CHARACTERISTICS OF CHRONIC ANKLE INSTABILITY AND THE ROLE OF JOINT MOBILISATION

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This is to certify that the thesis entitled **'Characteristics of Chronic Ankle Instability and the Role of Joint Mobilisation'** submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (Physiotherapy) is in a form ready for examination.

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DECLARATION

I hereby certify that the work embodied in the thesis is my own work, conducted under normal supervision. The thesis contains no material which has been accepted, or is being examined, for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968 and any approved embargo.

I hereby certify that this thesis is in the form of a series of papers. I have included as part of the thesis a written declaration from each co-author, endorsed in writing by the Faculty Assistant Dean (Research Training), attesting to my contribution to any jointly authored papers.

Ishanka Weerasekara _____ 16 August 2019

Signature Date

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2. Weerasekara, I., Osmotherly, P., Snodgrass, S., Marquez, J., de Zoete, R., & Rivett, D. (2017, October 19-21). A systematic review and meta-analysis of the clinical benefits of passive joint mobilisation on ankle sprains. Paper presented at the *Australian Physiotherapy Association Conference*, Sydney, Australia.

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ADL	activities of daily living
AMI	axial malleolar index
ANZCTR	Australian New Zealand Clinical Trial Registry
AP	antero-posterior
APTA	American Physical Therapy Association
ATFL	anterior talofibular ligament
AUC	area under the curve
BMI	body mass index
CAI	chronic ankle instability
CAIT	Cumberland ankle instability tool
CFL	calcaneofibular ligament
CI	confidence interval
CoP	centre of pressure
CT	computed tomography
df	degrees of freedom
DFROM	dorsiflexion range of motion
FAAM	foot and ankle ability measure
FAOS	foot and ankle outcome score

GRADE	Grading of recommendations, assessment, development and evaluation
HVLA	high velocity low amplitude
IAC	International Ankle Consortium
ICC	intra-class correlation coefficient
ICF	International classification of functioning, disability and health
IMI	intermalleolar index
ITT	intention to treat
IV	inverse variance
LR	likelihood ratio
MCID	minimal clinically important difference
MD	mean difference
MDC	minimal detectable change
ML	medio-lateral
MRI	magnetic resonance imaging
MWM	mobilisation with movement
N/A	not applicable
OR	odds ratio
PL	postero-lateral
PM	postero-medial
POLICE	protection, optimal loading, ice, compression and elevation

PPT	pressure pain threshold
PTFL	posterior talofibular ligament
QOL	quality of life
RCT	randomised controlled trial
RICE	rest, ice, compression and elevation
ROC	receiver operating characteristic
ROM	range of motion
SD	standard deviation
SE	standard error
SEBT	star excursion balance test
SEM	standard error of measurement
SMD	standard mean difference
TCJ	talocrural joint
TFJ	tibiofibular joint
TTS	time to stabilisation
VAS	visual analogue scale
WHO	World Health Organisation

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Abstract

Chronic ankle instability (CAI) is the occurrence of giving way and/or recurrent sprain and/or feelings of instability of a previously injured ankle. Compared to a simple ankle sprain, the additional morbidity and additional costs incurred due to diagnostic imaging related to CAI create significant economic and other societal consequences. Direct costs can include consultations with physicians, physiotherapists and other health professionals, diagnostic imaging and various hospital expenses, while indirect costs may arise from productivity losses, absenteeism (from school, work and sports) and diminished levels of physical activity resulting in economic burden on the healthcare system and for the individual patient. Rehabilitation of CAI commonly involves manual therapy procedures applied to joints in the ankle region, such as non-thrust passive joint mobilisation, high-velocity thrust manipulation and mobilisation with movement (MWM) as described by Brian Mulligan. These techniques largely involve a continuum of skilled passive movements of joints that are applied at different speeds and amplitudes. The overall aims of this thesis were to explore the clinical characteristics of CAI and to determine the effects of joint mobilisation in CAI. This thesis comprises four studies designed to meet these aims, presented as five manuscripts which have either been published in peer-reviewed journals or are in the process of review or submission.

Study 1 is a systematic review and meta-analysis undertaken to evaluate the current evidence for joint mobilisation in the clinical rehabilitation of ankle sprains, using the previously published body of literature. Based upon this investigation, joint mobilisation appears to be beneficial for improving dynamic balance immediately after application and dorsiflexion range of movement in the short-term

in chronic ankle sprains. The results of this study also suggested that the combination of MWM and associated fibular repositioning taping is more likely to exhibit a clinical benefit than other assessed mobilisation techniques, and potentially supporting the hypothesis of Brian Mulligan that the distal fibula is displaced anteriorly in CAI.

Study 2 explored the position of the distal fibula in relation to the position of the distal tibia in CAI using weight-bearing radiographs. The findings of this study indicated that there is a more anteriorly positioned fibula in individuals with CAI compared to individuals with healthy ankles when assessed in a weight-bearing position, consistent with Mulligan's hypothesis. Notably, this study was the first to use weight-bearing radiographs to measure the fibula position in CAI.

Study 3 investigated other clinical characteristics of CAI including ankle dorsiflexion range of motion, balance, self-reported function, pain and pressure pain threshold which have not been consistently reported, or for which little research has been published in the previous literature. It was found that individuals with CAI exhibit a multi-factorial presentation including impaired ankle dorsiflexion range, reduced static and dynamic balance, lower self-reported function and greater pain intensity, compared to individuals with healthy ankles. Despite the persistence of pain often reported in CAI, no evidence was found to suggest maladaptive central nervous system sensitisation (nociplastic pain).

Study 4 involved a randomised controlled trial (RCT) to investigate the effects of MWM of the distal tibio-fibular joint with fibular repositioning taping on fibular position and other clinical characteristics of CAI. The protocol for this study was published, and in contrast to almost all previously published studies of this manual therapy technique, highlighted the long-term nature of the trial with a one year follow-up. The immediate and short-term findings revealed no significant differences in any of the outcomes measured except for improvements in two self-reported function subscales (pain and sports on the foot and ankle outcome score (FAOS) questionnaire) in the placebo (detuned laser) intervention group. The long-term results were still being collected at the time of the submission of this thesis so are not reported or considered in the discussion.

The body of work contained in this thesis extends our current understanding of CAI and its clinical management. The results have implications for the identification of the features of CAI and for improving its treatment using joint mobilisation. Reproduction of the contained research using more homogeneous samples of CAI may permit a greater understanding of this persistent condition and how it responds to manual therapy. In addition, the use of weight-bearing radiographs in future studies to assess fibula position may be a more functional method. Other future directions for research and implications for clinical practice are discussed in detail in relation to the results of each of the studies in this thesis.

Chapter 1 Introduction

1.1 Background and context

1.1.1 Chronic ankle instability (CAI)

Lateral ankle sprains are among the most common sports-related injuries and also have high recurrence rates (Attenborough et al., 2014; Hiller et al., 2012; Simon et al., 2014). A large percentage of individuals with lateral ankle sprains develop chronic ankle instability (CAI) (Kobayashi & Gamada, 2014; Vicenzino et al., 2006; Wikstrom & Brown, 2014). Chronic ankle instability, chronic lateral ankle instability, ankle instability, residual ankle instability, chronic instability, recurrent instability, recurrent lateral ankle instability, and chronic ankle sprain have all been used interchangeably in the literature to describe the condition referred to as CAI (Hiller et al., 2011).

Two main subgroups of CAI are widely accepted; those with mechanical instability and those with functional ankle instability (Freeman, 1965; Hertel, 2002; Hiller et al., 2011). These are not mutually exclusive but part of a continuum (Hertel, 2002; Hiller et al., 2011). Functional instability is proposed to result from functional insufficiencies such as impaired proprioceptive and neuromuscular control, while mechanical instability is thought to result from isolated or combined anatomical changes occurring after an initial sprain (Hertel, 2002; Hiller et al., 2011). These anatomical changes include impaired arthrokinematics, pathological laxity, synovial tissue changes, and the development of degenerative joint disease. Altered fibular position at the inferior tibio-fibular joint is one arthrokinematic restriction proposed to be related to recurrent ankle sprains in CAI (Hertel, 2002).

Due to inconsistency in participant selection criteria for CAI in published studies, and the associated limitations in generalising to the target population, the International Ankle Consortium (IAC) has published standard criteria for inclusion and exclusion of participants with CAI when recruiting for research (Gribble et al., 2013). These inclusion and exclusion criteria, based on the ankle injury history and the timing of the ankle sprain, provide a broader description of the condition despite not quantifying any associated disability.

1.1.2 Prevalence, effects and burden of CAI

Epidemiological studies investigating ankle sprains in various countries highlight the high incidence during sports training and games, with rates reported in person years as 7 per 1000 in Denmark, 6.09 per 1000 in the United Kingdom, and 2.15 per 1000 in the United States (Bridgman et al., 2003; Holmer et al., 1994; Waterman, Belmont, et al., 2010). In Sri Lanka in 2015, 4.6% of adults in the community were affected by ankle sprains which lead to chronicity, suggesting a similar picture overall between developing and developed countries (Weerasekara & Hiller, 2017). Persistent residual symptoms of an initial ankle sprain including recurrent sprains, episodes of giving way at the ankle joint, pain, swelling, and decreased function have been termed CAI (Delahunt, Coughlan, et al., 2010; Gribble et al., 2013; Hubbard & Hicks-Little, 2008). It has been reported that up to 70% of these ankle sprains lead to CAI in the short-term (Gribble et al., 2016a). CAI may lead to articular degeneration of the ankle joint, increasing the risk of secondary osteoarthritis (Fong et al., 2009; Gribble et al., 2016a;

Hiller et al., 2012; Hubbard & Hicks-Little, 2008), which can adversely impact on quality of life (QOL) (Hiller et al., 2012).

The high prevalence and long-term deficits associated with CAI produce a large societal and economic burden (Fong et al., 2007; Gribble et al., 2016a). Generally, most ankle injury direct costs are spent on consultations with physicians and physiotherapists, diagnostic imaging and hospital facility usage (Bielska et al., 2017; Gribble et al., 2016a). The combined direct and indirect costs of ankle sprain rehabilitation has been reported as ranging from $1809 to $5271 per person (2016 USD) (Bielska et al., 2017). The overall healthcare cost of the management of CAI is thought to be greater than this, as it is associated with additional morbidity and additional diagnostic testing, such as advanced imaging procedures (Gribble et al., 2016b; Soboroff et al., 1984). Moreover, with CAI being the second leading cause of post-traumatic ankle osteoarthritis (Saltzman et al., 2005), it contributes substantially to osteoarthritic surgical cases (Delco et al., 2017). The estimated 4400 total ankle replacements and 25,000 ankle fusions carried out in the United States each year reflects the economic burden associated with ankle osteoarthritis (Delco et al., 2017). Further, productivity loss (with a mean duration of unemployment of 7-29 days), absenteeism (from school, work and sports), loss of leisure time, diminished level of physical activity, and cost of travel all contribute to the indirect costs associated with CAI (Bielska et al., 2017; Fong et al., 2007; Gribble et al., 2016a; Waterman, Belmont, et al., 2010).

Impairments related to CAI such as increased ligament laxity and proprioceptive deficits may lead to activity limitations, and consequently participation restrictions occupationally or in some sports. This reflects the potential impact of CAI in line with the International classification of functioning, disability and health (ICF) of the World health organisation (WHO) (Hiller et al., 2011).

1.1.3 Rehabilitation of CAI

Clinical practice guidelines linked to the ICF from the orthopaedic section of the American Physical Therapy Association (APTA) recommends manual therapy, therapeutic exercises and activities, and sports related activity training in the progressive loading rehabilitation phase of ankle sprain, based on the scientific literature accepted for publication prior to April 2012 (Martin et al., 2013). Further, this conservative treatment may be supported by proprioceptive training and external ankle support such as taping and braces (De Vries et al., 2003). Various manual therapy procedures, including graded passive joint mobilisation, joint manipulation, and non weight-bearing and weight-bearing mobilisations with movement (MWM) have all been recommended during the progressive phase loading of ankle sprain rehabilitation (Cruz-Diaz et al., 2015; Doherty et al., 2017; Loudon et al., 2014).

1.1.3.1 Joint mobilisation

Mobilisation is defined as “comprising a continuum of skilled passive movements to the joints and/or related soft tissues that are applied at varying speeds and amplitudes, including a small-amplitude and high-velocity therapeutic movement” (American Physical Therapy Association, 2003, p2). A variety of

mobilisation techniques are commonly used by physiotherapists based upon varying approaches and paradigms for the treatment of ankle sprains and ankle instability.

A number of studies have investigated the effects of joint mobilisation and manipulation on ankle sprains using a variety of outcome measures including pain, range of motion (ROM), and restricted function from the acute to chronic stages of recovery, and these have shown mixed findings (Collins et al., 2004; Cosby et al., 2011; Cruz-Diaz et al., 2015; Delahunt et al., 2013; Gilbreath et al., 2014; Gómez et al., 2015; Green et al., 2001; O'brien & Vicenzino, 1998; Penso, 2008; Vicenzino et al., 2006; Woodman et al., 2013). These studies have mostly investigated MWM, the mobilisation intervention which was introduced by New Zealand physiotherapist Brian Mulligan in the latter part of the 20th century (Mulligan, 1993; Mulligan, 1995).

1.1.4 Principles of MWM

MWM techniques as described in the Mulligan Concept of manual therapy, have been reported to be effective in improving clinically important outcomes of CAI including dorsiflexion ROM (DFROM), postural control, and self-reported instability (Cruz-Diaz et al., 2015; Reid et al., 2007; Vicenzino et al., 2006). The original proposed mechanism of action of MWM is known as the 'positional fault hypothesis.' In this hypothesis, it is postulated that MWM works by correcting a minor bony incongruity which is at the source of the patient's presenting painful movement problem (Hing et al., 2015).

In the application of MWM, a pain-free passive accessory joint mobilisation/glide is sustained while the patient performs an active or passive physiological movement/task which was previously painfully limited (Hoch & Mckeon, 2010; Vicenzino et al., 2011) . This problematic movement or task is also referred to as the client specific impairment measure, and most frequently this is a movement or muscle contraction performed to the onset of pain, or to the end of the available ROM or maximum muscle contraction if no pain is produced during the technique. Vicenzino et al (2011) have proposed a model to explain the effects of MWM. These authors propose that the underpinning mechanism has both a biomechanical component (which results in a corrective transient bony displacement) and a neurophysiological component (which results in non-opioid hyperalgesia), together producing the observable clinical benefits to the patient (Vicenzino et al., 2011). The capacity of MWM to reverse any bony positional displacement has not been well investigated and remains controversial, with long-term effects unknown.

Similarly, the effects of MWM on investigated clinical deficits in individuals with CAI compared to individuals with healthy ankles, such as in dorsiflexion range of motion (DFROM), balance and function have not been consistently detected at any time point, including from immediately after application to the longer term.

1.2 Research aims

The overall aim of this thesis is to determine the clinical benefits of ankle joint mobilisation on CAI. Specifically, the aims of the planned studies are as follows:

1. To perform a systematic review of the literature on the clinical benefits of joint mobilisation including MWM on ankle sprains and CAI
2. To determine the presence of fibular displacement as an anatomical characteristic of ankles with chronic instability
3. To determine the clinical characteristics of ankles with chronic instability
4. To assess the effect of MWM on fibular position in CAI
5. To evaluate the effectiveness of MWM on the immediate, short and long term clinical outcomes of CAI.

1.3 Significance

This thesis is significant in addressing several deficiencies in the literature related to CAI. First, it remains unclear exactly which anatomical and clinical characteristics contribute to CAI, and whether, and in what circumstances, joint mobilisation (including MWM) is effective in the management of CAI. It is also unknown which joint mobilisation techniques might provide the best balance of beneficial and adverse effects. Considering this, a systematic and up to date review of the scientific evidence is important. Further, studies investigating the anatomical and clinical characteristics of CAI might be helpful in understanding the underpinning mechanisms by which joint mobilisation including MWM may produce any effects. Finally, there is a dearth of sufficiently powered, high quality and

well reported RCTs with a long-term follow-up, evaluating the effects of MWM in the treatment of CAI and providing trustworthy guiding evidence for clinicians.

This PhD project comprises a systematic review and meta-analysis, a case-control study and a randomised controlled trial (RCT). The systematic review and meta-analysis is the first review of the literature in which joint mobilisation is investigated as the sole intervention to determine its clinical benefits in the management of ankle sprains. In particular, evidence for the effects of MWM are evaluated for individuals with ankle sprains, including CAI. The next study uses a case-control design to develop a better understanding of the anatomical and clinical characteristics of CAI. This study explores fibular displacement in relation to the tibia in CAI in the more functional weight-bearing position, and for the first time in the literature. It reports a discrimination (or cut-off) scores for an abnormally positioned fibula in relation to the tibia that best differentiates individuals with and without ankle instability. Further, it assesses specific clinical outcome measures, including that of pressure pain threshold (PPT) to investigate whether there is any centrally driven pain response in CAI. As the final study of the thesis, the RCT aims to determine the effectiveness of MWM on various clinically relevant outcomes in CAI, including long-term benefits which have not previously been investigated. Moreover, the capacity of MWM to reverse any displacement of the fibula is assessed and this is the first study to investigate the effect of joint mobilisation on fibular displacement. The overall thesis will summarise the current research about the effects of joint mobilisation on ankle sprains, report the anatomical and clinical characteristics of CAI compared to healthy ankles, and measure the effects of MWM on various clinical outcomes of CAI.

1.4 Overview of the thesis

This thesis investigates the clinical benefits of the MWM joint mobilisation on CAI. It comprises a narrative literature review followed by a series of research papers (both published peer-reviewed articles and journal manuscripts under review) which describe the four studies undertaken, the overall findings of which are consolidated in a concluding discussion chapter.

The chapter outlines are as follows:

- Chapter 1 provides introductory information regarding CAI, joint mobilisation and details the aims and significance of the thesis
- Chapter 2 describes the available literature on the characteristics of CAI and the potential role of joint mobilisation in the rehabilitation of CAI
- Chapter 3 details Study 1 which reviews the current evidence for the clinical benefits of joint mobilisation for ankle sprains, in the form of a systematic review and meta–analysis (Weerasekara et al., 2018)
- Chapter 4 details Study 2, a case-control study exploring changes in fibular position compared to the position of the tibia as an anatomical characteristic of CAI, in order to investigate whether there is a difference in the fibular positon in CAI compared to healthy individuals.
- Chapter 5 details Study 3, a case-control study exploring clinical characteristics of CAI, in order to investigate whether individuals with CAI have specific deficits in terms of ankle DFROM, balance, self-reported function, pain and PPT compared to healthy matched controls, and do any of these differentiate between individuals with CAI and healthy individuals.

- Chapter 6 reports the protocol for Study 4, an interventional study to assess the effect of MWM on the anatomical and clinical properties of CAI (Weerasekara, Osmotherly, Snodgrass, et al., 2019b). This RCT is designed to investigate the immediate, short and long term effects of MWM on fibular position and clinical outcomes (ankle DFROM, balance, self- reported function, PPT, and pain intensity) in individuals with CAI, as well as identify any prognostic factors indicating recovery from CAI using MWM.
- Chapter 7 reports the actual findings of Study 4, that is the results of the interventional study to assess the effects of MWM on the anatomical and clinical properties of CAI. The immediate and short-term effects are reported in this chapter, but at the time of submission of the thesis the long-term data were still being collected.
- Chapter 8, the final chapter, provides a concluding summary and overarching discussion of the key findings and limitations of the various studies comprising the thesis, as relevant to the potential role of joint mobilisation in CAI and its pathophysiology, with recommendations for future research and implications for clinical practice.

1.5 Scope/delimitations

Whilst many joint mobilisation/manual therapy techniques have been suggested as useful in the rehabilitation of individuals with CAI, the scope of this thesis became increasingly focussed on the MWM joint mobilisation technique. This decision was made because the initial study, the systematic review and meta-analysis of previously published studies, suggested that the combination of Mulligan's MWM and associated fibular repositioning taping is more likely to produce a clinical

benefit than the other assessed joint mobilisation techniques (Weerasekara et al., 2018). Other physical interventions commonly employed in the treatment of CAI were not within the scope of this thesis. Finally, the decision was made to focus most of the research conducted in the thesis on CAI, because typically joint mobilisation including MWM is not the preferred choice of treatment in the acute stage of ankle sprain (Van Den Bekerom et al., 2013), and because CAI poses a greater burden to society and the individual.

Chapter 2 Literature review

2.1 Chronic ankle instability (CAI)

2.1.1 General description of CAI

The most frequently occurring acute sporting injury is reported to be the acute ankle sprain, accounting for about 14% of all sporting injuries (Fong et al., 2009; Garrick, 1977; Hertel, 2002; Powden et al., 2016). The acute ankle sprain is regularly under-treated, or even not treated at all as it is often not considered a severe or debilitating injury (Hertel, 2002; Mckay et al., 2001; Weerasekara & Hiller, 2017; Weerasekara et al., 2016). However, twenty to forty percent of individuals with acute ankle sprains are considered to be at risk of developing CAI due to varying factors such as inadequate rehabilitation or persistent deficits developed as a long-term sequela of the initial sprain (Hershkovich et al., 2015; Kobayashi & Gamada, 2014; Miklovic et al., 2018; Weerasekara, Tennakoon, et al., 2019).

The occurrence of repetitive bouts of lateral ankle instability, resulting after a single severe sprain or after numerous minor sprains is clinically considered to indicate CAI (Guillo et al., 2013; Hertel, 2002). Persistent pain, 'giving way' and feelings of instability in the ankle, and recurrent sprains, potentially leading to persistent disability are some of the key features of CAI (Attenborough et al., 2014; Gribble et al., 2016a). Although acute lateral ankle sprains occur at approximately the same rate between males (78.8%) and females (77.3%) (Tummala et al., 2018). CAI has been shown to have a comparatively greater prevalence among males (males, 1.1%; females, 0.7%) (Hershkovich et al., 2015).

Soccer, basketball and volleyball are the most represented sports in cases of CAI (Attenborough et al., 2014), and increased body mass index (BMI) and greater body height have also been associated with an increased incidence of CAI (Hershkovich et al., 2015). Commonly the mechanism of ankle sprains involves a sudden violent inversion or supination movement (Fong et al., 2009; Powden et al., 2016), however the mechanism by which CAI develops remains somewhat unclear.

While the direct costs for rehabilitation of acute lateral ankle sprains are relatively low, the indirect costs from follow-up rehabilitation and injury-associated time loss result in a higher financial impact (Gribble et al., 2016a; Weerasekara & Hiller, 2017). Importantly, the impacts on patient QOL, including on leisure time and work productivity are considerable (Gribble et al., 2016a).

2.1.2 Defining CAI

CAI has been defined in many ways but is mostly described as "an encompassing term used to classify an individual with both mechanical and functional instability of the ankle joint" (Gribble, Philip A et al., 2013, p. 583; Hertel, 2002). The original model, as proposed by Hertel explains CAI as resulting from both mechanical instability and functional instability (Hertel, 2002). Hertel's model of CAI has been commonly used in research, with modifications later added by Hiller et al (Hiller et al., 2011). According to the revised Hertel model, CAI is a heterogeneous condition of perceived instability, which may include mechanical or functional instability or a combination of both (Hertel, 2002; Hiller et al., 2011). Notably, no correlation has been found between mechanical and functional instabilities,

though they may both be present as parallel phenomena (Peters et al., 1991). Recently, selection criteria for patients with CAI in controlled research have been published, focused on defining a history of acute lateral ankle sprains and subsequent functional limitations as indicated by episodes of 'giving way' and validated self-reported outcome tools (Gribble et al., 2013). Interestingly, measures to evaluate mechanical instability were not considered amongst these criteria (Lohrer et al., 2015).

Functional instability has been proposed to result from functional insufficiencies such as impaired proprioception, neuromuscular control, postural control or strength, while mechanical instability is thought to result from isolated or combined structural changes after the initial sprain (Hertel, 2002). These structural changes may include impaired arthrokinematics, pathological laxity, synovial tissue changes, and the development of degenerative joint disease which can cause alteration of the mechanics of one or more joints within the ankle complex (Hertel, 2002; Hiller et al., 2011).

2.1.3 Mechanism of CAI

The initial tissue damage during the first episode of a lateral ankle sprain may develop into a combination of deficits such as sensory impairments and motor impairments that eventually can influence the clinical outcomes in a patient with CAI (Hertel & Corbett, 2019). The development of CAI following a lateral ankle sprain may be related to both personal (e.g. age and sex) and environmental (e.g. physical activity and sports participation) factors (Mccann & Gribble, 2016). Extensive research has been carried out to explore the alterations of anatomical structures and function in CAI, but the reasons for persistence of the impairments in some people but not others have not been

clearly explained (Mccann & Gribble, 2016). Further, development of CAI is impacted by patient resilience and self-efficacy, social attitudes, and rehabilitation adherence (Mccann & Gribble, 2016). Underlying central nervous system changes related to pain in CAI remain unclear, but central sensitisation may be a possible factor for the persistence of pain.

A recent update to the Hertel model has attempted to explain the development of CAI according to the ICF classification of the WHO, utilising some more contemporary injury models such as the biopsychosocial model, dynamic systems theory and the neuromatrix of pain theory (Hertel & Corbett, 2019). Essentially, it is a longstanding failure to cope with specific impairments resulting from the initial trigger of sensorimotor changes (via inflammatory and pain mediators) which occurred during the acute injury (Hertel & Corbett, 2019).

2.2 Anatomy and pathophysiology of CAI

The ankle joint complex comprises three major articulations: the talocrural joint, the subtalar joint, and the distal tibiofibular syndesmosis (Fong et al., 2009).

2.2.1 Talocrural joint

The talocrural joint behaves like a hinge joint and is formed by the articulation of the dome of talus, the tibial plafond, the medial malleolus and the lateral malleolus. The talocrural joint is supported laterally by three main ligaments; the anterior talofibular ligament (ATFL), the calcaneofibular ligament (CFL)

and the posterior talofibular ligament (PTFL) (Figure 2.1). Medially it is supported by the deltoid ligament (Fong et al., 2009; Hintermann, 2005). The ATFL runs from the anterior rim of the lateral malleolus to the lateral aspect of the talar neck. The CFL originates from tip of the lateral malleolus and inserts onto the lateral face of the calcaneus where it lies between the calcaneus and the peroneal tendons. The PTFL originates from the posterior part of the lateral malleolus and inserts into the posterior part of the talus. Two other ligaments are also located laterally; the anterior inferior tibiofibular ligament (origin, anterior part of the distal fibula; insertion, anterior part of the tibia) and the posterior inferior tibiofibular ligament (origin, posterior tibia; insertion, posterior malleolus) (Mckiernan et al., 2017). Each of the lateral ligaments has a role in stabilising the talocrural joint and/or the subtalar joint, depending on the position of the ankle (Hintermann, 2005). The medial ligament complex is composed of superficial and deep portions of the deltoid ligament. The tibiocalcaneal, tibiospring and tibionavicular ligaments comprise the superficial portion, and span from the medial malleolus to insert broadly onto the calcaneus, navicular, talar neck and spring ligament. The deep anterior tibiotalar, superficial posterior tibiotalar and deep posterior tibiotalar ligaments constitute the deep deltoid complex (Hintermann, 2005).

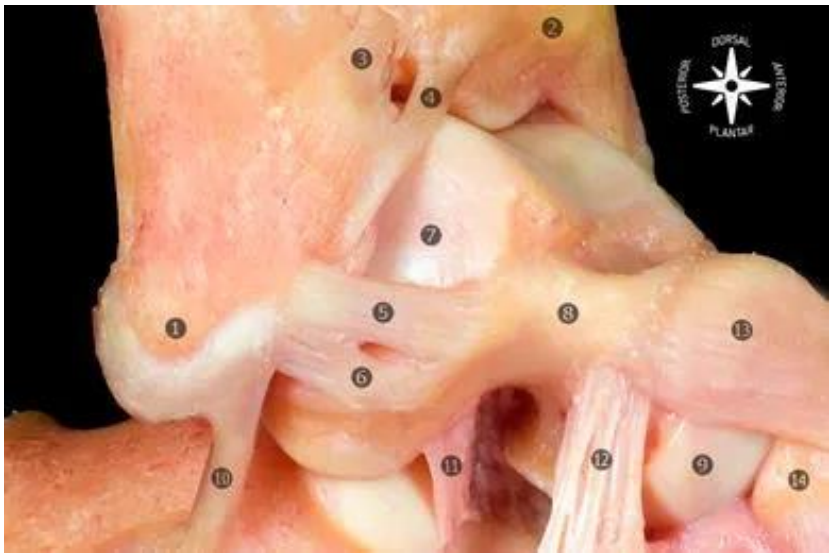

Figure 2. 1 The lateral ligaments of the foot and ankle joint. The anterior talofibular ligament is typically composed of two separate bands (1) Tip of the lateral malleolus; (2) tibia; (3) anterior tibiofibular ligament; (4) distal fascicle of the anterior tibiofibular ligament; (5) superior band of the anterior talofibular ligament; (6) inferior band of the anterior talofibular ligament; (7) lateral articular surface of the talus; (8) neck of the talus; (9) head of the talus; (10) calcaneofibular ligament; (11) talocalcaneal interosseous ligament; (12) cervical ligament; (13) talonavicular ligament; (14) navicular (Golanó et al., 2010).

2.2.2 Subtalar joint

The subtalar joint is a gliding joint formed by the articulation between the talus and the calcaneus (Norkus & Floyd, 2001). The anterior compartment of the subtalar joint is formed by the talocalcaneonavicular joint and the posterior component is formed by the talocalcaneal joint, separated by the canalis and sinus tarsi. The talocalcaneonavicular joint may be characterised as a ball-and-socket

joint (Bartoníček et al., 2018; Schuenke et al., 2009). The talocalcaneal joint of the subtalar complex is reinforced by anterior, posterior, lateral, medial, and interosseous talocalcaneal ligaments (Norkus & Floyd, 2001). The talocalcaneonavicular joint of the subtalar complex is supported by the spring ligament, the medial part of the bifurcate ligament (calcaneonavicular ligament) and the dorsal talonavicular ligament. The spring ligament is formed collectively by the superomedial ligament (largest), the medial plantar oblique ligament (thinnest) and the inferior plantar ligament (shortest) (Bartoníček et al., 2018). The bifurcate ligament is assumes a typical Y or V shape, and originating from the anteromedial edge of the anterior calcaneal process and inserting onto the lateral pole of the navicular close to the edge of its talar articular surface. The talonavicular ligament runs from the superior and partly from the lateral aspect of the neck of the talus into the upper surface of the navicular (Bartoníček et al., 2018). The canalis and sinus tarsi contain a complex system of ligaments and the roots of the inferior extensor retinaculum, the cervical ligament, the interosseous talocalcaneal ligament, and the anterior talocalcaneal ligament can be seen (Bartoníček et al., 2018).

2.2.3 Distal tibiofibular syndesmosis

The distal tibiofibular syndesmosis is formed by the articulation between the distal tibia and fibula (Fong et al., 2009; Schuenke et al., 2009). This articulation is further subdivided according to region into the superior tibiofibular joint, the interosseous membrane, and the inferior tibiofibular joint (Norkus & Floyd, 2001). The superior and inferior tibiofibular joints of distal tibiofibular syndesmosis are syndesmotic articulations between the convex surface of the fibula and the concave surface of the tibia, where the superior tibiofibular joint is located proximally and the inferior tibiofibular joint is located distally (Norkus & Floyd, 2001). The interosseous membrane is a thick osseofascial structure

extending from the tibial periosteum to the fibula and anchors the fibula and tibia together (Norkus & Floyd, 2001). The superior tibiofibular joint of the distal tibiofibular syndesmosis is stabilised by the anterior superior tibiofibular and posterior superior tibiofibular ligaments (Norkus & Floyd, 2001). The interosseous ligament binds the tibia and fibula, and is continuous with the interosseous membrane at the syndesmosis (De Vries, 2009; Norkus & Floyd, 2001). The inferior tibiofibular joint is reinforced by the anterior inferior tibiofibular ligament, the posterior inferior tibiofibular ligament, and the interosseous ligament (Norkus & Floyd, 2001).

With regard to the lateral ligaments which are relevant for inversion injuries, the ATFL is on maximum tension when the foot is in plantarflexion and supination, the CFL in dorsiflexion and supination, and the PTFL in dorsiflexion (De Vries, 2009). Lateral ankle sprains account for 80-85% of all ankle sprain injuries (Ferran & Maffulli, 2006) and 65-73% involve an isolated injury to the ATFL (Fong et al., 2009; Lynch, 2002). Combined injury of the ATFL and CFL is reported as being 20-25% of cases, and the PTFL has a lesser involvement of around 10% (Lynch, 2002; Renström & Konradsen, 1997). Another 3-10% of all ankle sprains are syndesmosis injuries or 'high ankle' sprains (Dubin et al., 2011; Renström & Konradsen, 1997), which may also involve a partial tear of the anterior deltoid ligament or malleolus fractures (Lynch, 2002; Renström & Konradsen, 1997). Only 3-33% of all ankle sprains involve the medial aspect of the ankle as the strong medial deltoid ligament is quite resistant to tearing (Fallat et al., 1998; Lynch, 2002; Ribbans & Garde, 2013). Most ankle sprains recover within several weeks to 2-3 months depending on the grade and site of the sprain, although 20-40% result in chronic sequelae (Krabak & Baima, 2008).

2.3 Clinical evaluation and diagnosis of CAI

A history of an ankle sprain preludes the signs and symptoms of CAI. A lateral ankle sprain is usually associated with an episode of an acute inversion/supination injury to the ankle, with or without an audible 'snapping' sound or feeling of a 'tearing' sensation (Lynch, 2002). Generalised pain and swelling are also present (Guillo et al., 2013; Lynch, 2002). CAI is accompanied by the perception of an abnormal ankle with a combination of symptoms reported, including recurrent sprains, pain, swelling, and avoidance of activities (Guillo et al., 2013). Provisional diagnosis is reliant on the patient's reported findings, with physical and radiological examinations used to confirm the diagnosis of CAI. During the assessment of patient reported findings, standard questions aiming to capture the presentation of CAI are used to establish a provisional diagnosis clinically. The key criteria to establish in the questioning include recurrence of acute ankle sprains, giving way of the ankle, avoidance or adaptation to daily or sporting activities, perception of an unstable ankle, and a perceived abnormal ankle indicated by factors such as pain or swelling (Guillo et al., 2013). There are also some self-reported scoring tools available to quantify the severity of ankle instability (including the Cumberland ankle instability tool [CAIT]), and to assess the functional impairments associated with CAI (including the foot and ankle ability measure [FAAM], and the foot and ankle outcome score [FAOS]), however they may not appropriate for everyday clinical use (Guillo et al., 2013).

During the physical examination, a comparative assessment of both ankles is undertaken, including assessing the alignment of the lower leg and foot while standing and during gait, and isolating the location of any tenderness. In addition, assessment of the range of ankle movements, ligament stress tests such as the talar tilt test and anterior drawer test, and stability measures such as single-leg stance

are usually important components of the physical examination (Gribble, 2019; Guillo et al., 2013). Standard plain radiographs, including anteroposterior, lateral and mortise views, as well as a comparative Saltzmann view to assess hindfoot alignment, may be ordered if indicated (Guillo et al., 2013). Comparative stress radiographs of the anterior drawer test and talar tilt test are also commonly performed. Advanced imaging procedures such as magnetic resonance imaging (MRI), ultrasonography and computed tomography (CT) may be helpful in some cases, though they are not routinely performed (Gribble, 2019; Guillo et al., 2013). Each of these assessment procedures are further discussed in the following sections.

2.3.1 Patient reported findings

Usually reports of pain, swelling, a feeling of giving way, or actual re-injury predominate the patient interview. These may occur during sporting activities, walking on uneven ground, or activities of daily living (ADL) (Peters et al., 1991). Questioning may reveal a history of recurrent acute ankle sprains, giving way of the ankle without a new sprain, perceptions of an insecure or unstable ankle, avoidance of or adaptation to daily or sporting activities, and the general perception of an abnormal ankle (Guillo et al., 2013). Several self-reported questionnaires may be used to quantify the functional impairments associated with CAI including the FAAM questionnaire, the FAOS questionnaire, and the CAIT questionnaire to assess the severity of the disorder and monitor progress following treatment.

2.3.1.1 Foot and ability measure (FAAM) questionnaire

The FAAM questionnaire is one of two general self-reported foot and ankle function questionnaires used to describe the level of disability recommended by the IAC in the selection of participants with CAI in controlled research (Gribble et al., 2013). This 29-item questionnaire was developed by Martin et al., and consists of two subscales: a 21-item ADL subscale and a 8-item sports subscale (Martin et al., 2005). Each item is scored on a 5 point Likert scale whereby 4 indicates 'no difficulty at all' and 0 indicates 'unable to do'. Total scores range from 0 to 84 for the ADL subscale and from 0 to 32 for the sports subscale, and these scores are converted to percentages. A higher percentage represents a higher level of function (Carcia et al., 2008), with 0% indicating an inability to perform the task and 100% indicating a level of function equivalent to before the injury. In addition, the perception of the participant about their ankle is rated as normal, nearly normal, abnormal, or severely abnormal on a categorical scale.

This instrument has been examined for reliability and validated in various languages including Brazilian, Dutch, English, French, German, Italian, Japanese, Persian, Spanish, Thai and Turkish (Arunakul et al., 2015; Borloz et al., 2011; Celik et al., 2016; Cervera-Garvi et al., 2017; Mazaheri et al., 2010; Moreira et al., 2016; Nauck & Lohrer, 2011; Sartorio et al., 2014; Uematsu et al., 2015; Weel et al., 2016). Responsiveness of this instrument has been evaluated for various ankle conditions including diabetes, achilles tendon diseases, and CAI (Carcia et al., 2008; Hoch et al., 2016; Kivlan et al., 2011; Reb et al., 2017). The questions were formed from a review of the literature and input from an expert panel. Initial item reduction was carried out with expert clinicians from the APTA. The participants involved in final item reduction included 1027 patients referred to physical therapy by a

physician and who were receiving treatment for a leg, ankle, or foot musculoskeletal disorder (Martin et al., 2005). The FAAM was validated for CAI using 30 young athletes and it is suggested that this instrument may be used to detect self-reported functional deficits related to CAI (Carcia et al., 2008). The minimal detectable change (MDC) and minimal clinically important difference (MCID) calculated for this questionnaire are 5.7 and 8 points, and 12.3 and 9 points, respectively, for the ADL and sports subscales (Martin et al., 2005).

2.3.1.2 Foot and ankle outcome score (FAOS) questionnaire

The FAOS questionnaire is the other of the two IAC endorsed general self-reported foot and ankle function questionnaires used to describe the level of disability in the selection of participants with CAI in controlled research (Gribble et al., 2013). This is a 42-item questionnaire assessing five separate subscales: pain (nine items), other symptoms (seven items), ADL (17 items), sport and recreational activities (five items), and QOL (four items) (Roos et al., 2001). Each item is scored on a 5 point Likert scale ranging from 0 to 4. A normalised score is calculated with lower percentage scores representing extreme symptoms for each subscale (Roos et al., 2001).

This instrument has been tested for reliability and validated in various languages including Dutch, Iranian and Thai (Angthong; Negahban et al., 2010; Van Den Akker-Scheek et al., 2013). Responsiveness of this instrument has been tested for various ankle conditions including acquired flatfoot deformity, ankle osteoarthritis, and hallux rigidus (Hogan et al., 2016; Mani et al., 2013; Mani et al., 2015). Questions were adapted from the knee injury and osteoarthritis outcome score and

validated using the responses of 213 participants who had undergone an anatomical reconstruction of the lateral ankle ligaments on average 12 years prior to study enrolment (Roos et al., 2001). The MDC and MCID have not been reported.

2.3.1.3 Cumberland ankle instability tool (CAIT) questionnaire

The CAIT has been designed to evaluate the severity of functional ankle instability (Hiller et al., 2006). The CAIT questionnaire is one of the three recommended questionnaires used to confirm the 'presence of self-reported ankle instability' which is one of the IAC inclusion criteria for participants with CAI in controlled research (Gribble et al., 2013). A cut-off score ≤ 24 identifies a 'self-reported unstable ankle' (Gribble et al., 2013). The maximum score is 30 for this 9-item questionnaire, and a low score represents more severe functional ankle instability. This instrument has been tested for reliability and validated in various languages including Dutch, Persian, Japanese, Korean, Spanish and Brazilian-Portuguese (Cruz-Diaz et al., 2013; De Noronha et al., 2008; Hadadi et al., 2017; Ko et al., 2015; Kunugi et al., 2017; Vuurberg et al., 2016). The questions included in the CAIT were identified from previous studies on ankle injury and from focus group interviews with people with CAI. The final version of CAIT was devised with 236 participants from a university campus, the general community and from among dance students at a performing arts high school (Hiller et al., 2006), and was validated with 177 participant responses. Participants with a score of 27 or lower were found to be likely to have functional ankle instability (Hiller et al., 2006). The CAIT has an MDC and MCID of ≥ 3 points (Wright et al., 2017).

2.3.2 Physical examination and tests

Comparative assessment of both ankles is necessary during physical examination and testing. Gait, alignment of the lower leg and hind foot, precise location of tenderness, ankle ROM, calf muscle tightness, and strength and pain on resisted function of the peroneal and tibialis posterior tendons are all assessed during the physical examination (Guillo et al., 2013). In addition, the Beighton scale tests are used to identify general ligament laxity (Guillo et al., 2013). The anterior drawer and talar tilt stress tests for the lateral ligaments can be used to establish the presence of mechanical instability (Guillo et al., 2013). However, the descriptions of the amount of translation considered physiologically normal for these tests are conflicting. Published normal responses have ranged from 2mm to 9mm for the anterior drawer test (Gould et al., 1980; Johannsen, 1978; Karlsson et al., 1989; Lynch, 2002), and 5° to 23° for the talar tilt test (Cox, 1985; Lynch, 2002; Rubin & Witten, 1960). Comparison of the amount of pathologic anterior laxity with the opposite normal ankle is generally recommended for the anterior drawer test, with a between limb difference exceeding 3mm being considered a positive anterior drawer test (Jolman et al., 2017; Lynch, 2002). More than 10° difference from the opposite normal side is generally considered abnormal when interpreting the outcome of the talar tilt test (Lynch, 2002). Stability and proprioceptive control of the ankle can also be assessed using single-leg stance with eyes open and then eyes close (Guillo et al., 2013).

The benefits and limitations of the physical examination tests used for outcome measurements within this thesis, including related common methods of measurement, normal ranges of values, reliability and MDC values are discussed below, where they have been previously reported.

2.3.2.1 Weight-bearing DFROM

Dorsiflexion ROM deficits may have implications for a patient sustaining future lower extremity injuries, including plantar fasciopathy, ankle sprains, and patellofemoral pain syndrome (Hoch et al., 2015; Pope et al., 1998; Rabin & Kozol, 2012; Riddle et al., 2003). Relationships between weight-bearing DFROM, sagittal plane kinematics at the knee and hip, and vertical ground reaction forces during single-leg landing have been observed in individuals with CAI (Hoch et al., 2015). Further, relationships have been observed between ankle DFROM and the anterior reach direction of the star excursion balance test (SEBT) which indicate that ankle DFROM may influence dynamic balance (Basnett et al., 2013). Identification of dorsiflexion deficits in individuals with CAI may potentially assist clinicians to modify the landing biomechanics of these individuals, potentially reducing the likelihood of further injury (Hoch et al., 2015).

Several methods and tools are available to measure ankle DFROM in both non weight-bearing and weight-bearing positions. Weight-bearing measures of dorsiflexion have been suggested to be advantageous over non weight-bearing measures as they are easy to perform, provide the ability to obtain full ROM with the participant's own body weight, and because they are more functional (Rabin & Kozol, 2012). A weight-bearing lunge position using a standard goniometer, digital inclinometer, or a tape measure using the distance-to-wall technique are all common, reliable methods to obtain ankle DFROM with low measurement error (Konor et al., 2012). One limitation of this method is the

difficulty of performing this manoeuvre on weight-bearing restricted individuals, such as immobilised patients (Rabin & Kozol, 2012).

Weight-bearing measures including goniometric, inclinometric and tape measure methods may be used to reflect the available ROM during functional activities. Each involves an individual performing a weight-bearing lunge (Konor et al., 2012). The goniometric method is commonly used clinically, however requires a greater degree of technical proficiency (Konor et al., 2012). The inclinometric method is easy to use, however the cost of equipment is usually higher than for a standard goniometer (Konor et al., 2012). The tape measure method is inexpensive, can be used in a variety of settings and does not require the technical proficiency of goniometric or inclinometric methods (Konor et al., 2012). During the tape measure method, the patient is instructed to lunge towards the wall, touching their knee to the wall, whilst keeping their heel in contact with the floor. They are then asked to move their foot away from the wall in 1cm increments until the heel no longer maintains contact with the floor or the knee is no longer in contact with the wall. Maximal dorsiflexion is considered to be the greatest distance between the great toe and wall with the participant's knee maintaining contact with the wall (Gilbreath et al., 2014; Hoch, Staton, et al., 2012; Konor et al., 2012). The same procedure is followed for the opposite side. Each centimetre away from the wall in the lunge test represents approximately 3.6° of ankle dorsiflexion (Bennell et al., 1998).

Individuals with CAI have been shown to have a mean 1.7cm deficit in the weight-bearing lunge test (Hoch, Staton, et al., 2012) compared to healthy matched individuals (Drewes et al., 2009). Both the

inter-rater reliability (intra-class correlation coefficient (ICC)=0.65-0.99) and intra-rater reliability (ICC=0.80-0.99) of the weight-bearing lunge test have been reported as good (Powden et al., 2015). Average MDC scores for inter-clinician and intra-clinician weight-bearing lunge test are 4.6° in goniometric method (1.6cm in tape measure method) and 4.7° (1.9cm) respectively (Powden et al., 2015).

2.3.2.2 Static balance

Postural control impairments in CAI have not been detected consistently with the use of traditional instrumented measures (Mckeon & Hertel, 2008). No differences have been revealed in single-leg stance balance measures between individuals with non-injured ankles after a primary ankle sprain and individuals with CAI (De Vries et al., 2010; Isakov & Mizrahi, 1997). Further, no differences have been demonstrated between individuals with and without functional ankle instability (Ross & Guskiewicz, 2004). However, stabilometry scores were reported as reduced among soccer players with functional instability, but were not apparently affected in those with mechanical instability (Tropp et al., 1985). Similarly, no differences in stabilometry measures were demonstrated between mechanically stable and mechanically unstable ankles in a latter study (Leanderson et al., 1993).

A number of non-instrumented and instrumented single-leg stance balance measures for ankle instability have been reported, with instrumented force plate measures more recently becoming the gold standard of assessment (Mckeon & Hertel, 2008). The balance error scoring system, timed balance test, and foot lift test are some available clinical tests used in measuring static balance. The

timed balance test was found to not be ideal in detecting a significant decline in balance until the age range of 60 to 70 years and also for athletes with mild concussion, suggesting a lack of sensitivity in detecting mild changes in balance (Browne & O'hare, 2001; Clark, 2007). Potentiometric displacement transducers, mechanical ataxia meters, sway magnetometry, multi-sensor polymer insoles and three-dimensional video analysis are some tools that have been used to record sway patterns of individuals (Browne & O'hare, 2001). Precise measurements of static balance with centre of pressure (CoP) data using force plates is now commonly the method used in research to quantify balance deficits associated with CAI (Linens et al., 2014).

When measuring static balance using CoP data obtained with the participant standing on the centre of a force plate, a standardised single-leg stance position is maintained. The individual is instructed to flex the non-tested leg slightly at the hip, whilst flexing the knee to 90°. The arms are crossed at the chest with each hand resting on the opposite shoulder. Measurements are recorded in both 'eyes open' and 'eyes close' positions. For 'eyes open', the individual is asked to maintain a fixed gaze on a cross marked on the wall five metres in front of them and remain as still as possible for 10 seconds (Karlsson & Frykberg, 2000).

The most commonly assessed CoP variable is sway velocity calculated as the absolute mean value of the instantaneous velocity of the CoP in a given direction during a given period (Ross et al., 2009), which indicates how quickly a person shifts and is able to control their CoP (Childs, 2016). A cut-off score of $\geq$ 1.56cm/s for CoP velocity measures in the single-leg stance position has been used to

distinguish individuals with and without CAI (Linens et al., 2014). Measurement of sway area in weight-bearing has been demonstrated to be reliable with an ICC ≥ 0.70 (Golriz et al., 2012). MDC values are estimated at 12mm/sec, 39mm, 4303mm^2 for CoP mean velocity, average location of CoP, and sway area respectively, for one repetition on the force plate (Golriz et al., 2012).

2.3.2.3 Dynamic balance

Some studies which have used force plate data alone have identified dynamic balance deficits in individuals with CAI (Brown & Mynark, 2007; Groters et al., 2013; Ross & Guskiewicz, 2004; Wikstrom et al., 2007), while other studies have reported no differences (Bernier et al., 1997; Shiravi et al., 2017). These conflicting findings may be due to the various activities researchers have chosen to use to assess dynamic balance on force plates (i.e. multiple hop test, single-leg hop, weight shifting tasks, and perturbations through the use of a tilting platform). In addition, the two studies with non-significant findings had comparatively small sample sizes raising the possibility of insufficient statistical power leading to a null result (Bernier et al., 1997; Shiravi et al., 2017). Poor dynamic balance has been observed in individuals with CAI compared to both lateral ankle sprain copers (described as perceiving a successful recovery from initial lateral ankle sprain with no or minimal symptoms within a year post-injury) (Hertel & Corbett, 2019; Wikstrom & Brown, 2014) and healthy controls (Doherty et al., 2016). When considering subgroups of CAI, individuals with mechanical instability have demonstrated increased postural sway compared to those with functionally unstable (and healthy) ankles. Postural control in individuals with functional instability has not been shown to be different to those with healthy ankles (Chen et al., 2014). When SEBT data were combined with force plate measures, method that which excludes any influence by the researcher the velocity of the

CoP was found to be lower in individuals with CAI compared to those without CAI in the medio-lateral component (Pionnier et al., 2016), indicating balance deficits are associated with CAI.

Dynamic balance tests have been suggested to provide a better means for identifying CAI over static balance tests as they assess balance during a functional task performance (Linens et al., 2014). There are several instrumented and non-instrumented methods available to measure dynamic balance, including the side hop test, SEBT test, and figure-of-8 hop test (Arnold et al., 2009; Linens et al., 2014). Time to stabilisation (TTS) in a single-leg jumping task and the SEBT are commonly used functional measures to assess dynamic balance in CAI (Arnold et al., 2009; Gribble et al., 2012). TTS provides better measures with larger effect sizes compared to SEBT alone, however it requires a force plate and analytical software (Arnold et al., 2009). Use of CoP measures during the SEBT to assess dynamic postural control has been introduced using movement analysis tools (optoelectronic cameras and force platforms) in some recent studies (Doherty et al., 2015; Pionnier et al., 2016).

Combining SEBT (in anterior, postero-lateral and postero-medial directions) with CoP data from force plate measures could assess balance more objectively than clinical tests alone, and could precisely quantify the balance measures (Bansbach, 2017). To do this, the individual is asked to establish a stable base of support on the stance limb in the middle of the testing grid on a force plate. While standing on a single limb, the individual is instructed to reach as far as possible with the reaching limb along each line (anterior, postero-medial and postero-lateral directions), lightly touching the line with the most distal portion of the reaching foot without shifting weight or coming to rest on the foot of the

reaching limb. The reaching limb is then returned to the starting position on the centre of the grid. If the individual lifts or shifts any part of the foot of the stance limb during the trial, the trial is not considered as complete (Gribble et al., 2012). After performing a maximum of four non-recorded trials for familiarisation, the next trial for each direction is recorded (Pionnier et al., 2016; Robinson & Gribble, 2008). Normalised SEBT values are obtained by dividing the excursion distance by the participant's leg length (the distance between the anterior superior iliac spine and the ipsilateral medial malleolus), and then multiplying by 100 (Gribble & Hertel, 2003; Pionnier et al., 2016). Data for CoP velocity, area and amplitude to quantify spatio-temporal parameters (medio-lateral and antero-posterior) are acquired at 100Hz, under the foot during single-leg stance (Pionnier et al., 2016).

The intra-rater and inter-rater reliability of the SEBT are both reported as good to excellent for both legs (ICC values ranging from 0.87 to 0.90), and the MDC values are calculated as 7.2% for the right leg and 6.2% for the left (Van Lieshout et al., 2016).

2.3.2.4 Pain intensity and pain distribution

One common residual symptom following a lateral ankle injury is reported to be pain. In a recent study of individuals with CAI, 12.4%, 47.7% and 39.9% reported constant pain, pain during physical activities, and no pain respectively (Adal et al., 2019). It is therefore important to understand the pain characteristics and distribution of pain in patients with CAI.

Various pain intensity measures are available including the visual analogue scale (VAS), point numerical rating scale, box scale, behavioural rating scale, verbal rating scale, McGill pain questionnaire and chronic pain grade scale (Hawker et al., 2011; Jensen et al., 1986). The pain scale used does not influence the pain intensity reported (Kremer et al., 1981). However, the numerical pain scale appears to be the most practical index both clinically and in research (Jensen et al., 1986). Further, in a recent study on osteoarthritic knee pain, the VAS was found to be the most reliable measure of pain (Alghadir et al., 2018). The VAS is easy to administer, complete and score (Hawker et al., 2011), and has been widely used in adult populations in research, including those with rheumatic disease. However, difficulty in understanding the concept and requirements of the VAS may impact studies involving older pain populations. Significant correlations have been found between age and incorrect responses to the VAS (Jensen et al., 1986; Kremer et al., 1981). Nonetheless, the VAS is considered to be a valuable instrument to assess pain intensity and changes in pain when respondents are given sound instructions (Haefeli & Elfering, 2006).

The VAS consists of a 100mm horizontal line, with ‘no pain’ anchoring the left of the line and ‘worst possible pain’ anchoring the right. The patient is asked to place a line perpendicular to the VAS line at the point that represents the pain intensity at rest. A higher score indicates greater pain intensity.

The recommended categorisation for VAS scores are no pain (0-4mm), mild pain (5-44mm), moderate pain (45-74mm), and severe pain (75-100mm) (Jensen et al., 2003). The validity of the VAS for detecting changes in pain intensity has been supported by several studies (Ferreira-Valente et al., 2011;

Price et al., 1983). The test-retest reliability of the VAS was reported as excellent (0.97), and the MDC as 0.08 (Alghadir et al., 2018).

2.3.2.5 Pressure pain threshold (PPT)

Chronic pain in CAI may result from increased nociceptor sensitivity known as peripheral sensitisation which is restricted to the site of tissue injury (Giesbrecht & Batti , 2005), or as a result of central sensitisation due to an increase in the excitability of neurons within the central nervous system, contributing to diffuse hypersensitivity in regions beyond the damaged tissue (Giesbrecht & Batti , 2005; Starkweather et al., 2016; Woolf, 1983; Wright, 1999). Distinguishing between peripheral (nociceptive) pain mechanisms and central nervous system (nociplastic) pain processing alterations/maladaption in musculoskeletal pain is important as central sensitisation is considered a potential influence in the development and maintenance of chronic/persistent pain (Coronado et al., 2014; Woolf, 1983; Wright, 1999). More personalised methods for monitoring the trajectory of chronic pain and responses to treatment may also improve outcomes for patients with CAI. Such individually specific clinical data may result in better long-term prediction of health outcomes by the potential provision of important diagnostic and prognostic information. Further, these data might also assist in assessing the severity of the condition and its response to a particular intervention (Bedson et al., 2019).

Clinically, central sensitisation results in increased pain sensitivity, spreading of hyperalgesia to surrounding areas, and spontaneous pain (Arendt-Nielsen et al., 2010). Widespread pressure

hypersensitivity is considered an indicator of central sensitisation. Thus, increased pressure pain sensitivity is indicated by decreased pain threshold measures in algometry (Ramiro-Gonzalez et al., 2012). Evidence of central sensitisation is usually tested by assessing PPT (Coronado et al., 2014), with methods including cuff algometry, pressure algometry, and algometry with electric stimulation (Mutlu & Ozdincler, 2015). PPT measurements for ankle conditions are obtained in each leg from two local points (to assess local hypersensitivity) and one remote body area (to assess central sensitisation) (Ramiro-Gonzalez et al., 2012). The recommended points are anterior to the lateral malleolus over the ATFL, inferior to the medial malleolus over the deltoid ligament, and over the proximal third of the tibialis anterior muscle belly. The algometer probe (contact surface of $1cm^2$) is placed perpendicular to the skin and pressure is applied (40kPa/s). The individual is asked to indicate when the feeling of the stimulus changes from 'pressure only' to 'discomfort' by pressing an indicator switch (Arendt-Nielsen et al., 2010; Rebbeck et al., 2015). This process is performed three consecutive times and a 10 second rest period is allowed between each set of measurements.

Pressure algometry is considered a stable and reliable measure of PPT (Frank et al., 2013). The inter-rater reliability of pressure algometry has been reported to be high when the algometer pressure is applied at a consistent rate (ICC 0.91, 95% (confidential interval) CI 0.82–0.97) (Chesterton et al., 2007).

2.3.3 Radiological examination

Although the patient reported findings, physical examination and specific clinical tests may provide a diagnosis in certain cases of ankle injury, complementary radiological tests are important in defining joint laxity and to assist in confirming some diagnoses. Stress radiographs, MRI and ultrasonography are often used to assess or to confirm ligamentous or tendinous pathology (Guillo et al., 2013; Peters et al., 1991; Tourné et al., 2010). Comparative stress radiographic images with the anterior drawer test and talar tilt test can be performed to confirm mechanical instability (Guillo et al., 2013; Peters et al., 1991). Commonly hind foot alignment is assessed using standard pain radiographs which may include standing antero-posterior, lateral and mortise views, and a comparative Saltzmann view (or Méary view) (Guillo et al., 2013).

Plain films are used in initial screening in diffuse ankle pain and for detection of gross bony lesions, while ultrasonography is utilised as a primary tool of investigation in imaging focal soft tissue abnormalities. MRI is found to be effective for those cases with an uncertain diagnosis, as it can exclude most clinically relevant pathologies (El-Liethy & Kamal, 2016). Magnetic resonance arthrogram and CT are also recommended in cases of high clinical suspicion meniscal or ligamentous injury. However, in order to localise a particular structure in chronic foot or ankle pain presentations, magnetic resonance imaging is generally recommended because of its ability to detect both soft tissue and bone lesions. Further, ultrasonography is particularly useful in dynamic evaluation (Aagesen & Melek, 2013).

2.3.3.1 Stress radiography tests

Several clinical tests can be used to assess the integrity of the key ligaments. The anterior drawer test is utilised to assess the integrity of the ATFL by assessing the amount of anterior translation of the talus under the tibia, and the talar tilt test stresses the CFL using passive adduction of the calcaneus to detect any excessive movement (Lynch, 2002). Stress radiography techniques are more often used for research purposes or to diagnose ankle joint mechanical instability and this involves specialised instruments and standardised loads (Lynch, 2002; Wheeless, 2016). Radiological evaluation of the amount of anterior translation of the talus, or talar tilt angle during a ligament stress test, is a widely accepted method to quantify any mechanical laxity in CAI (Hoffman et al., 2011; Hubbard & Hicks-Little, 2008).

Known limitations of stress radiography are that the testing may be influenced by pain, as well as the risk of exposure of the subject or provider to ionising radiation. The use of a standardised stress force has been shown to reduce measurement error (Sisson et al., 2011). Stress radiographs have been found to have moderate sensitivity, high specificity and a high positive predictive value for the evaluation of lateral ankle instability (Jolman et al., 2017). An absolute anterior displacement of 10mm or a between-limb difference of 3mm in anterior translation of the talus is considered clinically significant (Jolman et al., 2017; Lynch, 2002). A talar tilt angle of more than 10° of difference between limbs is generally considered abnormal (Lynch, 2002).

2.3.3.2 Position of the fibula in lateral ankle sprains including CAI

The 'positional fault' theory was introduced by Brian Mulligan to explain persistent pain after joint injury. According to this hypothesis, injuries or sprains might result in a minor positional fault (bony incongruence) of a joint causing pain and restriction in physiological movement (Mulligan, 1995). Mulligan specifically hypothesised that following an ankle inversion injury, the distal fibula may in some cases be malpositioned anteriorly due to forces transmitted through the attachment of the ATFL, leading to chronic ankle pain and impairment (Mulligan, 1995). Whether a pre-existing fibular 'positional fault' predisposes the patient to the injury, or whether the injury results in the fibular 'positional fault' is yet to be thoroughly examined (Hubbard et al., 2006).

The presence of fibula displacement has been investigated radiologically (Berkowitz & Kim, 2004; Eren et al., 2003; Hubbard & Hertel, 2008; Hubbard et al., 2006; Kobayashi et al., 2014; Li et al., 2017; Mavi et al., 2002; Merlin et al., 2005; Scranton et al., 2000; Wikstrom, Tillman, et al., 2010) and non-radiologically in ankle ligament injuries, including acute, sub-acute and chronic sprains, including CAI (Table 2.1). The findings of these studies have not been consistent, with evidence reported of an anteriorly positioned fibula, posteriorly positioned fibula, laterally positioned fibula, and no positional abnormality at all.

Radiographic measurement of fibular position is the most common method employed in studies to date, using lateral X-ray images with the measurement being the distance between the most anterior margin of the tibia and the most anterior margin of the fibula (Hubbard & Hertel, 2008; Hubbard et al.,

2006; Wikstrom, Tillman, et al., 2010). Measurements are made perpendicular to a line drawn vertically from the most anterior part of the tibia (Hubbard & Hertel, 2008; Hubbard et al., 2006). Due to individual anatomical variations, a normalisation technique has been proposed which reports fibular position as a percentage of tibial width (Wikstrom, Tillman, et al., 2010). The test-retest reliability $ICC_{3,1}$ has been calculated as 0.98 with a SEM of 0.64mm for this measurement, and for intra-tester reliability the $ICC_{3,1}$ is 0.92 and SEM is 0.72mm (Hubbard et al., 2006). However, these reliability values are reported for non weight-bearing positions. Considering that weight-bearing forces may cause widening of the distal tibiofibular joint, it is plausible that fibular position measures may detect greater differences in weight-bearing (Kobayashi et al., 2014). No reliability, validity or MDC values have been reported for weight-bearing radiographs used to measure fibular position, which are arguably more functional. However, there is a potential for rotation of the tibia and fibula in a weight-bearing radiograph which might introduce minor variability in fibular positional measurements, if the individual is not meticulously positioned.

Table 2.1 Reported abnormalities of fibula position in lateral ankle ligament injuries

Study	**Participants**	**Measurement method**	**Fibular positional abnormality**	**Mean (SD) value of displacement**	
				symptomatic	**control**
Berkowitz & Kim, 2004	CAI (patients with instability, n=65; uninjured controls, n=65)	radiological (CT/MRI scans)	posterior	17 (6)°	9 (4)°
Eren et al., 2003	acute ankle sprains (patients with ankle sprain, n=61; uninjured controls, n=101)	radiological (CT scans)	posterior	11.5 (7)°	5.85 (4.9)°
Fukuhara et al., 2012	sub-acute lateral ankle sprains (patients with unilateral sub-acute lateral ankle sprain, n=10; uninjured controls, n=10)	non-radiological (instrument consists of a pedestal and 2 devices incorporating a caliper)	anterior	43.7 (8.3)mm	37.4 (4.2)mm

Hubbard et al., 2006	CAI (patients with unilateral CAI, n=30; uninjured controls, n=30)	radiological (fluoroscopic lateral images)	anterior	14.3 (3.1)mm	16.1 (4.6)mm
Hubbard & Hertel, 2008	sub-acute lateral ankle sprains (patients with sub-acute lateral ankle sprain, n=11; uninjured controls, n=11)	radiological (fluoroscopic lateral images)	anterior	14.2 (3.4)mm	16.8 (2.3)mm
Kavanagh, 1999	acute or chronic ankle sprains (patients with ankle sprains, n=8 [chronic, n=2; acute, n=6]; uninjured controls, n=17)	non-radiological (instrument consisting of two potentiometers, a wooden bar with a strain gauge attached to an amplifier and circuit box)	anterior	7.5mm (greatest amount)	10mm (greatest amount)

Kobayashi et al., 2014	CAI (patients with unilateral CAI, n=17; control-contralateral side, n=17)	radiological (3-D analysis of CT-based bone models)	lateral	at lateral malleolus 0.60 (1.09)mm; at 5cm 0.57 (0.81)mm; at 10cm 0.68 (1.15)mm	not reported
Li et al, 2017	CAI (patients with mechanical ankle instability, n=54; patients for reasons unrelated to ankle instability, n=51)	radiological (MRI)	inconclusive (AMI significant and IMI non-significant)	AMI 11.06 (5.62)° IMI 9.97 (4.48)°	AMI 7.89 (4.41)° IMI 9.23 (4.09)°
Mavi et al., 2002	recurrent sprained ankles (patients with recurrent sprained ankles, n=18; uninjured controls, n=75)	radiological (MRI)	anterior	male 11.8 (1.4)mm; female 11.2 (1.3)mm	male 14.3(3.5)mm; female 12.5 (2.9)mm
Merlin et al., 2005	lateral ankle sprains (patients with sprained ankles, n=8; uninjured controls, n=30)	radiological (MRI)	superior	6.19 (0.28)cm	not reported
Scranton & Rogers, 2000	CAI (patients undergoing a	radiological (CT)	posterior	not reported	not reported

	Brostrom procedure for ankle instability, n=23; uninjured controls, n=100)				
Wikstrom et al., 2010	CAI (patients with CAI, n=24; uninjured controls, n=24; copers, n=24)	radiological (X-ray)	no abnormality	non-normalised 12.8 (4.2)mm; normalised 29.1 (8.2)%	non-normalised 12.2 (3.3)mm; normalised 29.2 (7.1)%

AMI, axial malleolar index; CAI, chronic ankle instability; CT, computed tomography; IMI, intermalleolar index; MRI, magnetic resonance imaging; SD, standard deviation

2.3.4 Other tools to assess CAI

Due to popularity and convenient application, smart phone-based systems have also been developed to assess postural control ability in individuals with CAI. Acceleration data is used to represent postural control performance during eyes open and close conditions (Chiu et al., 2017). However, the role of smartphone applications in the actual diagnosis of CAI is yet to be ascertained.

In summary, the clinical assessment of CAI should include a combination of factors; (i) patient history including injury mechanism and patient reported outcome measures, (ii) physical examination and tests including a comprehensive assessment of clinical characteristics such as deficits in DFROM and balance, and (iii) conventional radiography examination techniques, as appropriate.

