Optimising mobility outcomes after severe ankle injury in adults

David John Keene

Wadham College

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences

University of Oxford

A thesis submitted in part fulfilment of the requirements for the degree of

Doctor of Philosophy in Musculoskeletal Sciences

Trinity term 2014

Abstract

Severe ankle injuries can result in ligament rupture or a fracture. A major problem after such injuries is limitation in mobility. Weight bearing tasks, such as walking, become a problem because of pain, deficits in joint range of motion and muscle strength. This thesis studies a key dilemma in early rehabilitation, whether to immobilise the ankle or allow joint motion to improve mobility outcomes. Studies have focused on two scenarios, severe ligament rupture, and unstable fractures managed through open reduction and internal fixation (ORIF). The analysis of gait outcomes was an important component of this thesis and a novel analytical method was developed to normalise gait velocity in the estimation of speed-dependent gait outcomes.

A systematic review and meta-analysis was conducted including evidence to July 2014. The reporting and design of trials was universally poor. In the 6 weeks of recovery following ankle ORIF surgery, there was insufficient evidence that early ankle movements offered a benefit to mobility recovery compared with immobilisation in a cast. Ankle movements compared with immobilisation reduced the risk of venous thrombosis/thromboembolism. However, compared with cast immobilisation, the risk of deep and superficial surgical site infection and fixation-related complications were higher when ankle movements were permitted.

To investigate the role of ankle supports in rehabilitation of walking after ORIF, two randomised cross-over studies were completed. In healthy participants with non-pathological gait, a walker boot induced gait abnormalities when compared with Tubigrip (elasticated bandage). There were no important differences in gait between a stirrup brace and Tubigrip. In people who had undergone ankle ORIF 6 weeks previously, a walker boot and to a lesser extent a stirrup brace offered improvements in gait symmetry and lower pain scores when compared with Tubigrip. Finally, a secondary analysis of the Collaborative Ankle Support Trial cohort (n=584) was conducted, which concluded that, in comparison to Tubigrip, 10 days of cast immobilisation provided greater probability of recovery of a range of mobility outcomes 4 weeks following injury.

This thesis contributes evidence favouring a role for ankle immobilisation in improving mobility following severe ankle injury in adults. Clinicians should be aware of the benefits and risk of harms outlined, as well as the limitations in the current evidence base.

Acknowledgements

First and foremost I offer my gratitude to my academic supervisors, Professors Sallie Lamb and Keith Willett, for their generosity in time and knowledge. Their insights and support have enabled me to travel further than I could have imagined over the course of this thesis.

My sincere thanks also go to all the patients and volunteers that agreed to participate in the studies included in this thesis. To the clinicians and patients of the Trauma Unit, Oxford University Hospitals NHS Trust, for their support in conducting the clinical study. Special thanks to the trauma research team, Susanna Symonds, Louise Spoors and Vivienne Fairclough, for their assistance and expertise in recruiting participants.

To the additional members of the systematic review team, Dr Julie Bruce and Dr Esther Williamson, who gave their time so generously. Thanks also to Tatjana Petrinic, Outreach Librarian, Bodleian Health Care Libraries, for her advice on developing electronic search strategies.

To Professor Rolf Moe-Nilssen and his group at the University of Bergen, Norway, for sharing their expertise in gait analysis and Christopher Knox, medical statistician at the University of Warwick, for introducing me to statistical computing. To Dr Deborah Brown, who kindly proof read this thesis prior to submission.

To my colleagues, Lesley Morgan and Emma Roberts, who have shared many of the highs and lows of my DPhil experience and offered much encouragement along the way. To my friends, Dr Anand Segar and Dr Mark Williams, who with good humour made the writing up phase of this thesis all the more positive.

My appreciation to Health Education Thames Valley for financially supporting this research.

To my close family, I thank you for all for your support over the years. Especially my parents, Graham and Rosemary, who have given so much to enable me to reach my goals.

Finally, I dedicate this thesis to my wife Niki, without whom completion of this research would not have been possible. Her boundless support as a partner, friend and as mother to our young daughter, Olivia Mae, has been overwhelming.

Declaration

This thesis is the candidate's own work except where it contains work based on collaborative research. The nature and extent of the contributions of others have been indicated where applicable.

Chapter 2: The original experimental and statistical method for adjusting for walking velocity in gait analysis was developed by Professor Rolf Moe-Nilssen, University of Bergen, the candidate was not involved in this early stage of development. The concept for normalising walking velocity in gait analysis using multi-level modelling was originally from Professors Moe-Nilssen and Lamb. The candidate operationalised the concept and developed the code, programming and analytic approach, and undertook all analyses.

Chapter 3: The candidate designed and conducted the systematic review, which involved establishing a review team for secondary data extraction and agreements on risk of bias assessments and analytical decisions.

The systematic literature review was presented at the 5th National Institute for Health Research (NIHR) Infrastructure Doctoral Training Camp and won an award for best research poster. The review was also published as a manuscript in a peer-reviewed journal: Keene, D.J., Williamson, E., Bruce, J., Willett, K., Lamb, S.E. Early ankle movement versus immobilization in the post-operative management of ankle fracture in adults: a systematic review and meta-analysis. *J Orthop Sports Phys Ther.* 2014;44(9):690-C7.

Chapter 4: The study concept, design, approvals, participant recruitment, data collection and analysis were entirely the work of the candidate. The study was presented as a research poster at the 3rd International Scientific Tendinopathy Symposium, September 2014, Oxford, UK: Keene, D.J., Willett, K., Lamb, S.E. The effects of different types of ankle support on gait: a randomised cross-over study. *Br J Sports Med.* 2014;48:A31.

Chapter 5: The study concept, design, approvals, data collection and analysis were entirely the work of the candidate.

Chapter 6: The candidate was not involved in the design and conduct of the original trial but was entirely responsible for the design and conduct of the secondary analysis. It had been intended to use a final analysis of an ankle fracture trial the candidate was involved in but this was not possible. Hence the use of another ankle injury cohort that investigated the role of externally applied immobilisation.

Contents

List of Tables

List of Figures

Abbreviations

ANOVA	Analysis of variance
AO/ASIF	Arbeitsgemeinschaft für Osteosynthesefragen/Association of the Study of Internal Fixation
CAST	Collaborative Ankle Support Trial
CI	Confidence interval
EMG	Electromyography
FAOS	Foot and Ankle Outcome Score
FWS	Fast walking speed
HUI3	Health Utilities Index mark 3
ICC	Intra-class correlation coefficient
IQR	Inter quartile range
LEFS	Lower Extremity Functional Scale
LR	Likelihood ratio
MANOVA	Multivariate analysis of variance
MD	Mean difference
MLM	Multilevel modelling
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NNTB	Number Needed to Treat for one additional Beneficial outcome
NNTH	Number Needed to Treat for one additional Harmful outcome
OA	Osteoarthritis
OMAS	Olerud and Molander Ankle Score
OR	Odds ratio
ORIF	Open reduction and internal fixation
PROM	Patient-reported outcome measure
PWS	Preferred walking speed
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RR	Risk ratio
SD	Standard deviation
SI	Symmetry index/indices
SMD	Standardised mean difference
SSI	Surgical site infection
SWS	Slow walking speed
VAS	Visual analogue scale

Chapter 1

1 Introduction

This thesis concerns the recovery of mobility following severe ankle injury in adults. In particular in this thesis 1) ankle fractures requiring open reduction and internal fixation (ORIF) surgery and 2) severe ankle ligament sprains resulting in an inability to weight bear through the injured limb in the acute phase. The comparison of interventions central to all studies herein is externally applied ankle joint immobilisation versus ankle joint movement. The decision whether to use ankle supports, splints or casts to immobilise the ankle joint following ankle fracture and ORIF surgery or severe ligament sprain is one of the key issues in injury management.[108, 122]

The primary outcome for this thesis is mobility, as it is the main cause of disability after ankle injury.[123, 138, 214] Mobility is the capacity of an individual to move from place to place, or one posture to another, for example sit to stand, walking, climbing stairs and running. The main mobility tasks that are limited after severe ankle injury are those involving bipedal locomotion, in particular walking.[117, 237, 257, 273] Secondary outcomes relating to physical impairments associated with mobility limitations after severe ankle injury are also included.[125, 138, 213, 230] These impairments include deficits in range of motion, muscle strength and pain in the injured ankle. The following sections outline the context and basis of the thesis and conclude with the aims and objectives.

1.1 Clinically orientated anatomy and biomechanics of the ankle

The ankle joint is the articulation between the distal tibia and fibula, forming a mortise shape, with the talus (Figure 1). The ankle is a simple hinge joint that is highly stable due to the congruency of the bones and the extent of ligamentous support. The ligaments most commonly injured are the

lateral collateral ligaments (Figure 2).[96] The medial collateral ligament, known as the deltoid ligament, is far stronger and more extensive than the lateral ligament complex.[163] The ankle is most stable in the close packed position of dorsiflexion.[170] The primary movements of the ankle joint are dorsiflexion and plantar flexion, which functionally couple with subtalar joint eversion and inversion.[163] The main muscles acting about the ankle are detailed in Table 1. The triceps surae muscle complex, responsible for propulsion, is shown in Figure 3. The normal ankle range of motion is over 25° dorsiflexion and approximately 50° plantar flexion.[163] At normal walking speed the ankle requires up to 10° dorsiflexion and 20° plantar flexion.[163] The ankle, along with the foot, offers the lower limb a mechanically efficient interface with the ground.[170, 178] The human ankle has evolved to its current form and function in order that it can efficiently fulfil its primary role in enabling efficient bipedal mobility.[41, 240] Therefore, the range of motion, joint stability and muscle synergy of the ankle play a critical role in normal mobility.[178]

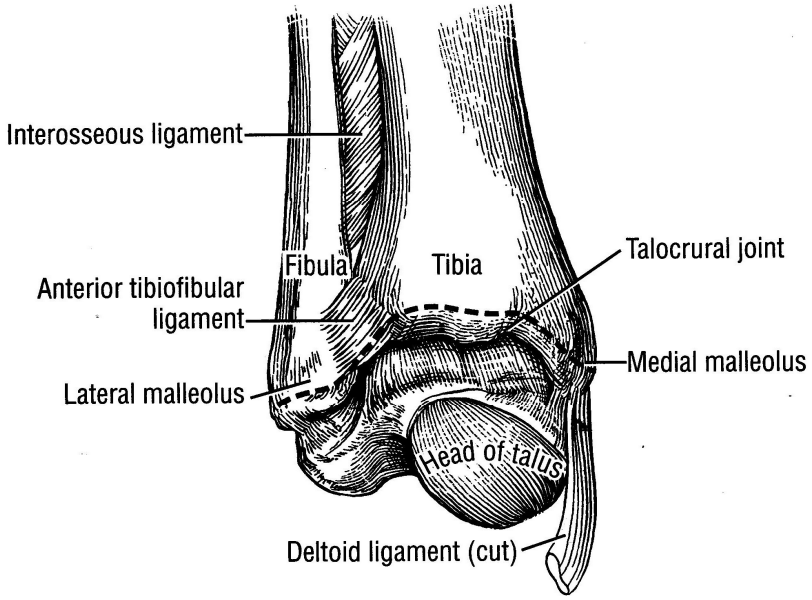


Figure 1: The anterior view of the distal end of the right tibia, fibula and talus. The articulation of the 3 bones forms the talocrural (ankle) joint.The dashed line shows the attachment of the joint capsule. This figure was published in Kinesiology of the Musculoskeletal System, D.A. Neumann, Copyright Elsevier (2002).

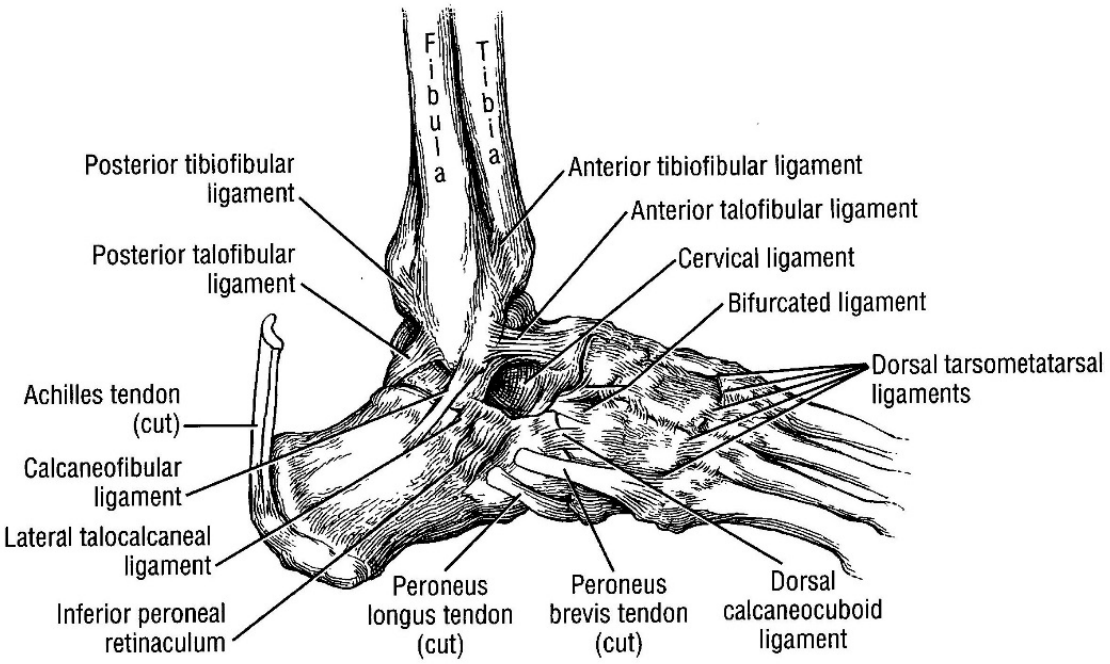


Figure 2: The lateral view of the right ankle showing the lateral collateral ligaments. This figure was published in Kinesiology of the Musculoskeletal System, D.A. Neumann, Copyright Elsevier (2002).

Table 1: Muscles of the lower leg acting on the ankle and subtalar joints by compartment and action.

Compartment of the lower leg (action)	**Muscle**
Anterior (dorsiflexors)	Tibialis anterior Extensor digitorum longus Extensor hallucis longus Peroneus tertius
Lateral (evertors)	Peroneus longus Peroneus brevis
Posterior (plantar flexors)	*Superficial group:* Gastrocnemius Soleus Plantaris
(invertors)	*Deep group:* Tibialis posterior Flexor digitorum longus Flexor hallucis longus

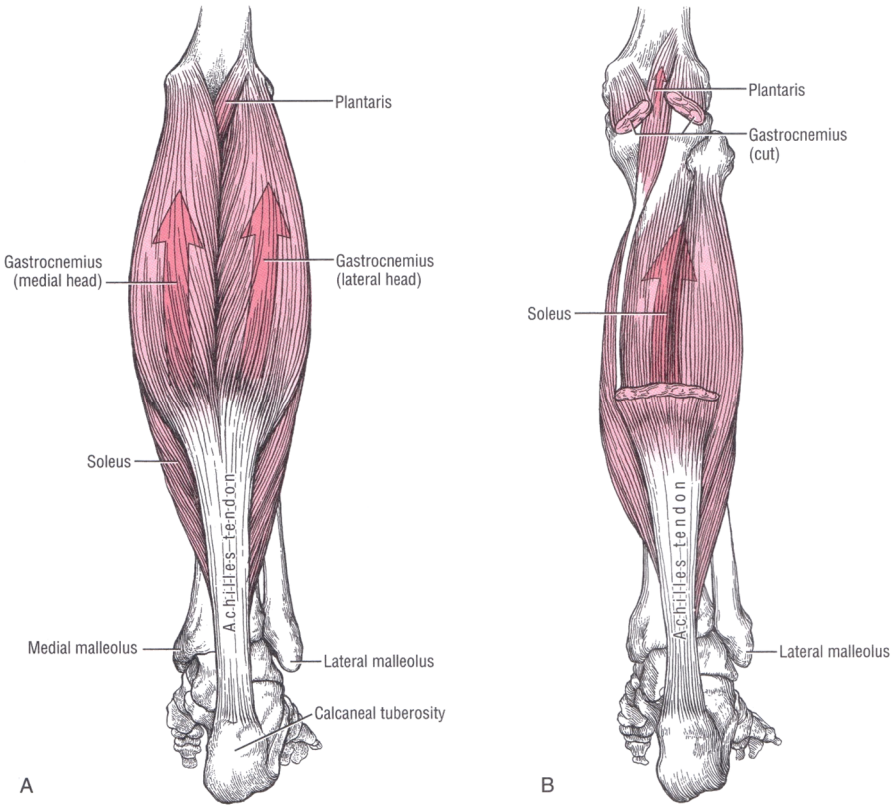


Figure 3: The posterior view of the muscles of the triceps surae complex; A, the gastrocnemius and B, the soleus. This figure was published in Kinesiology of the Musculoskeletal System, D.A.Neumann, Copyright Elsevier (2002).

1.2 Epidemiology

Ankle sprain

Ankle sprains are a common injury with an estimated incidence in the general population of 215 per 100,000 person-years.[259] It has been suggested that ankle sprains account for approximately 3 to 5% of all attendances at emergency departments in the UK.[38]

Ankle fracture

Ankle fracture incidence is much lower at 71 per 100,000 person-years.[235] There are age and gender differences, with peak incidence in younger men aged between 15 to 29 years, whereas in women, incidence peaks over the age of 50 years.[235] For ankle fractures in older people, osteoporosis is an important contributor.[120] Ankle fractures place considerable burden on the National Health Service (NHS) as they account for approximately 9% of all fractures[40] and many require surgical fixation,[75, 200] which costs £4,500 per procedure.[157] Projections from Scandinavia suggest the number of ankle fractures will increase 3 fold between 2006 and 2030, driven by the aging population[102] and increased participation of older people in sporting activities.[5]

1.3 Mechanism and grading of injury

When forces are applied to the ankle causing the talus to tilt or rotate, the ligaments are the first structures to strain. When the force exceeds the ligament's physiological limits, it can 1) fail 2) avulse the bone to which it is attached or 3) lead to fracture of the related bone.[271] If forces continue after failure of the first anatomic structure, the next structure loaded is injured.

Whether a ligament and/or bone are involved depends on the mechanism of injury.
Ankle sprains most commonly occur as a result of ankle inversion and plantar flexion. Initially the anterior talofibular ligament fails; the calcaneofibular ligament becomes involved if the injury is more severe.[105] Ankle fracture is an injury to one or more of the malleoli of the ankle. Severe fractures compromise the stability and alignment of the talocrural and/or distal tibiofibular joints of the ankle complex.[75] The fracture pattern depends on the direction and magnitude of forces on the

ankle and the extent of tissue failure. Unstable fractures are frequently associated with ligament injury.[70] As a result, fracture management needs to address the bone and soft tissue injuries that have occurred.

Ankle sprains are graded based on clinical criteria that indicate the extent of ligamentous disruption.[39, 138] Fractures are graded based on radiographic imaging using the mechanism of injury classification of Lauge-Hansen, or more commonly in clinical practice, the Danis-Weber classification system, which is based on anatomical injury characteristics (Table 2).[75]

Table 2: Classifications of ankle sprain and fracture.

Injury classification	Characteristics
Ankle sprain	
Grade I	No loss of mechanical function or ligamentous laxity. Can weight bear. Ligament stretched not torn.
Grade II	Some loss of function, partial or non-weight bearing. Ligament partially torn, some ligamentous laxity but firm end feel on testing
Grade III	Near total loss of function, unable to weight bear, severe pain, swelling and bruising. Joint unstable due to complete rupture, laxity without end feel on testing.
Ankle fracture	
Danis-Weber	
A	Fracture below the syndesmosis
B	Fracture at the level of the tibial plafond and syndesmosis
C	Fracture above the syndesmosis

1.4 Management of ankle injuries

The primary management of ankle injuries depends on injury severity.

Ankle sprain

Grade I ankle sprains often do not receive intervention beyond simple advice on self-management.[187] For more severe injuries, grades II and III, there is much debate as to whether the

ankle joint should be allowed to start moving or be immobilised by some form of externally applied cast, support, or splint. Immobilisation forms part of the recommendations for managing acute soft tissue injuries with the aim of reducing the risk of bleeding and disruption of new collagen and to control inflammation.[103, 105] The acute inflammatory phase of ligament healing lasts approximately 10 days,[103] therefore immobilisation of grade II or III ligament ruptures is often recommended to help stabilise an otherwise unstable joint during initial healing.[39] However, some clinicians advocate early ankle movement, often referred to as 'functional treatment'.[109] Functional treatment is an ambiguous term, so the direct description of 'early ankle movement' is the preferred term used throughout this thesis. Surgical reconstruction of the lateral ankle ligaments is not usually considered in the acute phase of management.[183]

Ankle fracture

Ankle fractures are initially reduced to the anatomical position, if displaced, and then held in a cast or splint until definitive management is implemented. Stable and undisplaced fractures are typically treated conservatively in an ankle splint or cast. Displaced and/or unstable ankle fractures often require surgery to restore and maintain congruence of the ankle mortise.[75] The recommended surgical technique in developed countries over the last few decades has been open reduction and internal fixation (ORIF).[200]

The rationale is that ORIF surgery will optimise outcome by reducing complications from malunion, particularly post-traumatic osteoarthritis (OA).[49, 137] This is because it is widely thought that malunion of weight-bearing joints directly leads to post-traumatic OA, which can result in persistent symptoms and disability and potentially the need for further surgery.[23, 92] There are several plausible explanations for the aetiology of post-traumatic OA. These include the biomechanical model in addition to genetic factors and direct damage caused by the initial trauma.[67]

In older adults, those over 60 years, there is more controversy in the management of unstable ankle fracture compared with younger adults. There is uncertainty regarding the relative benefits of surgical treatment compared with conservative cast immobilisation in older adults. The benefits of surgery are less clear due to the substantially increased risk of complications such as infection, wound breakdown and fixation failure.[277]

Ankle immobilisation in the first 6 weeks of recovery after ankle ORIF surgery

Usually surgery is followed by a period of complete ankle immobilisation and partial or non-weight bearing. The aim of joint immobilisation during this recovery phase after ORIF surgery is to protect surgical wounds and limit pain during the initial phase of fracture healing.[126] Complete immobilisation of the ankle, restraining ankle movement in a neutral position, can be achieved through various types of non-removable casting generally used for up to 6 weeks after surgery.[122] The potential negative effects of ankle immobilisation in the recovery phase after ankle fracture and ORIF surgery include loss of muscle strength and mass, reduced range of joint motion, and the consequential impact on mobility.[166, 192, 213]

Different recovery protocols after surgery have been investigated in clinical trials, many of these being summarised in the Cochrane review of rehabilitation for ankle fracture.[122, 126] The main comparison in the literature to date is ankle immobilisation versus early ankle movement in the 6 weeks following surgery. Early ankle range of motion exercises have been introduced on the premise that the deleterious effects of the immobilisation period could be reduced.[121] Unfortunately the Cochrane review does not distinguish between important clinical differences in immobilisation protocols such as whether there was also weight bearing. Non-weight bearing versus early weight bearing is a potentially important confounding factor as a systematic review comparing these elements of postoperative recovery have found some evidence, albeit of low quality, for differences in functional recovery favouring early weight bearing.[14] The Cochrane review also does not separate estimates for the risk of minor adverse events (e.g. skin irritation and

sores) from more serious events (e.g. venous thrombosis and deep surgical site infection). An updated review addressing these limitations is therefore required to guide clinical practice.

Rehabilitation of mobility at 6 weeks after ankle ORIF surgery

After 6 weeks of ankle protection and recovery following ankle ORIF surgery, patients commence rehabilitation of weight bearing mobility. Patients may be permitted to start fully weight bearing without restrictions on ankle motion as this coincides with clinical union of the fracture, although this decision can be influenced by surgeon preference and progress of fracture healing.[134] The role of different types of ankle supports, which vary in their design, in aiding rehabilitation of weight bearing mobility is unclear. Ankle supports are usually worn for the first few weeks of weight bearing and are gradually withdrawn as rehabilitation progresses. There are no studies into the effects of different types of ankle support used in clinical practice on walking or pain at this stage of recovery following ankle ORIF surgery. A support for the ankle in the first few weeks of weight bearing may improve gait, have no effect, or indeed make walking gait worse. Developing evidence of the effects of ankle supports currently used in clinical practice would enable clinicians and patients to make more informed choices during rehabilitation of walking.

1.5 Physical impairments and mobility limitations after ankle injury

Due to a range of physical impairments after severe ankle injury, the main loss of function is mobility.

Ankle sprain

Pain, loss of ankle range of motion and deficits in muscle function are major clinical features of acute ankle sprains.[18, 138, 230] A systematic review including 31 studies found that after ankle sprain up to 30% of patients were experiencing pain at 1 year after injury and only 36 to 85% reported full recovery within 3 years.[247] Recovery is slow, with the average absence from work of more than a week, which has substantial economic implications given the high incidence of ankle sprains.[39] The approximate proportion of individuals who have not returned to sport within 6

weeks is 50% and within one year, 10%.[108] Many of those with persistent symptoms have ankle instability, which is more likely after higher severity ankle sprains.[189]

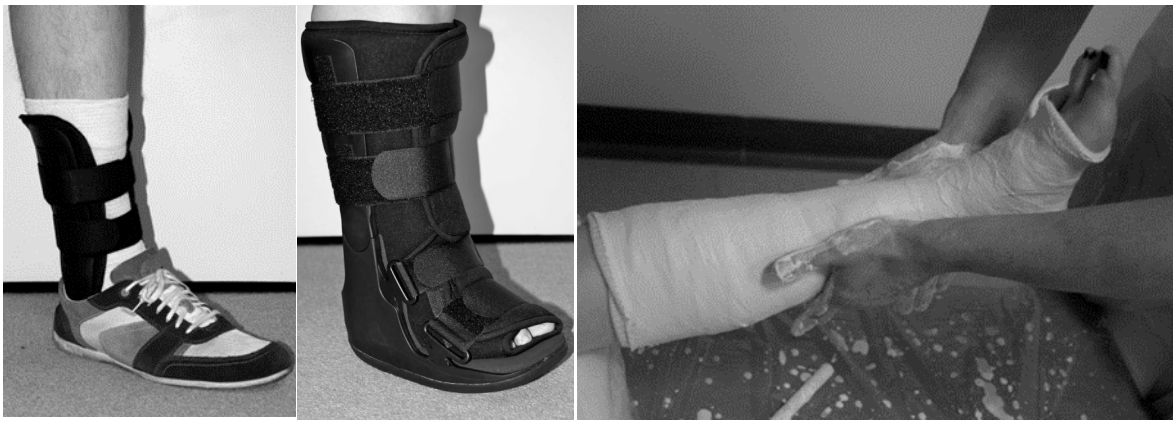
Ankle fracture

The main impairments of the ankle in the early phases of recovery from ankle fracture and subsequent ORIF surgery are pain and a loss of ankle range of motion[125] and deficits in muscle strength.[192, 224] These impairments result in mobility limitations[74, 125] and abnormalities of walking gait.[273] The rates of functional recovery and return to work and sport after ankle ORIF surgery vary substantially in the current literature. McPhail et al.[147] summarised long-term outcome studies of ankle ORIF patients, with reports of between 50 to 85% having good to excellent recovery and 50% reporting persistent problems with sport related activities. Nilsson et al.[168] conducted a patient-reported and physical performance-based follow up of ankle ORIF patients 14 months following surgery. They found over 50% of patients reported ongoing pain, stiffness and swelling in the ankle and observed impaired mobility and triceps surae muscle strength in the injured limb. The impact of mobility limitations was illustrated by a follow-up study investigating employment status after ankle fracture; those patients with physically demanding job roles were particularly at risk of work capacity limitations after ankle fracture.[232]

In the longer-term, the main complication following severe ankle fracture or sprain is post-traumatic osteoarthritis.[241] Unlike hip (2%) and knee (10%) osteoarthritis, most ankle osteoarthritis is post-traumatic (80%).[23] Ankle osteoarthritis sufferers present in lower numbers to secondary care orthopaedic clinics than those with hip and knee osteoarthritis, but experience comparable disability.[71] The burden of post-traumatic ankle osteoarthritis is probably underestimated. A recent study in Australia reported chronic musculoskeletal ankle disorders in approximately 20% of adults aged 18-65, of which most had problems for more than 10 years and a history of injury.[85] The estimated 30,000 patients seen in secondary care each year in the UK with severe ankle osteoarthritis[72] may therefore reflect a limited proportion of those with post-traumatic ankle osteoarthritis in the wider population.

1.6 Externally applied ankle immobilisation versus ankle movement

Externally applied immobilisation encompasses a range of interventions that offer 1) protection of soft tissue injuries and surgical site wounds after surgery for the injured limb, 2) control of joint motion during early rehabilitation of walking and 3) possibly psychological benefits, including greater confidence. Immobilisation limits motion of bones, joints and neurovascular and musculotendinous tissues. Ankle immobilisation is typically achieved by various types of supports or splints, including braces, boots and casts, examples of which are shown in Figure 4. The ankle 'stirrup' brace (e.g. protect.Ankle air foam, Medi, Germany) is formed by two rigid plastic strips with an inner lining on the medial and lateral sides of the lower leg and ankle complex. The stirrup fastens to the leg with Velcro straps. The stirrup primarily limits motion in the frontal plane (inversion and eversion) and is worn with normal footwear. The removable below-knee 'walker' boot (e.g. Jura Walker Fixed, Promedics, UK) is formed by an internal liner and an external plastic sole, with rigid vertical struts medially and laterally, a rocker bottom sole and Velcro fastening straps. The sole of the design of walker boot shown is approximately 4 cm in depth in the mid-section. The walker boot is designed to limit motion at the ankle in all planes. A cast (e.g. plaster of Paris or synthetic casting), is a rigid support that limits ankle motion in all planes. Casts can be non-removable, or can be bivalved, enabling removal to allow ankle movements.



i. ii. iii.

Figure 4: Ankle supports and splints used to limit motion of the ankle. i. ankle stirrup brace, designed to limit ankle inversion and eversion, ii. walker boot, a removable support designed to limit motion in all directions, iii. moulding of plaster of Paris cast, limits motion in all directions.

The earliest recorded use of immobilisation for injured limbs by means of external splinting was by the ancient Egyptians approximately 3000 years B.C.[217] Ever since there has been ongoing refinement and use of external splinting to manage musculoskeletal injury, either in addition to surgical fracture fixation or in isolation.[46, 200] Casting and splints remain an important part of modern clinical practice, with 2.3% of over 18 million treatments in NHS emergency departments in 2012/13 involving some form of plaster cast or splint.[95] There have been many basic and clinical research studies comparing the effects of immobilisation with movement on the musculoskeletal system, which are summarised in the following sections.

1.7 Basic research comparing immobilisation with movement

A wide range of effects of externally applied immobilisation have been studied in animal and human models (Table 3). What is evident is that the musculoskeletal system is responsive to mechanical loading, or stress.[111] Absence or diminished mechanical loading below habitual levels is detrimental to healthy tissues as they enter a catabolic state, or degradation. Mechanical loading is required for musculoskeletal tissue homeostasis and if increased within physiological limits, is an anabolic, or biosynthesis, stimulus.[76, 134] The overall positive influence of mechanical loading

on the musculoskeletal system is being increasingly recognised within the growing field of science known as *mechanobiology*.[58] Early work in this field has shown that loading of musculoskeletal tissues stimulates upregulation of growth factors associated with cellular proliferation and matrix remodelling.[111] The evidence from basic research has led to the recommendation of mobilising injured tissues early after injury. [16, 103]

Basic research into the effects of mechanical loading of musculoskeletal connective tissues such as ligament and tendon can be conducted *in vitro* using cell cultures, but the majority are *in vivo* using animal models.[128] The methods of mechanically unloading musculoskeletal tissues in animal models are summarised by Turner,[238] they include sciatic neurectomy, tenotomy, casting, hind limb taping, hind limb suspension and space flight. The heterogeneity in unloading methods in animal models makes direct transferability of findings into externally applied immobilisation for joint injury in humans questionable. There is a need to assess the effects of immobilisation versus movement in the clinical management of severely injured limbs.

Table 3: Summary of the effects of immobilisation on musculoskeletal tissues from basic research.[81, 100, 134, 181]

Domain	Effect of immobilisation
Ligament	• Lower quality ligament material and scar tissue produced, materially weaker. • Extracellular matrix decreases in quantity. • Reduction in ligament strength and stiffness (slightly reduced in the first few weeks after immobilisation, then exponential). • Structural orientation of scar laid down by fibroblasts is less aligned with functional demands of the tissues.
Bone	• Increased reabsorption and decreased depositing of bone tissue. • Decreased bone stiffness and strength.
Joint capsule and cartilage	• Cross-linking of fibres within the connective tissue limits joint compliance and range of motion. • Fibrofatty connective tissue appears in joint. • Adhesions form between fibrofatty connective tissue and cartilage. • If joint unstable, there is some evidence that short-term. immobilisation of the joint can reduce short-term cartilage damage (shown in the knee in an animal model). • Immobilisation of over one month has been shown to cause atrophy of articular cartilage (decrease in proteoglycan synthesis, softening, decreased thickness, chondrocyte death).
Musculotendinous tissue	• Sarcomeres at the myotendinous junction increase in number if immobilised in a lengthened position and reduce if in a shortened position (starts within 12 to 24 hours of immobilisation). • Atrophy of contractile and non-contractile components. • Reduced muscle fibre size. • Reduced muscle cross-sectional area. • Reduced muscle stiffness and tensile strength. • Reduced number of collagen fibres in tendon. • Diminished neural recruitment of motor units. • Decrease in motor cortex map area of immobilised muscles. • Decreased excitability of corticospinal pathway for immobilised muscles. • Deficits in muscle strength and endurance.

1.8 Clinical research comparing ankle immobilisation with movement

A systematic review including 49 clinical trials (3,366 patients) compared immobilisation versus movement for the early management of all extremity soft tissue injuries. The review found early movement protocols resulted in better outcomes when compared with immobilisation for many types of injury, and in others, found no differences in outcomes.[162] Benefits for the early movement protocols were a faster return to function and reduced joint stiffness and pain. The main limitation of the review was the heterogeneity in the injuries studied, for example, upper and lower limb, and the lack of consideration of severity of injury.

Clinical trials comparing ankle immobilisation with ankle movement have been conducted for the management of ankle sprain and in the postoperative recovery period following ankle ORIF surgery.[123] As discussed above in section 1.4, clinical trial evidence varied and as a result there is controversy as to the optimal treatment strategy after severe injury. The clinical evidence is considered in detail within the individual chapters as it forms the context on which the studies presented in this thesis are based.

1.9 The importance of optimising mobility after ankle injury

Improving patient outcomes after injury is an important personal and public health priority. The Global Burden of Disease Study 2010 found that musculoskeletal disorders account for 21% of years lived with disability worldwide[253] and injuries cost the global population 300 million years of healthy life each year, accounting for 11% of disability-adjusted life years.[158] Optimising early management to maximise mobility recovery and capacity to be physically active is important to reduce disability after injury.

A relationship between physical impairments, limitations in physical activity and participation restrictions is illustrated within the context of the wider health state by the World Health Organisation International Classification of Functioning, Disability and Health (ICF) in Figure 5.[267]

The ICF model highlights the complex relationship of the factors contributing to participation restrictions such as loss of capacity to work or participate in sport. After ankle injury, physical impairments impact on functional activities related to mobility, which in turn affects capacity to participate in activities of daily life. Additionally, environmental and personal factors interplay with these relationships, highlighting the complexity of disability. Of central importance in the return to participation in life roles is the capacity to be mobile. Therefore, optimising recovery of mobility should reduce the burden of ankle injury.

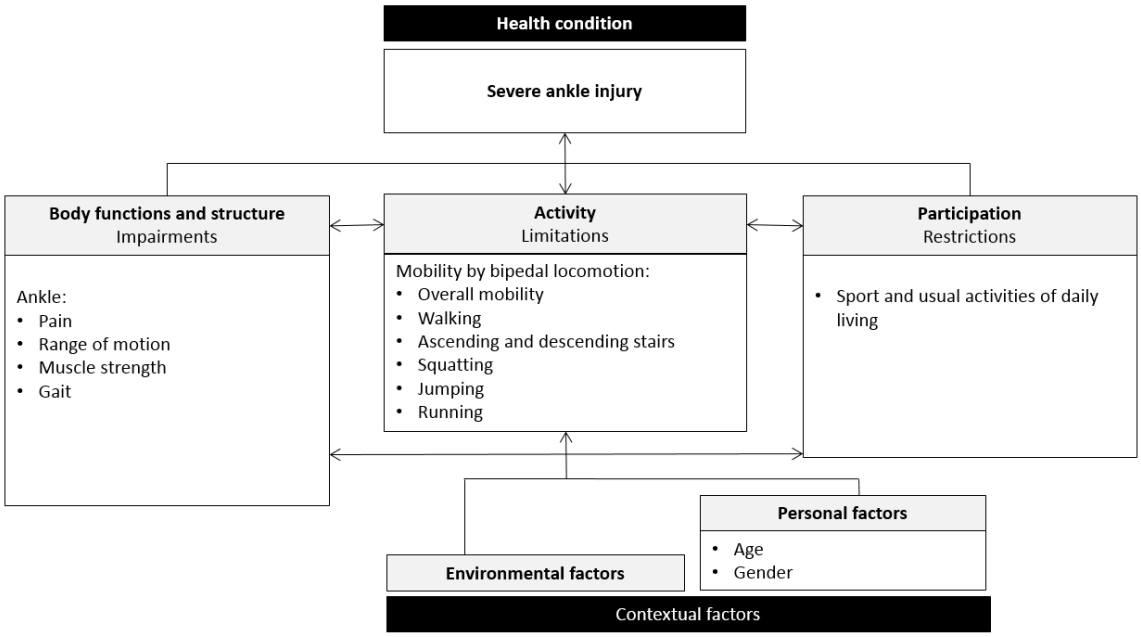


Figure 5: The World Health Organisation International Classification of Functioning (ICF) [267] *adapted with specific elements included within this thesis below the major headings.*

1.10 Recovery of mobility following severe ankle injury

Physical therapy, involving movement, exercise and manual manipulation of the body, is recommended to address ankle impairments with the aim of improving mobility after severe ankle injury.[123] However, evidence supporting the use of manual therapy and exercise interventions used by physical therapists following ankle injury is limited.[18, 124] There is a rationale for initially optimising protocols for immobilisation after injury prior to investigating physical therapy further.

Once the effectiveness of initial injury management is established it would provide a foundation from which physical therapy rehabilitation can be evaluated.

Severe ankle injuries result in the higher levels of limitation of mobility unlike less severe injuries that do not disrupt the stability of the talocrural joint.[45, 169, 173, 189] This thesis focusses on the role of externally applied immobilisation in the management of the severely injured joint involving separate studies of recovery and rehabilitation after a) severe ankle sprain b) recovery and rehabilitation after the period of surgical management (ORIF).

1.11 Summary

The evidence overall for benefits of early movement over immobilisation after musculoskeletal injuries is compelling both from basic science and clinical trials. However, there is less certainty regarding the relative merits of movement or immobilisation after severe ankle injuries. Severity of injury is an important clinical factor when considering the options of treatment. Minor sprains and fractures (stable and/or undisplaced) tend to have a better prognosis and the rates and degree of long-term disability are low. In contrast, severe sprains can result in persistent symptoms, joint instability, decline in function and also be prone to reoccurrence.[138, 247] Higher severity of ankle fracture (unstable and/or displaced) often necessitates surgical management to hold reduction of the fracture and recovery of mobility is often limited.[168, 262]

1.12 Aims and objectives

The overall research question for this thesis was:

Does immobilisation of the ankle compared with ankle movement improve recovery of mobility after severe ankle injury in adults?

1.12.1 Research Aims

The principal aims of this research thesis were:

- To investigate the effects of ankle immobilisation compared with ankle movement on mobility outcomes after severe ankle injury (ligament sprain and fracture).
- To develop experimental and analytical techniques to estimate the effects of different types of ankle support on walking gait.
- To make recommendations on ankle immobilisation interventions for research and clinical practice.

1.12.2 Objectives

- To conduct a systematic review and meta-analysis of the effects of ankle immobilisation versus early ankle movement in the recovery phase after ORIF surgery for ankle fracture in adults.
- To investigate the effects of different types of ankle support on non-pathological walking gait.
- To investigate the effects of different types of ankle support on walking gait and pain in the rehabilitation of walking at 6 weeks after ankle ORIF surgery in adults.
- To quantify muscle strength impairment in adults at 6 weeks after ankle ORIF surgery.
- To determine the effects of different types of ankle support on short- and medium-term recovery of a range of mobility outcomes after severe ankle sprain using the Collaborative Ankle Support Trial (CAST) cohort.
- To use and develop robust research methodology and techniques to generate high quality evidence to support clinical practice and on-going research.

Chapter 2

2 Measurement of mobility after ankle injury

In the preceding chapter, the focus of this thesis on mobility outcomes after ankle injury was introduced. Here the approaches to measurement of mobility, the primary role of ankle function, are considered. Assessment of mobility after ankle injury can involve patient-reported outcome measures (PROMs) or more direct measures of performance such as gait analysis. In this chapter, the merits and challenges of different methods of measurement are discussed. A detailed commentary regarding the development of novel analytical methods for gait analysis developed as part of this thesis is also included.

2.1 Measurement of ankle function

The ICF model of disability (Figure 5, p.16) highlights the central role of mobility in human functioning. An illustration of the importance of mobility is that it is frequently the primary outcome to assess ankle function in clinical trials.[108, 122] There are two main types of instruments used in the literature to measure mobility 1) patient-reported outcome measures 2) objective mobility performance measures.

2.2 Patient-reported outcome measures (PROMs)

PROMs are subjective responses to questions that are scored to provide a quantitative measure of single or multiple domains of health and importantly are assessed by the patient.[144, 226] Patient-reported outcomes are measures of health that can be used to assess the outcome of care received.[15] In the study of ankle injury, PROMs capture some aspects of the ICF domains of activity limitations and participation restrictions. However, some disease-specific PROMs for ankle injury

also include symptoms such as ankle swelling and stiffness that cover another ICF domain, impairments of body functions and structure.

When investigating one specific condition, such as ankle injury, disease-specific or body region-specific PROMs tend to have more clinical focus than generic health measures.[15] The instruments used to evaluate health outcomes require several key properties to be established, these are:[226]

- Content validity, whether the instrument measures all important domains.
- Construct validity, whether the instrument measures what it intends to measure.
- Reliability, the extent to which measurements of individuals are similar when obtained in different conditions.

Examples of disease-specific PROMs for ankle injury and region-specific measures for the lower limb are shown in Table 4. The scores shown are those reported in recent systematic reviews as being frequently used for ankle injury[98] and having evidence as to their properties as measurement tools.[139] It can be seen that the instruments vary in their evidence-base for measurement properties. Two scores, the FAAM and FAOS, use subscale scores, whereas the other PROMs sum the scores from all of the items in the questionnaire. Interestingly in the case of ankle injury, the disease-specific measures do not have as much evidence to support their use as the region-specific instruments.

An issue with the outcome measures for the ankle region when aiming to measure mobility is the diversity of items in each instrument. Few scores focus on mobility in isolation. The disease-specific PROMs for ankle function are multi-item scores that include domains covering symptoms as well as mobility. Region-specific scores also assess diverse mobility and activities of daily living, making measurement of mobility challenging. For example, the FAOS activities of daily living subscale includes questions relating to climbing stairs, walking, shopping, bed mobility and domestic duties. The sports subscale includes questions as varied as kneeling and running.[199]

These issues with using validated PROMS do not negate the value of their use but does highlight their limitations when used to measure mobility specifically.

2.3 Objective mobility performance measures

Performance measures of mobility are objective quantitative assessments of an individual's capacity to perform certain tasks that enable movement of an individual from one place to another. Performance measures are focussed on the ICF domain of impairments of body functions and structure. These performance measures include analysis of walking gait, which is the pattern of movement adopted in human locomotion.[114] Impairments of the ankle region such as pain, muscle weakness and limited joint motion contribute to disorders of gait after injury.[9, 193, 213] The ICF model shows the inter-dependent relationship between these impairments of body functions and structure and activity limitations related to mobility.

Mobility can be measured by different methods of performance measurement. As discussed in Chapter 1, the main initial mobility task of clinical interest after injury is recovering the capacity to walk and this is the focus of this section. Walking is the basic form of mobility that enables movement of an individual around their environment. There are physical performance measures of other mobility tasks such as stair climbing and running, however these activities can be viewed as extensions the base task of walking.[178]

Simple walking measurements following ankle injuries have focused on gait velocity.[213] Although gait velocity is a strong indicator of pathology,[66, 227] individuals with physical impairments will often adopt a compensatory gait pattern in order to maintain velocity.[114] Therefore, despite simple timed walk tests being practical and easily administered in clinical environments, there are limitations in their ability to discriminate between normal and pathological gait. These limitations can be overcome with the use of gait analysis using modern measurement apparatus, which can capture detailed aspects of movement during walking.[178]

Table 4: Evidence for frequently used ankle injury and general lower limb patient-reported outcome measures. Based on Martin and Irrgang.[139]

Measure	Focus	Items	Reliability	Content validity	Construct validity	MCID
AAOS-FA	Regional	20 items including pain, function, stiffness, swelling, giving way	+	+	+	
FAAM*	Regional	2 subscales: ADL (21 items), sport (8 items)	+	+	+	+
FAOS	Regional	5 subscales: pain (9 items), other symptoms (7 items), ADL (17 items), sports and recreation (5 items), foot and ankle QoL (4 items)	+	+	+	
KAFS	Ankle sprain	8 items including instability, pain, swelling, stiffness, stair climbing, running, work activities, ankle support use.			+	
LEFS	Regional	20 items covering a diverse range of physical activities and participation.	+	+	+	+
OMAS	Ankle fracture	9 items including pain, stiffness, swelling, stair climbing, running, jumping, squatting, use of supports for ankle or walking, work and ADL.			+	

AAOS-FA – American Academy of Orthopaedic Surgeons lower limb outcomes assessment instruments Foot and Ankle module. ADLs – Activities of Daily Living. FAAM – Foot and Ankle Ability Measure. FADI – Foot and Ankle Disability Index. FAOS – Foot and Ankle Outcome Score. KAFS – Karlsson Ankle Function Score. LEFS – Lower Extremity Functional Scale. MFS - Maryland Foot Score. MCID – Minimal Clinically Important Difference. OMAS – Olerud-Molander Ankle Score. QoL – Quality of Life. *previous version was the Foot and Ankle Disability Index.

2.3.1 The gait cycle and gait analysis

Walking gait is the *'repetitious sequence of limb motions to simultaneously move the body forward while also maintaining stance stability'*.[178] The role of a lower limb during a gait cycle changes from being a dynamic support of body weight to the advancement of the limb to a new support location. A normal gait pattern is characterised by reciprocal and symmetrical timing and spacing of the two lower limbs as they move between these two roles.[178] As such, symmetry is a widely accepted indicator of normal walking gait.[231] The gait cycle is illustrated in Figure 6 and the divisions of the gait cycle are defined in Table 5.

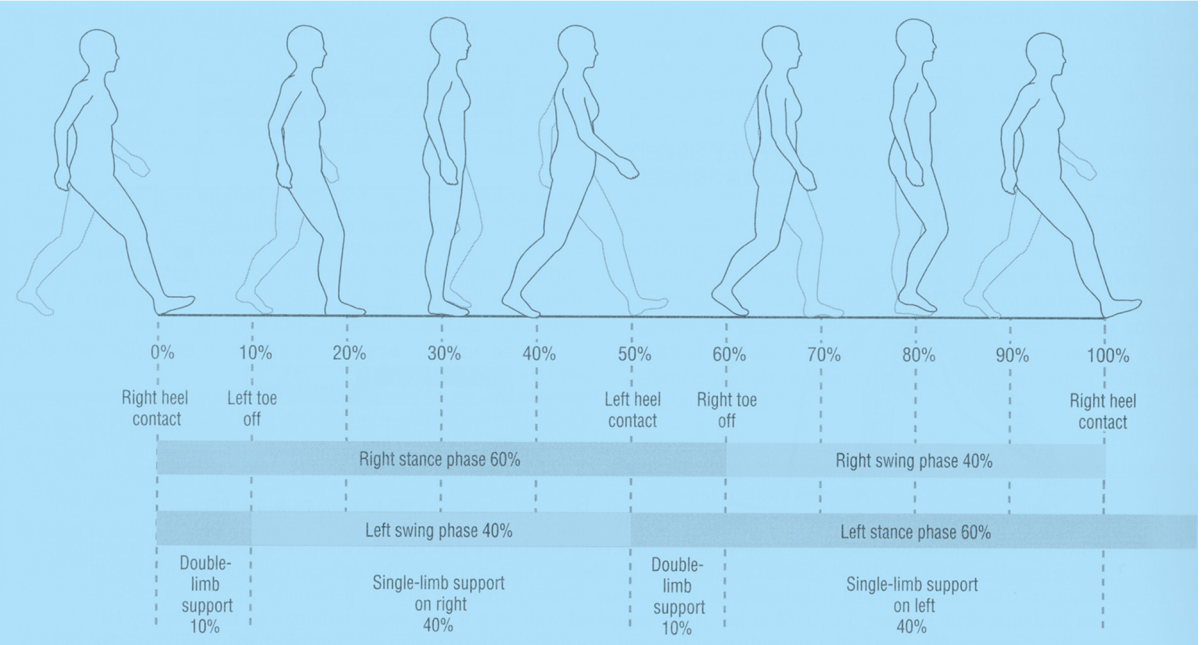


Figure 6: The gait cycle. This figure was published in Kinesiology of the Musculoskeletal System, D.A.Neumann, Copyright Elsevier (2002).

Table 5: Divisions of the gait cycle. [163]

Phase of gait cycle	Description
Stance phase	Foot in contact with the ground.
Double-limb support / double support	Both feet in contact with the ground simultaneously.
Single-limb support /single support	Only one foot in contact with the ground.
Swing phase	Foot is in the air advancing to next location for stance.

In healthy individuals, the duration of the phases of gait for both limbs can increase or decrease as a proportion of the overall gait cycle due to changes in walking velocity required for different mobility tasks. For example, as walking velocity increases the duration of double-limb support reduces, until there is no longer a double support phase and running begins as both feet are off the ground simultaneously.[163] Despite this ability to vary the velocity and the duration of the phases of the gait cycle, healthy individuals maintain a high level of symmetry between the left and right limbs.[114]

The symmetry of gait in humans results in efficient bipedal locomotion.[178] Symmetry reduces energy expenditure, aids balance control and distributes mechanical load on the musculoskeletal system evenly between the lower limbs.[266] Perfect symmetry is not normal, even in non-pathological gait.[201] However, unilateral pathologies have larger magnitudes of asymmetry that are clinically obvious, for example in hemiplegia,[87] hip and knee osteoarthritis[88, 152] and lower extremity fractures.[10, 179]

The main disturbance in walking gait that presents after severe ankle injury is asymmetry in the characteristics of gait between the injured and uninjured limbs.[9, 257] Gait asymmetry is a result of the unilateral physical impairments such as pain, an inability to weight bear, limited joint range of motion, diminished proprioception and muscle atrophy and weakness.[99, 125, 173, 224] When restricted by pain, this is referred to as *antalgic* gait.[114]

2.3.2 Methods of assessing gait asymmetry

Assessment of gait asymmetry requires the use of quantitative gait analysis, as changes in gait are not always evident during clinical observation.[114] There are five main methods of gait analysis:[178]

1. Motion analysis measures the magnitude and timing of joint movements. Measurement systems use 3D motion capture using body markers and multiple cameras in a fixed gait analysis laboratory system (e.g. VICON®, Oxford, UK)

2. Force plates quantify ground reaction forces during weight bearing. Ground reaction forces provide an indication of the functional demands on the foot during weight bearing. Closely related is plantar pressure measurement, which can identify regions of high pressure across the interface between the ground and foot.[178]
3. Electromyography (EMG) captures the co-ordination and timing of muscle activity.
4. Energy expenditure can be used to examine the efficiency of gait mechanics.
5. Temporo-spatial footfall analysis provides an overall robust measure of gait quality, as it is the combined result of gait muscle kinetics (effect of muscle forces on joints) and arthrokinematics (movement of the joints).[163, 178] These are most commonly measured using an electronic walkway containing pressure sensors to capture the timing and spacing of footfalls (e.g. GAITRite®, CIR Symptoms, Havertown, PA).[178]

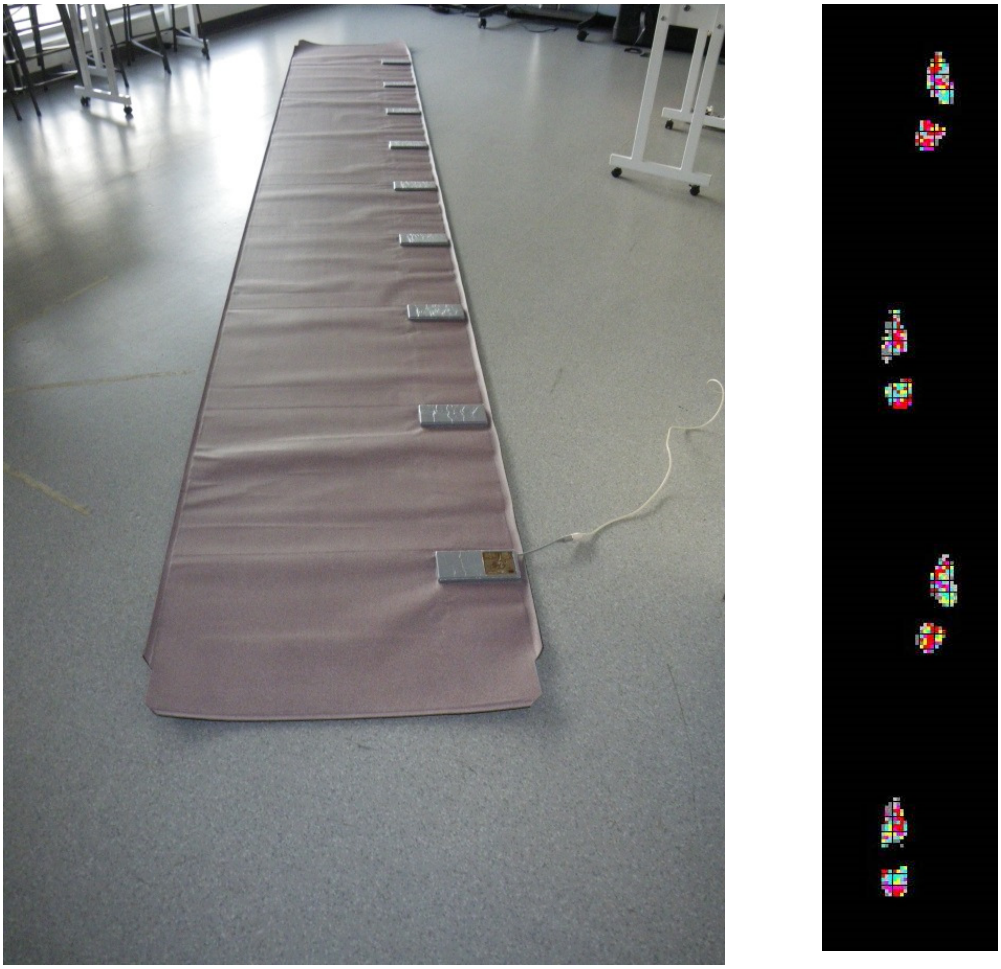
The equipment required for sophisticated motion analysis is not practical within the acute clinical environment where ankle injuries are managed. Force plates require fixed systems in specialised gait laboratories. Plantar-pressure measurements are used for assessing foot mechanics and detecting abnormalities in pressure distribution rather than gait cycle asymmetry. EMG technologies are developing but are time-consuming and the most accurate assessments require invasive needle electrodes. Energy cost is a key factor when examining the restrictions of mobility related to fatigue secondary to a lack of mechanical efficiency, but this does not offer a quantification of walking asymmetry. As symmetry of walking gait is a rehabilitation objective[231] the mode of analysis needs to be able to compare lower limb performance of the injured and uninjured limbs. Portable systems have been developed to measure temporo-spatial gait characteristics, which enable assessment of gait cycle asymmetry in clinical environments. Therefore, for clinical and pragmatic considerations, temporo-spatial footfall analysis was selected as the mode of gait analysis employed in the experimental studies in this thesis investigating the effects of ankle supports on walking gait (Chapters 4 and 5).

2.3.3 Temporo-spatial footfall analysis

Temporo-spatial footfall analysis is the measurement of 1) temporal observations, which concerns the timing of events during a gait cycle and 2) spatial analysis, the distance parameters between footfalls during the gait cycle.

The instrument used in Chapters 4 and 5 for measurement of temporo-spatial footfalls is the GAITRite® portable electronic walkway. The 16ft version has 18,432 integrated sensors with an active area 61cm wide and 4.88m long (Figure 7). The upper surface of the walkway is made of anti-slip vinyl and the underside is neoprene rubber. The sensor pads within the electronic walkway have a spatial resolution of 1.27cm. As a participant steps onto the mat, the sensors detect pressure contact from the foot. Signals are converted into a graphical trace of the footfall contacts as the participant ambulates over the walkway. These footfall traces are used by the algorithms within the system to calculate distance parameters. When combined with measurements of the timing of footfalls, complete assessment of spatial and temporal aspects of gait can be integrated.

Concurrent validity of the GAITRite® system has been investigated by comparing temporo-spatial measurements with the VICON® system[260] and the Clinical Stride Analyzer®.[12] Excellent test-retest reliability on measures 2 weeks apart has been demonstrated for step length and walking velocity in healthy young and older adults.[148]



i. ii.

Figure 7: The GAITRite® system i. the electronic walkway (16ft/4.9m); ii. graphical display of footfalls detected by the pressure sensors.

Guidelines for temporo-spatial footfall measurements using GAITRite® have been developed by a European network of clinicians and researchers.[115] The purpose of these guidelines was to improve the reproducibility of gait measurements. The guidelines indicated the need to standardise lighting, to minimise audio-visual distractions, to allow participants to wear their own footwear and to take precautions to reduce risk of falls in clinical populations. It was also recommended that participants should not use walking aids if possible, if not, the type of aid used should be noted and included in the study report. There is also a need to ensure that measurements are not taken from static standing, as a steady state of walking is not achieved until after 2 complete gait cycles.

2.3.4 Key temporo-spatial gait variables

Two interdependent gait outcomes, step length and single support time, were selected as the key spatial and temporal footfall characteristics respectively for the purposes of this thesis. These two outcomes are equally important when interpreting gait asymmetry outcomes. Step length is the distance one part of the foot moves during a step in relation to the same part of the foot in the contralateral limb (Figure 8).[114] Single support time is the duration of time in the gait cycle when a single lower limb is in contact with the ground and solely supporting body weight (Figure 6).

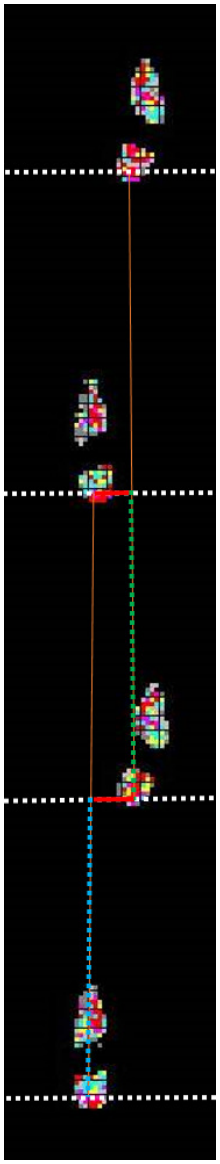
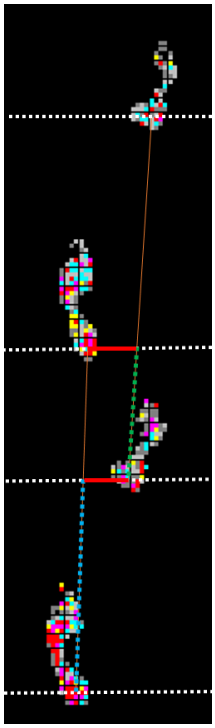
i.  ii. 