2.4 Management of CAI

A large number of treatment strategies for ankle sprains and CAI are detailed in the literature. An overview of systematic reviews with meta-analysis indicated strong evidence for exercise therapy and bracing in preventing ankle sprain recurrence, although the optimal treatment strategy remains unclear (Doherty et al., 2017). However, studies of manual therapy interventions have been limited by short timeframes for follow-up (Doherty et al., 2017). Neuromuscular training also appears to improve ankle function in patients with CAI (De Vries et al., 2011), along with weight loss, activity appropriate footwear and external restraints recommended in athletic patient populations (Mccriskin et al., 2015). Patients with functional instability are more likely to benefit from non-surgical measures (Mccriskin et al., 2015). Generally, patients with CAI who fail functional rehabilitation progress to surgical

management (Chan et al., 2011). With early mobilisation of the ankle joint (rather than six weeks of immobilisation), functional rehabilitation is recommended in the post-surgical management of CAI to ensure early return to work and sports (De Vries et al., 2011).

2.4.1 Conservative interventions

Acute management of recurrent sprains in CAI has long been considered to involve rest, ice, compression and elevation (RICE) as the standard approach (Ajis & Maffulli, 2006; Herb & Hertel, 2014). Joint protection, optimal loading, ice, compression and elevation (POLICE) was introduced later for acute ankle sprain management (Bleakley et al., 2012), however there is limited evidence to support this regime (Herb & Hertel, 2014). Generally, the clinical rehabilitation of CAI aims to restore the identified deficits such as in ROM, balance and function with differing clinical interventions (Ajis & Maffulli, 2006). A plethora of therapeutic interventions for CAI have been proposed including joint mobilisation (e.g. MWM, manipulation), balance retraining (e.g. single-leg standing balance exercises, dynamic balance tasks), peroneal muscle strengthening (e.g. resistance exercises), proprioceptive retraining (e.g. wobbleboard exercises), soft-tissue mobilisation, passive calf stretching and orthotics (Ajis & Maffulli, 2006; Kosik et al., 2016; Mccriskin et al., 2015). These are generally applied in combination depending on the deficits with which the individual patient presents. For example, joint mobilisation has been shown to improve DFROM (Hoch, Andreatta, et al., 2012), while strength training and proprioceptive retraining have been shown to improve muscle weakness and function in CAI (Kaminski et al., 2003). Various electrophysical modalities (e.g. ultrasound, contrast therapy), oral anti-inflammatory medication, injectable steroid medication, elastic bandaging and strapping are also often clinically used in combination with rehabilitation programs (Ajis & Maffulli, 2006).

A variety of joint mobilisation techniques, including manipulation are commonly practised to manage ankle sprains. Joint mobilisation is suggested as being effective at restoring objective impairments such as reduced ankle ROM or decreased dynamic postural control, and the combination of mobilisation with other conservative interventions is endorsed (Kosik et al., 2016). In a large scale study of patients with lateral ankle sprains in the United States who received physiotherapy, 52% received manual therapy with joint mobilisation/manipulation being the most commonly applied manual therapy technique (51.7%) (Feger et al., 2017). However, there is limited supportive evidence for the use of joint mobilisation in isolation for improving outcomes of patients with CAI, including self-reported function (Kosik et al., 2016).

2.4.1.1 Mobilisation with movement (MWM)

Several trials and systematic reviews have investigated the effects of manual therapy on CAI. No studies have actually assessed joint mobilisation as the sole intervention nor undertaken a meta-analysis, except for one very recent systematic review (Vallandingham et al., 2019). However, this study assessed MWM for only two outcomes of CAI; DFROM and dynamic balance (Vallandingham et al., 2019). Further, it is not clear which joint mobilisation technique is more likely to produce a clinical benefit for people with CAI. MWM is a mobilisation technique recommended in the rehabilitation of CAI (Vicenzino et al., 2011) which concurrently uses a pain-free sustained passive accessory joint mobilisation with an active or passive physiological movement during application (Hoch & Mckeon, 2010).

MWM was introduced by New Zealand physiotherapist Brian Mulligan (Mulligan, 1993), and has been applied to improve pain, swelling, function, feelings of instability, postural control, and ankle DFROM following lateral ankle sprains (Collins et al., 2004; Cruz-Diaz et al., 2015; Gilbreath et al., 2014; Gómez et al., 2015; Reid et al., 2007; Vicenzino et al., 2006). Similar symptoms are widely existent individually or in combination in individuals with CAI. According to Mulligan, rather than tearing or rupturing the ATFL, in some cases an inversion injury exerts an anterior and slightly caudad force on the fibula via the ATFL, thus creating a 'positional fault' in that direction. Therefore, the fibula may be mobilised using a MWM technique incorporating a sustained postero-cephalad glide, while asking the patient to simultaneously repeat the previously symptomatic movement, such as active inversion or dorisflexion (Hing et al., 2015; Mulligan, 1995).

For patients with CAI, the inferior tibio-fibular joint may be mobilised using a 'fibular MWM for dorsiflexion and/or inversion in non weight-bearing' according to Mulligan's paradigm. The technique is initially applied in supine lying, with the tibia resting on the treatment table and the ankle and foot unsupported off the edge of the table. The therapist applies a sustained anteroposterior glide to the fibula, with some inclination slightly cephalad and laterally, while stabilising the tibia. While the therapist maintains this glide in a pain-free manner, the patient is instructed to perform active ankle inversion or dorsiflexion to the first onset of pain or end of range. At this point, if there is no pain, the therapist can apply overpressure to the active movement for a few seconds (Hing et al., 2015; Vicenzino et al., 2006). Treatment is recommended to be applied with 6-10 repetitions in a set, with 3-5 sets in a treatment session depending on the pain response of the patient (Hing et al., 2015). The patient may be reassessed using the active physiological movement or functional task with which they

are most painfully restricted, known as the client specific impairment measure. If there is a clinical indication, MWM can be progressed to a weight-bearing position in some cases.

Mulligan ankle taping, or fibular repositioning taping, is an intervention which may be used to enhance the effect of the MWM technique described in the previous section by using tape to maintain the glide component of the MWM (Someeh et al., 2015b). In addition, the potential of fibular repositioning taping to enhance proprioception is suggested to improve stability and confidence, and also decrease feelings of instability in individuals with CAI (Someeh et al., 2015b). Non-stretchable tape is applied to the ankle starting 2cm anterior to the fibula and 1cm proximal to the tip of the lateral malleolus. The tape is spiralled obliquely around the lower leg while applying the pain-free fibula glide and the taping is finished on the anterior aspect of the skin (Hing et al., 2015).

2.4.2. Surgical interventions

If CAI is unresponsive to a three month rehabilitation program, then surgical treatment may be indicated (Giannini et al., 2014). Numerous anatomic and non-anatomic procedures have been described in the surgical management of CAI in the literature. Anatomic techniques generally consist of direct repair of injured ligaments, while non-anatomic procedures consist of tenodesis in order to substitute for the injured ligaments and to address pathological ankle mobility (Chan et al., 2011; Giannini et al., 2014). However, these techniques often result in joint stiffness and limited ROM of the ankle and subtalar joints. Non-anatomic techniques are associated with an increased rate of complications compared to anatomic reconstruction (Giannini et al., 2014).

Management of CAI may vary depending on the impairment, or combination of impairments, that the individual with CAI clinically presents with, including pathomechanical impairments, sensory-perceptual impairments, and/or motor-behavioural impairments. Personal factors such as age, BMI and environmental factors such as social support, access to health service may affect the severity of these impairments. Therefore, the clinical outcome of management could end up being a coper who perceives a full recovery or with CAI who perceives recurrent ankle sprains (Hertel & Corbett, 2019. The management of CAI is generally based both on the clinical judgement of the practitioner from their assessment of the condition, and also the application of evidence-based practice recommendations, as appropriate. The options for management range from conservative (e.g., manual therapies, electrotherapeutic modalities, thermal therapies, orthotics, exercise therapies [including strengthening, stretching, proprioceptive training, range of motion exercises, balance exercises, neuro-muscular training, gait training and functional exercises]), to pharmaceutical interventions and surgery.

2.5 Summary

Ankle sprains are a common musculoskeletal injury and often develop into CAI. Along with its high prevalence, recurring episodes of injury in CAI contribute to its high healthcare cost. The mechanism for development of CAI, whether mechanical or functional remains unclear in the literature. Identification of the anatomical and clinical characteristics specific to CAI, may assist in better defining this debilitating condition and its subgroups. The pain mechanism(s) involved in CAI should also be specifically investigated, and whether there are underlying central changes related to the chronic pain in CAI. While the literature supports that joint mobilisation helps to improve some

clinically relevant outcomes in CAI, the underpinning mechanism by which joint mobilisation may work is not clearly understood, nor are the long-term effects known. In particular, the clinical benefits of MWM in the management of CAI and its subgroups remain unclear, including if or how MWM may alter fibular position.

Chapter 3 Clinical benefits of joint mobilisation on ankle sprains: a systematic review and meta–analysis

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The work presented in this manuscript was completed in collaboration with the co-authors (Appendix 1). The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews on January 12, 2016 (CRD42016030194) (Appendices 7 and 16).

Overview

The epidemiologic findings and socio-economic burden associated with lateral ankle sprains and CAI suggest that current rehabilitation approaches may be inadequate. The aim of the study presented in this chapter is to synthesise the best available evidence for joint mobilisation, as a common rehabilitation approach in managing patients with acute to chronic ankle sprains including CAI. Previous systematic reviews which have evaluated the evidence on the effectiveness of manual therapies for ankle sprains or CAI have included multi-modal studies that involved co-interventions such as RICE and home exercise programs, as an adjunct to joint mobilisation. At the time of the

study, no systematic reviews have actually assessed joint mobilisation as the sole intervention for ankle sprains or CAI, or indeed undertaken a meta-analysis, despite it being a common intervention in the rehabilitation of a number of ankle conditions. Therefore, the systematic review presented in this chapter aimed to synthesise and meta-analyse the available evidence for ankle joint mobilisation in grade I or II ankle sprains of the medial or lateral ligaments in the acute to chronic stages of rehabilitation in any ambulant setting.

This chapter describes a systematic investigation of the current published evidence for various joint mobilisation techniques on ankle sprains including CAI, as found in 11 databases from inception to June 2017. At the time of the study, this is the first systematic review and meta-analysis to only include studies in which joint mobilisation is the sole intervention, thus providing a clearer understanding of the effects of mobilisation in isolation. The current review did not identify any studies evaluating the clinical benefits of joint mobilisation on acute ankle sprains. The quantitative analysis was therefore conducted using data from studies involving chronic ankle sprains including CAI, and thus the findings of the meta-analysis may be applicable to the joint mobilisation treatment of chronic ankle sprains including CAI. This chapter also assesses the immediate, short-term and long-term clinical benefits of joint mobilisation on ankle sprains and persistent ankle instability, as described in the reviewed body of literature.

3.1 Introduction

Ankle sprains are a common injury in sports and the general community, and may lead to chronic pain, functional limitations and physical disability (Parker & Jelsma, 2010; Woolf, 2003). Epidemiological studies conducted in various countries highlight the high incidence of ankle sprains during sports training and competition with rates reported as 7 per 1000 in Denmark, 6.09 per 1000 in United Kingdom, and 2.15 per 1000 in the United States in person years (Bridgman et al., 2003; Holmer et al., 1994; Waterman, Owens, et al., 2010). Plantarflexion inversion sprain or lateral ankle sprain, is the most common type of ankle sprain (Doherty et al., 2014). It typically results in either an injury of the inferior tibiofibular ligament, ATFL or the bifurcate ligament (Hing et al., 2015). Eversion injuries often result in damage to the deltoid and spring ligaments of the medial aspect of the ankle (Hing et al., 2015).

According to the clinical practice guidelines linked to the ICF from the Orthopaedic Section of The APTA, manual therapy is recommended for both the acute and progressive loading phases of rehabilitation (Martin et al., 2013). Management of ankle sprains commonly involves mobilisation procedures applied to the joint, such as non-thrust joint mobilisation, high velocity thrust manipulation, and MWM.

The mechanisms by which these techniques are purported to work are biomechanical (such as stretching/tearing tissue, inducing cavitation within the joint, reducing muscle hypertonicity/stiffness)

and neurophysiological, potentially including spinal cord and supra-spinally mediated mechanisms (Mccarthy et al., 2015; Vicenzino et al., 2011).

Several studies have investigated the effects of manual therapy on ankle sprains using a variety of outcome measures including pain, ROM and function from the acute to chronic stages of recovery, with different results reported (Collins et al., 2004; Cosby et al., 2011; Cruz-Diaz et al., 2015; Delahunt et al., 2013; Gilbreath et al., 2014; Green et al., 2001; Marron-Gomez et al., 2015; O'brien & Vicenzino, 1998 ; Penso, 2008; Vicenzino et al., 2006; Woodman et al., 2013). Several systematic reviews have attempted to collate this evidence but have been limited by their narrow focus on lateral ankle sprains and restricted outcome measures (Bleakley et al., 2008; Hoch & Mckeon, 2010; Loudon et al., 2014; Terada et al., 2013; Van Der Wees et al., 2006). Previous systematic reviews have all included some studies which involved other interventions such as RICE and home exercise programs, as an adjunct to mobilisation. Therefore, they have not actually assessed mobilisation as the sole intervention. Moreover, the clinical benefits of joint mobilisation have not yet been evaluated through meta-analysis, despite it being a common intervention used in the rehabilitation of a number of ankle conditions and despite the growing body of empirical literature.

The present systematic review aims to address these limitations by synthesising and meta-analysing the available evidence for ankle joint mobilisation (including high velocity thrust manipulation) in grade I or II ankle sprains of the medial or lateral ligaments in the acute/sub-acute/chronic stages of rehabilitation in any ambulant setting.

3.2 Method

3.2.1 Registration

The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on January 12, 2016 (CRD42016030194).

3.2.2 Search strategy

A search of electronic databases, including MEDLINE, MEDLINE In Process, Embase, AMED, PsycINFO, CINAHL, Cochrane library, PEDro, Scopus, SPORTDiscus, and Dissertations and Thesis was conducted from inception to June, 2017. In addition to the database search, a hand search of the reference lists of identified studies was also carried out. A search strategy (Table 3.1) was developed for the main search strings of ankle sprain and mobilisation. Keywords used for 'ankle sprain' included sprain, talocrural joint, ligament injuries, lateral ligament, medial ligament, deltoid ligament, collateral ligament, ATFL, PTFL, sprain and strain, and ankle twist. Key words used for 'mobilisation' included manual therapy, joint mobilisation, manipulation, MWM, Maitland, Mulligan, and rehabilitation. These terms were used alone and in combinations during the search.

Table 3.1 Search strategy

#	Searches
1	Ankle Injuries/
2	ankle sprain.mp.
3	(ankle* adj5 injur*).tw.
4	(ankle* adj5 sprain*).tw.
5	(ankle* adj5 twist*).tw.
6	(injur* adj5 ligament*).tw.
7	lateral ligament*.mp. or Collateral Ligaments/
8	Ankle Joint/ or medial ligament*.mp.
9	Ankle Joint/ or deltoid ligament*.mp.
10	ATFL.mp.
11	PTFL.mp.
12	"Sprains and Strains"/
13	talocrural.tw.
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	Chiropractic/ or Manipulation, Orthopedic/
16	musculoskeletal manipulation.mp. or Musculoskeletal Manipulations/
17	(joint* adj5 manipul*).tw.
18	(ankle* adj5 rehab*).tw.
19	Mulligan*.mp.
20	Maitland*.mp.

21	MWM*.mp.
22	manual therap*.mp.
23	manual technique*.mp.
24	(joint* adj5 mobili?ation*).tw.
25	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26	Randomized controlled trial.pt.
27	clinical trial.pt.
28	random*.tw.
29	trial*.tw.
30	group*.tw.
31	case series.tw.
32	cross-over studies/
33	Cross-Sectional Studies/
34	exp Cohort Studies/
35	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36	14 and 25 and 35
37	limit 36 to humans

3.2.3 Identification and selection of studies

Full text RCTs, crossover studies, cross-sectional studies, cohort studies, and case series published in peer reviewed journals and dissertations were considered for the present review. Studies were not restricted by language, provided the title and abstract were in English. Studies not involving live

human participants (e.g., model-based, animal and cadaveric investigations) were excluded. Conference proceedings, commentaries, research notes, editorials, and letters were also excluded. To be included, studies were required to meet the following criteria:

Participants

Live humans (without any age limitation) with a grade I or II lateral or medial ligament sprain of the ankle at any stage of recovery (acute to chronic) in any ambulant setting who have been treated with joint mobilisation. Studies involving grade III sprains, fractures (other than Weber type A), and syndesmotic injuries were excluded from this review.

Intervention

Studies reporting any type of joint mobilisation techniques applied to the talocrural joint, subtalar joint, or inferior tibiofibular joint by a physiotherapist, medical practitioner, osteopath, chiropractor or athletic trainer were eligible for inclusion in the review. Interventions other than therapist performed joint mobilisation were excluded from the review.

Comparators

Studies reporting any conservative intervention for comparison, such as exercise therapy, elevation and icing, supportive strapping, sham intervention, or no treatment, were eligible for inclusion. Control

groups with healthy subjects were also eligible as a comparator. Studies which compared mobilisation techniques to surgical interventions were excluded.

Outcome measures

All commonly reported clinical impairments (pain, swelling, balance, proprioception, strength, stability, and gait), activity restriction and self-reported confidence, community participation, QOL, re-injury rate, function, and return to sport were considered for the review. The primary outcomes of interest were ankle ROM, pain, QOL, and function.

Timing of the measurement of the outcomes was categorised as either 'immediate', measured immediately following the intervention (Southerst et al., 2015), 'short-term' measured up to 3 months following the intervention (Van Ochten et al., 2014), and 'long-term' measured at 3 or more months (Bleakley et al., 2008) following the intervention.

Identified studies were exported to reference management software (EndNote X7.3.1, Ontario, Canada) and duplicate records were manually removed. Study titles and abstracts were initially screened by two independent reviewers, followed by screening of full text papers, to determine the eligibility of the identified studies. Disagreement between the reviewers was resolved by consensus or involvement of a third reviewer. The level of agreement between reviewers was assessed using Cohen's Kappa (Viera & Garrett, 2005).

3.2.4 Assessment of methodological quality

The methodological quality of individual studies was assessed using the PEDro scale for RCTs and the Quality Assessment Tool for Observational Cohort and Cross-sectional Studies (Higgins et al., 2011; National Institutes of Health, 2014; Pedro-Scale, 1999). Two independent reviewers assessed the methodological quality and the level of agreement between reviewers was assessed using Cohen's Kappa.

3.2.5 Assessment of the quality of evidence

The overall quality of evidence was assessed at the stage of meta- analysis, using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (Atkins et al., 2004). The quality of the evidence was classified as either high, moderate, low, or very low (Guyatt et al., 2008). Risk of bias, consistency of results, directness (e.g. generalisability) and precision (e.g. sufficient data) were considered in assessing the overall quality (Armijo-Olivo et al., 2016).

3.2.6 Data extraction and statistical analysis

Descriptive data were extracted using an extraction table (Table 3.2). Authors were contacted if possible where there were difficulties extracting data from the published paper. Where feasible, study data that were comparable in terms of participant characteristics, outcome measures and follow-up periods, were pooled and a meta-analysis was performed.

For the meta-analysis, the standard mean difference (SMD) was calculated for the outcomes where the means and standard deviations were provided pre- and post-intervention. This conversion of the data to a common scale permitted comparison of studies that used different tools to measure the same outcome. This review followed the general practice of interpretation for small, medium, and large effect sizes (0·2=small effect, 0.5=medium effect, 0.8=large effect) (Cohen, 1988; Valentine & Cooper, 2013). The mean difference (MD) was calculated for studies using the same instrument for measurement. The results were reported in forest plots with 95% CI. The MCID was used to interpret the clinical meaningfulness of the findings. Inconsistency was quantified by calculating I^2 and interpreted as follows: 30% to 59% may represent moderate heterogeneity, 60% to 89% substantial heterogeneity, and 90% to 100% considerable heterogeneity between studies. If I^2 was greater than 30%, a random effects model was used to incorporate intertrial heterogeneity (Higgins et al., 2011).

In the instance of multiple comparison groups, the sham group was selected as the control condition. For the outcome of 'static balance', studies with eyes closed balance were selected to maintain the homogeneity of the analysis. Further, in studies with multiple time points, measurements taken at 2-3 weeks were selected for the meta-analysis (e.g., if effects were measured at the time points of 2 days, 3 weeks and at 2 months in a single study, data from measurements at 3 weeks were selected for the analysis). All statistical analyses were conducted using RevMan 5.3, Copenhagen (Revman, 2014).

Table 3.2 Description of the eligible studies

Study	Design	Sample	Intervention and dosage	Comparator	Measurement time points	Outcomes	Results
Alanson et al, 2012	RCT	17 (10M) grade 1/2 chronic lateral ankle sprains	TCJ (antero-posterior)-mobilisation + TCJ traction 30s	sham	immediate	non weight-bearing DFROM, proprioception (joint position sense)	non weight-bearing DFROM, significantly improved across time (p=0.04) joint position sense significantly improved across time at target angle 10° plantarflexion (p=0.03)
Beazell et al, 2012	RCT	43 chronic ankle sprains	distal TFJ manipulation + HVLA thrust 1 repetition	no intervention	immediate, short-term (1, 2 and 3 wk)	weight-bearing DFROM, static balance (single-leg stance), function (step down test, self-reported function, FAAM sports)	weight-bearing DFROM not significant (p=0.82) single-leg stance not significant (p=0.42) function not significant-step down test (p=0.76), self-reported function

							(p=0.61), FAAM sports (p=0.83)
Collins et al, 2004	randomised cross over	16 (8M) grade 2 sub-acute lateral ankle sprains	weight- bearing MWM TCJ (posterior talar glide, postero anterior tibial glide) 3 sets of 10 repetitions	placebo, no interventio n	immediate	weight-bearing DFROM, pressure pain threshold, thermal pain threshold	weight-bearing DFROM significantly improved across time (p=0.013) and no significant group difference (vs placebo p=0.202, vs control p=0.208) pressure pain threshold and thermal pain threshold not significant (p<0.05)
Cruz-Díaz et al, 2015	RCT	81 (47M) chronic ankle sprains	weight-bearing MWM TCJ (posterior talar glide, postero-anterior tibial glide-)	sham, no interventio n	immediate, short-term (3 wk), long-term (6 mo)	weight-bearing DFROM, dynamic balance (SEBT)	weight-bearing DFROM significantly improved p<0.0001 (at each time point) dynamic balance significantly improved

			2 sets of 10 repetitions 2 sessions/wk for 3 wk				p<0.0001 (each direction of SEBT)
Gilbreath et al, 2014	prospective longitudinal	11 (5M) chronic ankle sprains	weight –bearing MWM TCJ (posterior talar glide, postero anterior tibial glide) 2 sets of 4 repetitions 4m of MWM X 3 sessions over a 1 wk	no control group	short-term (after 24-48 h)	weight –bearing DFROM,dynamic balance (SEBT), function (FAAM)	weight-bearing DFROM not significant (p=0.69) dynamic balance not significant (SEBT-anterior p=0.99; postero-medial - p=0.15; postero-lateral p=0.24). FAAM ADL not significant (p=0.19). FAAM SPORTS significantly improved across time (p=0.01)
Harkey et al, 2014	RCT	30 (14M)	Maitland mobilisation	No interventio	immediate	non weight-bearing DFROM, dynamic	non weight- bearing DFROM significantly

		chronic ankle sprains	TCJ (antero-posterior grade III) 3 sets of 60s	n		balance (SEBT)	improved (p=0.049) dynamic balance no improvement (p >0.05)
Hoch & McKeon, 2011	randomised cross over	20 (9M) chronic ankle sprains	Maitland mobilisation TCJ-(anterior posterior III) 50 ± 5 of 1s oscillations X2	no interventio n	immediate	weight-bearing DFROM, static balance dynamic balance (SEBT), talar stiffness	weight-bearing DFROM significantly improved (p=0.01) static balance significantly improved time to boundary antero-posterior minima significantly improved (p<0.0001) dynamic balance-not significant (p=0.98) (normalised reach distance) talar stiffness not significant (p=0.08)
Hoch et al, 2012	prospective longitudinal	12 (6M)	Maitland mobilisation	no control group	short-term (24–48 h and	Weight-bearing DFROM,dynamic	weight-bearing DFROM significantly improved

		chronic ankle sprains	TCJ (antero-posterior III)+ TCJ traction 2 sets of 2min traction and 4 sets of 2min mobilisation		1wk follow-up)	balance, function (FAAM)	across time (p<0.0001) dynamic balance significantly improved across time (SEBT anterior- p<0.0001); postero-medial- p=0.003; postero-lateral- p<0.0001) FAAM ADL and SPORTS significantly improved across time (p=0.001)
Hoch et al, 2014	prospective longitudinal	12 (6M) chronic ankle sprains	Maitland Mobilisation TCJ (antero posterior III) + TCJ traction 2 sets of 2min traction and 4 sets of 2min	no control group	short-term (24–48h, and 1 wk follow-up)	static balance, talar stiffness	static balance not significant. time to boundary antero-posterior and time to boundary medio-lateral not significant (p >0.05) talar stiffness not significant (p>0.05)

Hopper et al., 2009	randomised controlled within-subjects design	20 (8M) chronic ankle sprains	Mulligan ankle taping not explicitly stated	injured taped, injured un-taped, uninjured taped, uninjured un-taped	immediate	static balance, dynamic balance (wandering, overshoot, reaction time)	static balance significantly improved in postural sway recovery across time ($p<0.001$) single-leg stance not significant (0.792), dynamic tracking balance not significant ; wandering ($p=0.559$), overshoot- ($p=0.547$), reaction time- $p=0.142$.
Houstan et al, 2013	prospective longitudinal	12 (6M) chronic ankle sprains	Maitland mobilisation TCJ (antero-posterior III) + TCJ traction 4min of traction	no control group	immediate, short-term (1 wk follow-up)	function (FAAM sports)	FAAM ADL some components significantly improved across time; walking on even ground ($p=0.06$); going down stairs ($p=0.07$); walking on

			and 8min of mobilisation 6 sessions over 2 wk.				uneven ground (p=0.03); light to moderate work (p=0.06); heavy work (p=0.03); recreational activity (p=0.07) FAAM SPORTS some components significantly improved across time; landing (p=0.03); low impact activities (p=0.07); cutting p =0.02)
Joshep et al., 2010	RCT	40 (19M) grade 1/2 chronic lateral ankle sprains	ankle axial elongation TCJ (superior inferior)-HVLA thrust 6 sessions over 3 wk	muscle energy technique	short-term (1 mo)	DFROM, plantarflexion ROM, static balance, pain quality and intensity, function (functional evaluation scale)	DFROM significantly improved across time (p<0.001) and no significant group differences (p=0.713). Plantarflexion ROM significantly improved across time (p<0.001) and

			no significant group differences (p=0.300) single-leg stance eyes closed significantly improved across time (p<0.001) and no significant group differences (p=0.344) single-leg stance eyes open significantly improved across time (p<0.001) and no significant group differences (p=0.413) McGill significantly improved across time (p<0.001) and no significant group differences (p=0.077) Functional evaluation scale significantly improved

							across time (p<0.001) and no significant group differences (p=0.144)
Kohne, et al 2007	RCT	30 (21M) grade 1/2 chronic recurrent lateral ankle sprains	ankle axial elongation TCJ (superior inferior by a mortise separation)- 6 manipulations over 4 wk)	single manipulation on treatment	short-term (fifth wk follow-up)	DFROM, proprioception (joint position sense), pressure pain threshold, pain intensity	DFROM significantly improved-p=0.028 (across time) joint position sense at 5° plantarflexion error significantly improved p=0.029 (across time) pressure pain threshold (p value not reported) pain intensity (p value not reported)
Lopez-Rodrıguez et al, 2007	randomised controlled within-subject repeated	52 (35M) grade 2 chronic lateral	TCJ Manipulation (caudal) HVLA thrust + posterior	placebo	immediate	proprioception	proprioception significantly improved; load support bilateral posterior load (p=0.016), anterior load (p=0.04),

	measures	ankle sprains	gliding manipulation TCJ -HVLA thrust 1min				posterior load (p=0.043), posterior anterior load (p=0.016)
Marron-Gomez, 2015	RCT	52 (31M) chronic ankle sprains	weight – bearing MWM TCJ (posterior talar glide, postero-anterior tibial glide) 1 set of 10 repetitions TCJ HVLA distraction thrust x 3	placebo	immediate, short-term (24 and 48 h)	weight-bearing DFROM	MWM- weight-bearing DFRFOM significantly greater than placebo- p< 0.05 (immediately and short-term) HVLA- weight-bearing DFROM significantly greater than placebo- p<0.001(immediately) and p=0.001(short-term)
Pellow et al., 2001	RCT	30 (19M) grade	ankle axial alongation (TCJ- superior	detuned ultrasound treatment	short-term (1 mo follow-up)	non weight-bearing DFROM, pain threshold, pain quality	non weight- bearing DFROM significantly improved across time

	1/2 sub-acute and chronic lateral ankle sprains	inferior by a mortise separation) 8 manipulations over 4 wk	and intensity, function (functional evaluation scale)	(p=0.001) and between groups-(p=0.001) pain threshold significantly improved across time (p=0.002) and no significant group differences (p=0.395). McGill significantly improved across time (p=0.001) and between groups-(p=0.004) pain intensity significantly improved across time (p=0.002) and between groups-(p=0.004) functional evaluation scale significantly improved across time (p=0.001) and between groups-(p<0.001)

Plante, 2012	RCT	20 (12M) chronic ankle sprains	TCJ (antero-posterior) 10 oscillations	healthy subjects	immediate	Weight-bearing DFROM, static balance, function (dynamic functional tasks)	weight-bearing DFROM significantly improved across time ($p<0.0001$) single-leg stance; centre of pressure significantly improved ($p<0.04$) dynamic functional task (centre of pressure medial-lateral during jump task significantly improved [$p<0.00$]; centre of pressure medial- lateral during squat significantly improved [$p< 0.022$]; centre of pressure medial – lateral during stance task significantly improved [$p<0.0.039$])
Reid et al, 2007	randomised cross over	23 (8M)	weight-bearing MWM	sham	immediate	weight-bearing DFROM	weight-bearing DFROM significantly improved

		chronic lateral ankle	(posterior talar glide, postero-anterior tibial glide) 10 repetitions X 2				(p=0.02)
Someeh et al, 2015	experimental study design- within subjects	32 (20M) chronic ankle sprains	Mulligan ankle taping/ Fibular repositioning taping not explicitly stated	healthy subjects	immediate	dynamic balance (SEBT)	dynamic balance significantly improved across time- SEBT overall reach (p=0.001)

Someeh et al, 2015	experimental study design- within subjects	32 (20M) chronic ankle sprains	Mulligan ankle taping not explicitly stated	healthy subjects	immediate	function (dynamic functional tasks), participants perceptions of stability and confidence	function significantly improved across time; single-leg hopping (p=0.014); figure of 8 hopping (p=0.05); side hopping- (p=0.001) confidence in above mentioned functional tests significantly improved across time; p=0.023, 0.048, and 0.038, respectively
Vicenzino et al, 2006	randomised cross over	16 (8M) chronic lateral ankle sprains	non weight-bearing MWM (antero posterior talar glide for DF), 4 glides of 10s 4 sets	no interventio n	immediate	weight-bearing DFROM, talar stiffness	weight-bearing DFROM significantly improved (p=0.017) talar glide significantly improved (p<0.001)

			weight-bearing MWM (posterior talar glide, postero anterior tibial glide) 4 sets of 10 glides				
Wells, 2012	RCT	17 (7M) chronic ankle sprains	Maitland mobilisation (TCJ-antero-posterior IV) 3 repetitions, 60s	no intervention	immediate	weight-bearing DFROM, non weight-bearing BDFROM, dynamic balance, pain intensity, static balance, stiffness, function (self-reported function)	weight bearing DFROM not significant (p=0.95) non weight-bearing DFROM not significant (p=0.1) dynamic balance not significant; SEBT composite (p=0.8); anterior (p=0.07); postero-medial (p=0.79); postero lateral (p=0.73) pain not significant

							(p=0.06). stiffness not significant (p=0.59) stability not significant (p=0.40) function (VAS) not significant (p=0.44)
Yeo et al, 2011	randomised controlled within-subject repeated measures	13 (10M) grade 2 sub-acute lateral sprain	Maitland mobilisation (distal TFJ antero-posterior) 3 sets of 1min mobilisation	placebo, no intervention	immediate	weight-bearing DFROM, pressure pain threshold, pain intensity, function (functional evaluation scale)	weight-bearing DFROM significantly improved (p<0.0001) pressure pain threshold significantly improved (p<0.0001) pain intensity not significant (p=0.369) functional evaluation scale not significant (p=0.475)

Note: “immediate”, measured immediately following the intervention. “short-term”, measured up to 3 months following the intervention.

“long-term”, measured at 3 or more months following the intervention.

ADL, activities of daily living; DFROM, dorsiflexion range of motion; FAAM, Foot and ankle ability measure; HVLA, high velocity low amplitude; M, Male; MWM, mobilisation with movement; RCT, randomised controlled trial; SEBT, star excursion balance test; TCJ, talocrural joint; TFJ, tibiofibular joint

3.3 Results

3.3.1 Selection and characteristics of included studies

The database search identified 1521 studies after duplicate removal and a further nine studies were identified through citation tracking and hand searching of reference lists (Figure 3.1). Following the first stage of screening (using study title and abstract), 56 studies (database search- n=47, hand search- n=9) were identified as eligible for inclusion from the original 1530 (database search- n=1521, hand search- n=9) studies. Common reasons for exclusion following title and abstract screening included; ineligible study design, joint mobilisation was not assessed in isolation, and the study aim was not relevant to the review research question. A further 33 studies were excluded in second stage (full text) screening, and reasons for exclusion included; study aim not relevant to research question (Ambarish et al., 2008; Baker, 2013; Cosby, 2012; Cosby et al., 2011; Delahunt et al., 2013; Eisenhart et al., 2003; Estrade, 2013; Fisher et al., 2009; Green et al., 2001; Hedlund et al., 2014; Kumari et al., 2014; Landrum et al., 2008; Lee et al., 2012; Lubbe et al., 2015; Nambi & Shah, 2012; Nilsson, 1983; Rashid et al., 2013; Silva et al., 2017; Teixeira et al., 2013) (n=19), conference proceedings, commentaries and research notes (Andersen et al., 1987; Ayad et al., 2015; Clinch, 1986; Fay & Egerod, 1984; Hart & Macintyre, 2002; Rundle, 1988; Vicenzino et al., 2005) (n=7), not peer reviewed (Andersen et al., 2003; Chen et al., 2012; Yu, 2007) (n=3), full text not available (Diebschlag, 1987; Lee & Kim, 2005) (n=2), study protocol only (Davenport et al., 2010) (n=1), and thesis removed as the relevant published paper was included (Hoch, 2011) (n=1). Twenty-three studies (including three theses) were therefore included in the current review. The inter-reviewer agreement for the title/abstract and full text screenings was considered to be very good (k=0.80, 95% CI 0.72-0.89) and good (k=0.71, 95% CI 0.52-0.90) respectively. All disagreements were resolved by consensus. The data from 11 studies (including two theses (Plante,

2012; Wells, 2012)) were available and deemed appropriate for inclusion in the meta-analysis (Figure 3.1). Publication bias was visually observed using funnel plots (Figure 3.2).

The included studies were conducted in seven countries (Australia, Canada, Iran, New Zealand, South Africa, Spain, and United States) and involved a total of 585 participants. Twenty- one studies evaluated chronic ankle sprains and three studies investigated sub-acute sprains. Outcomes measured varied widely and included DFROM, proprioception, stability/balance, pain threshold (pressure and thermal), pain intensity and quality, function, talar stiffness, postural sway, and patient confidence. A range of joint mobilisation techniques were used and these included MWM in both weight-bearing or/and non weight-bearing (n=6) (Collins et al., 2004; Cruz-Diaz et al., 2015; Gilbreath et al., 2014; Marron-Gomez et al., 2015; Reid et al., 2007; Vicenzino et al., 2006), antero-posterior talocrural mobilisation (Maitland grades III and IV (Maitland, 2005), (n=4) (Harkey et al., 2014; Hoch & Mckeon, 2011; Plante, 2012; Wells, 2012), high velocity low amplitude (HVLA) ankle axial elongation manipulation and manipulation of the talocrural joint (n=6) (Alanson, 2012; Joseph et al., 2010; Kohne et al., 2007; Lopez-Rodriguez et al., 2007; Marron-Gomez et al., 2015; Pellow & Brantingham, 2001), Mulligan ankle taping (MAT) (n=3) (Hopper et al., 2009; Someeh et al., 2015a, 2015b), distal tibiofibular joint manipulation or mobilisation (n=2) (Beazell et al., 2012; Yeo & Wright, 2011), and combined mobilisation and traction of the talocrural joint (n=4) (Alanson, 2012; Hoch, Andreatta, et al., 2012; Hoch et al., 2014; Houston et al., 2013). MAT was included because it aims to mimic a MWM by sustaining the fibula glide during daily activities (Hing et al., 2015). These techniques were variously applied by physiotherapists, medical practitioners, chiropractors and athletic trainers. Table 3.2 describes the participants, interventions, comparators, outcome measures and results of the included studies.

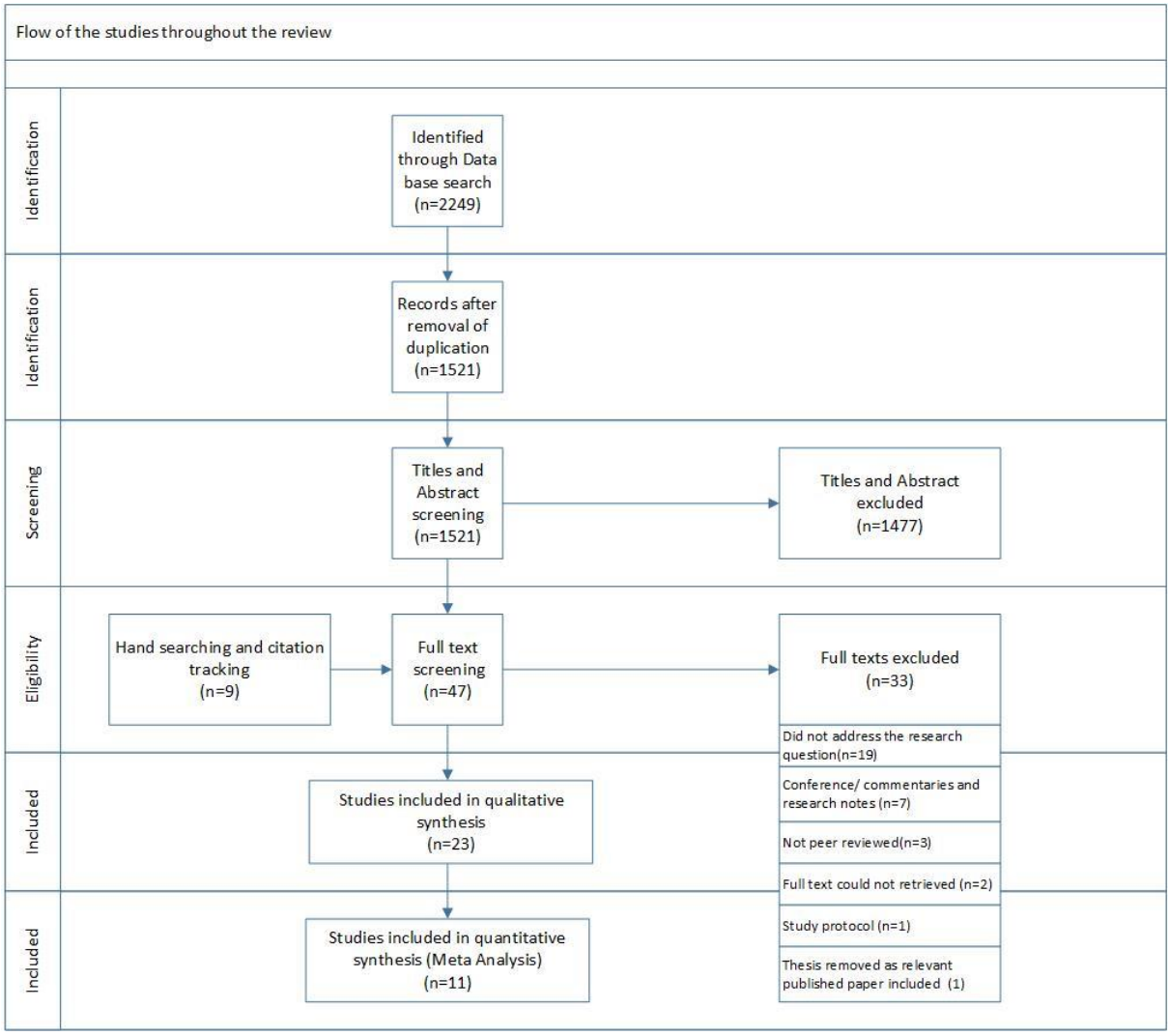
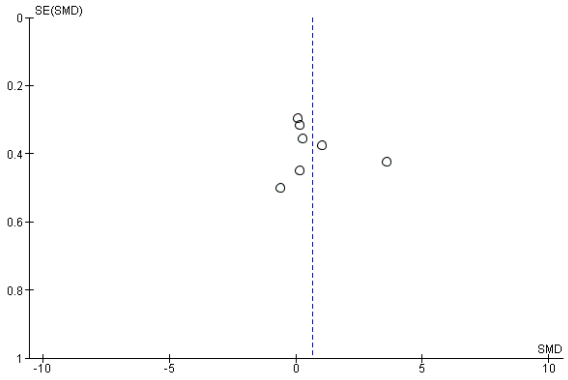
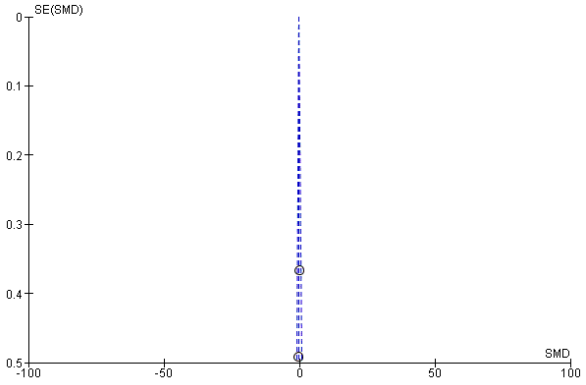


Figure 3.1 Flow chart of study selection

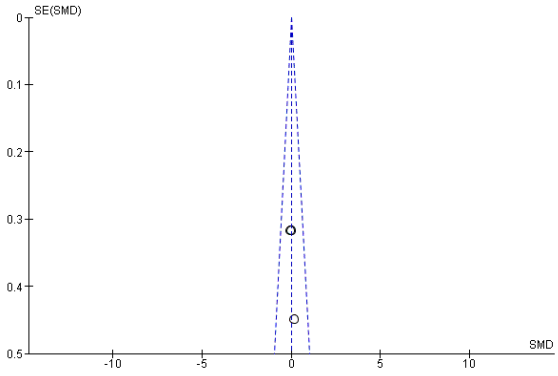
Immediate effect of mobilisation on weight-bearing dorsiflexion, pain, static balance and dynamic balance



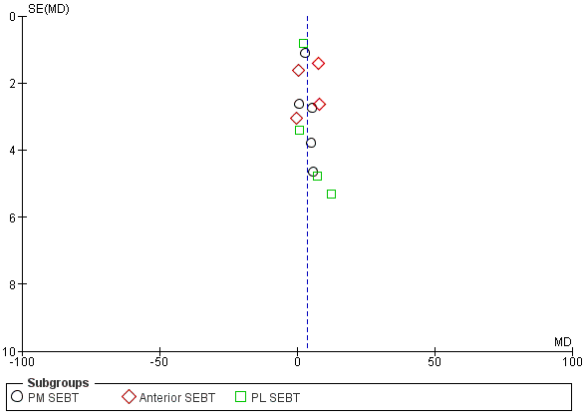
a) Weight-bearing dorsiflexion



b) Pain

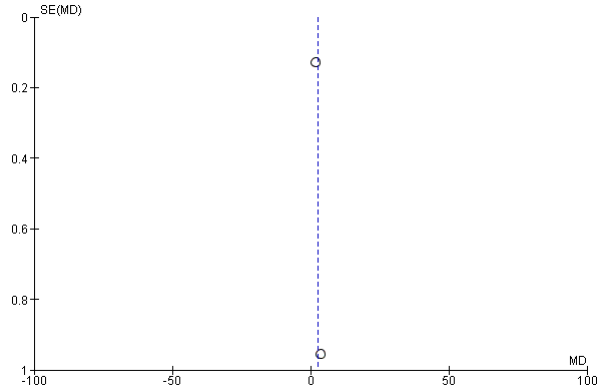


c) Static balance



d) Dynamic balance

Short-term effect of mobilisation on weight-bearing dorsiflexion



a) Weight-bearing dorsiflexion

SE=Standard Error; SMD=standard mean difference; MD=mean difference, PM=postero-medial; PL=postero-lateral; SEBT star excursion balance test

Figure 3.2 Funnel plots

The immediate effects of joint mobilisation were evaluated in 17 studies, short-term effects in 10 studies, and the long-term effects were assessed in only one study (Table 3.3). No studies evaluating effects on gait parameters, QOL, re-injury rate or strength were located in our search. In this systematic review, participants with chronic ankle sprains were included in 21 studies and three studies included participants with sub-acute sprains. No studies measuring the effectiveness of mobilisation in isolation for acute ankle sprains were able to be found. A meta-analysis was conducted using 11 studies, all involving participants with chronic ankle sprains.

3.3.2 Common mobilisation techniques used in rehabilitation of ankle sprains

Five combinations of mobilisation techniques were used in the 23 studies, including Mulligan MWM and taping techniques, Maitland mobilisation with and without traction, and manipulation.

The number of studies with positive effects on any clinically relevant outcome are contrasted against the number of studies with no positive effects, for each mobilisation technique (Figure 3.3). The findings also suggest that the combination of Mulligan MWM and taping is more likely to produce a clinical benefit than the other three mobilisation combinations, as more (17) of the studies using MWM techniques found positive outcomes compared to other techniques (Maitland mobilisation 12, manipulation 14). Further, studies reporting no positive outcomes with MWM techniques are fewer in number (6) compared with the other techniques (Maitland mobilisation 14, manipulation 13).

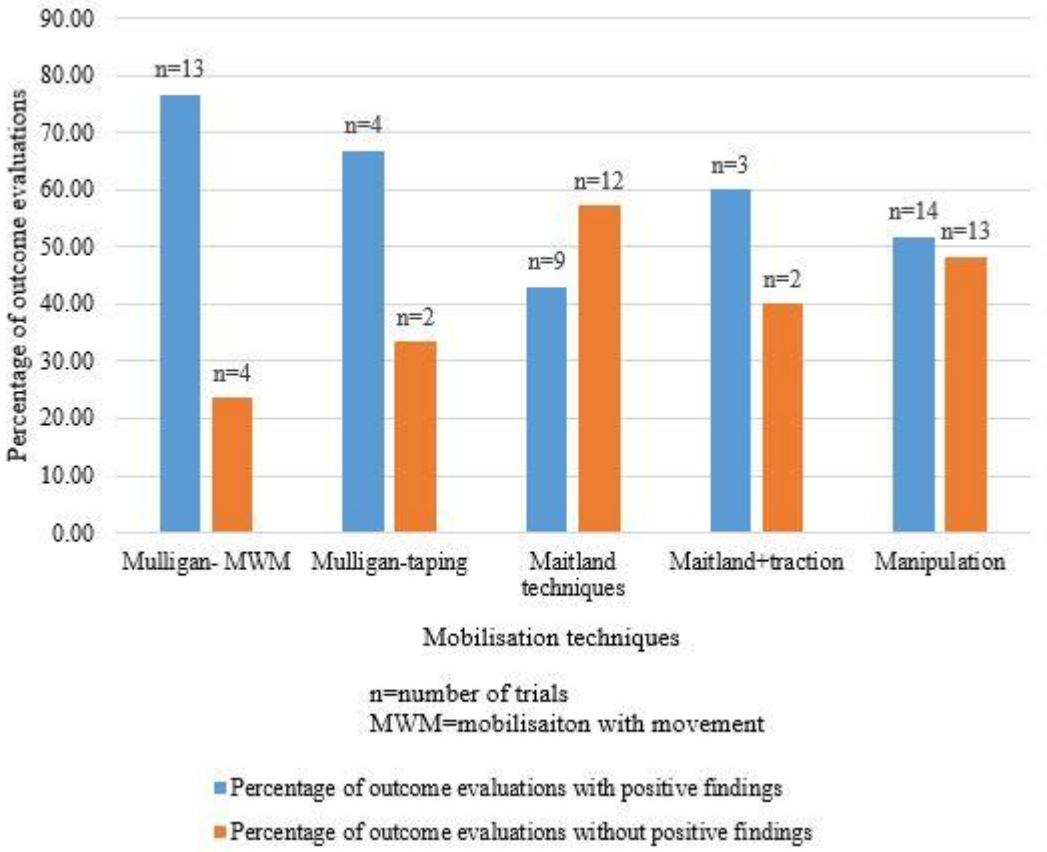


Figure 3.3 Percentage and number of outcome evaluations with and without positive findings following each technique combination of mobilisation for any clinically relevant outcome at any time point

3.3.3 Quality of studies

Due to differences in study design, two tools were used to assess the methodological quality of the included studies. PEDro was used for the assessment of RCTs (n=19) and the quality assessment tool for observational cohort and cross-sectional studies was used for all other study types (n=4). The level of agreement between reviewers for the quality assessment was considered to be high (k=0.63, 95% CI=0.53-0.73) and all disagreements were resolved by consensus.

Most studies scored well on random allocation, adequate follow-up, and for providing both point measures and measures of variability for at least one key outcome. In studies assessed using the PEDro scale (Figure 3.4), the most common risk of bias was for therapist and subject blinding. For the Quality assessment tool for observational cohort and cross-sectional studies, all four studies demonstrated bias in terms of insufficient timeframe, different levels of exposures as related to the outcome examined, and clearly defined valid and reliable exposure measures (Figure 3.5). All studies scored at least moderate in terms of the overall quality of the methodology for both the scales utilised (Figure 3.6 and 3.7).

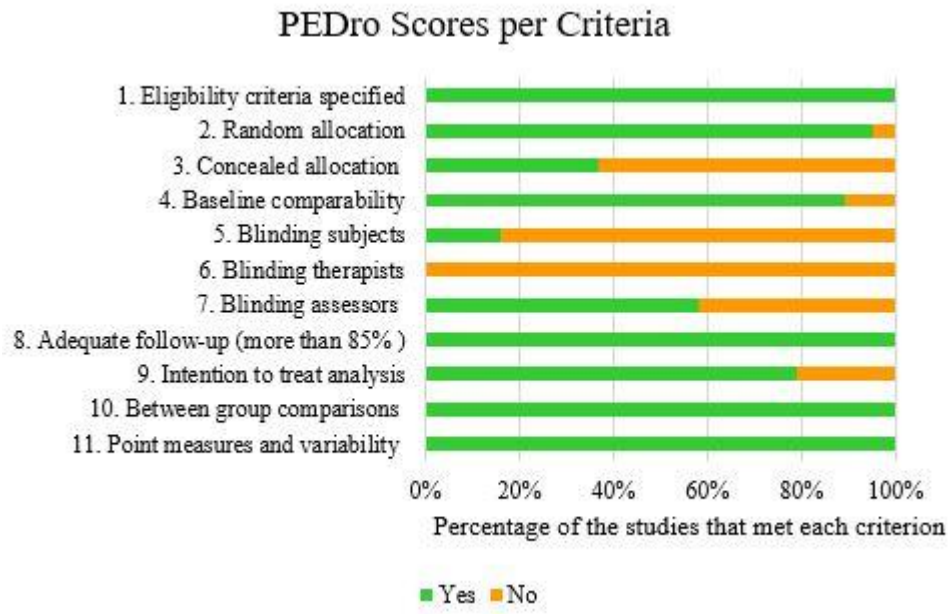


Figure 3.4 PEDro scores for assessment of quality of individual criteria (Pedro-Scale, 1999). Details about criteria: 1, Eligibility criteria were specified (Explanation: This criterion influences external validity, but not the internal or statistical validity of the trial. It has been included in the PEDro Scale so that all items of the Delphi Scale are represented on the PEDro Scale. This item is not used to calculate the PEDro score) (PEDro Scale); 2, Participants were randomly allocated to groups; 3, Allocation was concealed; 4, Groups were similar at baseline regarding most important prognostic indicators; 5, Blinding of all participants; 6, Blinding of therapists who administered the therapy; 7, Blinding of all assessors who measured at least 1 key outcome; 8, Measures of at least 1 key outcome were obtained from more than 85% of the participants; 9, All participants for whom outcome measures were available received the treatment or control condition as allocated; 10, Results of between-group statistical comparisons are reported for at least 1 key outcome; 11, Study provides both point measures and measures of variability for at least 1 key outcome.

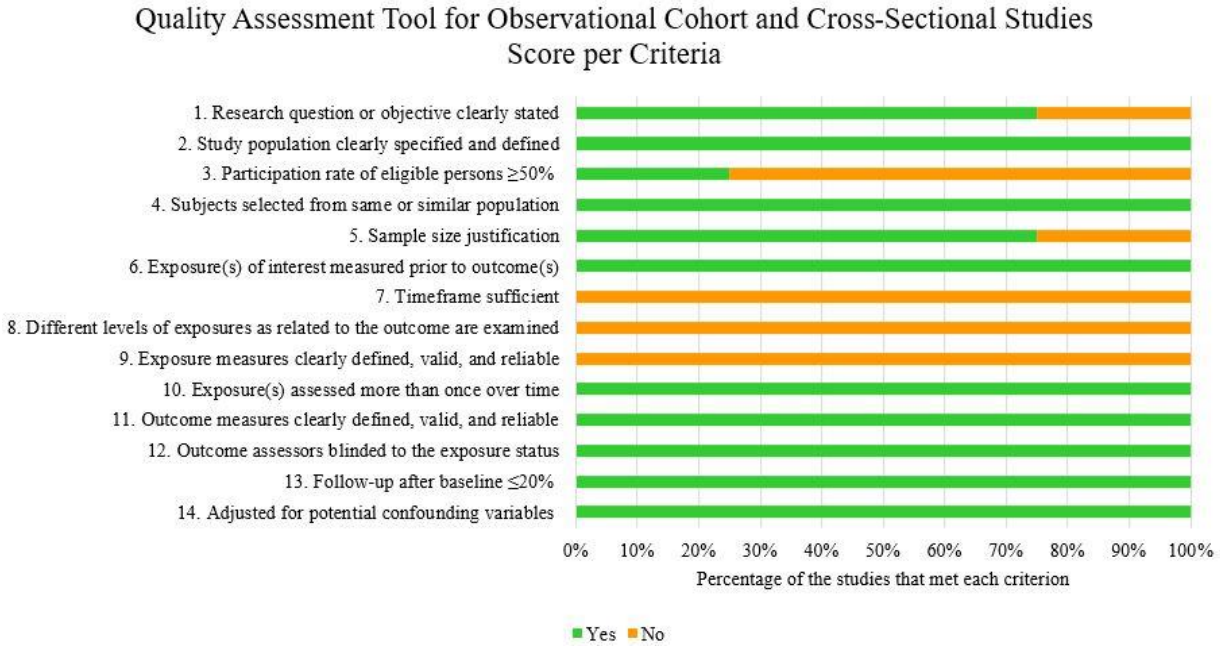


Figure 3.5 Quality assessment tool for observational cohort and cross-sectional studies (National Institutes of Health, 2014)

PEDro scale												
Study	**1) Eligibility criteria**	**2) Random allocation**	**3) Concealed allocation**	**4) Baseline comparability**	**5) Blinding subjects**	**6) Blinding therapists**	**7) Blinding assessors**	**8) Adequate follow-up (than 85% of subjects)**	**9) Intention to treat analysis**	**10) Between-group comparisons**	**11) Point measures and variability**	**Total Score out of 10**
Alanson 2012	+	+	+	-	-	-	+	+	+	+	+	7
Beazell, Grindstaff et al. 2012	+	+	-	+	-	-	+	+	+	+	+	7
Collins, Teys et al. 2004	+	+	-	+	+	-	+	+	-	+	+	7
Cruz-Diaz, Lomas Vega et al. 2015	+	+	+	+	-	-	+	+	-	+	+	7
Harkey, McLeod et al. 2014	+	+	+	+	-	-	+	+	+	+	+	8
Hoch and McKeon 2011	+	+	+	+	-	-	+	+	+	+	+	8
Hopper, Samsson et al. 2009	+	+	-	+	-	-	-	+	+	+	+	6
Joseph, de Busser et al. 2010	+	+	+	+	-	-	-	+	+	+	+	7
Kohne, Jones et al. 2007	+	+	+	-	-	-	-	+	+	+	+	6
Lopez-Rodriguez, de-Las-Penas et al. 2007	+	-	-	+	-	-	-	+	+	+	+	5
Marron-Gomez, Rodriguez-Fernandez et al. 2015	+	+	-	+	+	-	+	+	+	+	+	8
Pellow and Brantingham 2001	+	+	-	+	-	-	-	+	-	+	+	5
Plante 2012	+	+	-	+	-	-	-	+	+	+	+	6
Reid, Birmingham et al. 2007	+	+	-	+	-	-	+	+	-	+	+	6
Someeh, Norasteh et al. 2015	+	+	-	+	-	-	-	+	+	+	+	6
Someeh, Norasteh et al. 2015	+	+	-	+	-	-	-	+	+	+	+	6

Vicenzino, Branjerdporn et al. 2006	+	+	-	+	+	-	+	+	+	+	+	8
Wells 2012	+	+	+	+	-	-	+	+	+	+	+	8
Yeo and Wright 2011	+	+	-	+	-	-	+	+	+	+	+	7

Figure 3.6 PEDro scores for assessment of quality of individual intervention studies

+ meet criteria, - do not meet criteria

1, eligibility criteria were specified (*Explanation: This criterion influences external validity, but not the internal or statistical validity of the trial. It has been included in the PEDro scale so that all items of the Delphi scale are represented on the PEDro scale. This item is not used to calculate the PEDro score*) (PEDro Scale); 2, participants were randomly allocated to groups; 3, allocation was concealed; 4, groups were similar at baseline regarding most important prognostic indicators; 5,blinding of all participants; 6, blinding of therapists who administered the therapy; 7, blinding of all assessors who measured at least one key outcome; 8, measures of at least one key outcome were obtained from more than 85% of the participants; 9, all participants for whom outcome measures were available received the treatment or control condition as allocated; 10, results of between-group statistical comparisons are reported for at least one key outcome; 11, study provides both point measures and measures of variability for at least one key outcome (Pedro-Scale, 1999).

	Quality assessment tool for observational cohort and cross-sectional studies scale														
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Score out of 14**
(Gilbreath, Gaven et al. 2014)	+	+	+	+	+	-	-	-	+	+	+	-	+	+	10
(Hoch, Andreatta et al. 2012)	+	+	+	+	+	-	-	-	+	+	+	+	+	+	11
(Hoch, Mullineaux et al. 2014)	+	+	+	+	+	-	-	-	+	+	+	-	+	+	10
(Houston, McKeon et al. 2013)	+	+	+	+	-	-	-	-	+	-	+	-	+	-	7

Figure 3.7 Quality assessment tool for observational cohort and cross-sectional studies scores for assessment of quality of individual cohort studies

+ meet criteria, - do not meet criteria

1, Research question or objective clearly stated; 2, Study population clearly specified and defined; 3, Participation rate of eligible persons ≥50% ; 4, Subjects selected from same or similar population; 5, Sample size justification; 6, Exposure(s) of interest measured prior to outcome(s); 7,Timeframe sufficient; 8, Different levels of exposures as related to the outcome are examined; 9, Exposure measures clearly defined, valid, and reliable;10, Exposure(s) assessed more than once over time; 11,Outcome measures clearly defined, valid, and reliable; 12, Outcome assessors blinded to the exposure status; 13, Follow-up after baseline ≤ 20% ; 14, Adjusted for potential confounding variables Total (0 to 14) (Higgins et al., 2011; National Institutes of Health, 2014)

3.3.4 Effects of mobilisation on sub-acute/chronic ankle sprains

The outcome measures of DFROM, proprioception, stability/balance, pain threshold, pain intensity and quality, function, talar stiffness, postural sway, and patient's confidence towards stability were assessed at varying time points across the studies after application of joint mobilisation. Table 3.3 lists each outcome evaluation, indicating positive effects of mobilisation at each of the three time points of interest.

Eleven studies on chronic sprains reported quantitative data on five different outcomes, including weight-bearing DFROM, static balance, dynamic balance, pain intensity and pain threshold. However, due to study heterogeneity and a lack of useable data for some outcomes, data could only be pooled for weight-bearing DFROM, static balance, dynamic balance and pain intensity in order to evaluate immediate effects, and weight-bearing DFROM was the only outcome measure available to assess the short-term effects of ankle mobilisation.

Table 3.3 Number of outcome evaluations investigating at each time point of interest, listed by the reported positive effects

Outcome	Positive findings					
	Immediate		Short-term		Long-term	
	Yes	No	Yes	No	Yes	No
1. DFROM	11	3	4	4	1	0
weight bearing DFROM	9	2	3	2	1	0
non weight bearing DFROM	2	1	0	1	0	0
unspecified	0	0	1	1	0	0
2. Proprioception	2	0	1	0	0	0
3. Stability/balance	3	7	3	3	1	0
static balance	1	3	1	3	0	0
dynamic balance	2	4	2	0	1	0
4. Pain threshold	1	1	1	1	0	0
5. Pain intensity	0	2	2	1	0	0
6. Functional outcomes	2	4	4	2	0	0
7. Talar stiffness	1	2	0	1	0	0
8. Recovery from postural sway	1	0	0	0	0	0
9. Patient's confidence towards stability	1	0	0	0	0	0

DFROM, dorsiflexion range of motion

Note: "Immediate'', measured immediately following the intervention, "Short-term", measured up to 3 months following the intervention, "Long-term", measured at 3 or more months following the intervention

3.3.5 Immediate effects of mobilisation on ankle sprains

The immediate effects on DFROM were assessed in 14 outcome evaluations, of which 11 reported improvement with mobilisation techniques (Table 3.3). The findings for other outcomes were less notable. Of the 10 studies which investigated the immediate effects of mobilisation on stability/balance, three had demonstrable improvement (Cruz-Diaz et al., 2015; Hoch & Mckeon, 2011; Someeh et al., 2015a). Similarly, studies which assessed pain, talar stiffness and function revealed inconsistent results. When considering the immediate effects of mobilisation on functional outcomes, two outcome evaluations out of six demonstrated that it was effective (Houston et al., 2013; Someeh et al., 2015b). A summary of the reported immediate effects is provided in Table 3.3.

Pooled data from five studies with a total of 180 participants were grouped for analysis of the effects of mobilisation on each direction of the SEBT; anterior, postero-medial, and postero-lateral. This analysis provided significant findings for the postero-medial direction of the SEBT (MD=3.22, CI=1.43-5.01, p=0.0004), however the postero-lateral direction (MD=3.55, CI=-0.18-7.28, p=0.06) and the anterior direction (MD=4.10, CI=-0.35- 8.54, p=0.07) results of the SEBT, were not significant (Figure 3.8). Pooled data for static balance from three studies with a total of 100 participants indicated there were no significant immediate benefits following mobilisation of individuals with chronic sprains, when compared to control participants (SMD=0.01, CI=-0.38-0.40, p=0.96) (Figure 3.9).

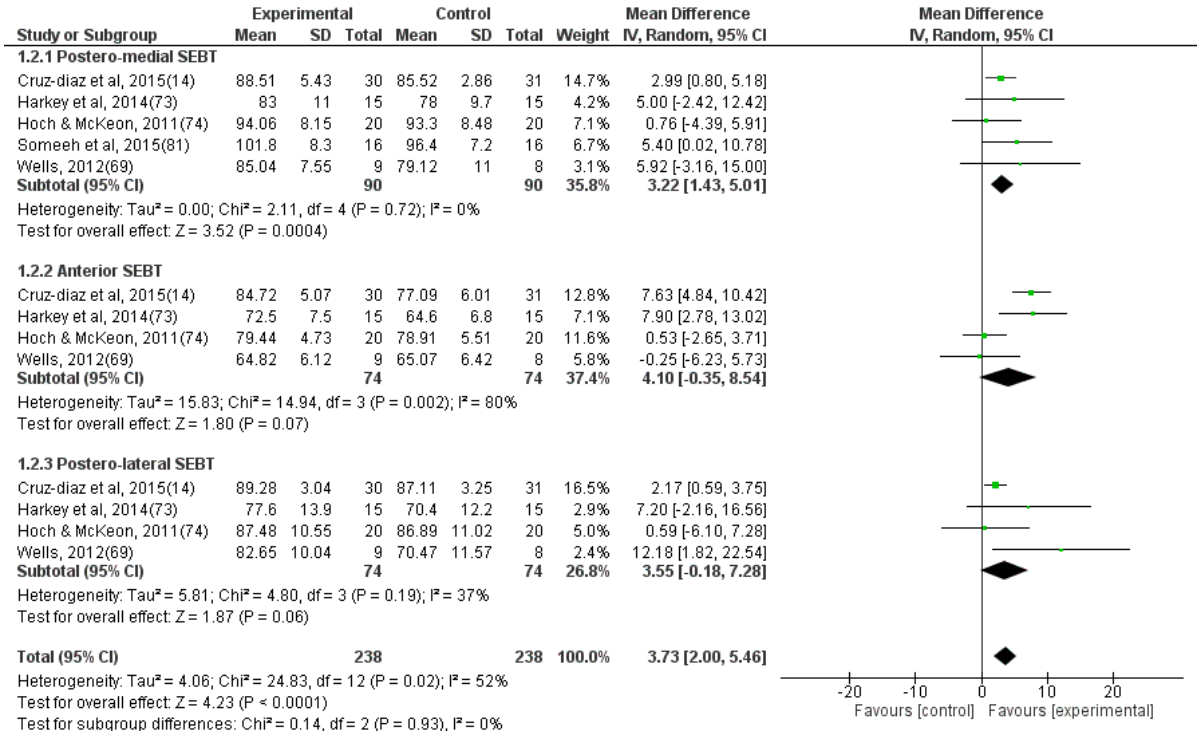


Figure 3.8 MD (95% CI) of the immediate effect of joint mobilisation on dynamic balance by pooling data from 5 studies (n=180). Abbreviations: df, degrees of freedom; IV, inverse variance

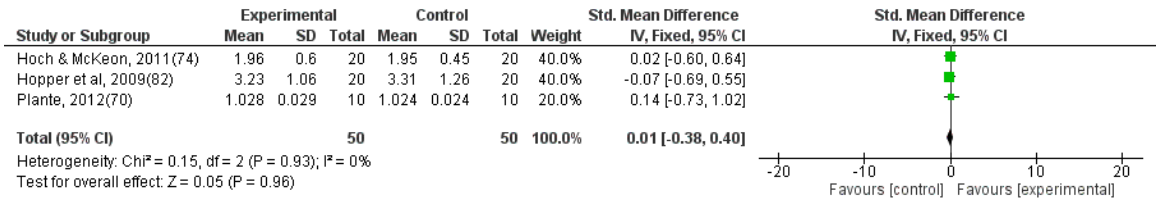


Figure 3.9 SMD (95% CI) of the immediate effect of joint mobilisation on static balance by pooling data from 3 studies (n=100). Abbreviations: df, degrees of freedom; IV, inverse variance; Std., standardised

Similarly, data from seven studies with a total of 249 participants indicated there were no significant immediate effects of mobilisation on the weight-bearing DF-ROM of individuals with chronic sprains (SMD=0.66, CI=-0.25-1.58, p=0.16) (Figure 3.10). For pain intensity, pooled data from two studies with a total 47 participants indicated mobilisation had no immediate effect on individuals with chronic sprains (SMD=-0.21, CI=-0.78-0.37, p=0.48) (Figure 3.11). There were insufficient data to analyse the immediate benefits of mobilisation on pain threshold.