Figure 8: Two consecutive footfalls of the left and right feet during walking gait in i. non-pathological gait and ii. right ankle impairment (images not on same scale, for illustrative purposes only). Step length for the left is represented by the green line and the right by the blue line. The distance perpendicular to these lines is the step width, represented by the red lines. The orange line represents the line of progression between consecutive footfalls of the same foot. These variables are calculated relative to the centre of the heel and the line of progression.

Non-pathological gait is characterised by near perfect symmetry in step length and single support time between the lower limbs.[178] Step length and single support time in normal gait are usually interrelated.

After ankle injury the limitations in ability to weight-bear and achieve stability on the injured limb may reduce the duration of single limb support.[42] Reduced single support time can lead to reduced step length in the contralateral limb as a means of returning the uninjured limb back to a weight-bearing role as soon as possible. Step length can increase or decrease in an injured limb relative to an uninjured limb as individuals try to compensate for impairments. As a result, symmetry indices rather than absolute values for each limb tend to be the most clinically useful metrics as indicators of recovery.[114] Symmetry indices have been selected as primary outcomes in previous studies investigating temporo-spatial footfall characteristics in unilateral musculoskeletal impairment.[88] The relationship between the injured and uninjured limb are expressed as a symmetry index (SI).[88]. SI calculations vary in the literature but one that overcomes the issue of positive and negative indices cancelling out when making comparisons between tests is used in this thesis:[86]

$$SI = 1 - \left(\frac{value\ for\ limb\ with\ lowest\ measure\ of\ gait\ outcome}{value\ for\ limb\ with\ highest\ measure\ of\ gait\ outcome}\right)$$

The SI has a minimum of 0 (perfect symmetry) and 0.1 is equivalent to 10% asymmetry, 0.5 is 50% asymmetry and so on. Values over 1.0 are only possible for the step length SI, where the foot of one limb does not progress past the same part in the opposite foot. A SI of over 1.0 indicates substantial gait asymmetry.

2.3.5 Accounting for the influence of walking velocity when assessing gait asymmetry

A major methodological challenge when measuring gait asymmetry is dealing with the influence of walking velocity.[3] Velocity of walking can influence the magnitude of gait asymmetry.[88] The speed-dependent nature of asymmetry measures means observed asymmetry under different

conditions (repeated measures or between individuals) may be explained by differences in gait velocity. Therefore, walking velocity needs to be accounted for in experimental design and analysis. However, there is not a universally accepted approach in the literature.[3]

2.3.6 Development of an analytical approach to obtain velocity normalised effect estimates

Approaches to normalising gait speed involve either experimentally setting walking velocity or using statistical procedures. The approaches typically used to normalise speed have major limitations. Experimental options include participants walking at a range of speeds with the walk nearest a pre-selected speed being used in the analysis. Alternatively, cadence (steps per minute) pacing can be attempted using a metronome.[3] Both of these approaches rely on all participants to walk at a common speed in all experimental conditions, which may not be practical or possible as self-selected speed varies markedly between people – some people naturally walk slowly and others do not. It also imposes an abnormal cognitive demand that can influence gait performance.[275]

Statistical methods are sometimes used to adjust for the effect of velocity:

- Repeated measures analysis of variance (ANOVA): One of the main limitations of ANOVA is the assumption of sphericity.[90] Sphericity is the assumption that the variance in the differences between observations from the same participants is equal.[60] Sphericity is a strict assumption in the context of gait performance over time as the stability of individual variability is not certain.
- Multivariate analysis of variance (MANOVA): This approach avoids the assumption of sphericity but does not account for the nesting of gait observations within individuals, violating the independence assumption.[90]

2.3.7 Combined experimental and statistical methods to normalise walking speed

A technique has been developed by Moe-Nilssen and colleagues, which combines experimental and statistical approaches.[80] The technique involves asking participants to walk deliberately at their self-selected slow, preferred and fast speeds over a series of tests.

Experimental procedure

Participants are asked to walk back and forth across an electronic walkway at Preferred Walking Speed (PWS), followed by measurements at Slow Walking Speed (SWS) and then Fast Walking Speed (FWS). Therefore, 2 walks are recorded at each speed, 6 walks in total. The purpose of 2 walks at each speed is to reduce random error.

Statistical procedure

Speed normalised estimates for speed-dependent gait variables such as step length symmetry indices are obtained using the data from the 6 walks, to construct a linear regression plot across all conditions. A curvilinear regression plot is used instead if adding a quadratic term improves the fit of the model (see Figure 9 for a detailed illustration and explanation of this technique).[80]

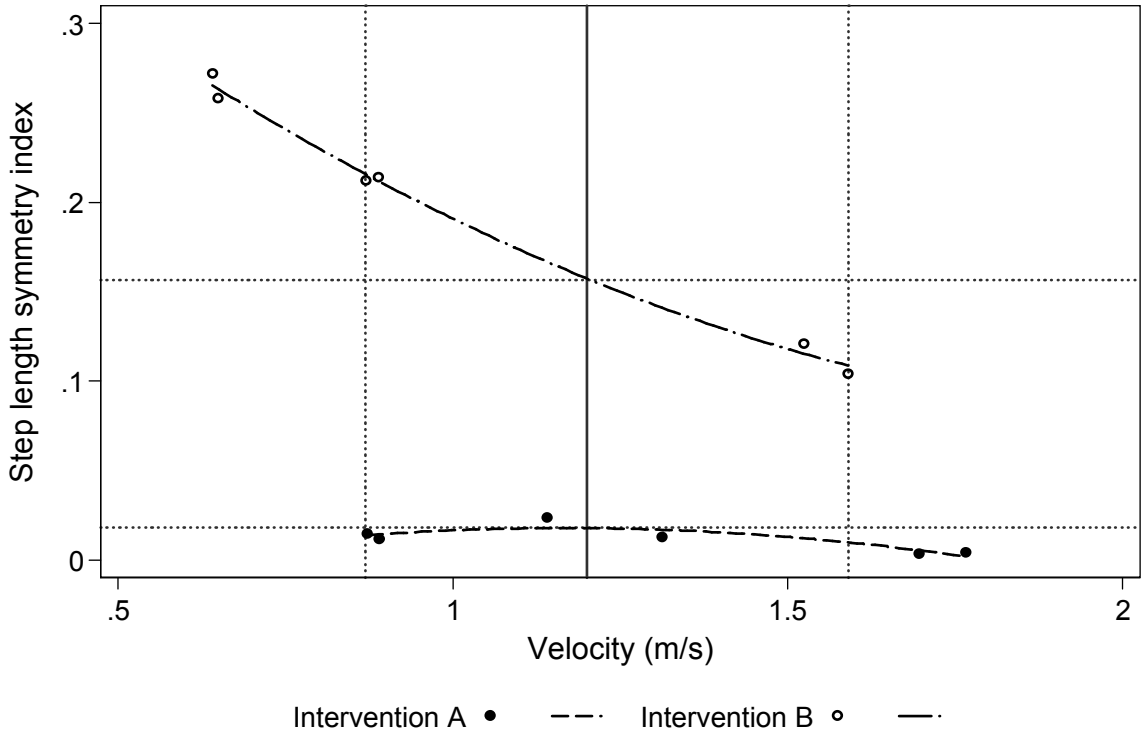


Figure 9: Example of step length symmetry indices by velocity (m/s) for one participant during two different interventions (A and B). 6 observations per intervention are shown by the larger dots. Pairs of larger dots in close proximity represent the two test walks at each test speed, from left to right, slow, preferred and fast test speeds. The dashed lines represent the quadratic regression lines for the two different interventions. An estimate of step length symmetry indices is obtained at a point within the range of overlapping walking velocities for each intervention. The range of overlap is between the two x-axis dotted reference lines. An estimate of step length symmetry indices for the two interventions is taken a selected point, in this example at 1.2m/s, represented by the x-axis solid reference line. The estimates for each intervention at 1.2 m/s is shown by the y-axis dotted reference lines

As shown in Figure 9, the reference walking velocity is taken at a point of convenience somewhere within the range of observed speeds common to all test conditions. The advantage of this method is the normalisation of speed using an estimate from the regression plots within the range of speeds observed across the experimental conditions. However, to utilise this technique, all participants require an overlap in the range of walking velocities. If an intervention is being studied there needs to be an overlap between the ranges of gait velocities within and between participants for all interventions. This can be problematic in clinical populations, or when assessing the effect of different interventions, as large differences in walking capacity can make this requirement

impractical. To date there have been no satisfactory solutions to this limitation. An example later in this thesis illustrates how the requirement to obtain an overlap in the range of speeds walked across all participants and with different interventions being applied is not always possible (Chapters 4 and 5).

An additional issue with this method during analysis is that gait asymmetry can vary at different parts of the range of walking velocity. Figure 9 shows an example of gait measurements during two interventions. The size of difference in estimated step length symmetry indices between interventions varies across the range of walking velocity. The implications of this is that normalising effect estimates using a point-estimate means that differences in gait performance between the two interventions will vary depending on what reference velocity is chosen. These analytical issues necessitated the development of a novel alternative analytical method to improve the estimates of treatment effect for studies using gait analysis in this thesis (Chapters 4 and 5). Techniques were needed that could 1) utilise the data from the experimental procedure outlined by Moe-Nilssen, 2) account for the effect of walking velocity, 3) not require overlapping ranges of walking velocity for each support and each intervention and 4) not be reliant on a single point-estimate.

2.3.8 Multilevel modelling for gait analysis

Multilevel modelling (MLM), otherwise known as hierarchical modelling, offers an alternative approach to the analytical issues identified.[194, 239] Literature searches indicate that this method has not been widely applied in temporo-spatial gait analysis. Searching Medline in July 2014, using terms for gait and hierarchical/multilevel models, found 12 results. No results were returned when searching for 'gaitrite' and the model terms. Multilevel models may be limited in their use due to the relative complexity of the analysis when compared with ANOVA and multiple linear regression.[194] Many of the specialised software packages also require statistical programming to optimise analysis.[239] In the case of GAITRite® data, there is also no existing statistical computing code to automate all of the steps in the analysis.

2.3.9 Developing a novel application of multilevel modelling in gait analysis

The repeated-measures from gait analysis are clustered within subject. Due to the repeated within-subject measurements, and therefore correlated observations, the use of multilevel modelling is appropriate. Twisk[239] and Rabe-Hesketh and Skrondal[194] provide detailed explanations of MLM which can be applied to the circumstances in gait analysis. MLM is an extension of linear regression modelling, the main difference being that the models account for hierarchy in the data. In the context of repeated measures in gait analysis, the measures are level 1 data and these observations are clustered by participant, the level 2 data. Accounting for the hierarchy in the data brings several advantages. The use of MLM to account for walking velocity in the analysis enables the intervention effect on, for example step length asymmetry, to be distinguished from the effect of walking speed. To illustrate the functions and advantages of MLM, the stages of building of the models is described below.

2.3.10 Multilevel models for repeated-measures gait analysis

Simple linear regression (Figure 10) does not account for the clustering of observations in repeated measures within-subject (incorrect standard errors and variance at participant and observation levels).

Equation for a simple linear regression model:

$$Y = \beta_0 + \beta_1 X_1 + \varepsilon$$

Where Y = outcome variable; β_0 = intercept; β_1 = regression coefficient for X_1; X_1= time-dependent independent variable; and ε = error/residual

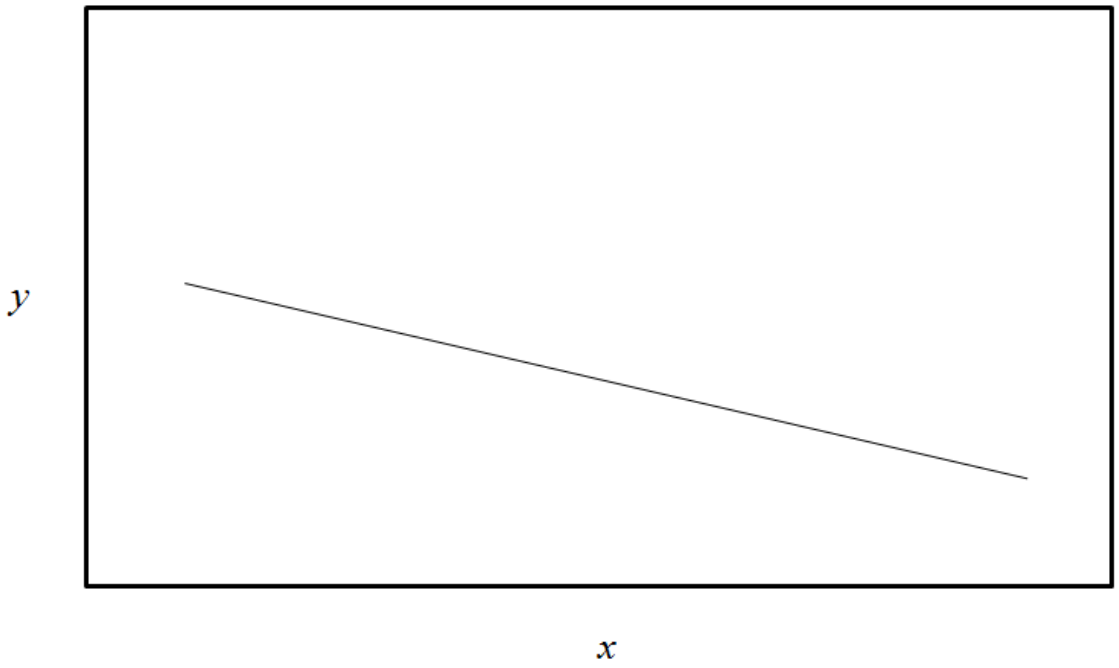


Figure 10: Illustration of a simple linear regression plot for the relationship between two variables.

Multilevel modelling deals with the clustering of observations from repeated measures by accounting for the variance of the intercepts i.e. variance parameter is estimated for the random intercept (Figure 11).

Random intercept model:

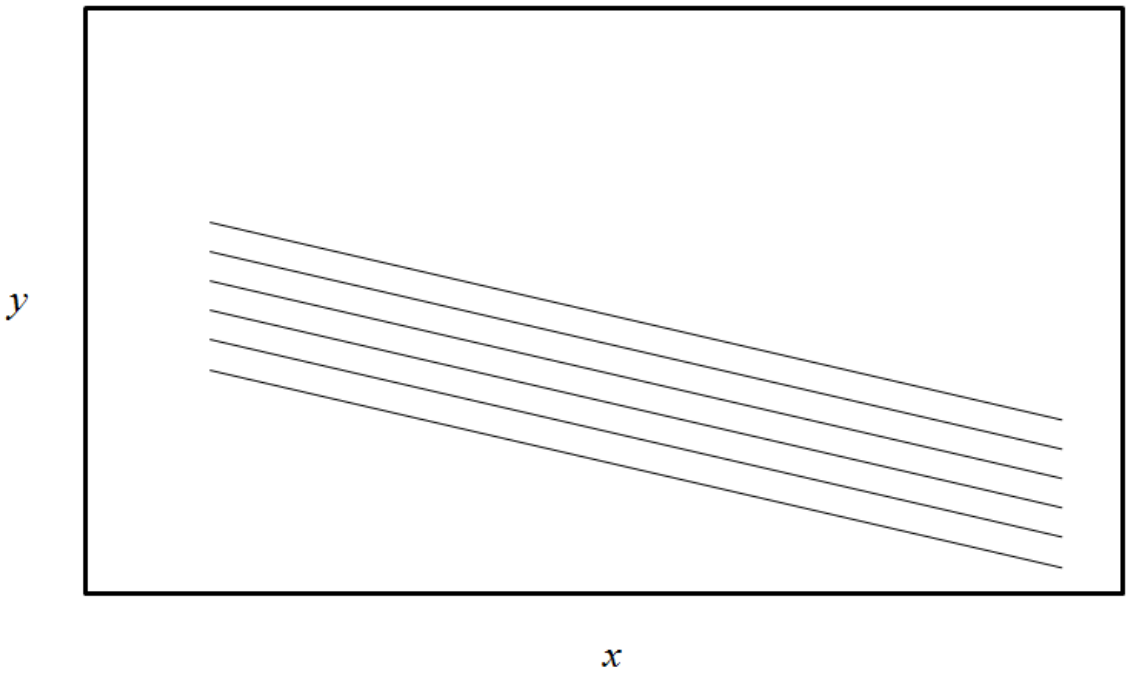


Figure 11: Illustration of a random intercept model of the relationship between two variables with a different intercept for each participant.

Equation for a random intercept model:

$$Y_{ij} = \beta_0 + \beta_1 X_{1ij} + u_j + \varepsilon_{ij}$$

Y_{ij} =gait variable outcome for the ith measurement occasion and jth participant.

i= measurement occasion

j= participant

Fixed part

β_0 = intercept for overall regression line (intercept for each participant is $\beta_0 + u_j$)

β_1 = increase in Y for a 1 unit increase in X.

Random part

u_j = random term for participant (random intercept): unexplained variation at level 2 after controlling for the explanatory variables

ε_{ij}= random term for observations: unexplained variation at level 1 after controlling for the explanatory variables.

One assumption of the random intercept model is that the effect of the explanatory variable(s) is the same in every participant. This may not be a valid assumption and this can be seen visually when comparing regression lines for each participant (Figure 12). In these circumstances, exploring the use of a random slope model is recommended.[194, 239]

Random coefficient/slope model:

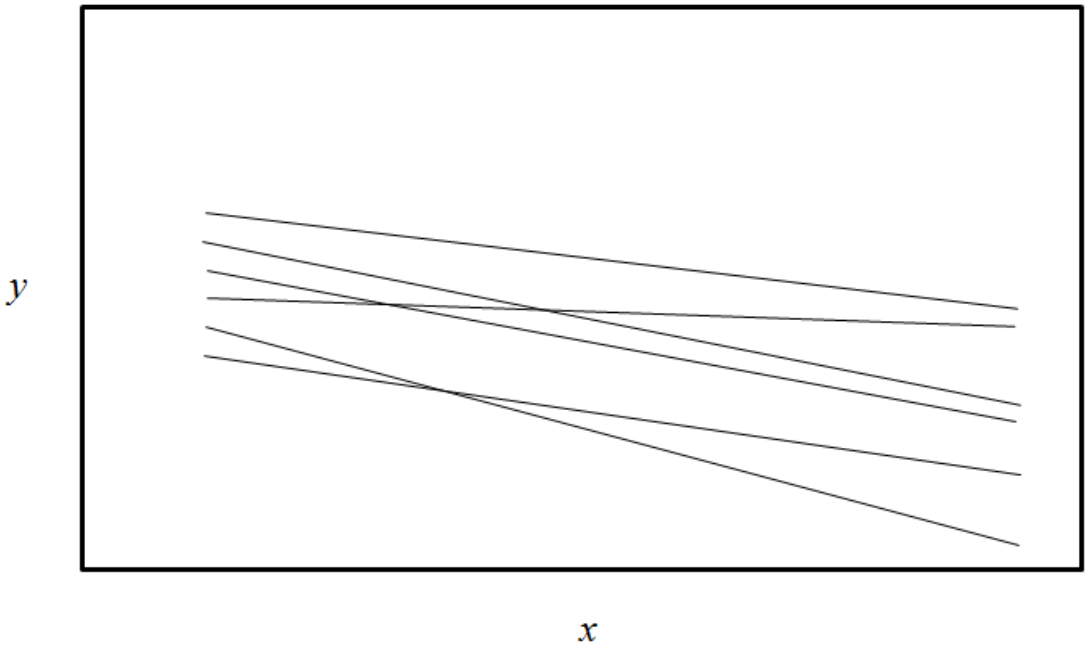


Figure 12: Illustration of a random coefficient/slope model of the relationship between two variables with a different intercept for each participant.

Equation for a random coefficient/slope model:

$$Y_{ij} = \beta_0 + \beta_1 X_{1ij} + u_{0j} + u_{1j} X_{1ij} + \varepsilon_{0ij}$$

Fixed part

β_0 = intercept for overall regression line (intercept for each participant is $\beta_0 + u_{0j}$)

β_1 = slope of the average line i.e. the mean change across all participants in Y for a 1 unit change in X_1

Random part

u_{0j} = random term for intercept: unexplained variation at level 2 after controlling for the explanatory variables

u_{1j}= random term for slopes between participant lines and the slope of the overall line

ε_{ij}= random term for observations: unexplained variation at level 1 after controlling for the explanatory variables.

Explanatory variables are added to these models to control for differences in the conditions for each participant (e.g. ankle support used and velocity of walk). A further model adding a variance parameter can also be added for random curve using a quadratic term (velocity^2).

In the context of gait analysis the use of MLM has several advantages over other statistical methods:

1. Reduces the confounding effect of walking velocity.
2. Offers a closer model of the true treatment effect on a speed-dependent gait outcome as walking velocity is accounted for.
3. Does not violate the assumptions of independence or sphericity.
4. Utilises the information on repeated gait measurements at a range of walking velocities.
5. Allows adjustment for participant level variability in gait performance over different walking velocities (intercepts and slope variance for each participant).
6. Does not require overlap of walking speeds as per the Moe-Nilssen method described in section 2.3.7, p.32.
7. The models are robust in situations where missing data could present, as is often an issue in clinical research.[239]

The novel application of MLM approach to gait data analysis described here is applied in two studies in this thesis, see Chapters 4 and 5.

2.4 Strength and limitations of PROMs and gait analysis

Beyond the main issues in measurement of mobility discussed above, there are also differences in the strengths and limitations for PROMs and gait analysis. These differences are compared in Table 6.

Table 6: Strengths and limitations of PROMs and gait analysis in the measurement of aspects of mobility. [15, 44, 114, 144, 178, 226]

	Strengths	Limitations
PROMs	• Patient's perspective is central. • Pragmatic measure of mobility outcome. • Requires little or no clinician or researcher involvement or training. • Can be administered remotely or independently to reduce risk of bias in responses. • Relatively low cost to administer. • Large numbers of study participants can be assessed.	• Response rates to questionnaires used remotely can be low. • Domains measured in a tool may not match with the objectives of a particular research question. • Responses can be influenced by other factors than health state.

Performance tests of mobility	• Direct measurement of mobility task, can detect subtle changes in performance.
	• Useful as an outcome in explanatory trials where surrogate markers of mobility outcome are appropriate.
	• Precision of measure can reduce the number of participants required to detect meaningful differences in outcome (if the method has high reliability).
		• Equipment can be costly.
		• Resources can be intensive, requires:
		  o Technical expertise.
		  o Designated space.
		  o Patient attendance.
		  o Significant time from participant and researcher.
		• Higher resource requirements make use on large numbers of participants burdensome.
		• Investigator often conducts measurements therefore open to observer or Hawthorne effect biases.
		• Experimental and analytic challenges.

2.5 Conclusion

While PROMs and physical performance measures such as gait analysis have differences in their strengths and weaknesses, ultimately they complement each other as measures of outcome.[47] However, the choice between using PROMs and physical performance measures is mainly guided by the objectives of the research question.[44] If the focus is on mobility outcomes more broadly in a pragmatic clinical setting then PROMs are usually indicated. When studying the efficacy or mechanism of an intervention on mobility, in earlier developmental research, the use of physical performance measures such as gait analysis may be the preferred outcome. A novel approach to overcoming a major limitation to gait analysis of speed-dependent gait measurements has been outlined. This analytical development is employed in Chapters 4 and 5.

Chapter 3

3 Early ankle movement versus ankle immobilisation in the postoperative management of ankle fracture in adults: a systematic review and meta-analysis.

This chapter reports a systematic review and meta-analysis of current knowledge regarding early ankle movement compared with ankle immobilisation in the postoperative management of ankle fracture in adults. The review was focussed on patient-reported physical function/mobility and pain outcomes as well as adverse events. The clinical and research implications are discussed in relation to the findings of the review.

3.1 Background

As introduced in section 1.4, p.6, a Cochrane systematic review included trials up to July 2011, which compared early ankle movement versus ankle immobilisation after ankle ORIF surgery.[122] The authors concluded that a removable ankle splint/support may reduce activity limitation, improve pain and ankle range of movement, but was also associated with an increase in postoperative adverse events, mainly surgical wound problems. Although the Cochrane review was thorough, the approach taken limits the clinical application of findings. For example, heterogeneous data from a broad range of postoperative time points were pooled so that outcomes from 10 weeks to 2 years were summarised within an 'end of follow-up' estimate.[122] Similarly, pooling of all postoperative adverse events, including clinically serious complications (e.g. venous thrombosis/thromboembolism) and less serious complications (e.g. superficial surgical site infection), into a single adverse event estimate limits clinical interpretation of the risk of harms. An earlier systematic review [233] aimed to identify the risk of different postoperative complications but did not report effect sizes and was methodologically limited by including retrospective data from non-randomised patients.[31]

3.2 Objectives

The aim of the review presented in this thesis was to update and synthesise all eligible randomised and quasi-randomised controlled trials (RCTs) to investigate whether early ankle movement, compared with immobilisation, improved clinical and patient-reported outcomes in adults undergoing surgery for ankle fracture. Importantly the aim was to evaluate treatment effects by severity and impact of postoperative complications. An alternative approach to previous reviews was used to synthesise the literature, by considering important functional and physical outcomes by clinical time point after surgery (acute, sub-acute, and long-term outcome). This approach was taken to provide clinicians and patients with information on the risks and benefits of alternative treatment strategies during different stages of the recovery pathway.

3.3 Methods

The review is reported as per PRISMA reporting guidelines for systematic reviews and meta-analyses.[156] In accordance with good practice guidelines, the review was registered and published on the PROSPERO database 2012:CRD42012002639. Available at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002639#.UqmBN-LwhvY

3.3.1 Eligibility criteria

Randomised and quasi-randomised[83] (e.g. allocation by date of birth) clinical trials were included.

Participants

Studies involving skeletally mature adults (majority of participants aged 18 years or over) with surgically treated ankle fractures were eligible for inclusion. Studies of fractures to the tibial plafond (pilon fractures) and talus were excluded, as were studies of pathological fractures (except osteoporotic fractures) and exercise-related stress fractures.

Interventions

One of the trial interventions was a type of externally applied immobilisation (e.g. splint, cast or brace).

Comparators

The comparator intervention was any treatment protocol that allowed ankle movement (e.g. no externally applied immobilisation, or a splint or brace that did not immobilise the ankle, or a removable cast/brace to allow ankle motion exercises).

Outcomes

Studies were not selected based on the outcomes reported. The primary and secondary outcomes for the review were selected before conducting the search, as outlined below.

Date restriction was imposed to include studies from the last 3 decades of medical literature from 1982 to 2013. This reflects a period when ankle fracture fixation principles were widely disseminated and adopted through the AO (Arbeitsgemeinschaft für Osteosynthesefragen [association of the study of internal fixation]) Foundation.[200] The search was not limited by language of publication, duration of follow-up, or by outcomes reported.

3.3.2 Search

Search strategies were developed and applied to the following databases: The Cochrane Library (Wiley InterScience), MEDLINE, AMED, EMBASE (via Ovid), CINAHL, SPORTDiscus (via EBSCO), trials registers (CENTRAL and WHO International Clinical Trials Registry), and PEDro (Physiotherapy Evidence Database). An example of the electronic search strategy for MEDLINE is shown in Table 7. The other search strategies are included in Appendix 1. The search strategy was peer-reviewed by an experienced medical librarian (Tatjana Petrinic, Outreach Librarian, Bodleian Health Care Libraries). Searches were completed in September 2012; a limited update search[156] was conducted July 2014 which yielded no additional studies. Reference lists of included trials and systematic reviews were checked for potentially eligible studies.

Table 7: Example of electronic search strategy.

MEDLINE via OVID	
1.	(distal and (fibula* or tibia*)).mp.
2.	(ankle* or malleol* or unimalleol* or bimalleol* or trimalleol* or potts or weber or lauge-hansen).mp.
3.	fracture*.mp.
4.	(1 or 2) and 3
5.	exp Ankle Injuries/
6.	exp Fractures, Bone/
7.	5 and 6
8.	4 or 7
9.	limit 8 to yr="1982 - 2012"
10.	(randomized controlled trial pt or controlled clinical trial pt or randomized ab or placebo ab or randomly ab or trial ab or groups ab).af.
11.	randomized controlled trial.pt.
12.	controlled clinical trial.pt.
13.	randomized.ab.
14.	randomly.ab.
15.	trial.ab.
16.	10 or 11 or 12 or 13 or 14 or 15
17.	9 and 16

3.3.3 Study selection

The screening of studies was conducted by one reviewer (David J. Keene) inspecting titles and abstracts. Full-text publications were then obtained as required. Any query regarding eligibility was resolved by discussion with other reviewers (Dr Esther Williamson and Professor Sarah E. Lamb).

3.3.4 Data collection

Primary outcomes included patient-reported physical function/mobility, postoperative pain, and different types of complication. In line with recommendation in the Cochrane Handbook,[83] primary outcomes included two potential positive intervention outcomes, functional/mobility recovery and pain, and an adverse effect outcome, postoperative complications. Postoperative complications were categorised into 4 types: superficial and deep surgical site infection (SSI); postoperative venous thrombosis/thromboembolism (all confirmed on diagnostic investigation but not systematically screened); other non-infected skin or wound complications; and fixation related complications (i.e. failure of fixation or reoperation to remove metalwork). Secondary outcomes included ankle range of movement, ankle swelling, muscle function, physical performance

measures, duration of hospital stay, return to work and leisure activities/sports, quality of life, and patient satisfaction.

3.3.5 Data extraction and management

Study characteristics, participant characteristics, intervention, control or comparator treatment, and outcome data were extracted using a standardised data extraction form based on Cochrane recommendations (Appendix 2).[83] Data extraction was performed by 2 independent reviewers (DJK and EW). Where events were only reported for 1 intervention arm, it was assumed no events occurred in the comparator group.

3.3.6 Risk of bias in individual studies

Risk of bias in the individual studies was assessed with the Cochrane risk of bias assessment tool for two main reasons. Firstly, this method of appraisal is standardised and includes all major evidence-based methodological elements that can increase the risk of bias in RCT results. Secondly, recent studies evaluating the tool have identified high levels of acceptability by researchers.[83, 202] Six assessment domains were assessed by the 2 independent reviewers: sequence generation, allocation concealment, outcome assessor blinding, incomplete reporting, selective reporting, and other potential sources of risk of bias (Appendix 3). Discordance in assessment was resolved by discussion, with a third reviewer (SEL) acting as adjudicator. Unless explicitly stated, it was assumed that outcome assessors were not blinded to intervention allocation.

3.3.7 Measures of treatment effect

The synthesis of the current evidence was supplemented by meta-analysis where appropriate using RevMan v5.2 (The Nordic Cochrane Centre, Copenhagen, Denmark). Risk ratios (RR) and absolute risks (%) for dichotomous outcomes and mean differences (MD) with 95% confidence intervals, or standardised mean differences (SMD) where different outcome measure scales were used, were calculated. The Peto odds ratio (OR) was used for dichotomous outcomes with rare

events (low event rates and a high frequency of zero events).[21, 83] Differences in the direction of different outcome scales included within the meta-analysis were adjusted by multiplying data values by -1 where necessary.[63] Number needed to treat for one additional beneficial outcome (NNTB) or harmful outcome (NNTH) was also calculated where appropriate.

3.3.8 Strategy for data synthesis

Pooling of data by meta-analysis was conducted when the participants, interventions and outcomes were clinically comparable. Outcomes also needed to be measuring the same construct for meta-analysis to be conducted. Data were pooled from 3 time-points for analysis of postoperative function/mobility; at the end of the intervention (all immobilisation interventions were 6 weeks in duration), short-term (9-12 weeks), and longer-term outcome (1 year). Studies were not included in meta-analysis if there was uncertainty over key components of the early ankle movement intervention. Studies were also not included in meta-analyses when measures of dispersion (e.g. standard deviation) were not reported or could not be calculated.

Each trial was the unit of analysis. Statistical heterogeneity was assessed using 2 statistical tests, Chi^2 (statistical significance indicating heterogeneity of intervention effects) and I^2, defined as the percentage variability in effects due to heterogeneity, broadly interpreted as: 0% to 40%, may not be important; 30% to 60%, moderate; 50% to 90%, substantial; 75% to 100%, considerable.[83] A fixed effect approach was the primary meta-analysis method, except where there was evidence of high levels of statistical heterogeneity where a random effects model was used.[83]

Sensitivity analyses

One *a priori* sensitivity analysis was conducted to investigate differences in the early ankle movement intervention between trials. The analysis explored the impact of removable splints versus no ankle splint from 3 days after surgery between the early ankle movement interventions in the superficial SSI analysis. In addition, 2 post-hoc stratified analyses were undertaken: firstly, a need to conduct an analysis by non-weight bearing or early weight bearing became apparent during

data extraction and synthesis. Basic research has shown that joint movement and weight bearing are mechanical musculoskeletal loads that can influence healing of soft tissues and bone.[100, 176] Clinical evidence has also indicated weight bearing status as a potentially important confounding factor after ankle ORIF surgery.[14] Secondly, the impact of trials reporting particularly high complication rates was assessed to investigate their contribution to overall pooled estimates.

3.4 Results

3.4.1 Study selection and characteristics

Searches of electronic databases yielded 2070 citations with 2 additional citations identified from checking reference lists. There were 1763 citations after duplicates were removed. After screening of titles and abstracts, 103 articles were potentially eligible and obtained in full-text. Of these, 84 studies were assessed and excluded; a total of 14 trials published in 19 articles were included in the systematic review. Of the included studies, 6 were reported as published journal papers only, 4 had results reported in journal papers and conference abstracts, 1 had results in 2 journal papers and 3 were only reported in conference abstracts. The process of study selection is outlined in the PRISMA flow diagram in Figure 13.

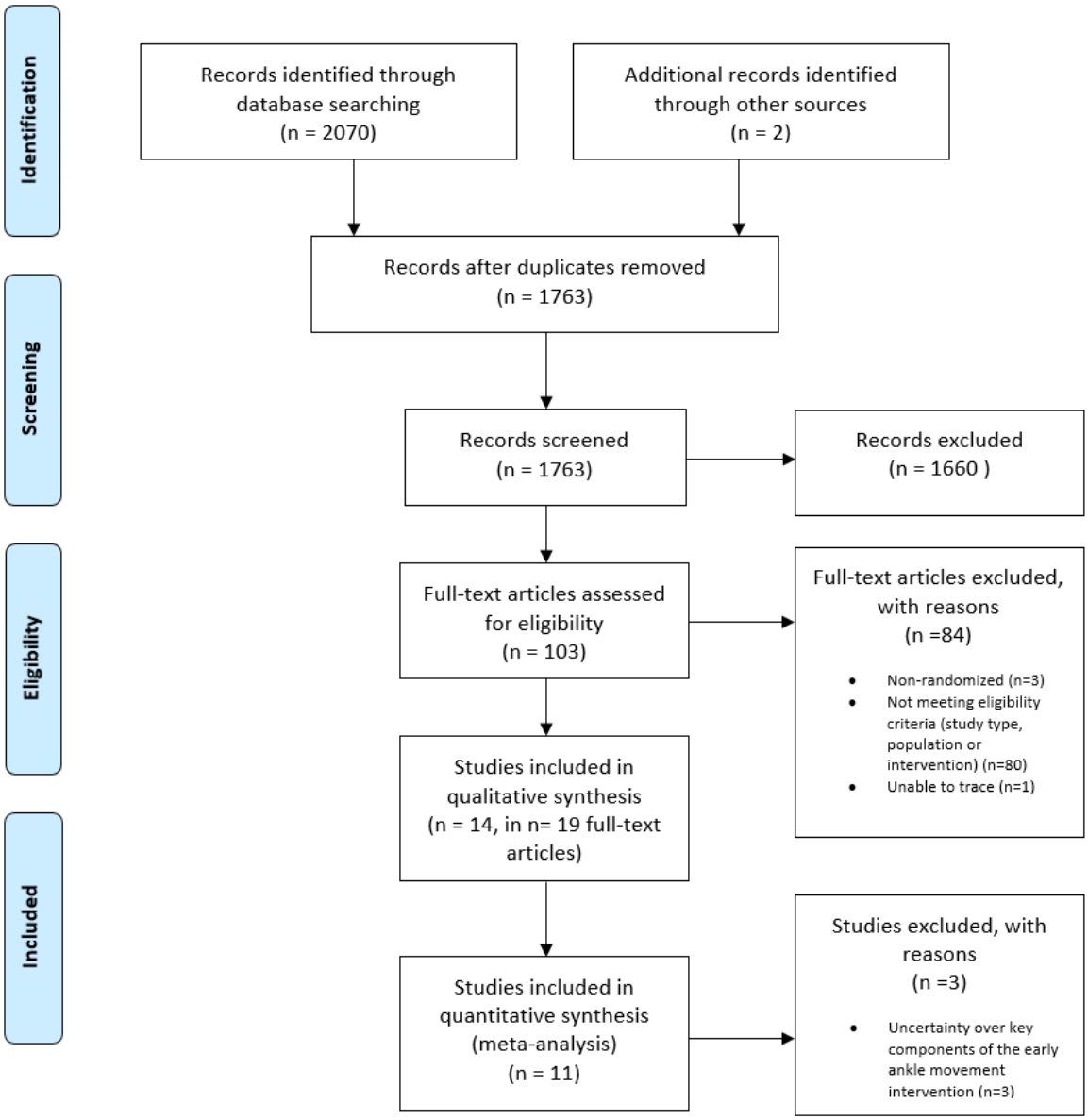


Figure 13: PRISMA flow diagram.

3.4.2 Characteristics of included studies

The characteristics of the 14 studies are shown in Table 8. Trials were published between 1986 and 2008. Overall, 705 participants were included with sample sizes of the individual trials ranging from 27 to 100 participants. All trials were single centre studies. Studies were conducted in developed countries, and all reported in English except 2 trials published in German, which were translated.[133, 225] Two studies were publically funded,[63, 121] 1 was funded by the military[50] and the remaining trials did not report a source of funding. Randomisation occurred postoperatively in 11 studies reporting timing of randomisation. Length of participant follow-up ranged from 1 week to 2 years after surgery.

Participants

The average age of participants included within trials varied from 35 to 50 years, and the age range varied from 15 to 77 years. All studies recruited both genders and all participants required surgical fixation. Eight studies indicated the need for stable or rigid internal surgical fixation in their inclusion criteria.

Interventions

Across the 14 trials, ankle immobilisation interventions were broadly similar. All immobilisation interventions involved casting of the ankle for 6 weeks following ankle ORIF surgery. There was more variability in the early ankle movement treatment protocols. In the early ankle movement interventions, a removable ankle splint was used in all but 2 trials.[63, 219] In these 2 trials the ankle was splinted for the first 3 days only following surgery, no further splints were applied. One study allowed ankle movements during the first 2 weeks postoperatively and then ankles were placed in a below-knee walking cast for 4 weeks.[52] Although there was a level of variability in the early ankle movement interventions it was agreed by the review team that there was acceptable clinical similarity in key elements of the trials for it to be reasonable to conduct meta-analysis. The exceptions were 3 studies[65, 249, 263] not entered into quantitative synthesis due to concerns over clinical heterogeneity, as there was no explicit reporting on the performance of purposeful ankle

movements. No studies compared ankle immobilisation versus ankle movement at or beyond 6 weeks after ankle ORIF surgery.

One aspect of postoperative regimes that varied between studies was weight-bearing restriction in the 6 weeks after surgery. Although weight bearing was the same for both treatment groups within each trial, 7 studies allowed weight bearing in the first 6 weeks, 5 restricted participants to non-weight bearing, and 2 did not report weight bearing status. These variations in weight bearing guidelines were explored in sensitivity analyses described below.

Outcomes

Patient-reported functional/mobility outcomes were reported in 10 of the 14 trials. The most commonly used patient-reported outcome measure was the Olerud and Molander Ankle Score (OMAS)[174] which was used in 6 trials.[52, 65, 78, 121, 236, 250] The OMAS is scored from 0-100 with higher scores indicating better ankle-related function. Other measures of function/mobility used were an ankle grading system,[53, 141] 'Maryland foot score' (0-100, higher scores indicating better outcome),[50] a Modified Weber Scale (0-24, higher scores indicating a worse outcome),[63] and 1 study failed to describe the method of function/mobility outcome measurement.[263]

Seven studies reported postoperative pain outcomes, although timing and detail of reporting varied. Two studies used a 10-point visual analogue scale (VAS) at 10 weeks[65] or 12 weeks[52] whereas 2 other studies reported proportion of participants with persistent pain or pain intensity - mild, moderate, or severe pain.[219, 249] Two studies reported pain sub-scores from other outcome scales (Weber/OMAS).[63, 78] One study described postoperative pain but failed to detail the method used.[263] Due to differences in pain reporting, it was not possible to calculate a pooled estimate. Postoperative complications were reported by 13 trials. However, not all complications were reported by intervention group. Further details of the secondary outcomes and follow-up time points are shown in Table 8.

Table 8: Study characteristics

Study (country)	Eligibility – surgically treated ankle fractures	Participant characteristics	Randomised	Loss to follow-up	Intervention: Early ankle movement	Comparator: Ankle immobilisation	Both groups	Outcomes and follow-up time points.
DiStasio et al. 1994 [50] (USA)	Inclusion: -isolated closed fractures -active military duty -stable fixation	Age: overall mean 25.6 years (range 19-41) Gender (male/female): 54/7 Fracture classification: NR but report no difference between groups	Overall: 61 Ankle movement: NR Immob.: NR	Ankle movement: states 1 (ROM data for 11). Immob. states 3 (ROM data for 10).	Removable short-leg orthosis for 6 weeks. *Rehabilitation:* PT immediately. *Device:* Donjoy Fixed Walker (Donjoy, Carlsbad, CA, USA).	Below-knee short-leg cast for 6 weeks. *Rehabilitation:* PT at 6 weeks.	*Weight bearing:* NWB for 6 weeks. *A*t 6 weeks issued Air Stirrup (Aircast, Summit, NJ, USA) and PWB to FWB. *Surgery:* syndesmosis screws removed at 6-8 weeks (if used).	Follow-up: up to 6 months Function (MFS) Complications ROM (method NR) Swelling (compared to uninjured) Muscle strength (manual muscle test, toe-raises) Duration of hospital stay Return to work
Dogra and Rangan 1999 [51, 52] (UK)	Inclusion: -bimalleolar fractures -16-65 years old Exclusion: -previous ankle disease or other concomitant injury	Age: overall mean 47.2 years (range 18-65) Gender (male/female): 25/27 Fracture classification: all bimalleolar	Overall: 52 Ankle movement: 26 Immob.: 26	Ankle movement: 0 Immob.: 0	Plaster slab and exercise for 2 weeks followed by below-knee walking cast for 4 weeks. *Rehabilitation:* From 24 hours post-op. to 2 weeks, repeated DF and PF, 4 sessions a day,	Plaster slab and no exercise for 2 weeks followed by below-knee walking cast for 4 weeks.	*Rehabilitation:* At 6 weeks advice on ankle remobilisation. *Weight bearing:* graduated.	Follow-up: 12 weeks Function (OMAS) Pain (VAS) Complications ROM (compared to uninjured) Walking performance (subjective

					each lasting 10 minutes.			assessment of symmetry)
Egol et al. 2000 [53, 54] (USA)	Inclusion: -skeletally mature -closed isolated fracture -non-neuropathic joint	Age: *ankle movement* mean 39.5 years (SD 17.2, range 15-77) *immobilisation* mean 45.6 years (SD 17.5, range 16-76) Gender (male/female): *ankle movement* 13/14, *immobilisation* 10/18 Fracture classification: Lauge-Hansen‡: *ankle movement* Sup-ev. 24, Sup-add. 1, Pro-ev. 1, Pro-add. 1, *immobilisation* Sup-ev. 22, Sup-add. 1, Pro-ev. 1, Pro-add. 4	Overall: 60 Ankle movement: Results for 27 Immob.: Results for 28	Overall: 5 (8%).	Removable functional brace for 6 weeks. *Device:* 'functional brace' (Aircast) *Rehabilitation:* instructed on active and passive ankle/subtalar exercises by PT. Continued exercises at home out of brace 3 times daily.	Short-leg cast for 6 weeks. *Materials:* fibre-glass *Duration:* 6 weeks *Rehabilitation:* PT after 6 weeks.	Interventions applied 2-3 days after surgery, initially into plaster A-O splint. *Weight bearing:* started at 6 weeks (those with syndesmosis screw started at 8 weeks whether screw removed or not, n=7 groups not reported).	Follow-up: 6, 12, 24, 52 weeks Function (AGS) Complications Return to work Quality of life (SF-36)
Finsen et al. 1989 [62, 63] (Norway)	Inclusion: -displaced fracture including lateral malleolus -operation within 1 week -stable fixation	Age: *ankle movement* mean 43 years (SE 3.2), *immobilisation* mean 40 years (SE 3.3) Gender (male/female):	Overall: 56† Ankle movement: 18 Immob.: 19	Overall: 8 months = 4/56 (7%), 12 months = 10 (19%)	Removable POP splint removed 3 days postoperatively, for 6 weeks. *Rehabilitation:* written instructions to	Lightweight POP cast, for 6 weeks.	*Weight bearing:* NWB for 6 weeks *Surgery:* syndesmosis repaired with sutures supported with cortical screw (removed at 9	Follow-up: 9, 18, 36 weeks and years 1 and 2. Function (modified WS) Pain (subscale of WS)

	-no concomitant injury Exclusion: -isolated medial malleolus fracture	*ankle movement* 8/10, *immobilisation* 8/11 Fracture classification: *ankle movement* Weber B/C 15/3, *immobilisation* Weber B/C 16/3			DF/PF/invert/evert ankle repeatedly each day.		weeks). Other ligamentous injuries not sutured. All other osteosynthesis material removed under local anaesthesia approx.36 weeks post-op.	Complications Return to work
Franke 2008 [65] (Germany)	Inclusion: -isolated Weber B fractures (providing Volkmann's triangle did not require treatment) - simple and bi-malleolar fractures -18-65 years old Exclusion: -open or multi-fragmentary fractures - requiring positioning screw - disorders restricting mobility or affecting healing process -limited ambulation with crutches	Age: *ankle movement* median 44.3 years (range 20.3-59.4) *immobilisation* median 40.8 years (range 25-64.1) Gender (male/female): *ankle movement* 7/7, *immobilisation* 8/5 Fracture classification: *ankle movement* Simple 13, Bi-malleolar 1, *immobilisation* Simple 13, Bimalleolar 0	Overall: 27 Ankle movement: 14 Immob.: 13	Ankle movement: 1 (7%) at 2 weeks Immob.: 2 (15%) at 2 weeks	Dynamic vacuum orthosis with ankle mobilisation for 6 weeks. *Weight-bearing:* PWB second day, FWB day 15 onwards. *Device:* Vacoped, allowed 10-0-10 degrees ankle motion.	Circular synthetic cast then a plastic supportive bandage (Baycast) for 6 weeks. *Weight bearing:* window cut into post-op. cast on 2nd day to allow dorsiflexion, NWB until change of cast (at time of wound healing), then PWB until 14th day, FWB from day 15. *Rehabilitation:* After cast removal, attended PT 3	*Thrombosis prophylaxis:* daily low-weight heparin until WB for the vacuum orthosis group or for the duration of cast immobilisation.	Follow-up: 6 and 10 weeks. Function (OMAS) Pain (VAS) Complications Patient satisfaction (VAS) ROM (compared to uninjured) Return to work Quality of life (SF-12) Treatment costs

						times/week for 4 weeks.		
Hedström et al. 1994 [78] (Sweden)	Inclusion: -lateral malleolar fracture Exclusion: -open fractures -children -unable to cooperate	Age: *ankle movement* mean 44 years (range 15-70), *immobilisation* mean 41 years (range 16-71) Gender (male/female): *ankle movement* 13/15, *immobilisation* 11/14 Fracture classification: Lauge-Hansen‡: *ankle movement* Sup-ev. II 13 III 2 IV 8, Pro-abd. III 1, Pro-ev. III 1 IV 3, *immobilisation* Sup-ev. II 10 III 5 IV 7, Pro-abd. III 1, Pro-ev. III 1 IV 1	Overall: 53 Ankle movement: 28 Immob.: 25	Overall: Ankle movement: 3 and 6 months = 0, 18 months = 2 (7%) Immob. 3 and 6 months = 0, 18 months = 4 (16%)	Removable orthosis *Rehabilitation:* PT instructed unloaded DF/PF at least 5 times daily.	Walking plaster cast	*Duration:* NR. *Weight bearing:* WB. *Surgery:* internal fixation using cerclage wires and staples.	Follow up: 3 months, 6 months, 18 months Function (OMAS, also a disability VAS). Pain (subscale of OMAS) Complications ROM (compared to uninjured)
Lehtonen et al. 2003 [121] (Finland)	Inclusion: -seen <72 hours after injury -displaced or unstable -Weber A or B Exclusion: -insufficiently stable	Age: *ankle movement* mean 41 years (SD 13), *immobilisation* mean 41 years (SD 13) Gender (male/female):	Overall: 100 Ankle movement: 50 Immob.: 50	Overall: Ankle movement: 6 weeks = 0, 12 weeks = 1 (2%), 52 weeks = 1 (2%), 2	Removable functional Air-Stirrup ankle brace (Aircast) for 6 weeks *Rehabilitation:* Daily active and passive ankle exercises	Plaster cast for 2 weeks then fiberglass cast for further 4 weeks	*Weight bearing:* PWB started at 2 weeks, FWB at 4 weeks. *Surgery:* no soft tissue repair. *Rehabilitation:* until randomisation all	Follow-up: 6, 12, 52 weeks and 2 years Function (OMAS, KS) Complications ROM (compared to uninjured)

	-open/Pilon or Weber C fracture -other severe injuries -unable to cope with postoperative protocols	*ankle movement* 25/25, *immobilisation* 31/19 Fracture classification: *ankle movement* Weber A/B 2/48, *immobilisation* Weber A/B 2/48		years = 4 (8%) Immob. 6 weeks = 0, 12 weeks = 0, 52 weeks = 3 (6%), 2 years = 8 (16%)	immediately postoperatively until normal gait was achieved.		were in a FoamWalker leg brace (Aircast,). Cast/brace removed at 6 weeks, exercise, strapping/orthosis and advice same for both groups.	Swelling (cm difference compared to uninjured ankle, malleolar circumference) Duration of hospital stay Return to work
Losch 2002* [133] (Germany)	Inclusion: -isolated Weber C ankle fracture	Age: *ankle movement* mean 37 years, *immobilisation* mean 38 years Gender (male/female): *ankle movement* 8/12, *immobilisation* 8/12 Fracture classification: All Weber C (inclusion criteria)	Overall: 40 Ankle movement: 20 Immob.: 20	Ankle movement: 1 (2.5%) Immob.: 6 (15%)	Combi-cast orthosis. *Duration and weight bearing:* NR. *Rehabilitation:* PT for functional rehabilitation 3 times/week for 3 hours.	Walking cast for 6 weeks. *WB status not specified but 'walking'.* *Rehabilitation:* report group received non-standardised ambulation.	-	Follow-up: 10 weeks ROM (compared to uninjured) Stair climbing ability Return to work Treatment costs
Sondenaa et al. 1986 [218, 219] (Norway)	Exclusion: - reduction/rigidity of the fixation not satisfactory -open fracture -compression fracture	Age: *ankle movement* median 35 years (range 16-59), *immobilisation* median 37 years (range 16-66) Gender (male/female): *ankle movement* 9/11,	Overall: 43 Ankle movement: 20 Immob.: 23	Overall: NR Ankle movement: NR Immob.: NR	Immobilisation in backslab for approximately 3 days then active exercises were allowed. *Rehabilitation:* 12 appointments with PT.	Plaster cast for 6 weeks *Duration:* 1st day post-op until 6 weeks. *Rehabilitation:* After 6 weeks active exercises and 12	*Weight-bearing:* FWB at 6 weeks. *Rehabilitation:* PT 'standardised'.	Follow-up: 6, 12, 18 weeks and 1 year. Pain (method NR) Complications ROM (compared to uninjured)

		immobilisation 9/14 Fracture classification: *ankle movement* Weber A/B/C 2/8/10, *immobilisation* Weber A/B/C 0/15/8				appointments with PT.		Swelling (number of participants with positive finding, criteria NR) Muscle strength (method NR)
Stockle 2000* [225] (Germany)	Inclusion: -closed fractures -isolated injury -no previous ankle fracture -18-65 years	Age: Overall mean 45 years (range 20-65) Gender (male/female): Overall 21/19 Fracture classification: *ankle movement* Weber B/C 15/5, *immobilisation* Weber B/C 12/8	Overall: 40 Ankle movement: 20 Immob.: 20	Overall: 0 Ankle movement: 0 Immob.: 0	Removable vacuum orthosis (Vacoped) for 6 weeks. Orthosis removed for wound check, hygiene, and intermittent PT (details of PT not reported).	Walking plaster cast for 6 weeks.	*Weight bearing:* PWB for 6 weeks. *Surgery:* heparin post-op.	Follow-up: 6 and 12 weeks. Complications ROM (compared to uninjured) Return to work
Tropp and Norlin 1995 [236] (Sweden)	Inclusion: -Weber B or C -no large posterior tibial fragment (>1/4 of the sagittal joint line) -age 18-60 years -stable fixation -satisfactory reduction	Age: Overall median 26 years (range 19-60) Gender (male/female): NR Fracture classification: 11 involved medial malleolus, 4 posterior process of tibia. Report no difference between groups.	Overall: 30 Ankle movement: 15 Immob.: 15	Overall: NR Ankle movement: NR Immob.: NR	Removable hinged brace. *Duration:* 10 weeks. *Weight-bearing:* encouraged, crutches first 2 weeks. *Rehabilitation:* DF and PF and normal gait pattern	Conventional plaster cast boot with a sole for 6 weeks. *Weight bearing:* WB and walking, with crutches. After removal, crutches for another 2- 4 weeks, then FWB allowed.	*Surgery:* within 24 hours using rigid or non-rigid fibular fixation. Syndesmosis secured by staples and osteosutures (if possible). *Rehabilitation:* program for self-training of mobility, muscular	Follow-up: 10 weeks and 1 year. Function (OMAS) Complications ROM (injured ankle) Swelling (malleolar circumference compared to uninjured)

					encouraged immediately.	*Rehabilitation:* as per other group but started at 6 weeks.	strength, and function.	Muscle strength (isokinetic DF)
Venesmaa 2004 [249] (Finland)	Inclusion: -low energy uni- or bi-malleolar fracture	Age: *ankle movement* mean 41 years (range 20-63), *immobilisation* mean 48 years (range 19-69) Gender (male/female): *ankle movement* 8/10, *immobilisation* 6/8 Fracture classification: NR	Overall: 32 Ankle movement: 18 Immob.: 14	Overall: NR Ankle movement: NR Immob.: NR	Aircast splint for 6 weeks	Standard cast for 6 weeks	*Weight-bearing:* NR	Follow-up: 9 and 26 weeks. Pain (categorical scale) Complications ROM (DF, method NR). Physical performance assessments
Vioreanu et al. 2007 [250, 251] (Ireland)	Inclusion: -acute closed fractures -age 14 to 65 years -non-neuropathic joint -Weber A/B/C fracture -uni-, bi- or tri-malleolar fracture -fibular displacement >2mm Exclusion:	Age: *ankle movement* mean 37.2 years (SD 12.9) *immobilisation* mean 34.9 years (SD 16) Gender (male/female): *ankle movement* 21/10 (2 missing) *immobilisation* 20/9 Fracture classification: *ankle movement* Weber B/C 29/4,	Overall: 66 Ankle movement: 33 Immob.: 29	Overall: 4 excluded after randomisation but group allocation NR	Removable cast, non-weight bearing for 6 weeks *Materials:* fiberglass cast with Velcro straps. *Rehabilitation:* active and passive exercises of the ankle and subtalar joint without the brace (open and closed chain exercises),	Below-knee cast, non-weight bearing for 6 weeks *Materials:* fiberglass cast. *Rehabilitation:* exercises as per other group started at 6 weeks.	*Surgery:* prophylactic intravenous antibiotics preoperatively. *Weight bearing:* Initial 10-14 days NWB in POP splint with ankle in neutral position until primary wound healing. At 6 weeks, PWB, progress to achieve FWB over 2 weeks.	Follow up: 6, 9, 12, 24 weeks Function (OMAS and AOFASS) Complications ROM (maximal range of injured ankle) Swelling (malleolar circumference compared to uninjured) Return to work

	-concomitant severe injuries -Pilon or isolated medial malleolar fractures -Diabetes mellitus -insufficiently stable fixation	*immobilisation* Weber B/C 21/8			supervised by PT.			Quality of life (SF-36, at 6 months only)
Wetzler 1991 [263] (USA)	Inclusion: -closed rigidly fixed adult ankle fractures	Age: NR Gender (male/female): NR Fracture classification: NR	Overall: 45 Ankle movement: 20 Immob.: 25	Overall: NR Ankle movement: NR Immob.: NR	Walker 1 to 2 weeks until suture removal then pneumatic walker and brace (duration not reported).	Short-leg cast for 6 weeks.	*Weight bearing:* WB.	Follow-up: 1, 2, 4, 6, 12 weeks, 6 months, 1 year. Function (average - method NR) Pain (average - method NR) Complications ROM (compared to uninjured) Return to work Treatment costs

*German language. †additional group of non-removable immobilisation but included variation in weight-bearing, 6 additional participants later excluded but not given by group allocation. ‡ Lauge-Hansen classification: Pro-abd. (Pronation-Abduction), Pro-Ev. (Pronation-Eversion), Sup-Add. (Supination-Adduction), Sup-Ev. (Supination-Eversion). AGS – Ankle Grading System. AOFASS - Am. Ortho. Foot and Ankle Society Score. DF – Dorsiflexion. KS - Kaikonen score. MRS – Maryland Foot Score. NR – not reported. OMAS - Olerud-Molander Ankle Score. ORIF – Open Reduction Internal Fixation. PF – Plantar flexion. POP – Plaster of Paris. PT – Physical Therapy/Therapist. ROM – range of movement. WB/NWB/PWB/FWB – Weight bearing/Non-weight bearing/Partial weight bearing/Full weight bearing. WS – Weber Scale.

3.4.3 Risk of bias within included studies

The risk of bias assessment is shown in Table 9. All included studies had unclear or high risk of bias assessments in at least 3 of the 6 categories, and so were deemed to be at high risk of bias overall. As a result, a sensitivity analysis by risk of bias was not undertaken. Only 3 studies achieved adequate sequence generation and allocation concealment and were graded at low risk of selection bias. Limitations in reporting of the studies resulted in unclear risk of bias for many domains. The most common categories judged to be of high risk of bias, for all but 2 studies, were outcome assessor blinding or other sources of risk of bias e.g. concerns regarding methods of analysis.

Table 9: Risk of bias assessments

Study	Sequence generation	Allocation concealment	Outcome assessor blinding	Incomplete reporting	Selective reporting	Other source of risk of bias
DiStasio 1994	×*	×*	×	×	?	×
Dogra 1999	✓*	?	✓	✓	?	×
Egol 2000	✓*	✓*	×	?	?	×
Finsen 1989	?	?	×	×	?	×
Franke 2008	✓	✓*	×*	?	×	×
Hedstrom 1994	?	?	×	?	?	×
Lehtonen 2003	?	?	?	?	?	?
Losch 2002	?	?	×	×	?	×
Sondenaa 1986	✓*	?	×	?	×	×
Stockle 2000	×	×	×	?	×	×
Tropp 1995	✓*	✓*	✓*	?	?	×
Venesmaa 2004	?	?	×	?	?	?
Vioreanu 2007	×	×	×	?	×	×
Wetzler 1991	×*	×*	×	?	?	?