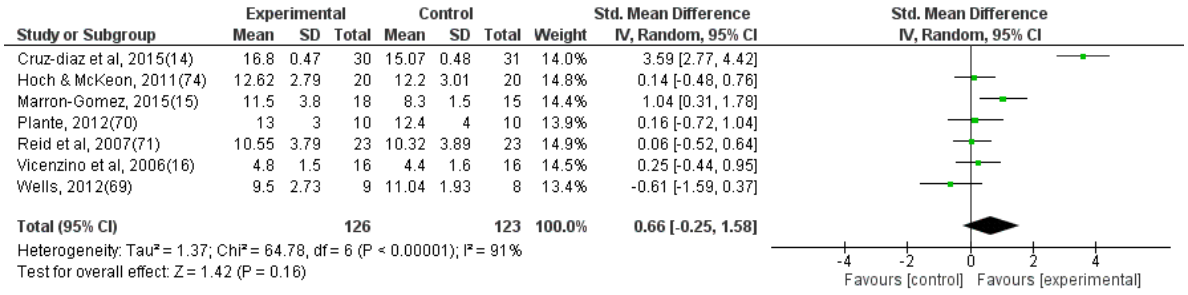


Figure 3.10 SMD (95% CI) of the immediate effect of joint mobilisation on weight-bearing DFROM by pooling data from 7 studies (n=249). Abbreviations: df, degrees of freedom; IV, inverse variance; Std., standardised

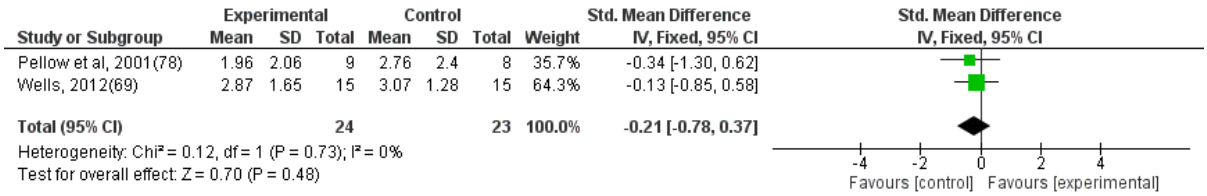


Figure 3.11 SMD (95% CI) of the immediate effect of joint mobilisation on pain intensity by pooling data from 2 studies (n=47). Abbreviations: df, degrees of freedom; IV, inverse variance; Std., standardised

3.3.6 Short-term effects of mobilisation on ankle sprains

Half of the outcome evaluations reported that mobilisation improved DFROM, stability/balance and pain threshold in the short-term (Table 3.3). Demonstrable improvement was also observed in pain intensity and function (Table 3.3), and two studies (Hoch et al., 2014; Kohne et al., 2007) which evaluated short-term outcomes on talar stiffness and proprioception reported improvements. No studies reported short-term findings on postural sway or patient's balance confidence.

Pooled data from two studies with 94 participants with chronic sprains indicated joint mobilisation was effective in the short-term for improving weight-bearing DFROM (MD=2.56, CI=0.89- 4.23, p=0.003) (Figure 3.12). There were insufficient data evaluating static balance, dynamic balance, pain threshold and pain intensity to permit analysis of the short-term benefits of mobilisation on these outcomes.

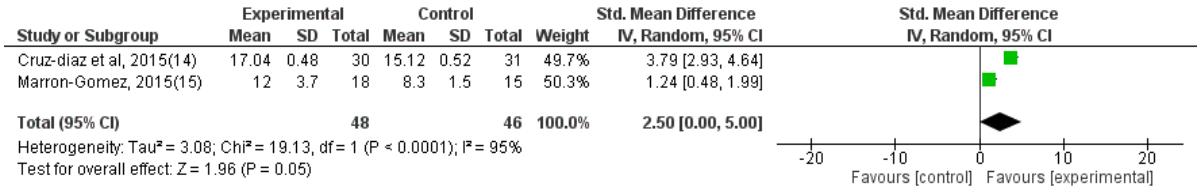


Figure 3.12 SMD (95% CI) of the short-term effect of joint mobilisation on weight-bearing DFROM by pooling data from 2 studies (n=94). Abbreviations: df, degrees of freedom; IV, inverse variance; Std., standardised

3.3.7 Long-term effects of mobilisation on ankle sprains

Only one study evaluated the long-term effects of mobilisation on ankle sprains. Long-term improvement in DFROM and stability/balance were reported in the single included study (Cruz-Diaz et al., 2015).

3.3.8 Quality of evidence

According to the GRADE assessment (Table 3.4), the evidence for DFROM (immediate and short term), static balance and dynamic balance can be considered to be of moderate quality. The evidence for pain was considered to be of low quality due to lack of generalisability of one of the included studies. Overall, the evidence included in this meta-analysis was considered to be of moderate quality, with the risk of bias and the level of heterogeneity the main factors influencing the quality of the evidence.

Table 3.4 Assessment of the quality of evidence

Number of studies **(sample size, n)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality of evidence**
Immediate effects					
Outcome: DFROM					
7 studies (n; experimental=126 : control=123)	low risk of bias (Pedro scores: 6,6,7,8,8,8 and 8)	p value on test for heterogeneity p<0.00001, I^2=91% high inconsistency	low indirectness	low imprecision	moderate quality (low risk of bias and high inconsistency)

Outcome: dynamic balance					
5 studies (n; experimental=90: control=90)	low risk of bias (Pedro scores: 6,7,8,8 and 8)	p value on test for heterogeneity p=0.02, I^2=52% moderate inconsistency	low indirectness	low imprecision	moderate quality (low risk of bias and moderate inconsistency)
Outcome: static balance					
3 studies (n; experimental=50: control=50)	moderate risk of bias (Pedro scores: 6,6 and 8)	p value on test for heterogeneity p=0.93, I^2=0% low inconsistency	low indirectness	low imprecision	moderate quality (moderate risk of bias and low inconsistency)
Outcome: pain intensity					
2 studies (n; experimental=24: control=23)	moderate risk of bias (Pedro scores: 5 and 8)	p value on test for heterogeneity p=0.73, I^2=0% low inconsistency	moderate indirectness (less generalisable)	low imprecision	low quality (moderate risk of bias, moderate inconsistency and low indirectness)
Short-term effects					
Outcome: DFROM					
2 studies (n; experimental=48: control=46)	low risk of bias (Pedro scores: 7 and 8)	p value on test for heterogeneity p<0.0001, I^2=95% high inconsistency	low indirectness	low imprecision	moderate quality (low risk of bias and high inconsistency)

DFROM, Dorsiflexion range of movement

3.4 Discussion

This is the first systematic review to assess the clinical benefits of joint mobilisation in the management of either lateral or medial ankle ligament sprains at all stages of recovery. Importantly, this is the first review to only include studies in which joint mobilisation is the sole intervention. The current review did not identify any studies evaluating the clinical benefits of joint mobilisation on acute ankle sprains, perhaps because mobilisation is not typically the preferred choice of management in the acute stage of ankle sprains (Van Den Bekerom et al., 2013). Findings about the clinical benefits of mobilisation on the majority of outcome measures were inconsistent across studies, and a lack of reported quantitative data, heterogeneity of subjects and the differing types of joint mobilisation applied made direct comparisons difficult. Despite this, meta-analysis indicated there are immediate benefits of mobilisation for improving dynamic balance, and a short-term benefit in improving weight-bearing DFROM in chronic ankle sprains. These results provide compelling evidence that joint mobilisation may be effective in improving balance immediately and in increasing DFROM in the short-term in chronic ankle sprains.

Dynamic balance and weight-bearing DFROM improvements following joint mobilisation were both associated with clinically meaningful changes. The modified SEBT test assesses performance during single-leg balance with reaching in three directions (anterior, postero-medial, postero-lateral) (Chimera et al., 2015; Rehabilitation-Measures-Database, 2010). The MCID for this test is reported as being 3.5%, and therefore the immediate effect on dynamic balance found in the meta-analysis (MD=3.73) can be considered as clinically meaningful (Chimera et al., 2015; Rehabilitation-Measures-Database, 2010). It is plausible that the immediate improvements in dynamic balance following joint mobilisation may increase the individual's balance confidence and

perhaps reduce the risk of re-injury. Clinically, this may assist the individual with an ankle sprain to more safely proceed to the next level of functional exercise in the rehabilitation process.

There were no immediate improvements in either anterior SEBT performance or DFROM. Interestingly, previous research supports the existence of a correlation between anterior SEBT performance and the weight-bearing lunge test (Hoch, Staton, et al., 2012). This correlation could help explain the current review's findings on immediate anterior SEBT performance and DF-ROM. Notably, the MCID for ankle DFROM has not been established (Young et al., 2013). However, approximately 3.6˚ of DFROM is associated with 1cm in distance from the wall in the lunge test (Hoch & Mckeon, 2011). The MD in the short-term measurement of weight-bearing DFROM from the current meta-analysis was 2.56cm and this equates to 9.2° of dorsiflexion, which can be considered as clinically meaningful given that the normal total range is only 15- 20° (Hallaceli et al., 2014; Roaas & Andersson, 1982).

Joint mobilisation techniques are aimed at restoring the normal joint ROM (Hertling & Kessler, 2006; Oatis, 2004), and indeed this review found DFROM improved following mobilisation. However, the mechanisms by which restoring ankle ROM may assist other impairments is unclear, as are the underlying mechanisms by which mobilisation may actually work (Marron-Gomez et al., 2015; Vicenzino et al., 2006). It has been proposed that increased ankle ROM is due to the correction of a bony positional fault (Vicenzino et al., 2011). It is further postulated that the correct alignment of the articular surfaces may help to restore normal biomechanics, as well as sensorimotor function (Vicenzino et al., 2011). However, it may be that mobilisation produces less impact on pain, as evidenced by the lack of improvement in ankle pain outcome measures in this

review. Potential underlying central nervous system changes related to persistent pain in chronic sprains remain unclear, but central sensitisation may be a possible factor for persistence of chronic pain. If central sensitisation is actually a key factor contributing to chronic ankle sprain pain, then changing the bony alignment would be unlikely to improve pain in chronic sprains as it is not the usual localised pressure pain hypersensitivity (Ramiro-Gonzalez et al., 2012) experienced immediately after a sprain.

According to the Clinical Practice Guidelines Linked to the ICF from the APTA, clinicians should use joint mobilisation to improve ankle dorsiflexion, proprioception, and weight-bearing tolerance in patients recovering from a lateral sprain (Martin et al., 2013). Of these three outcomes, the findings of the current review only support the benefit of mobilisation for dorsiflexion. There was insufficient research available to conclude whether mobilisation is effective for improving proprioception or weight-bearing tolerance. However, the current review found clinically meaningful evidence for the effect of mobilisation on dynamic balance, an outcome not mentioned in the Clinical Practice Guidelines from the APTA. One explanation for this difference may be that the Guidelines only included literature published prior to April 2012, while the current review has included seven more recently published studies.

The inclusion and exclusion criteria of the current review differ in important ways from previous systematic reviews on this topic. In contrast to these prior reviews, our search criteria included both lateral and medial ligament sprains, covered all stages of recovery from acute to chronic, and encompassed all clinically relevant outcomes used to assess the effects of mobilisation. Importantly, of the six prior reviews which have evaluated the efficacy of mobilisation techniques

on ankle sprains, all included studies which did not evaluate joint mobilisation as a unique intervention, but rather as an adjunct to other interventions (such as home exercise programs, RICE protocol and external supports included in their review (Bleakley et al., 2008; Loudon et al., 2014; Southerst et al., 2015; Terada et al., 2013; Van Der Wees et al., 2006; Wikstrom & Mckeon, 2011). The current review excluded these multi-modal studies to ensure the homogeneity of the included studies, and to increase the precision of the results in relation to the effects of joint mobilisation. Compared to the recent review by Loudon et al (Loudon et al., 2014), the present review included almost three times more studies (23), with all of these only investigating the clinical effects of joint mobilisation techniques in isolation. In the review by Loudon et al (Loudon et al., 2014), only eight studies were included, and of those mobilisation was used as the sole intervention in only five (Loudon et al., 2014). This disparity in the number of included studies may be due to our searching a greater number of databases (11), including medial ankle sprains in the search criteria, by reviewing dissertations and theses, and by not limiting clinical outcomes.

This review includes the first meta-analysis undertaken to assess the clinical benefits of joint mobilisation for ankle sprains. When comparing the findings of the current review to previous systematic reviews, there were some agreements and some inconsistent results. When considering the immediate effects of mobilisation, the review by van der Wees et al (Van Der Wees et al., 2006) reported an improvement in DFROM (Van Der Wees et al., 2006). However, the current review did not support an immediate effect on weight-bearing DFROM, with mobilisation providing only a short-term effect. Pain and function are concluded to improve immediately in the review by Southerst et al (Southerst et al., 2015), but in our review immediate pain relief was not evident and inconclusive results were found for immediate function. When considering the short-term effects, the effectiveness of mobilisation in increasing ankle ROM was supported in the

review of Bleakely et al (Bleakley et al., 2008), and this was consistent with the findings of the current review (Bleakley et al., 2008). The review by van Ochten et al (Van Ochten et al., 2014) reported positive changes in short-term pain and function in chronic sprains, however the findings of the present review were inconclusive for both of these outcomes (Van Ochten et al., 2014). When considering the long-term effects of mobilisation, pain and function are improved according to the review by Southerst et al (Southerst et al., 2015). The findings of the current review on these outcomes were inconclusive due to lack of data. Different definitions of inclusion criteria for mobilisation techniques included within reviews (e.g., including other therapies such as home exercise or RICE treatment along with mobilisation), as well as differences in the databases searched and the periods of the data searches, are all factors contributing to these differing findings.

3.4.1 Study limitations

Limitations of this review include the wide variation in follow-up time points that we defined as short-term (from one day to less than three months). Additionally, the included studies have used a range of different mobilisation techniques and comparators. It was beyond the scope of this review to attempt to determine the independent merits of individual techniques. In particular, there may be value in analysing joint mobilisation and high velocity thrust manipulation techniques separately rather than together, but given the lack of available research at this time directly comparing these two manual therapy approaches this level of scrutiny is not possible. In addition, it was not possible to pool data to analyse the effectiveness of mobilisation for some important outcomes that were reported in single studies. Despite attempts to contact authors of included studies, data were insufficient to analyse immediate effects on PPT and short-term effects on PPT and pain intensity. Finally, no high quality evidence was found, to provide robust evidence for the effectiveness of joint mobilisation for ankle sprains.

Further research is required to determine the mechanisms by which mobilisation improves dynamic balance and weight-bearing DFROM. Also, the long-term effects of mobilisation on ankle sprains should be further investigated using clinically relevant outcomes.

3.5 Conclusion

Joint mobilisation appears to clinically benefit individuals with chronic ankle sprains, improving dynamic balance immediately and weight-bearing DFROM in the short-term. It is unlikely to have an immediate effect on static balance, pain intensity, and weight-bearing DFROM. Other clinical outcomes that have been reported following mobilisation demonstrate an inconsistent response to mobilisation, and this may be a reflection of previous study designs or of the intervention itself.

Chapter 4 Is the fibula positioned anteriorly in weight-bearing in individuals with chronic ankle instability?

This chapter has been has been submitted (10 July 2019) for publication in a peer-reviewed journal as:

> Weerasekara, I., Osmotherly, P., Snodgrass, S., Tesseir, J., & Rivett, D. A. (2019). Is the fibula positioned anteriorly in weight-bearing in individuals with chronic ankle instability? (under review).

The work presented in this manuscript was completed in collaboration with the co-authors (Appendix 1). The ethics approval and supporting documents for the study reported in this chapter appear in Appendices 2, 4, 5, 9, 10, 13 and 15.

Overview

The findings of the systematic review described in Chapter 3 did not identify any studies evaluating the clinical benefits of joint mobilisation on acute ankle sprains, and all studies included in the meta-analysis were on chronic recurrent sprains or on CAI. Other than development of residual symptoms such as a subjective feeling of 'giving way' and a history of recurrent sprains, various anatomical and clinical deficits have been purported to be associated with CAI. However, these deficits have not been consistently reported in the literature and there is no agreement as to the clinical features of CAI. Chapters 4 and 5 together aim to further investigate the identifying characteristics of CAI.

The presence and direction of a fibular positional abnormality in CAI remains controversial, although this could be one of the key potential anatomical characteristics of CAI. All previous studies examining fibular position in participants with ankle injuries have used non-functional (non weight-bearing) radiographs. Therefore, the purpose of the case-control study described in this chapter was to determine any differences in normalised fibular position in a weight-bearing position between participants with CAI and healthy volunteers, and to establish diagnostic utility measures.

This chapter presents the findings of the case-control study with respect to a comparison of the position of the fibula of individuals with CAI, to those with healthy ankles. Importantly, this is the first study to assess fibular position using weight-bearing radiographs, arguably a more functional position. Utility data for normalised fibular position including a discrimination score, reliability values, specificity and sensitivity are also discussed in this chapter.

4.1 Introduction

The ‘positional fault hypothesis’ was proposed in 1993 by Brian Mulligan (Mulligan, 1993) to explain the benefits of MWM in the treatment of joint injuries. According to this hypothesis, joint injuries or sprains might result in a minor bony incongruence. In relation to ankle joint inversion injuries, the distal fibula may become anteriorly positioned in relation to the tibia following injury (Vicenzino et al., 2011), causing painful restrictions in physiological movement (Mulligan, 1995). The presence of such a fibular positional abnormality remains controversial. Whether an abnormally positioned fibula predisposes to injury, or whether inversion injury may result in an anteriorly positioned fibula, is yet to be examined (Hubbard et al., 2006).

The presence of an abnormally positioned fibula has been explored in acute to chronic ankle sprains and also in CAI (Berkowitz & Kim, 2004; Eren et al., 2003; Fukuhara et al., 2012; Hubbard & Hertel, 2008; Hubbard et al., 2006; Kavanagh, 1999; Kobayashi et al., 2014; Li et al., 2017; Mavi et al., 2002; Merlin et al., 2005; Scranton et al., 2000), using fibular movement measured by potentiometer, 3D CT-based bone models, and radiological investigations involving MRI, CT, fluoroscopy and X-rays. These studies utilised different indices to determine fibular position including axial malleolar index (AMI) and intra–malleolar index (IMI) (Berkowitz & Kim, 2004; Eren et al., 2003; Mavi et al., 2002; Scranton et al., 2000). Fibular position has also been measured radiographically as the distance between the most anterior margin of the tibia and the most anterior margin of the fibula on a lateral view (Hubbard et al., 2006; Vicenzino et al., 2011). Because of possible superimposition of anatomy (fibular position by the size of the tibia) on the lateral projection, a normalisation technique has been suggested which reports fibular position as a percentage of tibial width (Wikstrom, Tillman, et al., 2010).

While some studies support the presence of an alteration in fibular position in CAI, others indicate no such findings (Li et al., 2017; Wikstrom et al., 2012). Where a fibular positional anomaly has been detected, there are mixed findings regarding the direction of the displacement, including anterior (Hubbard et al., 2006), posterior (Berkowitz & Kim, 2004), lateral (Kobayashi et al., 2014) and antero-inferior (Merlin et al., 2005). These inconsistencies may possibly be due to different radiological methods or methods of measurement (Vicenzino et al., 2011) used across the various studies. It is also possible that alterations in fibular position may be better observed in functional positions (such as standing). However, all studies undertaken to date have utilised non weight-bearing positions.

It may be important to assess the position of the fibula in a weight-bearing position as this is a more functional position and likely more clinically relevant. A detectable difference in fibular position in a weight-bearing position in patients with CAI, as compared to healthy individuals could well be important in their clinical management. Demonstration of the existence of an altered fibular position could provide some support for physical interventions aimed at 'correcting a fibular positional fault', and provide a possible explanation for persistent ankle pain and dysfunction following injury in some cases (Vicenzino et al., 2011).

To date, researchers have not investigated differences in fibular position between injured and healthy individuals in a weight-bearing position, or adequately demonstrated the diagnostic utility of any imaging method of fibular position. Quantifying values for reliability, specificity and

sensitivity measures, and cut-off scores for fibular positional changes that may be clinically relevant, could be of assistance in the therapeutic management of CAI.

The purpose of this study was to determine any differences in normalised fibular position in a weight-bearing position between participants with CAI and healthy volunteers, and to establish diagnostic utility measures including inter-rater and intra-rater reliability, specificity and sensitivity, and cut-off scores for normalized fibular position.

4.2 Materials and methods

Participants with CAI and healthy ankles aged 18 years and over were recruited through posted flyers, social media and using media releases (from October, 2017 to April, 2018). The volunteers with CAI were considered eligible if they satisfied the inclusion and exclusion criteria as endorsed by the IAC (Gribble et al., 2013), with the exception that the duration for undergoing at least two episodes of giving way of the ankle was changed from six to 12 months considering the seasonal nature of some sports. Individuals with a history of at least one significant ankle sprain and of the ankle giving way, and/or a recurrent sprain, and/or a feeling of instability, were included in the CAI group. Individuals were excluded from the CAI group if they reported a history of previous surgery or fractures in the lower extremity, current or previous injury to the ankle, neuromuscular disorders causing problems in the lower limb, conditions contraindicating radiological imaging, and an inability to read English. A significant ankle sprain was defined as an initial sprain occurring at least 12 months prior to study enrolment associated with inflammatory symptoms and which created at least one day of interrupted desired physical activity, with the most recent injury occurring more than three months prior to study enrolment (Gribble et al., 2013). Volunteers with

healthy ankles (age and gender matched) were accepted into the study if they had no prior history of ankle problems, lower limb surgery or other ankle treatment, and reported no current pain or problems in or around the ankle while performing daily activities. The same exclusion criteria were applied for volunteers with both CAI and healthy ankles. The University of Newcastle Human Research Ethics Committee granted ethical approval for the study (H-2017-0217). Informed consent was obtained from all participants and the rights of them were protected.

An X-ray (55k Vp and 2.1 mAs) was taken of the most affected ankle of the individuals with CAI to measure the fibular position with respect to the tibia in weight-bearing (neutral ankle in standing position). The most affected side was determined using the CAIT (Hiller et al., 2006). CAIT is a self-reported questionnaire used to determine the presence of ankle instability, with a cut-off score ≤ 24 indicating an individual's ankle is unstable (Gribble et al., 2013). If participants presented with a similar score for both ankles, they were asked to verbally nominate the most problematic ankle. If they were unable to distinguish between ankles, the dominant side was imaged. Volunteers with healthy ankles were age and gender matched to the participants with CAI, with the same ankle (left, right) imaged.

Each participant was instructed to stand on the affected foot with the knee slightly flexed representing mid-stance of the gait cycle, with the foot of the other leg hanging relaxed. Approximately 2cm distance was maintained between the imaged foot and the parallel image receptor. All participants were provided with similar instructions and the position of the leg was monitored throughout the procedure. The X-ray was repeated once if any leg rotation was observed on imaging. The central ray was directed to the base of the metatarsals and perpendicular to the

image receptor. The focal-film distance was set to 110cm. To ensure the lateral X-ray was acceptable, each individual radiograph was viewed immediately after exposure, while the participant maintained the same position of the imaged foot but could take some weight back on the other foot if desired. As the image was visible after approximately 10 seconds, this allowed for adjustments to the participant's position and a new image to be taken if required. As the radiograph was a lateral view, it was considered acceptable if superimposition of the talar domes was present, thus permitting a clear view of an open tibio-talar joint and allowing planned measurements to be undertaken. The participant was permitted to lightly hold the body of the X-ray machine for balance, if necessary (Weerasekara, Osmotherly, Snodgrass, Tesseir, et al., 2019).

Merge PACS software (Merge Health Care, 2012) was used to digitally record all radiographic images. The distance between the anterior edges of the distal fibula and the distal tibia was recorded as the fibular position (Figure 4.1) (Hubbard et al., 2006). Measures of fibular position were normalised to tibial width, and the tibial width defined as the maximum distance between the anterior and posterior tibial processes within the distal epiphysis, in a lateral view X-ray image. Normalisation of measurements was undertaken to minimise the potential error that could be introduced due to anatomical variation between individuals. All the radiographs were performed by a registered diagnostic radiographer (JT) with over 30 years of clinical experience.

A random selection of 24 ankle X-rays (CAI=12, healthy=12) were used to determine the reliability measures. These radiographs were independently evaluated by two assessors (a registered physical therapist [SW], and a registered radiographer [JT]) for reliability measures. Both the assessors were experienced in the use of the Merge PACS software (Merge Health Care, 2012). Each tester

individually completed measurements on one occasion to determine inter-rater reliability measures, and one tester (IW) undertook further blinded measurements on a second occasion (two weeks later) for intra-rater reliability measures. The standard error of measurement (SEM) was calculated for each reliability measure.

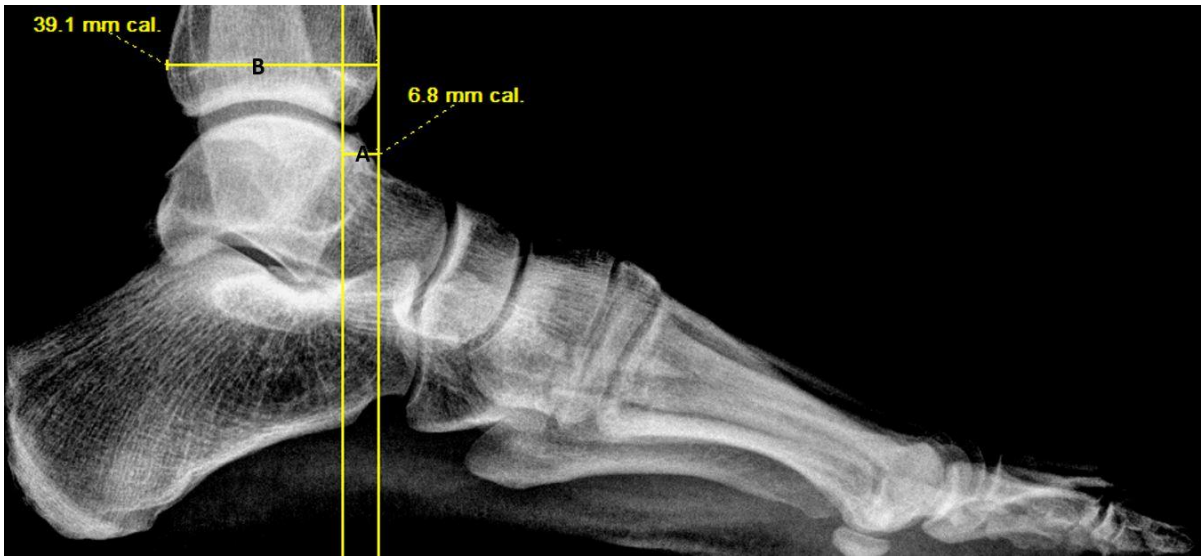


Figure 4.1 Measurement of normalised fibular position (normalised to tibial width; normalised fibular position, 17.39% =(fibular position [A], 6.8mm / maximum tibial width [B], 39.1mm) x 100. (A)=distance between the anterior edge of the distal fibula and the anterior edge of the distal tibia. (B)=maximum distance between the anterior tibial process and the posterior tibial process within the distal epiphysis

4.2.1 Analysis

The primary outcome measures of fibular position (Hubbard et al., 2006) and self-reported function (FAAM subscales) (Croy et al., 2012) were used in sample size calculations. The largest sample size estimation (MD=2.5, SD=3.4) (Hubbard et al., 2006) resulted in a minimum sample size of 33 participants per group allowing for a 10% for data loss, alpha of 0.05, and achieving power of 0.80.

Baseline data were assessed for normality using the Shapiro-Wilk normality test. Descriptive statistics were calculated for all variables. Comparison of means between the normal and CAI groups were analysed using independent t-tests. The effect size was calculated using Cohen's d for normalised fibular position.

Relative reliability of the measures was assessed using $ICC_{2,1}$ and 95% CIs. The SEM was calculated to assess measurement precision using the formula, $SEM=SD \times \sqrt{(1 - ICC)}$, with SD representing the standard deviation of the measure (Powden et al., 2015).

The ability of the measures of normalised fibular position to identify individuals with CAI was calculated using the area under the curve (AUC) for receiver operating characteristic (ROC) curves and the 95% CIs of the AUC. A traditional academic point scale was utilised to determine the accuracy of the AUC and the 95% CIs of the AUC for discriminating between healthy participants and those with CAI (0.90 - 1.00, excellent; 0.80 - 0.89, good; 0.70 - 0.79, acceptable; 0.60 - 0.69, poor; and 0.00 - 0.59, failure) (Wikstrom et al., 2012). In addition, a cut-off score (for discriminating individuals with CAI from healthy individuals) with resulting likelihood ratios and 95% CIs were quantified for normalised fibular position. The cut-off score was determined by calculating the Youden index (J) for fibular position along the ROC curve, with the largest J value representing the cut-off score (Beninato et al., 2014; Wikstrom et al., 2012). Further, positive (LR+) and negative (LR−) likelihood ratios were produced (LR+=(sensitivity /(1 – specificity), LR−=(1–sensitivity)/specificity) (Beninato et al., 2014; Powers et al., 2017). All statistical analyses were performed using IMB SPSS (Version 23.0, Armonk, NY, IBM Corp).

4.3 Results

Sixty-six participants were included in the study after assessing eligibility. An outline of the recruitment process is provided in Figure 4.2. Common reasons for exclusion included previous ankle injury (n=13 in CAI group) and unable to match with CAI group (n=6 in healthy group).

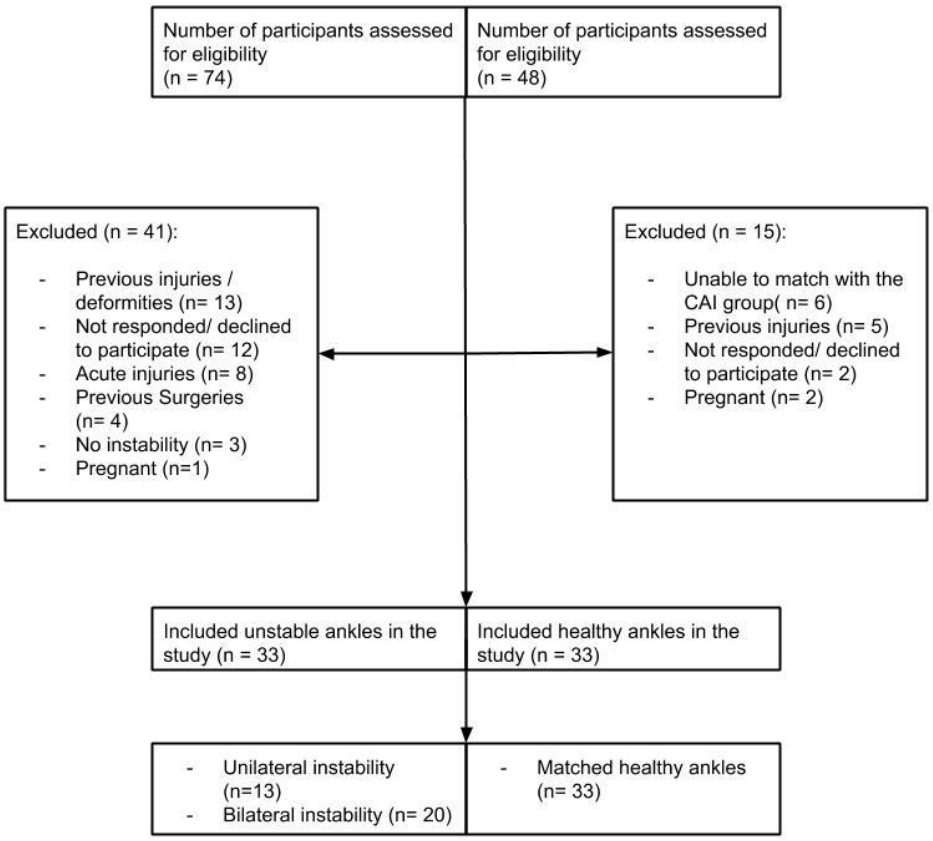


Figure 4.2 Overview of the recruitment process

4.3.1 Participant characteristics

Data from 33 individuals with chronic unstable ankles (11 males; mean (SD) age 30.24 ± 8.70 years; mean (SD) BMI 25.30 ± 4.46 kgm^{-2}) and 33 age and gender matched healthy controls (11 males; mean (SD) age 30.45 ± 8.71 years; mean (SD) BMI 23.47 ± 3.51 kgm^{-2}) were included in the study. Participant characteristics are presented in Table 4.1.

The height, weight and BMI measures were similar in both groups. The CAI group was functionally impaired with a significantly different mean FAAM score (Table 4.1). Further, in the CAI group, the dominant leg was unstable in 20 participants and 26 of them had sprained their other ankle even though it was not reported by them as unstable.

4.3.2 Comparison of fibular position

No significant difference between the two groups was noted for non-normalised fibular position (MD=-1.24mm [95% CI=-2.85 - 0.37], p=0.13). However, there was a significant difference in normalised fibular position (MD=-3.01% [95% CI =-5.83- -0.19], p=0.04) (Table 4.2). The effect size was d=0.53 for normalised fibular position.

4.3.3 ROC analysis

The AUC for the ROC curve (Figure 4.3) was not significant indicating that the fibular position values cannot independently predict having CAI. The largest Youden index value indicated that a normalised fibular position value of greater than 27% was the cut-off score to distinguish the CAI group (Table 4.3). Moderate sensitivity (70%) and fair specificity (55%) were calculated at this cut-

off for normalised fibular position. Resulting positive and negative likelihood ratios were 1.53 and 0.56 respectively.

Table 4.1 Characteristics of the participants

Baseline data	**Healthy (n=33) mean (SD)**	**95% CI**	**CAI (n=33) mean (SD)**	**95% CI**	**p value**
age	30.5 (8.7)	27.4-33.5	30.2 (8.7)	27.2-33.3	0.92
height	169.5 (9.2)	166..3-172.8	170.6 (7.6)	167.9-173.3	0.61
weight	67.8 (13.6)	63.0-72.6	73.7 (14.3)	68.7-78.8	0.09
BMI	23.5 (3.5)	22.2-24.7	25.3 (4.5)	23.7-26.9	0.07
CAIT score affected/ matched side	29.0 (1.5)	28.5-29.6	13.8 (4.3)	12.3-15.3	<0.01
CAIT score other side	29.0 (1.5)	28.5-29.5	21.1 (6.7)	19.7-23.4	<0.01
FAAM ADL score	99.9 (0.4)	99.8-100.0	89.1 (8.5)	86.1-92.1	<0.01
FAAM	99.4	98.6-100.1	70.1	65.7-74.4	<0.01

Sports score	(2.2)	(2.3)

ADL, activities of daily living; BMI, body mass index; CAI, chronic ankle instability; CAIT, Cumberland Ankle Instability Tool; FAAM, Foot and Ankle Ability Measure; SD, standard deviation

Table 4.2 Comparison of fibular position between individuals with unstable ankles and healthy ankles

Fibular position	**Healthy (n=33) mean (SD)**	**CAI (n=33) mean (SD)**	**p value (MD, 95% CI)**
non-normalised fibular position (mm)	11.54 (2.89)	12.78 (3.63)	0.13 (1.24, -0.37 to 2.85)
normalised fibular position (%)	26.69 (4.78)	29.7 (6.55)	0.04 (3.01, 0.19 to 5.8)

CAI, chronic ankle instability; MD, mean difference; SD, standard deviation

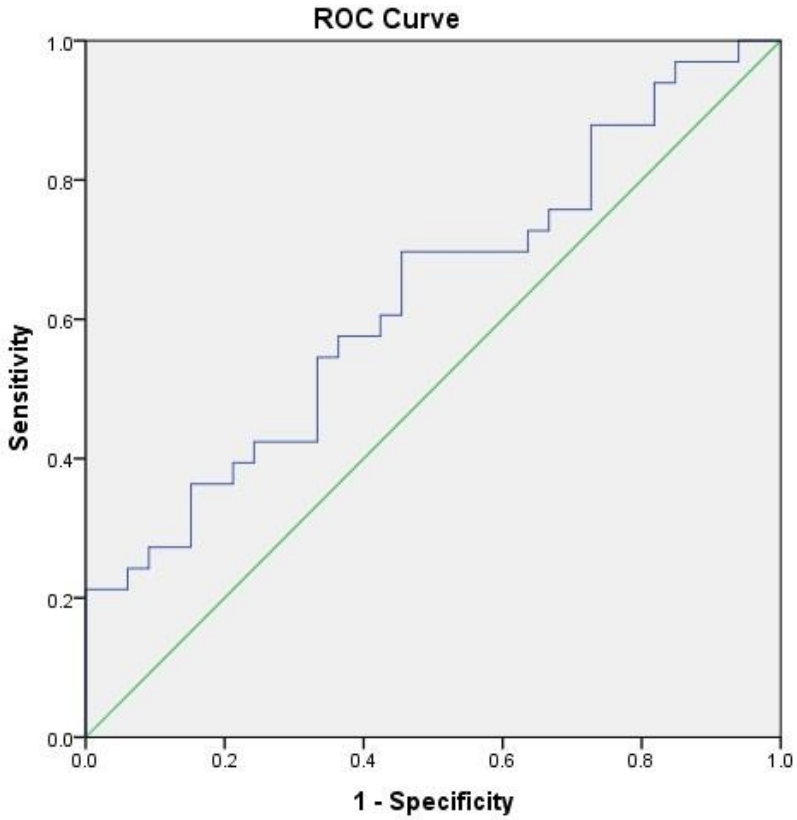


Figure 4.3 Receiver operating characteristic (ROC) curve used to calculate the area under the curve and cut-off score for normalised fibular position

Table 4.3 Characteristics of receiver operating characteristic (ROC) curve for fibular position

Fibular positon	**Non-normalised fibular position**	**Normalised fibular position**
Area under the curve (95% CI)	0.60 (0.46-0.73)	0.63 (0.50-0.77)
p value	0.18	0.07
Sensitivity (95% CI)	0.49	0.70
Specificity (95% CI)	0.73	0.55

Positive likelihood ratio (LR^+)	1.78	1.53
Negative likelihood ratio (LR^-)	0.71	0.56
Cut–off value	12.70	26.81

CI, confidence interval; LR, likelihood ratio

4.3.4 Reliability of the weight-bearing X-Ray measures of fibular position

Inter-rater reliability and intra-rater reliability were excellent for all the fibular position measures with high ICC $_{(2,1)}$ values, and low SEM values (Table 4.4).

Table 4.4 Intra-class correlation coefficient ($ICC_{2,1}$) and standard error of measurement (SEM) with 95% CI for inter-rater and intra-rater reliability of measurements of fibular position

Measurement	Intra-rater reliability	Inter-rater reliability
Non-normalised fibular position		
ICC (95% CI)	1.00 (0.99-1.00)	0.98(0.96-0.99)
SEM	0.56	0.97
95% CI (1.96 x SEM)	1.10	1.91
Tibial width		
ICC (95% CI)	1.00 (1.00)	0.98(0.96-0.99)

SEM	0.57	
95% CI (1.96 x SEM)	1.12	1.12
		2.19
Normalised fibular position		
ICC (95% CI)	0.99(0.98-1.00)	0.98(0.96-0.99)
SEM	1.33	1.75
95% CI (1.96 x SEM)	2.60	3.43

ICC, intra-class correlation coefficient; SEM, standard error of measurement; CI, confidence interval

4.5 Discussion

The present study of fibular position in individuals with CAI is the first to be conducted with participants weight-bearing in standing. A significant difference in fibular position in individuals with CAI was found compared to individuals with healthy ankles when normalised for tibial width, which may suggest CAI is associated with a slight anterior position of the fibula in a weight-bearing position. Although the magnitude of detected difference in the current study were small, the effect size was moderate (d=0.53). This indicates that individuals with CAI have a more anteriorly displaced fibula (0.53 standard deviations higher) than individuals with healthy ankles (Cohen, 1988). Clinically, this may be a factor contributing to the persistence of pain, ROM restriction and other symptoms and signs of CAI. The finding of an anteriorly positioned fibula in the present study lends support to Mulligan's hypothesis of a fibular 'positional fault' in chronic cases of injury or sprain of the ankle (Vicenzino et al., 2011). It also supports the biological rationale for MWM which attempts to correct the 'positional fault' through the pain-free application of a manual glide (usually a posteriorly directed mobilisation) of the fibula while the

patient performs the impaired active or functional movements. While the mechanism leading to the observed anterior fibular positional change in CAI is unclear, it may be associated with mechanical instability in some cases. The incidence of isolated distal tibiofibular syndesmotic sprains is reported as being between 1% and 11% (Hopkinson et al., 1990). Any change in fibular position could potentially be due to an undiagnosed syndesmotic sprain or instability of the anterior syndesmosis of the ankle in certain individuals.

In our study, the distance between the anterior margin of the tibia and the anterior margin of the fibula was measured to determine the fibular position, using lateral X-rays taken in a weight-bearing position. To allow for individual morphological differences, this measurement was also normalised by calculating it as a percentage of the tibial width. No previous studies have investigated fibular position in a weight-bearing position to facilitate comparison of our findings. However, there are a few studies investigating fibular positional changes conducted in non weight-bearing positions using radiological methods, such as fluoroscopy (Hubbard et al., 2006), X- ray generators (Wikstrom, Tillman, et al., 2010), MRI (Berkowitz & Kim, 2004; Mavi et al., 2002; Merlin et al., 2005) and CT (Berkowitz & Kim, 2004; Eren et al., 2003; Kobayashi et al., 2014; Scranton et al., 2000), and non-radiological methods, such as a potentiometer (Kavanagh, 1999). In these studies, participants were positioned in either side-lying or supine lying. In addition, the ankle was held in a variety of positions, including maximal dorsiflexion in one study (Hubbard et al., 2006), neutral in the majority of studies (Eren et al., 2003; Kavanagh, 1999; Kobayashi et al., 2014; Mavi et al., 2002; Merlin et al., 2005) and was not mentioned in one study (Wikstrom, Tillman, et al., 2010).

Previous research on the existence of an altered fibular position in CAI is somewhat conflicting. Two studies found no fibular positional differences between healthy and CAI participants (Kavanagh, 1999; Wikstrom, Tillman, et al., 2010), however the others all support the existence of a fibular positional change. However the direction of this change varies between these studies, with most finding either an anteriorly positioned (Hubbard et al., 2006; Kavanagh, 1999; Mavi et al., 2002) (consistent with the present study) or a posteriorly positioned fibula (Berkowitz & Kim, 2004; Eren et al., 2003; Scranton et al., 2000). Further, an antero-inferior displacement (Merlin et al., 2005) and a laterally positioned fibula have also been observed (Kobayashi et al., 2014). Some of the differences in findings across studies may be due to the use of different measures. The AMI (Berkowitz & Kim, 2004; Eren et al., 2003; Scranton et al., 2000) is most commonly utilised in MRI studies where it shows the position of the fibula in relation to the tibia at the ankle mortise (Berkowitz & Kim, 2004). In radiographic studies, the 'distance between anterior margin of the tibia and anterior margin of the fibula' is commonly used (Hubbard et al., 2006; Mavi et al., 2002; Wikstrom, Tillman, et al., 2010). The studies of Kobayashi et al (Kobayashi et al., 2014) and Kavanagah et al (Kavanagh, 1999) used other customised measures. Moreover, normalisation of fibular position was used in only one previous study because of possible superimposition of fibular position by the size of the tibia on the lateral projection (Wikstrom, Tillman, et al., 2010), making this just the second study to do so.

Consistent with previous research using fluoroscopic non weight-bearing images (Hubbard et al., 2006), weight-bearing lateral X-ray measures in the current study demonstrated excellent reliability for both normalised and non-normalised fibular positon. A weight-bearing lateral X-ray is arguably more functional and more clinically relevant than other available methods for measuring fibular position. Further, the low SEM values (Table 4.4) indicate good precision for estimation of both

normalised and non-normalised fibular position. On the other hand, only moderate sensitivity (70%) and fair specificity (55%) were observed at the cut-off value for identifying the individuals with CAI using normalised fibular position (≥ 27%) in the current findings. These sensitivity and specificity values demonstrate a moderate ability of the normalised fibular position to predict the presence of CAI when the test is positive (≥ 27%), and a minimal ability to exclude the presence of CAI when the test is negative (Lalkhen & Mccluskey, 2008).

Given that the mechanism of CAI may sometimes be multifactorial (mechanical and/or functional), it is perhaps not surprising that the normalised fibular position measure discriminated between the two groups (CAI and healthy) with a point estimate accuracy of 0.63 for the AUC (95% CI 0.50-0.77, p=0.07) (Table 4.3). Thus, only 63% of participants were correctly classified according to CAI status using 'normalised fibular position' as the predictor alone. Moreover, the lack of statistical significance of the AUC could indicate that this finding is simply due to chance. The positive and negative likelihood ratios of 1.53 and 0.56 (respectively) do not provide a strong indication for ruling CAI in or out in these individuals, further suggesting that normalised fibular position alone is not an appropriate sole predictor of CAI (Jaeschke et al., 1994; Wright et al., 2014). Therefore, utilisation of normalised fibular position measures combined with other clinical findings, might be helpful in identifying individuals with CAI.

Future research should investigate whether lateral X-ray findings of fibular position may effectively be used in determining the appropriate application of MWM techniques in rehabilitating CAI. Potentially the practitioner could choose whether or not to apply MWM as a treatment for the client based on the amount of displacement. Further, they could also potentially choose the

direction of the MWM glide so as to reverse the evident direction of positional displacement. Whether MWM treatment actually reverses fibular displacement on imaging may also merit investigation using the method employed in this study. However, the clinical utility of this method should consider the ease of obtaining an accurate X-ray image and the time spent on taking the fibular position measures. Finally, it would be interesting to measure fibular displacement of the other ankle of individuals with CAI to explore whether the fibular position was present before the injury or if it resulted from the injury.

First, although every effort was made to minimise axial rotation of the lower limb during radiographs, possible rotation of the tibia and fibula may have introduced minor variability in the fibular positional measurements. Second, a priori sample size estimation was not conducted for the ROC analysis because it was a planned but secondary objective. Third, the study was not powered to explore weight-bearing fibular position in subgroups (mechanical and functional instability) of CAI, and thus the potential for heterogeneity of the study sample may have influenced the results. Fourth, the assessor was not blinded to group allocation during the measurements, however fibular position measures were obtained using a computer program. Fifth, in positioning the knee of the non-imaged limb (slightly flexed, representing mid-stance of the gait cycle) some variability may have been introduced, and in future researchers should consider standardising this. Finally, the case-control design of the study precludes any cause and effect relationship being ascribed to the fibular positional difference.

As a conclusion, an anteriorly positioned distal fibula in relation to the tibia was observed in participants with CAI compared with healthy controls. This fibular positional difference may

contribute to the persistence and recurrence of pain and dysfunction in some cases of CAI. Weight-bearing lateral radiographic measurements of fibular position can be performed reliably and reproducibly. However, the low specificity and sensitivity utility scores for normalised fibular position indicate that it has very little ability to predict CAI alone.

Chapter 5 Clinical characteristics of chronic ankle instability: a case-control study

This chapter has been submitted (03 June 2018) for publication in a peer-reviewed journal as:

> Weerasekara, I., Snodgrass, S., Osmotherly, P., Tessier, J., & Rivett, D. A. (2019). Clinical characteristics of chronic ankle instability: a case-control study (under review).

The work presented in this manuscript was completed in collaboration with the co-authors (Appendix 1). The ethics approval and supporting documents for the study reported in this chapter appear in Appendices 2, 4, 5, 9, 10, 13 and 15.

Overview

The case-control study detailed in Chapter 5 is intended to address the inconsistency of evidence for common clinical characteristics of CAI, by evaluating differences in ankle dorsiflexion range, balance, self-reported function, pain and PPT between individuals with CAI and those with healthy ankles. In this regard, it is an extension of and complementary to the study reported in Chapter 4 investigating displacement of the fibula as an anatomical characteristic of CAI.

This chapter therefore presents the findings of the case-control study comparing the aforementioned proposed clinical characteristics of individuals with CAI to those with healthy ankles. In addition, the association of each of these clinical features with CAI are described in this chapter.

5.1 Introduction

The ankle is the second most commonly injured body area in sport with ankle sprain being the most common type of ankle injury (Fong et al., 2007). Up to 40% of individuals who sprain their ankles may develop CAI (Miklovic et al., 2018). Other than development of residual symptoms such as a subjective feeling of 'giving way' and recurrent sprains, other deficits have been purported to be associated with CAI, including reduced ankle dorsiflexion range, impaired balance and compromised function (Hertel, 2002). However, these deficits have not been consistently reported in the literature and clinical relationships are yet to be investigated between these deficits. Moreover, little research has been conducted to identify pain (Adal et al., 2019) and PPT characteristics in CAI. Better understanding of the major clinical differences between individuals with CAI as compared to healthy ankles, may assist in the design of more effective treatment and prevention programs for this condition.

Assessing pain, functional assessment tool scores (such as weight-bearing dorsiflexion range and balance tests), and self-reported functional assessment tool scores, as well as exploring the existing associations between these measures may be clinically relevant in interpreting the nature and presentation of this condition. Reduced ankle dorsiflexion range has been demonstrated to impact on dynamic balance in an anterior direction as measured by the SEBT in individuals with CAI compared with healthy controls (Hoch, Staton, et al., 2012). The SEBT has been recommended as a highly representative non-instrumental measure of dynamic balance for physically active people (Gribble et al., 2012). However, anterior direction balance deficits identified by this test can be due to ankle DFROM restriction rather than any balance impairment. Previously reported positive correlations between dorsiflexion range restriction and anterior direction balance deficit measured using the SEBT (Basnett et al., 2013; Terada et al., 2014), has raised questions regarding the

appropriateness of SEBT as a representative test for dynamic balance alone. Notably, CoP during performance of the on the SEBT has been quantified in individuals with acute first-time lateral ankle sprains (Doherty et al., 2015) and individuals with recurrent sprains in previous studies (Nakagawa & Hoffman, 2004). Thus exploring the performance of individuals with CAI on the SEBT combined with CoP measures, may be of greater value in quantifying dynamic balance impairments than with the SEBT alone. Further, static balance deficits associated with CAI have not been consistently reported in the previous literature (De Vries et al., 2010; Nakagawa & Hoffman, 2004).

Both self-report and objective measures of pain characteristics are similarly important in understanding the clinical presentation of CAI. The importance of investigating the impact of pain on individuals with CAI was highlighted in a recent study with 1147 participants, in which 60% reported ankle pain (Adal et al., 2019). Self-perceived pain in CAI has been previously reported to not correlate with SEBT performance (Terada et al., 2014), and it would be clinically interesting to further explore whether pain actually limits the functional ability of individuals with CAI. Further, no previous study has investigated peripheral and central sensitisation pain mechanisms in CAI despite it being documented in acute ankle sprains (Ramiro-Gonzalez et al., 2012). Clinical recognition of central sensitisation in patients with persistent musculoskeletal pain is essential in appropriately applying the growing knowledge of pain neurophysiology in clinical practice (Nijs et al., 2010).

This study aimed to explore whether people with CAI have specific deficits in terms of ankle dorsiflexion range, balance, self-reported function, pain and PPT compared to healthy matched

controls. Further, the study aimed to investigate whether any of these measures may be associated with the presence of CAI.

5.2 Methods

5.2.1 Participants

From October 2017 to April 2018, participants with CAI (n=33) and age, gender and side matched individuals with healthy ankles (n=33) were recruited into this case-control study. Recruitment was from a university and the general community in the Newcastle area of New South Wales, Australia through flyers, social media, media release and web posts. All volunteer participants over 18 years of age with CAI were considered eligible if they satisfied the inclusion and exclusion criteria as endorsed by the IAC, one with modification; the period for experiencing at least two episodes of giving way was changed to 12 months instead of six to account for the seasonal nature of some sports (Figure 5.1) (Gribble et al., 2013; Weerasekara, Osmotherly, Snodgrass, et al., 2019b). Volunteers with healthy ankles were eligible for the study provided they had not experienced previous ankle problems, lower limb surgeries, or other treatment for an ankle problem, and had no current pain or problems in or around the ankle while performing daily activities. The same exclusion criteria applied to CAI participants were also applied to the volunteers with healthy ankles (Weerasekara, Osmotherly, Snodgrass, et al., 2019b). Written informed consent was obtained from all participants and ethics approval (H-2017-0217) was obtained from the Human Research Ethics Committee of The University of Newcastle, Australia.

Inclusion criteria
• A history of at least one significant ankle sprain; - Initial sprain must have occurred at least 12 months prior to study enrolment - Was associated with inflammatory symptoms - Created at least one interrupted day of desired physical activity - The most recent injury must have occurred more than three months prior to study enrolment • A history of the previously injured ankle joint 'giving way' and/or recurrent sprain and/or 'feelings of instability' - Participants should report at least two episodes of giving way in the 12 months prior to study enrolment - Self-reported ankle instability should be confirmed with the Cumberland Ankle Instability Tool (CAIT) (≤ 24)
Exclusion criteria
1. A history of previous surgeries to the musculoskeletal structures (i.e., bones, joint structures, nerves) in either lower extremity 2. A history of a fracture in either lower extremity requiring realignment 3. Acute injury to musculoskeletal structures of other joints of the lower extremity in the previous three months that impacted joint integrity and function (i.e., sprains, fractures), resulting in at least one interrupted day of desired physical activity 4. Any previous injuries still causing problems to lower limb (i.e., balance issues) 5. Any neuromuscular disorder that may affect lower limb (i.e., muscle weakness, balance issues) 6. Have conditions for which radiological imaging is contraindicated (e.g., pregnancy) 7. Inability to read English

Figure 5.1: Inclusion and exclusion criteria for individuals with CAI (Gribble et al., 2013)

In cases of bilateral CAI, the CAIT was utilised to screen for the most affected side. Greater instability is represented by a lesser score in this questionnaire (Hiller et al., 2006). The cut-off score of ≤ 24 was taken to indicate a self-reported unstable ankle (Gribble et al., 2013). If both ankles had a similar score, the participant was asked to select their most problematic ankle. If they were unable to distinguish between their ankles, the dominant side was selected for the measurement. Individuals with healthy ankles were age and gender matched to individuals with CAI. Clinical characteristics including ankle DFROM, balance (static and dynamic), and PPT were measured by the same researcher throughout the study. The sequence of testing was randomised and the sound side (or less unstable) was measured first in every measure in individuals with CAI.

5.2.3 Procedures

Static balance:

The participant was instructed to stand barefoot on the marked centre of the force plate (KISTLER 9260AA6, Winterthur, Switzerland), assuming a single-leg stance position. Each participant was then asked to bend the non-stance leg slightly at the hip, with the knee bent to approximately 90 degrees, representing mid-stance of the gait cycle. Their arms were crossed on their chest during both eyes close and open balance tests. The participant was asked to remain as still as possible for 10 seconds in both static balance tests (eyes open, eyes close), and maintaining a fixed gaze on a cross marked on the wall six metres in front of them during the eyes open balance test. If the participant was unable to stand for 10 seconds, the total standing time completed was recorded. Averaged CoP data for sway velocity (absolute mean value of the instantaneous velocity of the CoP in a given direction during a given period) (Ross et al., 2009) and sway area (rectangular area defined by the maximum anterior, posterior, medial, and lateral sways during a given time) (Ross et

al., 2009) per second were recorded and used in the analysis. Prior to each data collection session the force plate was calibrated automatically, and CoP data were acquired at 100Hz.

Dynamic balance (SEBT):

The participant was instructed to stand on a stable base of support on the stance limb in the middle of the testing grid on a force plate. The force plate was calibrated prior to each data collection session. Then the participant was asked to reach as far as possible with the reaching limb along each of the lines marked on the platform in anterior, postero-medial and postero-lateral directions. They were then asked to tap the line with the great toe of the reaching foot, and to return the reaching limb to the starting position in the centre of the grid. The great toe of the reaching foot was painted with a washable paint, so the researcher could easily measure how far the limb had reached. The shortest distance from the centre to the paint print was taken as the measure. The balance time was the time spent from the moment the participant lifted their limb until they returned to the starting position (Jaber et al., 2018). If the participant lifted or shifted any part of the foot of the stance limb during the trial, the trial was not considered complete. After performing a maximum of four non-recorded trials for familiarisation, one trial per direction was recorded (Pionnier et al., 2016). Normalised SEBT values were taken as the ratio between excursion distance and the participant's leg length (the distance between the anterior superior iliac spine and the ipsilateral medial malleolus) (Pionnier et al., 2016). Sway velocity (Ross et al., 2009) measures to quantify spatio-temporal parameters were acquired at 100Hz, under the foot during single-leg stance (Pionnier et al., 2016).

Self-reported function:

The FAAM (Martin et al., 2005) and FAOS questionnaires (Roos et al., 2001) for self-reported foot and ankle function were used to describe the level of disability of the cohort, as endorsed by the IAC (Gribble et al., 2013). The participants were asked to answer the questions with responses that most closely described their condition during the last week. The FAAM consists of two sub-scales to assess function during usual ADL and during sports-related activities. The FAOS consists of five sub-scales to assess symptoms, pain, function related to ADL, function related to sports and recreational activities, and QOL.

Pain:

Pain intensity during rest was assessed using a VAS which consisted of a 100mm horizontal line, with 'no pain' anchoring the left side of the line and 'worst possible pain' anchoring the right. The validity of the VAS for detecting changes in pain intensity has been supported by numerous studies (Ferreira-Valente et al., 2011; Price et al., 1983).

Pressure pain threshold (PPT):

PPT measurements were obtained in each leg from two points around the ankle (anterior to the lateral malleolus over the ATFL, inferior to the medial malleolus over the deltoid ligament) and one remote point over the proximal third of the tibialis anterior muscle belly (Ramiro-Gonzalez et al., 2012). A Freedom Tracker hand-held algometer (JTECH Medical, Salt Lake City, UT, USA) was used during measurement, and a probe with a contact surface of $1cm^2$ was placed perpendicular to the skin and pressure applied at 40kPa/s. The least affected/not affected leg was

measured first, and the order of the measurement sites was randomised. The tested leg was rested on the bed, and calibration was carried out prior to each data collection session. The participant was instructed to indicate when the feeling of the stimulus changed from 'pressure only' to 'pressure and discomfort' by pressing an indicator switch. This process was repeated three consecutive times at each measurement site and a 10s rest time was allowed between each measure. Pressure algometry is considered a stable and reliable measure of PPT (Frank et al., 2013).

Weight-bearing dorsiflexion range of motion (DFROM):

The participant was instructed to perform a weight-bearing lunge by bringing their knee towards the wall until they lightly touched the wall, whilst maintaining their heel in contact with the floor. Then the participant was asked to move their foot away from the wall in 1cm increments until the heel no longer maintained contact with the floor or the knee was no longer in contact with the wall. Participants were instructed to keep their hands on their hips and to avoid twisting their trunk during the test. Maximal dorsiflexion was measured by the greatest distance between the great toe and wall with the participant's knee maintaining contact with the wall (Gilbreath et al., 2014). The same procedure was followed for the opposite leg. The weight-bearing lunge test is reported as a reliable measure (Powden et al., 2015).

5.2.3 Analysis

The sample size was calculated using an alpha significance level of 0.05 and a power of 0.80, in relation to the largest estimation resulted for primary outcome measures (MD=2.5, SD=3.4) of self-reported function and fibular position (Hubbard et al., 2006). This resulted in a minimum sample size of 33 per group, while allowing for a 10% dropout rate. Statistical analyses were

performed using SPSS Statistics for Windows (Version 23.0, Armonk, NY, IBM Corp). Descriptive statistics were calculated for all variables.

Mean comparison

Data were assessed for normality both visually and using the Shapiro-Wilk test. The comparison of means between normal and CAI groups were analysed using independent t-tests, and comparison of means between the CAI affected side and the other side were analysed using paired t-tests. When the condition of normality was not met, non parametric equivalent tests were applied. The level of significance was set at $\alpha = 0.05$.

Regression analysis

The variables were selected for the regression model according to the assumptions of regression analysis, and highly correlated (over 0.7-1) variables were removed from the model. Univariate regression was carried out between each variable (BMI, weight-bearing DFROM, normalised anterior SEBT scores, antero-posterior sway velocity recorded during both postero-lateral and postero-medial SEBT testing, and both antero-posterior and medio-lateral eyes open balance scores, and fibular position normalised to tibial width), and those with $p < 0.2$ were retained for inclusion in the multivariate model. Logistic regression was carried out using a backwards-stepwise Wald selection method. The level of significance was set at $\alpha = 0.05$.

5.3 Results

A total of 66 participants (CAI=33, healthy=33) who met the eligibility criteria were included in the study (Figure 5.2).

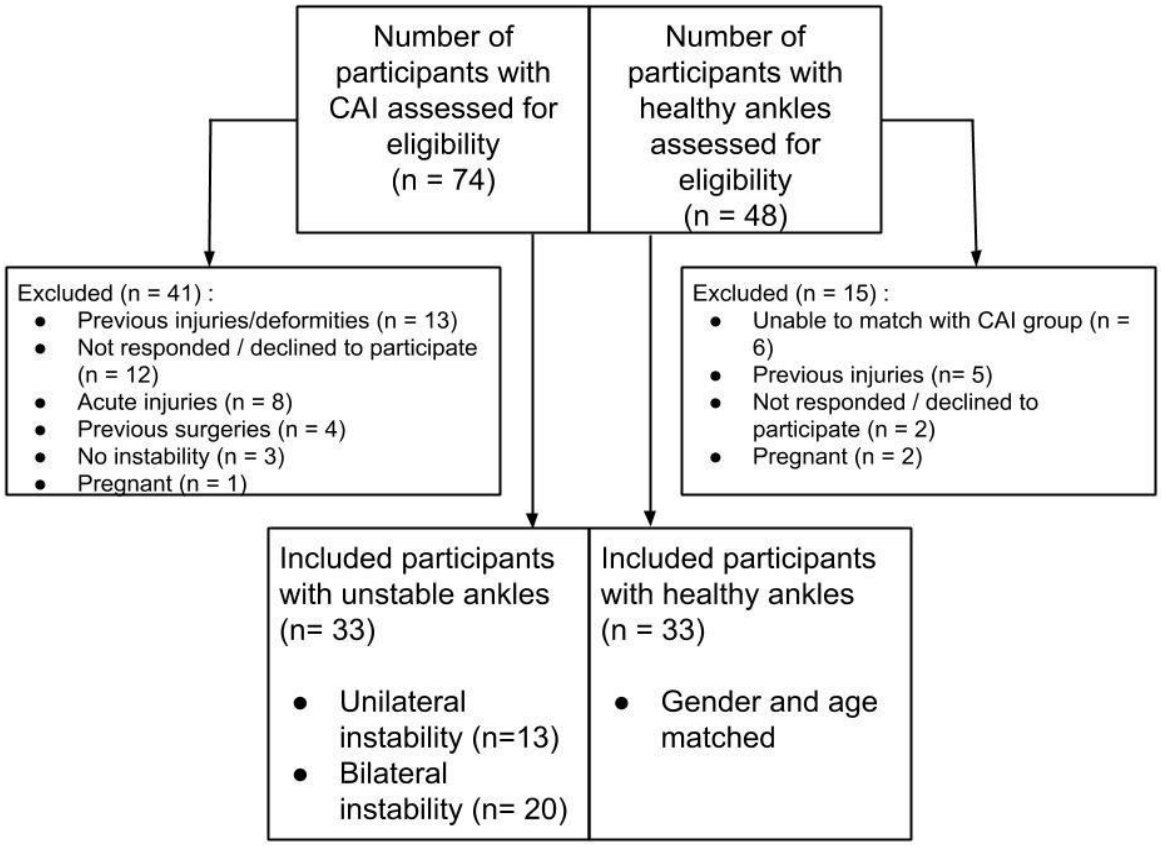


Figure 5.2 Flow chart of participants in the selection process

5.3.1 Participant characteristics

Results of the comparison between group characteristics are presented in Table 5.1. There were 22 females and 11 males in each group. In 18 individuals with CAI, the most affected side was the right. The right side was dominant in 27 participants in the CAI group, and in 31 with healthy

ankles. Age, height, weight and BMI were normally distributed in the two groups, and no statistical differences were found in participant characteristics between the groups except for CAIT score ($p < 0.01$). All of the self-reported outcomes in relation to the FAAM and FAOS sub-scales were significantly lower in the CAI group compared to the healthy group ($p > 0.01$) (Table 5.1).

Table 5.1 Characteristics of the participants in each group

	Groups		**Difference between groups**
	CAI (n=33) mean (SD)	Healthy (n=33) man (SD)	**MD (95% CI)**
age (years)	30.2 (8.7)	30.5 (8.7)	0.2 (4.1-4.5)
height (cm)	170.6 (7.6)	169.5 (9.2)	-1.1 (-5.2-3.1)
weight (kg)	73.7 (14.3)	67.8 (13.6)	-5.9 (-12.8-0.9)
BMI (kgm^{-2})	25.3 (4.5)	23.5 (3.5)	-1.8 (-3.8-0.1)
CAIT score	13.8 (4.30)	29.0 (1.5)	15.2 (13.6-16.8)*
FAOS symptoms	66.2 (15.8)	96.8 (4.2)	30.6 (24.9-36.4)*
FAOS pain	77.3 (14.1)	99.5 (0.8)	22.4 (17.4-27.4)*
FAOS sports	59.2 (22.0)	99.6 (2.0)	37.2 (29.9-44.5)*
FAOS ADL	88.7 (11.5)	99.9 (0.3)	11.3 (7.3-15.3)*
FAOS QOL	56.4 (14.9)	99.4 (1.8)	43.0 (37.8-48.3)*
FAAM ADL	89.1 (8.5)	99.9 (0.4)	10.9 (7.9-13.9)*
FAAM sports	70.1 (12.3)	99.4 (2.2)	29.3 (24.9-33.6)*

ADL, activities of daily living; BMI, body mass index; CAI, chronic ankle instability; CAIT, Cumberland ankle instability tool; FAAM, foot and ankle ability measure; FAOS, foot and ankle outcome score; QOL, quality of life

*Significant difference ($p < 0.05$)

5.3.2 Comparison of the characteristics

A significantly lower normalised anterior SEBT score was observed in the affected ankle of the CAI group compared to the healthy group (MD=-5.8, 95% CI -9.5 to -2.1) and also compared to the other ankle of the CAI group (MD=-2.5, 95% CI -4.5 to -0.5) (Table 5.2). The normalised postero-medial SEBT score was significantly less in the affected ankle of participants with CAI, compared to their other ankle (MD=-4.0, 95% CI -6.8 to -1.2). All the other SEBT measures were found to be non-significant (Table 5.2). A significantly lower weight-bearing DFROM was found between the ankles of individuals with CAI and between the two groups (MD=-2.6, 95% CI -4.2 to -1.0; MD=-1.0, 95% CI -1.7 to -0.4, respectively) (Table 5.2). Pain during rest was significantly higher in the affected ankle of CAI participants compared to healthy individuals ($p<0.01$), as well as compared to the other ankle of the CAI participants ($p=0.06$) (Table 5.2). None of the PPT values were significantly different, except for a lower threshold over the lateral ligament on the affected side compared to the other ankle of CAI participants (MD=-2.5, 95% CI -4.8 to -0.2) (Table 5.2).