Key:
✓= Low risk of bias. ?= Unclear risk of bias. ×=High risk of bias
*=Additional information obtained from authors by Cochrane review[122] contributed to assessment

3.4.4 Primary outcomes

Patient-reported function/mobility

Of the 10 studies reporting functional outcomes, only 2 studies (155 participants) reported functional outcomes using comparable scales at 6 weeks after surgery.[53, 121] The pooled estimate showed no difference in functional outcome after early ankle movement versus ankle immobilisation (MD 1.39, 95% CI -4.55 to 7.33, I^2=80%). The 2 studies had divergent results and there was very high statistical heterogeneity (I^2=80%), so this estimate should be interpreted with caution. At 9 to 12 weeks after surgery, pooled data from 5 studies (283 participants)[53, 63, 121, 236, 250] also showed no difference in functional outcomes between treatment groups (SMD 0.46, 95% CI -0.02 to 0.93, *P*=.06, I^2=72%) (Figure 14). At 1 year after surgery, pooled data from 4 studies (218 participants),[53, 63, 121, 236] showed there was no evidence of a difference in function after early ankle movement compared to ankle immobilisation (SMD 0.04 95% CI -0.23 to 0.31, *P*=.77, I^2=0%) (Figure 14).

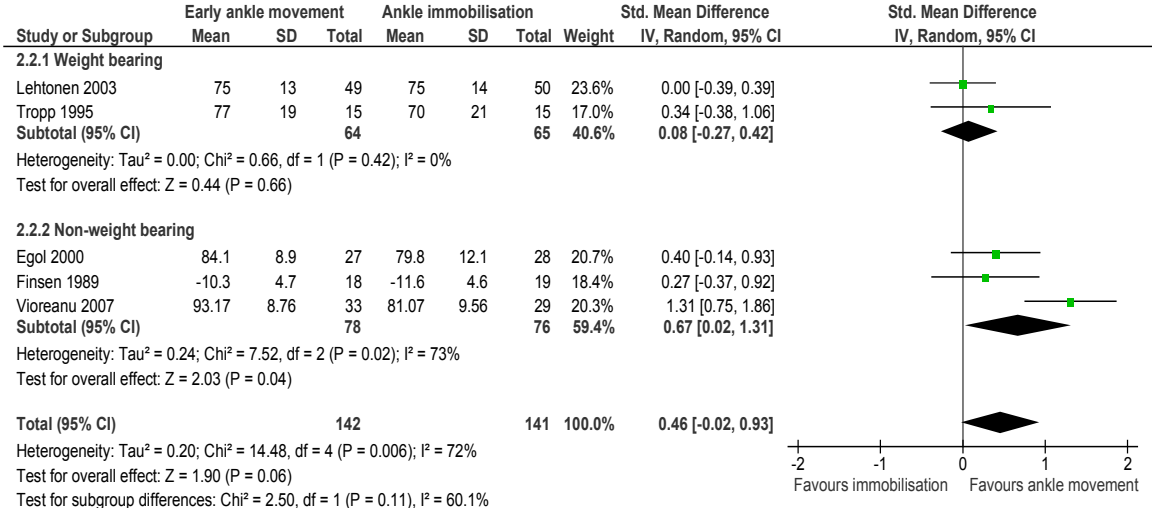
The 5 trials that were not included in any of the function meta-analyses had varied results. Two trials found no differences in function between treatment groups[52, 78] and 1 reported a statistically significant difference in favour of the early ankle movement group compared to immobilisation at 12 weeks.[50] An additional trial found no difference in function between treatment groups at 6 weeks, but did find a statistically significant difference in favor of the removable orthosis group compared to immobilisation at 10 weeks.[65] In contrast, another trial found a statistically significant difference in favour of the removable brace group compared to immobilisation at 6 weeks but no differences were found at 12 weeks or 1 year after surgery.[263]

Sensitivity analysis

Results were stratified by weight bearing and non-weight bearing status. At 9-12 weeks after surgery there was an effect favoring early ankle movement in the non-weight bearing subgroup,

but this estimate had high statistical heterogeneity (SMD 0.67, 95% CI 0.02 to 1.31, *P*=.02, I^2=73%). There was no evidence that weight bearing status had an impact on outcome at 1 year.

i. Function at 9-12 weeks.



ii. Function at 1 year.

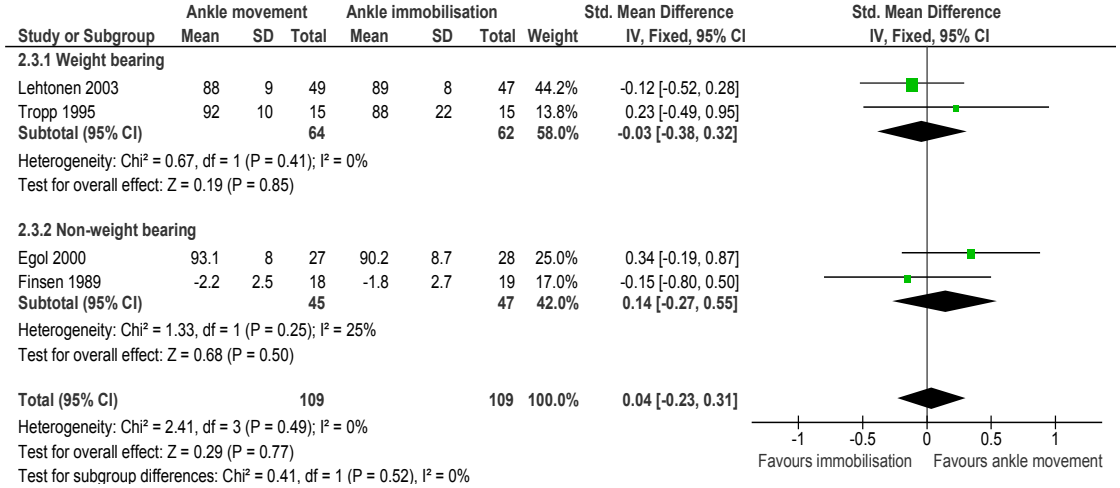


Figure 14: Forest plots and meta-analyses for function i. at 9-12 weeks, ii. at 1 year.

Postoperative pain

Seven studies (286 participants) reported 'acute' postoperative pain,[52, 63, 65, 78, 219, 249, 263] defined as pain within 3 months of surgery. Four studies (178 participants) reported chronic pain outcomes,[63, 78, 219, 263] defined as pain persisting for 6 months or longer. With regard to acute pain, 4 studies described statistically significant differences between groups, all in favor of early ankle movement and 3 studies reported no difference in acute pain outcomes between treatment arms. No differences in chronic pain outcomes were reported.

3.4.5 Postoperative complications

Surgical site infection (SSI)

Three studies (206 participants) reported deep SSIs by treatment group (Figure 15.i).[50, 121, 250] Overall, 6 deep SSIs occurred in 104 participants (5.8%) after early ankle movement compared to no deep infections in 102 participants in the ankle immobilisation group. Odds of developing a deep SSI were significantly higher after early ankle movement compared to ankle immobilisation (Peto OR 7.08 95% CI 1.39 to 35.99, P=.02, I^2=0%). The number needed to treat with early ankle movement for an additional harmful outcome was 18 (95% CI 9 to 50).

Superficial SSIs were reported by group in 5 studies (296 participants, Figure 15.ii).[50, 78, 121, 219, 250] Overall, 21 superficial SSIs occurred in 150 participants (14%) in the early ankle movement group compared to 7 SSIs in 146 participants (4.8%) randomised to ankle immobilisation. Risk of superficial SSI with early ankle movement was more than 2.5 times that of ankle immobilisation (RR 2.62 95% CI 1.21 to 5.68, P=.01, I^2=0%). The number needed to treat with early ankle movement for an additional harmful outcome was 11 (95% CI 7 to 38).

Sensitivity analyses

One study had a very high overall rate of postoperative wound infection (5% deep SSIs and 23% superficial SSIs).[121] When this trial was removed from the meta-analysis, the effect estimates were not statistically significant for deep SSI (Peto OR 6.75 95% CI 0.41 to 111.14, P=.18) or

superficial SSI (RR 1.52 95% CI 0.43 to 5.35, *P*=.52). Results were stratified by weight bearing and non-weight bearing status. There were no significant differences between early ankle movement and immobilisation groups in both weight bearing or non-weight bearing protocols, so weight bearing status did not appear to modify deep SSI outcomes (Figure 15.ii). The difference in risk of superficial SSI was statistically significant in the weight bearing subgroup, showing an effect favoring immobilisation (RR 3.23 95% CI 1.29 to 8.09, *P*=.01). The weight bearing subgroup contained the study with higher rates of postoperative wound infection.[121] There was no difference in superficial SSI risk in the non-weight bearing subgroup. An additional sensitivity analysis on the superficial SSI meta-analysis was conducted, removing a trial in which ankle splinting was used for only 3 days in the ankle movement group,[219] this did not impact the direction of results (RR 2.57 95% CI 1.16 to 5.71, *P*=.02).

Venous thrombosis/thromboembolism

Four studies (245 participants) reported postoperative thrombosis/thromboembolism.[53, 121, 225, 250] Of the 5 events reported, 4 were deep vein thrombosis and 1 was pulmonary embolism. All thrombotic/thromboembolic events occurred in the ankle immobilisation group (5/119; 4.2%). The risk of thrombosis/thromboembolism for early ankle movement was significantly lower compared to ankle immobilisation (Peto OR 0.12 95% CI 0.02 to 0.71, *P*=.02, I^2=0%) (Figure 15, iii.). The estimated number needed to treat with early ankle movement to prevent a harmful outcome was 24 (95% CI 11 to 86).

Sensitivity analyses

When stratified by weight bearing status, there were no significant differences between early ankle movement and immobilisation groups, so weight bearing status did not appear to modify the overall result (Figure 15.iii).

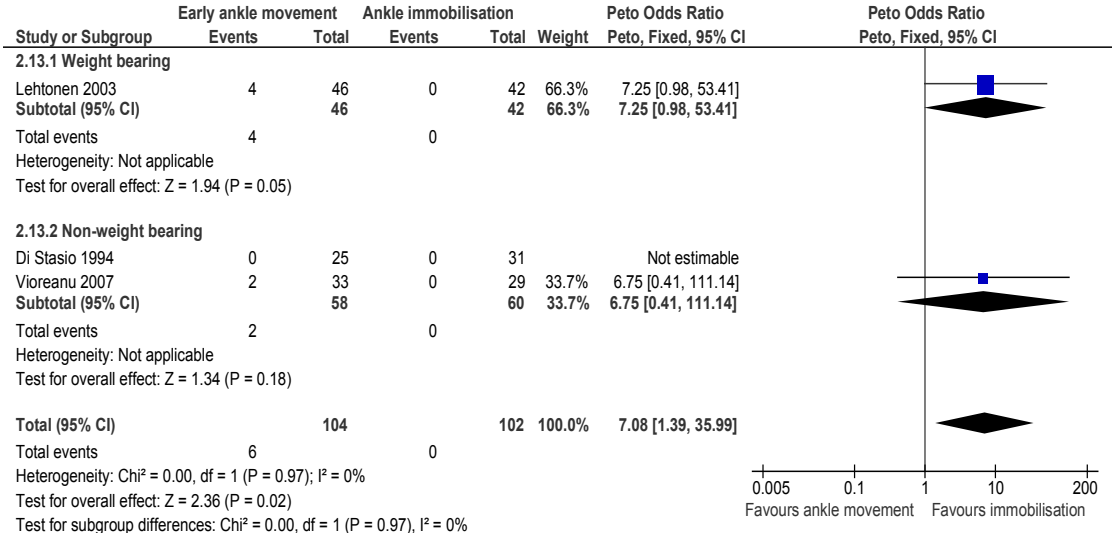
Fixation-related complication (failure of fixation or reoperation for removal of metalwork)

Seven studies (390 participants) reported 8 fixation failures and 2 reoperations to remove metalwork after deep SSI in the early ankle movement group (10/198; 5.1%), compared to 1 failure of fixation in the immobilisation group (1/192; 0.5%).[50, 52, 53, 78, 121, 236, 250] Fixation-related complications were significantly more common after early ankle movement compared to ankle immobilisation (Peto OR 6.56 95% CI 1.84 to 23.41, *P*=.004, I^2=0%) (Figure 15, iv.). The number needed to treat with early ankle movement for an additional harmful outcome was 23 (95% CI 12 to 65).

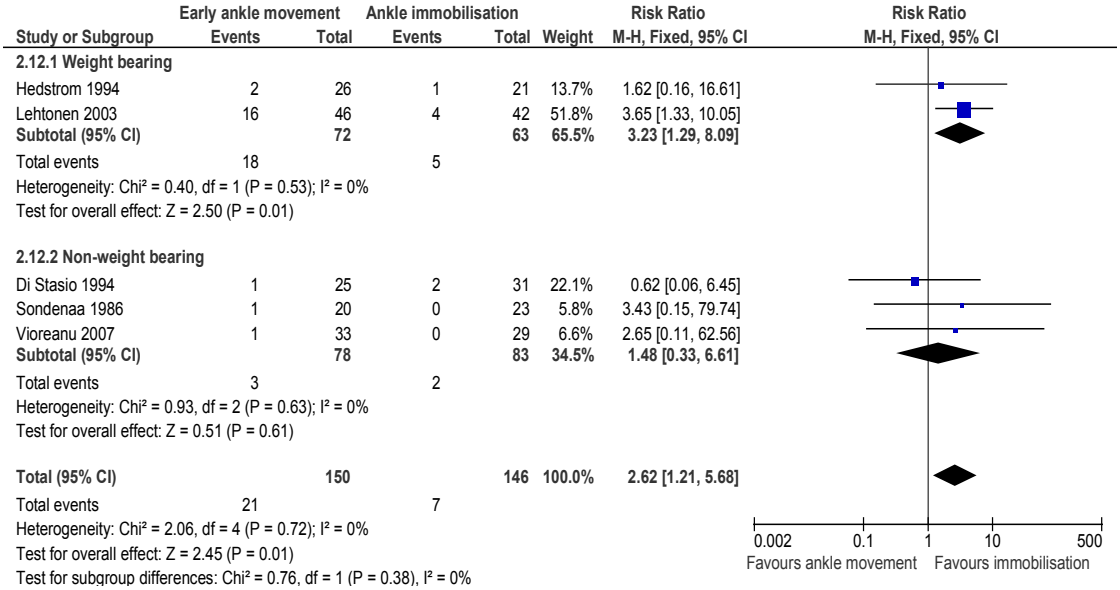
Sensitivity analysis

One study reported a high level of fixation failure, with 6 participants having failure of syndesmotic staples out of 15 participants (40%) in the early ankle movement group.[236] However, when this study was removed in a sensitivity analysis, the effect estimate remained statistically significant (Peto OR 7.34 95% CI 1.02 to 52.82, *P*=.05). Results were stratified by weight bearing and non-weight bearing status. The difference in risk of fixation-related complications was statistically significant in the weight bearing subgroup, showing an effect favoring immobilisation (Peto OR 6.16 95% CI 1.33 to 28.5, *P*=.02). This subgroup contained the study with higher rates of fixation failure.[236] There was no difference in fixation-related complication risk in the non-weight bearing subgroup.

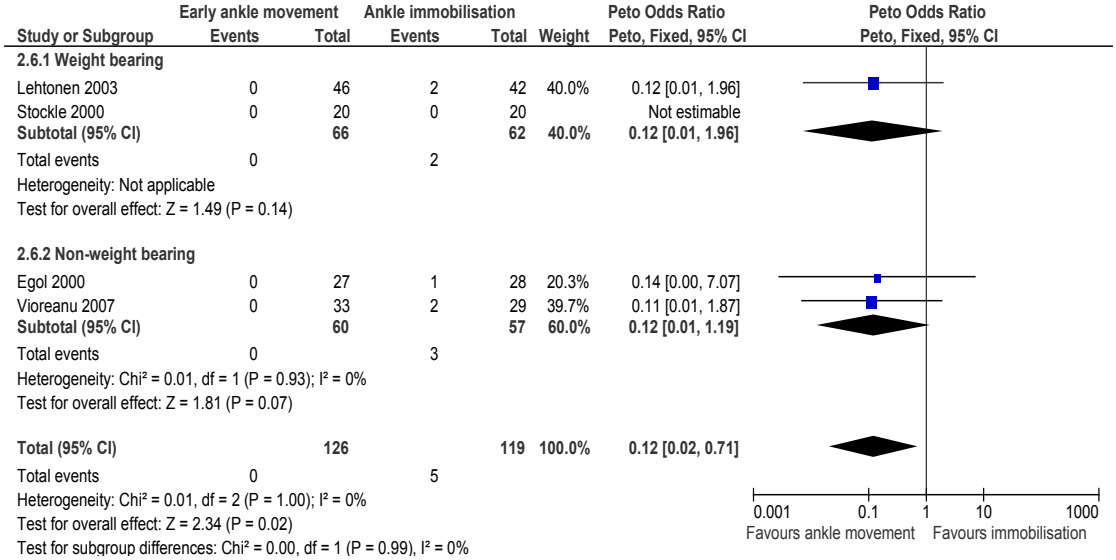
i. Deep surgical site infection



ii. Superficial surgical site infection



iii. Venous thrombosis/thromboembolism



iv. Fixation-related complication (failure of fixation or reoperation to remove metalwork)

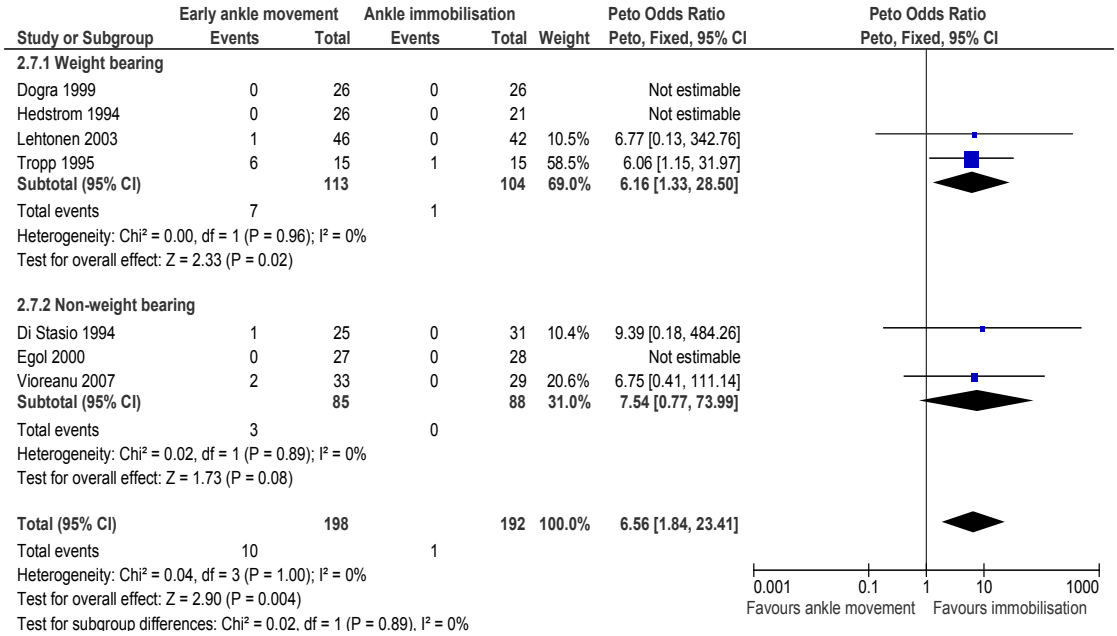


Figure 15: Forest plots and meta-analyses for different types of postoperative complications i. deep surgical site infection, ii. superficial surgical site infection, iii. venous thrombosis/thromboembolism, iv. fixation-related complication

Skin / wound related complications

Five studies reported other non-infectious complications including local skin necrosis, wound secretion (negative cultures), dehiscence, postoperative haematoma, secondary suturing, and chronic skin irritation and dysaesthesia. Pooled data from 3 studies (158 participants) showed that these postoperative complications were more common after early ankle movement although this finding was not statistically significant (RR 3.09 95% CI 0.97 to 9.86, P=.06, I^2=0%).[121, 225, 236] Two studies where participants were non-weight bearing reported no events, therefore pooled risks were not estimable.

Three trials[50, 52, 63] reported complications without specifying the intervention group, including 8 operations to remove metal work and 4 postoperative surgical site infections (superficial or unspecified).

3.4.6 Secondary outcomes

The results for secondary outcomes are summarised in Table 10.

Table 10: Result for secondary outcomes.

Outcome	Summary of findings
Ankle range of movement - dorsiflexion	8 studies (412 participants)[52, 78, 121, 133, 219, 225, 236, 250] were pooled for outcome at 9-12 weeks postoperatively. Statistically significant difference in favor of early ankle movement but this was a small mean difference of 1.9 degrees dorsiflexion (95% CI 0.5 to 3.3, *P*=.008, I^2=46%).
Ankle range of movement – plantar flexion	7 studies (369 participants) were pooled for outcome at 9-12 weeks postoperatively. An estimate was not calculated due to the very high levels of statistical heterogeneity (I^2=87%). 3 studies found statistically significant differences in favour of early ankle movement compared to immobilisation.[133, 225, 250] 4 studies found no difference between treatment groups.[52, 78, 121, 236]
Postoperative swelling	5 studies reported postoperative swelling. 3 studies were pooled (192 participants).[225, 236, 250] No statistically significant difference between treatment groups in ankle circumference (difference between injured and uninjured in cm) at 6-10 weeks postoperatively (MD -0.04 95% CI -0.32 to 0.25, *P*=.83, I^2 0%). 1 study reported a statistically significant difference in favor of early ankle movement compared to immobilisation for number of participants with swelling at 12 weeks.[219] 1 study did not follow up the treatment groups at equal time points.[50]
Muscle function	3 studies (134 participants)[50, 219, 236] reported muscle strength measurements postoperatively. Not possible to pool data due to differences in the measures used. 1 study [236] reported isokinetic dorsiflexion muscle strength at 10 weeks and 1 year. Descriptive data for strength (Nm) indicated there were no consistent clinically important differences in strength between groups. 1 study [219] assessed strength but methods and results were not reported, only that there were no statistically significant differences. 1 study [50] did not follow up the treatment groups at equal time points.
Physical performance measures	3 studies (124 participants)[52, 133, 249] reported physical performance outcomes. Not possible to pool data due to limitations in reporting and differences in the methods of assessment. 1 study [52] assessed walking symmetry 12 weeks postoperatively; 20/26 in the early ankle movement group and 6/26 in the immobilisation group were assessed as walking with symmetry. 1 study[133] reported a statistically significant difference in favor of early ankle movement compared to immobilisation for ability to descend stairs at 10 weeks. 1 study[249] reported no significant differences between groups for a range of physical performance abilities (including running, stair climbing, and single limb stance) but data were not reported.

Duration of hospital stay	2 studies (161 participants) reported length of hospital stay, with no differences found between groups.[50, 121]
Time to return to work and leisure activities/sports	9 studies (429 participants) reported return to work outcomes. Not possible to pool data due to differences in data capture and reporting. 3 studies[50, 53, 250] reported a statistically significant difference in favor of the early ankle movement (or removable orthosis) compared to immobilisation for earlier return to work. 3 studies[63, 121, 263] reported no statistically significant differences between treatment groups. 3 studies[65, 133, 225] found an earlier return to work after early ankle movement but failed to report if the differences were statistically significant. No studies reported time to return to leisure activities/sport.
Quality of life	3 studies (153 participants) used the Short-Form (SF) quality of life instruments (SF-36 and SF-12). 1 study[250] reported no statistically significant differences between the groups in the SF-36 at 6 months. 1 study[53] reported statistically significant differences in favor of the early ankle movement group in SF-36 domains of vitality and perceptions of general health at 1 year. 1 study[65] found a statistically significant difference in favor of the removable orthosis group compared to immobilisation for the SF-12 mental component score.
Patient satisfaction	1 study (27 participants)[65] reported patient satisfaction with treatment. It measured satisfaction on a visual analogue scale (VAS) and found results in favor of the vacuum orthosis group compared to ankle immobilisation at 10 weeks and discharge, but no data were reported.

3.5 Discussion

Overall, current evidence indicates that the effect of early ankle movement after surgery for ankle fracture on function/mobility is inconclusive in the short-term and there is no evidence of difference in the longer term. There is evidence of a lower risk of thrombotic/thromboembolic events after early ankle movement. However, this needs to be considered in the context of a clinically important increased risk of other complications, including deep and superficial SSIs and fixation failure/reoperation for removal of metalwork. The poor quality of existing trials indicates a need for caution when applying these findings in clinical practice. The evidence for all outcomes is weak due to high risk of bias, small trial sample sizes with low statistical power, limitations in reporting of results, and inconsistency amongst outcome measures used.

Short-term improvement in recovery of range of ankle dorsiflexion with early ankle movement is, in part, consistent with previous reviews and the theoretical benefits of movement after injury.[122, 162, 233] However, the improvement in short-term dorsiflexion range recovery is limited (mean 1.9°). The lower risk of thrombosis/thromboembolism with early ankle movements is consistent with recognised benefits of movement in preventing deep vein thrombosis.[69] Only 1 of the 4 studies reporting thrombosis/thromboembolism events described the use of thrombo-prophylaxis.[225] Immobilisation protocols may therefore benefit from thrombo-prophylaxis where indicated, an important factor to consider in future studies.

The increased risk of deep and superficial SSIs with early movement may be due to disturbance or exposure of the healing wound, compounded by the limited soft tissue envelope at the ankle. However, detection bias could have influenced this finding as ankle immobilisation limits observation of wounds, especially when casts do not require reapplication or undergo routine removal for wound inspection. One study had an important influence on the pooled infection risk estimates due to a higher infection rate compared to other trials.[121] The strong influence of a single study could indicate local clinical issues, or it could be argued that this study undertook meticulous

assessment and detailed reporting of adverse events thus may reflect higher reporting standards and careful follow-up. Vioreanu et al.[250] was the only study in the meta-analysis to describe prophylactic antibiotic use (administered intravenously pre-operatively), however there were still 3 infections in the early ankle movement group compared with none in the ankle immobilisation group. The increased risk of deep infections in the early ankle movement group is clinically important given the increased morbidity associated with this late infection. The consequences from deep infection are potentially serious, as illustrated by 2 of 6 participants with deep infection requiring additional surgery to remove metalwork.[250]

The increased rate of fixation-related complications with early ankle movement occurred in postoperative regimes that encouraged either early weight bearing or non-weight bearing. One trial had a higher rate of failure of syndesmotic staples seen on radiographs (6 out of 15 participants in the early ankle movement group).[236] Staples have performed comparably to other metalwork in biomechanical studies;[136] it is therefore not certain why so many events were observed. It may relate to the motion induced at the distal tibio-fibular joint during ankle movement.[163] Movement of the distal tibio-fibular joint may loosen the staples, however, the morbidity, if any, associated with this complication is uncertain as none of the participants with failure of the staples had widening of the ankle mortise on radiographs at 1 year. The number of fixation failures and additional surgeries observed across the trials may have been influenced by varied duration of follow-up as intolerance of metalwork and decisions to remove metalwork can be delayed.[22]

It was not possible to calculate a pooled estimate for the effects of different treatment protocols on postoperative pain outcomes. Of the secondary outcomes, individual studies suggested that overall there may be an earlier return to work for those starting early ankle movements, but this was not consistent across the trials, nor was it possible to quantify this benefit so the clinical importance is inconclusive. Only three studies reported physical performance measurements of mobility outcomes. These included a subjective clinical assessment of walking symmetry and objective

assessments of running, stair climbing, and single limb stance performance but details on how these were assessed were limited.

No studies were found that compared different types of ankle supports that offer ankle immobilisation versus allowing ankle movements at 6 weeks after ankle ORIF surgery. At 6 weeks, the fracture should be united and the focus of recovery shifts from protection of the injured joint to the rehabilitation of walking and a rapid return to function.[134] A removable ankle support is often used to aid the transition from cast immobilisation and limited weight bearing towards the goal of unsupported full weight bearing ankle function.[50] This thesis investigated the effects of different types of ankle support used in clinical practice on physical performance measures of walking in healthy participants (Chapter 4) and in adults 6 weeks after ankle ORIF surgery (Chapter 5).

3.5.1 Limitations

The main limitation of the presented meta-analysis, common to all quantitative syntheses of trial data, was that to estimate the effect of early ankle movement after surgery, data were pooled from studies with differences in participants, interventions, comparator treatments, and outcomes. Although it was judged that there was acceptable clinical similarity in these key elements in the included trials, the variation should be taken into account when interpreting the clinical implications. Furthermore, despite issues with meta-analysis, the benefits of pooling trial data was the inclusion of all available trial evidence and therefore, when compared to results from individual studies, there was increased statistical power and precision of the treatment effect estimates. In addition, the meta-analyses are supported by 1) detailed reporting of the search, methods, participants, interventions, outcomes and analyses according to guidelines, 2) sensitivity and stratified analyses to explore the influence of differences in the interventions or outcomes, 3) exclusion of trials with insufficient information to characterise the comparator intervention, 4) appropriate choice of modelling according to the level of statistical heterogeneity, 5) cautious interpretation of the results based on risk of bias assessments.

There are some limitations in the generalisability of this review, as few older persons were included in the trials. As per recommendations in the Cochrane Handbook, the use of funnel plots to detect publication bias was also not conducted due to there being fewer than 10 studies included in each meta-analysis.[83] It was not possible to obtain 1 abstract which was identified within another review.[196] This trial included 40 participants and has not been published in full. Data extraction and risk of bias assessment was hampered by limitations in reporting for all trials. The reporting of postoperative complications was generally inadequate, with events not being fully reported by treatment group. No studies reported factors with the potential to influence healing or risk of complications, including smoking, alcohol use, or the presence of diabetes or other co-morbidities. Only 3 of 14 included trials were considered at low risk of selection bias, having adequately generated random sequences and concealed allocation to treatment group. No trials clearly reported sample size calculations, or declared primary outcomes or use of intention-to-treat analysis. Key aspects of trial conduct that require consideration in future are trial design, to reduce risk of bias (e.g. independent evaluation of outcomes via blinded assessors), reporting consistent with CONSORT guidelines,[206] and conducting sample size calculations to ensure there is adequate statistical power to provide precise effect size estimates.

3.6 Conclusion

Overall trial evidence indicates that the effects of early ankle movement on recovery of function/mobility within 12 weeks of surgery, when compared to ankle immobilisation, are inconclusive, and there is no evidence of difference in function at 1 year. The results are to be interpreted with caution due to the low quality of evidence. Evidence of a reduced risk of thrombosis/thromboembolism with early ankle movement in the short term needs to be weighed up against the increased risk of developing deep/superficial SSIs and failure of fixation and need for additional surgery. Due to the limitations of the current evidence there is a need for adequately powered, high quality clinical trials to evaluate the clinical and cost effectiveness of early ankle movement compared to immobilisation after surgery for ankle fracture.

Chapter 4

4 The effects of ankle supports on non-pathological gait in adults: a randomised cross-over study.

The range of ankle supports used after severe ankle injury has been introduced in the previous chapters. The aim of this chapter was to investigate the effects of ankle supports on walking in healthy adults. The chapter concludes with a discussion of the clinical and research implications before presenting a clinical study on the effects of ankle supports on walking at 6 weeks after ankle open reduction and internal fixation (ORIF) surgery.

4.1 Background

Ankle supports are routinely issued to patients after acute ankle injuries and surgery.[123] The rationale for ankle support use is to aid pain relief, control loading of the injured tissues and facilitate weight bearing and rehabilitation of walking.[108] The types of ankle support described in the literature as being used after severe ankle sprain[38, 117] and after ORIF surgery for ankle fracture[50] vary greatly in their design. The primary differences in the designs are the extent and direction of mechanical limitation to ankle joint motion. Patients may be advised to use Tubigrip (elasticated tubular bandage), a stirrup brace or a type of removable walker boot (Figure 16). Tubigrip offers global compressive support without physically limiting motion. The stirrup brace and walker boot were introduced in section 1.6, p.11. In summary, a stirrup brace limits ankle motion in the frontal plane and less so in the sagittal plane. The walking boot limits motion in both planes and typically has a rocker bottom sole.

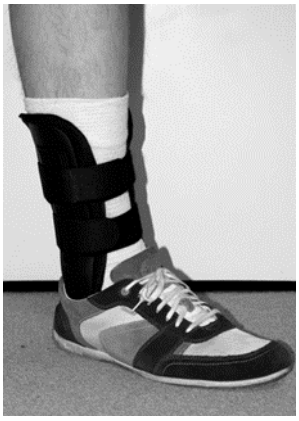
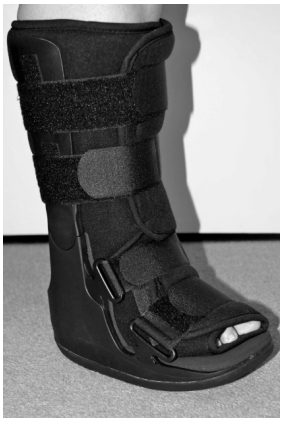
i.  ii.  iii. 

Figure 16: Ankle supports : i. Tubigrip ii. stirrup brace iii. walker boot.

One of the main aims of the initial phase of rehabilitation after severe ankle injury is to optimise the recovery of a normalised walking gait pattern for a timely restoration of ambulatory function and balance.[105] As discussed in Chapter 2, after ankle injury the main disturbance in walking gait that presents is asymmetry[9, 257] due to unilateral impairments including pain, inability to weight bear, limited joint range of motion, diminished proprioception and muscle atrophy and weakness.[99, 125, 173, 224] Determining which type of ankle support optimally reduces asymmetry of gait is therefore of clinical importance.

4.1.1 The effects of ankle supports on gait

There are currently no studies directly comparing the effects of different types of ankle supports on walking quality in either healthy adults or in clinical populations. In cadaver models of complete lateral ligament tear, ankle stirrup braces have been shown to mechanically limit inversion.[175] Stirrup braces have also been found to restrict ankle range of motion in all directions *in vivo*, but the primary limit is to inversion.[55] Ankle stirrup braces increase step length by a small magnitude in the paretic limb in those with hemiplegia.[25] Several studies have investigated the effect of walker boots on plantar pressures in healthy adults.[48, 171] Plantar pressures provide information about asymmetry and distribution of load within the feet but not about gross gait asymmetry, which is often of clinical importance after ankle injury. Hutchins et al.[101] conducted a literature review on

the effect of rocker soles on gait outcomes. They found no overall evidence of rocker soles significantly altering kinematics, kinetics or temporal parameters of gait. However, a toe-only curved rocker, as commonly used in walker boots, was found to reduce stride length. The use of this sole profile unilaterally could therefore contribute to asymmetry of gait.

It is plausible that there is a limit to the gait symmetry that can be achieved while wearing ankle supports that are designed to limit ankle range of motion such as ankle stirrup braces and walker boots. Subtalar and talocrural motion are both required for normal ankle motion. The ankle complex is formed of two functionally dependent articulations, the ankle (tibiotalar/talocrural) and subtalar (calcaneotalar) joints.[170] The axis of motion at the ankle is not exactly aligned to the sagittal and coronal planes, resulting in biplanar motion at the ankle complex. Plantar flexion at the talocrural joint occurs with some inversion at the subtalar joint and dorsiflexion occurs with some eversion. In the foot support phase of gait, 15° of motion occurs, from 5° plantar flexion at heel contact to 10° dorsiflexion at terminal stance. The ankle then moves from 10° dorsiflexion to 15° plantar flexion in the pre-swing phase and the foot rotates over the great toe.[178] Comparing gait in Tubigrip with stirrup braces and walker boots in healthy adults would indicate whether there is a limit to the quality of walking possible in these supports, even in the absence of injury. Quantifying the magnitude of asymmetry in non-pathological gait in different types of ankle support would also inform interpretation in clinical populations. The effects of the supports and the clinical impairments after injury on the presenting asymmetry would be more readily discerned with data from healthy adults.

Research question

Do ankle supports designed to limit ankle motion (ankle stirrup brace and walker boot) have different effects on gait characteristics compared with a non-limiting ankle support (Tubigrip) in healthy adults?

4.2 Objectives

Primary Objective:

- To determine the effects of ankle supports on gait characteristics in healthy adults.

Secondary Objectives:

- To develop analytical procedures to account for the effect of gait velocity on speed-dependent gait characteristics.
- To establish the test-retest reliability of gait assessments in different types of ankle support.

4.3 Methods

4.3.1 Study overview and design

The design was a randomised three-treatment, three-period, cross-over trial. Each participant was tested walking in all 3 types of ankle support. The within-subject design enhanced the estimation of the effect of different ankle supports on walking gait by increasing statistical power, reducing error due to individual participant differences.[106] The within-subject design controlled for important influences on gait such as age and gender, as each participant acted as their own control. A cross-over trial is ideal for gait analysis where between-individual variation can be higher than within-individuals.[114, 178] The increased precision requires fewer participants and therefore resources. A cross-over trial was deemed appropriate as the mechanical effects of applying the ankle support were expected to have an immediate impact on walking.

4.3.2 Design considerations

The issues specific to cross-over designs are potential order and carry-over effects, which may bias estimates of treatment effect.[61, 212] Carry-over effects are the influences of one intervention persisting during the application and assessment of the next intervention. Order-effects relate to the influence of the sequence of intervention application on outcomes.

It was considered unlikely that carry-over effects would be problematic between interventions. The effect of mechanical limitations to ankle range of motion from an ankle support would immediately be eliminated on removal. It was anticipated that the patient's ankle condition would be relatively stable during the single testing session. In effect this eliminated the need for a washout period between measurements in each support. Formal statistical testing for carry-over effects were not undertaken based on the recommendations of Senn[211, 212] who argues that cross-over designs should not be used if carry-over effects are likely, and that statistical testing for this are not validated and usually inconclusive.

An order-effect was considered more likely, as during repeated measures of gait, participants may become more practiced or fatigued. Several design and analytical strategies were employed to minimise risk of bias from order-effects. The participants had a minimum rest period between tests in each support. The sequence of testing the ankle supports was also randomised to further reduce bias (see section 4.3.13 below). A sensitivity analysis was included to adjust intervention estimates for the order of testing. A single session of testing also reduced the risk of bias from protocol violations and withdrawals which would have further risked bias in the cross-over design.[184]

4.3.3 Setting

The study took place from February to May 2012 in the laboratory in the Kadoorie Centre for Critical Care Research and Education, John Radcliffe Hospital, Oxford, UK.

4.3.4 Study Participants

Screening and recruitment

Participants were volunteers sought through posters in public spaces (Appendix 4). Potential participants were given the opportunity to discuss the study with the investigator and were issued a participant information sheet (Appendix 5) so that they could consider participation and ask

questions. Participants gave written informed consent prior to study registration and randomisation.

4.3.5 Eligibility criteria

Eligible participants were healthy volunteers who fulfilled the following eligibility criteria:

Inclusion Criteria

- Aged 18 years or over
- Able to give informed consent and to understand and respond appropriately to verbal instructions
- Able to walk a minimum of 10m (with or without a walking aid)

Exclusion Criteria

The participants were not entered into the study if any of the following applied:

- Open wounds below the knee (preventing application of the supports)
- Neurological disorder or previous major lower limb fracture (potentially limiting symmetry of gait)
- Systemically unfit to undergo testing (i.e. nausea, fever, active infection requiring antibiotics)
- Unable to walk safely without physical support from another person
- Uncontrolled health disorder (e.g. respiratory or cardiovascular instability)

4.3.6 Interventions

The three ankle supports evaluated in this study varied in their design and ankle motion limitations offered (Figure 16). The standard intervention was Tubigrip (Mölnycke Health Care, Sweden), which is an elasticated compressive tubular bandage applied in a double layer from the level of the tibial tuberosity to the metatarsophalangeal joints of the injured leg and the patient wears normal footwear with the support. The ankle 'stirrup' brace (protect.Ankle air foam, Medi, Germany) and the removable below-knee 'walker' boot (Jura Walker Fixed, Promedics, UK) are described in section 1.6, p.11. The participant wore the ankle support on their right foot and their normal

footwear on the left foot. The supports were applied according to manufacturer guidelines by the lead investigator (an experienced musculoskeletal physiotherapist).

4.3.7 Outcome Measures

4.3.8 Primary outcome

Step length and single support time asymmetry

As discussed in section 2.3.4, p.28, step length is the distance one part of the foot moves during a step in relation to the same part of the foot in the contralateral limb. Single support time is the duration of time in the gait cycle when a single lower limb is in contact with the ground and solely supporting body weight. Step length and single support time are measurements for each lower limb. The relationship between the right and left limb was expressed as a symmetry index (SI) using the equation detailed in section 2.3.4, p.28.[88] The SI has a minimum of 0 (perfect symmetry) and 0.1 is equivalent to 10% asymmetry, 0.5 is 50% asymmetry and so on.

4.3.9 Secondary outcomes

Step width (cm)

Step width is the medial-lateral distance between the heels in double support.[114] The mean of right and left 'heel-to-heel base of support' data from the electronic walkway was used to measure step width (see Figure 8, p.29). Step width tends to increase to widen base of support, an adaptive response in impaired balance.[114]

Walking velocity (m/s)

Walking velocity at slow, preferred and fast walking speeds.

4.3.10 Instrumentation

All outcomes were measured using the GAITRite® electronic walkway (CIR Symptoms, Havertown, PA, USA), as described in section 2.3.2, p.24.

4.3.11 Overview of study procedures

After screening for eligibility and consent the participants underwent baseline assessments and then had a trial walk over the electronic walkway. Randomisation then took place, followed by gait analysis in each ankle support (Figure 17).

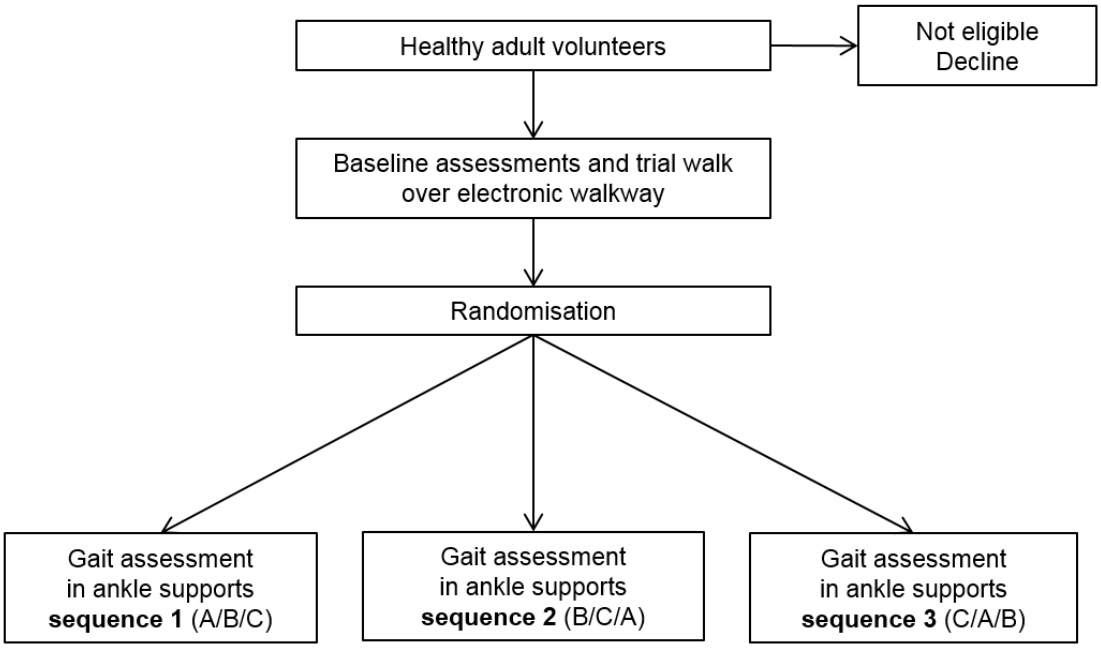


Figure 17: Overview of the stages of the study procedures.

4.3.12 Baseline assessments

A baseline questionnaire was completed on the day of the gait measurements (Appendix 6). Data were collected on the participants' age, gender and current lower limb function (Lower Extremity Functional Scale [LEFS]).[13, 127] The LEFS is a self-report questionnaire consisting of 20 items with a maximum score of 80, indicating a high functional level. Items include difficulty with walking tasks, light and heavy activities around the home, recreation and sport. Measurement properties for the LEFS are shown in Table 4, p.22.

4.3.13 Randomisation of sequence of ankle supports tested

In this within-subject design study comparing 3 ankle supports, there was a need to control for order-effects.[61, 212] It is feasible that participants may respond differently to the first, second and third supports as they become more familiar with the tests, but also potentially develop fatigue with more ambulation. Simple randomisation does not guarantee an even balance between the orders of testing of the ankle supports. To deal with a potential systematic order-effect, a Latin square design was utilised, as shown in Table 11.[61, 212] These sequences ensured an even number of participants were tested in each support first, second or third.

Table 11: The Latin Square randomisation sequences for the study.

	Period		
	1	2	3
Sequences	Intervention		
I	A	B	C
II	B	C	A
III	C	A	B

4.3.14 Allocation concealment

The sequence of randomisation needed to be undecipherable, therefore safeguards known as allocation concealment were required to ensure participants, clinicians and investigators were unable gain knowledge of future allocations.[83] The allocation concealment method used was based on strategies recommended by Schulz and Grimes.[207] A layer of aluminium foil was inserted into the pre-prepared envelopes containing an allocation card. The foil is inserted to ensure the envelope is not permeable to a light source. Sequentially numbered, opaque, sealed envelopes were opened once the participant information had been written on the front, with carbon paper inside transferring information onto the assignment card. This pragmatic but relatively strict procedure was utilised in this study as the lead investigator was randomising participants during the gait analysis procedures with the participant present.

4.3.15 Blinding

It was not practical to blind the allocated treatments as the support was applied by both the investigator and participant.

4.3.16 Gait analysis procedures on the electronic walkway

Steady state gait was facilitated by participants walking 2.5m before and continuing 2m beyond the active sensors.[115, 129] The participants walked 9.4 metres over the electronic walkway system for each test (with an active length of sensors in the mid-section of 4.88m). In accordance with guidelines developed by the European GAITRite® network, several methodological, environmental and safety considerations were observed.[115] The testing was performed in controlled well-lit conditions in a research laboratory. Testing occurred at times where there were limited sources of audio-visual distraction.

One preliminary trial of walking over the electronic walkway, back and forth, was conducted at the participant's preferred walking speed in their own footwear prior to commencing full measurements. The purpose of this was to acclimatise the participant to the test conditions before proceeding with further measurements.

Once allocation was revealed, the first ankle support was applied. This support was then tested at three walking speeds as described in section 2.3.7, p.32. The measurements stopped automatically as soon as the participant left the electronic walkway after the first walk. The participant then turned and walked back across the mat. The order of walking speeds tested (preferred, slow then fast) was not randomised, as the first speed of walking tested was the reference speed, with the aim of maximising the range of speeds achieved in subsequent tests.

The actual speed achieved was self-limited. Participants regulated the range of speeds that they achieved safely. Standardised instructions were given to participants as per the European GAITRite® network guidelines,[115] which were: *'Walk at your own preferred speed'* for PWS,

'Now try and walk slower, take your time' for SWS and then *'Now try to walk as fast as you can safely'* for FWS.

There was a rest period for a minimum of 3 minutes before testing the second and third ankle supports with the same protocol. Participants were able to stop the testing procedure at any time at their own request or if deemed necessary by the investigator due to concerns (e.g. fatigue), but this was not necessary.

4.3.17 Sample size

Published estimates to inform the minimal clinically important difference in temporo-spatial gait characteristics and the effect size for ankle support use on the primary outcomes were not available. Therefore the effect size assumption was developed based on pragmatic clinical considerations. A minimum of 18 participants were required to complete the series of gait assessments to match the target sample size for the clinical study in Chapter 5 (see p.131). Precision from a limited sample was enhanced by repeated measures and a within-subject design (n=6 observations per participant in each support).

4.3.18 Analysis strategy

Descriptive statistics

Baseline characteristics of participants and all primary and secondary outcome data were summarised as counts (%), means (SD) and range, as appropriate. Box and whisker plots were used to show distributions of continuous data. The top line of the box in the plot is the 75th percentile (upper quartile), the middle bar the 50th percentile (median) and the bottom line the 25th percentile (lower quartile). The ends of the box are the interquartile range (IQR). The whiskers extend to the upper and lower adjacent values (most extreme data point from the upper and lower quartiles within 1.5 times the IQR) and values outside these (outliers) are shown by markers.[153]

Gait data were collected by the GAITRite system on a connected laptop and were stored on the system's software in an integrated database (GAITRite® v3.8E, CIR Systems, Peekskill, NY, USA). The GAITRite® system has an internal algorithm to calculate velocity, step length, single support time and step width. Gait data were then exported to Excel 2010 (Microsoft, Redmond, WA, USA) to transfer into a format suitable for analysis in STATA version 12 (StataCorp, College Station, TX, USA). The steps of data manipulation, calculation of symmetry indices, multilevel modelling and post-estimation diagnostics were programmed within the STATA interface.

4.3.19 Reliability

The two gait assessments at each test speed in each ankle support were subjected to a single analysis of reliability of walking velocity. This was an efficient and more valid approach to exploring a reliability analysis than conducting separate measurements to assess if participants could replicate their performance in each pair of tests at the same speed and with the same ankle support.[154] The reliability of the repeated measures were analysed by intra-class correlation coefficients ($ICC_{1,1}$) from one-way analysis of variance (ANOVA), where all within-subject variability is treated as measurement error[79, 215]:

$$\text{ICC}\ (1,1) = \frac{\text{BMS} - \text{WMS}}{BMS + (k-1)WMS}$$

Where BMS is between-subject mean squares, WMS is within-subject mean squares and k is the number of measurements.[195]

4.3.20 Walking velocity

Walking velocity in each ankle support and test speed was calculated using a random intercept model. The model was used to enable the repeated gait measures to be used to compare walking velocity in the different ankle supports and walking test speeds (slow, preferred and fast). A random intercept model was also used to explore the relationship between gait velocity and step length symmetry indices, single support time symmetry indices and step width. The aim of this

analysis was to determine whether these gait parameters were related to walking velocity and therefore required speed-normalisation.

4.3.21 Analysis of primary endpoint

As discussed in Chapter 2, temporo-spatial gait outcomes required an analytical approach that accounted for the effect of velocity to enable valid intervention effect estimates. A novel approach to accounting for velocity was developed using multilevel modelling, as described in section 2.3, p.31.

Models were fitted via maximum likelihood estimation. The modelling was developed in stages during the analysis.

4.3.22 Stages of model building

The model was developed in stages:

- **Model 0:** random intercept model with fixed treatment effect unadjusted for velocity
- **Model 1:** random intercept model with fixed intervention effect, adjusted for velocity, random effect at the participant level
- **Model 2:** random slope model for velocity with fixed intervention effect, adjusted for velocity, random effect at the participant level
- **Model 3:** random curve model for velocity with fixed intervention effect, adjusted for velocity, random effect at the participant level

The chi-square likelihood-ratio test was used to assess if additional components were required. Likelihood ratio (LR) test is a test statistic to compare the fit of a model with the previous one to see whether adding parameters improved the model.[194] The LR test compared log-likelihood (measure of error or unexplained variation) of two models and determined if there is a statistically significant difference.[60] If it was not statistically significant (P<0.05), the previous model was the

final model used to estimate the treatment effect. Level 1 residual standard deviation (SD) reducing with the addition of terms was also used as an indicator of improvement in the fit of the model.

For the final model, post-regression diagnostics were conducted to check key assumptions:[194]

- Homoscedasticity (assumption of homogeneity of variance) was explored using scatterplot of standardised residuals and predicted values.
- As the outcome variable was continuous, a check for normally distributed residuals using a plot of quantiles of standardised residuals against quantiles of normal distribution (Q-Q plot of level 1 residuals).

4.3.23 Interpretation of multilevel modelling output

The relative contributions of each predictor were interpreted (coefficient and 95% CI and *P* value). For the intervention effect, coefficients were produced for the stirrup brace and walker boot compared with the reference condition of Tubigrip (set at 0). The relationship between velocity and the gait outcome was interpreted for every 1m/s change in velocity. A 1m/s change is a normal range between slow and fast walking velocity in healthy populations.[178]

4.3.24 Sensitivity analysis

A sensitivity analysis to assess for a period effect was conducted by adding terms for each period into the final model.

Statistical significance was set at α 0.05 (two-sided) for all analyses.

4.3.25 Reporting

The study was reported based on recommendations from the CONSORT guidelines for randomised clinical trials.[155, 206] The CONSORT guidelines facilitate completeness and clarity of trial reports, enhancing utility of research findings.[216]

4.3.26 Ethical approval

This study was conducted according to Good Clinical Practice guidelines and approval was obtained from the Central University Research Ethics Committee (Ref: MSD/IDREC/C1/2012/17, Appendix 7).

4.4 Results

4.4.1 Participant characteristics

The flow of participants through the stages of the study is reported in a CONSORT flow diagram (Figure 18). The 18 participants were an average age of 42 (SD 13) years and 14 (88%) were female. All participants had good patient-reported lower limb function/mobility status, as indicated by the LEFS scores. The average walking velocity at baseline was within normal range for adults, but the fastest and slowest speeds were slightly outside normative ranges (1.2-1.6 m/s) (Table 12).[114] None used walking aids for the testing procedures or in normal activities of daily living. All volunteers were able to complete the testing procedures.

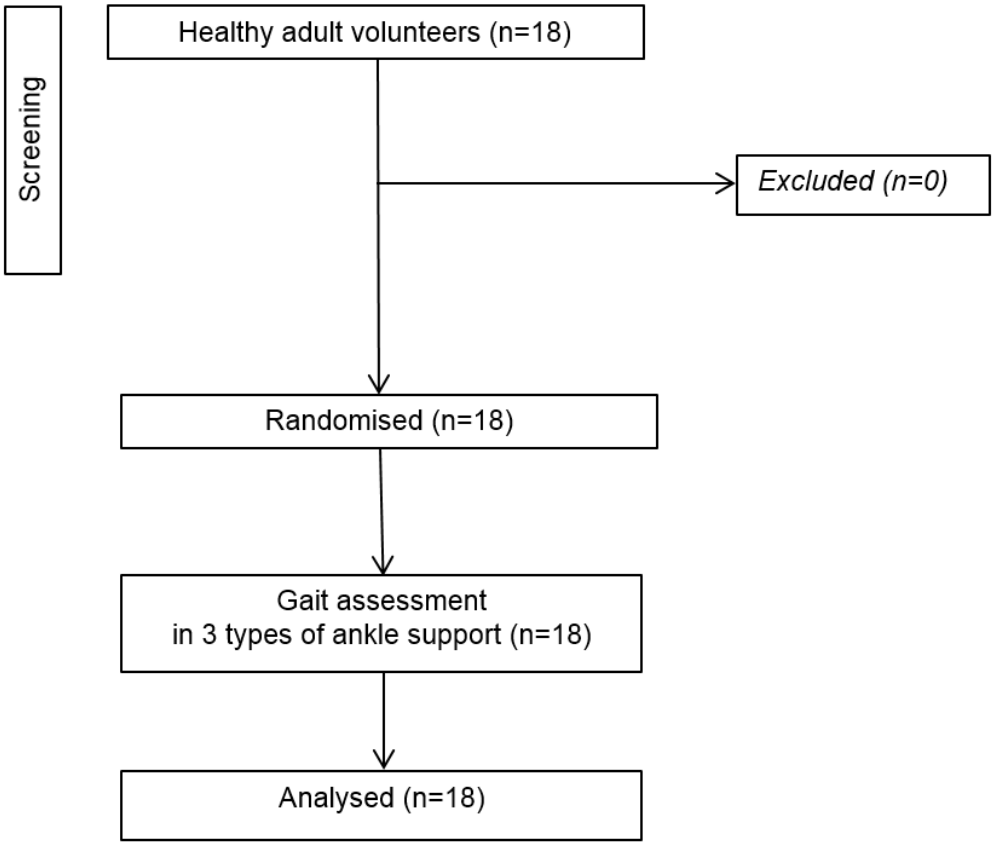


Figure 18: Flow chart of participants through the study.

Table 12: Baseline characteristics of study participants (n=18).

Characteristic	Mean (SD) range (unless otherwise stated)
Age (years)	42(13) 24-62
Gender (Male/Female)	4/14 (88% female)
Lower Extremity Functional Scale (LEFS)	76 (6) 60-80
Walking velocity at preferred speed in no support (m/s)	1.38 (0.16) 1.05-1.71

4.4.2 Walking velocity

The reliability of walking velocity for the two gait measurements for each test speed and ankle support were excellent (Table 13).

Table 13: Intraclass correlation coefficients (ICC) and 95% confidence intervals (CI) for the two walks in each test condition. Participants (n=18) were tested in 3 ankle supports at 3 different speeds.

	Tubigrip		Stirrup		Walker	
	ICC	(95% CI)	ICC	(95% CI)	ICC	(95% CI)
Velocity (m/s)						
Slow	0.95	(0.90 to >0.99)	0.85	(0.71 to 0.98)	0.95	(0.91 to >0.99)
Preferred	0.92	(0.85 to 0.99)	0.92	(0.86 to 0.99)	0.94	(0.88 to 0.99)
Fast	0.92	(0.85 to 0.99)	0.95	(0.90 to >0.99)	0.95	(0.91 to >0.99)

Participants varied their walking velocity when asked to walk at slow, preferred and fast speeds in all 3 supports (Table 14 and Figure 19). Walking velocity was statistically significantly faster at preferred (0.45 m/s, 95% CI 0.42 to 0.49, $P<0.001$) and fast (0.87 m/s, 95% CI 0.83 to 0.90, $P<0.001$) test speeds compared to the slow test (Table 15). The variability in walking velocity increased in the fast speed tests compared with tests conducted at slow and preferred speeds (Table 14). There were no overlaps in the range of walking velocities achieved for two participants when wearing a walker boot (Figure 20), which highlighted the need for developing the use of MLM, as described in section 2.3. Walking velocity in the Tubigrip and stirrup brace were comparable at all 3 test speeds and there was no statistically significant difference (Table 15). Walking velocity was

statistically significantly slower in the walker boot when compared with the Tubigrip (-0.19 m/s, 95% CI -0.23 to -0.16, P<0.001).

A relationship between gait velocity and the other gait outcomes was evident, indicating these measures were speed-dependent. With increasing walking velocity, asymmetry between limbs lessened for step length (β=-0.08, 95% CI -0.10 to -0.06, P<0.001) and single support time (β=-0.05, 95% CI -0.06 to -0.03, P<0.001), and step width narrowed (β=-2.27cm, 95% CI -2.92 to -1.62, P<0.001).

Table 14: Gait outcomes in each ankle support and test condition (speeds slow, preferred and fast). Participants (n=18) were tested in 3 ankle supports at 3 different speeds.