In the SEBT tests, greater postero-medial sway velocity in the postero-medial direction were observed in the CAI group (MD 7.8, 95% CI 0.2 to 15.5), with all the other sway velocity measures (in any group comparison) non-significant (Table 5.2). When comparing CoP data for the eyes

open standing balance tests of the healthy and CAI groups, all were significantly higher in both the antero-posterior and medio-lateral directions for sway velocity ($p=0.02$ and $p<0.01$, respectively), and medio-lateral sway area per second ($p<0.01$) in individuals with CAI (Table 5.2). However, no differences were found between the affected and the other ankle for CAI participants (Table 5.2). In eyes close balance, only antero-posterior sway area per second was significantly higher in the CAI group (Table 5.2). Interestingly, antero-posterior and medio-lateral sway velocity were significantly greater in the other ankle of CAI participants compared to the affected ankle ($p=0.03$ and $p=0.02$, respectively) (Table 5.2).

Table 5.2 Comparison of characteristics between individuals with CAI and healthy individuals, and between the affected ankle and other ankle of CAI participants

Clinical characteristic	**CAI group (affected ankle) (n=33)** **mean (SD)**	**CAI group (other ankle) (n=33)** **mean (SD)**	**Healthy group (n=33)** **mean (SD)**	**MD (CAI affected ankle - healthy group)** **(p value [95% CI])**	**MD (CAI affected ankle - CAI other ankle)** **(p value [95% CI])**
dynamic balance (non-normalised) (cm)					
SEBT anterior	54.3 (7.0)	56.5 (6.5)	58.0 (5.6)	-3.7 (0.02, -6.8 to -0.6)*	-2.1 (0.02, -3.9 to -0.3)*
SEBT postero-lateral	73.8 (9.2)	75.8 (9.2)	75.5 (8.0)	-1.7 (0.43, -5.9 to 2.5)	-1.9 (0.12, -4.4 to 0.5)
SEBT postero-medial	59.4 (13.1)	62.9 (12.4)	60.8 (13.3)	-1.4 (0.66, -7.9 to 5.1)	-3.4 (0.01, -6.0 to -0.9)*
dynamic balance (normalised)					
SEBT anterior	61.1	63.7	66.9	-5.8 (> 0.01,	-2.5 (0.02,

	(8.0)	(8.5)	(6.9)	-9.5 to -2.1)*	-4.5 to -0.5)*
SEBT postero-lateral	83.0 (10.5)	85.3 (11.2)	87.2 (9.9)	-4.1 (0.11, -9.1 to 0.9)	-2.3 (0.09, -5.0 to 0.4)
SEBT postero-medial	66.9 (15.2)	70.9 (15.1)	70.1 (15.4)	-3.3 (0.39, 10.8 to 4.2)	-4.0 (0.01, -6.8 to -1.2)*
weight-bearing DFROM (cm)	9.4 (3.9)	10.4 (3.4)	12.0 (2.4)	-2.6 (> 0.01, -4.2 to -1.0)*	-1.0 (> 0.01, -1.7 to -0.4)*
PPT (kPa)					
Tibialis anterior	27.4 (13.8)	27.2 (10.1)	26.9 (18.5)	p=0.33[#]	0.2 (0.85, -2.1 to 2.6)
medial ligament	27.9 (9.4)	30.4 (11.4)	26.5 (12.6)	p=0.21[#]	-1.7 (0.38, -5.6 to 2.2)
lateral ligament	24.9 (10.0)	26.58 (10.6)	24.0 (12.4)	p=0.43[#]	-2.5 (0.04, -4.8 to -0.2)*
pain at rest (mm)	7.8 (11.1)	4.8 (10.4)	0 (0)	p<0.01[#]*	p=0.06[#]

SEBT tests: sway velocity measures (mm/s)					
anterior direction-sway velocity AP	78.7 (23.9)	74.4 (20.8)	80.6 (22.0)	-1.9 (0.74, -13.1 to 9.4)	4.4 (0.18, -2.1 to 10.8)
anterior direction-sway velocity ML	54.2 (18.7)	55.4 (17.2)	53.0 (54.2)	1.2 (0.79, -7.2 to 9.5)	-1.2 (0.77, -9.3 to 6.9)
postero-medial-sway velocity AP	73.7 (20.6)	77.1 (24.7)	69.4 (18.7)	4.2 (0.39, -5.4 to 13.9)	-3.4 (0.44, -12.3 to 5.4)
postero-medial-sway velocity ML	62.4 (16.9)	58.6 (14.5)	54.5 (14.3)	7.8 (<0.05, 0.2 to 15.5)*	3.8 (0.25, -2.7 to 10.3)
postero-lateral-sway velocity AP	73.1 (23.6)	75.6 (20.1)	70.1 (16.2)	3.0 (0.55, -7.0 to 13.0)	-2.5 (0.40, -8.4 to 3.4)
postero-lateral-sway velocity ML	60.1 (21.7)	59.2 (21.4)	53.6 (16.4)	6.4 (0.18, -3.0 to 15.9)	0.8 (0.86, -8.6 to 0.3)
eyes open balance - sway velocity (mm/s) and sway area (mm) measures					
sway velocity AP	31.8 (16.0)	33.0 (24.0)	24.8 (6.3)	p=0.02#*	p=0.64#

sway velocity ML	35.5 (7.7)	35.9 (11.0)	29.6 (6.5)	p<0.01[#*]	p=0.78[#]
sway area per second AP	8.1 (5.3)	9.6 (7.3)	6.1 (2.2)	p=0.10[#]	p=0.09[#]
sway area per second ML	7.7 (3.5)	8.6 (5.7)	5.5 (1.8)	p<0.01[#*]	p=0.81[#]
eyes close balance - sway velocity (mm/s) and sway area (mm) measures					
sway velocity AP	62.5 (20.0)	74.1 (33.4)	57.0 (20.0)	p=0.18[#]	p=0.03[#*]
sway velocity ML	63.4 (17.4)	70.8 (14.1)	60.5 (17.8)	p=0.73[#]	p=0.02[#*]
sway area per second AP	13.0 (4.0)	14.1 (7.7)	11.2 (4.3)	p=0.04[#*]	p=0.69[#]
sway area per second ML	10.77 (4.22)	13.6 (8.9)	10.3 (3.3)	p=0.73[#]	p=0.07[#]

[#]non-parametric tests were used (Wilcoxon Signed Ranks Test for paired comparison, Mann Whitney Test for independent group comparison)

*Significant difference ($p < 0.05$)

AP, antero-posterior; CAI, chronic ankle instability; ML, medio-lateral; PPT, pressure pain threshold; SEBT, star excursion balance test; DFROM, dorsiflexion range of motion

5.3.3 Regression analysis

Results of correlation analyses between each variable are shown in Supplemental Digital Content 2 (Table 5.3). Significantly high correlations ($r > 0.70$) were found between anterior SEBT and postero-lateral SEBT, and between postero-medial SEBT and postero-lateral SEBT variables. Significantly moderate correlations ($0.50 < r < 0.70$) were found between antero-posterior sway velocity of postero-medial SEBT and antero-posterior sway velocity of postero-lateral SEBT, antero posterior sway velocity of eyes open standing balance and medio-lateral sway velocity of eyes open standing balance; weight-bearing DFROM and anterior SEBT; and anterior SEBT and postero-medial SEBT variables (Table 5.3).

Table 5.3: Bivariate correlations identified as being statistically significant ($p<.05$) for the CAI affected ankle

Variable 1	**Variable 2**	r	**p value**
BMI	– weight-bearing DFROM	-0.26	0.03
	– PL SEBT: ML sway velocity	0.35	<0.01
	– eyes open: AP sway velocity	0.35	<0.01
	– eyes open: ML sway velocity	0.29	0.02
weight-bearing DFROM	– normalised SEBT anterior	0.55	<0.01
	– normalised SEBT PL	0.37	<0.01
	– normalised SEBT PM	0.33	0.01
normalised SEBT anterior	– normalised SEBT PL	0.76	<0.01
	– normalised SEBT PM	0.58	<0.01
	– PM SEBT: AP sway velocity	0.25	<0.05
	– eyes open: AP sway velocity	-0.31	0.01
	– eyes open: ML sway velocity	-0.32	0.01

normalised SEBT PL	–	normalised SEBT PM	0.76	<0.01
	–	eyes open: AP sway velocity	-0.29	0.02
	–	eyes open: ML sway velocity	-0.31	0.01
normalised SEBT PM	–	eyes open: AP sway velocity	-0.32	0.01
anterior SEBT: AP sway velocity	–	anterior SEBT: ML sway velocity	0.31	0.01
	–	PL SEBT: AP sway velocity	0.48	<0.01
	–	PL SEBT: ML sway velocity	0.31	0.01
	–	PM SEBT: AP sway velocity	0.42	<0.01
	–	PM SEBT: ML sway velocity	0.25	<0.05
	–	eyes open: AP sway velocity	0.41	<0.01
	–	eyes close: AP sway velocity	0.25	<0.05
anterior SEBT: ML sway velocity	–	eyes close: ML sway velocity	0.28	0.02
	–	fibular position	0.44	<0.01
PM SEBT: AP sway velocity	–	PL SEBT: AP sway velocity	0.60	<0.01
	–	PM SEBT: ML sway velocity	0.38	<0.01
	–	eyes open: AP sway velocity	0.28	0.02
	–	eyes close: AP sway velocity	0.32	0.01
PM SEBT: ML sway velocity	–	PL SEBT: AP sway velocity	0.29	0.02
	–	PL SEBT: ML sway velocity	0.43	<0.01
	–	eyes open: AP sway velocity	0.29	0.02
PL SEBT: AP sway velocity	–	PL SEBT: ML sway velocity	0.41	<0.01
	–	eyes close: AP sway velocity	0.36	<0.01
PL SEBT: ML sway velocity	–	eyes open: AP sway velocity	0.27	0.03
eyes open: AP sway velocity	–	eyes close: AP sway velocity	0.41	<0.01
	–	eyes open: ML sway velocity	0.56	<0.01
eyes open: ML sway velocity	–	eyes close : ML sway velocity	0.27	0.03
	–	fibular position	0.28	0.03

eyes close: AP sway velocity	–	eyes open: ML sway velocity	0.43	<0.01
	–	eyes close: ML sway velocity	0.58	<0.01
eyes close: ML sway velocity	–	fibular position	0.33	0.01

AP, antero-posterior; BMI, body mass index; ML, medio-lateral; PL, postero-lateral; SEBT, star excursion balance test; DFROM, dorsiflexion range of motion

The logistic regression model used the predictor variables of BMI, normalised fibular position, weight-bearing DFROM, anterior excursion of the SEBT, medio-lateral sway velocity of postero-lateral and postero-medial SEBT excursions, and antero-posterior and medio-lateral sway velocity of eyes open standing balance (Table 5.4). The final regression model demonstrated that reduced weight-bearing DFROM is associated with having CAI (OR 0.72, 95% CI 0.58 to 0.88, p<.001), and greater medio-lateral sway velocity of eyes open balance is also associated with having CAI (OR 1.17, 95% CI 1.06 to 1.29, p<.001).

Table 5.4 Results of final multivariate regression model (backwards Wald method, R^2=.413) indicating variables predicting group membership of CAI (n=66)

Variable	**Group**	**OR (95% CI)**	**p-value**
BMI	Healthy	1	0.60
	CAI	1.04 (0.88-1.25)	
weight-bearing DFROM	Healthy	1	0.03
	CAI	0.74 (0.57-0.97)	
normalised SEBT anterior excursion	Healthy	1	0.80
	CAI	0.99 (0.89-1.09)	
medio-lateral sway velocity of postero-lateral excursion of SEBT	Healthy	1	0.74
	CAI	0.99 (0.95-1.03)	
medio-lateral sway velocity of postero-medial excursion of SEBT	Healthy	1	0.34
	CAI	1.02 (0.98-1.07)	
antero-posterior sway velocity of eyes open standing balance	Healthy	1	0.62
	CAI	0.98 (0.91-1.06)	
medio-lateral sway velocity of eyes open standing balance	Healthy	1	0.03
	CAI	1.17 (1.10-1.35)	
normalised fibular position	Healthy	1	0.63
	CAI	1.03 (0.91-1.17)	

BMI, body mass index; CAI, chronic ankle instability; OR, odds ratio; SEBT, star excursion balance test; weight-bearing DFROM, weight-bearing dorsiflexion range of motion

5.4 Discussion

There are several key findings from this study. First, individuals with CAI achieved a smaller excursion in the anterior direction during the SEBT, demonstrated restricted weight-bearing DFROM, reported greater functional impairment with both self-reported functional outcome questionnaires, and indicated greater resting pain, both compared to healthy individuals and to their other leg. Second, there were no differences in PPT in any of the tested locations, other than locally over the lateral ligament in individuals with CAI as compared to their other ankle. Third, there was a clearly observed pattern in all force plate parameters of CoP during both eyes open and close balance tests, possibly due to some individuals with bilateral ankle injuries in the CAI group. Alternatively, the pattern may possibly be due to changes in the central nervous system and motor control affecting both limbs. However, analysis of balance in participants with unilateral CAI (excluding bilateral CAI participants) was not undertaken due to the small sample size for a per-protocol post hoc analysis (unilateral CAI, n = 10). Generally, this was lower CoP measures in healthy individuals compared to individuals with CAI, but not on the affected side of individuals with CAI compared to their other side. Finally, weight-bearing DFROM and eyes open standing balance medio-lateral sway velocity parameters were associated with ankle instability in this sample. Overall, these findings suggest that there are multiple differences in CAI compared to healthy ankles, including restriction in dorsiflexion, a balance deficit in anterior directions, greater resting pain, higher functional impairment, and higher sway velocity and sway area measures in eyes open balance.

Some of the SEBT reach performance differences between groups are consistent with previous research, including a reduction in anterior SEBT reach distance (Hoch, Staton, et al., 2012; Jaber et al., 2018) and postero-medial reach distance during the SEBT in individuals with CAI, as

previously reported by Plante et al (Plante & Wikstrom, 2013). Similarly, a reduced DFROM of the affected ankle in individuals with CAI has been reported in previous studies (Hoch, Staton, et al., 2012; Plante & Wikstrom, 2013; Terada et al., 2014). It is plausible that the observed reduction in SEBT reach distance may be related to the reduced available weight-bearing DFROM. Some possible reasons for the limitation in dorsiflexion may include soft tissue dysfunction or tissue adhesions around the ankle (Nyska & Mann, 2002), incongruences of the bones in and around the foot and ankle (Del Buono et al., 2013), foot or ankle muscle strength deficits (Guillén-Rogel et al., 2017), and various other biomechanical influences (Baumbach et al., 2014; Brockett & Chapman, 2016). Clinically, this range limitation may contribute to an increased risk of injury recurrence in CAI, particularly when it is associated with a balance deficit (Basnett et al., 2013).

Other studies have also found a correlation between SEBT performance and DFROM. In our study, a significant positive correlation was observed between every direction of the SEBT and weight-bearing DFROM (anterior, r=0.55, p<0.01; postero-lateral, r=0.37, p<0.0; postero-medial, r=37, p=0.01) (Table 5.3). Very similar findings were noted in the study of Basnett et al (Basnett et al., 2013), and in some other studies weight-bearing DFROM was correlated with the anterior direction of the SEBT, but not with the postero-lateral or postero-medial directions (Hoch, Staton, et al., 2012; Terada et al., 2014). The correlation of weight-bearing DFROM with anterior SEBT reach distance observed in our study may therefore provide one possible reason for the significant reduction in anterior SEBT reach distance in the CAI group. Although SEBT is recommended as a non-instrumented dynamic balance test for physically active people (Gribble et al., 2012), it appears a restriction in weight-bearing DFROM could affect excursions in some or all the directions of the SEBT (Hoch, Staton, et al., 2012; Terada et al., 2014). Therefore, the SEBT may not purely assess balance because a weight-bearing DFROM restriction may impact the results.

Within this context, introducing CoP measures during the SEBT may enhance the accuracy of assessing balance.

A combination of CoP measures (using force plate platforms) with the SEBT has been previously utilised in two studies investigating CAI (Jaber et al., 2018; Pionnier et al., 2016). Both of those studies reported significant differences in all sway velocity measures during the SEBT (Jaber et al., 2018; Pionnier et al., 2016), which contrasts with the results of the present study. However, there were several differences in the measures in these studies compared to the present study. In one study, balance time for CoP velocity was the time interval between toe-off and touchpoint, whereas in our study it was toe-off to the touchpoint and then back to mid-stance. In that study a significant reduction of CoP velocity of the medio-lateral component was reported for CAI participants, but no changes were found in the antero-posterior component (Pionnier et al., 2016). In the other study, single-leg stance balance was measured for about 10 seconds before resting after each excursion of the SEBT, and the sway velocity values were significantly higher in each of the three SEBT directions in individuals with CAI (Jaber et al., 2018). The non-significant findings in our study may have been because CAI participants felt less confident in moving (or perhaps experienced kinesiophobia due to fear of a recurrent sprain) when performing functional or sports tasks, as compared to healthy individuals. Thus, future research could consider assessing individuals with CAI for kinesiophobia during functional or sports tasks.

In sports medicine settings, the most frequent measures of postural-control assessment using CoP based variables have shown contradictory findings on altered postural stability in CAI (Ross et al., 2009). The most commonly assessed CoP variable is sway velocity (the absolute mean value of the

instantaneous velocity of the CoP in a given direction during a given period) (Ross et al., 2009) which indicates how quickly a person shifts and is able to control the CoP (Childs, 2016). In our study, both sway velocity parameters and ML sway area were significantly greater in CAI participants in eyes open balance when compared between groups, but not when compared between ankles in CAI participants. In eyes close balance, sway velocity was not significantly different between groups, but was significantly different between ankles within the CAI participants. The unaffected side exhibited greater sway velocity than the affected side. Some previous studies similarly report a significantly greater sway velocity measures in antero-posterior (Wikstrom, Fournier, et al., 2010) and medio-lateral directions (Chen et al., 2014; Wikstrom, Fournier, et al., 2010), whereas in contrast to our findings, no significant difference in postural sway has also been reported (Bernier et al., 1997; Chen et al., 2014). Small sample sizes (Bernier et al., 1997) and the use of CAI subgroups (functionally (Bernier et al., 1997) or mechanically unstable ankle (Chen et al., 2014)) may account for some of the differences in findings between studies.

The significant difference within groups in sway velocity measures for eyes close balance suggests that proprioception is impaired as a part of compensation mechanism where contralateral ankle counteract the balance insufficiency. Impaired anterior-posterior measures may indicating the increased antero-posterior movements due to lack of movement control by injured lateral ligament (Chen et al., 2014). In addition, having a more antero-lateral sway measures likely explains, the closed-packed ankle joints assist the unstable ankle to maintain a more stable position (Pope et al., 2011). Also, the greater sway velocity of the unaffected side suggests that local impairments in proprioception may be related to the original injury to local tissues that contain proprioceptive organs. This bilaterally poor proprioception may be centrally driven, however due to the small sample size was unable to be tested. Notably, poor postural control has previously been found to be

related to an increased risk of ankle sprain (Chen et al., 2014; McKeon & Hertel, 2008), and this may therefore be one of the possible causes for the common occurrence of bilateral instability.

The presence of ankle pain has been found to be common (>60%, n=689) in patients with CAI (Adal et al., 2019). In our sample, 60.1% (n=20) of individuals with CAI reported a mean (SD) resting ankle pain of 7.8 (11.1) mm on the VAS scale. Therefore, pain-relieving interventions may sometimes be clinically indicated, along with other interventions to address impairments associated with CAI. Persistent or chronic pain is one common complaint of CAI, (Konradsen et al., 2002) and it was expected that the presence of central sensitisation would be indicated by generalised lower PPT (Ramiro-Gonzalez et al., 2012). So far as we are aware this is the first study to assess the role of central sensitisation in CAI using PPT, and our study found no evidence suggestive of central sensitisation, other than a local pressure pain hypersensitivity over the lateral ligament. This is consistent with some peripheral musculoskeletal conditions such as acute ankle sprain ((Ramiro-Gonzalez et al., 2012) and shoulder pain (Coronado et al., 2014), however differs to other musculoskeletal conditions such as knee osteoarthritis (Fingleton et al., 2015) and chronic low back pain (Corrêa et al., 2015). Possibly the occurrence of recurrent acute sprains within the course of CAI is key. Potentially, activated nociceptors due to recurrent injuries, ongoing inflammation and mechanical irritancy in CAI can prolong the pain experience and may perpetuate peripheral sensitisation, without any central sensitisation (Chimenti, Frey-Law, & Sluka, 2018). The conflicting findings of bilateral changes in CoP measures and reduced PPT measures over the affected area suggest the need for assessing more than one aspect of sensorimotor function, and also for investigating specific subgroups of CAI.

Patient-reported outcome tools could provide clinicians with some insight into the disability experienced by patients with CAI. The two self-reported functional questionnaires endorsed by the IAC and used in the present study (Gribble et al., 2013), demonstrated significantly lower self-reported function in participants with CAI, consistent with the findings of the systematic review by Houstan et al (Houston et al., 2015). Several clinical factors may have contributed to the decreased function in the CAI group, including impaired weight-bearing DFROM, impaired balance measures and pain. This suggests the need for a comprehensive treatment plan to address the various clinical characteristics of this multifactorial problem.

One limitation of this study is that for the eyes close balance test, the participant was asked to remain as still as possible for 10 seconds. However, some participants were unable to stand for this long, therefore averaged CoP data were used in analysis to maintain consistency. A further limitation is that some participants with CAI reported bilateral ankle injuries, and this may have affected comparisons undertaken within the CAI group. Additionally, differences between subgroups of CAI were not able to be investigated due to an insufficient sample size required for subgroup analysis. Finally, the assessor was not blinded to the group allocation, however all the measures except for DFROM were obtained using a computer program.

5.5 Conclusion

The findings of this study support the multi-faceted nature of CAI, including reduced weight-bearing DFROM, impaired static and dynamic balance, decreased self-reported function, and increased resting pain as compared to individuals with healthy ankles. However, there was no difference in PPT in individuals with CAI, suggesting central sensitisation may not be a component

in their chronic pain. Further, impaired weight-bearing DFROM and eyes open medio-lateral sway velocity are the variables most associated with having CAI.

Chapter 6 Effects of mobilisation with movement (MWM) on anatomical and clinical characteristics of chronic ankle instability: a randomised controlled trial protocol.

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The work presented in this manuscript was completed in collaboration with the co-authors (Appendix 1). The ethics approval, clinical trial registration and supporting documents for the study reported in this chapter appear in Appendices 3, 6, 8, 11, 12 and 14-16.

Overview

The systematic review presented in Chapter 3 suggested that MWM and associated fibular repositioning taping may produce greater clinical benefits in chronic ankle sprains than other common joint mobilisation techniques. Further, there is a notable paucity of RCTs investigating the efficacy of manual therapies for CAI, especially in the long-term. The RCT protocol described in this chapter is designed to assess the immediate to long-term effects of MWM (with fibular repositioning taping) on the anatomical and clinical characteristics of CAI, as identified within the studies described in Chapters 4 and 5.

This chapter outlines the study design for the RCT that is the basis for the final study of the thesis. This RCT is designed to compare the effects of MWM (with fibular repositioning taping) to a placebo intervention on fibular position and clinical outcomes including ankle dorsiflexion range, balance, self-reported function, pain and PPT immediately post-intervention, at 12 weeks and at 12 months.

6.1 Introduction

Up to 40% of patients with an initial ankle sprain develop CAI, which is frequently associated with recurrent sprains and persistent pain (Doherty et al., 2014; Hershkovich et al., 2015). A recurrent subjective perception of the ankle joint 'giving way' is clinically indicative of CAI (Gigi et al., 2015), which is defined as "repetitive bouts of lateral ankle instability resulting in numerous ankle sprains" (Hertel, 2002). Clinical management of CAI often involves balance and sport-related activity training (Martin et al., 2013). In a recent meta-analysis, preliminary evidence was also found supporting joint mobilisation as a clinically effective intervention in improving dynamic balance and DFROM in CAI (Weerasekara et al., 2018).

Several ankle joint mobilisation procedures have been developed and described by renowned manual therapists such as Geoffrey Maitland, Freddy Kaltenborn and Brian Mulligan, and are commonly used in rehabilitation (Pettman, 2007). These procedures are applied to a joint, either in the form of non-thrust passive joint mobilisations, high velocity thrust manipulation, or MWM. MWM is defined as the application of a sustained passive accessory movement to a joint while the patient actively performs a task/movement that was previously identified as being painful or limited (Vicenzino et al., 2011). After manual application of MWM, tape is applied to help maintain the glide and corrected fibular position (Mau & Baker, 2014). Biomechanically and neurophysiologically mediated mechanisms have been proposed to explain how these joint mobilisation procedures may work (Mccarthy et al., 2015; Vicenzino et al., 2011). The proposed neurophysiological mechanisms are based on animal (Chien et al., 2009) and human experiments (Sterling et al., 2001) related to pain science and motor systems (Vicenzino et al., 2011). These have shown that joint manual therapy techniques including MWM, activate a descending pain inhibitory pathway which is non-opioid mediated (Vicenzino et al., 2011). One proposed

biomechanical mechanism relates to a reduction of an entrapped meniscoid or synovial fringe by a specifically directed MWM glide particularly in those instances where only one repetition is required to bring about a substantial and long lasting effect (Vicenzino et al., 2011).

Our recent systematic review and meta-analysis identified greater effects for MWM and Mulligan taping compared to Maitland joint mobilisation (with and without traction) and joint thrust manipulation (Beazell et al., 2012; Weerasekara et al., 2018). DFROM and self-reported instability were some of the outcomes for which there was evidence of improvement from MWM, although the long-term benefits were unclear (Cruz-Diaz et al., 2015; Reid et al., 2007; Vicenzino et al., 2006). Most of the previous studies on chronic ankle sprains have applied MWM to the talocrural joint (Cruz-Diaz et al., 2015; Gilbreath et al., 2014; Marron-Gomez et al., 2015; Reid et al., 2007; Vicenzino et al., 2006), and few studies have applied MWM taping (Hopper et al., 2009; Someeh et al., 2015a, 2015b). However Mulligan proposes that an anterior fibular positional fault commonly results from ankle inversion sprains, and that a MWM using a posterior glide of the fibula to correct this should be trialled after 48 hours following such an injury (Hing et al., 2015). Patients with recurrent ankle sprains may also benefit from this MWM treatment combined with taping aimed at maintaining the posterior fibula glide, with reportedly less ‘giving way’ and greater confidence in using the ankle in patients with functional instability and pain (Hing et al., 2015). Therefore this study is designed to evaluate the clinical benefits of the fibular posterior glide MWM with Mulligan taping, and whether it corrects any demonstrable positional fault which may exist. The prevalence of pain in people with CAI is high (60.1%) (Adal et al., 2019) and to our knowledge no studies have assessed the effect of MWM on pain. In addition, the present study will assess the effects of MWM on PPT in CAI. The presence of localised peripheral sensitisation has been previously identified in acute inversion ankle sprains (Ramiro-Gonzalez et al., 2012) and in

sub-acute ankle sprains (Collins et al., 2004). Balance impairments in CAI are frequently reported in the literature and MWM has been found to be effective immediately after application, but there is presently insufficient research to determine the short-term benefits of MWM for balance impairments (Weerasekara et al., 2018). The present study plans to address this deficiency in the literature as well.

A positional fault at the inferior tibio-fibular joint, is one arthrokinematic abnormality proposed to be related to persistent/recurrent symptoms and repetitive ankle sprains in CAI (Hertel, 2002). In the case of an ankle joint sprain, Mulligan suggests that the distal fibula is 'mal-positioned' anteriorly (anterior positional fault) following an inversion injury and that chronicity may result if this remains uncorrected (Hing et al., 2015; Mulligan, 1995). Preliminary evidence for such an anterior fibular positional fault was identified in Hubbard et al's study of individuals with CAI (Hubbard et al., 2006). However it is unclear whether ankle instability caused the anterior fibular position or whether the fault itself was actually the predisposing factor to re-injury. Also, the clinical importance of an anterior fibular positional fault in relation to other potential contributors to CAI remains unclear. Further, the mechanism(s) of changes in CAI outcomes after MWM needs to be further investigated (Cruz-Diaz et al., 2015; Hoch et al., 2014). It has been proposed by Mulligan in his positional fault hypothesis, that MWM effects an immediate and lasting improvement by correcting a minor bony incongruity which is the source of the patient's presenting problem (Hing et al., 2015). However, the capacity of MWM to reverse any positional fault remains unclear and further studies are required to assess the effectiveness of this technique.

The objective of this study is to determine the effect of MWM on anatomical and clinical characteristics of CAI, and to determine the long-term effectiveness of this treatment.

The specific aims of the study are therefore:

To evaluate the effectiveness of MWM on clinically relevant outcomes, including patient-reported outcomes (dorsiflexion range, pain intensity, self-reported function, PPT, static and dynamic balance), including long lasting benefits assessed at 12 months post treatment.

To assess the effect of MWM on changing the fibular position relative to the position of the tibia in CAI.

6.2 Methods

6.2.1 Design

This randomised controlled study has been registered in the Australian New Zealand Clinical Trial Registry (ANZCTR) and ethical approval has been granted by the Human Research Ethics Committee of The University of Newcastle, Australia (H-2017-0354). Informed consent will be obtained in writing from all participants.

6.2.2 Participants

Participants aged 18 years or over will be recruited from the general community in the Newcastle area of New South Wales, Australia through flyers posted on noticeboards in shopping centres, the University of Newcastle main campus, and various other public places. Recruitment advertising will also be via University of Newcastle social media channels. Volunteers with CAI will be

accepted into the study if they satisfy the inclusion and exclusion criteria as endorsed by the IAC (Gribble et al., 2013), except the time period for experiencing at least two episodes of giving way is changed from six months to 12 months to account for the seasonal nature of some sports (Table 6.1).

Data collection will be carried out at the physiotherapy and radiography research laboratories of the School of Health Sciences, The University of Newcastle, Australia.

6.2.3 Procedure

This trial will adopt a pragmatic RCT design to allow for real world application of MWM in a randomised setting (Alsop et al., 2016). This design has been used by previously published trials of manual therapy to better reflect routine clinical practice (Deyle et al., 2016; Groeneweg et al., 2017; Reid et al., 2015). It enhances the external validity, but still controls for threats to internal validity.

The initial screening will be performed over the telephone after the potential participant contacts the research team. The screening questions are to determine if the potential participant meets some of the inclusion/exclusion criteria (Table 6.1). If a potential participant appears eligible following the telephone interview, further screening will be carried out using two standardised questionnaires: the FAAM (Martin et al., 2005), which measures function, and the CAIT (Hiller et al., 2006), which measures ankle instability. A link to access these questionnaires on the Qualtrics online survey platform (Qualtrics, Provo, Utah, USA) will be sent to the potential participant, along with the participant information statement and the consent form, through an email. Once the potential participant returns their completed forms, their final eligibility will be determined

according to their scores (FAAM: ADL subscale <90%, sport subscale <80%; CAIT ≤ 24) on the two screening questionnaires. The participant will then be contacted to schedule an appointment for data collection.

Table 6.1 Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
• A history of at least one significant ankle sprain; - Initial sprain must have occurred at least 12 months prior to study enrolment - Was associated with inflammatory symptoms - Created at least one interrupted day of desired physical activity - The most recent injury must have occurred more than three months prior to study enrolment	• A history of previous surgeries to the musculoskeletal structures (i.e., bones, joint structures, nerves) in either lower extremity • A history of a fracture in either lower extremity requiring realignment • Acute injury to musculoskeletal structures of other joints of the lower extremity in the previous three months that impacted joint integrity and function (i.e., sprains, fractures), resulting in at least one interrupted day of desired physical activity

	• Have conditions for which manual therapy is generally contraindicated (such as the presence of a tumour, fracture, rheumatoid arthritis, osteoporosis, prolonged history of steroid use, or severe vascular disease)
• A history of the previously injured ankle joint 'giving way' and/or recurrent sprain and/or 'feelings of instability' - Participants should report at least two episodes of giving way in the 12 months prior to study enrolment	• Have conditions for which radiological imaging is contraindicated (e.g., pregnancy)
• Self-reported ankle instability should be confirmed with the Cumberland ankle instability tool (CAIT) (≤ 24)	• Have conditions for which taping is contraindicated (e.g., allergy to strapping tape)
• General self-reported foot and ankle function questionnaire minimum score (foot and ankle ability measure (FAAM): activities of daily living (ADL) subscale <90%, sport subscale <80%)	• Receiving concurrent treatment - The most recent treatment for the ankle condition should have been received at least a week prior to study enrolment
	• Inability to read English

Consenting participants will be randomised into two groups: an experimental group who will receive MWM, and a control group who will receive a placebo (detuned laser). All of the participants will be assessed for general joint hypermobility using the Beighton score (Smits-Engelsman et al., 2011). Mechanical ankle instability will be tested separately for each ankle using an X-ray while undergoing an anterior drawer stress test (Hubbard & Cordova, 2009). The clinically important outcome measures will include; radiological imaging of fibular position with

respect to the tibia (positional fault), DFROM, PPT, pain intensity, function, static balance and dynamic balance. These procedures and outcome measures are further explained below. The researcher who collects the clinical measurements, and the radiographer taking the X-rays, will be blinded to the participant's group (intervention) allocation. This researcher will remain blinded to the group allocation until the three month follow-up. The 12 month follow-up data will be collected using online questionnaires.

Each participant will be randomly allocated to a group to receive either MWM (active) treatment or detuned laser treatment (placebo) (these interventions are fully explained below). The participant will be blinded as to whether they are receiving an active or placebo intervention, however due to the nature of the interventions, the treating practitioner cannot be blinded. Participants will be randomly allocated to groups according to a computer generated (GraphPad Software, Inc., CA, USA) randomisation schedule by another researcher not involved in data collection using sealed opaque envelopes. Each envelope will contain a piece of paper printed with either '1' or '0', for which '1' denotes 'MWM' group and '0' denotes 'placebo' group. The treating practitioner will open the envelope and allocate the participant to a group according to the number in the envelope, and deliver the designated treatment accordingly.

Participants of both groups will attend for 2-8 treatment sessions over 4 weeks. The exact number of treatments needed to achieve an optimal change is not presently known, so a range allows the practitioner to exercise their clinical judgement. We have chosen two as the minimum number of treatments, because usual clinical practice would involve a minimum of two visits to enable re-assessment following the initial treatment (Maitland, 2005). The actual number of treatment

sessions delivered to participants in each group will be determined according to the clinical judgement of the treating practitioner, who is a registered physiotherapist with a post-professional tertiary qualification in the field of manual therapy and more than 20 years of clinical experience in treating musculoskeletal conditions. The physiotherapist will also be individually instructed in the MWM intervention by an accredited member of the Mulligan Concept Teachers Association. The physiotherapist will conclude the course of intervention if the patient reports they have fully recovered or if no further improvement is possible up to a limit of eight sessions over a four week period. The number of sessions and the duration of each session will be recorded. The same measures taken at baseline will be repeated at the conclusion of the course of intervention, within a maximum of four days after the participant's last intervention session. Further measurements will be repeated at the twelfth week with the exception of the imaging, and only self-report outcomes will be assessed at 12 months. Participants will be contacted by telephone every four weeks after finishing treatment for up to one year to record any new ankle injuries, any treatments undertaken, and their level of engagement in sport and other activities. Figure 6.1 describes the flow of the study.

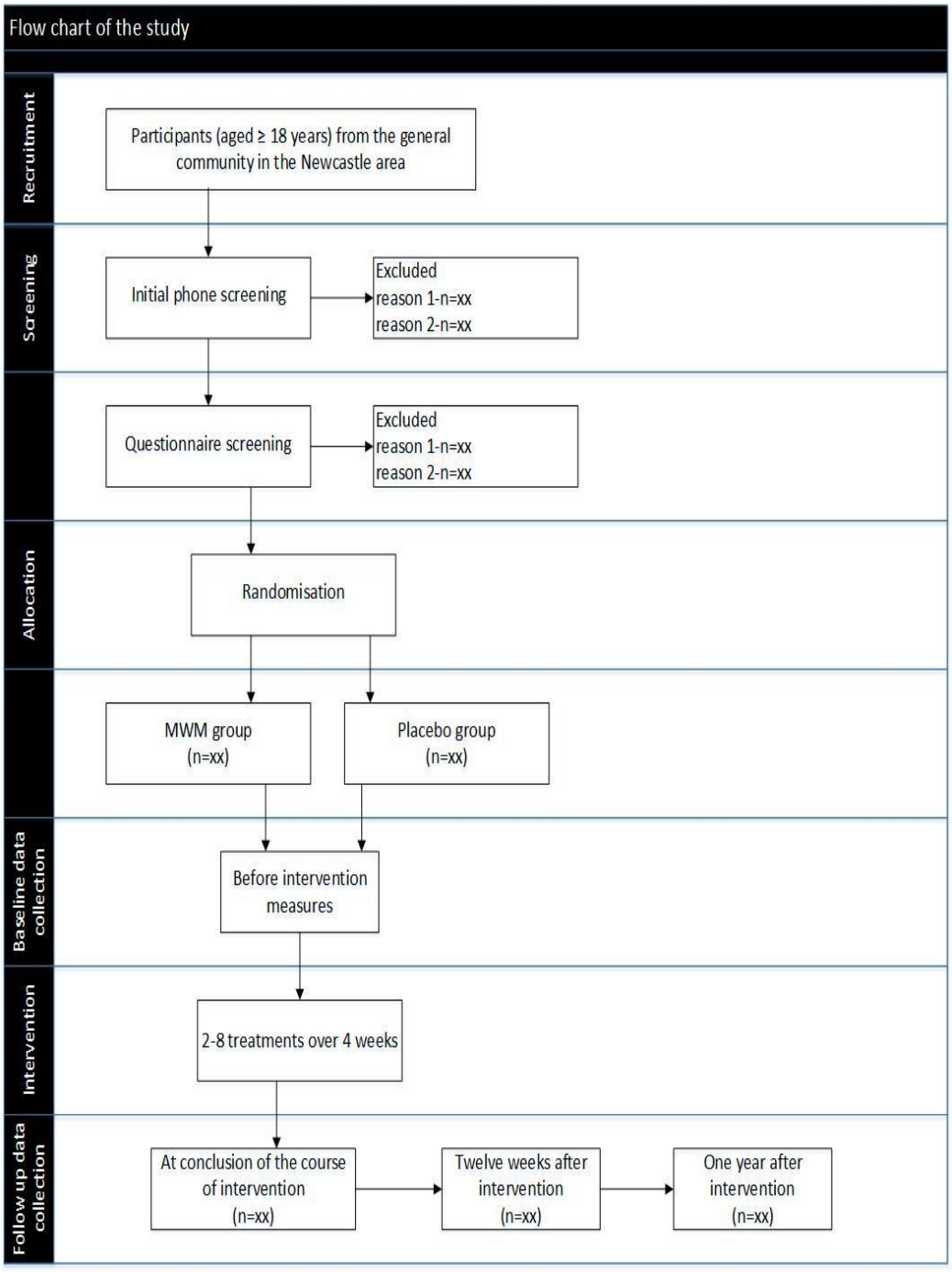

Figure 6.1 Flow of the study

6.2.4 Outcome measures

6.2.4.1 Measurement of fibular positional fault from radiograph

A weight-bearing (neutral ankle in standing position) X-ray (55k Vp and 2.1 mAs) will be taken of the affected ankle of the participant. The participant will be asked to stand on the foot to be imaged on a wooden box with the knee slightly flexed to simulate mid-stance of the gait cycle, with the foot of the non-stance leg hanging in a relaxed manner. The imaged leg will be maintained ~2cm away and parallel to the image receptor. The same instructions will be given to all participants and the participant's leg position will be monitored throughout the procedure. If any leg rotation is noted on imaging, the X-ray will be redone. The central ray will be centred at the base of the metatarsals and perpendicular to the image receptor, and the focal-film distance will be set to 110cm. The participant will be allowed to hold on to body of the X-ray machine for balance if required.

Radiographic images will be digitally obtained using Merge PACS^{TM} software (Merge Health Care, 2012). The fibular position will be measured as the distance between the anterior edge of the distal fibula and the anterior edge of the distal tibia (Hubbard et al., 2006) (Figure 6.2). The test-retest reliability $ICC_{3,1}$ has been estimated as 0.98, with a SEM of 0.64mm for this measurement, and for intra-tester reliability, the $ICC_{3,1}$ is 0.92 and SEM is 0.72mm (Hubbard et al., 2006).

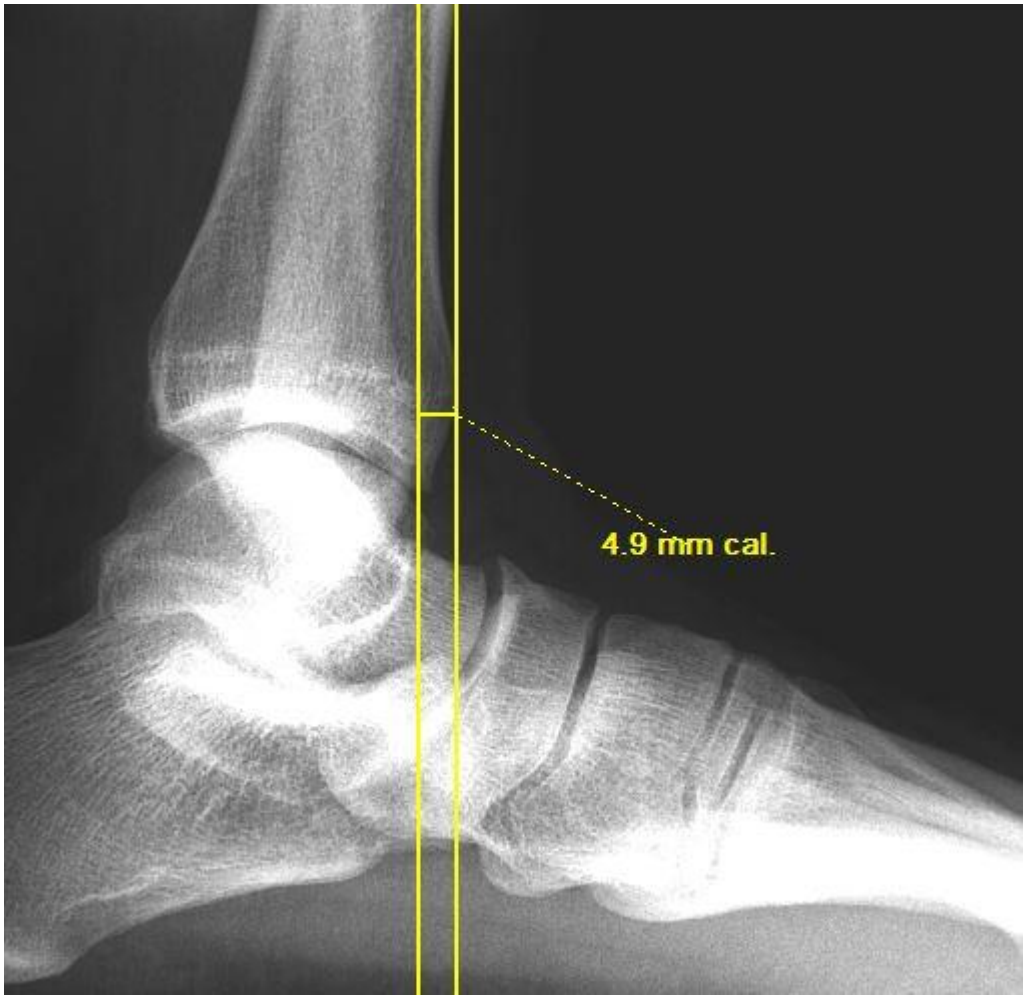

Figure 6.2 Fibular position measurement; the distance between the anterior edge of the distal fibula and the anterior edge of the distal tibia (right ankle, 4.2mm in this image)

6.2.4.2 Weight-bearing dorsiflexion range of movement

Weight-bearing DFROM will be measured using the weight-bearing lunge test. The participant will be instructed to lunge towards the wall, touch their knee to the wall, and keep their heel in contact with the floor. Then the participant will be asked to move their foot away from the wall in 1cm increments until the heel no longer maintains contact with the floor or the knee is no longer in contact with the wall. Maximal dorsiflexion will be considered to be the greatest distance between

the great toe and wall with the participant's knee maintaining contact with the wall (Gilbreath et al., 2014; Hoch, Andreatta, et al., 2012). Both inter-rater reliability (ICC=0.80-0.99) and intra-rater reliability (ICC=0.65-0.99) have been reported as high for this test (Powden et al., 2015). The same procedure will be followed for the opposite leg. Each centimetre away from the wall in the lunge test represents approximately 3.6 degrees of dorsiflexion (Bennell et al., 1998). Three test attempts will be performed and the average value will be used for analysis.

6.2.4.3 Pressure pain threshold (PPT)

PPT measurements will be obtained in each leg from two local points (to assess local hypersensitivity) and one remote body area (to assess central sensitisation), in accordance with the method used in a previous study on acute ankle sprain (Ramiro-Gonzalez et al., 2012). The points include anterior to the lateral malleolus over the ATFL, inferior to the medial malleolus over the deltoid ligament, and over the proximal third of the tibialis anterior muscle belly.

A Freedom Tracker hand-held algometer (JTECH Medical, Salt Lake City, UT, USA) will be used for measuring PPT. A probe (contact surface of $1cm^2$) will be placed perpendicular to the skin and pressure will be applied (40kPa/s). The participant will be asked to indicate when the feeling of the stimulus changes from 'pressure only' to 'discomfort' by pressing an indicator switch (Arendt-Nielsen et al., 2010; Rebbeck et al., 2015). This process will be performed three consecutive times and a 10 second rest period will be allowed between each set of measurements. Pressure algometry is considered a stable and reliable measure of PPT (Frank et al., 2013). The inter-rater reliability of pressure algometry has been reported to be high when the algometer pressure is applied at a consistent rate (ICC 0.91, 95% CI 0.82–0.97) (Chesterton et al., 2007).

6.2.4.4 Pain intensity

Current pain intensity will be assessed using the VAS which consists of a 100mm horizontal line, with ‘no pain’ anchored on the left of the line and ‘worst possible pain’ anchored on the right. The validity of the VAS for detecting changes in pain intensity has been supported by several studies (Ferreira-Valente et al., 2011; Price et al., 1983).

The participant will also be asked to indicate all areas in which they currently feel symptoms on a body chart. The areas in which they feel ‘pain’ will be shaded; the areas in which they feel ‘tingling, pricking, or burning’ will be circled; and the areas where they feel ‘numbness, heaviness or other sensations’ will be indicated on the chart by an ‘N’.

6.2.4.5 Function

Self-reported physical function of the participant will be evaluated using the FAAM which consists of a 21-item ADL subscale and an 8-item sport subscale (Martin et al., 2005). This tool has been documented as a reliable, responsive and valid measure of physical function for individuals with a broad range of musculoskeletal disorders of the lower leg, foot and ankle (Martin et al., 2005). The FAOS questionnaire comprising 42 items will also be used, and has been reported as also being a reliable and valid measure (ICCs reported as 0.78, 0.86, 0.70, 0.85, 0.92 for the five subscales of pain, symptoms, ADL, sport and recreation function, and foot and ankle related QOL, respectively) (Roos et al., 2001).

Further, the participant will be asked to identify up to three important activities that they are unable to perform or are having moderate to extreme difficulty performing due to pain. For each activity, the participant will be asked to rate between 0 and 10 the level of difficulty they experience performing that activity using the patient-specific functional scale (PSFS) (Stratford et al., 1995). The construct validity of the PSFS is well supported, and the test-retest reliability has been assessed as moderate to good ($ICC_{2,1}$=0.713) (Hefford et al., 2012).

6.2.4.6 Static balance

For static balance, the participant will stand barefoot on the centre of a force plate (KISTLER 9260AA6, Winterthur, Switzerland), assuming a standardised single-leg stance position. The participant will then be instructed to flex the other leg slightly at the hip, with the knee flexed to 90 degrees. Their arms will be crossed at their chest with each hand resting on the opposite shoulder. Measurements will be recorded with both 'eyes open' and 'eyes close'. For 'eyes open', the participant will be asked to maintain a fixed gaze on a cross marked on the wall three metres in front of them and remain as still as possible for 10 seconds (Trojian & Mckeag, 2006). For 'eyes close', the participant will be asked to close their eyes and remain as still as possible for 10 seconds (Trojian & Mckeag, 2006). If the participant is unable to stand for 10 seconds, the standing time achieved will be recorded. Only averaged CoP data including sway velocity, sway area per second, sway average amplitude and sway maximal amplitude will be used in the analysis to maintain consistency. CoP data obtained through the force platform will be acquired at 100Hz (Hopper et al., 2009).

6.2.4.7 Dynamic balance

Dynamic balance will be assessed using the SEBT which has been shown to be a reliable measure to identify dynamic balance deficits in patients with a variety of lower extremity conditions (Gribble et al., 2012). The participant will be asked to establish a stable base of support on the stance limb in the middle of the testing grid on a force plate (KISTLER 9260AA6, Winterthur, Switzerland). While standing on a single limb, the participant will be asked to reach as far as possible with the reaching limb along each line (anterior, postero-medial and postero-lateral directions), lightly touching the line with the most distal portion of the reaching foot without shifting weight or coming to rest on the foot of the reaching limb. The participant will then be asked to return the reaching limb to the starting position in the centre of the grid. If the individual lifts or shifts any part of the foot of the stance limb during the trial, the trial will be not considered as complete (Gribble et al., 2012).

After performing a maximum of four non-recorded trials for familiarisation, the next trial for each direction will be recorded for the purpose of analysis (Pionnier et al., 2016; Robinson & Gribble, 2008). Normalised SEBT values will be obtained by dividing the excursion distance by the participant's leg length (the distance between the anterior superior iliac spine and the ipsilateral medial malleolus), and then multiplying by 100 (Gribble & Hertel, 2003; Pionnier et al., 2016). Data for CoP velocity (V) to quantify spatio-temporal parameters (VCoP-total, VCoP-mediolateral, VCoP-anteroposterior) will be acquired at 100Hz, under the foot during unipodal stance (Pionnier et al., 2016).

6.2.4.8 Perceptions of the credibility of the placebo

At the data collection session at the conclusion of course of intervention, the participant will be asked to indicate which intervention (active or placebo) they thought they had received during the last four weeks and to give a confidence rating on a scale of 0–10 (with 0='not at all confident' and 10='extremely confident' (Owens & Menard, 2011)). Global perceived effect will also be measured using a self-assessment of improvement on a seven point rating scale (1=completely recovered, 2=much improved, 3=slightly improved, 4=not changed, 5=slightly worsened, 6=much worsened, 7=worse than ever) in response to the question 'How would you rate the course of your ankle complaints since the start of this study?' (Kamper et al., 2010; Van Der Windt et al., 1998).

6.2.4.9 Other measures

Telephone interviews will be conducted monthly after enrolment up to one year to record any new injuries, any treatments undertaken, and the level of engagement in sports and other activities. These variables will be used as covariates in the analysis of the 12 month follow-up data as they are possible confounders. Further, the Beighton score for hypermobility and radiographic measurement of the anterior drawer stress test will be recorded.

6.2.4.10 Beighton score

Scoring for joint hypermobility will be undertaken according to previously published methods(Smits-Engelsman et al., 2011). Each participant will be assessed in five test positions, as follows:

1. Passive extension of the fifth metacarpophalangeal (MCP) joint to ≥ 90 degrees. The participant sits on a chair at the short side of the table with the shoulder in 80 degrees abduction, elbow flexed at 90 degrees, and the forearm resting on the table in a pronated

position. The fifth MCP joint is passively extended by the researcher and a goniometer is used to measure the angle.

2. Passive hyperextension of the elbow ≥ 10 degrees. The participant sits on a chair with the shoulder at 90 degrees of flexion and the forearm supinated. A goniometer is placed at the lateral epicondyle and the measurement is taken at maximum elbow extension.
3. Passive hyperextension of the knee ≥ 10 degrees. The participant lies supine with their legs in the horizontal plane. The goniometer is placed at the lateral femoral condyle and the measurement taken at maximum knee extension.
4. Passive apposition of the thumb to the flexor side of the forearm. The score is positive if the entire thumb touches the flexor side of the forearm while the shoulder is flexed at 90 degrees, the elbow extended, and the forearm pronated.
5. Forward flexion of the trunk with the knees straight. The score is positive if the participant's hand palms rest easily on the floor.

6.2.4.11 Anterior drawer stress test with radiographic measurement

Ankle joint mechanical instability will be assessed using a lateral X-ray to measure the amount of anterior translation of the talus during a ligament stress test for each ankle. The radiograph will be taken while the ankle is undergoing a simulated anterior drawer test using 125N (Maitland, 2005). The stress radiograph will be taken with the participant in a supine lying position with the foot relaxed in a resting position and the lower leg resting on a support, with the hip and knee each flexed approximately 45 degrees. The heel will be supported on a dynamometer (Lafayette Manual Muscle Tester, Model 01165, Lafayette, IN, USA) attached to a customised device which produces the anteriorly directed force. The distal tibia will be fixed on the support using a stabilising belt placed over the distal aspect of the tibia (Seebauer et al., 2013). The central ray will be centred just

above the tip of the lateral malleolus and perpendicular to the image receptor (Johannsen, 1978). Then an anterior force of 125N will be applied (Hubbard & Cordova, 2009) to the heel of the participant at an angle of 20 degrees to the vertical plane as per recommended clinical practice (Dutton, 2017), using the customised device. The force will be monitored using the digital display of the dynamometer attached to the customised device, and the radiograph will be taken at 125N. The ankle radiograph will be taken at the focal-film distance of 110cm (Lee et al., 2013) and will set to 55 kVp and 2.1 mAs. The same procedure will be applied to the other ankle. These images will be taken at the baseline data collection session to assess mechanical instability for use in subgroup analysis.

Radiographic images will be digitally obtained using Merge PACS^{TM} software (Merge Health Care, 2012). Anterior translation of the talus will be measured between the posterior lip of the tibial articular surface and the nearest point of the talar dome (Figure 6.3) (Beynnon et al., 2005; Ellis et al., 2011; Lee et al., 2013; Prado et al., 2013) to identify any mechanical instability. Anterior drawer stress radiographs have been found to have moderate sensitivity, high specificity and a high positive predictive value for the evaluation of lateral ankle instability (Jolman et al., 2017). A between-limb difference of 3mm in anterior translation of the talus or an absolute value of 10mm is considered clinically significant (Jolman et al., 2017).

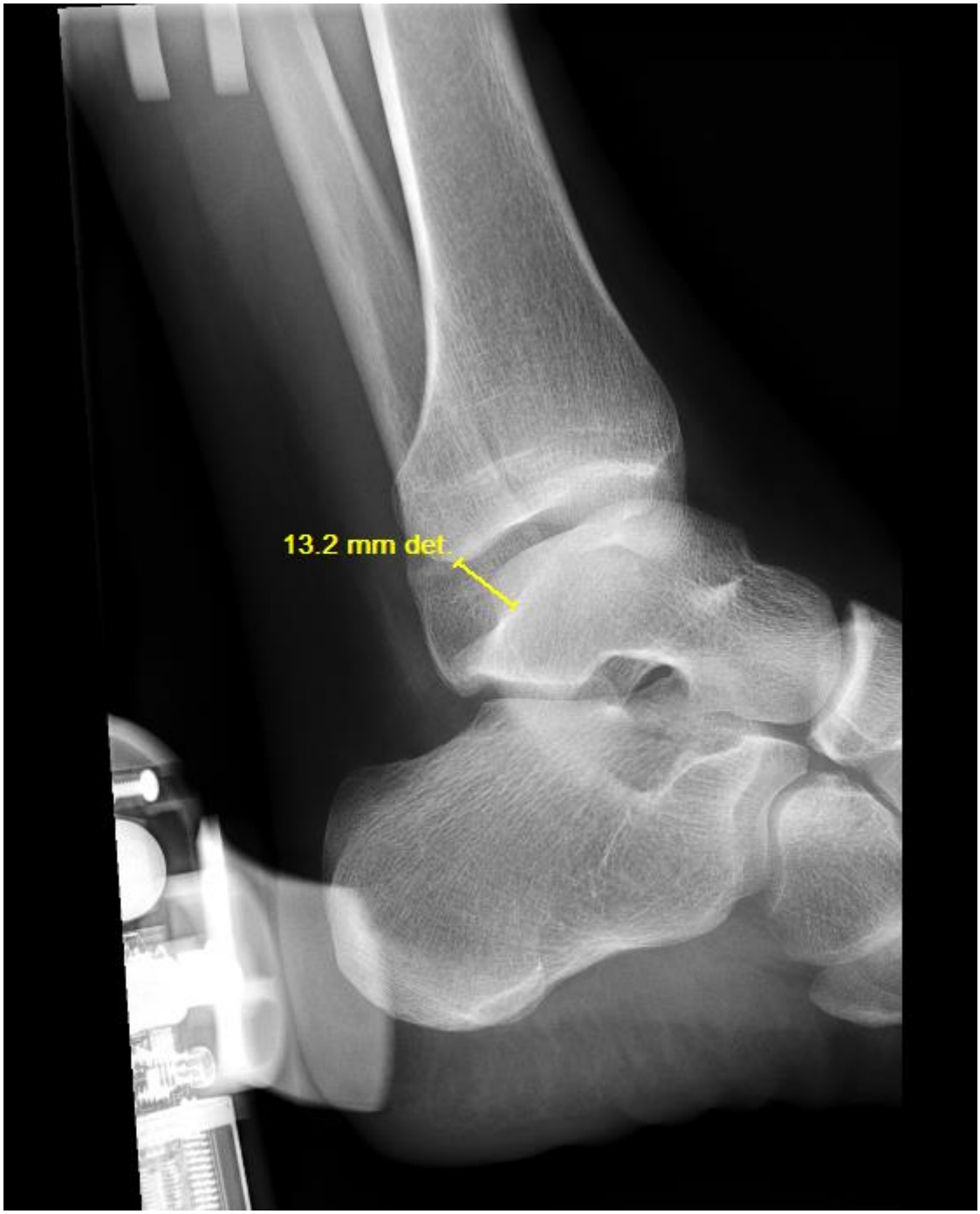

Figure 6.3 Anterior translation of the talus during the anterior drawer stress test is measured as the distance on X-ray from the posterior lip of the tibial joint surface to the nearest point of the talar dome (left ankle, 13.2mm in this image)

6.2.5 Application of the intervention

Participants in the experimental group will be treated with a manual MWM technique to the ankle and will be taped after the intervention using the Mulligan approach (Hing et al., 2015) to attempt to maintain the effects of the MWM. The control group will receive a detuned (inactive) therapeutic laser treatment to the lateral region of the ankle. The number of treatment sessions delivered for each participant will be based on their symptomatic response to treatment, as determined by the clinical judgement of the treating practitioner. Each participant will be asked to avoid concurrent interventions during their participation in the study.

6.2.5.1 MWM intervention

The participant's inferior tibio-fibular joint will be mobilised using Mulligan's fibula MWM for dorsiflexion and/or inversion (Hing et al., 2015). Initially, the technique will be performed in supine lying with the tibia resting on the treatment table and the foot unsupported off the table's edge. The practitioner applies a sustained pain-free anteroposterior glide with a slight cephalad and lateral inclination to the distal fibula (lateral malleolus). This glide is maintained while the participant performs active inversion or dorsiflexion (depending on which is more limited in range) to end of range. There should be no pain with the active movement. At the end of range, the practitioner will apply and sustain overpressure to the active movement for a few seconds (or the participant will do so after appropriate instruction) (Hing et al., 2015; Vicenzino et al., 2006). If dorsiflexion remains restricted, this technique can be progressed and performed in partial and/or full weight-bearing.

One treatment session will consist of three to five sets, with six to ten repetitions of the active movement in each set, with the actual dosage depending on the individual response of the participant (Hing et al., 2015). Participants will receive between two to eight sessions according to the clinical reasoning of the practitioner, over a period of four weeks. After each session, Mulligan MWM taping will be applied in an attempt to replicate the sustained fibula glide (Vicenzino et al., 2011). Non-elastic tape will be applied to the ankle starting 2cm anterior to the fibula and 1cm proximal to the tip of the lateral malleolus. The tape will be spiralled obliquely around the lower limb while the fibula glide is sustained, finishing on the anterior aspect of the leg (Hing et al., 2015). The participant will be instructed to keep the tape on for 24 hours. In the case of an adverse reaction, they will be advised to remove the tape immediately and note the length of time the tape was in place.

6.2.5.2 Detuned laser intervention

The placebo intervention will be applied using a detuned therapeutic laser device (Meyer Medical Electronics, Mordialloc, Australia) for five minutes to the lateral region of the ankle, maintaining the probe 0.5-1cm away from the skin (De Bie et al., 1998; Kingsley et al., 2014; Reid et al., 2015; Teo et al., 2010). The detuned laser device will appear to function normally (both audibly and visually) to participants, but no effective emission will be produced. Both the participant and the practitioner will be required to wear protective glasses as per normal clinical practice (Cotler et al., 2015). Participants will receive two to eight treatments over four weeks, according to the clinical judgement of the treating practitioner. Detuned laser has been used in several other studies assessing manual therapy including for chronic ankle sprains. It avoids any possible direct mechanical effects to the ankle being treated and also does not activate somatosensory receptors (Irnich et al., 2001; Pellow & Brantingham, 2001; Reid et al., 2008). Further, it has been shown to

have a strong placebo effect (Reid et al., 2008). Scheduling of participant appointments will be arranged to avoid interaction between participants.

6.2.6 Sample size and data analysis

Previously published data related to the primary outcome measure of function (FAAM subscales, ADL and sports) (Gilbreath et al., 2014; Martin et al., 2005) (MCID=8.0, SD=5.68; MCID=9.0, SD=7.42 respectively) were used in sample size calculations (Gilbreath et al., 2014; Martin et al., 2005; Merlin et al., 2005). A sample size of 16 per group allowing for a 30% drop-out rate was estimated, for a minimal statistical power of 0.80 and an alpha significance level of 0.05. Secondary analysis based on the subgroups of ankle instability (mechanical, functional) will be preliminary in nature as the study is not powered for this aim. Data will be analysed using SPSS Statistics for Windows (Version 23.0, Armonk, NY, IBM Corp). Continuous data will be assessed for normality using the Shapiro-Wilk test.

Baseline comparability between groups will be analysed using the independent t-test or non-parametric equivalent, as appropriate. Linear mixed models will be used to analyse the outcome measures. For the primary outcome measure, 'function' will be the outcome variable and time, group and an interaction term for time by group will be the predictors. Any statistically significant difference in change in the outcome variable over time between the groups will be indicated by the p value for the interaction term. Pairwise Bonferroni comparisons will be performed to explore the differences between time points and between groups if a significant interaction is identified. Independent t-tests will be used to compare outcome measures between groups at each time point and the changes of the scores will be used to detect any changes in the outcomes of interest.

Intention to treat (ITT) analysis will be performed with all participants allocated to each group condition to evaluate the effect of the independent variable. For missing data in ITT analysis, a participant's last observation for each outcome measure will be carried forward. The average number and the average duration of intervention sessions between groups will be compared. If any significant difference observed, secondary analysis will be taken to find any correlation between the treatment volume and the outcomes.

Additional variables recorded during monthly phone interviews (new injuries, changes in activity level, and occurrence of other treatments) will be used as covariates in the analysis of the 12 month follow-up data as they are possible confounders. Further, the Beighton score for hypermobility will also be included in regression analysis as a covariate. Radiographic measurement of the anterior drawer stress test will be used to differentiate subgroups of CAI in potential sub group analysis.

6.3 Discussion

One proposed anatomical mechanism underpinning MWM is theorised to be a correction of a minor bony incongruity (positional fault) which is at the source of the patient's presenting problem (Hing et al., 2015; Vicenzino et al., 2007). The existence of an anterior fibular 'positional fault' in individuals with CAI has some preliminary radiological support (Hubbard et al., 2006). There are also limited MRI data supporting Mulligan's positional fault hypothesis in cases of lateral ankle pain (Merlin et al., 2005), however there is no evidence to date that MWM reverses any positional anomaly. Further, should any fibular positional anomaly be reversed immediately after the application of MWM, the length of time this reversal or correction is maintained is unknown. The proposed study protocol is designed to determine the presence of any positional fault of the fibula

in CAI, and whether MWM can reverse this, and if so, whether this reversal is evident four weeks after treatment commences. Moreover, this study protocol will explore the correlation between an anatomical measure (fibular position) and other clinical outcomes (pain, function, PPT, DFROM, static and dynamic balance). Potential relationships between these measures may help explain how changing an anatomical measure may effect a clinically meaningful outcome. The effect of MWM in CAI will also be explored in relation to the presence or not of radiologically measurable mechanical instability.

There are very few clinical trials with long-term follow-ups which have assessed MWM for any musculoskeletal condition, and only one for CAI which had a six month follow-up (Cruz-Diaz et al., 2015; Weerasekara et al., 2018). The proposed study protocol is therefore the first designed to evaluate the long-term effectiveness of MWM on CAI. Moreover, the treatment effect may depend on the type of instability present (mechanical or functional), and this study protocol may evaluate the efficacy of MWM on these two subgroups of CAI. However, the subgroup analysis will be exploratory as the study was only powered to detect the main effect being the intervention on the functional outcome.

Chapter 7 Mobilisation with movement with taping is not effective in changing fibular position or improving clinical outcomes in chronic ankle instability: a randomised controlled trial

This chapter has been prepared in accordance with the requirements for manuscript submission to a peer-reviewed journal. For the purpose of this thesis, only immediate post-intervention and 12 week follow-up data are presented in this chapter as 12 month data were still being collected at the time of thesis submission. The manuscript to be submitted for publication will be finalised after the completion of the 12 month follow-up data collection and analysis.

The ethics approval, clinical trial registration and supporting documents for the study reported in this chapter appear in Appendices 3, 6, 8, 11, 12, 14 and 15.