	Tubigrip		**Stirrup**		**Walker**	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Velocity (m/s)						
Slow	0.88	(0.19)	0.90	(0.18)	0.75	(0.22)
Preferred	1.39	(0.20)	1.35	(0.22)	1.14	(0.25)
Fast	1.78	(0.21)	1.76	(0.22)	1.58	(0.32)
Step length symmetry index						
Slow	0.030	(0.022)	0.033	(0.027)	0.170	(0.157)
Preferred	0.021	(0.015)	0.021	(0.015)	0.162	(0.135)
Fast	0.018	(0.014)	0.026	(0.022)	0.092	(0.083)
Single support time symmetry index						
Slow	0.042	(0.059)	0.065	(0.085)	0.101	(0.108)
Preferred	0.036	(0.022)	0.033	(0.029)	0.099	(0.114)
Fast	0.031	(0.027)	0.029	(0.025)	0.091	(0.155)
Step width (cm)						
Slow	8.71	(2.66)	10.20	(2.48)	14.28	(2.93)
Preferred	8.63	(1.81)	9.48	(2.16)	12.99	(2.36)
Fast	8.75	(2.30)	9.18	(2.26)	12.15	(2.48)

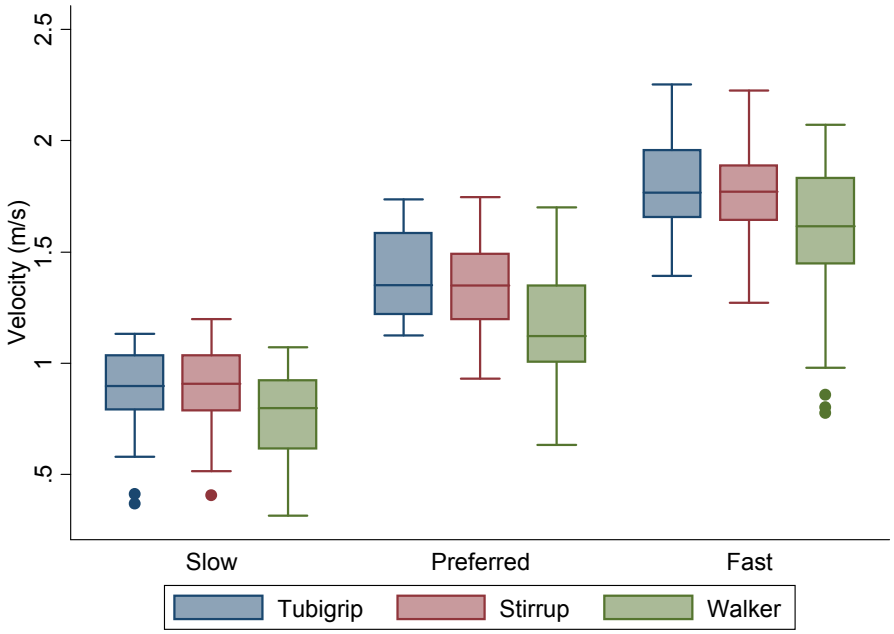


Figure 19: Box and whisker plot of velocity (m/s) of walking in each ankle support by test speed (n=18 participants with 18 observations each). The middle line of the box is the median, the top line is the upper quartile and the bottom line is the lower quartile. The error bars indicate the greatest and smallest values except outliers, which are represented by dots.

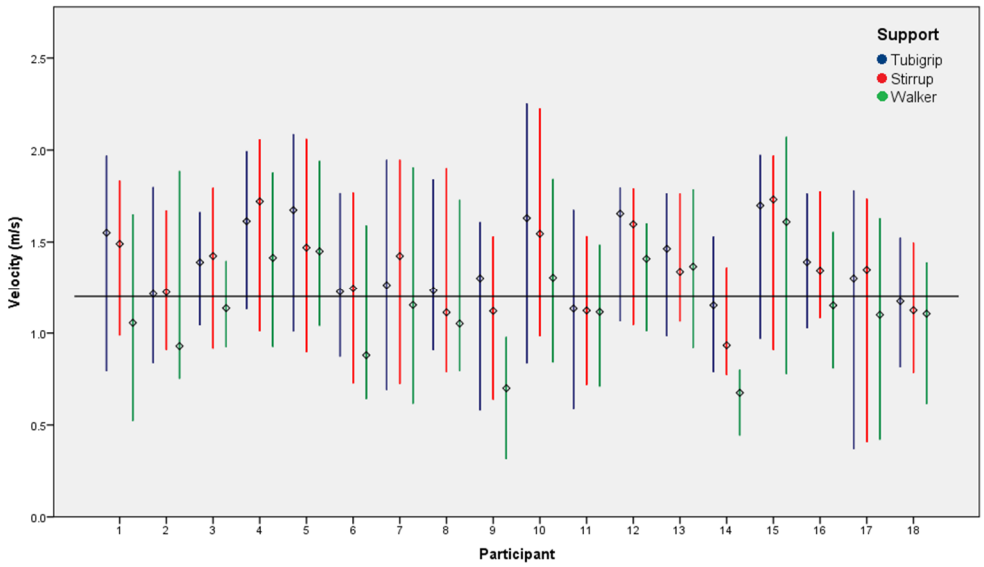


Figure 20: Line graph of the range of walking velocity (with median marker) (m/s) for each participant (n=18) by ankle support. The reference line is set at 1.2 m/s. The range of walking velocities for all participants in all ankle supports overlap except for participants 9 and 14 in a walker boot.

Table 15: Multilevel model for walking velocity in each ankle support, compared with Tubigrip, and test speed, compared with the slow speed test (n=18).

Variable	β	95% CI		*P* value
Fixed effects				
Ankle support				
Tubigrip*	0.00			
Stirrup	-0.01	-0.05	0.02	0.45
Walker	-0.19	-0.23	-0.16	<0.001
Test speed				
Slow**	0.00			
Preferred	0.45	0.42	0.49	<0.001
Fast	0.87	0.83	0.90	<0.001
Constant (β_0)	0.91	0.82	1.00	<0.001
Random effects	Estimate			
Intercept SD	0.18	0.13	0.25	
Level 1 residuals SD	0.14	0.13	0.15	
Likelihood-ratio test[a]				

CI: Confidence Interval; SD: Standard Deviation.
*Ankle support reference category.
**Test speed reference category.
Random intercepts with fixed treatment and test speed effect at level 1.
$\beta < 0.0$ = velocity slower than reference category, $\beta > 0.0$ = velocity faster than reference category.

4.4.3 Step length asymmetry

Step length SI at each test speed by ankle support is shown in Figure 21. The step length SI by gait velocity by participant is shown in Figure 22. The participant level variability in gait performance in each ankle support across the range of velocities highlighted the indication for use of MLM to estimate the effect of ankle supports.

Multilevel modelling: When compared with Tubigrip, step length asymmetry between limbs was 10% worse (95% CI 9 to 12, $P<0.001$) in the walker boot (Table 16). There was no difference in step length asymmetry between walking in the stirrup brace and Tubigrip. There was an overall negative relationship between walking velocity and step length asymmetry. Step length asymmetry was reduced by 30% (-30%, 95% CI -41 to -10, $P<0.001$) for 1m/s increase in velocity (in a random curve model). Figure 23 shows the predicted step length SI from the final model by walking velocity in each ankle support. It can be seen that asymmetry was greater at slower and faster walking velocities and that step length asymmetry was markedly greater in the walker boot compared with the other two supports.

Random effect results: Allowing both the intercept and curve for each participant to vary improved the fit of the model.

Sensitivity analyses: The order in which the ankle supports were tested was not a statistically significant factor and had a negligible effect on the final model estimates of step length SI (<1%).

Model diagnostics: The diagnostic plots (Figure 24 and Figure 25) identified some limitations of the final model. The inflection in the Q-Q plot deviating from the normal distribution indicates that the model fits well with most of the range but does not fit as well with predictions of greater asymmetry and for the extreme observations. Transformations did not substantially improve the model fit. Removing the observations for one participant, who had the largest residuals and also the largest degree of step length asymmetry, did not alter the conclusions. When these outlying observations were removed from the analysis, the walker remained the only support that was different from Tubigrip and the margin of asymmetry in the Walker boot reduced by only 1%, which is not clinically significant.

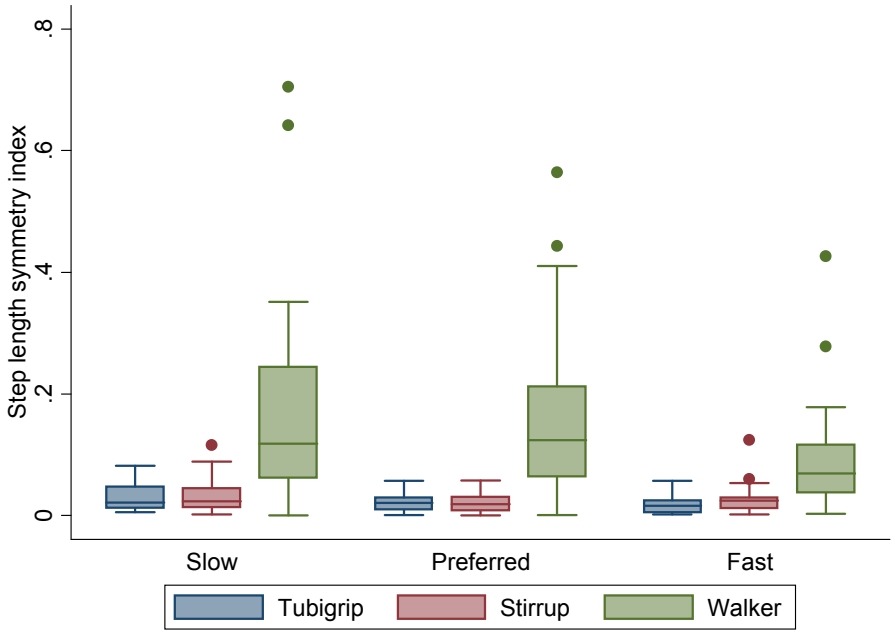


Figure 21: Box and whisker plot of step length symmetry index in each ankle support by test speed (n=18 participants with 18 observations each). The middle line of the box is the median, the top line is the upper quartile and the bottom line is the lower quartile. The error bars indicate the greatest and smallest values except outliers, which are represented by dots.

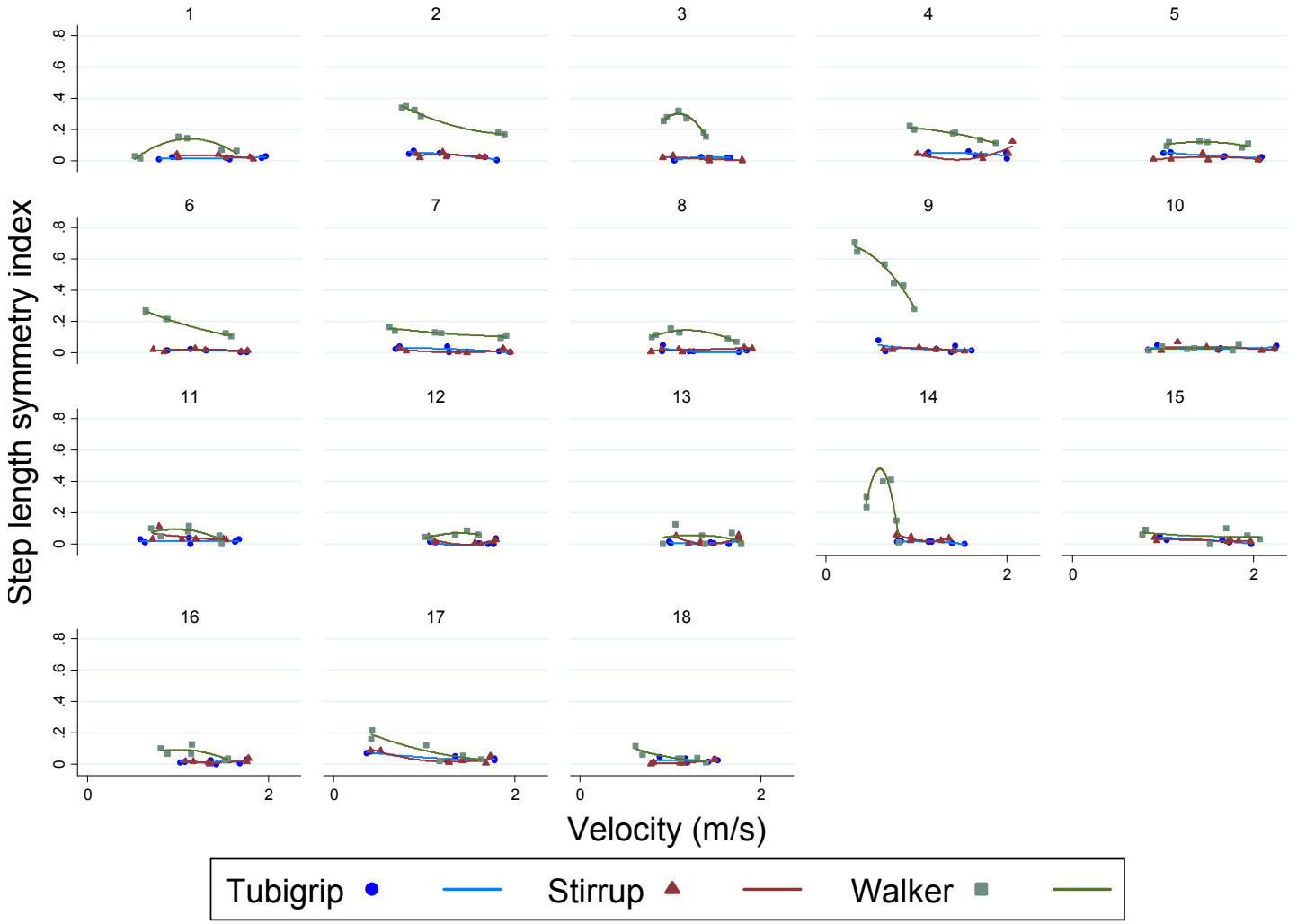


Figure 22: Two-way scatter plot with quadratic prediction plot of step length SI and walking velocity (m/s) by participant (n=18). There are 6 data points representing the 6 walking tests for each ankle support by participant. The quadratic prediction curve is plotted to fit these data points for each ankle support. The relationship between single support symmetry and velocity varies between participants and the support used.

Table 16: Multilevel modelling results for step length SI. Level 1 was the repeated measurement occasions (n=18) and level 2 was the participant (n=18).

Variable	**Model 0**[#]				**Model 1**[##]				**Model 2**[###]				**Model 3**[####]			
	β	95% CI		*P* value	*β*	95% CI		*P* value	*β*	95% CI		*P* value	*β*	95% CI		*P* value
Fixed effects																
Velocity	.	.	.	.	-0.05	-0.07	-0.03	<0.001	-0.05	-0.09	-0.01	0.02	-0.30	-0.41	-0.19	<0.001
Velocity^2	.	.	.	.	.	.	.	.	.	.	.	.	0.10	0.06	0.14	<0.001
Stirrup[*]	0.00	-0.02	0.02	0.72	0.00	-0.02	0.02	0.77	0.00	-0.01	0.02	0.81	0.00	-0.01	0.02	0.67
Walker[*]	0.12	0.10	0.14	<0.001	0.11	0.09	0.13	<0.001	0.10	0.09	0.12	<0.001	0.10	0.09	0.12	<0.001
Constant (β_0)	0.02	0.00	0.04	0.03	0.09	0.06	0.12	<0.001	0.08	0.02	0.14	0.01	0.23	0.15	0.31	<0.001
Random effects	Estimate				Estimate				Estimate				Estimate			
Slope SD (velocity)	.	.	.		.	.	.		0.08	0.05	0.11		0.06	0.04	0.09	
Intercept SD	0.04	0.02	0.05		0.03	0.02	0.05		0.12	0.08	0.17		0.10	0.07	0.15	
Level 1 residuals SD	0.07	0.06	0.07		0.07	0.06	0.07		0.06	0.05	0.06		0.06	0.05	0.06	
Likelihood-ratio test[a]					χ^2= 26.27	*P*<0.001			χ^2= 67.87	*P*<0.001			χ^2= 19.04	*P*<0.001		

CI: Confidence Interval; SD: Standard Deviation.
[*]Compared with Tubigrip (reference category).
[#] Random intercepts with fixed treatment effect at level 1.
[##] Added covariate (velocity) at Level 1.
[###] Random intercepts and slopes (as a function of velocity).
[####] Random intercepts and curves (as a function of velocity^2).
[a] vs. previous model.
β < 0.0 = step length SI better than reference category (Tubigrip), β > 0.0 = step length SI worse than reference category (Tubigrip).

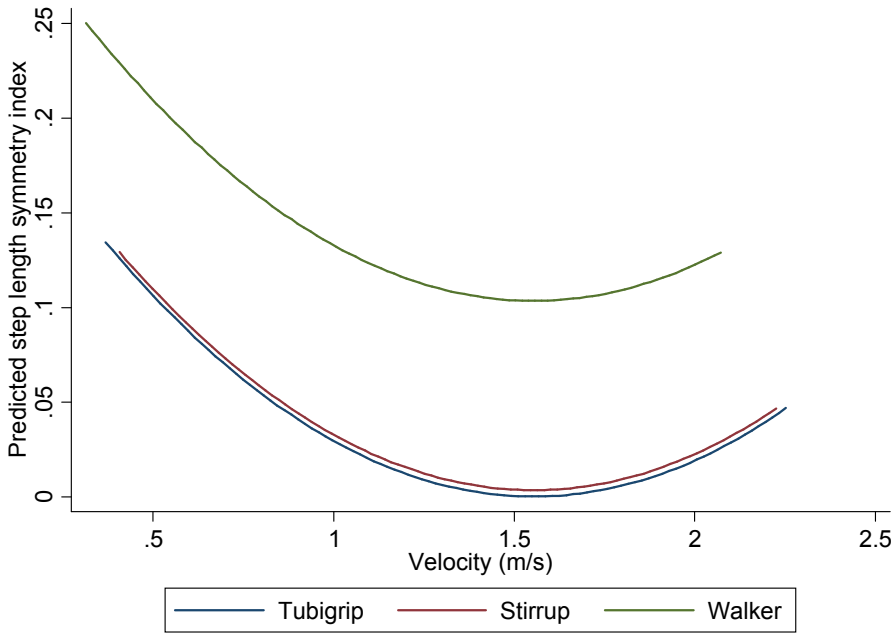


Figure 23: The final model predicted step length symmetry by walking velocity (m/s) in each type of ankle support. There was a statistically significant in favour of Tubigrip compared with the walker boot (P<0.001).

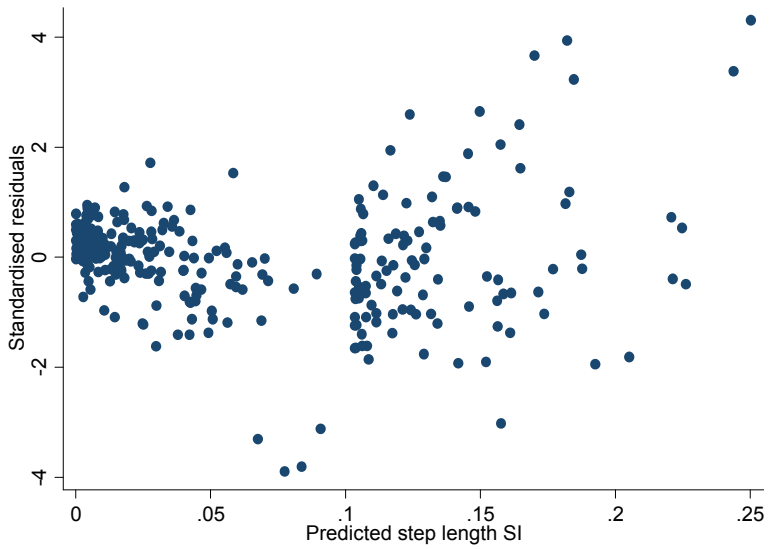


Figure 24: Scatterplot of standardised residuals and predicted values (Level 1) (n=324).

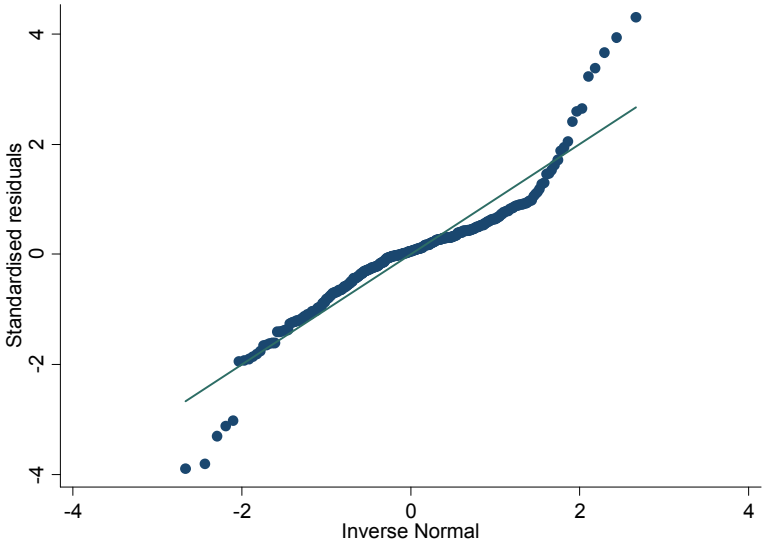


Figure 25: Q-Q plot of standardised residuals against normal distribution (level1) (n=324).

4.4.4 Single support time asymmetry

Single support time SI at each test speed by ankle support is shown in Figure 26. The single support time SI by gait velocity by participant is shown in Figure 27. The participant level variability in gait performance in each ankle support in the range of velocities again highlighted the indication for MLM to estimate the effect of the ankle supports.

Multilevel modelling: When the walker boot was compared with Tubigrip, asymmetry between limbs in single support time was 5% (95% CI 3 to 7, $P<0.001$) worse (Table 17). There was no difference in single support time asymmetry between Tubigrip and the stirrup brace. There was an overall negative relationship between walking velocity and single support time asymmetry. Single support time asymmetry between limbs reduced by 3% (-3%, 95% CI -7 to 0) for a 1m/s increase in velocity. Figure 28 shows the predicted single support time SI by walking velocity in each ankle support. It can be seen that single support time asymmetry was greater at slower walking velocities and that this lessened as velocity increased. Single support time asymmetry was markedly greater the walker boot than the other two supports.

Random effect results: Allowing both the intercept and slope for each participant to vary improved the fit of the model.

Sensitivity analyses: The order in which the ankle support was tested was not a statistically significant factor and had a negligible effect on the final model estimates (<1%) when added to the final model in a sensitivity analysis.

Model diagnostics: The diagnostic plots (Figure 29 and Figure 30) identified some limitations of the final model. The inflection in the Q-Q plot deviating from the normal distribution indicates the model fits well with most of the range but does not fit as well with greater asymmetry or for the extreme observations. Transformations did not substantially improve the model fit. Removing the extreme observations for the participant with largest residuals (participant 5 had one asymmetry value of over 80% in the walker, Figure 27) did not alter the conclusions.

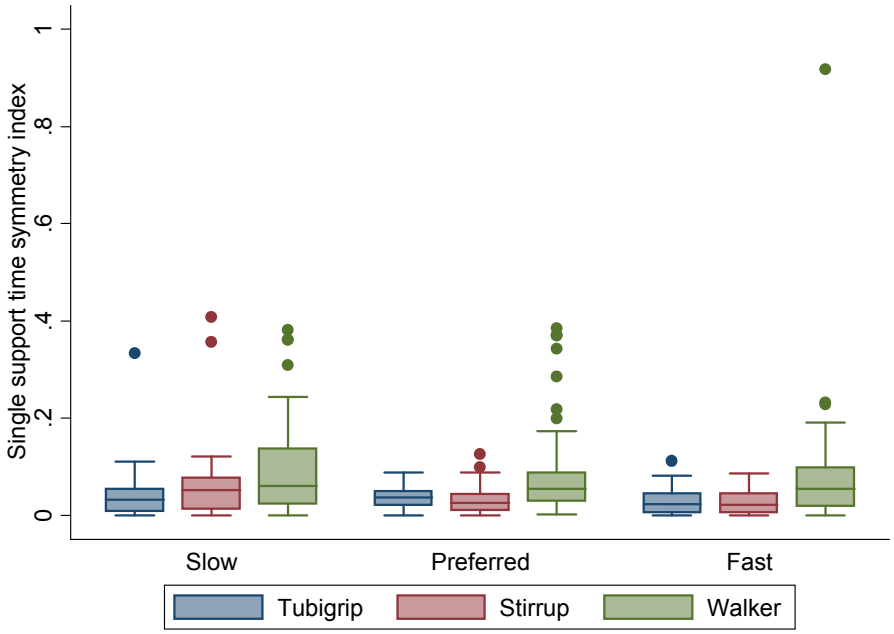


Figure 26: Box and whisker plot of single support time symmetry index in each ankle support by test speed (n=18 participants with 18 observations each). The middle line of the box is the median, the top line is the upper quartile and the bottom line is the lower quartile. The error bars indicate the greatest and smallest values except outliers, which are represented by dots.

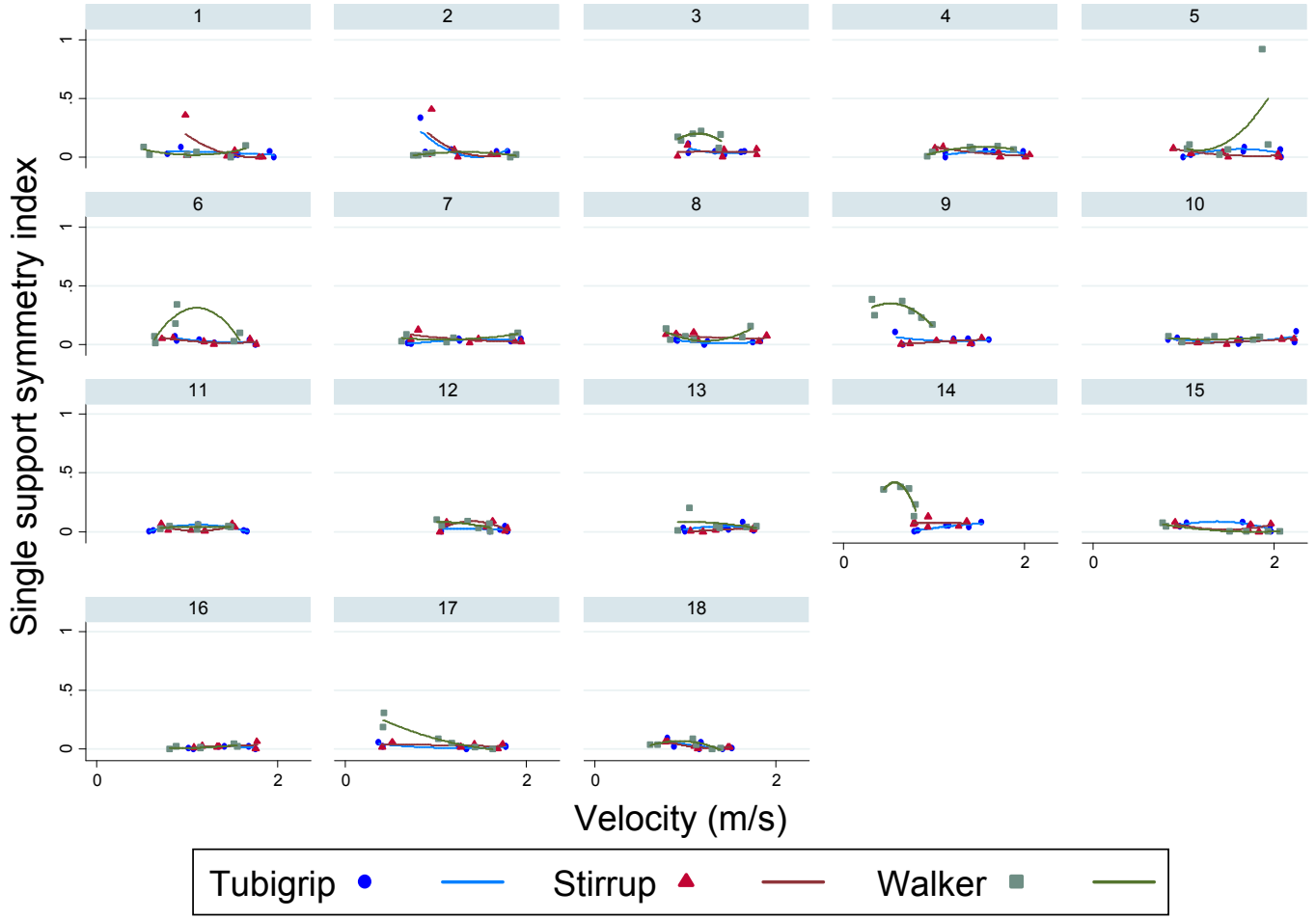


Figure 27: Two-way scatter plot with quadratic prediction plot of single support time SI and walking velocity (m/s) by participant (n=18). There are 6 data points representing the 6 walking tests for each ankle support by participant. The quadratic prediction curve is plotted to fit these data points for each ankle support. The relationship between single support symmetry and velocity varies between participants and the support used.

Table 17: Multilevel modelling results for single support time SI. Level 1 was the repeated measurement occasions (n=18) and level 2 was the participant (n=18).

Variable	**Model 0**[#]				**Model 1**[##]				**Model 2**[###]			
	β	95% CI		*P* value	β	95% CI		*P* value	β	95% CI		*P* value
Fixed effects												
Velocity	.	.	.	.	-0.03	-0.05	-0.01	0.002	-0.03	-0.07	0.00	0.09
Velocity^2	.	.	.	.								
Stirrup[*]	0.01	-0.02	0.03	0.58	0.01	-0.02	0.03	0.60	0.00	-0.02	0.02	0.65
Walker[*]	0.06	0.04	0.08	<0.001	0.05	0.03	0.08	<0.001	0.05	0.03	0.07	<0.001
Constant (β_0)	0.04	0.02	0.05	<0.001	0.08	0.05	0.12	<0.001	0.07	0.02	0.13	0.01
Random effects	Estimate				Estimate				Estimate			
Slope SD (velocity)	.	.	.		.	.	.		0.06	0.04	0.10	
Intercept SD	0.02	0.01	0.04		0.02	0.01	0.04		0.09	0.06	0.14	
Level 1 residuals SD	0.08	0.07	0.09		0.08	0.07	0.08		0.08	0.07	0.08	
Likelihood-ratio test[a]					χ^2=8.93	*P*=0.003			χ^2=19.38	*P* <0.001		

CI: Confidence Interval; SD: Standard Deviation.
[*]Compared with Tubigrip (reference category).
[#] Random intercepts with fixed treatment effect at level 1.
[##] Added covariate (velocity) at Level 1.
[###] Random intercepts and slopes (as a function of velocity).
[a] vs. previous model.
β < 0.0 = single support time SI better than reference category (Tubigrip), β > 0.0 = single support time SI worse than reference category (Tubigrip).