Overview

This chapter reports some of the findings of the RCT study for which the protocol is described in Chapter 6, including at baseline, immediately post-intervention and at 12 week follow-up. Data for 12 month follow-up were incomplete as they were still being collected at the time of submission of the thesis, and therefore are not included in this chapter.

An average of six sessions of 'MWM with fibular repositioning taping', which included four sets of eight repetitions, was compared to an average of five sessions of '6 minutes of detuned placebo laser' in assessing their effects on fibular displacement and common clinical characteristics of CAI. The clinical characteristics of self-reported function, weight-bearing dorsiflexion range, static and

dynamic balance, PPT and pain intensity were assessed in both groups up to 12 weeks, and the results are described in this chapter.

7.1 Introduction

Chronic ankle instability is typically a result of recurrent ankle sprains and long-term weakness in surrounding supporting structures, particularly the lateral ligament complex (Hertel, 2002). It can present bilaterally or unilaterally and is often accompanied by weakness, chronic ankle pain, and a feeling of giving-away (Fong et al., 2007; Hiller et al., 2011). CAI may also disrupt regular daily activities, including potential lost time from sporting activities, and may result in both direct and indirect costs of management (Childs, 2016; Gribble et al., 2016b). There are two widely accepted subgroups of CAI, mechanical ankle instability and functional ankle instability (Hiller et al., 2011).

Conservative interventions are applied alone or as a combination of strategies to manage ankle instability (Ajis & Maffulli, 2006), and often include manual therapy (Weerasekara et al., 2018). Brian Mulligan's MWM and fibular repositioning taping is a frequently used manual therapy combination for managing CAI (Marron-Gomez et al., 2015; Vicenzino et al., 2006), and has been suggested to be more beneficial when compared to other forms of manual therapy, a placebo or no intervention controls (Weerasekara et al., 2018; Westad et al., 2019). The fibula has been reported to be more anteriorly positioned compared to the tibia in CAI in the weight-bearing position (Weerasekara, Osmotherly, Snodgrass, et al., 2019a). To date, there have been no studies investigating the effectiveness of Mulligan's MWM with taping on correcting the displaced fibular position in CAI.

The effects of MWM have been examined previously in individuals with CAI using DFROM (Cruz-Diaz et al., 2015; Gilbreath et al., 2014; Marron-Gomez et al., 2015; Reid et al., 2007; Vicenzino et al., 2006), dynamic balance (Cruz-Diaz et al., 2015; Gilbreath et al., 2014) and self-

reported function (Gilbreath et al., 2014). Mulligan's fibular repositioning taping has also been examined for its effects on static balance (Hopper et al., 2009), dynamic balance (Hopper et al., 2009; Someeh et al., 2015a) and function (Someeh et al., 2015b) in participants with CAI. These studies have reported inconsistent conclusions on improvement of measured outcomes. The potential to alter fibular position using MWM with fibular repositioning taping, could impact on other clinical outcomes for CAI. While there is a growing evidence for the use of MWM alone for CAI (Weerasekara et al., 2018), the evidence for the efficacy of a combination of Mulligan's MWM with taping to improve clinical outcomes is currently lacking. Further, it may be insightful to explore the effect of MWM on a group of individuals with CAI that present with a displaced fibula at the distal tibio-fibular joint.

Therefore, the research questions for this study were:

1. Is there a significant difference in the immediate effect of Mulligan's MWM with fibular repositioning taping and a placebo intervention on fibular position in individuals with CAI?
2. Is there a significant difference in the immediate or short-term effects of Mulligan's MWM with fibular repositioning taping and a placebo intervention on measures of weight-bearing DFROM, static balance, dynamic balance, PPT, pain intensity and self-reported function in individuals with CAI?
3. Is there any effect of Mulligan's MWM with fibular repositioning taping on a subgroup of CAI (mechanically unstable vs mechanically stable, or displaced fibula vs non-displaced fibula), using primary outcome measures (fibular position, self-reported function)?

7.2 Materials and Methods

This study has been registered in the Australian New Zealand Clinical Trials Registry (ACTRN12617001467325) and granted ethical approval by the Human Research Ethics Committee of The University of Newcastle, Australia (approval no. H-2017-0354). Written consent was obtained from all participants.

7.2.1 Design

A detailed protocol of this study has been published together with prospective registration (Weerasekara, Osmotherly, Snodgrass, et al., 2019b). The current study used a pragmatic RCT, assessor-blinded design. The participants were blinded as to whether they were receiving an active or placebo intervention, however, in keeping with any trial using manual therapy, the therapist was not able to be blinded. After completion of baseline measurements, the participants were randomly allocated to groups according to a computer-generated random number schedule (GraphPad Software, Inc., CA, USA) by a researcher not involved in data collection, using sealed opaque envelopes. The therapist allocated the participant to the group and delivered the designated intervention according to the number in the envelope.

Once the therapist concluded the course of intervention up to a maximum of eight sessions over a four week period, the baseline assessment was repeated. The endpoint of treatment was decided by the therapist based on their clinical judgement, using a pragmatic approach within this time frame (Weerasekara, Osmotherly, Snodgrass, et al., 2019b). The same assessment was repeated at the twelfth week with the exception of the radiographic measures (Figure 7.1). Further, the participants were telephoned every four weeks following the completion of the intervention to determine any

new ankle or leg injuries, any treatment undertaken, and their level of engagement in activities.

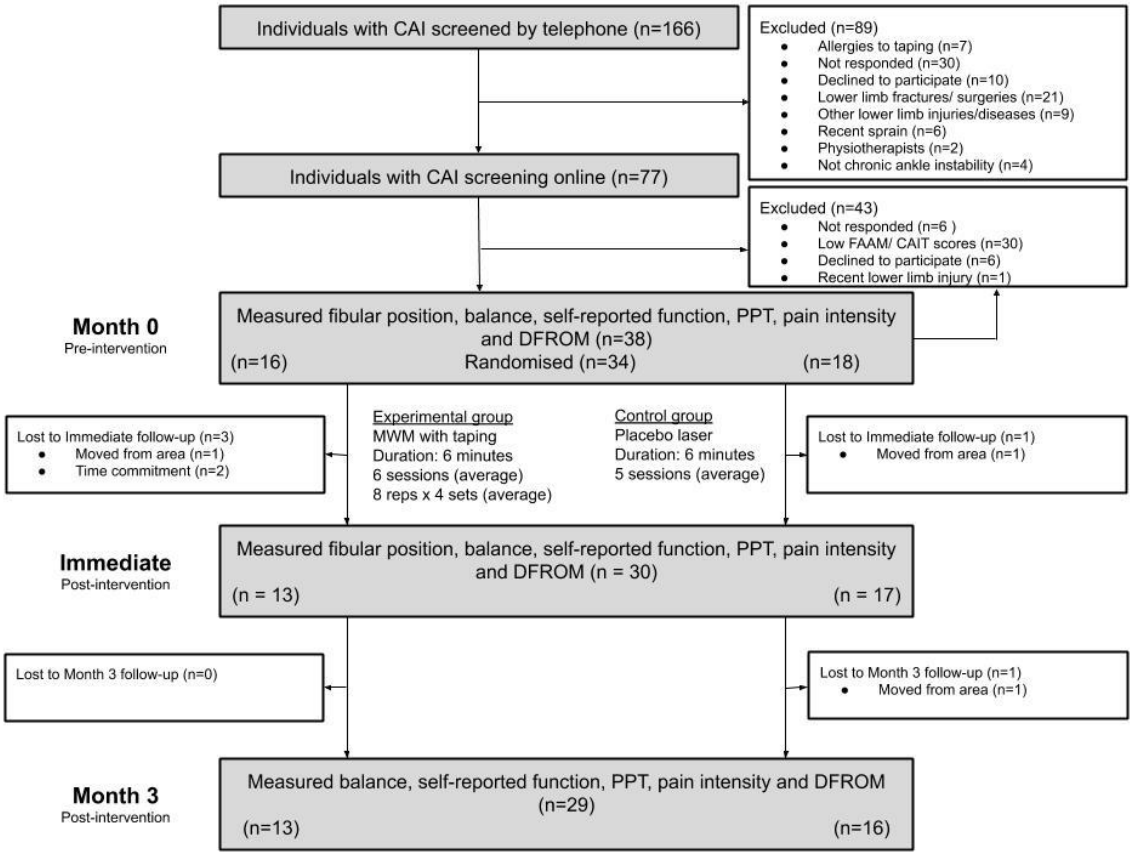

Figure 7.1 Design and flow of participants through the trial

CAI, chronic ankle instability; CAIT, Cumberland Ankle Instability Tool; DFROM, dorsiflexion range of motion; FAAM, foot and ankle ability measure; MWM, Mobilisation with movement; PPT, pressure pain threshold

7.2.2 Participants, therapists, centres

Participants were recruited via flyers and social media channels. Inclusion criteria included aged 18 years or over, a history of at least one significant ankle sprain, a history of ankle joint 'giving way'

and/or recurrent sprain and/or ‘feelings of instability’ confirmed with a CAIT score of ≤ 24 (Gribble et al., 2013). and cut-off scores of ADL scale < 90% and sport scale < 80% in the FAAM questionnaire (Gribble et al., 2013; Weerasekara, Osmotherly, Snodgrass, et al., 2019b). A history of previous surgeries or fractures requiring realignment in the lower extremity, an acute injury to the lower extremity in the previous three months, any condition for which manual therapy, taping or radiological imaging is generally contraindicated, receiving concurrent treatment, and an inability to read English were the exclusion criteria for the study (Gribble et al., 2013).

Questionnaires were completed through the Qualtrics online survey platform (Qualtrics, Provo, Utah, USA) and other data were collected at the physiotherapy and radiography research laboratories of The University of Newcastle, Australia.

7.2.3 Intervention

Participants in both groups received 2-8 treatments over four weeks, according to the clinical judgement of the therapist based on their symptomatic response to treatment. Both interventions involved approximately the same amount of treatment time. The participant appointments were arranged in a way to avoid interactions between the participants of the two groups. The interventions for both groups were delivered by a registered physiotherapist with a post-professional qualification in manual therapy and more than 20 years of musculoskeletal clinical experience. An honorary member of the Mulligan Concept Teachers Association instructed the physiotherapist in the MWM intervention. Including an adjunct intervention such as home exercise was avoided in the current study to increase the precision of the results in relation to the effects of joint mobilization as a unique intervention, and also to ensure the homogeneity of the sample.

7.2.3.1 Experimental group

Participants in this group were treated with a manual MWM technique to the ankle region and taped after the intervention, as described by Mulligan (Hing et al., 2015; Weerasekara, Osmotherly, Snodgrass, et al., 2019b). The inferior tibio-fibular joint of the supine lying participant was mobilised using Mulligan's fibula MWM for dorsiflexion and/or inversion (Hing et al., 2015), with the tibia resting on the treatment table and the foot unsupported off the edge of the table. A sustained pain-free anteroposterior glide with a slight cephalad and lateral inclination was then applied to the distal fibula. The participant was then asked to perform active inversion or dorsiflexion (whichever was most limited) to end of range, while the physiotherapist maintained the glide. An overpressure was applied at the end of the range and maintained by the physiotherapist for a few seconds (Hing et al., 2015; Vicenzino et al., 2006). Consistent with MWM treatment principles, this technique was performed pain free. The technique was progressed to partial and/or full weight-bearing if dorsiflexion remained restricted. Three to five sets of eight repetitions were included in an intervention session, depending on the individual response of the participant (Hing et al., 2015; Weerasekara, Osmotherly, Snodgrass, et al., 2019b).

After each session, taping was applied to maintain the pain-free fibula glide (Vicenzino et al., 2011). Non-elastic tape was spiralled obliquely starting 2cm anterior to the fibula and 1cm proximal to the tip of the lateral malleolus, while the fibula glide was manually sustained by the therapist (Hing et al., 2015; Weerasekara, Osmotherly, Snodgrass, et al., 2019b). The participant was instructed to keep the tape on for 24 hours. In the case of an adverse reaction to the tape, the

participant was asked to remove the tape immediately and note the length of time the tape had been in place.

7.2.3.2 Control group

Participants in the control group received a detuned (inactive) therapeutic laser (Meyer Medical Electronics, Mordialloc, Australia) treatment to the lateral region of the ankle. The detuned laser device functioned with visual and audible parameters, but did not produce any emission. As per normal clinical practice, both the participant and the practitioner wore protective glasses (Cotler et al., 2015; De Bie et al., 1998).

7.2.4 Outcome measures

The primary outcomes of this study were fibular position and self-reported function. In addition, there were several secondary outcomes including weight-bearing DFROM, balance (static and dynamic), PPT and pain intensity. Further, radiographic assessment of the anterior drawer stress test of the ankle and an assessment of overall joint hypermobility using the Beighton score (hypermobility defined as a Beighton scale score of ≥ 4) (Clinch et al., 2011) were undertaken. Due to ethical considerations of the radiation exposure from repeated X-rays and the related cost, we chose not to follow up fibular position measures beyond the 12 week follow-up. All other measures were followed up for 12 months. All these measurements have been explained in detail in the protocol paper of this RCT (Weerasekara, Osmotherly, Snodgrass, et al., 2019b), but are briefly outlined below. This paper reports the results obtained up to the 12 week follow-up.

7.2.4.1 Primary measures

The position of the fibula was measured with the participant standing on the affected foot, representing mid-stance of the gait cycle. A digital lateral radiographic image was obtained using Merge PACS software (Merge Health Care, 2012). The fibular position was recorded as the distance between the anterior edges of the distal fibula and the distal tibia (Hubbard et al., 2006). These measurements were then normalised for tibial width, defined as the maximum distance between the anterior and posterior tibial processes within the distal epiphysis (Weerasekara, Osmotherly, Snodgrass, et al., 2019b). A cut-off for normalised fibular position of ≥ 27 was used to distinguish a displaced fibula (Weerasekara, Osmotherly, Snodgrass, et al., 2019a). All radiographic assessments were performed by the same radiographer.

Self-reported function was measured using the FAAM (Martin et al., 2005) and the FAOS (Roos et al., 2001; Weerasekara, Osmotherly, Snodgrass, et al., 2019b).

7.2.4.2 Secondary measures

Weight-bearing DFROM was measured using the weight-bearing lunge test. Maximal dorsiflexion was recorded as the greatest distance between the great toe and the wall (Gilbreath et al., 2014; Hoch, Andreatta, et al., 2012; Weerasekara, Osmotherly, Snodgrass, et al., 2019b).

Static balance measurements were recorded in ‘eyes open’ and ‘eyes close’ conditions for 10 seconds. The participant was asked to stand barefoot assuming a single-leg stance position on the centre of a force plate (KISTLER 9260AA6, Winterthur, Switzerland). Averaged CoP data during these measures, including sway velocity and sway area per second acquired at 100Hz, were used in

the analysis (Hopper et al., 2009; Weerasekara, Osmotherly, Snodgrass, et al., 2019b).

The SEBT was performed on a force plate to measure dynamic balance. The SEBT reach distances were normalised by dividing the excursion distance by the participant's leg length, and then multiplying by 100 (Gribble & Hertel, 2003; Pionnier et al., 2016; Weerasekara, Osmotherly, Snodgrass, et al., 2019b). CoP data were recorded during these excursions (Weerasekara, Osmotherly, Snodgrass, et al., 2019b).

PPT was measured using a Freedom Tracker hand-held algometer (JTECH Medical, Salt Lake City, UT, USA). Measurements were obtained at local points anterior to the lateral malleolus and inferior to the medial malleolus, and from one point remote to the ankle (over the proximal third of the tibialis anterior muscle belly) (Ramiro-Gonzalez et al., 2012; Weerasekara, Osmotherly, Snodgrass, et al., 2019b).

Each participant was asked to indicate their pain intensity at rest using a VAS, by marking a 100mm line anchored with 'no pain' at one end and 'worst possible pain' at the other (Weerasekara, Osmotherly, Snodgrass, et al., 2019b).

Ankle joint mechanical instability was measured during the anterior drawer test using a lateral X-ray for each ankle. The amount of anterior translation of the talus for each ankle was measured while a 125N force was applied (Hubbard & Cordova, 2009).Where the participant could not tolerate 125N of force, the maximum force they could tolerate was applied to both ankles. Anterior

translation of the talus was recorded as the distance between the posterior lip of the tibial articular surface and the nearest point of the talar-dome (Beynnon et al., 2005; Ellis et al., 2011; Lee et al., 2013; Prado et al., 2013; Weerasekara, Osmotherly, Snodgrass, et al., 2019b). A difference between the limbs of 3mm or more in anterior translation of the talus was considered indicative of a mechanically unstable ankle (Jolman et al., 2017).

7.2.5 Data analysis

The sample size calculation used both self-reported function (FAAM) and fibular position as the primary outcome measures (Gilbreath et al., 2014; Merlin et al., 2005). The largest estimation was 17 participants per group providing 80% power to detect a 3.5mm between-group difference for fibular position, assuming a standard deviation of 3.1mm (Merlin et al., 2005), a dropout rate of 30% and an alpha of 0.05.

The normal distribution of quantitative data was assessed graphically and by normality tests. Baseline comparability between groups was analysed using the independent t-test or non-parametric equivalent, as appropriate. A general linear model repeated measures with time (pre-intervention, immediately post-intervention, 12 week follow-up) as the within-subject factor, and group (MWM or placebo) as the between-subject factor (independent variable), was applied. An ITT analysis was utilised, with imputation using last observation carried forward (Salkind, 2010). Effect sizes for within-group and between-group were calculated. Further, changes in outcome measures were compared between groups using independent t-tests, and between time points using paired t tests. Non-parametric tests were used appropriately when assumptions were violated for parametric tests. Further, subgroups (displaced vs non-displaced fibula; mechanically unstable vs

mechanically stable ankle) were compared *post hoc*.

Data were analysed using IMB SPSS (Version 24.0, Armonk, NY, IBM Corp) software. The statistical analysis was conducted using a 95% CI, with a p value of less than 0.05 considered statistically significant.

7.3 Results

7.3.1 Flow of participants, therapists, centres through the study

Recruitment occurred between February-July 2018. Twelve week follow-up assessments were completed in November 2018. A total of 166 participants were screened over the phone and 89 were excluded. Common reasons for exclusion were non-response, lower limb fractures and surgeries. The online screening excluded a further 43 participants, with the most common reason for exclusion being below the FAAM cut-off score required to be eligible for the study. A total of 34 participants were randomly assigned to the experimental group (n=16) or control group (n=18). However, four participants (experimental=3, control=1) did not continue the intervention and were considered as lost to follow-up (Figure 7.1). All participants received the correct intervention as per the randomisation schedule. Table 7.1 presents the baseline characteristics of the participants. No differences were found in baseline characteristics between the two groups.

Table 7.1 Participants characteristics

Characteristic	**Randomised (n=34)**		**Lost to follow up (n=4)**	
	Exp (n=16)	**Con (n=18)**	**Exp (n=3)**	**Con (n=1)**
age (years), mean (SD)	33.1 (8.1)	31.9 (11.8)	29.7 (8.1)	20.0 (0)
female, n (%)	8 (50)	13 (72.2)	2 (66.7)	0 (0)
height (cm), mean (SD)	172.5 (8.5)	168.7 (5.2)	172.5 (1.8)	166.0 (0)
weight (Kg), mean (SD)	75.5 (16.1)	71.5 (17.7)	72.7 (19.8)	53.0 (0)
BMI ($Kg.m^{-2}$), mean (SD)	26.8 (5.2)	25.1 (5.9)	24.3 (6.2)	19.2 (0)
other ankle sprained, n (%)	13 (81.3)	16 (88.9)	3 (75)	1 (0)
hypermobile, n (%)	3 (18.8)	6 (33.3)	2 (50)	1 (0)
CAIT score (affected) (SD)	8.1 (3.5)	8.8 (5.1)	9 (6.1)	7 (0)
CAIT score (other) (SD)	19.6 (7.8)	15.3 (5.8)	27.0 (5.2)	18.0 (0)
FAAM score (ADL) (SD)	72.9 (8.7)	73.7 (15.6)	74.3 (10.3)	62.0 (0)
FAAM score (sports) (SD)	54.5 (12.7)	54.8 (15.8)	66.7 (8.0)	56.0 (0)

ADL, activities of daily living; BMI, body mass index; CAIT, Cumberland ankle instability tool; Con, control group (placebo, detuned laser); Exp, experimental group (MWM with taping); FAAM, foot and ankle ability measure

7.3.2 Compliance with trial method

The 13 participants who were randomized into the experimental group (MWM) each received an average of 6 (1.5 SD) sessions, consisting of an average of 4 (0.5 SD) sets of eight repetitions. The 17 participants in the placebo (detuned laser) group underwent an average of 5 (1.9 SD) sessions per participant. Both groups received the intervention for approximately the same duration (six minutes). No adverse effects were reported. The same physiotherapist was responsible for all intervention sessions for both groups.

During the 12 week follow-up, eight new ankle injuries (MWM, n=5; laser, n=3) and eight other leg injuries (MWM, n=6; laser, n=2) were reported. Compared to the levels reported during the intervention period, 14 participants (MWM, n=5; laser, n=7) increased their activity levels and eight (MWM, n=6; laser, n=2) decreased their activity levels. Eleven participants (MWM, n=3; laser, n=8) underwent other treatments for their ankle (massage therapy, n=2; non-steroidal anti-inflammatory medication, n=5; orthostatic support, n=1); physiotherapy, n=2; surgery, n=1).

7.3.3 Effect of 'Mulligan's MWM with fibular repositioning taping' intervention

No differences were found between groups in all variables at baseline, except for higher weight-bearing DFROM of the ankle in the placebo group (p=0.01, MD=-2.7cm, 95% CI=-4.6 to -0.8). In the group-by-time interaction, no significant difference was found in any of the outcomes (Table 7.2).

7.3.4 Effect on fibular position in individuals with CAI

No significant changes between the two groups were identified in fibular position or normalised fibular position following completion of the intervention (p=0.61, effect size=0.01; p=0.81, effect size=<0.01, respectively). No significant interaction effect and no significant effect for time was detected (Table 7.2). No difference was found in the relative change of fibular position between or within groups at any of the time points (Table 7.3).

7.3.5 Effect on common clinical measures in individuals with CAI

In the comparison between the two interventions, significant improvements were observed in the FAOS pain (p=0.02, effect size=0.18) and sports (p< 0.01, effect size=0.23) subscales in the placebo group (Table 7.2). Significant improvements were reported across time in the placebo group; for pain intensity (p=0.03, effect size=0.23), SEBT normalised postero-medial reach distance (p< 0.01, effect size=0.33), FAAM sports subscale (p=0.02, effect size=0.24), FAOS sports subscale (p=0.03, effect size=0.22), FAOS quality of life (QOL) subscale (p=0.03, effect size=0.22), antero-posterior sway velocity of postero-lateral excursion (p=0.03, effect size=0.24) and medio-lateral sway velocity of eyes close balance (p=0.03, effect size=0.23) (Table 7.2). In the group-by-time interaction, no significant difference was found in any of the outcomes (Table 7.2).

In the comparison between the two groups, a significant increase of the relative change of the antero-posterior sway velocity of anterior excursion of the SEBT was observed in the placebo group immediately after application (MD=-28.5; 95CI% 53.6 to -3.4). No difference was found in the relative change of any of the outcomes after immediate measurement (immediately post-intervention minus pre-intervention) in either of the groups. Twelve weeks after application, the

MWM group demonstrated improvement in relative change of scores of the FAOS pain and ADL subscales, as well as the medio-lateral sway velocity of anterior excursion and antero-posterior sway velocity of postero-medial excursion of the SEBT across time. The placebo group demonstrated improvements in the FAAM sports subscale and eyes close balance, both antero-posterior sway velocity and antero-posterior sway area per second (Table 7.3).

7.3.6 Effect on subgroups

None of the primary outcome measures were found to be significantly different between the subgroups with a displaced fibula (n=8) and non-displaced fibula (n=8) (Table 7.4), or between the subgroups with a mechanically unstable ankle (n=8) and mechanically stable ankle (n=8) (Table 7.5).

Table 7.2 Effect of MWM with taping on outcomes in individuals with CAI. The results of the general linear model repeated measures are presented as the mean (SD) of groups, mean (SD) difference within groups, and mean (95% CI) difference between groups (n, MWM=13; placebo=17)

Variable	**Descriptive statistics (mean, SD)**						**Interaction effect** (p value, effect size)	**Main effects** (p value, effect size)	**Between-subject effect** (p value, effect size)
	Pre-intervention		**Immediately post-intervention**		**12 week follow-up**				
	Exp	**Con**	**Exp**	**Con**	**Exp**	**Con**			
fibular position (mean, SD) cm	11.5 (3.0)	10.6 (4.6)	11.9 (3.4)	11.3 (5.3)	N/A	N/A	0.83 (< 0.01)	0.37 (0.03)	0.61 (0.01)
normalised fibular position (mean, SD) %	26.2 (5.7)	25.3 (9.2)	27.2 (6.9)	26.7 (10.1)	N/A	N/A	0.82 (< 0.01)	0.34 (0.03)	0.81 (< 0.01)
weight-bearing DFROM (mean, SD) cm	7.1 (3.3)	9.7 (2.0)	8.3 (3.3)	9.8 (2.4)	8.3 (2.9)	9.5 (2.5)	0.37 (0.07)	0.31 (0.08)	0.05 (0.13)
pain intensity (mean, SD)	27.1 (19.9)	31.4 (28.4)	18.8 (14.3)	15.9 (15.0)	12.9 (11.1)	17.8 (19.6)	0.10 (0.16)	0.03* (0.23)	0.70 (< 0.01)
PPT (mean, SD) kPa									

over Anterior Tibialis	20.7 (10.4)	17.9 (6.5)	22.2 (14.5)	18.4 (9.8)	21.4 (11.3)	21.0 (12.9)	0.50 (0.05)	0.60 (0.04)	0.52 (0.02)
over medial ligament	25.7 (8.6)	19.7 (9.9)	25.1 (12.5)	19.9 (8.6)	23.0 (10.7)	18.2 (10.7)	0.93 (0.01)	0.25 (0.10)	0.11 (0.09)
over lateral ligament	22.6 (8.7)	15.2 (5.5)	23.8 (13.1)	18.3 (7.9)	22.0 (10.0)	19.0 (9.6)	0.26 (0.10)	0.44 (0.06)	0.09 (0.10)
Non normalised dynamic balance (mean, SD) cm									
SEBT Anterior	55.1 (8.3)	50.6 (5.8)	55.4 (8.2)	53.5 (6.7)	55.1 (7.1)	53.4 (6.7)	0.15 (0.13)	0.08 (0.17)	0.27 (0.04)
SEBT Post-lateral	74.2 (10.6)	68.1 (9.1)	77.0 (11.7)	72.4 (9.4)	75.9 (11.6)	71.6 (8.8)	0.79 (0.02)	0.05 (0.2)	0.15 (0.07)
SEBT Post-medial	58.4 (15.5)	49.0 (11.8)	62.2 (16.7)	59.5 (11.0)	64.6 (18.6)	59.1 (13.7)	0.32 (0.08)	<0.01* (0.34)	0.21 (0.06)
Normalised dynamic balance (mean, SD) %									
SEBT Anterior	62.0 (8.5)	59.1 (6.2)	62.4 (8.1)	62.4 (7.7)	62.2 (8.6)	62.3 (7.0)	0.15 (0.13)	0.08 (0.17)	0.71 (<0.01)

SEBT Post-lateral	83.5 (10.0)	79.6 (11.1)	86.8 (12.9)	84.1 (11.1)	85.7 (13.4)	83.6 (9.8)	0.85 (0.01)	0.05 (0.19)	0.46 (0.02)
SEBT Post-medial	65.5 (15.5)	58.8 (13.6)	70.0 (18.1)	69.8 (14.1)	72.9 (20.9)	69.6 (14.6)	0.40 (0.67)	<0.01* (0.33)	0.51 (0.02)
FAAM score (mean, SD)									
ADL	72.6 (8.7)	74.4 (15.8)	74.8 (13.0)	80.8 (12.5)	75.6 (11.7)	80.5 (14.1)	0.80 (0.02)	0.36 (0.07)	0.26 (0.05)
sports	51.7 (12.0)	54.3 (16.3)	54.7 (18.8)	60.0 (17.4)	59.2 (18.8)	68.1 (18.8)	0.69 (0.03)	0.02* (0.24)	0.24 (0.05)
FAOS score (mean, SD)									
symptoms	58.5 (12.3)	63.9 (19.0)	59.6 (17.6)	71.0 (13.9)	58.8 (17.5)	70.1 (19.8)	0.66 (0.03)	0.46 (0.06)	0.07 (0.11)
pain	67.7 (13.9)	72.5 (13.8)	65.0 (11.9)	77.8 (11.5)	70.8 (11.3)	78.8 (15.7)	0.26 (0.10)	0.16 (0.13)	0.02* (0.18)
sports	50.4 (14.9)	59.1 (16.1)	55.4 (16.3)	69.1 (15.7)	60.4 (15.2)	73.2 (20.2)	0.85 (0.01)	0.03* (0.22)	<0.01* (0.23)

ADL	77.2 (14.1)	80.6 (15.6)	76.9 (10.9)	85.5 (11.1)	82.0 (10.3)	84.9 (14.3)	0.17 (0.12)	0.20 (0.11)	0.16 (0.07)
QOL	39.9 (16.6)	41.9 (15.1)	45.7 (18.0)	55.5 (18.2)	46.2 (22.0)	60.3 (22.3)	0.43 (0.06)	0.03* (0.22)	0.11 (0.09)
CoP measures during SEBT									
anterior reach excursion-sway velocity AP (mm/s)	76.7 (16.1)	72.8 (15.9)	74.9 (23.8)	99.7 (45.7)	81.6 (23.8)	79.5 (25.9)	0.09 (0.16)	0.11 (0.15)	0.40 (0.03)
anterior reach excursion-sway velocity ML (mm/s)	50.6 (14.7)	57.3 (19.5)	44.2 (12.0)	57.4 (24.5)	53.2 (15.0)	51.6 (15.9)	0.21 (0.11)	0.72 (0.02)	0.20 (0.006)
postero-lateral reach excursion-sway velocity AP (mm/s)	65.8 (17.4)	69.1 (19.9)	68.0 (19.9)	86.6 (31.3)	81.5 (31.4)	84.2 (36.2)	0.23 (0.10)	0.03* (0.24)	0.30 (0.04)
postero-lateral reach excursion-sway velocity ML (mm/s)	60.1 (26.1)	49.7 (14.7)	56.6 (21.6)	59.1 (41.5)	77.2 (48.5)	60.0 (44.1)	0.46 (0.06)	0.31 (0.08)	0.37 (0.03)
postero-medial reach excursion-sway velocity AP (mm/s)	77.0 (30.5)	72.0 (19.5)	72.8 (17.7)	72.9 (24.3)	79.8 (15.9)	79.0 (27.0)	0.89 (0.01)	0.20 (0.11)	0.80 (<0.01)
postero-medial reach excursion-sway velocity ML (mm/s)	58.7 (18.4)	55.3 (19.8)	52.7 (15.9)	61.0 (28.1)	52.8 (14.0)	62.1 (23.6)	0.35	1.00	0.31

							(0.08)	(<0.01)	(0.40)
CoP measures during static balance tests									
eyes open- sway velocity AP (mm/s)	33.5 (12.7)	34.8 (10.1)	27.4 (6.6)	30.6 (13.6)	28.6 (6.1)	33.7 (11.8)	0.52 (0.05)	0.13 (0.14)	0.32 (0.04)
eyes open-sway velocity ML (mm/s)	33.8 (8.8)	38.5 (9.5)	29.5 (6.3)	33.9 (13.9)	30.3 (6.3)	35.8 (11.8)	0.93 (<0.01)	0.19 (0.12)	0.11 (0.09)
eyes open-sway area AP (mm/s)	7.5 (3.2)	7.3 (2.7)	18.0 (43.6)	6.3 (2.3)	6.5 (1.3)	6.9 (2.8)	0.52 (0.05)	0.34 (0.08)	0.29 (0.04)
eyes open-sway area ML (mm/s)	7.7 (4.2)	9.6 (13.7)	5.6 (1.2)	5.4 (1.4)	5.8 (1.9)	5.9 (2.1)	0.85 (0.01)	0.26 (0.10)	0.65 (0.01)
eyes close-sway velocity AP (mm/s)	63.7 (10.7)	77.8 (33.9)	60.6 (5.6)	65.0 (19.9)	61.0 (12.8)	70.0 (32.5)	0.39 (0.07)	0.10 (0.16)	0.23 (0.05)
eyes close-sway velocity ML (mm/s)	72.7 (25.9)	83.9 (37.6)	63.1 (18.6)	69.2 (24.3)	64.6 (16.0)	96.1 (51.1)	0.12 (0.15)	0.03* (0.23)	0.12 (0.09)
eyes close-sway area AP (mm/s)	14.1 (5.4)	14.7 (4.9)	82.2 (250.9)	12.8 (4.4)	12.8 (3.5)	16.7 (7.6)	0.26 (0.09)	0.56 (0.04)	0.29 (0.04)

eyes close-sway area ML (mm/s)	12.4 (4.4)	38.6 (110.0)	11.4 (2.9)	11.5 (3.1)	9.9 (2.0)	11.6 (5.0)	0.45 (0.06)	0.51 (0.05)	0.37 (0.03)

ADL, activities of daily living; AP, antero-posterior; CAI, chronic ankle instability; Con, control group (placebo, detuned laser); CoP, centre of pressure; Exp, experimental group (MWM, mobilisation with movement); FAAM, foot and ankle ability measure; FAOS, foot and ankle outcome score; ML, medio-lateral; N/A, not applicable; PPT, pressure pain threshold; QOL, quality of life; SEBT, star excursion balance test; weight-bearing DFROM, weight-bearing dorsiflexion range of motion

*significantly different, $p < 0.05$

Table 7.3 Effect of MWM with taping on the changes in outcomes at each time point in individuals with CAI.

Data are presented as mean (SD) of groups, mean (SD) difference within groups, and mean (95% CI) difference between groups

Outcome	**Groups**						**Difference within groups (paired t test)**				**Difference between groups (independent-t test)**	
	Pre-intervention		**Immediately post-intervention**		**12 week follow-up**		**Immediately post-intervention-Pre-intervention**		**12 week follow-up-Pre-intervention**		**Immediately post-intervention-Pre-intervention**	**12 week follow-up-Pre intervention**
	Exp (n=16)	**Con (n=18)**	**Exp (n=13)**	**Con (n=17)**	**Exp (n=13)**	**Con (n=16)**	**Exp (n=13)**	**Con (n=17)**	**Exp (n=13)**	**Con (n=17)**	**Exp minus Con**	**Exp minus Con**
fibular position (cm)	11.3 (3.1)	10.4 (4.5)	11.9 (3.4)	11.3 (5.3)	N/A	N/A	0.4 (3.5)	0.7 (2.8)	N/A	N/A	-0.3 (-2.6 to 2.1)	N/A
normalised fibular position (%)	25.6 (5.9)	25.0 (9.1)	27.2 (6.9)	26.7 (10.1)	N/A	N/A	0.9 (7.4)	1.5 (5.8)	N/A	N/A	-0.5 (-5.5 to 4.4)	N/A
weight-bearing DFROM (cm)	7.2 (3.2)	9.8 (2.1)	8.3 (3.3)	9.8 (2.4)	8.3 (2.9)	9.5 (2.5)	0.8[m] (2.4)	-0.4[p] (3.0)	0.7[m] (1.9)	0.4[p] (1.3)	1.7 (-0.5 to 3.9)	0.2[m,p] (-1.0 to 1.5)

pain intensity	23.4 (19.6)	32.0 (27.7)	18.8 (14.3)	15.9 (15.0)	12.9 (11.1)	17.8 (19.6)	-8.2 (18.5)	-14.2 (21.6)	15.5 (25.2)	-13.5 (29.4)	7.2 (-9.1 to 23.6)	-0.6 (-20.5 to 19.2)
PPT (kPa)												
over tibialis anterior	20.7 (10.4)	18.0 (6.5)	22.2 (14.5)	18.4 (9.8)	21.4 (11.3)	21.0 (12.9)	1.5 (8.3)	0.4 (9.2)	0.7 (5.9)	3.0 (11.7)	1.1 (-5.6 to 7.7)	-2.3 (-9.6 to 4.9)
over medial ligament	25.7 (8.6)	19.7 (9.9)	25.1 (12.5)	19.9 (8.6)	23.0 (10.7)	18.2 (10.7)	-0.6 (9.4)	0.2 (6.8)	-2.7 (7.7)	-1.4 (9.2)	-0.9 (-6.9 to 5.2)	-1.2 (-7.7 to 5.3)
over lateral ligament	20.8 (9.8)	15.4 (5.4)	23.8 (13.1)	18.3 (7.9)	22.0 (10.0)	19.0 (9.6)	1.2 (11.5)	3.1 (6.4)	-0.5 (6.7)	3.8 (8.5)	-1.9 (-8.7 to 4.9)	-4.3 (-10.2 to 1.6)
non-normalised SEBT (cm)												
anterior	54.8 (7.6)	51.2 (6.1)	55.4 (8.2)	53.5 (6.7)	55.1 (7.1)	53.4 (6.7)	0.3 (3.4)	2.8 (4.2)	0.0 (5.5)	2.8 (5.3)	-2.5 (-5.4 to 0.4)	-2.8 (-6.8 to 1.3)
postero-lateral	73.6 (9.8)	68.8 (9.4)	77.0 (11.7)	72.4 (9.4)	75.9 (11.6)	71.6 (8.8)	2.8 (7.3)	4.3 (7.4)	1.7 (7.3)	3.5 (7.4)	-1.5 (-7.1 to 4.0)	-1.8 (-7.4 to 3.7)
postero-medial	58.1 (15.5)	50.1 (12.4)	62.2 (16.7)	59.5 (11.0)	64.6 (18.6)	59.1 (13.7)	3.8 (11.4)	10.5 (11.6)	6.2 (11.0)	10.1 (15.4)	-6.7 (-15.4 to 2.0)	-3.8 (-14.1 to 6.5)

normalised SEBT (%)												
anterior	62.2 (7.8)	59.8 (6.8)	62.4 (8.1)	62.4 (7.7)	62.2 (8.6)	62.3 (7.0)	0.3 (4.0)	3.3 (4.9)	0.2 (6.2)	3.2 (6.4)	-3.0 (-6.4 to 0.4)	-3.0 (-7.8 to 1.8)
postero-lateral	83.4 (9.3)	80.6 (11.5)	86.8 (12.9)	84.1 (11.1)	85.7 (13.4)	83.6 (9.8)	3.3 (8.3)	4.5 (8.2)	2.1 (8.3)	4.0 (8.6)	-1.2 (-7.4 to 5.0)	-1.9 (-8.3 to 4.6)
postero-medial	65.7 (14.2)	60.1 (14.3)	70.0 (18.1)	69.8 (14.1)	72.9 (20.9)	69.6 (14.6)	4.7 (12.5)	10.9 (12.6)	7.4 (13.0)	10.8 (17.3)	-6.5 (-15.9 to 3.0)	-3.4 (-15.2 to 8.4)
FAAM score												
ADL	72.9 (8.7)	73.7 (15.6)	74.8 (13.0)	80.8 (12.5)	75.6 (11.7)	80.5 (14.1)	2.2 (8.4)	6.4 (21.4)	3.0 (10.2)	6.1 (20.5)	-4.2 (-17.1 to 8.7)	-3.1 (-15.8 to 9.6)
sports	51.7 (12.0)	54.3(16. 3)	54.7 (18.8)	60.0 (17.4)	59.2 (18.8)	68.1 (18.8)	3.0 (16.6)	5.7 (24.7)	7.5 (18.3)	13.8* (27.2)	-2.7 (-19.0 to 13.6)	-6.3 (23.4 to 10.7)
FAOS score												
symptoms	58.5 (12.3)	64.3 (18.5)	59.6 (17.6)	71.0 (13.9)	58.8 (17.5)	70.1 (19.8)	1.1 (14.8)	7.1 (19.3)	0.3 (13.2)	6.3 (26.0)	-6.0 (-19.2 to 7.2)	-6.1 (-21.0 to 8.9)

pain	69.8 (13.7)	73.0 (13.6)	65.0 (11.9)	77.8 (11.5)	70.8 (11.3)	78.8 (15.7)	-2.8 (14.8)	5.3 (20.2)	3.1* (13.1)	6.2 (22.9)	-8.0 (-21.7 to 5.6)	-3.1 (-16.8 to 10.5)
sports	50.4 (14.9)	59.1 (16.1)	55.4 (16.3)	69.1 (15.7)	60.4 (15.2)	73.2 (20.2)	(5.0) (21.7)	10.1 (25.5)	10.0 (16.8)	14.2 (27.7)	-5.0 (-23.1 to 13.0)	-4.2 (-22.0 to 13.7)
ADL	78.1 (13.5)	81.0 (15.2)	76.9 (10.9)	85.5 (11.1)	82.0 (10.3)	84.9 (14.3)	-0.2 (14.1)	4.8 (21.0)	4.8* (9.9)	4.3 (23.0)	-5.0 (-18.9 to 8.8)	0.5 (-12.3 to 13.4)
QOL	40.3 (15.1)	43.4 (16.0)	45.7 (18.0)	55.5 (18.2)	46.2 (22.0)	60.3 (22.3)	5.7 (16.8)	13.6 (23.9)	6.3 (18.0)	18.4 (28.7)	-7.9 (-23.8 to 7.4)	-12.1 (-30.8 to 6.5)
CoP measures during SEBT												
anterior reach excursion												
sway velocity AP (mm/s)	75.0 (15.0)	73.5 (15.7)	75.0 (23.8)	100.0 (45.7)	81.6 (23.8)	79.5 (25.9)	-1.7 (25.4)	26.8 (38.0)	5.0 (28.7)	6.7 (26.5)	-28.5* (-53.6 to -3.4)	-1.7 (-22.3 to 9.2)
sway velocity ML (mm/s)	50.3 (14.6)	55.4 (20.6)	44.2 (12.0)	57.4 (24.5)	53.2 (15.0)	51.6 (15.9)	-6.4 (21.7)	0.2 (19.4)	2.6* (21.7)	-5.7 (20.1)	-6.6 (-22.0 to 8.9)	8.3 (-9.0 to 25.6)
postero-lateral excursion												

sway velocity AP (mm/s)	62.5 (17.3)	68.8 (19.4)	68.0 (14.3)	86.6 (31.3)	81.5 (31.4)	84.2 (36.2)	2.2 (20.0)	17.5 (27.5)	15.7 (29.8)	15.1 (34.0)	-15.3 (-33.8 to 3.2)	0.7 (-23.7 to 25.0)
sway velocity ML (mm/s)	56.9 (24.6)	49.9 (14.3)	56.6 (21.6)	59.1 (41.5)	77.2 (48.5)	60.0 (44.1)	-3.5 (23.6)	9.4 (40.8)	17.1 (47.4)	10.3 (45.7)	-13.0 (-39.0 to 13.1)	6.8 (-28.2 to 41.9)
postero-medial excursion												
sway velocity AP (mm/s)	79.8 (29.3)	71.2 (19.2)	72.8 (17.7)	72.9 (24.3)	79.8 (15.9)	79.0 (27.0)	-3.8 (28.4)	1.0 (20.6)	3.2* (31.2)	7.1 (30.7)	-4.7 (-23.1 to 25.0)	-3.9 (-27.3 to 19.5)
sway velocity ML (mm/s)	61.6 (19.5)	54.8 (19.3)	52.7 (15.9)	61.0 (28.1)	52.8 (14.0)	62.1 (23.6)	-5.9 (21.6)	5.7 (27.5)	-5.8 (17.5)	6.8 (36.3)	-11.7 (-30.6 to 7.3)	-12.6 (-33.3 to 8.1)
CoP measures during static balance tests												
eyes open												
sway velocity AP (mm/s)	31.3 (12.5)	34.0 (10.3)	27.4 (6.6)	30.6 (13.6)	28.6 (6.1)	33.7 (11.85)	-6.1 (10.4)	-4.2 (15.6)	-4.9 (8.0)	-1.0 (10.5)	-2.0 (-12.3 to 8.3)	-3.9 (-11.1 to 3.3)
sway velocity ML (mm/s)	32.5 (8.5)	37.5 (10.2)	29.5 (6.3)	33.9 (13.9)	30.3 (6.3)	35.8 (11.8)	-4.3 (10.3)	-4.6 (14.7)	-3.5 (8.7)	-2.8 (10.6)	0.3 (-9.5 to 10.1)	-0.7 (-8.2 to 6.7)

sway area per second AP (mm/s)	7.2 (2.9)	7.1 (2.7)	18.0 (43.6)	6.3 (2.3)	6.5 (1.3)	6.9 (2.8)	-1.5[m] (3.7)	-0.9 (2.7)	-0.8[m] (3.1)	-0.4 (3.1)	-0.5 (-3.1 to 2.0)[m]	-0.6 (-2.9 to 1.8)
sway area per second ML (mm/s)	7.2 (4.0)	9.4 (13.3)	5.6 (1.2)	5.4 (1.4)	5.8 (2.1)	5.9 (2.1)	-2.1 (4.6)	-0.9[p] (2.7)	-1.9 (4.0)	-0.4[p] (3.1)	-1.2 (-4.0 to 1.6)[p]	-1.5 (-4.2 to 3.4)[p]
eyes close												
sway velocity AP (mm/s)	66.8 (226.5)	81.1 (38.2)	63.1 (18.6)	69.2 (24.3)	64.6 (16.0)	96.1 (51.1)	-9.6 (23.2)	-14.7 (30.4)	-8.1 (22.7)	12.2* (38.8)	5.1 (-12.3 to 8.3)	-20.3 (-43.5 to 3.0)
sway velocity ML (mm/s)	60.4 (12.2)	75.7 (34.0)	60.6 (5.6)	65.0 (19.9)	61.0 (12.8)	70.0 (32.5)	-3.2 (11.2)	-12.8 (24.0)	-2.7 (18.9)	-7.9 (26.5)	9.6 (-4.0 to 23.2)	5.1 (-12.6 to 22.9)
sway area per second AP (mm/s)	13.4 (5.7)	14.5 (4.9)	82.2 (12.8)	12.8 (4.4)	12.8 (3.5)	16.7 (7.6)	-1.6[m] (6.9)	-1.9 (5.9)	-1.4[m] (7.5)	-0.4* (4.6)	0.3 (-4.6 to 5.2)[m]	-3.3 (-9.0 to 2.4)
sway area per second ML (mm/s)	11.8 (4.4)	36.8 (106.9)	11.4 (2.9)	11.5 (3.1)	9.9 (2.0)	11.6 (5.0)	-1.0 (5.6)	-0.4[p] (4.6)	-2.5 (4.3)	-0.2[p] (6.1)	-0.6 (-4.5 to 3.2)[p]	-2.3 (-6.4 to 1.8)[p]

ADL, activities of daily living; AP, antero-posterior; CAI, chronic ankle instability; Con, control group (placebo, detuned laser); CoP, centre of pressure; Exp, experimental group (MWM with taping); FAAM, foot and ankle ability measure; FAOS, foot and ankle outcome score; ML, medio-lateral; N/A, not applicable; PPT, pressure pain threshold; QOL, quality of life; SEBT, star excursion balance test; weight-bearing DFROM, weight-bearing dorsiflexion range of motion

*significantly different, $p < 0.05$; [m] extreme outlier was identified in MWM group and removed (n=1); [p] extreme outlier was identified in placebo laser group and removed (n=1)

Table 7.4 Effects of MWM with taping on individuals with a displaced fibula (i.e. normalised fibular position ≥ 27), compared to individuals with a normally positioned fibular on the changes of primary outcomes at each time point

Outcome	**Groups (mean, SD)**						**Difference between groups (Mann - Whitney t test)**	
	Pre-intervention		**Immediately post-intervention**		**12 week follow-up**		**Immediately post-intervention-Pre-intervention (p value)**	**12 week follow-up-Pre-intervention (p value)**
	Displaced fibula (n=8)	**Non-displaced fibula (n=8)**	**Displaced fibula (n=7)**	**Non-displaced fibula (n=6)**	**Displaced fibula (n=7)**	**Non-displaced fibula (n=6)**		
fibular position (mm)	13.8 (1.8)	8.8 (1.9)	12.5 (3.9)	11.2 (3.0)	N/A	N/A	0.10	N/A
normalised fibular position (%)	30.9 (2.0)	20.3 (2.6)	28.4 (7.5)	25.8 (6.6)	N/A	N/A	0.10	N/A
FAAM score ADL								
	72.4 (8.7)	73.5 (9.2)	73.3 (13.3)	76.7 (13.5)	73.4 (12.0)	78.2 (11.8)	1.00	0.63

sports	52.8 (16.7)	56.3 (7.5)	50.6 (22.4)	59.5 (13.9)	53.6 (18.1)	65.7 (18.9)	0.95	0.63
FAOS score								
symptoms	57.6 (12.9)	57.6 (12.7)	58.1 (20.9)	61.3 (14.5)	57.7 (21.4)	60.1 (13.4)	0.63	0.63
pain	68.7 (13.7)	70.8 (14.5)	65.5 (10.2)	64.4 (14.7)	71.0 (12.7)	70.6 (10.7)	0.73	0.45
sports	50.6 (18.0)	52.5 (12.5)	58.6 (15.7)	51.7 (17.5)	53.6 (16.5)	68.3 (9.3)	0.37	0.45
ADL	76.3 (10.3)	80.0 (16.6)	78.8 (10.9)	74.8 (11.4)	80.0 (11.1)	84.3 (9.8)	0.84	0.45
QOL	34.4 (18.3)	46.1 (8.8)	42.8 (20.6)	49.0 (15.5)	37.5 (19.1)	56.3 (22.3)	0.73	0.95

ADL, activities of daily living; FAAM, foot and ankle ability measure; FAOS, foot and ankle outcome score; MWM, mobilisation with movement; N/A, not applicable; QOL, quality of life

Table 7.5 Effects of MWM with taping on individuals with a mechanically unstable ankle (i.e. positive anterior drawer stress test) compared to individuals with a mechanically stable ankle on the changes of primary outcomes at each time point

Outcome	**Groups (mean, SD)**						**Difference between groups (Mann - Whitney t test)**	
	Pre-intervention		**Immediately post-intervention**		**12 week follow-up**		**Immediately post-intervention-Pre-intervention (p value)**	**12 week follow-up-Pre-intervention (p value)**
	Mechanically unstable (n=8)	**Mechanically stable (n=8)**	**Mechanically unstable (n=6)**	**Mechanically stable (n=7)**	**Mechanically unstable (n=6)**	**Mechanically stable (n=7)**		
fibular position (mm)	8.7 (1.7)	13.9* (1.7)	10.2 (2.3)	13.4 (3.7)	N/A	N/A	0.45	N/A
normalised fibular position (%)	20.7 (3.2)	30.6* (2.7)	24.2 (6.5)	29.7 (6.7)	N/A	N/A	0.45	N/A
FAAM ADL	74.4 (9.6)	71.5 (8.0)	73.5 (12.8)	76.0 (14.0)	77.0 (11.0)	74.4 (12.9)	0.14	0.95
sports	59.0	50.0	57.5	52.3	64.7	54.4	0.45	0.95

	(6.3)	(16.0)	(12.0)	(23.9)	(18.1)	(19.4)		
FAOS symptoms	59.4 (12.5)	55.8 (12.8)	62.5 (14.1)	57.1 (20.9)	63.1 (14.1)	55.1 (20.0)	1.00	0.45
pain	74.0 (14.8)	65.6 (11.9)	61.1 (13.2)	68.3 (10.6)	71.5 (11.6)	70.2 (12.0)	0.30	1.00
sports	55.6 (13.5)	47.5 (16.3)	50.8 (16.9)	59.3 (15.9)	66.7 (8.8)	55.0 (18.0)	0.07	0.73
ADL	81.1 (16.9)	75.2 (9.3)	73.5 (10.6)	79.8 (11.0)	82.8 (8.9)	81.3 (12.1)	0.37	0.84
QOL	48.5 (8.7)	32.1 (16.2)	47.9 (14.1)	43.7 (21.7)	53. 2 (19.2)	40.2 (23.9)	0.37	0.53

ADL, activities of daily living; FAAM, foot and ankle ability measure; FAOS, foot and ankle outcome score; MWM, mobilisation with movement; N/A, not applicable; QOL, quality of life

*significantly different, $p < 0.05$

7.4 Discussion

This is the first mixed RCT which utilised a pragmatic application of 'Mulligan's MWM with fibular repositioning taping' for participants with CAI. In addition, this is the first mixed RCT to assess the capacity of MWM with taping to reverse a displaced fibular position. This study aimed to evaluate the effectiveness of this common clinical technique on fibular position and functional and other clinical outcomes in individuals with CAI, both immediately and at 12 weeks after treatment. On average, the participants in the MWM group underwent six sessions with four sets of eight repetitions of MWM and taping, over a maximum of four weeks. A recent meta-analysis has shown that six sessions of manual therapy is sufficient to improve functional performance of the ankle in individuals with CAI (Shi et al., 2019). Therefore this dosage of MWM with taping could be considered sufficient to demonstrate any improvement in outcomes resulting from this manual therapy treatment.

The results of the current study indicate that Mulligan's MWM with fibular repositioning taping has no immediate or short-term (12 weeks post intervention) effect on fibular position or clinical outcomes including weight-bearing DFROM, PPT, static and dynamic balance, pain intensity and any sub-scales of the self-reported function questionnaires. Interestingly, scores for subscales of self-reported function (FAOS pain and sports) were immediately improved after application of detuned laser. Further, the antero-posterior sway velocity of anterior excursion of the SEBT was found to be significantly higher in the placebo group immediately after intervention, whilst the MWM group remained unchanged. Postural performance has been suggested to be characterised by the ability to reduce postural sway (Thompson et al., 2017). However, the increased sway velocity observed in the placebo group may simply be explained as a possible Type 1 error. There were no statistically significant effects identified

on any of the other outcomes or change of any outcomes at any of the time points. Without a comparative 'no treatment' control group, it is unknown whether the outcomes for participants in either or both groups were superior to that of natural recovery (Bialosky et al., 2011). Ethical considerations precluded the inclusion of such a group in the study design. Further, it is also possible that MWM may be more or less effective in different stages of recovery following an ankle sprain (e.g., the sub-acute phase) and this may be worthy of future investigation.

Similarly, the subgroup analyses (displaced fibula vs non-displaced fibula; mechanically unstable vs mechanically stable ankle) failed to find any significant effect of MWM on the primary outcomes of fibular position and self-reported function. However, these findings should be considered as preliminary because the sample size was not powered for either subgroup analysis. The lack of any detectable effect of MWM on fibular position could also be due to the sample containing participants with both mechanically stable and unstable ankles, as demonstrated on the anterior drawer stress test (mechanically unstable, n=6; mechanically stable, n=7).

The findings of our study are supported by some previous investigations in which MWM and associated fibular repositioning taping have been assessed separately. In these studies, MWM applied in isolation was found to not demonstrate any significant immediate improvement in weight-bearing DFROM (Gilbreath et al., 2014), dynamic balance (Gilbreath et al., 2014) or self-reported function assessed using the FAAM in participants with CAI (Gilbreath et al., 2014). Taping alone has also not shown any significant immediate improvement in static balance (Alves et al., 2018; Hopper et al.,

2009), dynamic balance (Delahunt, Mcgrath, et al., 2010; Hopper et al., 2009) or dynamic functional tasks (Alves et al., 2018). However in other studies, MWM in isolation improved weight-bearing DFROM (Cruz-Diaz et al., 2015; Marron-Gomez et al., 2015; Reid et al., 2007; Vicenzino et al., 2006) and dynamic balance (Cruz-Diaz et al., 2015) immediately and/or in the short-term, and taping alone was shown to improve dynamic balance (Someeh et al., 2015a) and the performance of dynamic functional tasks (Someeh et al., 2015b). These contrasting results may to some degree be due to the different dosages (ranging from one to four sets of mobilization in one session) of intervention used (Gilbreath et al., 2014) or perhaps due to different control groups in each trial. Further, these findings may be influenced by differences in the baseline participant demographics and clinical characteristics.

Some limitations of our study need to be acknowledged. First, the method may have been strengthened if fibular position and the pain outcome measures had been included as inclusion criteria during recruitment. Similarly, variable duration of injury and ongoing pain or stiffness in participants may have had a potential impact on treatment response, and it is suggested that in future research greater homogeneity of the sample may better replicate clinical practise. Second, the effectiveness of blinding of participants may have been sub-optimal because the placebo intervention notably differed from the experimental treatment. However, the mechanism of fibular displacement with ankle injuries and the mechanical effects of MWM are not clearly understood, so it was not desirable to introduce any external force potentially creating a mechanical change to the ankle/fibula, as might occur with laying on of hands in other placebo or sham manual therapy treatments. Further, 52.9% of the laser group participants perceived that they had received the active intervention (compared with 46.2% of the MWM group participants), suggesting the placebo was effective. Third, the practitioner who applied

the treatment was not a Mulligan Concept Practitioner or Teacher as certified by the Mulligan Concept Teachers Association (Mulligan Concept Teachers Association, 2019). However, it is arguable that for a manual therapy intervention to be widely beneficial to a population with a given condition, it should be demonstrably effective when applied by a post-professionally trained and registered musculoskeletal/manual therapist, and not require significant additional educational certification. Notably, only one prior study stated that it utilized a certified Mulligan Concept Practitioner or Teacher as the treating practitioner (Reid et al., 2007). Further, the current study used a sustained anteroposterior glide of the fibula as the active intervention, and a different MWM technique may have produced different results. Finally, there remained the potential for anatomical rotation in the X-ray imaging, although the same instructions were given to all participants and the leg position was carefully monitored for this. If any leg rotation was observed on imaging, the radiograph was repeated.

In conclusion, individuals with CAI who underwent an average of six sessions of Mulligan's MWM with fibular repositioning taping over a maximum four week period, demonstrated no significant differences in any of the outcomes measured compared to a placebo intervention. Further powered trials with homogenous samples are recommended in order to assess the effectiveness of MWM with taping in specific CAI subgroups. Also, it may be worthwhile exploring fibular position changes in the longer term in future research.

Chapter 8 Discussion and conclusions

This chapter summarises the major overarching findings of the various studies comprising this thesis, and considers their collective clinical and research implications. This thesis includes a systematic review with meta-analysis, a case-control study, and an RCT with a one year follow-up in progress. The systematic review described in Chapter 3 is the first published study to assess the clinical benefits of joint mobilisation as the sole intervention in the management of ankle ligament sprains at all stages of recovery. It included the first meta-analysis undertaken to quantitatively evaluate the clinical benefits of joint mobilisation for ankle sprains. The case-control study assessed displaced fibular position as an anatomical characteristic of CAI (Chapter 4), and also some common clinical characteristics of CAI (Chapter 5). Fibular position was assessed using weight-bearing lateral X-rays, whereas previous studies had only assessed fibular position in non-weight-bearing positions. The weight-bearing position is more functional and easier to apply clinically than the methods used for measuring fibular position in prior research. In the RCT for which the protocol was published (Chapter 6), the effectiveness of an MWM intervention was evaluated in individuals with CAI immediately post-treatment, at 12 weeks, and at 12 months post treatment. This trial has a longer follow-up (one year) than any other study of MWM for CAI published to date. However, within this thesis outcomes data are presented only up to the 12 week follow-up, as described in Chapter 7. Twelve month follow-up data will be analysed when these are fully collected, and the findings will be added to the prepared manuscript (as presented in Chapter 7) before submission to a peer-reviewed journal. Further, this RCT is the first RCT to investigate the effects of MWM on antero-posterior fibular displacement relative to the tibia in CAI.

8.1 Summary of study findings

Chronic ankle instability and recurrent ankle sprains are extremely common in the community, both in Australia and around the world (Hertel, 2002; Hiller et al., 2012; Weerasekara & Hiller, 2017). Therefore, the findings of this series of studies have the potential to be advantageous for many people with this debilitating condition. Eligible participants were randomly recruited from the university population and general community in the Newcastle area of New South Wales, Australia and thus the findings can be generalised to the wider community.

The key findings presented in this thesis include:

From a systematic review and meta-analysis (Chapter 3) of 23 studies of joint mobilisation only for ankle sprains:

1. There are immediate (measured immediately after the intervention) benefits of joint mobilisation for improving dynamic balance in chronic ankle sprains including CAI.
2. There are short-term (measured up to 3 months after the intervention) benefits of joint mobilisation for improving ROM (specifically, weight-bearing DFROM) in chronic ankle sprains including CAI.
3. There are no immediate improvements in static balance, pain intensity, and weight-bearing DFROM following ankle joint mobilisation in chronic ankle sprains including CAI.

4. Other clinical outcomes (proprioception, PPT, pain intensity and quality, function, talar stiffness, postural sway, and patient's confidence toward stability) that have been reported after ankle sprains demonstrate an inconsistent response to joint mobilisation.

5. The combination of Mulligan MWM and associated fibular repositioning taping is more likely to produce a clinical benefit than Maitland joint mobilisation with and without traction, or joint manipulation in individuals with ankle sprains including CAI.

From a case-control study (Chapters 4 and 5) of 33 participants with CAI and 33 matched control participants:

6. A more anteriorly positioned fibula in relation to the tibia was observed in participants with CAI compared with healthy controls in weight-bearing radiographs.

7. Weight-bearing lateral radiographic measurements of fibular position can be performed reliably and reproducibly.

8. The normalised fibular position has very little ability to predict CAI alone.

9. CAI exhibits a multi-faceted nature including pain and impaired weight-bearing DFROM, static balance, dynamic balance, and self-reported function compared to individuals with healthy ankles.

10. The presence of localised peripheral pain (nociceptive mechanism) is associated with persistent pain in CAI, rather than central sensitisation.

11. Weight-bearing DFROM and eyes open medio-lateral sway velocity are most predictive of being in the CAI group.

From an RCT (Chapters 6 and 7) that included 34 participants with CAI:

12. Individuals with CAI, who have undergone an average of six sessions of 'Mulligan's MWM with fibular repositioning taping' demonstrated no significant immediate difference on fibular position compared to a placebo intervention.

13. Individuals with CAI, who have undergone an average of six sessions of 'Mulligan's MWM with fibular repositioning taping' compared to a placebo intervention, reported no significant immediate or short-term differences in any of the outcomes measured (weight-bearing DFROM, static or dynamic balance, pain intensity, PPT or self-reported function).

The studies completed in this thesis therefore answered the following four hypotheses as identified in Chapter 1:

1. Joint mobilisation has multiple clinical benefits for people with CAI.
2. Individuals with CAI are anatomically different with a more anteriorly positioned fibula, compared to individuals with healthy ankles.
3. Individuals with CAI are clinically different, with greater pain intensity and more impaired weight-bearing DFROM, dynamic balance, self-reported function and static balance (single leg

stance eyes open, measured using CoP measures on a force plate), compared to individuals with healthy ankles.

4. There are no immediate or short-term effects of MWM combined with fibular repositioning taping on anatomical or clinical outcomes of individuals with CAI, compared to a placebo intervention.

8.2 Significance of the findings of the thesis

The published systematic review presented in Chapter 3 of the thesis was the first systematic review to assess the clinical benefits of joint mobilisation as the sole intervention in the management of ankle sprains at all stages of recovery. The findings of this study provide compelling evidence to inform clinical practice that joint mobilisation may be effective in improving balance immediately and in increasing weight-bearing DFROM in the short-term in chronic ankle sprains, including CAI.

The case-control study described in this thesis presents the difference in fibular position between individuals with CAI and healthy ankles in a weight-bearing position, and adequately demonstrates the diagnostic utility of this imaging method of fibular position (Chapter 4). This imaging technique may be clinically relevant due to its easier application and more functional nature, and therefore could be of value in the therapeutic identification of CAI. The presence of an anteriorly positioned fibular may be a factor contributing to the persistence of pain, ROM restriction, and other symptoms and signs of CAI. This finding also lends support to Mulligan's hypothesis of a fibular 'positional fault' in chronic ankle sprains (Vicenzino et al., 2011). While the mechanism leading to the observed anterior fibular

positional change in CAI is unclear, it may be associated with mechanical instability in some cases. This case-control study was also the first to explore the involvement of central nervous system sensitisation in persistent pain in individuals with CAI, using PPT measures (Chapter 5). The main finding from this investigation was that there was evidence for the presence of localised peripheral sensitisation (nociceptive pain), with no evidence of central sensitisation (nociplastic pain). This suggests that management of CAI is less likely to require interventions to address psychosocial factors, as opposed to the physical impairments identified. However, future research should assess psychosocial factors (such as fear avoidance behaviour) to further explore this. Overall, this case-control study adds support for the multi-faceted anatomical and biological nature of CAI.

The final component of the thesis was an RCT to explore the effects of MWM with fibular repositioning taping on ankle instability (Chapters 6 and 7). This is the first RCT to investigate the potential of Mulligan's MWM with associate fibular repositioning taping on altering fibular position in CAI. The pragmatic RCT design used in this study utilised a real-world application of MWM with taping for participants with CAI, thus enhancing the generalisability of the findings to clinical practice. The RCT found no significant immediate or short-term (12 weeks) differences after undergoing a course of ‘Mulligan’s MWM with fibular repositioning taping’ in any of the outcomes measured. The heterogeneous nature of the sample, including participants with both mechanical and functional instability, and differing dosages as judged by the treating practitioner may have had an impact on the findings to date. Further, some participants with CAI may have experienced transient changes in fibular position (i.e. temporary alterations in fibular position due to recurrent sprains), and this may have led to intermittent and recurrent symptoms (Gilbreath et al., 2014). Despite these considerations,

and although the long-term findings are yet to be fully collected and analysed, those findings to date presented in Chapter 7 suggest that MWM with taping is unlikely to be any more effective than a placebo intervention in treating CAI. Interestingly, the few significant differences found in this RCT were in favour of the placebo group, suggesting that detuned laser may have a strong placebo effect (Howick et al., 2013). Therefore, it may be considered as a potential placebo for future research in manual therapy. There is currently no consensus on a placebo intervention for manual therapy studies.

8.3 Strengths and limitations of the studies

This thesis is comprised of four studies employing three study designs: i) a systematic review and meta-analysis (Weerasekara et al., 2018), ii) a case-control study, and iii) a RCT (using a pragmatic approach) (Weerasekara, Osmotherly, Snodgrass, et al., 2019b). The strengths and limitations of each study are discussed individually below.

8.3.1 Systematic review

A major strength of the systematic review reported in Chapter 3 was that data were able to be pooled for meta-analysis. This quantitatively summarised the results of all of the included studies and increased the precision of the estimate of the treatment effect of the interventions (Bartolucci & Hillegass, 2010). In addition, joint mobilisation was evaluated as a sole intervention to ensure homogeneity and to increase the precision of the findings on the effects of joint mobilisation.

However, the methodologies used by all studies included in the systematic review were found to be of moderate quality (Weerasekara et al., 2018), which limits the conclusions that can be drawn on the evidence for the effectiveness of joint mobilisation for ankle sprains. Some other limitations of this systematic review should be acknowledged, including the wide variety of follow-up time points that were defined as short-term (from one day up to three months), the wide variety of different mobilisation techniques in the included studies, and the insufficiency of data for quantitative analysis of some outcome measures (Weerasekara et al., 2018).

8.3.2 Case-control study

The case-control study compared individuals with CAI with age and gender matched individuals with healthy ankles. The major strengths of this study were randomisation of the measurements and the careful selection of the study sample according to IAC recommendations on selection criteria for participants with CAI in controlled research (Gribble et al., 2013). All the measurements were obtained in a randomised order within a single data collection session for each participant. The body sites of the measurements were also randomised when it was applicable (e.g. test locations in PPT measures). Further, the use of a force plate helped to assess balance more objectively, and also could precisely quantify the balance measurements.

In terms of limitations, two-thirds of the CAI group had bilateral ankle injuries, and this may have exerted a potential effect in all comparisons carried out within the CAI group. In addition, the study was not designed to perform a subgroup analysis to examine differences (anatomical and clinical)

between participants with mechanical and functional instabilities. Thus, the sample size was not adequately powered for this subgroup analysis and none of the outcomes were able to be compared between these two subgroups using appropriate statistical methods.

8.3.3 Randomised controlled trial

A strength of the RCT presented in this thesis is that a pragmatic approach was used. This utilised a pragmatic RCT design which allowed a routine clinical application of MWM combined with fibular repositioning taping (Alsop et al., 2016). This enhances the external validity and also controls for some threats to internal validity. Real-world application of the MWM, its dosage and the number of treatment visits were judged by the treating practitioner based on individual participant responses, and this enhanced the study's external validity by improving the extent the findings could be generalised to clinical practice. Internal validity of a study is typically threatened by bias (commonly selection bias, performance bias, detection bias, and attrition bias) and random error (Spieth et al., 2016). In this RCT, random allocation of the participants to the groups, concealed allocation, random allocation of the measurements and measurement locations, blinding of both the assessor and the participant, and ITT analysis strengthened the internal validity by controlling for the above sources of bias. Further, MWM combined with fibular repositioning taping was assessed as a unique intervention with no potential confounding effects from adjunct interventions, such as self-mobilisation or other home exercises.

Another strength was that a detuned laser was used as the placebo and has previously been shown to have a strong placebo effect (Reid et al., 2008). Though there was a different physical appearance to

the interventions, using a detuned laser prevents any potential direct mechanical effect to the ankle being treated and also does not activate somatosensory receptors. This avoids an external force potentially creating a therapeutic or deleterious mechanical change to the ankle/fibula, as might occur with the 'laying on of hands' in other placebo or sham manual therapy techniques. Due to the fact that alteration of fibular position in CAI is not well understood, precautions were taken to not introduce any external force which may potentially create a mechanical change to the fibula or ankle by manual handling or placing the participant in a different position, a common potential error in the placebo or control groups used in some other RCTs (Hancock et al., 2006; Pellow & Brantingham, 2001; Reid et al., 2008). This was to some degree controlled by the scheduling of participant appointments in a way that avoided interaction between participants.

As with any RCT in the field of manual therapy, an unavoidable design limitation is that the intervention practitioner could not be blinded, which had the potential to introduce bias if the practitioner has particular beliefs about the intervention. Another limitation was that there might also have been some outcome measures which were underpowered to detect a significant difference between groups, because the sample size was estimated using fibular position and self-reported function. Finally, if we had included some major measures such as fibular position in the inclusion criteria (i.e. by screening all potential participants radiographically), we may have recruited a more homogeneous group. However, this would not have been as generalisable to the clinical setting, as patients presenting for physiotherapy are not usually screened radiologically. Further, in future research the screening of people with CAI for ongoing pain or stiffness might better replicate clinical practise and ensure a more homogeneous sample. Similarly, the sample size was inadequate for

subgroup (mechanical and functional instability) comparisons as this was not a planned inclusion criteria, and any findings regarding subgroups should be considered preliminary in nature.

8.4 Clinical implications of findings

Clinicians may consider applying joint mobilisation when treating patients with chronic ankle sprains, as the meta-analysis from the systematic review revealed that it is immediately (measured immediately after the intervention) beneficial for dynamic balance and for DFROM in the short-term (measured up to three months after the intervention). Evidence for long-term (measured at three or more months after the intervention) benefits of joint mobilisation is lacking in the literature due to a paucity of RCTs assessing the long-term efficacy of joint mobilisation on CAI.

The case-control study presented in this thesis has led to the introduction of a simple and reliable method to assess fibular position in a weight-bearing position in individuals with CAI using plain film radiography. As it is not presently possible to precisely diagnose CAI with a single diagnostic test (Guillo et al., 2013; Rodriguez-Merchan, 2012), careful consideration (in terms of ease of obtaining an accurate X-ray and time spent on obtaining fibular position measures) of an anteriorly displaced fibula evident on weight-bearing lateral X-rays may improve the accurate diagnosis of patients with this condition. In addition, clinicians should consider the multi-faceted nature of CAI (such as balance, function and ROM deficits) when developing rehabilitation programs for individuals with CAI. They should be mindful when assessing dynamic balance with the SEBT in patients with CAI, that it may be impacted by restricted weight-bearing DFROM. It is unknown whether the observed differences in

clinical measures in the case-control study presented in this thesis may differ between subgroups of CAI, therefore each patient with CAI should be individually assessed.

The results of the RCT to date indicate that Mulligan's MWM with fibular repositioning taping is not superior to a placebo treatment in producing any immediate or short-term effect on fibular position or any of the clinical outcomes measured. However, this was based on a sample of participants with different sub-categories of CAI (i.e. this sample is a mix of mechanically unstable, functionally unstable, both mechanically and functionally unstable; fibular displaced and non-displaced ankles). It is possible the effects of MWM with taping in different subgroups may differ.

8.5 Future research

The series of studies described in this thesis raise a number of questions that could be addressed in future research. Identification of CAI subgroups with common clinical characteristics may in the future be linked to treatment outcomes. One or more CAI subgroups may respond better to MWM than others, for example MWM may be able to improve reduced DFROM in individuals with a displaced fibula by reversing the displacement. In this case, the presence of a displaced fibular position may be a common characteristic of mechanical instability. Therefore careful investigation of the use of normalised fibular position combined with other diagnostic tools in diagnosing individuals with this condition, may improve the accuracy of diagnosis of CAI or at least some subgroups of CAI. Further, research using an adequate sample size of individuals with CAI who have a displaced fibula with specific clinical deficits (e.g. reduced DFROM and impaired balance), may reveal differences between

individuals with CAI and healthy ankles not detected in this thesis. Therefore, more research is required to further determine the efficacy of joint mobilisation in the rehabilitation of CAI across its various subgroups. It is also possible that MWM may be more or less effective in different stages of recovery following an ankle sprain (e.g., the sub-acute phase) and could contribute to the prevention or reduction of recurrence of ankle instability, and this may be worthy of future investigation. In addition, researchers may also consider investigating the pros and cons of detuned laser as a placebo intervention in manual therapy studies.

8.6 Conclusions

Chronic ankle instability is a common musculoskeletal disorder that significantly affects the quality of life of affected individuals, and is also responsible for recurrent and persistent disability which potentially causes a substantial financial burden on society. It is an umbrella term which includes several different types of CAI, including mechanically unstable, functionally unstable, and both mechanically and functionally unstable ankles. This thesis on CAI and joint mobilisation including MWM, assesses the anatomical and clinical characteristics of individuals with CAI compared to individuals with healthy ankles, and also examines the efficacy of joint mobilisation in improving the outcomes of CAI. The series of studies presented in this thesis provide evidence that; (1) joint mobilisation provides both immediate and short-term benefits for people with chronic ankle sprains, including CAI; (2) there is an anteriorly positioned fibula in individuals with CAI compared to those with healthy ankles; (3) CAI is a multi-faceted disorder with residual symptoms such as impaired balance, function and ROM; and (4) MWM with fibular repositioning taping may not be helpful in improving a displaced fibula or common clinical outcomes of individuals with CAI. The dissemination

of results from this thesis will lead to benefits for patients suffering from CAI by improving our understanding of the nature of this condition and by providing high level evidence for its effective management using manual therapy.

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Appendices

Appendix 1 Statements of collaboration from co-authors

Statement from Darren A. Rivett relating to papers published with Ishanka Weerasekara

I, Darren A. Rivett, attest that Research Higher Degree candidate, Ishanka Weerasekara contributed to the listed publications by contributing to the conception and design of the studies, conducting and writing up the literature review, the collection of data, undertaking the statistical analysis, description and interpretation of the results, and writing the discussion and conclusions.

1. Weerasekara, I., Osmotherly, P., Snodgrass, S., Marquez, J., de Zoete, R., & Rivett, D. A. (2018). Clinical benefits of joint mobilisation on ankle sprains: a systematic review and meta-analysis. *Archives of physical medicine and rehabilitation, 99*(7), 1395-1412.e1395. doi:https://doi.org/10.1016/j.apmr.2017.07.019

2. Weerasekara, I., Osmotherly, P. G., Snodgrass, S. J., Tessier, J., & Rivett, D. A. (2019). Effects of mobilisation with movement (MWM) on anatomical and clinical characteristics of chronic ankle instability: a randomised controlled trial protocol. *BMC musculoskeletal disorders, 20*(1), 75. doi:10.1186/s12891-019-2447-x

3. Weerasekara, I., Osmotherly, P., Snodgrass, S., Tesseir, J., & Rivett, D. A. (2019). Is the fibula positioned anteriorly in weight-bearing in individuals with chronic ankle instability? (under review).

4. Weerasekara, I., Snodgrass, S., Osmotherly, P., Tessier, J., & Rivett, D. A. (2019). Clinical characteristics of chronic ankle instability: a cross sectional study (under review).

…….. Date: 15 August 2019

Professor Darren A. Rivett

…….. Date: 15 August 2019

Ishanka Weerasekara

…….. Date: 15 August 2019

Dr Lesley MacDonald-Wicks

Assistant Dean Research Training, Faculty of Health and Medicine

Statement from Peter G. Osmotherly relating to papers published with Ishanka Weerasekara

I, Peter G. Osmotherly, attest that Research Higher Degree candidate, Ishanka Weerasekara contributed to the listed publication by contributing to the conception and design of the studies, conducting and writing up the literature review, the collection of data, undertaking the statistical analysis, description and interpretation of the results, and writing the discussion and conclusions.

1. Weerasekara, I., Osmotherly, P., Snodgrass, S., Marquez, J., de Zoete, R., & Rivett, D. A. (2018). Clinical benefits of joint mobilization on ankle sprains: a systematic review and meta-analysis. *Archives of physical medicine and rehabilitation, 99*(7), 1395-1412.e1395. doi:https://doi.org/10.1016/j.apmr.2017.07.019

2. Weerasekara, I., Osmotherly, P. G., Snodgrass, S. J., Tessier, J., & Rivett, D. A. (2019). Effects of mobilisation with movement (MWM) on anatomical and clinical characteristics of chronic ankle instability: a randomised controlled trial protocol. *BMC musculoskeletal disorders, 20*(1), 75. doi:10.1186/s12891-019-2447-x

3. Weerasekara, I., Osmotherly, P., Snodgrass, S., Tesseir, J., & Rivett, D. A. (2019). Is the fibula positioned anteriorly in weight-bearing in individuals with chronic ankle instability? (under review).

4. Weerasekara, I., Snodgrass, S., Osmotherly, P., Tessier, J., & Rivett, D. A. (2019). Clinical characteristics of chronic ankle instability: a cross sectional study (under review).

…….. Date: 14 August 2019

Dr. Peter G. Osmotherly

…….. Date: 15 August 2019

Ishanka Weerasekara

…….. Date: 15 August 2019

Dr Lesley MacDonald-Wicks

Assistant Dean Research Training, Faculty of Health and Medicine

Statement from Suzanne J. Snodgrass relating to papers published with Ishanka Weerasekara

I, Suzanne J. Snodgrass, attest that Research Higher Degree candidate, Ishanka Weerasekara contributed to the listed publication by contributing to the conception and design of the studies, conducting and writing up the literature review, the collection of data, undertaking the statistical analysis, description and interpretation of the results, and writing the discussion and conclusions.

1. Weerasekara, I., Osmotherly, P., Snodgrass, S., Marquez, J., de Zoete, R., & Rivett, D. A. (2018). Clinical benefits of joint mobilization on ankle sprains: a systematic review and meta-analysis. *Archives of physical medicine and rehabilitation, 99*(7), 1395-1412.e1395. doi:https://doi.org/10.1016/j.apmr.2017.07.019

2. Weerasekara, I., Osmotherly, P. G., Snodgrass, S. J., Tessier, J., & Rivett, D. A. (2019). Effects of mobilisation with movement (MWM) on anatomical and clinical characteristics of chronic ankle instability: a randomised controlled trial protocol. *BMC musculoskeletal disorders, 20*(1), 75. doi:10.1186/s12891-019-2447-x

3. Weerasekara, I., Osmotherly, P., Snodgrass, S., Tesseir, J., & Rivett, D. A. (2019). Is the fibula positioned anteriorly in weight-bearing in individuals with chronic ankle instability? (under review).

4. Weerasekara, I., Snodgrass, S., Osmotherly, P., Tessier, J., & Rivett, D. A. (2019). Clinical characteristics of chronic ankle instability: a cross sectional study (under review).

…….. Date: 14 August 2019

A/ Professor Suzanne J. Snodgrass

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Ishanka Weerasekara

…….. Date: 15 August 2019

Dr Lesley MacDonald-Wicks

Assistant Dean Research Training, Faculty of Health and Medicine

Statement from John Tessier relating to papers published with Ishanka Weerasekara

I, John Tessier, attest that Research Higher Degree candidate, Ishanka Weerasekara contributed to the listed publication by contributing to the conception and design of the studies, conducting and writing up the literature review, the collection of data, undertaking the statistical analysis, description and interpretation of the results, and writing the discussion and conclusions.

1. Weerasekara, I., Osmotherly, P. G., Snodgrass, S. J., Tessier, J., & Rivett, D. A. (2019). Effects of mobilisation with movement (MWM) on anatomical and clinical characteristics of chronic ankle instability: a randomised controlled trial protocol. *BMC musculoskeletal disorders, 20*(1), 75. doi:10.1186/s12891-019-2447-x
2. Weerasekara, I., Osmotherly, P., Snodgrass, S., Tesseir, J., & Rivett, D. A. (2019). Is the fibula positioned anteriorly in weight-bearing in individuals with chronic ankle instability? (under review).
3. Weerasekara, I., Snodgrass, S., Osmotherly, P., Tessier, J., & Rivett, D. A. (2019). Clinical characteristics of chronic ankle instability: a cross sectional study (under review).

…….. Date: 14 August 2019

John Tessier

…….. Date: 15 August 2019

Ishanka Weerasekara

…….. Date: 15 August 2019

Dr Lesley MacDonald-Wicks

Assistant Dean Research Training, Faculty of Health and Medicine

Statement from Jodie Marquez relating to a paper published with Ishanka Weerasekara

I, Jodie Marquez, attest that Research Higher Degree candidate, Ishanka Weerasekara contributed to the listed publication by developing the systematic review protocol, conducting and writing up the literature review including interpreting the literature and writing the discussion and conclusions.

1. Weerasekara, I., Osmotherly, P., Snodgrass, S., Marquez, J., de Zoete, R., & Rivett, D. A. (2018). Clinical benefits of joint mobilization on ankle sprains: a systematic review and meta-analysis. *Archives of physical medicine and rehabilitation, 99*(7), 1395-1412.e1395. doi:https://doi.org/10.1016/j.apmr.2017.07.019

…….. Date: 15 August 2019

Dr. Jodie Marquez

…….. Date: 15 August 2019

Ishanka Weerasekara

..... Date: 15 August 2019

Dr Lesley MacDonald-Wicks

Assistant Dean Research Training, Faculty of Health and Medicine

Statement from Rutger de Zoete relating to a paper published with Ishanka Weerasekara

I, Rutger de Zoete, attest that Research Higher Degree candidate, Ishanka Weerasekara contributed to the listed publication by developing the systematic review protocol, conducting and writing up the literature review including interpreting the literature and writing the discussion and conclusions.

1. Weerasekara, I., Osmotherly, P., Snodgrass, S., Marquez, J., de Zoete, R., & Rivett, D. A. (2018). Clinical benefits of joint mobilization on ankle sprains: a systematic review and meta-analysis. *Archives of physical medicine and rehabilitation, 99*(7), 1395-1412.e1395. doi:https://doi.org/10.1016/j.apmr.2017.07.019

.....

Dr. Rutger de Zoete Date: 14 August 2019

..... Date: 15 August 2019

Ishanka Weerasekara

…….. Date: 15 August 2019

Dr Lesley MacDonald-Wicks

Assistant Dean Research Training, Faculty of Health and Medicine

Appendix 2 Human research ethics committee approval: case-control study

HUMAN RESEARCH ETHICS COMMITTEE

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

Notification of Expedited Approval

To Chief Investigator or Project Supervisor:	**Professor Darren Rivett**
Cc Co-investigators / Research Students:	**Doctor Peter Osmotherly** **Mr John Tessier** **Mrs Ishanka Madhurangani Rajapaksha Mudiyanselage** **Associate Professor Suzanne Snodgrass**
Re Protocol:	**Anatomical and clinical characteristics of the ankles of individuals with chronic ankle instability**
Date:	**19-Sep-2017**
Reference No:	**H-2017-0217**
Date of Initial Approval:	**19-Sep-2017**

Thank you for your **Response to Conditional Approval (minor amendments)** submission to the Human Research Ethics Committee (HREC) seeking approval in relation to the above protocol.

Your submission was considered under **Expedited** review by the Ethics Administrator.

I am pleased to advise that the decision on your submission is **Approved** effective **19-Sep-2017**.

In approving this protocol, the Human Research Ethics Committee (HREC) is of the opinion that the project complies with the provisions contained in the National Statement on Ethical Conduct in Human Research, 2007, and the requirements within this University relating to human research.

Approval will remain valid subject to the submission, and satisfactory assessment, of annual progress reports. *If the approval of an External HREC has been "noted" the approval period is as determined by that HREC.*

The full Committee will be asked to ratify this decision at its next scheduled meeting. A formal *Certificate of Approval* will be available upon request. Your approval number is **H-2017-0217**.

If the research requires the use of an Information Statement, ensure this number is inserted at the relevant point in the Complaints paragraph prior to distribution to potential participants You may then proceed with the research.

Conditions of Approval

This approval has been granted subject to you complying with the requirements for *Monitoring of Progress*, *Reporting of Adverse Events*, and *Variations to the Approved Protocol* as detailed below.

PLEASE NOTE:
In the case where the HREC has "noted" the approval of an External HREC, progress reports and reports of adverse events are to be submitted to the External HREC only. In the case of Variations to the approved protocol, or a Renewal of approval, you will apply to the External HREC for approval in the first instance and then Register that approval with the University's HREC.

- ***Monitoring of Progress***

Other than above, the University is obliged to monitor the progress of research projects involving human participants to ensure that they are conducted according to the protocol as approved by the HREC. A progress report is required on an annual basis. Continuation of your HREC approval for this project is conditional upon receipt, and satisfactory assessment, of annual progress reports. You will be advised when a report is due.

- ***Reporting of Adverse Events***

1. It is the responsibility of the person **first named on this Approval Advice** to report adverse events.
2. Adverse events, however minor, must be recorded by the investigator as observed by the investigator or as volunteered by a participant in the research. Full details are to be documented, whether or not the investigator, or his/her deputies, consider the event to be related to the research substance or procedure.
3. Serious or unforeseen adverse events that occur during the research or within six (6) months of completion of the research, must be reported by the person first named on the Approval Advice to the (HREC) by way of the Adverse Event Report form (via RIMS at https://rims.newcastle.edu.au/login.asp) within 72 hours of the occurrence of the event or the investigator receiving advice of the event.
4. Serious adverse events are defined as:
    - Causing death, life threatening or serious disability.
    - Causing or prolonging hospitalisation.
    - Overdoses, cancers, congenital abnormalities, tissue damage, whether or not they are judged to be caused by the investigational agent or procedure.
    - Causing psycho-social and/or financial harm. This covers everything from perceived invasion of privacy, breach of confidentiality, or the diminution of social reputation, to the creation of psychological fears and trauma.
    - Any other event which might affect the continued ethical acceptability of the project.

5. Reports of adverse events must include:
    - Participant's study identification number;
    - date of birth;
    - date of entry into the study;
    - treatment arm (if applicable);
    - date of event;
    - details of event;
    - the investigator's opinion as to whether the event is related to the research procedures; and
    - action taken in response to the event.

6. Adverse events which do not fall within the definition of serious or unexpected, including those reported from other sites involved in the research, are to be reported in detail at the time of the annual progress report to the HREC.

- ***Variations to approved protocol***

If you wish to change, or deviate from, the approved protocol, you will need to submit an *Application for Variation to Approved Human Research* (via RIMS at https://rims.newcastle.edu.au/login.asp). Variations may include, but are not limited to, changes or additions to investigators, study design, study population, number of participants, methods of recruitment, or participant information/consent documentation. **Variations must be approved by the (HREC) before they are implemented** except when Registering an approval of a variation from an external HREC which has been designated the lead HREC, in which case you may proceed as soon as you receive an acknowledgement of your Registration.

Linkage of ethics approval to a new Grant

HREC approvals cannot be assigned to a new grant or award (ie those that were not identified on the application for ethics approval) without confirmation of the approval from the Human Research Ethics Officer on behalf of the HREC.

Best wishes for a successful project.

Associate Professor Helen Warren-Forward
Chair, Human Research Ethics Committee

For communications and enquiries:
Human Research Ethics Administration

Research & Innovation Services
Research Integrity Unit
The University of Newcastle
Callaghan NSW 2308
T +61 2 492 17894
Human-Ethics@newcastle.edu.au

RIMS website - https://RIMS.newcastle.edu.au/login.asp

Linked University of Newcastle administered funding:

Funding body	Funding project title	First named investigator	Grant Ref

Appendix 3 Human research ethics committee approval: randomised controlled trial

HUMAN RESEARCH ETHICS COMMITTEE

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

Notification of Expedited Approval

To Chief Investigator or Project Supervisor:	**Professor Darren Rivett**
Cc Co-investigators / Research Students:	**Doctor Peter Osmotherly** **Associate Professor Suzanne Snodgrass** **Mrs Ishanka Madhurangani Rajapaksha Mudiyanselage** **Mr John Tessier**
Re Protocol:	**The effect of Mobilisation with Movement on Anatomical and Clinical Characteristics of Chronic Ankle Instability (CAI)**
Date:	**01-Feb-2018**
Reference No:	**H-2017-0354**
Date of Initial Approval:	**01-Feb-2018**

Thank you for your **Response to Conditional Approval (minor amendments)** submission to the Human Research Ethics Committee (HREC) seeking approval in relation to the above protocol.

Your submission was considered under **Expedited** review by the Ethics Administrator.

I am pleased to advise that the decision on your submission is **Approved** effective **01-Feb-2018**.

In approving this protocol, the Human Research Ethics Committee (HREC) is of the opinion that the project complies with the provisions contained in the National Statement on Ethical Conduct in Human Research, 2007, and the requirements within this University relating to human research.

Approval will remain valid subject to the submission, and satisfactory assessment, of annual progress reports. *If the approval of an External HREC has been "noted" the approval period is as determined by that HREC.*

The full Committee will be asked to ratify this decision at its next scheduled meeting. A formal *Certificate of Approval* will be available upon request. Your approval number is **H-2017-0354**.

If the research requires the use of an Information Statement, ensure this number is inserted at the relevant point in the Complaints paragraph prior to distribution to potential participants You may then proceed with the research.

Conditions of Approval

This approval has been granted subject to you complying with the requirements for *Monitoring of Progress*, *Reporting of Adverse Events*, and *Variations to the Approved Protocol* as detailed below.

PLEASE NOTE:
In the case where the HREC has "noted" the approval of an External HREC, progress reports and reports of adverse events are to be submitted to the External HREC only. In the case of Variations to the approved protocol, or a Renewal of approval, you will apply to the External HREC for approval in the first instance and then Register that approval with the University's HREC.

- ***Monitoring of Progress***

Other than above, the University is obliged to monitor the progress of research projects involving human participants to ensure that they are conducted according to the protocol as approved by the HREC. A progress report is required on an annual basis. Continuation of your HREC approval for this project is conditional upon receipt, and satisfactory assessment, of annual progress reports. You will be advised when a report is due.

- ***Reporting of Adverse Events***

1. It is the responsibility of the person **first named on this Approval Advice** to report adverse events.
2. Adverse events, however minor, must be recorded by the investigator as observed by the investigator or as volunteered by a participant in the research. Full details are to be documented, whether or not the investigator, or his/her deputies, consider the event to be related to the research substance or procedure.
3. Serious or unforeseen adverse events that occur during the research or within six (6) months of completion of the research, must be reported by the person first named on the Approval Advice to the (HREC) by way of the Adverse Event Report form (via RIMS at https://rims.newcastle.edu.au/login.asp) within 72 hours of the occurrence of the event or the investigator receiving advice of the event.
4. Serious adverse events are defined as:
    - Causing death, life threatening or serious disability.
    - Causing or prolonging hospitalisation.
    - Overdoses, cancers, congenital abnormalities, tissue damage, whether or not they are judged to be caused by the investigational agent or procedure.
    - Causing psycho-social and/or financial harm. This covers everything from perceived invasion of privacy, breach of confidentiality, or the diminution of social reputation, to the creation of psychological fears and trauma.
    - Any other event which might affect the continued ethical acceptability of the project.

5. Reports of adverse events must include:
    - Participant's study identification number;
    - date of birth;
    - date of entry into the study;
    - treatment arm (if applicable);
    - date of event;
    - details of event;
    - the investigator's opinion as to whether the event is related to the research procedures; and
    - action taken in response to the event.

6. Adverse events which do not fall within the definition of serious or unexpected, including those reported from other sites involved in the research, are to be reported in detail at the time of the annual progress report to the HREC.

- ***Variations to approved protocol***

If you wish to change, or deviate from, the approved protocol, you will need to submit an *Application for Variation to Approved Human Research* (via RIMS at https://rims.newcastle.edu.au/login.asp). Variations may include, but are not limited to, changes or additions to investigators, study design, study population, number of participants, methods of recruitment, or participant information/consent documentation. **Variations must be approved by the (HREC) before they are implemented** except when Registering an approval of a variation from an external HREC which has been designated the lead HREC, in which case you may proceed as soon as you receive an acknowledgement of your Registration.

Linkage of ethics approval to a new Grant

HREC approvals cannot be assigned to a new grant or award (ie those that were not identified on the application for ethics approval) without confirmation of the approval from the Human Research Ethics Officer on behalf of the HREC.

Best wishes for a successful project.

Associate Professor Helen Warren-Forward
Chair, Human Research Ethics Committee

For communications and enquiries:
Human Research Ethics Administration

Research & Innovation Services
Research Integrity Unit
The University of Newcastle
Callaghan NSW 2308
T +61 2 492 17894
Human-Ethics@newcastle.edu.au

RIMS website - https://RIMS.newcastle.edu.au/login.asp

Linked University of Newcastle administered funding:

Funding body	Funding project title	First named investigator	Grant Ref

Appendix 4 Safety review notification

THE UNIVERSITY OF NEWCASTLE
AUSTRALIA

University Drive, Callaghan
NSW 2308 AUSTRALIA
HUMAN RESOURCE SERVICES
HEALTH AND SAFETY

Contact Person: Liz Pilgrim

Telephone 02-4921 6542
Fax 02-4921 6982
E-mail: safetyclearance@newcastle.edu.au

14 February 2018

TO: **Professor D Rivett, School of Health Sciences**
COPY TO: A/Professor S Dempsey, HOS, School of Health Sciences
Professor D Rivett, A/Professor S Snodgrass, Dr P Osmotherly, Dr S Walmsley, Mr J Tessier, Ms I Weerasekara
Ms R Gibbins, Human Research Ethics Officer
Dr N Gerrand, Manager Research Ethics and Governance, HNE Research Ethics Unit
FROM: Ms Jane Hamson, Chairperson, Chemical/Radiation Technical Committee
SUBJECT: SAFETY REVIEW NOTIFICATION

Based on the information provided the following Research Project has been reviewed and may proceed subject to compliance with the review conditions and there being no variation to the research processes that have been indicated in the application. If there is any variation to the protocol that affects the safety outcomes an additional application for safety review is necessary.

PROJECT TITLE	CHEMICAL	INSTITUTIONAL BIOSAFETY COMMITTEE (IBC)	RADIATION	HRE NUMBER	GRANTING BODY
THE EFFECT OF MOBILISATION WITH MOVEMENT ON ANATOMICAL AND CLINICAL CHARACTERISTICS OF CHRONIC ANKLE INSTABILITY (CAI) **REF NO 11/2018**	NA	NA	REVIEWED 07.02.2018	H-2017-0354	NA

In order to comply with the Work Health and Safety Act 2011 Chief Investigators must ensure that all, reasonably foreseeable, occupational health and safety risks arising out of their research activities are effectively controlled. A risk assessment must be completed to achieve this control. Effective controls follow on through the elimination (preferable), or minimisation, of these risks. Risk assessments are only validated once they have been signed and dated by the author and authorising supervisor. They must be reviewed annually and the review process needs to be documented (signed and dated).

Control measures for research activities must include (but are not limited to):

- A site (documented) orientation/induction to be given to all personnel when they are attending a facility/location for the first time. This induction will include; local rules (eating, drinking, storage of bags, standard of dress, hand washing and Personnel Protective Equipment [PPE] required etc), location of amenities, location of emergency procedures flipchart (which must contain correct contact information), rundown of evacuation procedure including the location of the assembly area.
- Ongoing inductions as appropriate to ensure current legislative requirements are reinforced to all facility users.
- Written standard operating procedures (SOP's) for equipment and processes
- Current SDS's must be readily available for all hazardous substances associated with the activity
- Please ensure the chemicals in your facility have been entered onto the Chemical Manifest.
- Training in SOP's for all personnel engaged in hazardous operations (with appropriate records)
- All documented control measures must be implemented.
- The minimum requirements for PPE in a laboratory are laboratory clothing (lab coat), protective eyewear (safety glasses), and closed shoes unless lesser requirements can be justified by a risk assessment AS/NZS 2243.1 Safety in laboratories Part 1: Planning and operational aspects.

- When ordering hazardous substances with a hazard rating of high or extreme, consideration should be given to using safer alternate reagents (where available) and only amounts required for the project should be purchased- to prevent unnecessary stockpiles of hazardous reagents.
- Any injury/incident occurring during the activity is reported via the University Online Incident Reporting System

Please ensure that all staff involved in working on this project is aware of the requirements of this review and a copy of this memorandum is to be kept in the Laboratory Safety Manual/s of the facility/s where the work is performed.

If you have any enquiries in relation to this safety review (implications) please do not hesitate to contact me.

MS JANE HAMSON
CHAIRPERSON, CHEMICAL/RADIATION TECHNICAL COMMITTEE

U: SRA2018\Rivett, Professor D – 11/2018 - Safety review notification

Appendix 5 Dosimetry report: case-control study

Medical Physics Group
Nick Hille, Area Radiation Safety Officer

Jenny Diffey, Senior Medical Physics Specialist
Tel: 4921 3380 Fax: 4921 3392
Email: jennifer.diffey@health.nsw.gov.au

NSW GOVERNMENT Health
Hunter New England
Imaging

Dr John Tessier
School of Health Sciences
University of Newcastle
Callaghan
NSW 2308

Dear John,

Please find below a dosimetry report for the research study entitled *"Anatomical and clinical characteristics of the ankles of individuals with chronic ankle instability"*

Dosimetry information for a study involving exposure to an external source of ionising radiation:

Participant Age Range: > 18 years old
Source of Exposure: X-ray
Examinations: All participants: Weight bearing lateral x-ray
Symptomatic participants: Lateral stress views of both ankles

Examination	kVp	mAs	Entrance Skin Dose (mGy)	Effective Dose[1] (mSv)
Lateral Ankle X-ray	55	2.1	0.1	0.0001

Total Effective Dose from Study = 0.0001 mSv (asymptomatic) or 0.0003 mSv (symptomatic participants)

The dose received from this study, not including any exposures incurred as part of the normal clinical management of the participant, **does not exceed** the relevant dose constraint in Table 1 of the ARPANSA Code of Practice (RPS8)[2].

The recommended statement for inclusion in the patient information sheet for this study is as follows:

"This research study involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 to 3 millisieverts (mSv) each year. The effective dose from this study is about 0.0003 mSv. At this dose level, no harmful effects of radiation have been demonstrated as any effect is too small to measure. The risk is believed to be minimal."

26 May 2017
Dr Jenny Diffey, Senior Medical Physics Specialist
NSW EPA Consulting Radiation Expert No. 5025022
ACPSEM Accreditation # R00069

References

1. Hart D et al. Frequency and Collective Dose for Medical and Dental X-ray Examinations in the UK, 2008. Health Protection Agency Report HPA-CRCE-012
2. ARPANSA Code of Practice RPS 8: Exposure of Humans to Ionizing Radiation for Research Purposes

Hunter New England Area Health Service
Hunter New England Imaging
Locked Bag 1 HRMC Newcastle NSW 2310

Appendix 6 Dosimetry report: randomised controlled trial

Medical Physics Group
Nick Hille, Area Radiation Safety Officer

Jenny Diffey, Senior Medical Physics Specialist
Tel: 4921 3380 Fax: 4921 3392
Email: jennifer.diffey@health.nsw.gov.au

Health
Hunter New England
Imaging

Dr John Tessier
School of Health Sciences
University of Newcastle
Callaghan
NSW 2308

Dear John,

Please find below a dosimetry report for the research study entitled *"The effect of mobilisation with movement on anatomical and clinical characteristics of chronic ankle instability (CAI)"*

Dosimetry information for a study involving exposure to an external source of ionising radiation:

Participant Age Range: > 18 years old; all participants are symptomatic.
Source of Exposure: X-ray

Examinations will be carried out on a Philips Dura Diagnost X-ray unit with DR detector.

Examination		kVp	mAs	Entrance Skin Dose (mGy)	Effective Dose[1] (mSv)
1	Pre-intervention weight bearing lateral x-rays of the symptomatic ankle	55	2.1	0.1	0.0001
2	Lateral stress views of symptomatic ankle	55	2.1	0.1	0.0001
3	Lateral stress views of asymptomatic ankle	55	2.1	0.1	0.0001
4	Post-intervention weight bearing lateral x-rays of the symptomatic ankle	55	2.1	0.1	0.0001

Total Effective Dose from Study = 0.0004 mSv*

* Please note: some of the study participants will have taken part in a previous study entitled *"Anatomical and clinical characteristics of the ankles of individuals with chronic ankle instability"* (see Dosimetry Report dated 26 May 2017). As part of this previous study, they will have received Examinations 1 – 3 and will only receive Examination 4 as part of the current study. Therefore, the maximum dose received by a participant of both studies will be 0.0004 mSv.

The dose received from this study, not including any exposures incurred as part of the normal clinical management of the participant, **does not exceed** the relevant dose constraint in Table 1 of the ARPANSA Code of Practice (RPS8)[2].

The recommended statement for inclusion in the patient information sheet for this study is as follows:

"This research study involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 to 3

Appendix 7 PROSPERO systematic review registration notification

Dear Mrs Weerasekara

Thank you for submitting details of your systematic review *Clinical benefits of passive joint mobilisation on ankle sprains: a systematic review and meta-analysis* to the PROSPERO register. We are pleased to confirm that the record has been published on the database.

Your registration number is: CRD42016030194

You are free to update the record at any time, all submitted changes will be displayed as the latest version with previous versions available to public view. Please also give brief details of the key changes in the Revision notes facility. You can log in to PROSPERO and access your records at http://www.crd.york.ac.uk/PROSPERO

An email reminder will be sent to you on the anticipated completion date, prompting you to update the record.

Comments and feedback on your experience of registering with PROSPERO are welcome at: crd-register@york.ac.uk

Best wishes for the successful completion of your review.

Yours sincerely

Lesley Indge

PROSPERO Administrator
Centre for Reviews and Dissemination
University of York
York YO10 5DD
t: +44 (0) 1904 321040
f: +44 (0) 1904 321041
e: CRD-register@york.ac.uk
www.york.ac.uk/inst/crd

PROSPERO is funded by the National Institute for Health Research and produced by CRD, an academic department of the University of York.

Appendix 8 ANZCTR clinical trial registration notification

Dear Ishanka Weerasekara and Darren Rivett,

Re: Joint Mobilisation in Chronic Ankle Instability

Thank you for submitting the above trial for inclusion in the Australian New Zealand Clinical Trials Registry (ANZCTR).

Your trial has now been successfully registered and allocated the ACTRN: ACTRN12617001467325p

Web address of your trial: http://www.ANZCTR.org.au/ACTRN12617001467325p.aspx
Date submitted: 10/10/2017 12:04:43 AM
Date registered: 17/10/2017 12:10:22 PM
Registered by: Ishanka Weerasekara
Principal Investigator: Darren Rivett

If you have already obtained Ethics approval for your trial, please send a copy of at least one Ethics Committee approval letter to info@actr.org.au or by fax to (+61 2) 9565 1863, attention to ANZCTR.

Note that updates should be made to the registration record as soon as any trial information changes or new information becomes available. Updates can be made at any time and the quality and accuracy of the information provided is the responsibility of the trial's primary sponsor or their representative (the registrant). For instructions on how to update please see http://www.anzctr.org.au/Support/HowToUpdate.aspx.

Please also note that the original data lodged at the time of trial registration and the tracked history of any changes made as updates will remain publicly available on the ANZCTR website.

The ANZCTR is recognised as an ICMJE acceptable registry (http://www.icmje.org/faq.pdf) and a Primary Registry in the WHO registry network (http://www.who.int/ictrp/network/primary/en/index.html).

If you have any enquiries please send a message to info@actr.org.au or telephone +61 2 9562 5333.

Kind regards,
ANZCTR Staff
T: +61 2 9562 5333
F: +61 2 9565 1863
E: info@actr.org.au
W: www.ANZCTR.org.au

Appendix 9 Information statement: case-control study

Professor Darren A. Rivett
School of Health Sciences
Faculty of Health and Medicine
The University of Newcastle
University Drive
Callaghan NSW 2308
Phone: 02 49215642 Fax: 02 49217053
Darren.Rivett@newcastle.edu.au

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

Information Statement for the Research Project:
Anatomical and clinical characteristics of the ankles of individuals with chronic ankle instability (CAI)
Version 2 (04/09/17)

You are invited to participate in the research project identified above which is being conducted in the School of Health Sciences at The University of Newcastle. The research is part of Ishanka Weerasekara' s PhD studies and is supervised by Professor Darren Rivett, Dr. Peter Osmotherly, and Associate Professor Suzanne Snodgrass. Your eligibility to participate in the clinical/ lab data collection is dependent on the score obtained by the questionnaires attached herewith. You will be informed (over the phone or via email) as to your eligibility to participate once you return the attached questionnaires to the researcher, according to your preferred method of contact.

Why is the research being done?
The purpose of this study is to determine the basic characteristics of ankle joint instability compared to healthy ankles.
The feeling of ankle joint instability is 'the situation whereby during activities of daily living (ADL) and sporting activities the participant feels that the ankle joint is unstable and is usually associated with the fear of sustaining an acute ligament sprain."

Who can participate in the research?
There are two groups of participants in this study, who are 18 years of age or older. The first group is composed of people who have ankle joint instability as described above. The second group are those with no ankle symptoms.

If you have the feeling of ankle joint instability and would like to participate in the study, you must have:

- A history of at least one significant ankle sprain
- A history of the previously injured ankle joint "giving way" and/or recurrent sprain and/or "feelings of instability."

If you have a healthy ankle, you may participate in the study if you have:

- Not had ankle problems or surgeries previously.
- Not had treatments for an ankle problem previously.
- No pain or problems in or around the ankle while performing daily activities currently

You may not be able to participate in the study if you have or have had any of the following:

- A history of fracture, or surgery to your ankle
- Any recent injury other than ankle instability (within 3 months) to your lower limb
- Any previous injury still causing problems to the lower limbs
- Any neuromuscular disorders that may result in lower limb soft tissue anomalies i.e. muscle weakness
- Any conditions for which x-ray imaging is contraindicated (e.g., pregnancy)
- Inability to speak or write English

If you are unsure if one of these criteria applies to you, please ask the investigator.

What choice do you have?
Participation in this research is entirely your choice. Only those people who give their informed consent will be included in the project. Whether or not you decide to participate, your decision will not disadvantage you.

If you do decide to participate, you may withdraw from the project at any time without giving a reason and have the option of withdrawing any data which identifies you.

What would you be asked to do?

If you agree to participate, you will be asked to:

- Attend one data collection session lasting approximately one hour at the School of Health Sciences Research Laboratories at the University of Newcastle at Callaghan.

- During this session you will:
    - Have your age, gender, height and weight recorded by the researchers
    - Have a registered radiographer take up to three x-rays of your ankle
    - Undergo few clinical measures including general hypermobility, ankle range of motion, balance tests, pain scales and pressure pain thresholds.

What measurements will be performed?

If you are eligible to participate, you will be invited to the study at the Discipline of Physiotherapy in the Hunter building at the University of Newcastle at Callaghan. During the study, we will be recording your basic data including age, gender, height, weight, side of the dominant leg and completing clinical measures. Your ankles will be also x-ray filmed by a registered radiographer.

If you have the feeling of ankle joint instability:

- Two x-rays of the affected ankle will be obtained (one in lying position and one in standing) to determine the bony involvement related to the ankle condition. One x-ray will be obtained from the other ankle to compare the difference.
- Clinical measures will be taken including ankle range of motion, balance tests, pain scales and pressure pain thresholds.

If you have a healthy ankle:

- One x-ray of the dominant side ankle will be obtained (in standing position) to determine the bony alignment of the ankle.
- Clinical measures will be taken including ankle range of motion, balance tests, pain scales and pressure pain thresholds.

All these tests will be stopped if you feel pain.

How much time will it take?

- The session will take about an hour.

What are the risks and benefits of participating?

The procedures in this study are used routinely in clinical practice, and there have been no published reports of adverse effects or problems with any of these procedures, to the best of our knowledge.

You will be benefitted from participating in this research, as this is an opportunity to have your ankle evaluated using x-ray measurement. During the process of reviewing your x-ray, if any abnormality is detected you will be advised to seek further review with your local medical practitioner. In the case of any abnormality being found, you will be provided with a copy of the x-ray/s. You will be provided with a letter detailing the findings and a copy of them so that you can take them to your medical practitioner if you choose to do so. If you request, you will be provided an electronic copy of your x-ray/s. In addition, at the completion of the study you can receive, if you wish, a summary of the study results. There will be no cost to you for any of the procedures you may receive in this trial or any part of your participation.

The risks to participating are minimal. However, if you do experience any unpleasant sensations, you can stop the assessment procedures at any time and withdraw from the study. The researchers, who are

registered health professionals, will discuss any uncomfortable sensations with you, and if appropriate, will provide you with a letter for your medical practitioner.

This research study involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 to 3 millisieverts (mSv) each year. The effective dose from this study is about 0.0003 mSv. At this dose level, no harmful effects of radiation have been demonstrated as any effect is too small to measure. The risk is believed to be minimal. Also the ankle is away from vital organs of the body, which will not be exposed to radiation. The risk is, therefore, believed to be very low.

How will your privacy be protected?

Personally identifiable information that is provided will be confidential to the researchers. Non-identifiable data may be also be shared with other parties to encourage scientific scrutiny, and to contribute to further research and public knowledge, or as required by law. No identifying information will be included in any reports presented at a scientific meeting or published in a journal or thesis. Your x-ray images will be stored on a secure database only accessible to the researchers listed above. Paper copies of questionnaires and the other measurements will be stored in a locked cabinet in the School of Health Sciences offices and the information will only be accessed by the researchers unless you consent otherwise, except as required by law. All data collected from you will be labelled with a code on the day it is collected. Coded data will be stored in the ownCloud data management facility of The University of Newcastle that is password protected and is only accessible to the researchers listed above. If you choose to complete the questionnaires online, your information will be securely collected and transferred to ownCloud via the Qualtrics platform, and only you and the researchers have access to your information on this platform. The contact details that you provide will be stored separately to the data in a locked cabinet in the office of the School of Health Sciences. At the conclusion of the study all data will be downloaded to CD and stored in a locked cabinet in the office of the School of Health Sciences at the University of Newcastle. All information will be stored in the School of Health Sciences at The University of Newcastle for a minimum of 5 years, after which time it will be appropriately destroyed.

How will the information collected be used?

The results of this study will be submitted in a thesis for, Ishanka Weerasekara's PhD, and may be presented at conferences and in scientific journals. Individual participants will not be identified in any reports arising from this project. Further, de-identified data may be used in future research upon your consent. A summary of the study results can be provided to you, if you wish to receive this, at the completion of the study.

What do you need to do to participate?

If you would like to participate, please telephone or email your contact details to the research team. Once you contact the researchers, a preliminary telephone screening will be carried out and then, if you are potentially eligible to participate, you will be sent the information statement, consent form and three screening questionnaires. These documents will either be posted as hard copies or a link will be emailed to enable you to access them online, depending on your preference.

Please read this Information Statement and be sure you understand its contents before you consent to participate. If there is anything you do not understand, or you have questions, contact the researchers.

Please complete the attached consent form and return it in the reply paid envelope (or submit the online form) provided. Researchers will then contact you to arrange a time convenient to you for the screening. Also you can contact one of the researchers listed below either by telephone, email or in person. They will then answer any further queries, and confirm an appointment time for you to attend your data collection session.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not- for - profit sectors.

Further information

If you would like further information, you may contact the researchers directly:
Ishanka Weerasekara: tel. 0424208114 email: Ishanka.weerasekara@uon.edu.au
Professor Darren Rivett: tel: 049217220 email: Darren.rivett@newcastle.edu.au

Thank you for considering this invitation.

Professor Darren Rivett Ishanka Weerasekara

Project supervisor

Research Higher Degree Candidate

Complaints about this research

This project has been approved by the University's Human Research Ethics Committee, Approval No.H-2017-0217.

Should you have concerns about your rights as a participant in this research, or you have a complaint about the manner in which the research is conducted, it may be given to the researcher, or, if an independent person is preferred, to the Human Research Ethics Officer, Research & Innovation Services, The University of Newcastle, University Drive, Callaghan NSW 2308, Australia, telephone (02) 49216333, email Human-Ethics@newcastle.edu.au.

Appendix 10 Consent form: case-control study

Professor Darren A. Rivett
School of Health Sciences
Faculty of Health and Medicine
The University of Newcastle
University Drive
Callaghan NSW 2308
Phone: 02 49215642 Fax: 02 49217053
Darren.Rivett@newcastle.edu.au

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

Consent Form for the Research Project:
Anatomical and clinical characteristics of the ankles of individuals with chronic ankle instability (CAI)
Version 2 (04/09/17)

Chief Investigators: Professor Darren Rivett, Dr Peter Osmotherly, A/ Professor Suzanne Snodgrass
Student Researcher: Ms Ishanka Weerasekara

I agree to participate in the above research project and give my consent freely.

I understand that the project will be conducted as described in the Information Statement, a copy of which I have retained.

I understand I can withdraw from the project at any time and do not have to give any reason for withdrawing.

I consent to:

- Attend one data collection session lasting approximately one hour at the School of Health Sciences Research Laboratories at the University of Newcastle Callaghan Campus.
- Being tested to determine the whether I have chronic ankle instability.
- Have my age, gender, height and weight and hypermobility measurements recorded
- Have the clinical measures (balance, range of ankle, pain intensity and pain threshold) /assessments (x- rays of my ankle) explained in the information sheet recorded by the researchers.

I understand that my personal information will remain confidential to the researchers.

I have had the opportunity to have questions answered to my satisfaction.

Print Name: _____

Contact Phone: _____

Contact Address: _____

Email: _____

Signature: _____

Date: _____

Do you consent to be contacted for about potential participation in future research?	Yes / No
Do you consent to reuse of your de-identified data if required in future research?	Yes / No
Please indicate (circle) whether you would like a summary of the study findings	Yes / No
If you indicate yes, in any of the questions above, please select the preferred method of contact	Email / Post

Appendix 11 Information statement: randomised controlled trial

Professor Darren A. Rivett
School of Health Sciences
Faculty of Health and Medicine
The University of Newcastle
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Callaghan NSW 2308
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THE UNIVERSITY OF NEWCASTLE AUSTRALIA

Information Statement for the Research Project:
The effect of Mobilisation with Movement on Anatomical and Clinical Characteristics of Chronic Ankle Instability (CAI)
Version 3 (23/01/18)

You are invited to participate in the research project identified above which is being conducted in the School of Health Sciences at The University of Newcastle. The research is part of Ishanka Weerasekara' s PhD studies and is supervised by Professor Darren Rivett, Dr. Peter Osmotherly, and Associate Professor Suzanne Snodgrass. Your eligibility to participate in the clinical/ lab data collection is dependent on the score obtained by the questionnaires attached. You will be informed (over the phone or via email) as to your eligibility to participate once you return the attached questionnaires to the researcher, according to your preferred method of contact. If you do participate, you are advised to retain this Information Statement for at least 5 years so that it can be provided to researchers in any future research project involving radiation.

Why is the research being done?
The purpose of this study is to determine the effectiveness of two procedures performed by physiotherapists as treatment for ankle joint instability.

The feeling of ankle joint instability is 'the situation whereby during activities of daily living (ADL) and sporting activities the participant feels that the ankle joint is unstable and is usually associated with the fear of sustaining an acute ligament sprain."

Who can participate in the research?
The group of participants is composed of people who have ankle joint instability as described above, who are more than 18 years of age.

If you would like to participate in the study, you must have:

- A history of at least one significant ankle sprain
- A history of the previously injured ankle joint "giving way" and/or recurrent sprain and/or "feelings of instability."

You may not be able to participate in the study if you have or have had any of the following:

- A history of fracture, or surgery to your lower limb
- Any recent injury other than ankle instability (within 3 months) to your lower limb
- Any previous injuries (other than ankle instability), still causing problems to the lower limb
- Any neuromuscular disorders that may result in lower limb soft tissue anomalies ie. muscle weakness
- Any conditions for which manual therapy is not recommended (e. g.: tumour, rheumatoid arthritis, or osteoporosis)
- Any conditions for which x-ray imaging is not recommended (e.g., pregnancy)
- Any allergies to adhesive strapping tape
- Inability to speak or write English

If you are unsure if one of these criteria applies to you, please ask the investigator.

What choice do you have?
Participation in this research is entirely your choice. Only those people who give their informed consent will be included in the project. Whether or not you decide to participate, your decision will not disadvantage you.

If you do decide to participate, you may withdraw from the project at any time without giving a reason and have the option of withdrawing any data which identifies you. Also it will not disadvantage you or impact on any relationship you may have with the University of Newcastle and its staff.

What would you be asked to do?

If you agree to participate, you will be asked to:

- Complete screening questionnaires, and if it is determined that you are eligible you will then proceed to the next phase of the study.

- If you are eligible to participate, you will be invited to attend a data collection session at the Physiotherapy Research Laboratory in the Hunter Building at the University of Newcastle at Callaghan. During the first visit you will:
    - Have your age, gender, height, weight and general joint mobility recorded by the researchers.
    - Have a registered radiographer (Mr John Tessier) take three x-rays of your ankle.
    - Undergo clinical measures including ankle range of motion, balance tests, pain scales, self- reported function questionnaires and pressure pain thresholds.

- Following the measurements, you will be:
    - Randomly allocated to one of the two possible groups. Each group will receive a different intervention from a registered Physiotherapist. You are requested not to discuss your intervention with other participants in the study.
    - Given this same intervention 2-8 times over 4 weeks. The number of sessions you attend will be determined by the physiotherapist based on your response to treatment, and sessions will be scheduled at a time convenient for you.

- Then follow up data will be collected during three occasions; at the 4th week after the enrolment (lab data collection), at the 12th week (lab data collection) and 12th month after the intervention (questionnaire based data collection).
    - At the 4th week after enrolment: One x-ray of your ankle will be obtained by a registered radiographer. Clinical measures including ankle range of motion, balance tests, pain scales, pressure pain thresholds and self- reported function questionnaires will be obtained.
    - At the 12th week of intervention: Clinical measures including ankle range of motion, balance tests, pain scales, self- reported function questionnaires and pressure pain thresholds will be obtained.
    - At the 52nd week of intervention: Fill three questionnaires to measure ankle instability, function and pain intensity (on hard copies posted or online survey link via email according to your preference).

You may stop these tests at any time you feel pain. You will be requested not to receive any additional treatment for the ankle during the study period, and the most recent treatment should have been received at least a week prior to study enrolment.

Your activity level, re-injuries and also regarding other treatments during the procedures will be recorded at each treatment visit and further you will be phone interviewed monthly for up to one year to record the same details.

(Note: If you have already participated in the study on 'Anatomical and clinical characteristics of the ankles of individuals with chronic ankle instability (CAI)' (ethics reference no: H-2017-0217), you do not have to undergo the measurements collected during the first visit, and will be directed to the treatment phase directly.)

The treatment procedures

You will be randomly allocated to one of two intervention groups, and you will not be able to choose which intervention you will receive. Some of you will receive an active intervention of unproven benefit, though this intervention is routinely used by physiotherapists and believed to help ankle symptoms. There is a chance of not receiving an intervention with any therapeutic benefit.

One group will receive laser to the lateral aspect of the ankle. Normally there is no sensation felt with laser. The other group will receive a mobilisation technique to the ankle region, which involves gentle pressure on one of your ankle bones while you move your ankle.

A registered and experienced physiotherapist will perform all interventions. If you experience any pain during either intervention you must tell the physiotherapist.

If you choose to participate in this research by completing and returning the consent form, you are agreeing to participate in all aspects of the study, as detailed above. You will be provided with parking vouchers or free parking for all treatment and measurement sessions that you attend. There will be no other reimbursements or payments for participating in this research.

How much time will it take?

To be involved in the study, you will need to be able to attend the 2-8 separate intervention sessions over a period of 4 weeks, and measurement sessions on 3 separate occasions over a period of twelve (12) months. The table below provides details on how long each session will take and where each will be held.

Week/s	Session	Time	Location
0	Questionnaire screening (3 questionnaires)	10 minutes	Online/ post
1	Measurement sessions (3 x-rays, clinical measures)	1.15 hours	Hunter Building, The University of Newcastle
1, 2, 3, 4	Treatment sessions (2-8 sessions) Injury, activity and treatment record	15 minutes	Hunter Building, The University of Newcastle
4	Measurement sessions (1 x-ray, 2 questionnaires, clinical measures)	1 hour	Hunter Building, The University of Newcastle
12	Measurement sessions (2 questionnaires, clinical measures)	45 minutes	Hunter Building, The University of Newcastle
52	Measurement sessions (3 questionnaires)	10 minutes	Online/ post
4, 8, 12, 16, 20, 24, 27, 32, 36, 40, 44, 48, 52	Injury, activity and treatment record (phone interview/online survey)	7 minutes	Over the phone

What are the risks and benefits of participating?

The procedures and interventions in this study are used routinely used in clinical practice, and there have been no published reports of adverse effects or problems with any of these procedures, to the best of our knowledge. Some participants will receive an active intervention of unproven benefit, though this intervention is routinely used by physiotherapists and believed to help ankle symptoms. Other participants will undergo an intervention that is not designed to be of any therapeutic benefit. Therefore researchers anticipate that some participants will benefit from the interventions used, but not all. If the active intervention is shown to be beneficial and you did not receive it, you will be offered the active intervention free of charge, after completion of your participation in the study. The request should be made within 12 months after their enrolment by the participant. Otherwise, there will be no continued access to the trial intervention you have received during the trial, after the completion of the trial. If treatment is offered after your participation in the study, it will be conducted at the University of Newcastle, Callaghan campus.

You will benefit from participating in this research, as this is an opportunity to have your ankle evaluated using x-ray measurement. During the process of reviewing your x-ray, if any abnormality is detected you will be provided with a copy of your x-ray/s and a letter detailing the findings, and advised to seek further review with your local medical practitioner. In addition, at the completion of the study you can request to receive a summary of the study results. There will be no cost to you for any of the procedures you may receive in this trial or any part of your participation.

The risks to participating are minimal. However, if you do experience any unpleasant sensations, you can stop the assessment procedures at any time and withdraw from the study. The researchers, who are registered health professionals, will discuss any uncomfortable sensations with you, and if appropriate, will provide you with a letter for your medical practitioner.

This research study involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 to 3 millisieverts (mSv) each year. The effective dose from this study is about 0.0004 mSv. At this dose level, no harmful effects of radiation have been demonstrated as any effect is too small to measure. The risk is believed to be minimal. Also the ankle is away from vital organs of the body, which will not be exposed to radiation. The risk of harm from exposure to radiation is, therefore, believed to be very low.

How will your privacy be protected?

Personally identifiable information that is provided will be confidential to the researchers. Non-identifiable data may be also be shared with other parties to encourage scientific scrutiny, and to contribute to further research and public knowledge, or as required by law. No identifying information will be included in any reports presented at a scientific meeting or published in a journal or thesis. Your x-ray images will be stored on a secure database only accessible to the researchers listed above. Paper copies of questionnaires and the other measurements will be stored in a locked cabinet in the School of Health Sciences offices and the information will only be accessed by the researchers unless you consent otherwise, except as required by law. All data collected from you will be labelled with a code on the day it is collected. Coded data will be stored in the ownCloud data management facility of The University of Newcastle that is password protected and is only accessible to the researchers listed above. If you choose to complete the questionnaires online, your information will be securely collected and transferred to ownCloud via the Qualtrics platform, and only you and the researchers have access to your information on this platform. The contact details that you provide will be stored separately to the data in a locked cabinet in the office of the School of Health Sciences. At the conclusion of the study all data will be downloaded to CD and stored in a locked cabinet in the office of the School of Health Sciences at the University of Newcastle. All information will be stored in the School of Health Sciences at The University of Newcastle for a minimum of 5 years, after which time it will be appropriately destroyed.

How will the information collected be used?

The results of this study will be submitted in a thesis for, Ishanka Weerasekara's PhD, and may be presented at conferences and in scientific journals. Individual participants will not be identified in any reports arising from this project. Further, de-identified data may be used in future research upon your consent. A summary of the study results can be provided to you, if you wish to receive this, at the completion of the study.

What do you need to do to participate?

Please read this Information Statement and be sure you understand its contents before you consent to participate. If there is anything you do not understand, or if you have any questions, please contact the researchers.

If you wish to participate, please complete the consent form and three screening questionnaires, and return these in the reply-paid envelope provided (or alternatively complete the documents online using the provided link). Once these are received, the researchers will contact you to confirm your eligibility and arrange an appointment time for you to attend your first session.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for profit sectors.

Further information

If you would like further information, you may contact the researchers directly:
Ishanka Weerasekara: tel. 0424208114 email: Ishanka.weerasekara@uon.edu.au
Professor Darren Rivett: tel: 49217220 email: Darren.rivett@newcastle.edu.au

Thank you for considering this invitation.

Professor Darren Rivett
Project supervisor

Ishanka Weerasekara
Research Higher Degree Candidate

Complaints about this research

This project has been approved by the University's Human Research Ethics Committee, Approval No. H-2017-0354.

Should you have concerns about your rights as a participant in this research, or you have a complaint about the manner in which the research is conducted, it may be given to the researcher, or, if an independent person is preferred, to the Human Research Ethics Officer, Research & Innovation Services, The University of Newcastle, University Drive, Callaghan NSW 2308, Australia, telephone (02) 49216333, email Human-Ethics@newcastle.edu.au .

Appendix 12 Consent form: randomised controlled trial

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Consent Form for the Research Project:
The effect of Mobilisation with Movement on Anatomical and Clinical Characteristics of Chronic Ankle Instability (CAI)
Version 2 (15/12/2017)

Chief Investigators: Professor Darren Rivett, Dr Peter Osmotherly, A/ Professor Suzanne Snodgrass
Student Researcher: Ms Ishanka Weerasekara

I agree to participate in the above research project and give my consent freely.

I understand that the project will be conducted as described in the Information Statement, a copy of which I have retained.

I understand I can withdraw from the project at any time and do not have to give any reason for withdrawing.

I consent to:

- Attend 3 data collection sessions lasting approximately one and half hour at the School of Health Sciences Research Laboratories at the University of Newcastle Callaghan Campus.
- Being tested to determine the whether I have chronic ankle instability.
- Attend 2-8 treatment sessions to receive an intervention which may treat my ankle instability
- Have my age, gender, height and weight and hypermobility measurements recorded
- Have the clinical measures (balance, range of ankle, pain intensity, function and pain threshold) recorded
- Have my ankle x-rayed and recorded
- Being contacted to record the details about my activity level, re-injuries and other treatments at each treatment visit and also to contact monthly after the treatments for one year.

I understand that my personal information will remain confidential to the researchers.

I have had the opportunity to have questions answered to my satisfaction.

Print Name: _____

Contact Phone: _____

Contact Address: _____

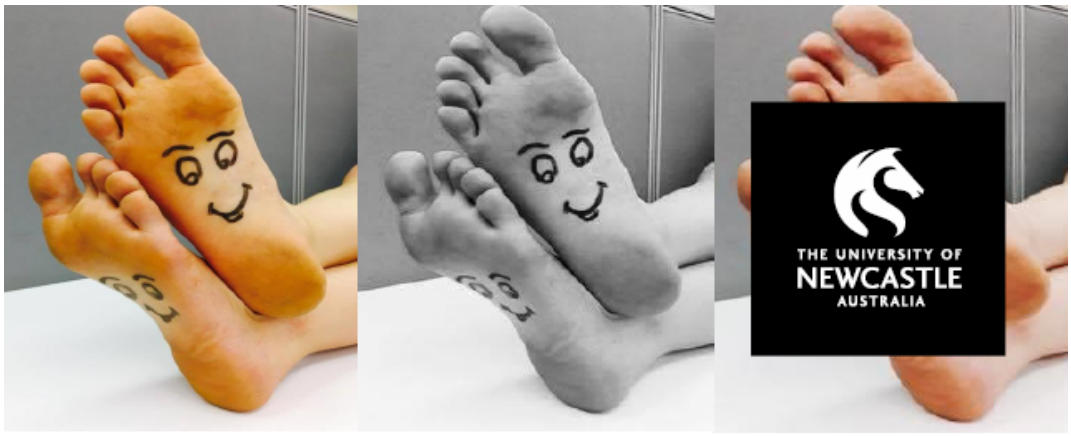
Email: _____

Signature: _____

Date: _____

Do you consent to reuse of your de-identified data if required in future research?	Yes / No
Please indicate (circle) whether you would like a summary of the study findings	Yes / No
If you indicate yes, in any of the questions above, please select the preferred method of contact	Email / Post

Appendix 13 Participant recruitment flyers: case-control study



SEEKING HEALTHY ANKLES…!

ARE YOU…

- **More than 18 years old**
- **Without any ankle pain or problem in the ankle now**
- **Without any history of previous ankle surgeries or any recent ankle problems**

This University of Newcastle based project on 'Anatomical and clinical characteristics of the ankles of individuals with chronic ankle instability (CAI)' will require you to attend the School of Health Sciences Research Laboratories in the Hunter Building to have ankle movement, balance, function, pain assessments, and X-ray examination measured.

If you would like to find our more information about the study please phone Ishanka in the Discipline of Physiotherapy, the University of Newcastle.

Research Higher Degree Candidate
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Project Supervision
Prof. Darren Rivett
T: 49217220
E: Darren.rivett@newcastle.edu.au

This project has been approved by the University of Newcastle Human Research Ethics Committee, HREC Approval No. H-2017-0217

Ankle instability study
Participants with/ without Ankle instability
Ishanka- 0424208114
Ishanka.weerasekara@uon.edu.au

KEEP ON SPRAINING YOUR ANKLE?

IS THIS YOU…?

- **More than 18 years old**
- **Have a history of the previously injured ankle joint "giving way" and/or recurrent sprain and/or "feelings of instability."**

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Appendix 14 Participant recruitment flyers: randomised controlled trial

Do you have an unstable ankle?

Does this sound like you?

- More than 18 years old
- Have you had repeated ankle sprains? and / or does your ankle 'give way' or feel unstable?
- Would you like to have the chance of free physiotherapy treatment for your ankle?

We are recruiting individuals to participate in a study to evaluate the effectiveness of two interventions in the management of chronic ankle instability.

This University of Newcastle based project on 'The effect of Mobilisation with Movement on Anatomical and Clinical Characteristics of Chronic Ankle Instability (CAI)' will require you to attend the School of Health Sciences Research Laboratories in the Hunter Building to have **ankle movement, balance, function, pain assessments, and an x-ray examination** measured before and after the treatment. You will **receive 2-8 intervention sessions** depending on the condition of your ankle.

If you would like to find out more information about the study please phone **Ishanka** in the Discipline of Physiotherapy, University of Newcastle on **0424208114**.

Research Higher Degree Candidate
Ishanka Weerasekara on 0424208114 or Ishanka.weerasekara@uon.edu.au
Project Supervisor
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This project has been approved by the University's Human Research Ethics Committee, Approval No. H-2017-0354.

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Ankle instability study
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Appendix 15 Data collection forms (both case-control and RCT studies) including questionnaires

Data Collection sheet

The information on this form will be kept strictly confidential and is used to research purposes.

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Before subject arrives:

Randomise the tests: (and keep a note here)

A-DFROM TEST (good leg first > affected next)

B-BALANCE TEST (good leg first > affected next)

C- PPT TEST (good leg first > affected next)

Randomise the three sites of algometer reading: (and keep a note here)

X- Lateral ankle

Y- Medial ankle

Z- Ant tibialis

PPT:

Ensure devices are charged and Freedom USB is attached to the laptop (Shortcut to open Tracker 5), 4 N/s using a 1 cm² indenter tip, corresponding to 40kPa/s. Software records the maximum force (N) generated; may want to convert to kPa for analysis for consistency with UQ literature; some others have used N.

Zero calibrate – to be done daily prior to patient arrival:

Select System (top left) – zero calibrate – algometer, Wake up device by pushing the on switch on the PPT, Click on "Zero" and then OK

***BALANCE**:*

Ensure Force plate is on and the USB attached. Short cut to MARS. Open the add details of the participants to be filled with height/weight/birthday.

Brief introduction about the study and the process

Data Collection sheet

The information on this form will be kept strictly confidential and is used to research purposes.

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Date: ---------- **Participant No:** ----------

General Information

Gender: ----------

Height: ----------

Weight: ----------

Dominant leg: ----------

Affected leg: ----------

Right leg length: ----------

Left leg length: ----------

Beighton test:

Description	Right	Left	Scoring max. points
1. Passive hyperextension of the knee ≥ 10 degrees			(2)
2. Passive dorsiflexion of the fifth metacarpophalangeal joint to ≥ 90 degrees			(2)
3. Passive hyperextension of the elbow ≥ 10 degrees			(2)
4. Passive apposition of the thumb to the flexor side of the forearm, while shoulder is flexed 90 degrees, elbow is extended, and hand is pronated			(2)
5. Forward flexion of the trunk, with the knees straight, so that the hand palms rest easily on the floor			(1)
Total			(9)

Weight bearing lunge test (cm)

Attempts	Right	Left
Read 1		
Read 2		
Read 3		

Data Collection sheet

The information on this form will be kept strictly confidential and is used to research purposes.

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

Balance tests

SEBT test (cm)

Side	Right	Left
Anterior		
Postero medial		
Postero lateral		

Pressure pain threshold (Kpa)

Set up patient:

Select Perform exam (bottom of screen)
Select Ankle study for the database
Enter patient enter their study number as their first and last name (or find them in the list if they have come before)
Enter Anklestudy1 as the incident
Enter the name of the exam into Exam: baseline

Collect PPT

Select 'Instrumented'
Select the "lightbulb" which is algometry
Click on custom tests
*Select the practice test on the first round, and then select all three tests (left and right versions) **in the order they are to be performed** (check data collection sheet for randomised order). We will randomised the 3 positions, and then do left and right in each position (also randomised), but will do one position at a time to reduce moving around.*
Rest time is set to 10 seconds (between repeated tests)

Location	Right			Left		
	Read 1	Read 2	Read 3	Read 1	Read 2	Read 3
Anterior to the lateral malleolus over the anterior talo-fibular ligament (ATFL)						
Inferior to the medial malleolus over the deltoid ligament						
over the proximal third of tibialis anterior muscle belly						

Data Collection sheet

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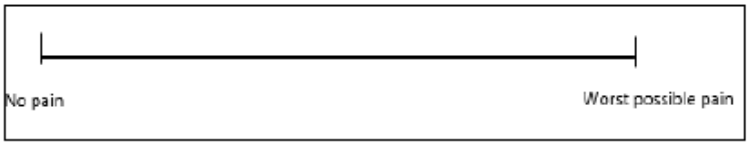
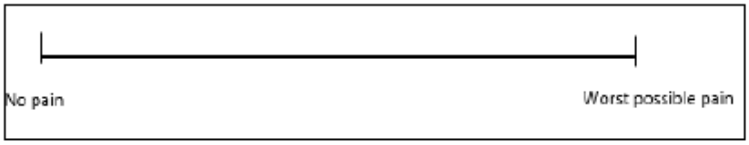
THE UNIVERSITY OF NEWCASTLE AUSTRALIA

Patient-Specific Functional Scale (PSFS) and body chart

At rest: (with 'no pain' on the left hand of the line and 'worst possible' on the right.)



Left leg



Right leg

List the three activities causes most pain?

Activity 1: .....

Activity 2: .....

Activity 3: .....

Data Collection sheet

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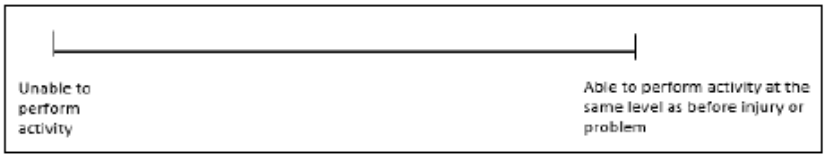
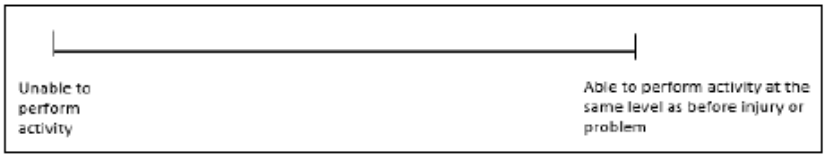
Mark the level of pain of each activity in below lines (with 'unable to perform the activity' on the left hand of the line and 'able to perform activity at the same levels as before injury or problem' on the right.)

Activity 1:

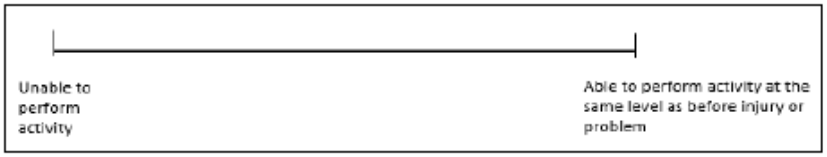


Left leg

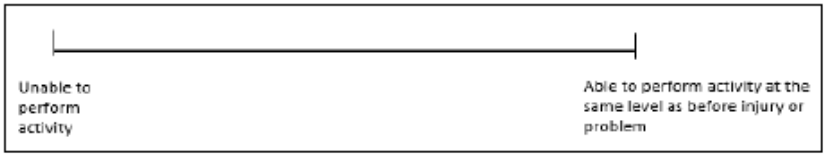


Right leg

Activity 2:

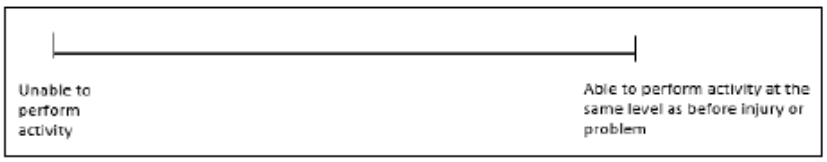


Left leg

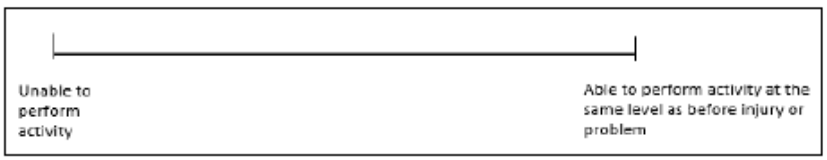


Right leg

Activity 3:



Left leg



Right leg

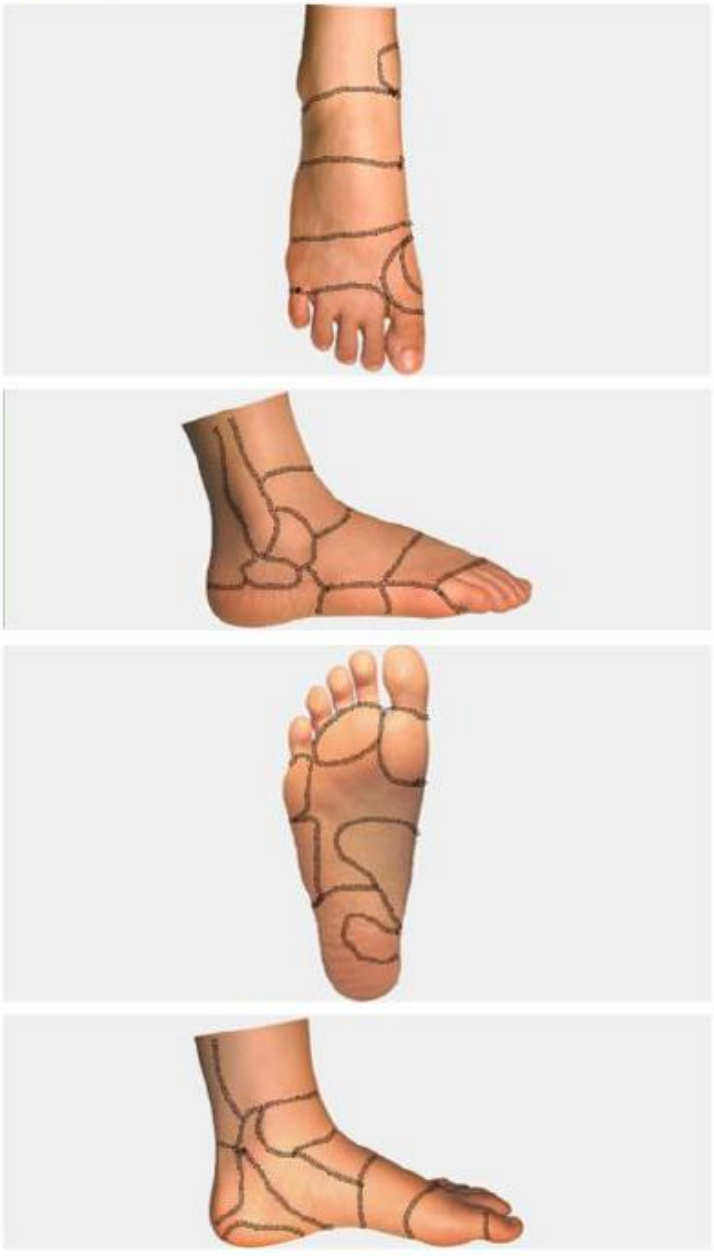
Data Collection sheet

The information on this form will be kept strictly confidential and is used to research purposes.

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

On the diagram below, please indicate the areas in which you are **currently** feeling symptoms.

1. First, **shade (colour)** the areas in which you are feeling pain.
2. Next, **circle** the area in which you are feeling tingling pricking, or burning.
3. Finally, **place an 'N'** near the area where you are feeling numbness, heaviness or other sensations.



Data Collection sheet

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THE UNIVERSITY OF NEWCASTLE AUSTRALIA

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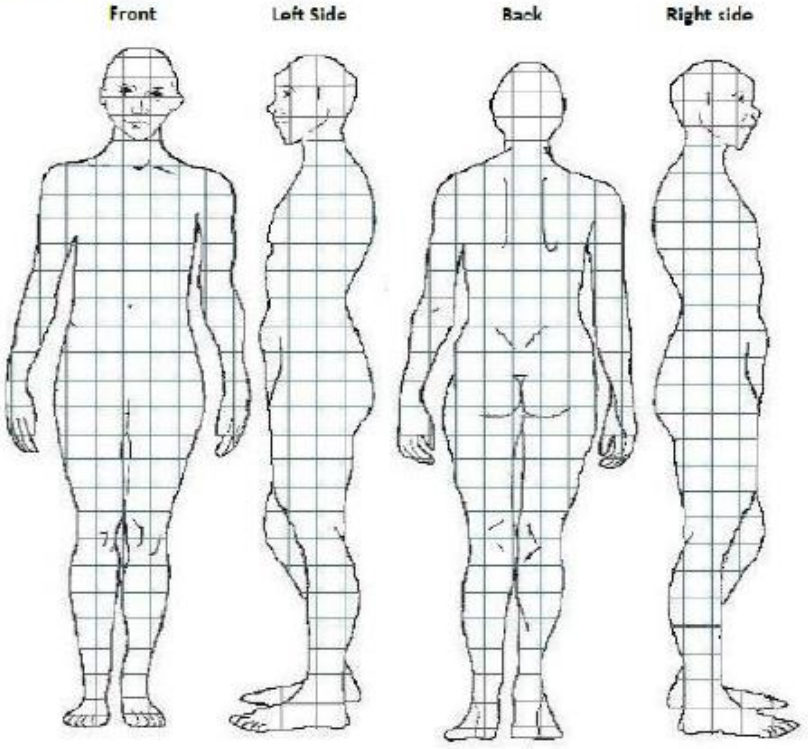


THE CAIT QUESTIONNAIRE

Please tick the **ONE** statement in **EACH** question that **BEST** describes your ankles.

1. I have pain in my ankle

	Left Ankle	Right Ankle
Never	○	○
During sport	○	○
Running on uneven surfaces	○	○
Running on level surfaces	○	○
Walking on uneven surfaces	○	○
Walking on level surfaces	○	○

2. My ankle feels UNSTABLE

	Left Ankle	Right Ankle
Never	○	○
Sometimes during sport (not every time)	○	○
Frequently during sport (every time)	○	○
Sometimes during daily activity	○	○
Frequently during daily activity	○	○

3. When I make SHARP turns, my ankle feels UNSTABLE

	Left Ankle	Right Ankle
Never	○	○
Sometimes when running	○	○
Often when running	○	○
When walking	○	○

4. When going down the stairs, my ankle feels UNSTABLE

	Left Ankle	Right Ankle
Never	○	○
If I go fast	○	○
Occasionally	○	○
Always	○	○

5. My ankle feels UNSTABLE when standing on ONE leg

	Left Ankle	Right Ankle
Never	○	○
On the ball of my foot	○	○
With my foot flat	○	○

6. My ankle feels UNSTABLE when

	Left Ankle	Right Ankle
Never	○	○
I hop from side to side	○	○
I hop on the spot	○	○
When I jump	○	○

7. My ankle feels UNSTABLE when

	Left Ankle	Right Ankle
Never	○	○
I run on uneven surfaces	○	○
I jog on uneven surfaces	○	○
I walk on uneven surfaces	○	○
I walk on a flat surface	○	○

8. TYPICALLY, when I start to roll over (or "twist") on my ankle, I can stop it

	Left Ankle	Right Ankle
Immediately	○	○
Often	○	○
Sometimes	○	○
Never	○	○
I have never rolled over on my ankle	○	○

9. After a TYPICAL incident of my ankle rolling over, my ankle returns to "normal"

	Left Ankle	Right Ankle
Almost immediately	○	○
Less than one day	○	○
1–2 days	○	○
More than 2 days	○	○
I have never rolled over on my ankle	○	○

Foot and Ankle Ability Measure (FAAM-ADL)

Please answer **every question** with **one response** that most closely describes your condition within the past week.

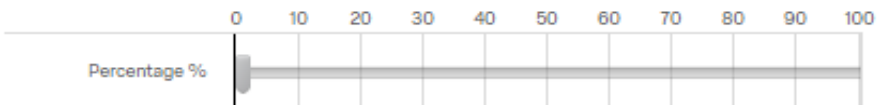
If the activity in question is limited by something other than your foot or ankle mark "Not Applicable" (N/A).

	No Difficulty at all	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	× Not applicable
Standing	○	○	○	○	○	○
Walking on even ground	○	○	○	○	○	○
Walking on even ground without shoes	○	○	○	○	○	○
Walking up hills	○	○	○	○	○	○
Walking down hills	○	○	○	○	○	○
Going up stairs	○	○	○	○	○	○
Going down stairs	○	○	○	○	○	○
Walking on uneven ground	○	○	○	○	○	○
Stepping up and down curbs	○	○	○	○	○	○
Squatting	○	○	○	○	○	○
Coming up on your toes	○	○	○	○	○	○
Walking initially	○	○	○	○	○	○
Walking 5 minutes or less	○	○	○	○	○	○
Walking approximately 10 minutes	○	○	○	○	○	○
Walking 15 minutes or greater	○	○	○	○	○	○

Because of your foot and ankle how much difficulty do you have with:

	No difficulty at all	Slight Difficulty	Moderate difficulty	Extreme Difficulty	Unable to do	× Not applicable
Home responsibilities	○	○	○	○	○	○
Activities of daily living	○	○	○	○	○	○
Personal care	○	○	○	○	○	○
Light to moderate work (standing, walking)	○	○	○	○	○	○
Heavy work (push/pulling, climbing, carrying	○	○	○	○	○	○
Recreational activities	○	○	○	○	○	○

How would you rate your current level of function during you usual activities of daily living from 0 to 100 with **100 being your level of function prior to your foot or ankle problem** and **0 being the inability to perform** any of your usual daily activities?

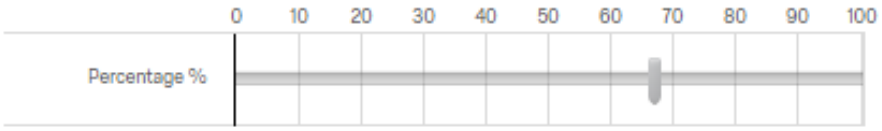


Foot and Ankle Ability Measure (FAAM-SPORTS)

Because of your foot and ankle how much difficulty do you have with:

	No Difficulty	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	× Not applicable
Running	○	○	○	○	○	○
Jumping	○	○	○	○	○	○
Landing	○	○	○	○	○	○
Starting and stopping quickly	○	○	○	○	○	○
Cutting/lateral movements	○	○	○	○	○	○
Low impact activities	○	○	○	○	○	○
Ability to perform activity with your normal technique	○	○	○	○	○	○
Ability to participate in your desired sport as long as you like	○	○	○	○	○	○

How would you rate your current level of function during your sports related activities from 0 to 100 with **100 being your level of function prior to your foot or ankle problem** and **0 being the inability to perform** any of your usual daily activities?



Overall, how would you rate your current level of function?

Normal	Nearly normal	Abnormal	Severely abnormal
○	○	○	○

Foot and Ankle Outcome Score (FAOS) questionnaire

This survey asks for your view about your foot/ankle. Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms

These questions should be answered thinking of your foot/ankle symptoms during the **last week.**

	Never	Rarely	Sometimes	Often	Always
S1. Do you have swelling in your foot/ankle?	○	○	○	○	○
S2. Do you feel grinding, hear clicking or any other type of noise when your foot/ankle moves?	○	○	○	○	○
S3. Does your foot/ankle catch or hang up when moving?	○	○	○	○	○

These questions should be answered thinking of your foot/ankle symptoms during the **last week.**

	Always	Often	Somtimes	Rarely	Never
S4. Can you straighten(ankle move towards ground) your foot/ankle fully?	○	○	○	○	○
S5. Can you bend (ankle move towards your face)your foot/ankle fully?	○	○	○	○	○

Stiffness

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

	None	Mild	Moderate	Severe	Click to write Scale point 5
S6. How severe is your foot/ankle stiffness after first wakening in the morning?	○	○	○	○	○
S7. How severe is your foot/ankle stiffness after sitting, lying or resting later in the day?	○	○	○	○	○

Pain

	Never	Monthly	Weekly	Daily	Always
P1. How often do you experience foot/ankle pain?	○	○	○	○	○

What amount of foot/ankle pain have you experienced the **last week** during the following activities?

	None	Mild	Moderate	Severe	Extreme
P2. Twisting/pivoting on your foot/ankle	○	○	○	○	○
P3. Straightening foot/ankle fully	○	○	○	○	○
P4. Bending foot/ankle fully	○	○	○	○	○
P5. Walking on flat surface	○	○	○	○	○
P6. Going up or down stairs	○	○	○	○	○
P7. At night while in bed	○	○	○	○	○
P8. Sitting or lying	○	○	○	○	○
P9. Standing upright	○	○	○	○	○

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 foot/ankle.

	None	Mild	Moderate	Severe	Extreme
A1. Descending stairs	○	○	○	○	○
A2. Ascending stairs	○	○	○	○	○

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

	None	Mild	Moderate	Severe	Extreme
A3. Rising from sitting	○	○	○	○	○
A4. Standing	○	○	○	○	○
A5. Bending to floor/pick up an object	○	○	○	○	○
A6. Walking on flat surface	○	○	○	○	○
A7. Getting in/out of car	○	○	○	○	○
A8. Going shopping	○	○	○	○	○
A9. Putting on socks/stockings	○	○	○	○	○
A10. Rising from bed	○	○	○	○	○
A11. Taking off socks/stockings	○	○	○	○	○
A12. Lying in bed (turning over, maintaining foot/ankle position)	○	○	○	○	○
A13. Getting in/out of bath	○	○	○	○	○
A14. Sitting	○	○	○	○	○
A15. Getting on/off toilet	○	○	○	○	○

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

	None	Mild	Moderate	Severe	Extreme
A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)	○	○	○	○	○
A17. Light domestic duties (cooking, dusting, etc)	○	○	○	○	○

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 foot/ankle.

	None	Mild	Moderate	Severe	Extreme
SP1. Squatting	○	○	○	○	○
SP2. Running	○	○	○	○	○
SP3. Jumping	○	○	○	○	○
SP4. Twisting/pivoting on your injured foot/ankle	○	○	○	○	○
SP5. Kneeling	○	○	○	○	○

Quality of Life

	Never	Monthly	Weekly	Daily	Constantly
Q1. How often are you aware of your foot/ankle problem?	○	○	○	○	○

	Not at all	Mildly	Moderately	Severely	Extremely
Q2. Have you modified your life style to avoid potentially damaging activities to your foot/ankle?	○	○	○	○	○
Q3. How much are you troubled with lack of confidence in your foot/ankle?	○	○	○	○	○

	None	Mild	Moderate	Severe	Exrteme
Q4. In general, how much difficulty do you have with your foot/ankle?	○	○	○	○	○

Perception about the intervention (to be distributed at the end of the intervention phase)

- What did you think of the intervention?

.....

.....

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.....

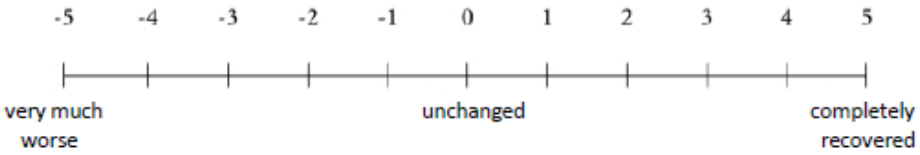
- Do you think that the intervention you received during the last 4 weeks is the active (genuine or true) intervention? Please answer the question by ticking the appropriate box below:

Yes ☐

No ☐

- Please mark the line that best indicates your confidence of above response in the scale from 1-10 (with 0='not at all confident' and 10='extremely confident)

- With respect to your ankle problem how would you describe yourself now compared to before you had the intervention to your ankle? (circle a number)



Appendix 16 Journal publications

ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

Archives of Physical Medicine and Rehabilitation 2018;99:1395-412

REVIEW ARTICLE (META-ANALYSIS)

Clinical Benefits of Joint Mobilization on Ankle Sprains: A Systematic Review and Meta-Analysis

Ishanka Weerasekara, MPhil, Peter Osmotherly, PhD, Suzanne Snodgrass, PhD, Jodie Marquez, MMgt(Health), Rutger de Zoete, MSc, Darren A. Rivett, PhD

From the School of Health Sciences, Faculty of Health and Medicine, The University of Newcastle, Callaghan, Australia.

Abstract

Objective: To assess the clinical benefits of joint mobilization for ankle sprains.

Data Sources: MEDLINE, MEDLINE In-Process, Embase, AMED, PsycINFO, CINAHL, Cochrane Library, PEDro, Scopus, SPORTDiscus, and Dissertations and Theses were searched from inception to June 2017.

Study Selection: Studies investigating humans with grade I or II lateral or medial sprains of the ankle in any pathologic state from acute to chronic, who had been treated with joint mobilization were considered for inclusion. Any conservative intervention was considered as a comparator. Commonly reported clinical outcomes were considered such as ankle range of movement, pain, and function. After screening of 1530 abstracts, 56 studies were selected for full-text screening, and 23 were eligible for inclusion. Eleven studies on chronic sprains reported sufficient data for meta-analysis.

Data Extraction: Data were extracted using the participants, interventions, comparison, outcomes, and study design approach. Clinically relevant outcomes (dorsiflexion range, proprioception, balance, function, pain threshold, pain intensity) were assessed at immediate, short-term, and long-term follow-up points.

Data Synthesis: Methodological quality was assessed independently by 2 reviewers, and most studies were found to be of moderate quality, with no studies rated as poor. Meta-analysis revealed significant immediate benefits of joint mobilization compared with comparators on improving posteromedial dynamic balance ($P=.0004$), but not for improving dorsiflexion range ($P=.16$), static balance ($P=.96$), or pain intensity ($P=.45$). Joint mobilization was beneficial in the short-term for improving weight-bearing dorsiflexion range ($P=.003$) compared with a control.

Conclusions: Joint mobilization appears to be beneficial for improving dynamic balance immediately after application, and dorsiflexion range in the short-term. Long-term benefits have not been adequately investigated.

Archives of Physical Medicine and Rehabilitation 2018;99:1395-412

Ankle sprains are a common injury in sports and the general community, and may lead to chronic pain, functional limitations, and physical disability.[1,2] Epidemiologic studies conducted in various countries highlight the high incidence of ankle sprains during sports training and competition, with rates reported as 7 per 1000 in Denmark, 6.09 per 1000 in the United Kingdom, and 2.15 per 1000 in the United States in person-years.[3-5] Plantarflexion inversion sprain or lateral ankle sprain is the most common type of ankle sprain.[6] It typically results in an injury of the inferior tibiofibular ligament, anterior tibiofibular ligament, or the bifurcate ligament.[7] Eversion injuries often result in damage to the deltoid and spring ligaments of the medial aspect of the ankle.[7]

According to the clinical practice guidelines linked to the *International Classification of Functioning, Disability and Health* from the Orthopaedic Section of the American Physical Therapy Association, manual therapy is recommended for both the acute and progressive loading phases of rehabilitation.[8] Management of

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International Prospective Register of Systematic Reviews (PROSPERO) Registration No.: CRD42016030194.

Disclosures: none.

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ankle sprains commonly involves mobilization procedures applied to the joint, such as nonthrust joint mobilization, high-velocity thrust manipulation, and mobilization with movement (MWM).

The mechanisms by which these techniques are purported to work are biomechanical (such as stretching/tearing tissue, inducing cavitation within the joint, reducing muscle hypertonicity/stiffness) and neurophysiological, potentially including spinal cord and supraspinally mediated mechanisms.[9,10]

Several studies[11-21] have investigated the effects of manual therapy on ankle sprains using a variety of outcome measures including pain, range of motion (ROM), and function from the acute to chronic stages of recovery, with different results reported. Several systematic reviews[22-26] have attempted to collate this evidence but have been limited by their narrow focus on lateral ankle sprains and restricted outcome measures. Previous systematic reviews have all included some studies that involved other interventions such as "rest, ice, compression, and elevation" (RICE) and home exercise programs as an adjunct to mobilization. Therefore, they have not actually assessed mobilization as the sole intervention. Moreover, the clinical benefits of joint mobilization have not yet been evaluated through meta-analysis, despite it being a common intervention used in the rehabilitation of a number of ankle conditions and despite the growing body of empirical literature.

The present systematic review aims to address these limitations by synthesizing and meta-analyzing the available evidence for ankle joint mobilization (including high-velocity thrust manipulation) in grade I or II ankle sprains of the medial or lateral ligaments in the acute/subacute/chronic stages of rehabilitation in any ambulant setting.

Methods

Registration

The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews on January 12, 2016 (CRD42016030194).

Search strategy

A search of electronic databases, including MEDLINE, MEDLINE In-Process, Embase, AMED, PsycINFO, CINAHL, Cochrane Library, PEDro, Scopus, SPORTDiscus, and Dissertations and Theses was conducted from inception to June 2017. In addition to the database search, a hand search of the reference lists of identified studies was also carried out. A search strategy (supplemental appendix S1, available online only at http://www.archives-pmr.org/) was developed for the main search strings of ankle sprain and mobilization. Keywords used for "ankle sprain" included sprain, talocrural joint, ligament injuries, lateral ligament, medial ligament, deltoid ligament, collateral ligament, anterior talofibular ligament, posterior talofibular ligament, sprain and strain, and ankle twist. Keywords used for "mobilization" included manual therapy, joint mobilization, manipulation, MWM, Maitland, Mulligan, and rehabilitation. These terms were used alone and in combinations during the search.

List of abbreviations:

CI	**confidence interval**
DFROM	**dorsiflexion range of motion**
MCID	**minimal clinically important difference**
MD	**mean difference**
MWM	**mobilization with movement**
RICE	**rest, ice, compression, and elevation**
ROM	**range of motion**
SEBT	**star excursion balance test**
SMD	**standardized mean difference**

Identification and selection of studies

Full-text randomized controlled trials, crossover studies, cross-sectional studies, cohort studies, and case series published in peer-reviewed journals and dissertations were considered for the present review. Studies were not restricted by language, provided the title and abstract were in English. Studies not involving live human participants (eg, model-based, animal, and cadaveric investigations) were excluded. Conference proceedings, commentaries, research notes, editorials, and letters were also excluded. To be included, studies were required to meet the criteria that follow.

Participants

Participants were live humans (without any age limitation) with a grade I or II lateral or medial ligament sprain of the ankle at any stage of recovery (acute to chronic) in any ambulant setting who have been treated with joint mobilization. Studies involving grade III sprains, fractures (other than Weber type A), and syndesmotic injuries were excluded from this review.

Intervention

Studies reporting any type of joint mobilization techniques applied to the talocrural joint, subtalar joint, or inferior tibiofibular joint by a physiotherapist, medical practitioner, osteopath, chiropractor, or athletic trainer were eligible for inclusion in the review. Interventions other than therapist-performed joint mobilization were excluded from the review.

Comparators

Studies reporting any conservative intervention for comparison, such as exercise therapy, elevation and icing, supportive strapping, sham intervention, or no treatment, were eligible for inclusion. Control groups with healthy subjects were also eligible as a comparator. Studies that compared mobilization techniques to surgical interventions were excluded.

Outcome measures

All commonly reported clinical impairments (pain, swelling, balance, proprioception, strength, stability, gait), activity restriction and self-reported confidence, community participation, quality of life, reinjury rate, function, and return to sport were considered for the review. The primary outcomes of interest were ankle ROM, pain, quality of life, and function.

Timing of the measurement of the outcomes was categorized as "immediate," measured immediately after the intervention[27]; "short-term," measured up to 3 months after the intervention[28]; and "long-term," measured at 3 or more months[22] after the intervention.

Identified studies were exported to reference management software (EndNote X7.3.1[a]), and duplicate records were manually removed. Study titles and abstracts were initially screened by 2 independent reviewers, followed by screening of full-text articles, to determine the eligibility of the identified studies. Disagreement between the reviewers was resolved by consensus or involvement of a third reviewer. The level of agreement between reviewers was assessed using Cohen's kappa.[29]

Table 1 Description of eligible studies

Study	Design	Sample	Intervention and Dosage	Comparator	Measurement Time Points	Outcomes	Results
Alanson et al,[36] 2012	RCT	17 (10M) Grade 1/2 Chronic lateral ankle sprains	TCJ (anteroposterior) mobilization + TCJ traction 30s	Sham	Immediate	Non–weight-bearing DFROM, proprioception (joint position sense)	Non–weight-bearing DFROM, significantly improved across time ($P=.04$). Joint position sense significantly improved across time at target angle 10° plantarflexion ($P=.03$).
Beazell et al,[37] 2012	RCT	43 Chronic ankle sprains	Distal TFJ manipulation + HVLA thrust 1 repetition	No intervention	Immediate, short-term (1, 2, and 3 wk)	Weight-bearing DFROM, static balance (single-limb stance), function (step down test, self-reported function, FAAM sports)	Weight-bearing DFROM not significant ($P=.82$). Single-limb stance not significant ($P=.42$). Function not significant—step down test ($P=.76$), self-reported function ($P=.61$), FAAM sports ($P=.83$)
Collins et al,[13] 2004	Randomized crossover	16 (8M) Grade 2 Subacute lateral ankle sprains	Weight- bearing MWM TCJ (posterior talar glide, posteroanterior tibial glide) 3 sets of 10 repetitions	Placebo No intervention	Immediate	Weight- bearing DFROM, pressure-pain threshold, thermal pain threshold	Weight- bearing DFROM significantly improved across time ($P=.013$) and no significant group difference (vs placebo, $P=.202$; vs control, $P=.208$). Pressure-pain threshold and thermal pain threshold not significant ($P<.05$).
Cruz-Díaz et al,[14] 2015	RCT	81 (47M) Chronic ankle sprains	Weight–bearing MWM TCJ (posterior talar glide, posteroanterior tibial glide) 2 sets of 10 repetitions, 2 sessions/wk for 3wk	Sham, no intervention	Immediate, short-term (3wk), long-term (6mo)	Weight–bearing DFROM, dynamic balance (SEBT)	Weight-bearing DFROM significantly improved–$P<.0001$ (at each time point). Dynamic balance significantly improved–$P<.0001$ (each direction of SEBT)
Gilbreath et al,[21] 2014	Prospective longitudinal	11 (5M) Chronic ankle sprains	Weight–bearing MWM TCJ (posterior talar glide, posteroanterior tibial glide) 2 sets of 4 repetitions 4min of MWM×3 sessions over 1wk	No control group	Short-term (after 24–48h)	Weight-bearing DFROM, dynamic balance (SEBT), function (FAAM)	Weight-bearing DFROM not significant ($P=.69$). Dynamic balance not significant (SEBT-anterior, $P=.99$; posteromedial, $P=.15$; posterolateral, $P=.24$). FAAM ADL not significant ($P=.19$). FAAM Sports significantly improved across time ($P=.01$).
Harkey et al,[38] 2014	RCT	30 (14M) Chronic ankle sprains	Maitland mobilization TCJ (anteroposterior grade III) 3 sets of 60s	No intervention	Immediate	Non–weight-bearing DFROM, dynamic balance (SEBT)	Non–weight-bearing DFROM significantly improved ($P=.049$). Dynamic balance no improvement ($P>.05$).

(*continued on next page*)

Table 1 (*continued*)

Study	Design	Sample	Intervention and Dosage	Comparator	Measurement Time Points	Outcomes	Results
Hoch and McKeon,[39] 2011	Randomized crossover	20 (9M) Chronic ankle sprains	Maitland mobilization TCJ (anterior posterior grade III) 50±5 of 1-s oscillations ×2	No intervention	Immediate	Weight- bearing DFROM, static balance, dynamic balance (SEBT), talar stiffness	Weight-bearing DFROM significantly improved ($P=.01$). Static balance significantly improved. Time to boundary anteroposterior minima significantly improved ($P<.0001$). Dynamic balance—not significant—$P=.98$ (normalized reach distance). Talar stiffness not significant ($P=.08$).
Hoch et al,[40] 2012	Prospective longitudinal	12 (6M) Chronic ankle sprains	Maitland mobilization TCJ (anteroposterior grade III) + TCJ traction 2 sets of 2min traction and 4 sets of 2min mobilization	No control group	Short-term (24–48h and 1-wk follow-up)	Weight-bearing DFROM, dynamic balance, function (FAAM)	Weight-bearing DFROM significantly improved across time ($P<.0001$). Dynamic balance significantly improved across time (SEBT anterior, $P<.0001$; posteromedial, $P=.003$; posterolateral, $P<.0001$). FAAM ADL and Sports significantly improved across time ($P=.001$).
Hoch et al,[41] 2014	Prospective longitudinal	12 (6M) Chronic ankle sprains	Maitland mobilization TCJ (anteroposterior grade III) + TCJ traction 2 sets of 2min traction and 4 sets of 2min	No control group	Short-term (24–48h, and 1-wk follow-up)	Static balance, talar stiffness	Static balance not significant. Time to boundary anteroposterior and time to boundary mediolateral not significant ($P>.05$). Talar stiffness not significant ($P>.05$).
Hopper et al,[42] 2009	Randomized controlled Within-subjects design	20 (8M) Chronic ankle sprains	Mulligan ankle taping Not explicitly stated	Injured taped, Injured untaped, Uninjured taped, Uninjured untaped	Immediate	Static balance, dynamic balance (wandering, overshoot, reaction time)	Static balance significantly improved in postural sway recovery across time ($P<.001$). Single-limb stance not significant- ($P=.792$), Dynamic tracking balance not significant; wandering ($P=.559$), overshoot ($P=.547$), reaction time ($P=.142$).
Houstan et al,[43] 2013	Prospective longitudinal	12 (6M) Chronic ankle sprains	Maitland mobilization TCJ (anteroposterior grade III) + TCJ traction 4min of traction and 8min of mobilization 6 sessions over 2wk.	No control group	Immediate, short-term (1-wk follow-up)	Function (FAAM Sports)	FAAM ADL some components significantly improved across time; walking on even ground ($P=.06$); going down stairs ($P=.07$); walking on uneven ground ($P=.03$); light to moderate work ($P=.06$); heavy work ($P=.03$); recreational activity ($P=.07$).

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Table 1 (*continued*)

Study	Design	Sample	Intervention and Dosage	Comparator	Measurement Time Points	Outcomes	Results
							FAAM Sports some components significantly improved across time; landing ($P=.03$); low impact activities ($P=.07$); cutting ($P=.02$).
Joseph et al,[44] 2010	RCT	40 (19M) Grade 1/2 Chronic lateral ankle sprains	Ankle axial elongation TCJ (superior inferior)-HVLA thrust 6 sessions over 3wk	Muscle energy technique	Short-term (1mo)	DFROM, plantarflexion ROM, static balance, pain quality and intensity, function (Functional Evaluation Scale)	DFROM significantly improved across time ($P<.001$) and no significant group differences ($P=.713$). Plantarflexion ROM significantly improved across time ($P<.001$) and no significant group differences ($P=.300$). Single-limb stance—eyes closed significantly improved across time ($P<.001$) and no significant group differences ($P=.344$). Single-limb stance—eyes open significantly improved across time ($P<.001$) and no significant group differences ($P=.413$). McGill significantly improved across time ($P<.001$) and no significant group differences ($P=.077$). Functional Evaluation Scale significantly improved across time ($P<.001$) and no significant group differences ($P=.144$).
Kohne, et al,[45] 2007	RCT	30 (21M) Grade 1/2 Chronic, recurrent lateral ankle sprains	Ankle axial elongation TCJ (superior inferior by a mortise separation)—(6 manipulations over 4wk)	Single manipulation treatment	Short-term (fifth week follow-up)	DFROM, proprioception (joint position sense), pressure-pain threshold, pain intensity	DFROM significantly improved: $P=.028$ (across time). Joint position sense at 5° plantarflexion error significantly improved: $P=.029$ (across time). Pressure-pain threshold (P value not reported), pain intensity (P value not reported).
Lopez-Rodrıguez et al,[46] 2007	Randomized controlled within-subject repeated measures	52 (35M) Grade 2 Chronic lateral ankle sprains	TCJ Manipulation (caudal) HVLA thrust + posterior gliding manipulation TCJ -HVLA thrust 1min	Placebo	Immediate	Proprioception	Proprioception significantly improved; load support—bilateral posterior load ($P=.016$), anterior load ($P=.04$), posterior load ($P=.043$), posterior-anterior load ($P=.016$).

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Table 1 (*continued*)

Study	Design	Sample	Intervention and Dosage	Comparator	Measurement Time Points	Outcomes	Results
Marron-Gomez et al,[15] 2015	RCT	52 (31M) Chronic ankle sprains	Weight-bearing MWM TCJ (posterior talar glide, posteroanterior tibial glide) 1 set of 10 repetitions TCJ HVLA distraction thrust ×3	Placebo	Immediate, short-term (24 and 48h)	Weight-bearing DFROM	MWM—Weight-bearing DFROM significantly greater than placebo —$P<.05$ (immediately and short-term). HVLA—weight-bearing DFROM significantly greater than placebo —$P<.001$ (immediately) and $P=.001$(short-term).
Pellow and Brantingham,[47] 2001	RCT	30 (19M) Grade 1/2 subacute and chronic lateral ankle sprains	Ankle axial elongation (TCJ— superior inferior by a mortise separation) 8 manipulations over 4wk	Detuned ultrasound treatment	Short-term (1-mo follow-up)	Non—weight-bearing DFROM, pain threshold, pain quality and intensity, function (Functional Evaluation Scale)	Non—weight-bearing DFROM significantly improved across time ($P=.001$) and between groups ($P=.001$). Pain threshold significantly improved across time ($P=.002$) and no significant group differences ($P=.395$). McGill significantly improved across time ($P=.001$) and between groups ($P=.004$). Pain intensity significantly improved across time ($P=.002$) and between groups ($P=.004$). Functional Evaluation Scale significantly improved across time ($P=.001$) and between groups ($P<.001$).
Plante,[48] 2012	RCT	20 (12M) Chronic ankle sprains	TCJ (anteroposterior) 10 oscillations	Healthy subjects	Immediate	Weight-bearing DFROM, static balance, function (dynamic functional tasks)	Weight-bearing DFROM significantly improved across time ($P<.0001$). Single-limb stance, center of pressure significantly improved ($P<.04$). Dynamic functional task (center of pressure medial-lateral during jump task significantly improved [$P<.001$]; center of pressure medial-lateral during squat significantly improved [$P<.022$]; center of pressure medial-lateral during stance task significantly improved [$P<.039$]).

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Table 1 (*continued*)

Study	Design	Sample	Intervention and Dosage	Comparator	Measurement Time Points	Outcomes	Results
Reid et al,[49] 2007	Randomized crossover	23 (8M) Chronic lateral ankle	Weight- bearing MWM (posterior talar glide, posteroanterior tibial glide) 10 repetitions ×2	Sham	Immediate	Weight-bearing DFROM	Weight-bearing DFROM significantly improved (P=.02).
Someeh et al,[50] 2015	Experimental study design—within subjects	32 (20M) Chronic ankle sprains	Mulligan ankle taping/ fibular repositioning taping Not explicitly stated	Healthy subjects	Immediate	Dynamic balance (SEBT)	Dynamic balance significantly improved across time—SEBT overall reach (P=.001).
Someeh et al,[51] 2015	Experimental study design—within subjects	32 (20M) Chronic ankle sprains	Mulligan ankle taping Not explicitly stated	Healthy subjects	Immediate	Function (dynamic functional tasks), participants' perceptions of stability and confidence	Function significantly improved across time; single leg hopping (P=.014); figure-of-8 hopping (P=.05); side hopping (P=.001). Confidence in abovementioned functional tests significantly improved across time; consequently, P=.023, .048, and .038, respectively.
Vicenzino et al,[16] 2006	Randomized crossover	16 (8M) Chronic lateral ankle sprains	Non—weight-bearing MWM (anteroposterior talar glide for dorsiflexion), 4 glides of 10s 4 sets Weight-bearing MWM (posterior talar glide, posteroanterior tibial glide) 4 sets of 10 glides	No intervention	Immediate	Weight-bearing DFROM, talar stiffness	Weight-bearing DFROM significantly improved (P=.017). Talar glide significantly improved (P<.001).
Wells,[52] 2012	RCT	17 (7M) Chronic ankle sprains	Maitland mobilization (TCJ—anteroposterior grade IV) 3 repetitions, 60s	No intervention	Immediate	Weight -bearing DFROM, non—weight-bearing DFROM, dynamic balance, pain intensity, static balance, stiffness, function (self-reported function)	Weight -bearing DFROM not significant (P=.95). Non—weight-bearing DFROM not significant (P=.1). Dynamic balance not significant; SEBT composite (P=.8); anterior (P=.07); posteromedial (P=.79); posterolateral (P=.73). Pain not significant (P=.06). Stiffness not significant (P=.59). Stability not significant (P=.40). Function (visual analog scale) not significant (P=.44).

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Table 1 (*continued*)

Study	Design	Sample	Intervention and Dosage	Comparator	Measurement Time Points	Outcomes	Results
Yeo et al,[53] 2011	Randomized, controlled, within-subject repeated measures	13 (10M) Grade 2 Subacute lateral sprain	Maitland mobilization (distal TFJ anteroposterior) 3 sets of 1min mobilization	Placebo No intervention	Immediate	Weight-bearing DFROM, pressure-pain threshold, pain intensity, function (Functional Evaluation Scale)	Weight-bearing DFROM significantly improved ($P<.0001$). Pressure-pain threshold significantly improved ($P<.0001$). Pain intensity not significant ($P=.369$). Functional Evaluation Scale not significant ($P=.475$).

NOTE. "Immediate," measured immediately after the intervention. "Short-term," measured up to 3 months after the intervention. "Long-term," measured at 3 or more months after the intervention.
Abbreviations: ADL, activities of daily living; FAAM, Foot and Ankle Ability Measure; HVLA, high velocity, low amplitude; M, male; RCT, randomized controlled trial; TCJ, talocrural joint; TFJ, tibiofibular joint.

Assessment of methodological quality

The methodological quality of individual studies was assessed using the PEDro Scale for randomized controlled trials and the Quality Assessment Tool for Observational Cohort and Cross-sectional Studies.[30-32] Two independent reviewers assessed the methodological quality, and the level of agreement between reviewers was assessed using Cohen's kappa.

Assessment of quality of evidence

The overall quality of evidence was assessed at the stage of meta-analysis, using the Grading of Recommendations, Assessment, Development, and Evaluation approach.[33] The quality of the evidence was classified as either high, moderate, low, or very low.[34] Risk of bias, consistency of results, directness (eg, generalizability), and precision (eg, sufficient data) were considered in assessing the overall quality.[35]

Data extraction and statistical analysis

Descriptive data were extracted using an extraction table (table 1). Authors were contacted if possible where there were difficulties extracting data from the published article. Where feasible, study data that were comparable in terms of participant characteristics, outcome measures, and follow-up periods were pooled, and a meta-analysis was performed.

For the meta-analysis, the standardized mean difference (SMD) was calculated for the outcomes where the means and SDs were provided pre- and postintervention. This conversion of the data to a common scale permitted comparison of studies that used different tools to measure the same outcome. This review followed the general practice of interpretation for small, medium, and large effect sizes (0.2, small effect; 0.5, medium effect; 0.8, large effect).[54,55] The mean difference (MD) was calculated for studies using the same instrument for measurement. The results were reported in forest plots with 95% confidence intervals (CIs). The minimal clinically important difference (MCID) was used to interpret the clinical meaningfulness of the findings. Inconsistency was quantified by calculating I^2 and interpreted as follows: 30% to 59% may represent moderate heterogeneity, 60% to 89% substantial heterogeneity, and 90% to 100% considerable heterogeneity between studies. If I^2 was >30%, a random-effects model was used to incorporate intertrial heterogeneity.[31]

In the instance of multiple comparison groups, the sham group was selected as the control condition. For the outcome of "static balance," studies with eyes-closed balance were selected to maintain the homogeneity of the analysis. Further, in studies with multiple time points, measurements taken at 2 to 3 weeks were selected for the meta-analysis (eg, if effects were measured at the time points of 2d, 3wk, and 2mo in a single study, data from measurements at 3wk were selected for the analysis). All statistical analyses were conducted using RevMan 5.3.[b]

Results

Selection and characteristics of included studies

The database search identified 1521 studies after duplicate removal, and a further 9 studies were identified through citation tracking and hand searching of reference lists (fig 1). After the first

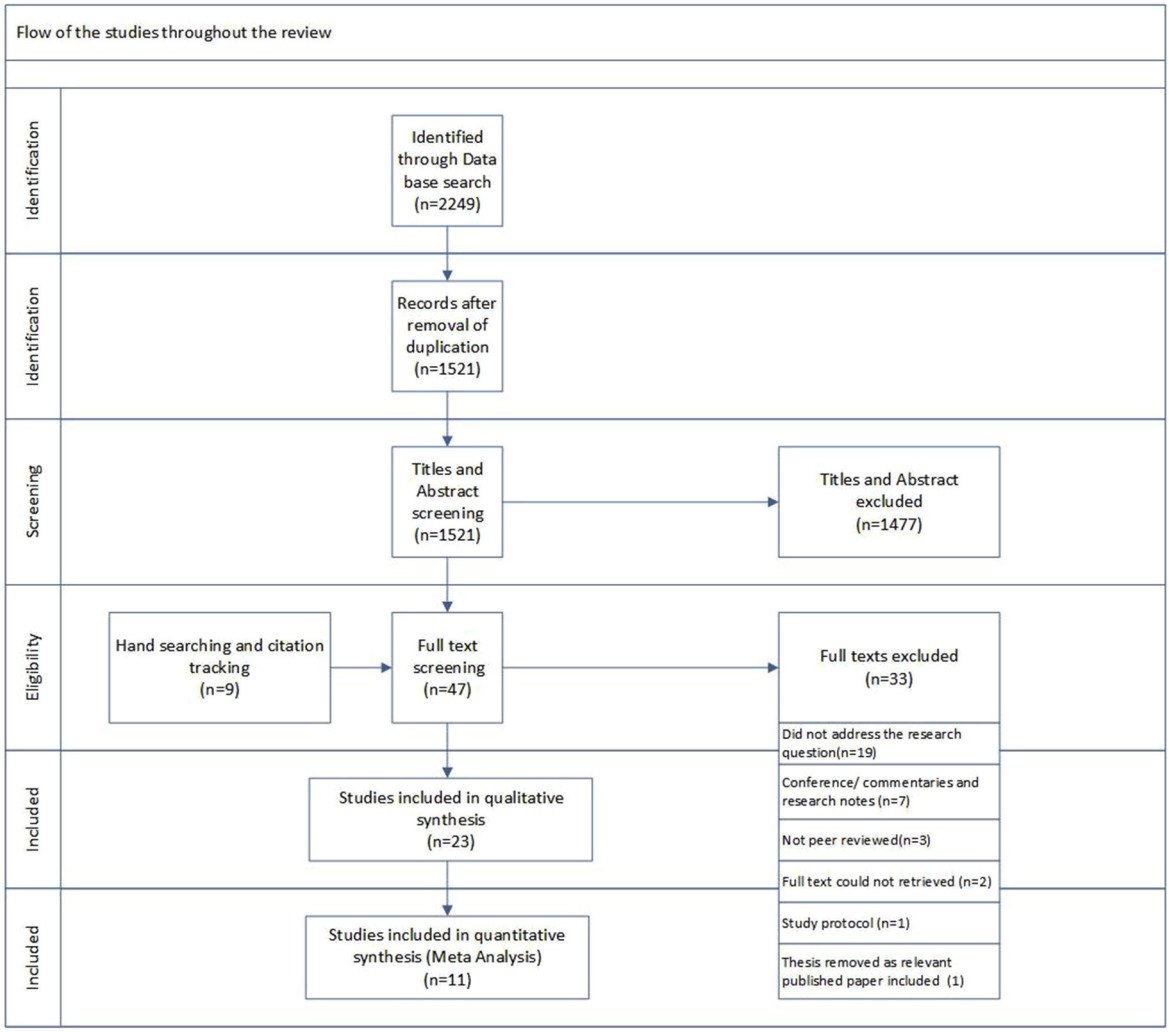

Fig 1 Flow chart of study selection.

stage of screening (using study title and abstract), 56 studies (database search, n=47; hand search, n=9) were identified as eligible for inclusion from the original 1530 (database search, n=1521; hand search, n=9) studies. Common reasons for exclusion after title and abstract screening included ineligible study design, joint mobilization not assessed in isolation, and study aim not relevant to the review research question. A further 33 studies were excluded in second stage (full text) screening, and reasons for exclusion included study aim not relevant to research question[12,18,19,56-71] (n=19); conference proceedings, commentaries, and research notes[72-78] (n=7); not peer reviewed[79-81] (n=3); full text not available[82,83] (n=2); study protocol only[84] (n=1); and thesis removed as the relevant published article was included[85] (n=1). Twenty-three studies (including 3 theses) were therefore included in the current review. The interreviewer agreement for the title/abstract and full-text screenings was considered to be very good (κ=.80; 95% CI, .72−.89) and good (κ=.71; 95% CI, .52−.90), respectively. All disagreements were resolved by consensus. The data from 11 studies (including 2 theses[48,52]) were available and deemed appropriate for inclusion in the meta-analysis (see fig 1). Publication bias was visually observed using funnel plots (supplemental appendix S2, available online only at http://www.archives-pmr.org/).

The included studies were conducted in 7 countries (Australia, Canada, Iran, New Zealand, South Africa, Spain, United States) and involved a total of 585 participants. Twenty-one studies evaluated chronic ankle sprains, and 3 studies investigated subacute sprains. Outcomes measured varied widely and included dorsiflexion range of motion (DFROM), proprioception, stability/balance, pain threshold (pressure and thermal), pain intensity and quality, function, talar stiffness, postural sway, and patient confidence. A range of joint mobilization techniques were used, and these included MWM in weight bearing and/or non−weight bearing (n=6)[13-16,21,49]; anteroposterior talocrural mobilization (Maitland grades III and IV)[86] (n=4)[38,39,48,52]; high-velocity, low-amplitude ankle axial elongation manipulation and manipulation of the talocrural joint (n=6)[15,36,44-47]; Mulligan ankle taping (n=3)[42,50,51]; distal tibiofibular joint manipulation or mobilization (n=2)[37,53]; and combined mobilization and traction of the talocrural joint (n=4).[36,40,41,43] Mulligan ankle taping was included because it aims to mimic a MWM by sustaining the fibula glide during daily activities.[7] These techniques were variously applied by physiotherapists, medical practitioners, chiropractors, and athletic trainers. Table 1 describes the participants, interventions, comparators, outcome measures, and results of the included studies.

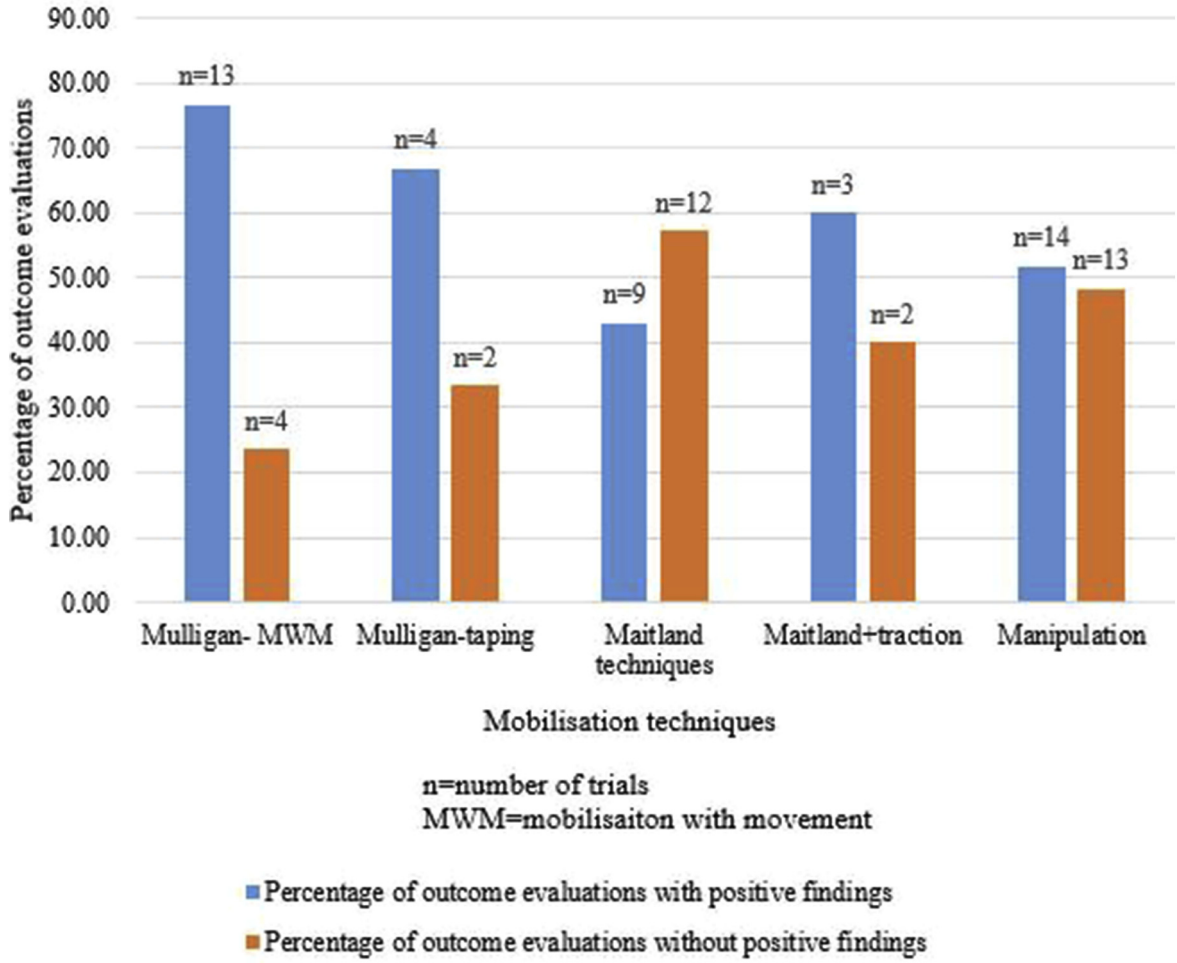

Fig 2 Percentage and number of outcome evaluations with and without positive findings following each technique combination of mobilisation for any clinically relevant outcome at any time point.

The immediate effects of joint mobilization were evaluated in 17 studies, short-term effects in 10 studies, and the long-term effects were assessed in only 1 study (see table 1). No studies evaluating effects on gait parameters, quality of life, reinjury rate, or strength were located in our search. In this systematic review, participants with chronic ankle sprains were included in 21 studies, and 3 studies included participants with subacute sprains. No studies measuring the effectiveness of mobilization in isolation for acute ankle sprains were able to be found. A meta-analysis was conducted using 11 studies, all involving participants with chronic ankle sprains.

Common mobilization techniques used in rehabilitation of ankle sprains

Five combinations of mobilization techniques were used in the 23 studies, including Mulligan MWM and taping techniques, Maitland mobilization with and without traction, and manipulation. The number of studies with positive effects on any clinically relevant outcome is contrasted against the number of studies with no positive effects, for each mobilization technique (fig 2). The findings also suggest that the combination of Mulligan MWM and taping is more likely to produce a clinical benefit than the other 3 mobilization combinations, as more (17) of the studies using MWM techniques found positive outcomes compared with other techniques (Maitland mobilization 12, manipulation 14). Further, studies reporting no positive outcomes with MWM techniques are fewer in number (6) compared with the other techniques (Maitland mobilization 14, manipulation 13).

Quality of studies

Because of differences in study design, 2 tools were used to assess the methodological quality of the included studies. PEDro was used for the assessment of randomized controlled trials (n=19), and the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used for all other study types (n=4). The level of agreement between reviewers for the quality assessment was considered to be high (κ=.63; 95% CI, .53−.73), and all disagreements were resolved by consensus.

Most studies scored well on random allocation, adequate follow-up, and for providing both point measures and measures of variability for at least 1 key outcome. In studies assessed using the PEDro Scale (fig 3), the most common risk of bias was for therapist and subject blinding. For the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, all 4 studies demonstrated bias in terms of insufficient time frame, different

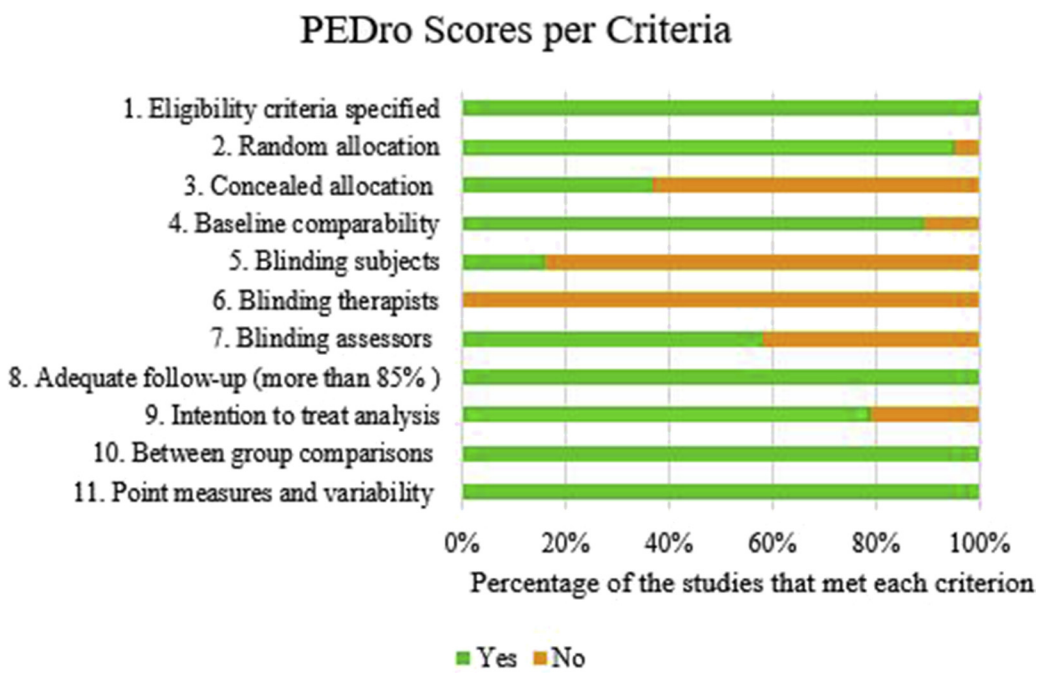

Fig 3 PEDro scores for assessment of quality of individual criteria.[30] Details about criteria: 1, Eligibility criteria were specified (Explanation: This criterion influences external validity, but not the internal or statistical validity of the trial. It has been included in the PEDro Scale so that all items of the Delphi Scale are represented on the PEDro Scale. This item is not used to calculate the PEDro score) (PEDro Scale); 2, Participants were randomly allocated to groups; 3, Allocation was concealed; 4, Groups were similar at baseline regarding most important prognostic indicators; 5, Blinding of all participants; 6, Blinding of therapists who administered the therapy; 7, Blinding of all assessors who measured at least 1 key outcome; 8, Measures of at least 1 key outcome were obtained from more than 85% of the participants; 9, All participants for whom outcome measures were available received the treatment or control condition as allocated; 10, Results of between-group statistical comparisons are reported for at least 1 key outcome; 11, Study provides both point measures and measures of variability for at least 1 key outcome.

levels of exposures as related to the outcome examined, and clearly defined valid and reliable exposure measures (fig 4). All studies scored at least moderate in terms of the overall quality of the methodology for both the scales used (supplemental appendixes S3 and S4, available online only at http://www.archives-pmr.org/).

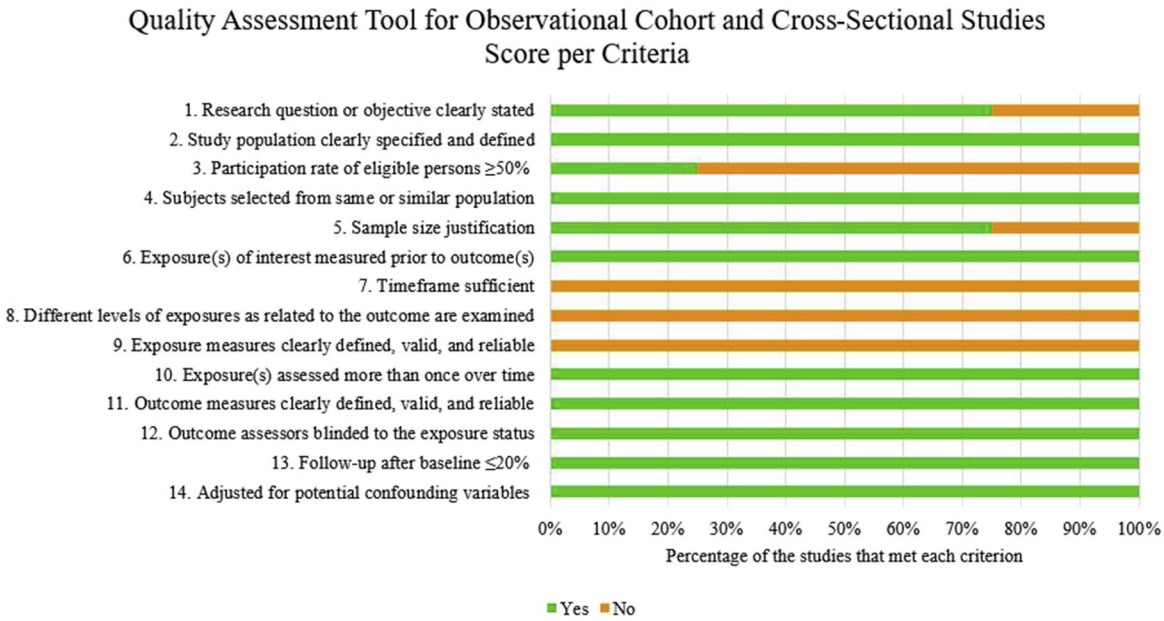

Fig 4 Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[32]

Table 2 Number of outcome evaluations investigating at each time point of interest, listed by the reported positive effects

	Positive Findings					
	Immediate		Short-Term		Long-Term	
Outcome	Yes	No	Yes	No	Yes	No
1. DFROM	11	3	4	4	1	0
Weight-bearing DFROM	9	2	3	2	1	0
Non—weight-bearing DFROM	2	1	0	1	0	0
Unspecified	0	0	1	1	0	0
2. Proprioception	2	0	1	0	0	0
3. Stability/balance	3	7	3	3	1	0
Static balance	1	3	1	3	0	0
Dynamic balance	2	4	2	0	1	0
4. Pain threshold	1	1	1	1	0	0
5. Pain intensity	0	2	2	1	0	0
6. Functional outcomes	2	4	4	2	0	0
7. Talar stiffness	1	2	0	1	0	0
8. Recovery from postural sway	1	0	0	0	0	0
9. Patient's confidence toward stability	1	0	0	0	0	0

NOTE. "Immediate," measured immediately after the intervention. "Short-term," measured up to 3 months after the intervention. "Long-term," measured at 3 or more months after the intervention.

Effects of mobilization on subacute/chronic ankle sprains

The outcome measures of DFROM, proprioception, stability/balance, pain threshold, pain intensity and quality, function, talar stiffness, postural sway, and patient's confidence toward stability were assessed at varying time points across the studies after application of joint mobilization. Table 2 lists each outcome evaluation, indicating positive effects of mobilization at each of the 3 time points of interest.

Eleven studies on chronic sprains reported quantitative data on 5 different outcomes, including weight-bearing DFROM, static balance, dynamic balance, pain intensity, and pain threshold. However, because of study heterogeneity and a lack of useable data for some outcomes, data could only be pooled for weight-bearing DFROM, static balance, dynamic balance, and pain

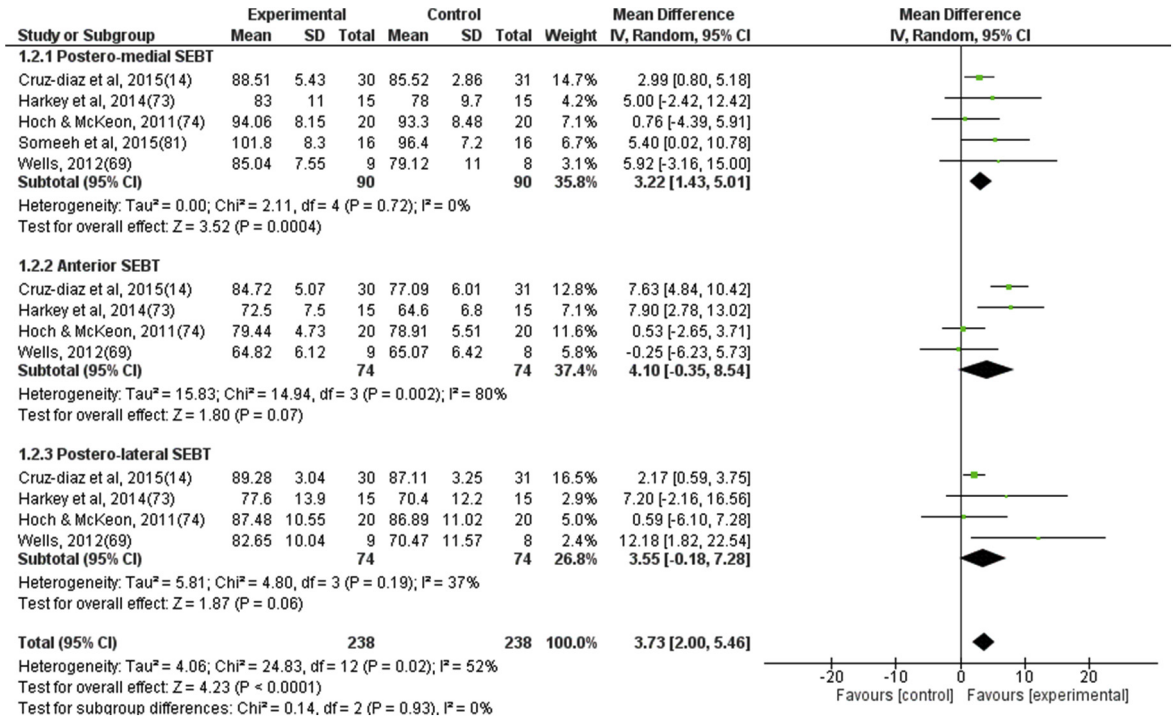

Fig 5 MD (95% CI) of the immediate effect of joint mobilization on dynamic balance by pooling data from 5 studies (n = 180). Abbreviations: df, degrees of freedom; IV, inverse variance.

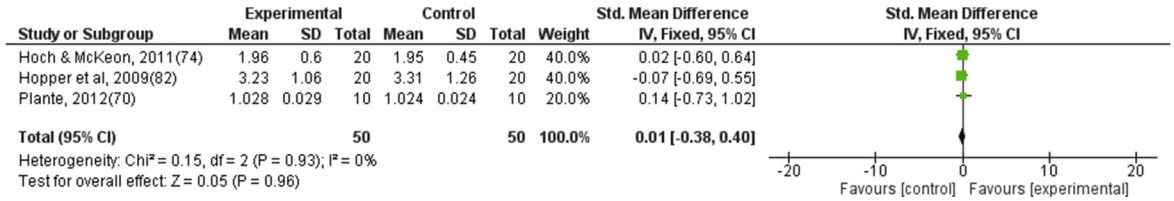

Fig 6 SMD (95% CI) of the immediate effect of joint mobilization on static balance by pooling data from 3 studies (n = 100). Abbreviations: df, degrees of freedom; IV, inverse variance; Std., standardized.

intensity in order to evaluate immediate effects, and weight-bearing DFROM was the only outcome measure available to assess the short-term effects of ankle mobilization.

Immediate effects of mobilization on ankle sprains

The immediate effects on DFROM were assessed in 14 outcome evaluations, of which 11 reported improvement with mobilization techniques (see table 2). The findings for other outcomes were less notable. Of the 10 studies that investigated the immediate effects of mobilization on stability/balance, 3[14,39,50] had demonstrable improvement. Similarly, studies that assessed pain, talar stiffness, and function revealed inconsistent results. When considering the immediate effects of mobilization on functional outcomes, 2 outcome evaluations out of 6 demonstrated that it was effective.[43,51] A summary of the reported immediate effects is provided in table 2.

Pooled data from 5 studies with a total of 180 participants were grouped for analysis of the effects of mobilization on each direction of the Star Excursion Balance Test (SEBT); anterior, posteromedial, and posterolateral. This analysis provided significant findings for the posteromedial direction of the SEBT (MD = 3.22; 95% CI, 1.43–5.01; $P = .0004$); however, the posterolateral direction (MD = 3.55; 95% CI, −.18 to 7.28; $P = .06$) and the anterior direction (MD = 4.10; 95% CI, −.35 to 8.54; $P = .07$) results of the SEBT were not significant (fig 5). Pooled data for static balance from 3 studies with a total of 100 participants indicated there were no significant immediate benefits after mobilization of individuals with chronic sprains when compared with control participants (SMD = .01; 95% CI, −.38 to .40; $P = .96$) (fig 6).

Similarly, data from 7 studies with a total of 249 participants indicated there were no significant immediate effects of mobilization on the weight-bearing DFROM of individuals with chronic sprains (SMD = .66; 95% CI, −.25 to 1.58; $P = .16$) (fig 7). For pain intensity, pooled data from 2 studies with a total of 47 participants indicated mobilization had no immediate effect on individuals with chronic sprains (SMD = −.21; 95% CI, −.78 to .37; $P = .48$) (fig 8). There were insufficient data to analyze the immediate benefits of mobilization on pain threshold.

Short-term effects of mobilization on ankle sprains

Half of the outcome evaluations reported that mobilization improved DFROM, stability/balance, and pain threshold in the short-term (see table 2). Demonstrable improvement was also observed in pain intensity and function (see table 2), and 2 studies[41,45] that evaluated short-term outcomes on talar stiffness and proprioception reported improvements. No studies reported short-term findings on postural sway or patient's balance confidence.

Pooled data from 2 studies with 94 participants with chronic sprains indicated joint mobilization was effective in the short-term for improving weight-bearing DFROM (MD = 2.56; 95% CI, .89–4.23; $P = .003$) (fig 9). There were insufficient data evaluating static balance, dynamic balance, pain threshold, and pain intensity to permit analysis of the short-term benefits of mobilization on these outcomes.

Long-term effects of mobilization on ankle sprains

Only 1 study[14] evaluated the long-term effects of mobilization on ankle sprains. Long-term improvement in DFROM and stability/balance were reported in the single included study.

Quality of evidence

According to the Grading of Recommendations, Assessment, Development, and Evaluation (supplemental appendix S5, available online only at http://www.archives-pmr.org/), the evidence for DFROM (immediate and short-term), static balance, and dynamic balance can be considered to be of moderate quality. The evidence for pain was considered to be of low quality because of lack of generalizability of 1 of the included studies. Overall, the evidence included in this meta-analysis was considered to be of

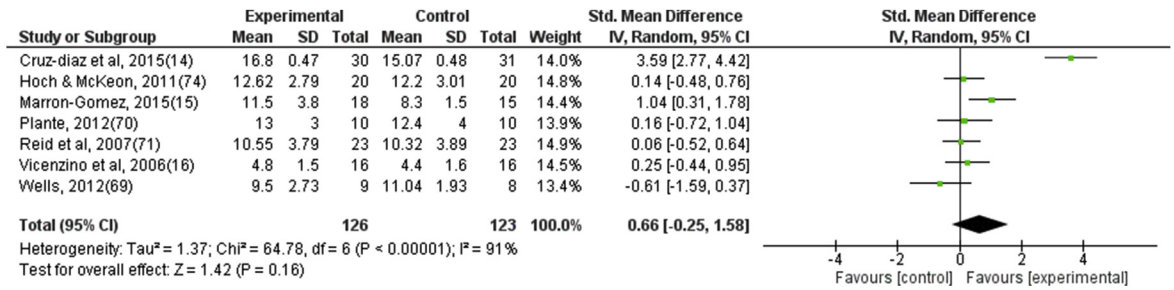

Fig 7 SMD (95% CI) of the immediate effect of joint mobilization on weight-bearing DFROM by pooling data from 7 studies (n = 249). Abbreviations: df, degrees of freedom; IV, inverse variance; Std., standardized.

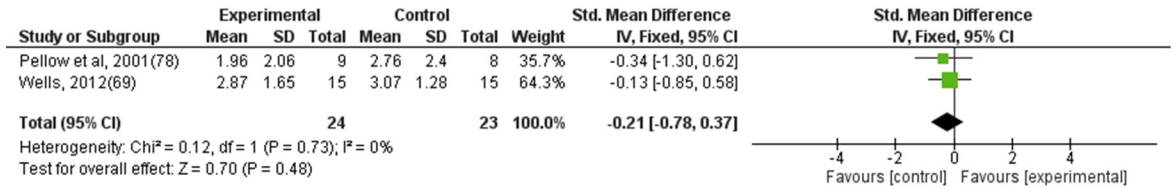

Fig 8 SMD (95% CI) of the immediate effect of joint mobilization on pain intensity by pooling data from 2 studies (n=47). Abbreviations: df, degrees of freedom; IV, inverse variance; Std., standardized.

moderate quality, with the risk of bias and the level of heterogeneity the main factors influencing the quality of the evidence.

Discussion

This is the first systematic review to assess the clinical benefits of joint mobilization in the management of either lateral or medial ankle ligament sprains at all stages of recovery. Importantly, this is the first review to only include studies in which joint mobilization is the sole intervention. The current review did not identify any studies evaluating the clinical benefits of joint mobilization on acute ankle sprains, perhaps because mobilization is not typically the preferred choice of management in the acute stage of ankle sprains.[87] Findings about the clinical benefits of mobilization on most outcome measures were inconsistent across studies, and a lack of reported quantitative data, heterogeneity of subjects, and the differing types of joint mobilization applied made direct comparisons difficult. Despite this, meta-analysis indicated there are immediate benefits of mobilization for improving dynamic balance, and a short-term benefit in improving weight-bearing DFROM in chronic ankle sprains. These results provide compelling evidence that joint mobilization may be effective in improving balance immediately and in increasing DFROM in the short-term in chronic ankle sprains.

Dynamic balance and weight-bearing DFROM improvements after joint mobilization were both associated with clinically meaningful changes. The modified SEBT assesses performance during single-leg balance with reaching in 3 directions (anterior, posteromedial, posterolateral).[88,89] The MCID for this test is reported as being 3.5%, and therefore the immediate effect on dynamic balance found in the meta-analysis (MD=3.73) can be considered as clinically meaningful.[88,89] It is plausible that the immediate improvements in dynamic balance after joint mobilization may increase the individual's balance confidence and perhaps reduce the risk of reinjury. Clinically, this may assist the individual with an ankle sprain to more safely proceed to the next level of functional exercise in the rehabilitation process.

There were no immediate improvements in either anterior SEBT performance or DFROM. Interestingly, previous research[90] supports the existence of a correlation between anterior SEBT performance and the weight-bearing lunge test. This correlation could help explain the current review's findings on immediate anterior SEBT performance and DFROM. Notably, the MCID for ankle DFROM has not been established.[91] However, approximately 3.6° of DFROM is associated with 1cm in distance from the wall in the lunge test.[39] The MD in the short-term measurement of weight-bearing DFROM from the current meta-analysis was 2.56cm, and this equates to 9.2° of dorsiflexion, which can be considered as clinically meaningful given that the normal total range is only 15° to 20°.[92,93]

Joint mobilization techniques are aimed at restoring the normal joint ROM,[94,95] and indeed this review found DFROM improved after mobilization. However, the mechanisms by which restoring ankle ROM may assist other impairments are unclear, as are the underlying mechanisms by which mobilization may actually work.[15,16] It has been proposed that increased ankle ROM is due to the correction of a bony positional fault.[10] It is further postulated that the correct alignment of the articular surfaces may help to restore normal biomechanics as well as sensorimotor function.[10] However, it may be that mobilization produces less impact on pain, as evidenced by the lack of improvement in ankle pain outcome measures in this review. Potential underlying central nervous system changes related to persistent pain in chronic sprains remain unclear, but central sensitization may be a possible factor for persistence of chronic pain. If central sensitization is actually a key factor contributing to chronic ankle sprain pain, then changing the bony alignment would be unlikely to improve pain in chronic sprains since it is not the usual localized pressure-pain hypersensitivity[96] experienced immediately after a sprain.

According to the clinical practice guidelines linked to the *International Classification of Functioning, Disability and Health* from the American Physical Therapy Association, clinicians should use joint mobilization to improve ankle dorsiflexion, proprioception, and weight-bearing tolerance in patients recovering from a lateral sprain.[8] Of these 3 outcomes, the findings of the current review only support the benefit of mobilization for dorsiflexion. There was insufficient research available to conclude whether mobilization is effective for improving proprioception or weight-bearing tolerance. However, the current review found clinically meaningful evidence

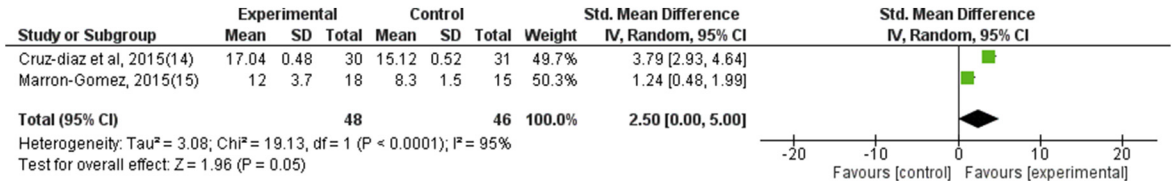

Fig 9 SMD (95% CI) of the short-term effect of joint mobilization on weight-bearing DFROM by pooling data from 2 studies (n=94). Abbreviations: df, degrees of freedom; IV, inverse variance; Std., standardized.

for the effect of mobilization on dynamic balance, an outcome not mentioned in the clinical practice guidelines from the American Physical Therapy Association. One explanation for this difference may be that the guidelines only included literature published before April 2012, while the current review has included 7 more recently published studies.

The inclusion and exclusion criteria of the current review differ in important ways from previous systematic reviews on this topic. In contrast to those prior reviews, our search criteria included both lateral and medial ligament sprains, covered all stages of recovery from acute to chronic, and encompassed all clinically relevant outcomes used to assess the effects of mobilization. Importantly, of the 6 prior reviews[22,24-27,97] that have evaluated the efficacy of mobilization techniques on ankle sprains, all included studies that did not evaluate joint mobilization as a unique intervention, but rather as an adjunct to other interventions (such as home exercise programs, RICE protocol, and external supports) included in their review. The current review excluded these multimodal studies to ensure the homogeneity of the included studies and to increase the precision of the results in relation to the effects of joint mobilization. Compared with the recent review by Loudon et al,[24] the present review included almost 3 times more studies (23), with all of these only investigating the clinical effects of joint mobilization techniques in isolation. In the review by Loudon,[24] only 8 studies were included, and of those, mobilization was used as the sole intervention in only 5.[24] This disparity in the number of included studies may be due to our searching a greater number of databases (11), including medial ankle sprains in the search criteria, by reviewing dissertations and theses, and by not limiting clinical outcomes.

This review includes the first meta-analysis undertaken to assess the clinical benefits of joint mobilization for ankle sprains. When comparing the findings of the current review to previous systematic reviews, there were some agreements and some inconsistent results. When considering the immediate effects of mobilization, the review by van der Wees et al[26] reported an improvement in DFROM.[26] However, the current review did not support an immediate effect on weight-bearing DFROM, with mobilization providing only a short-term effect. Pain and function are concluded to improve immediately in the review by Southerst et al,[27] but in our review immediate pain relief was not evident, and inconclusive results were found for immediate function. When considering the short-term effects, the effectiveness of mobilization in increasing ankle ROM was supported in the review of Bleakly et al,[22] and this was consistent with the findings of the current review.[22] The review by van Ochten et al[28] reported positive changes in short-term pain and function in chronic sprains; however, the findings of the present review were inconclusive for both of these outcomes. When considering the long-term effects of mobilization, pain and function are improved according to the review by Southerst.[27] The findings of the current review on these outcomes were inconclusive because of a lack of data. Different definitions of inclusion criteria for mobilization techniques included within reviews (eg, including other therapies such as home exercise or RICE treatment along with mobilization), as well as differences in the databases searched and the periods of the data searches, are all factors contributing to these differing findings.

Study limitations

Limitations of this review include the wide variation in follow-up time points that we defined as short-term (from 1d to <3mo). Additionally, the included studies have used a range of different mobilization techniques and comparators. It was beyond the scope of this review to attempt to determine the independent merits of individual techniques. In particular, there may be value in analyzing joint mobilization and high-velocity thrust manipulation techniques separately rather than together, but given the lack of available research at this time directly comparing these 2 manual therapy approaches, this level of scrutiny is not possible. In addition, it was not possible to pool data to analyze the effectiveness of mobilization for some important outcomes that were reported in single studies. Despite attempts to contact the authors of included studies, data were insufficient to analyze the immediate effects on the pressure-pain threshold, and the short-term effects on the pressure-pain threshold and pain intensity. Finally, no high-quality evidence was found to provide robust evidence for the effectiveness of joint mobilization for ankle sprains.

Further research is required to determine the mechanisms by which mobilization improves dynamic balance and weight-bearing DFROM. Also, the long-term effects of mobilization on ankle sprains should be further investigated using clinically relevant outcomes.

Conclusions

Joint mobilization appears to clinically benefit individuals with chronic ankle sprains, improving dynamic balance immediately and weight-bearing DFROM in the short-term. It is unlikely to have an immediate effect on static balance, pain intensity, and weight-bearing DFROM. Other clinical outcomes that have been reported after mobilization demonstrate an inconsistent response to mobilization, and this may be a reflection of previous study designs or of the intervention itself.

Suppliers

a. EndNote X7.3.1; Clarivate Analytics.
b. RevMan (Review Manager) 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. Available at: http://ims.cochrane.org/revman.

Keywords

Ankle injuries; Ankle joint; Joint instability; Musculoskeletal manipulations; Physical therapy modalities; Rehabilitation

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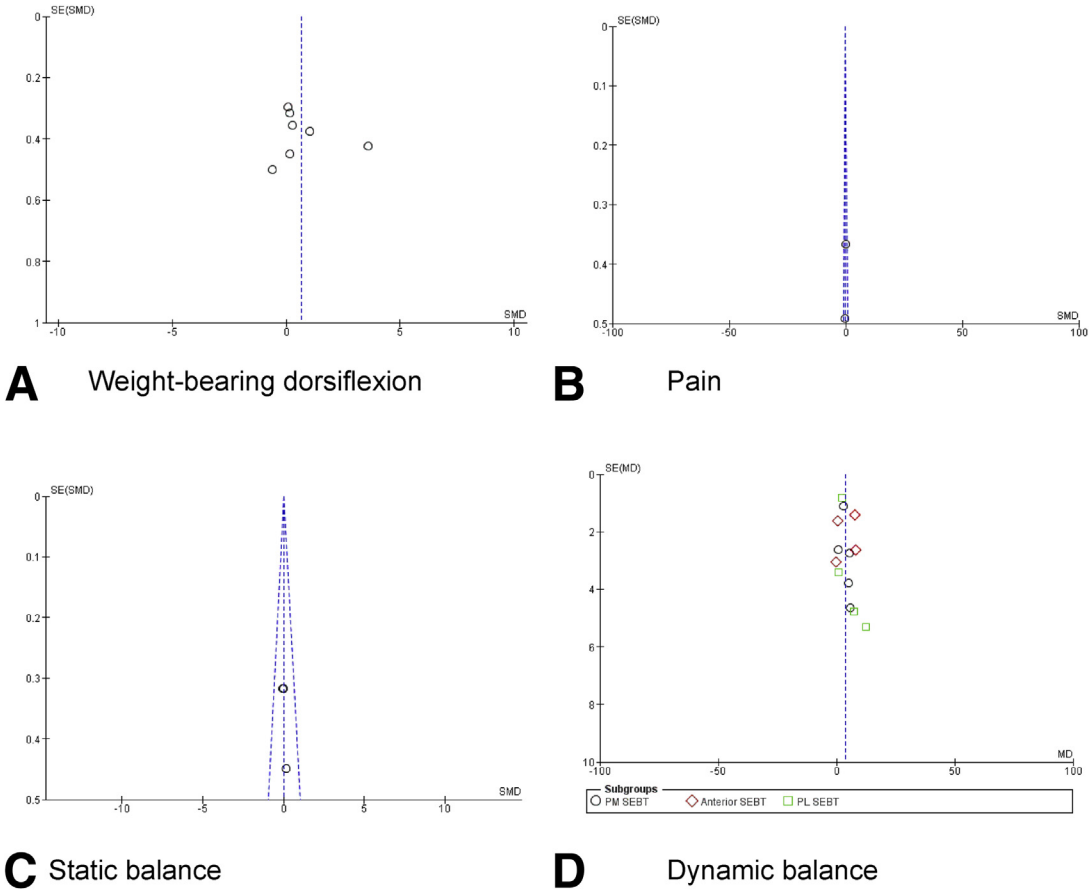
Supplemental Appendix S1 Search strategy

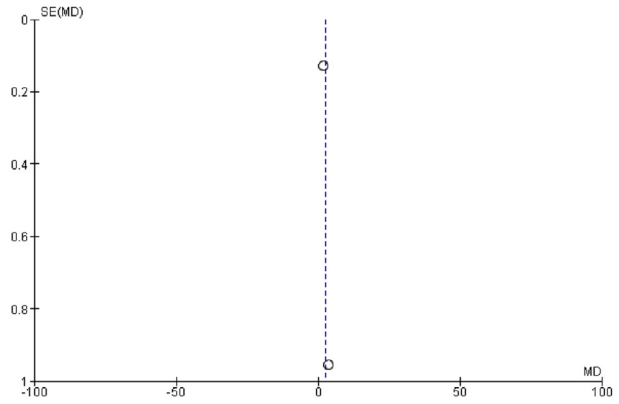
#	Searches
1	Ankle Injuries/
2	ankle sprain.mp.
3	(ankle* adj5 injur*).tw.
4	(ankle* adj5 sprain*).tw.
5	(ankle* adj5 twist*).tw.
6	(injur* adj5 ligament*).tw.
7	lateral ligament*.mp. or Collateral Ligaments/
8	Ankle Joint/or medial ligament*.mp.
9	Ankle Joint/or deltoid ligament*.mp.
10	ATFL.mp.
11	PTFL.mp.
12	"Sprains and Strains"/
13	talo crural.tw.
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	Chiropractic/or Manipulation, Orthopedic/
16	musculoskeletal manipulation.mp. or Musculoskeletal Manipulations/
17	(joint* adj5 manipul*).tw.
18	(ankle* adj5 rehab*).tw.
19	Mulligan*.mp.
20	Maitland*.mp.
21	MWM*.mp.
22	manual therap*.mp.
23	manual technique*.mp.
24	(joint* adj5 mobili?ation*).tw.
25	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26	Randomized controlled trial.pt.
27	clinical trial.pt.
28	random*.tw.
29	trial*.tw.
30	group*.tw.
31	case series.tw.
32	cross-over studies/
33	Cross-Sectional Studies/
34	exp Cohort Studies/
35	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36	14 and 25 and 35
37	limit 36 to humans

Supplemental Appendix S2 Funnel Plots

Immediate effect of mobilization on weight-bearing dorsiflexion, pain, static balance, and dynamic balance



Short-term effect of mobilization on weight-bearing dorsiflexion



a) Weight-bearing dorsiflexion

Abbreviations: MD, mean difference; PL, posterolateral; PM, posteromedial; SEBT, Star Excursion Balance Test; SMD, standardized mean difference.

Supplemental Appendix S3 PEDro scores for assessment of quality of individual intervention studies

	PEDro Scale											
Study	1) Eligibility Criteria	2) Random Allocation	3) Concealed Allocation	4) Baseline Comparability	5) Blinding Subjects	6) Blinding Therapists	7) Blinding Assessors	8) Adequate Follow-up (>85% of Subjects)	9) Intention-to-Treat Analysis	10) Between-Group Comparisons	11) Point Measures and Variability	Total Score Out of 10
Alanson,[36] 2012	+	+	+	−	−	−	+	+	+	+	+	7
Beazell et al,[37] 2012	+	+	−	+	−	−	+	+	+	+	+	7
Collins et al,[13] 2004	+	+	−	+	+	−	+	+	−	+	+	7
Cruz-Diaz et al,[14] 2015	+	+	+	+	−	−	+	+	−	+	+	7
Harkey et al,[38] 2014	+	+	+	+	−	−	+	+	+	+	+	8
Hoch and McKeon,[39] 2011	+	+	+	+	−	−	+	+	+	+	+	8
Hopper et al,[42] 2009	+	+	−	+	−	−	−	+	+	+	+	6
Joseph et al,[44] 2010	+	+	+	+	−	−	−	+	+	+	+	7
Kohne et al,[45] 2007	+	+	+	−	−	−	−	+	+	+	+	6
Lopez-Rodriguez et al,[46] 2007	+	−	−	+	−	−	−	+	+	+	+	5
Marron-Gomez et al,[15] 2015	+	+	−	+	+	−	+	+	+	+	+	8
Pellow and Brantingham,[47] 2001	+	+	−	+	−	−	−	+	−	+	+	5
Plante,[48] 2012	+	+	−	+	−	−	−	+	+	+	+	6
Reid et al,[49] 2007	+	+	−	+	−	−	+	+	−	+	+	6
Someeh et al,[50] 2015	+	+	−	+	−	−	−	+	+	+	+	6
Someeh et al,[51] 2015	+	+	−	+	−	−	−	+	+	+	+	6
Vicenzino et al,[16] 2006	+	+	−	+	+	−	+	+	+	+	+	8
Wells,[52] 2012	+	+	+	+	−	−	+	+	+	+	+	8
Yeo and Wright,[53] 2011	+	+	−	+	−	−	+	+	+	+	+	7

NOTE. 1, Eligibility criteria were specified (Explanation: This criterion influences external validity, but not the internal or statistical validity of the trial. It has been included in the PEDro Scale so that all items of the Delphi Scale are represented on the PEDro Scale. This item is not used to calculate the PEDro score) (PEDro Scale); 2, Participants were randomly allocated to groups; 3, Allocation was concealed; 4, Groups were similar at baseline regarding most important prognostic indicators; 5, Blinding of all participants; 6, Blinding of therapists who administered the therapy; 7, Blinding of all assessors who measured at least 1 key outcome; 8, Measures of at least 1 key outcome were obtained from more than 85% of the participants; 9, All participants for whom outcome measures were available received the treatment or control condition as allocated; 10, Results of between-group statistical comparisons are reported for at least 1 key outcome; 11, Study provides both point measures and measures of variability for at least 1 key outcome.[1]

Abbreviations: +, meet criteria; −, do not meet criteria.

Reference

1. PEDro Scale. 1999. Available at: http://www.pedro.org.au/english/downloads/pedro-scale/. Accessed May 12, 2015.

Supplemental Appendix S4 Quality assessment tool for observational cohort and cross-sectional studies scores for assessment of quality of individual cohort studies

	Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies Scale														
Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Score Out of 14
Gilbreath et al,[21] 2014	+	+	+	+	+	−	−	−	+	+	+	−	+	+	10
Hoch et al,[40] 2012	+	+	+	+	+	−	−	−	+	+	+	+	+	+	11
Hoch et al,[41] 2014	+	+	+	+	+	−	−	−	+	+	+	−	+	+	10
Houston et al,[43] 2013	+	+	+	+	−	−	−	−	+	−	+	−	+	−	7

NOTE. 1, Research question or objective clearly stated; 2, Study population clearly specified and defined; 3, Participation rate of eligible persons ≥50%; 4, Subjects selected from same or similar population; 5, Sample size justification; 6, Exposure(s) of interest measured before outcome(s); 7, Time frame sufficient; 8, Different levels of exposures as related to the outcome are examined; 9, Exposure measures clearly defined, valid, and reliable; 10, Exposure(s) assessed more than once over time; 11, Outcome measures clearly defined, valid, and reliable; 12, Outcome assessors blinded to the exposure status; 13, Follow-up after baseline ≤20%; 14, Adjusted for potential confounding variables. Total (0–14).[1,2]
Abbreviations: +, meet criteria; −, do not meet criteria.

References

1. National Institutes of Health. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies; 2014.
2. The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions; 2011.

Supplemental Appendix S5 Assessment of quality of evidence

No. of Studies (Sample Size, n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality of Evidence
Immediate effects					
Outcome: DFROM					
7 studies (n; experimental=126: control=123)	Low risk of bias (PEDro scores: 6, 6, 7, 8, 8, 8, and 8)	*P* value on test for heterogeneity $P<.00001$, $I^2=91\%$ High inconsistency	Low indirectness	Low imprecision	Moderate quality (low risk of bias and high inconsistency)
Outcome: dynamic balance					
5 studies (n; experimental=90: control=90)	Low risk of bias (PEDro scores: 6, 7, 8, 8, and 8)	*P* value on test for heterogeneity $P=.02$, $I^2=52\%$ Moderate inconsistency	Low indirectness	Low imprecision	Moderate quality (low risk of bias and moderate inconsistency)
Outcome: static balance					
3 studies (n; experimental=50: control=50)	Moderate risk of bias (PEDro scores: 6, 6, and 8)	*P* value on test for heterogeneity $P=.93$, $I^2=0\%$ Low inconsistency	Low indirectness	Low imprecision	Moderate quality (moderate risk of bias and low inconsistency)
Outcome: pain intensity					
2 studies (n; experimental=24: control=23)	Moderate risk of bias (PEDro scores: 5 and 8)	*P* value on test for heterogeneity $P=.73$, $I^2=0\%$ Low inconsistency	Moderate indirectness (less generalizable)	Low imprecision	Low quality (moderate risk of bias, moderate inconsistency, and low indirectness)
Short-term effects					
Outcome: DFROM					
2 studies (n; experimental=48: control=46)	Low risk of bias (PEDro scores: 7 and 8)	*P* value on test for heterogeneity $P<.0001$, $I^2=95\%$ High inconsistency	Low indirectness	Low imprecision	Moderate quality (low risk of bias and high inconsistency)

BMC Musculoskeletal Disorders

STUDY PROTOCOL Open Access

Effects of mobilisation with movement (MWM) on anatomical and clinical characteristics of chronic ankle instability: a randomised controlled trial protocol

Ishanka Weerasekara*, Peter Grant Osmotherly, Suzanne Jordan Snodgrass, John Tessier and Darren Anthony Rivett

Abstract

Background: Up to 40% of individuals who sprain their ankle develop chronic ankle instability (CAI). One treatment option for this debilitating condition is joint mobilisation. There is preliminary evidence that Mulligan's Mobilisation With Movement (MWM) is effective for treating patients with CAI, but the mechanisms by which it works are unclear, with Mulligan suggesting a repositioning of the fibula. This randomised controlled trial aims to determine the effects of MWM on anatomical and clinical characteristics of CAI.

Methods: Participants 18 years or over with CAI will be accepted into the study if they satisfy the inclusion and exclusion criteria endorsed by the International Ankle Consortium. They will be randomised into the experimental group (MWM) or the placebo group (detuned laser) and will receive the assigned intervention over 4 weeks. General joint hypermobility and the presence of mechanical instability of the ankle will be recorded during the first visit. Further, position of the fibula, self-reported function, ankle dorsiflexion range, pressure pain threshold, pain intensity, and static and dynamic balance will be assessed at baseline, and at the conclusion of course of intervention. Follow-up data will be collected at the twelfth week and at the twelfth month following intervention.

Discussion: Effectiveness of MWM on clinically relevant outcomes, including long term benefits will be evaluated. The capacity of MWM to reverse any positional fault of the fibula and the association of any positional fault with other clinically important outcomes for CAI will be explored. Proposed biomechanical mechanisms of fibular positional fault and other neurophysiological mechanisms that may explain the treatment effects of MWM will be further explored. The long term effectiveness of MWM in CAI will also be assessed.

Trial registration: Australian New Zealand Clinical Trials Registry; ACTRN12617001467325 (17/10/2017).

Keywords: Ankle sprain, Chronic ankle instability, Joint mobilisation, Mobilisation with movement, Fibular positional fault, Mechanical instability, Functional instability

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Background

Up to 40% of patients with an initial ankle sprain develop chronic ankle instability (CAI), which is frequently associated with recurrent sprains and persistent pain [1, 2]. A recurrent subjective perception of the ankle joint 'giving way' is clinically indicative of CAI [3], which is defined as "repetitive bouts of lateral ankle instability resulting in numerous ankle sprains" [4]. Clinical management of CAI often involves balance and sport-related activity training [5]. In a recent meta-analysis, preliminary evidence was also found supporting joint mobilisation as a clinically effective intervention in improving dynamic balance and dorsiflexion range of motion in CAI [6].

Several ankle joint mobilisation procedures have been developed and described by renowned manual therapists such as Geoffrey Maitland, Freddy Kaltenborn and Brian Mulligan, and are commonly used in rehabilitation [7]. These procedures are applied to a joint, either in the form of non-thrust passive joint mobilisations, high velocity thrust manipulation, or Mobilisation With Movement (MWM). MWM is defined as the application of a sustained passive accessory movement to a joint while the patient actively performs a task/movement that was previously identified as being painful or limited [8]. After manual application of MWM, tape is applied to help maintain the glide and corrected fibular position [9]. Biomechanically and neurophysiologically mediated mechanisms have been proposed to explain how these joint mobilisation procedures may work [8, 10]. The proposed neurophysiological mechanisms are based on animal [11] and human experiments [12] related to pain science and motor systems [8]. These have shown that joint manual therapy techniques including MWM, activate a descending pain inhibitory pathway which is non-opioid mediated [8]. One proposed biomechanical mechanism relates to a reduction of an entrapped meniscoid or synovial fringe by a specifically directed MWM glide particularly in those instances where only one repetition is required to bring about a substantial and long lasting effect [8].

Of our recent systematic review and meta-analysis identified greater effects for MWM and Mulligan taping compared to Maitland joint mobilisation (with and without traction) and joint thrust manipulation [6, 13]. Dorsiflexion range of motion and self-reported instability were some of the outcomes for which there was evidence of improvement from MWM, although the long term benefits were unclear [14–16]. Most of the previous studies on chronic ankle sprains have applied MWM to the talocrural joint [14–18], and few studies have applied MWM taping [19–21]. However Mulligan proposes that an anterior fibular positional fault commonly results from ankle inversion sprains, and that a MWM using a posterior glide of the fibula to correct this should be trialled after 48 h following such an injury [22]. Patients with recurrent ankle sprains may also benefit from this MWM treatment combined with taping aimed at maintaining the posterior fibula glide, with reportedly less 'giving way' and greater confidence in using the ankle in patients with functional instability and pain [22]. Therefore this study is designed to evaluate the clinical benefits of the fibular posterior glide MWM with Mulligan taping, and whether it corrects any demonstrable positional fault which may exist. The prevalence of pain in people with CAI is high (60.1%) [23] and to our knowledge no studies have assessed the effect of MWM on pain. In addition, the present study will assess the effects of MWM on pressure pain threshold in CAI. The presence of localized peripheral sensitization has been previously identified in acute inversion ankle sprains [24] and in subacute ankle sprains [25]. Balance impairments in CAI are frequently reported in the literature and MWM has been found to be effective immediately after application, but there is presently insufficient research to determine the short term benefits of MWM for balance impairments [6]. The present study plans to address this deficiency in the literature as well.

A positional fault at the inferior tibio-fibular joint, is one arthrokinematic abnormality proposed to be related to persistent/recurrent symptoms and repetitive ankle sprains in CAI [4]. In the case of an ankle joint sprain, Mulligan suggests that the distal fibula is 'mal-positioned' anteriorly (anterior positional fault) following an inversion injury and that chronicity may result if this remains uncorrected [22, 26]. Preliminary evidence for such an anterior fibular positional fault was identified in Hubbard et al's study of individuals with CAI [27]. However it is unclear whether ankle instability caused the anterior fibular position or whether the fault itself was actually the predisposing factor to re-injury. Also, the clinical importance of an anterior fibular positional fault in relation to other potential contributors to CAI remains unclear. Further, the mechanism(s) of changes in CAI outcomes after MWM needs to be further investigated [15, 28]. It has been proposed by Mulligan in his positional fault hypothesis, that MWM effects an immediate and lasting improvement by correcting a minor bony incongruity which is the source of the patient's presenting problem [22]. However, the capacity of MWM to reverse any positional fault remains unclear and further studies are required to assess the effectiveness of this technique.

The objective of this study is to determine the effect of MWM on anatomical and clinical characteristics of CAI, and to determine the long term effectiveness of this treatment.

The specific aims of the study are therefore:

1. To evaluate the effectiveness of MWM on clinically relevant outcomes, including patient-reported outcomes (dorsiflexion range, pain intensity, self- reported function, pressure pain threshold, static and dynamic balance), including long lasting benefits assessed at 12 months post treatment.
2. To assess the effect of MWM on changing the fibular position relative to the position of the tibia in CAI.

Methods

Design

This randomised controlled study has been registered in the Australian New Zealand Clinical Trial Registry (ANZTR) and ethical approval has been granted by the Human Research Ethics Committee of The University of Newcastle, Australia (H-2017-0354). Informed consent will be obtained in writing from all participants.

Participants

Participants aged 18 years or over will be recruited from the general community in the Newcastle area of New South Wales, Australia through flyers posted on noticeboards in shopping centres, the University of Newcastle main campus, and various other public places. Recruitment advertising will also be via University of Newcastle social media channels. Volunteers with CAI will be accepted into the study if they satisfy the inclusion and exclusion criteria as endorsed by the International Ankle Consortium [29], except the time period for experiencing at least two episodes of giving way is changed from 6 months to 12 months to account for the seasonal nature of some sports (Table 1).

Data collection will be carried out at the physiotherapy and radiography research laboratories of the School of Health Sciences, The University of Newcastle, Australia.

Procedure

This trial will adopt a pragmatic randomized controlled trial design to allow for real world application of MWM in a randomized setting [30]. This design has been used by previously published trials of manual therapy to better reflect routine clinical practice [31–33]. It enhances the external validity, but still controls for threats to internal validity.

The initial screening will be performed over the telephone after the potential participant contacts the research team. The screening questions are to determine if the potential participant meets some of the inclusion/exclusion criteria (Table 1). If a potential participant appears eligible following the telephone interview, further screening will be carried out using two standardised questionnaires: the Foot and Ankle Ability Measure (FAAM) [34], which measures function, and the Cumberland Ankle Instability Tool (CAIT) [35], which measures ankle instability. A link to access these questionnaires on the Qualtrics online survey platform (Qualtrics, Provo, Utah, USA) will be sent to the potential participant, along with the participant information statement and the consent form, through an email. Once the potential participant returns their completed forms, their final eligibility will be determined according to their scores (FAAM: activities of daily living (ADL) subscale < 90%, sport subscale < 80%; CAIT ≤24) on the two screening questionnaires. The participant will then be contacted to schedule an appointment for data collection.

Consenting participants will be randomised into two groups: an experimental group who will receive MWM, and a control group who will receive a placebo (detuned laser). All of the participants will be assessed for general joint hypermobility using the Beighton score [36]. Mechanical ankle instability will be tested separately for each ankle using an X-ray while undergoing an anterior drawer stress test [37, 38]. The clinically important outcome measures will include; radiological imaging of fibular position with respect to the tibia (positional fault), dorsiflexion range of motion (DFROM), pressure pain threshold (PPT), pain intensity, function, static balance and dynamic balance. These procedures and outcome measures are further explained below. The researcher who collects the clinical measurements, and the radiographer taking the X-rays, will be blinded to the participant's group (intervention) allocation. This researcher will remain blinded to the group allocation until the 3 month follow-up. The 12 month follow-up data will be collected using online questionnaires.

Each participant will be randomly allocated to a group to receive either MWM (active) treatment or detuned laser treatment (placebo) (these interventions are fully explained below). The participant will be blinded as to whether they are receiving an active or placebo intervention, however due to the nature of the interventions, the treating practitioner cannot be blinded. Participants will be randomly allocated to groups according to a computer generated (GraphPad Software, Inc., CA, USA) randomisation schedule by another researcher not involved in data collection using sealed opaque envelopes. Each envelope will contain a piece of paper printed with either '1' or '0', for which '1' denotes 'MWM' group and '0' denotes 'placebo' group. The treating practitioner will open the envelope and allocate the participant to a group according to the number in the envelope, and deliver the designated treatment accordingly.

Participants of both groups will attend for 2–8 treatment sessions over 4 weeks. The exact number of

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• A history of at least one significant ankle sprain; - Initial sprain must have occurred at least 12 months prior to study enrolment - Was associated with inflammatory symptoms - Created at least one interrupted day of desired physical activity - The most recent injury must have occurred more than 3 months prior to study enrolment	• A history of previous surgeries to the musculoskeletal structures (i.e., bones, joint structures, nerves) in either lower extremity • A history of a fracture in either lower extremity requiring realignment • Acute injury to musculoskeletal structures of other joints of the lower extremity in the previous 3 months that impacted joint integrity and function (i.e., sprains, fractures), resulting in at least one interrupted day of desired physical activity • Have conditions for which manual therapy is generally contraindicated (such as the presence of a tumour, fracture, rheumatoid arthritis, osteoporosis, prolonged history of steroid use, or severe vascular disease)
• A history of the previously injured ankle joint 'giving way' and/or recurrent sprain and/or 'feelings of instability' - Participants should report at least two episodes of giving way in the 12 months prior to study enrolment	• Have conditions for which radiological imaging is contraindicated (e.g., pregnancy)
• Self-reported ankle instability should be confirmed with the Cumberland Ankle Instability Tool (CAIT) (≤24)	• Have conditions for which taping is contraindicated (e.g., allergy to strapping tape)
• General self-reported foot and ankle function questionnaire minimum score (Foot and Ankle Ability Measure (FAAM): activities of daily living (ADL) subscale < 90%, sport subscale < 80%)	• Receiving concurrent treatment - The most recent treatment for the ankle condition should have been received at least a week prior to study enrolment
	• Inability to read English

treatments needed to achieve an optimal change is not presently known, so a range allows the practitioner to exercise their clinical judgement. We have chosen two as the minimum number of treatments, because usual clinical practice would involve a minimum of two visits to enable re-assessment following the initial treatment [39]. The actual number of treatment sessions delivered to participants in each group will be determined according to the clinical judgement of the treating practitioner, who is a registered physiotherapist with a post-professional tertiary qualification in the field of manual therapy and more than 20 years of clinical experience in treating musculoskeletal conditions. The physiotherapist will also be individually instructed in the MWM intervention by an accredited member of the Mulligan Concept Teachers Association. The physiotherapist will conclude the course of intervention if the patient reports they have fully recovered or if no further improvement is possible up to a limit of eight sessions over a 4 week period. The number of sessions and the duration of each session will be recorded. The same measures taken at baseline will be repeated at the conclusion of the course of intervention, within a maximum of 4 days after the participant's last intervention session. Further measurements will be repeated at the twelfth week with the exception of the imaging, and only self-report outcomes will be assessed at 12 months. Participants will be contacted by telephone every 4 weeks after finishing treatment for up to 1 year to record any new ankle injuries, any treatments undertaken, and their level of engagement in sport and other activities. Figure 1 describes the flow of the study.

Outcome measures

Measurement of fibular positional fault from radiograph

A weight-bearing (neutral ankle in standing position) X-ray (55 k Vp and 2.1 mAs) will be taken of the affected ankle of the participant. The participant will be asked to stand on the foot to be imaged on a wooden box with the knee slightly flexed to simulate mid-stance of the gait cycle, with the foot of the non-stance leg hanging in a relaxed manner. The imaged leg will be maintained ~ 2 cm away and parallel to the image receptor. The same instructions will be given to all participants and the participant's leg position will be monitored throughout the procedure. If any leg rotation is noted on imaging, the X-ray will be redone. The central ray will be centred at the base of the metatarsals and perpendicular to the image receptor, and the focal-film distance will be set to 110 cm. The participant will be allowed to hold on to body of the X-ray machine for balance if required.

Radiographic images will be digitally obtained using Merge PACS™ software (Merge Health Care, 2012). The fibular position will be measured as the distance between the anterior edge of the distal fibula and the anterior edge of the distal tibia [27] (Fig. 2). The test-retest reliability intra-class correlation coefficient $(ICC)_{3,1}$ has been estimated as 0.98, with a SEM of 0.64 mm for this measurement, and for intra-tester reliability, the $ICC_{3,1}$ is 0.92 and SEM is 0.72 mm [27].

Weight-bearing dorsiflexion range of movement

Weight-bearing DFROM will be measured using the weight-bearing lunge test. The participant will be

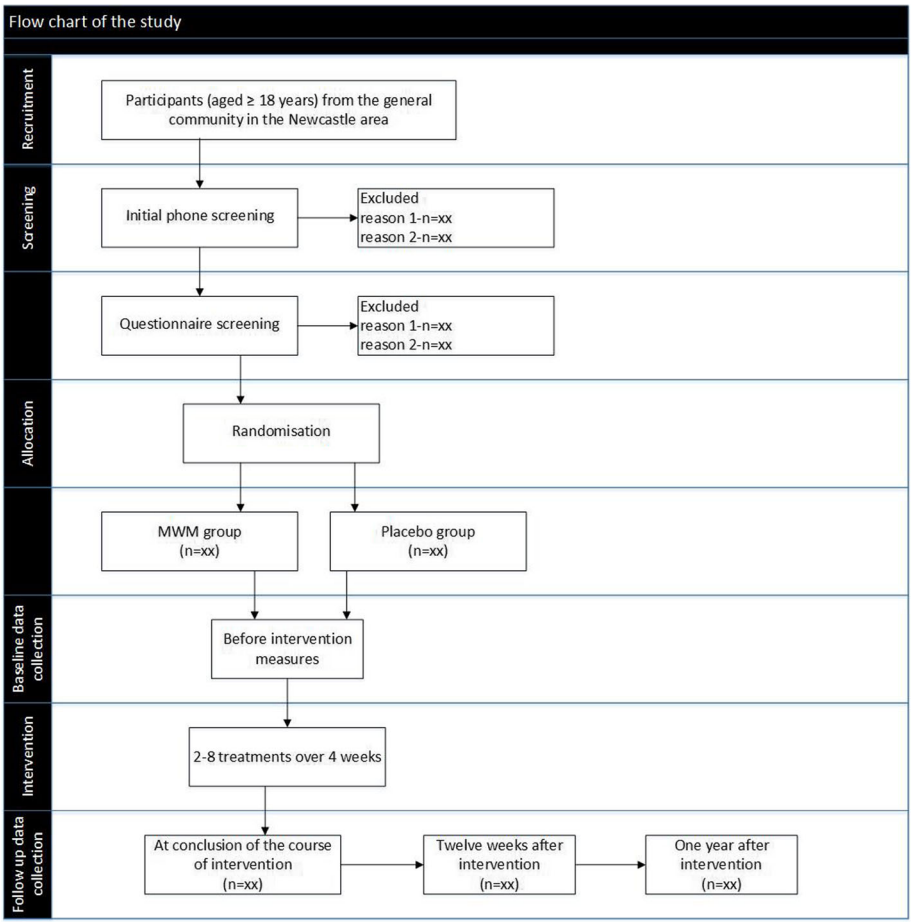

Fig. 1 Flow of the study

instructed to lunge towards the wall, touch their knee to the wall, and keep their heel in contact with the floor. Then the participant will be asked to move their foot away from the wall in 1 cm increments until the heel no longer maintains contact with the floor or the knee is no longer in contact with the wall. Maximal dorsiflexion will be considered to be the greatest distance between the great toe and wall with the participant's knee maintaining contact with the wall [18, 40]. Both inter-rater reliability (ICC = 0.80–0.99) and intra-rater reliability (ICC = 0.65–0.99) have been reported as high for this test [41]. The same procedure will be followed for the opposite leg. Each centimetre away from the wall in the lunge test represents approximately 3.6 degrees of dorsiflexion [42]. Three test attempts will be performed and the average value will be used for analysis.

Pressure pain threshold

PPT measurements will be obtained in each leg from two local points (to assess local hypersensitivity) and one remote body area (to assess central sensitisation), in accordance with the method used in a previous study on acute ankle sprain [24]. The points include anterior to the lateral malleolus over the anterior talo-fibular ligament, inferior to the medial malleolus over the deltoid ligament, and over the proximal third of the tibialis anterior muscle belly.

A Freedom Tracker hand-held algometer (JTECH Medical, Salt Lake City, UT, USA) will be used for measuring PPT. A probe (contact surface of 1 cm^2) will be placed perpendicular to the skin and pressure will be applied (40 kPa/s). The participant will be asked to indicate when the feeling of the stimulus changes from 'pressure only' to 'discomfort' by pressing an indicator switch [43, 44]. This process will be performed three consecutive times and a 10 s rest period will be allowed between each set of measurements. Pressure algometry is considered a stable and reliable measure of PPT [45]. The inter-rater reliability of pressure algometry has been reported to be high when the algometer pressure is applied at a consistent rate (ICC 0.91, 95% CI 0.82–0.97) [46].

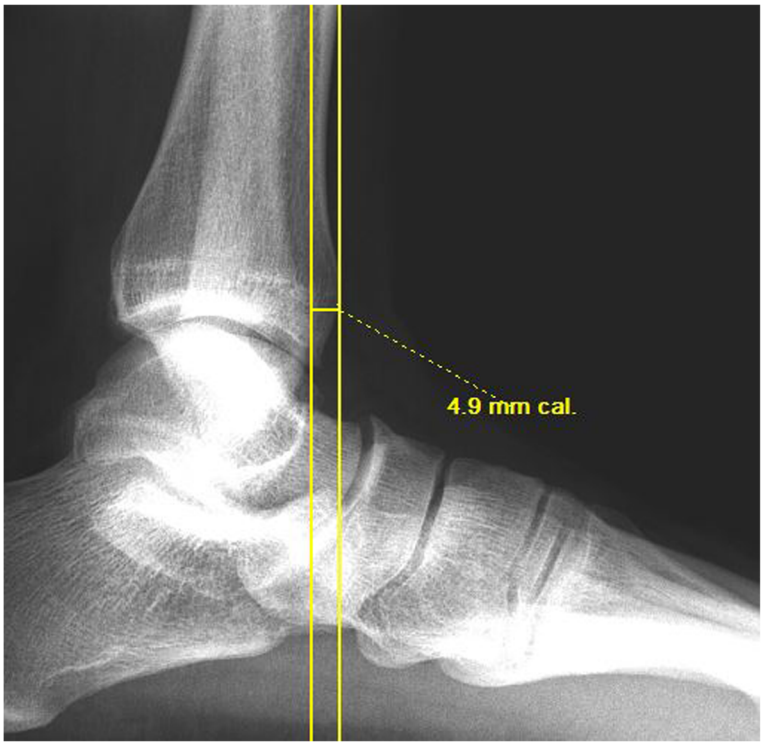

Fig. 2 Fibular position measurement; the distance between the anterior edge of the distal fibula and the anterior edge of the distal tibia (right ankle, 4.2 mm in this image)

Pain intensity

Current pain intensity will be assessed using the visual analogue scale (VAS) which consists of a 100 mm horizontal line, with 'no pain' anchored on the left of the line and 'worst possible pain' anchored on the right. The validity of the VAS for detecting changes in pain intensity has been supported by several studies [47, 48].

The participant will also be asked to indicate all areas in which they currently feel symptoms on a body chart. The areas in which they feel 'pain' will be shaded; the areas in which they feel 'tingling, pricking, or burning' will be circled; and the areas where they feel 'numbness, heaviness or other sensations' will be indicated on the chart by an 'N'.

Function

Self-reported physical function of the participant will be evaluated using the FAAM which consists of a 21-item ADL subscale and an 8-item sport subscale [34]. This tool has been documented as a reliable, responsive and valid measure of physical function for individuals with a broad range of musculoskeletal disorders of the lower leg, foot and ankle [34]. The Foot and Ankle Outcome Score (FAOS) questionnaire comprising 42 items will also be used, and has been reported as also being a reliable and valid measure (ICCs reported as 0.78, 0.86, 0.70, 0.85, 0.92 for the five subscales of pain, symptoms, ADL, sport and recreation function, and foot- and ankle-related quality of life, respectively) [49].

Further, the participant will be asked to identify up to three important activities that they are unable to perform or are having moderate to extreme difficulty performing due to pain. For each activity, the participant will be asked to rate between 0 and 10 the level of difficulty they experience performing that activity using the Patient-Specific Functional Scale (PSFS) [35]. The construct validity of the PSFS is well supported, and the test-retest reliability has been assessed as moderate to good (ICC2,1 = 0.713) [36].

Static balance

For static balance, the participant will stand barefoot on the centre of a force plate (KISTLER 9260AA6, Winterthur, Switzerland), assuming a standardized single leg stance position. The participant will then be instructed to flex the other leg slightly at the hip, with the knee flexed to 90 degrees. Their arms will be crossed at their chest with each hand resting on the opposite shoulder. Measurements will be recorded with both 'eyes open' and 'eyes closed'. For 'eyes open', the participant will be asked to maintain a fixed gaze on a cross marked on the wall three metres in front of them and remain as still as possible for 10 s [50]. For 'eyes closed', the participant will be asked to close their eyes and remain as still as

possible for 10 s [50]. If the participant is unable to stand for 10 s, the standing time achieved will be recorded. Only averaged Centre of Pressure (CoP) data including sway velocity, sway area per second, sway average amplitude and sway maximal amplitude will be used in the analysis to maintain consistency. CoP data obtained through the force platform will be acquired at 100 Hz [21].

Dynamic balance

Dynamic balance will be assessed using the Star Excursion Balance Test (SEBT) which has been shown to be a reliable measure to identify dynamic balance deficits in patients with a variety of lower extremity conditions [51]. The participant will be asked to establish a stable base of support on the stance limb in the middle of the testing grid on a force plate (KISTLER 9260AA6, Winterthur, Switzerland). While standing on a single limb, the participant will be asked to reach as far as possible with the reaching limb along each line (anterior, postero-medial and postero-lateral directions), lightly touching the line with the most distal portion of the reaching foot without shifting weight or coming to rest on the foot of the reaching limb. The participant will then be asked to return the reaching limb to the starting position in the centre of the grid. If the individual lifts or shifts any part of the foot of the stance limb during the trial, the trial will be not considered as complete [51].

After performing a maximum of four non-recorded trials for familiarisation, the next trial for each direction will be recorded for the purpose of analysis [52, 53]. Normalised SEBT values will be obtained by dividing the excursion distance by the participant's leg length (the distance between the anterior superior iliac spine and the ipsilateral medial malleolus), and then multiplying by 100 [52, 54]. Data for centre of pressure (CoP) velocity (V) to quantify spatio-temporal parameters (VCoP-total, VCoP-mediolateral, VCoP-anteroposterior) will be acquired at 100 Hz, under the foot during unipodal stance [52].

Perceptions of the credibility of the placebo

At the data collection session at the conclusion of course of intervention, the participant will be asked to indicate which intervention (active or placebo) they thought they had received during the last 4 weeks and to give a confidence rating on a scale of 0–10 (with 0='not at all confident' and 10 = 'extremely confident' [55]). Global perceived effect will also be measured using a self-assessment of improvement on a seven point rating scale (1 = completely recovered, 2 = much improved, 3 = slightly improved, 4 = not changed, 5 = slightly worsened, 6 = much worsened, 7 = worse than ever) in response to the question 'How would you rate the course of your ankle complaints since the start of this study?' [56, 57].

Other measures

Telephone interviews will be conducted monthly after enrolment up to 1 year to record any new injuries, any treatments undertaken, and the level of engagement in sports and other activities. These variables will be used as covariates in the analysis of the 12 month follow-up data as they are possible confounders. Further, the Beighton score for hypermobility and radiographic measurement of the anterior drawer stress test will be recorded.

Beighton score

Scoring for joint hypermobility will be undertaken according to previously published methods [36]. Each participant will be assessed in five test positions, as follows:

1. Passive extension of the fifth metacarpophalangeal (MCP) joint to ≥90 degrees. The participant sits on a chair at the short side of the table with the shoulder in 80 degrees abduction, elbow flexed at 90 degrees, and the forearm resting on the table in a pronated position. The fifth MCP joint is passively extended by the researcher and a goniometer is used to measure the angle.
2. Passive hyperextension of the elbow ≥10 degrees. The participant sits on a chair with the shoulder at 90 degrees of flexion and the forearm supinated. A goniometer is placed at the lateral epicondyle and the measurement is taken at maximum elbow extension.
3. Passive hyperextension of the knee ≥10 degrees. The participant lies supine with their legs in the horizontal plane. The goniometer is placed at the lateral femoral condyle and the measurement taken at maximum knee extension.
4. Passive apposition of the thumb to the flexor side of the forearm. The score is positive if the entire thumb touches the flexor side of the forearm while the shoulder is flexed at 90 degrees, the elbow extended, and the forearm pronated.
5. Forward flexion of the trunk with the knees straight. The score is positive if the participant's hand palms rest easily on the floor.

Anterior drawer stress test with radiographic measurement

Ankle joint mechanical instability will be assessed using a lateral x-ray to measure the amount of anterior translation of the talus during a ligament stress test for each ankle. The radiograph will be taken while the ankle is undergoing a simulated anterior drawer test using 125 N

force [38]. The stress radiograph will be taken with the participant in a supine lying position with the foot relaxed in a resting position and the lower leg resting on a support, with the hip and knee each flexed approximately 45 degrees. The heel will be supported on a dynamometer (Lafayette Manual Muscle Tester, Model 01165, Lafayette, IN, USA) attached to a customised device which produces the anteriorly directed force. The distal tibia will be fixed on the support using a stabilising belt placed over the distal aspect of the tibia [58]. The central ray will be centred just above the tip of the lateral malleolus and perpendicular to the image receptor [59]. Then an anterior force of 125 N will be applied [38] to the heel of the participant at an angle of 20 degrees to the vertical plane as per recommended clinical practice [60], using the customised device. The force will be monitored using the digital display of the dynamometer attached to the customised device, and the radiograph will be taken at 125 N. The ankle radiograph will be taken at the focal-film distance of 110 cm [61] and will set to 55 kVp and 2.1 mAs. The same procedure will be applied to the other ankle. These images will be taken at the baseline data collection session to assess mechanical instability for use in subgroup analysis.

Radiographic images will be digitally obtained using Merge PACS™ software (Merge Health Care, 2012). Anterior translation of the talus will be measured between the posterior lip of the tibial articular surface and the nearest point of the talar dome (Fig. 3) [61–64] to identify any mechanical instability. Anterior drawer stress radiographs have been found to have moderate sensitivity, high specificity and a high positive predictive value for the evaluation of lateral ankle instability [37]. A between-limb difference of 3 mm in anterior translation of the talus or an absolute value of 10 mm is considered clinically significant [37].

Application of the intervention

Participants in the experimental group will be treated with a manual MWM technique to the ankle and will be taped after the intervention using the Mulligan approach [22] to attempt to maintain the effects of the MWM. The control group will receive a detuned (inactive) therapeutic laser treatment to the lateral region of the ankle. The number of treatment sessions delivered for each participant will be based on their symptomatic response to treatment, as determined by the clinical judgement of the treating practitioner. Each participant will be asked to avoid concurrent interventions during their participation in the study.

MWM intervention

The participant's inferior tibio-fibular joint will be mobilised using Mulligan's fibula MWM for dorsiflexion and/or inversion [22]. Initially, the technique will be performed in supine lying with the tibia resting on the treatment table and the foot unsupported off the table's edge. The practitioner applies a sustained pain-free anteroposterior glide with a slight cephalad and lateral inclination to the distal fibula (lateral malleolus). This glide is maintained while the participant performs active inversion or dorsiflexion (depending on which is more limited in range) to end of range. There should be no pain with the active movement. At the end of range, the practitioner will apply and sustain overpressure to the active movement for a few seconds (or the participant will do so after appropriate instruction) [16, 22]. If dorsiflexion remains restricted, this technique can be progressed and performed in partial and/or full weight-bearing.

One treatment session will consist of three to five sets, with six to ten repetitions of the active movement in each set, with the actual dosage depending on the individual response of the participant [22]. Participants will receive between two to eight sessions according to the clinical reasoning of the practitioner, over a period of 4 weeks. After each session, Mulligan MWM taping will be applied in an attempt to replicate the sustained fibula glide [8]. Non-elastic tape will be applied to the ankle starting 2 cm anterior to the fibula and 1 cm proximal to the tip of the lateral malleolus. The tape will be spiralled obliquely around the lower limb while the fibula glide is sustained, finishing on the anterior aspect of the leg [22]. The participant will be instructed to keep the tape on for 24 h. In the case of an adverse reaction, they will be advised to remove the tape immediately and note the length of time the tape was in place.

Detuned laser intervention

The placebo intervention will be applied using a detuned therapeutic laser device (Meyer Medical Electronics, Mordialloc, Australia) for 5 min to the lateral region of the ankle, maintaining the probe 0.5–1 cm away from the skin [31, 65–67]. The detuned laser device will appear to function normally (both audibly and visually) to participants, but no effective emission will be produced. Both the participant and the practitioner will be required to wear protective glasses as per normal clinical practice [66, 68]. Participants will receive two to eight treatments over 4 weeks, according to the clinical judgement of the treating practitioner. Detuned laser has been used in several other studies assessing manual therapy including for chronic ankle sprains. It avoids any possible direct mechanical effects to the ankle being treated and also does not activate somatosensory receptors [69–71]. Further, it has been shown to have a strong placebo effect [70]. Scheduling of participant appointments will be arranged to avoid interaction between participants.

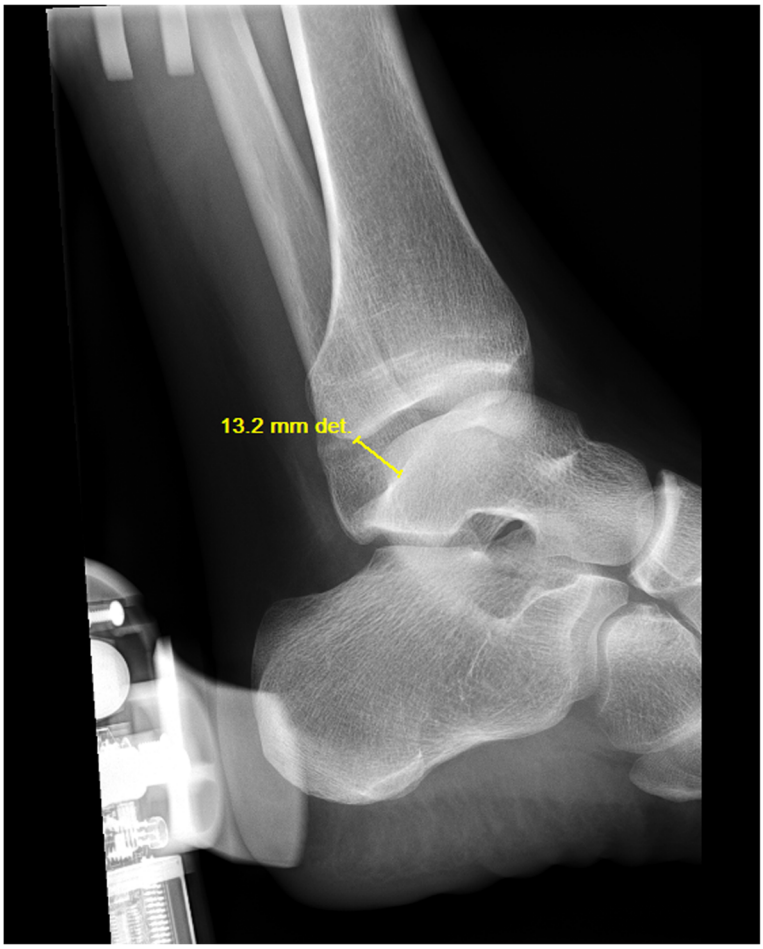

Fig. 3 Anterior translation of the talus during the anterior drawer stress test is measured as the distance on X-ray from the posterior lip of the tibial joint surface to the nearest point of the talar dome (left ankle, 13.2 mm in this image)

Sample size and data analysis

Previously published data related to the primary outcome measure of function (FAAM subscales, ADL and sports) [18, 34] (MCID = 8.0, SD = 5.68; MCID = 9.0, SD = 7.42 respectively) were used in sample size calculations [18, 34, 72]. A sample size of 16 per group allowing for a 30% drop-out rate was estimated, for a minimal statistical power of 0.80 and an alpha significance level of 0.05. Secondary analysis based on the subgroups of ankle instability (mechanical, functional) will be preliminary in nature as the study is not powered for this aim.

Data will be analysed using SPSS Statistics for Windows (Version 23.0, Armonk, NY, IBM Corp). Continuous data will be assessed for normality using the Shapiro-Wilk test.

Baseline comparability between groups will be analysed using the independent t-test or non-parametric equivalent, as appropriate. Linear mixed models will be used to analyse the outcome measures. For the primary outcome measure, 'function' will be the outcome variable and time, group and an interaction term for time by group will be the predictors. Any statistically significant difference in change in the outcome variable over time between the groups will be indicated by the p value for the interaction term. Pairwise Bonferroni comparisons will be performed to explore the differences between time points and between groups if a significant interaction is identified. Independent t-tests will be used to compare outcome measures between groups at each time point and the changes of the scores will be used to detect any changes in the outcomes of interest. Intention to treat analysis will be performed with all participants allocated to each group condition to evaluate the effect of the independent variable. For missing data in ITT analysis, a participant's last observation for each outcome measure will be carried forward. The average number and the average duration of intervention sessions between groups will be compared. If any significant difference observed, secondary analysis will be taken to find any correlation between the treatment volume and the outcomes.

Additional variables recorded during monthly phone interviews (new injuries, changes in activity level, and occurrence of other treatments) will be used as covariates in the analysis of the 12 month follow-up data as they are possible confounders. Further, the Beighton score for hypermobility will also be included in regression analysis as a covariate.

Radiographic measurement of the anterior drawer stress test will be used to differentiate subgroups of CAI in potential sub group analysis.

Discussion

One proposed anatomical mechanism underpinning MWM is theorised to be a correction of a minor bony incongruity (positional fault) which is at the source of the patient's presenting problem [22, 73]. The existence of an anterior fibular 'positional fault' in individuals with CAI has some preliminary radiological support [27]. There are also limited MRI data supporting Mulligan's positional fault hypothesis in cases of lateral ankle pain [72], however there is no evidence to date that MWM reverses any positional anomaly. Further, should any fibular positional anomaly be reversed immediately after the application of MWM, the length of time this reversal or correction is maintained is unknown. The proposed study protocol is designed to determine the presence of any positional fault of the fibula in CAI, and whether MWM can reverse this, and if so, whether this reversal is evident 4 weeks after treatment commences. Moreover, this study protocol will explore the correlation between an anatomical measure (fibular position) and other clinical outcomes (pain, function, pressure pain threshold, DFROM, static and dynamic balance). Potential relationships between these measures may help explain how changing an anatomical measure may effect a clinically meaningful outcome. The effect of MWM in CAI will also be explored in relation to the presence or not of radiologically measurable mechanical instability.

There are very few clinical trials with long term follow-ups which have assessed MWM for any musculoskeletal condition, and only one for CAI which had a 6 month follow-up [6, 15]. The proposed study protocol is therefore the first designed to evaluate the long term effectiveness of MWM on CAI. Moreover, the treatment effect may depend on the type of instability present (mechanical or functional), and this study protocol may evaluate the efficacy of MWM on these two subgroups of CAI. However, the subgroup analysis will be exploratory as the study was only powered to detect the main effect being the intervention on the functional outcome.

Abbreviations

ADL: Activities of daily living; ANZCTR: Australian New Zealand Clinical Trial Registry; AP: Antero-posterior; CAI: Chronic ankle instability; CAIT: Cumberland Ankle Instability Tool; CoP: Centre of pressure; DFROM: Dorsiflexion range of motion; FAAM: Foot and Ankle Ability Measure; FAOS: Foot and Ankle Outcome Score; MCID: Minimal clinically important difference; MCP: Metacarpophalangeal; ML: Medio-lateral; MWM: Mobilisation With Movement; PPT: Pressure pain threshold; PSFS: Patient-Specific Functional Scale; SD: Standard deviation; SEBT: Star Excursion Balance Test; VAS: Visual Analogue Scale

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Authors' contributions

IW, PO, JT, SS and DR contributed in designing the study. JT performed the radiological procedures. IW drafted the manuscript, and all authors (IW, PO, JT, SS and DR) read and approved the final manuscript.

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Ethics approval and consent to participate

This project has been approved by the Human Research Ethics Committee of The University of Newcastle, Australia (H-2017-0354). Written informed consent will be obtained from all participants.

Consent for publication

Not applicable.

Competing interests

Darren Rivett is an honorary member of the Mulligan Concept Teachers Association. The other authors declare that they have no competing interests.

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