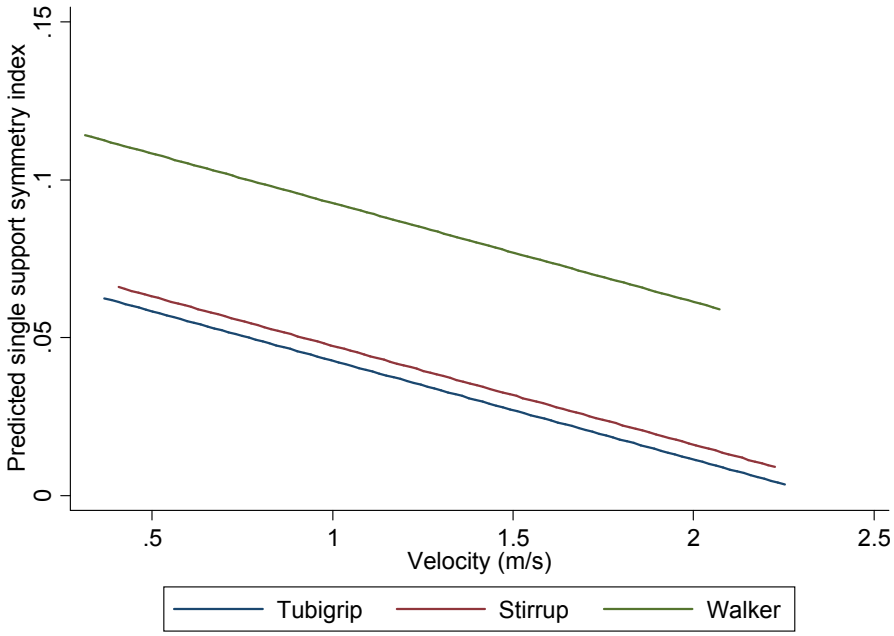


Figure 28: The final model predicted single support time symmetry by walking velocity (m/s) in each type of ankle support. There was a statistically significant difference in favour of Tubigrip compared with the walker boot (P<0.001).

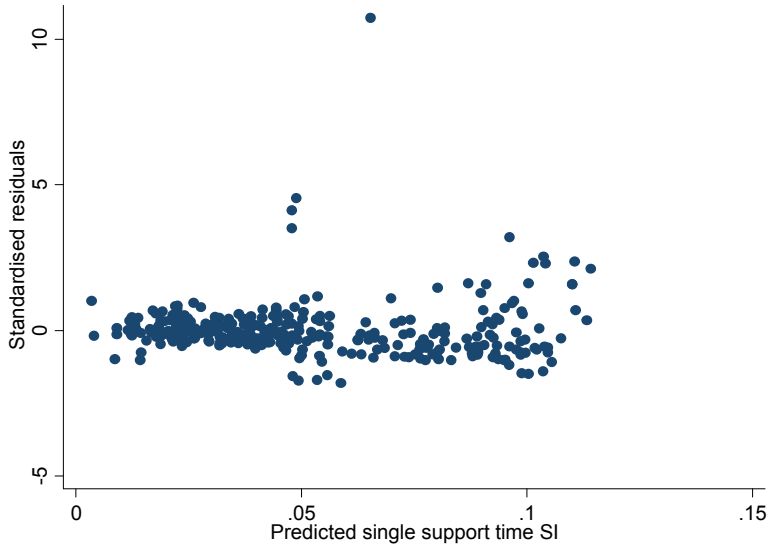


Figure 29: Scatterplot of standardised residuals and predicted values (Level 1) (n=324).

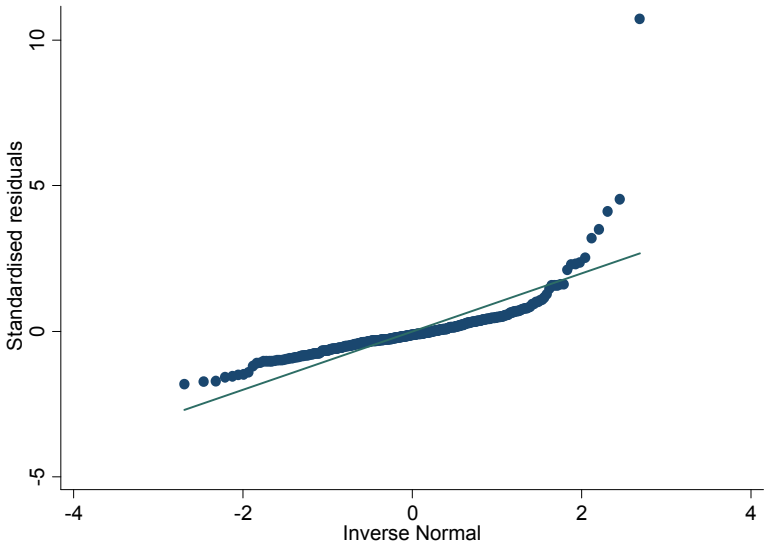


Figure 30: Q-Q plot of standardised residuals against normal distribution (level1) (n=324).

4.4.5 Step width

Step width at each test speed by ankle support is shown in Figure 31. The step widths by gait velocity by participant are shown in Figure 32.

Multilevel modelling: When compared with Tubigrip, step width was 0.9cm (95% CI 0.5 to 1.3, $P<0.001$) wider when walking in the stirrup brace and 4.1cm (95% CI 3.7 to 4.5, $P<0.001$) wider in the walker boot (Table 18). There was an overall negative relationship between walking velocity and step width. Step width was 5.1cm narrower (-5.1cm, 95% CI -7.9 to -2.3) for a 1m/s increase in velocity (in a curvilinear model). Figure 33 shows the predicted step width by walking velocity in each ankle support. It can be seen that there was wider step width at slower walking velocities and that this lessened as velocity increased, except for a small increase in step width again at the fastest walking velocities.

Random effect results: Allowing both the intercept and curve for each participant to vary improved the fit of the model.

Sensitivity analyses: The order in which the ankle support was tested was not a statistically significant factor and had a negligible effect (<0.1cm) on the final model estimates when added to the final model in a sensitivity analysis.

Model diagnostics: The diagnostic plots (Figure 34 and Figure 35) identified some minor limitations of the final model for the most negative residuals. Overall the model was a better fit than that for the symmetry indices. Transformations did not substantially improve the model fit.

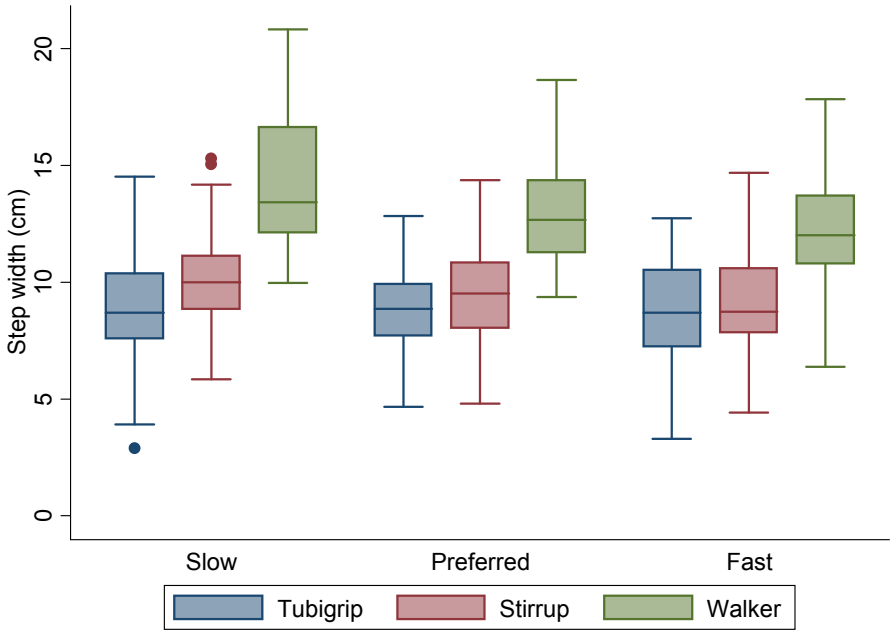


Figure 31: Box and whisker plot of step width (cm) in each ankle support by test speed (n=18 participants with 18 observations each). The middle line of the box is the median, the top line is the upper quartile and the bottom line is the lower quartile. The error bars indicate the greatest and smallest values except outliers, which are represented by dots.

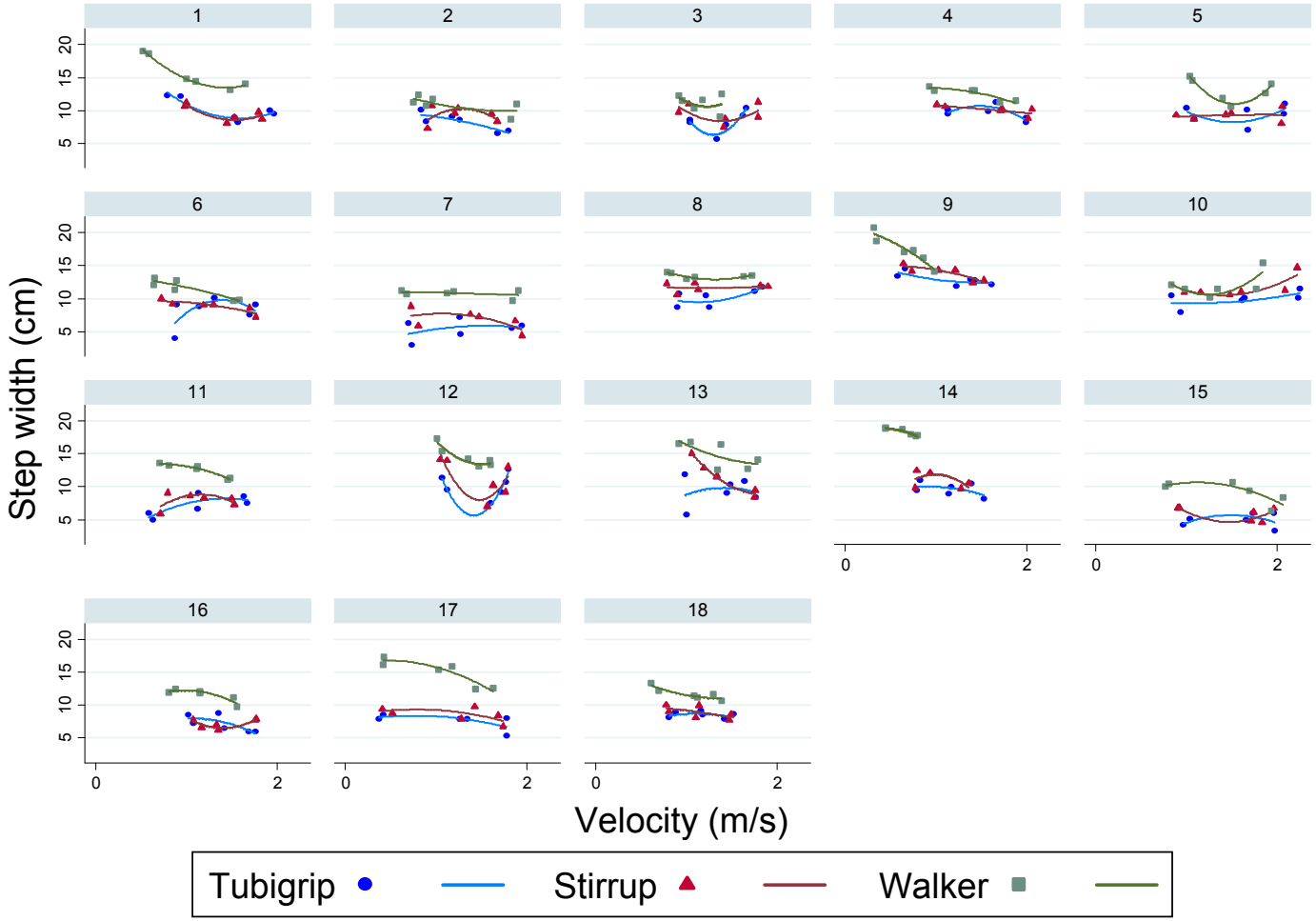


Figure 32: Two-way scatter plot with quadratic prediction plot of step width (cm) and walking velocity (m/s) (n=18 observations) by participant (n=18). There are 6 data points representing the 6 walking tests for each ankle support by participant. The quadratic prediction curve is plotted to fit these data points for each ankle support. The relationship between single support symmetry and velocity varies between participants and the support used.

Table 18: Multilevel modelling results for step width (cm). Level 1 was the repeated measurement occasions (n=18) and level 2 was the participant (n=18).

Variable	**Model 0**[#]				**Model 1**[##]				**Model 2**[###]				**Model 3**[####]			
	β	95% CI		*P* value	β	95% CI		*P* value	β	95% CI		*P* value	β	95% CI		*P* value
Fixed effects																
Velocity	.	.	.	.	-1.14	-1.58	-0.70	<0.001	-1.29	-2.14	-0.44	0.003	-5.10	-7.94	-2.26	<0.001
Velocity^2	.	.	.	.									1.48	0.42	2.54	0.01
Stirrup[*]	0.92	0.50	1.35	<0.001	0.91	0.50	1.31	<0.001	0.88	0.50	1.25	<0.001	0.90	0.53	1.27	<0.001
Walker[*]	4.44	4.01	4.86	<0.001	4.22	3.80	4.64	<0.001	4.09	3.70	4.48	<0.001	4.09	3.71	4.48	<0.001
Constant (β_0)	8.70	7.80	9.60	<0.001	10.24	9.18	11.29	<0.001	10.38	8.81	11.96	<0.001	12.62	10.43	14.80	<0.001
Random effects	Estimate				Estimate				Estimate				Estimate			
Slope SD (velocity)	.	.	.		.	.	.		1.60	1.04	2.46		1.36	0.84	2.21	
Intercept SD	1.84	1.31	2.59		1.78	1.27	2.50		3.11	2.14	4.52		2.89	1.97	4.25	
Level 1 residuals SD	1.59	1.47	1.72		1.53	1.41	1.66		1.40	1.29	1.52		1.39	1.28	1.51	
Likelihood-ratio test[a]					χ^2=24.86	*P* <0.001			χ^2=31.91	*P* <0.001			χ^2=9.92	*P*=0.009		

CI: Confidence Interval; SD: Standard Deviation.
[*]Compared with Tubigrip (reference category).
[#] Random intercepts with fixed treatment effect at level 1.
[##] Added covariate (velocity) at Level 1.
[###] Random intercepts and slopes (as a function of velocity).
[####] Random intercepts and curves (as a function of velocity^2).
[a] vs. previous model.
$\beta < 0.0$ = step width narrower than reference category (Tubigrip), $\beta > 0.0$ = step width wider than reference category (Tubigrip).

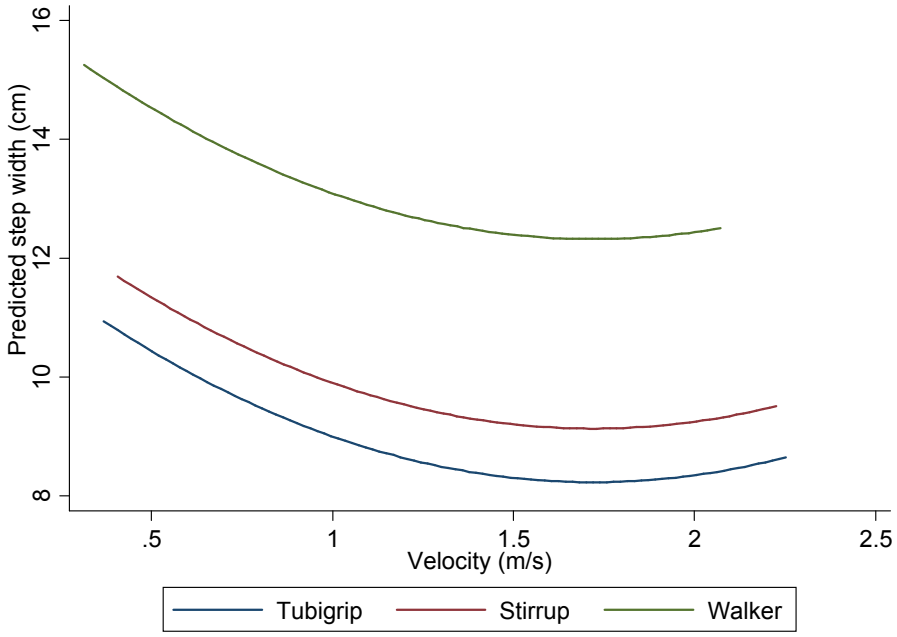


Figure 33: The final model predicted step width (cm) by walking velocity (m/s) in each type of ankle support. There was a statistically significant wider step width in the walker boot (P<0.001), and stirrup brace (P<0.001) compared with Tubigrip.

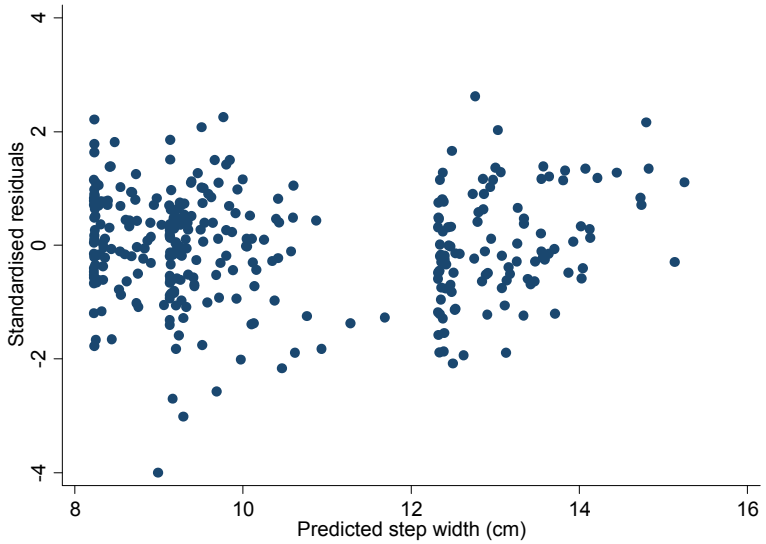


Figure 34: Scatterplot of standardised residuals and predicted values (Level 1) (n=324).

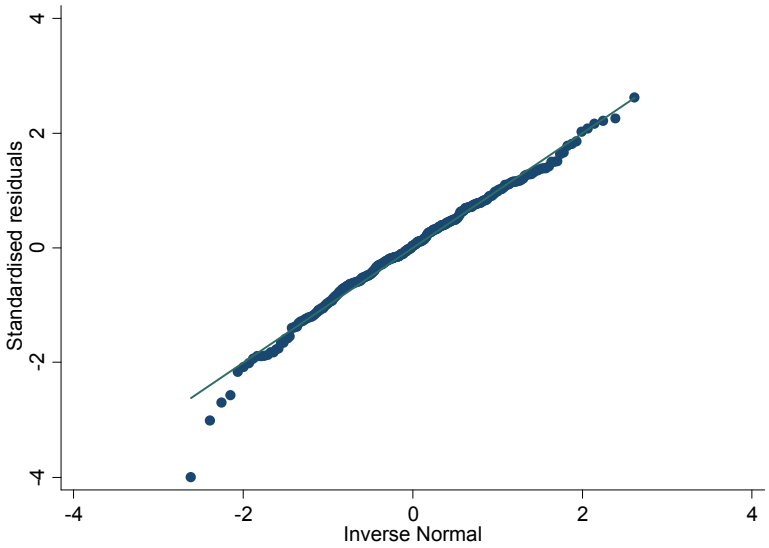


Figure 35: Q-Q plot of standardised residuals against normal distribution (level1) (n=324).

4.5 Discussion

4.5.1 Summary of findings

Temporo-spatial gait outcomes were speed-dependent, the effects of ankle supports on gait were therefore estimated accounting for walking velocity in multilevel models. The walker boot resulted in gait abnormalities compared with Tubigrip in non-pathological gait. There was greater asymmetry in step length in the walker boot by a 10% margin when compared to Tubigrip. Single support time was also more asymmetric in the walker boot than in Tubigrip, however this difference was smaller (5%). Step width was wider in the walker boot than in Tubigrip by a substantial 4cm margin. The only difference between the stirrup brace and Tubigrip was a wider step width but this was a small difference of 0.9cm. Compared to Tubigrip, walking velocity was slower in the walker boot, but similar in the stirrup brace.

4.5.2 Comparison with previous studies

Previous studies of walker boot use on walking gait have primarily examined within-foot plantar pressure changes in healthy adults. North et al.[171] found an increase in the proportion of weight bearing in healthy adults within the posterior part of the foot progressively from normal walking to walker boot use, 9kg partial weight-bearing and finally 27kg partial weight bearing with crutches. Weight bearing in the boot and partial weight bearing resulted in more even loading across the foot compared with normal walking where the heel and forefoot bear all of the weight at heel strike and toe-off respectively. In accordance with these findings, DiLiberto et al.[48] found a 37% reduction in peak forefoot pressure in a walker boot when compared with normal shoes in 26 healthy adults. These studies have indicated the within-foot changes associated with walker boot use, which is useful for conditions where high peak plantar pressures are critical, such as in patient with diabetic foot ulcers.[26] However, these studies have not contributed to the understanding of the effects of the walker boot on temporo-spatial gait outcomes.

The wider base of support in the walker boot may have been a result of leg length discrepancy induced by the height of the sole profile. The leg length discrepancy of approximately 4cm induced by the walker boot may be a crucial factor in the range of temporo-spatial outcomes found in this study. Mieras et al. found peak plantar pressures in the contralateral limb to the walker boot were normalised by correcting the leg length discrepancy in healthy adults.[150]

The effects of an ankle stirrup brace were not different from Tubigrip. This was unexpected given previous studies that have indicated that the stirrup braces restrict ankle range of motion.[55] The findings of this study imply that in non-pathological gait the limitations in ankle range of motion experienced with stirrup braces are not sufficient to induce gait asymmetry or change walking velocity compared to Tubigrip. The effects of ankle stirrup braces on gait in clinical populations are limited but have been found to increase step length in the paretic limb of people with hemiplegia, by a small but statistically significant amount.[25] Generalisation from central nervous system disorders to musculoskeletal injuries is problematic due to the fundamental differences in the pathophysiology that is responsible for the physical impairments in the affected lower limb. Additional investigation in clinical populations is required to establish if stirrup braces have a role in facilitating recovery of gait symmetry after severe ankle injury.

4.5.3 Reliability of gait measurements

The excellent reliability of the measures of walking velocity at each test speed (slow, preferred and fast) indicated that participants can walk at a similar velocity in two tests at the same test speed in each ankle support.

4.5.4 Novel application of multilevel modelling

The use of multilevel modelling in this study to account for the effects of walking velocity, when estimating the effects of ankle supports, deals with the analytical challenge of analysing speed-dependent gait variables. The use of models that allow for participant level intercepts, slopes and

in some cases curves, appeared to be validated by the observation of the plots for each participant, as it could be seen the regression lines were often neither parallel nor linear in nature.

4.5.5 Limitations

A limitation in the generalisability of findings of this study is that a single design of walker boot and stirrup brace were tested. Although broadly similar in key design features to other stirrup braces and walker boots on the market, there is a need to verify whether these findings are applicable to a wider range of designs. The profile of the walker boot sole may be influential in the gait characteristics produced. The importance of design variation is also highlighted by a study of 10 different designs of ankle braces that showed different effects on range of motion, depending on their construction.[55]

No large order-effects were detected in sensitivity analyses. This may not be a consistent finding in clinical populations, so was an important factor to consider in the related clinical study in Chapter 5.

4.6 Conclusion

Walker boots induced step length and single support time asymmetry and widened step width compared with Tubigrip in non-pathological gait. Ankle stirrup brace use did not differ from Tubigrip. Multilevel modelling is a flexible analytical option to account for the effects of walking velocity when estimating the effects of ankle supports on speed-dependent gait variables. Clinical research is required to directly compare the effects of these different types of ankle supports in patients after severe ankle injury to inform clinical decision making.

Chapter 5

5 The effect of ankle supports on walking gait and pain in the rehabilitation of walking after open reduction and internal fixation (ORIF) surgery for ankle fracture in adults: a randomised cross-over study.

The ankle supports tested in Chapter 4 are all used in clinical practice after open reduction and internal fixation (ORIF) surgery for ankle fracture. The main aim of this chapter was to determine which type of ankle support optimally reduces walking gait asymmetry and pain. The experimental and analytical methods developed in Chapter 4 were utilised. Clinical and research implications of the study findings are discussed and comparisons with the findings from Chapter 4 are included.

5.1 Background

In developed countries, unstable or displaced ankle fractures are managed with ORIF surgery using the universally accepted AO principles.[200] Ankle ORIF surgery is typically followed by a period of limited weight bearing and ankle immobilisation in a below-knee or removable cast for approximately 6 weeks (Chapter 3). After the fracture has united sufficiently, the focus of recovery shifts from protection of the injured joint to the rehabilitation of a normal gait pattern and return to function.[134] At 6 weeks after surgery, a removable ankle support is often used to aid the transition from ankle immobilisation and limited weight bearing towards the goal of unsupported full weight bearing ankle function.[50] Ankle supports are usually worn for the first few weeks of unrestricted weight bearing and gradually weaned as rehabilitation progresses.

5.1.1 Types of ankle supports used in rehabilitation of walking after ankle ORIF surgery

An informal survey of trauma staff at several NHS trusts and a systematic review of clinical trials of postoperative ankle fracture rehabilitation (Chapter 3) identified 3 common types of ankle support used in clinical practice. Patients may be advised to use Tubigrip, an ankle stirrup brace or a removable walking boot. The design and ankle motion limitations in each of these supports are discussed in sections 1.6, p.11 and 4.3.6, p.80. Although there is consistency in the time point in the recovery process when supports are provided, the type of support is determined by clinician preference and availability of supports. There are little data on how different types of support influence walking after removal of the cast. For example, it is unclear whether the degree of ankle movement restriction in an ankle support is associated with the extent and speed of recovery of mobility and a normal gait pattern.

5.1.2 Gait asymmetry after ankle ORIF

Patients starting to bear weight through their injured limb often present clinically with an asymmetrical gait pattern with a shortened stance phase on the injured limb. Asymmetry in gait can be a result of one or several impairments. Patients may have:

- Pain on weight bearing.[125]
- Limited joint range of motion due to stiffness.[123]
- Deficits in muscle strength.[213]
- Disorders of proprioception and balance.[167]
- Lack of confidence or fear of use of the limb.[57]

A limitation in ankle joint range of motion due to stiffness or pain decelerates the tibia on the talus during stance phase and limits progression of movement forward over the ankle.[178] The purpose of restoring gait symmetry after ankle ORIF surgery is to achieve efficient ambulation and normalise loading between the lower limbs, restoring motor control and balance. Therefore it is clinically important to determine which ankle support optimally improves gait symmetry.

Gait analysis investigations involving ankle fracture patients are limited to a few long-term outcome studies and none have studied the effects of different ankle supports. A retrospective study of 40 adult ankle fracture patients showed pressure across the foot to be asymmetrical between injured and non-injured limbs at 12-36 months.[9] In 18 adult participants one year after ankle fracture, reductions in talocrural joint range in the injured ankle compared with age and gender matched controls have been observed during gait analysis.[257] A gait analysis study of 20 adults 12 months after surgical fixation for ankle fracture reported significant stride length asymmetry between limbs and also reduced velocity compared with healthy controls.[132] These studies indicate that gait abnormities can persist in the longer term (one year).

In addition to investigating the effects of ankle supports on gait outcomes, it was hypothesised that there would be reduced ankle muscle strength in the injured ankle compared to the uninjured ankle and that this would be associated with gait abnormalities. Therefore, the feasibility of isometric ankle muscle strength measurements of injured and non-injured ankles for dorsiflexion and plantar flexion was also explored in this study. Muscle strength deficits in the injured limb after immobilisation for ankle fracture have previously been demonstrated using isokinetic dynamometry,[224] but not by portable hand-held dynamometers that are more practical in a clinical environment.

Research question

Does the use of ankle supports designed to limit ankle motion (ankle stirrup brace and walker boot), compared with Tubigrip, reduce gait asymmetry during the immediate period of unrestricted weight bearing after ankle ORIF surgery in adults?

5.2 Objectives

Primary Objective

- To determine the effects of ankle supports on gait characteristics during the immediate period of unrestricted weight bearing 6 weeks after ankle ORIF surgery in adults.

Secondary Objectives

- To assess the magnitude of temporo-spatial gait asymmetry 6 weeks after ankle ORIF surgery.
- To establish the reliability of gait measurements in different types of ankle support.
- To apply analytical procedures developed in Chapter 4 to estimate the effects of ankle supports on gait asymmetry.
- To explore whether the type of ankle support affects self-reported pain and perceived difficulty during walking.
- To assess the reliability and magnitude of ankle muscle strength asymmetry after 6 weeks of limited weight bearing after ankle ORIF surgery using hand-held dynamometry.
- To explore the relationship between gait characteristics and ankle pain, muscle strength and range of motion.

5.3 Methods

5.3.1 Study overview and design

The design of this study is similar to the previous chapter, as described in section 4.3, p.78. In addition to the cross-over design considerations outlined, a washout period was not deemed appropriate in this clinical study, at 6 weeks after ankle ORIF surgery. A washout period would have potentially increased bias in the assessments of gait as physical impairments of the ankle are unlikely to remain stable over the first few days of unrestricted weight bearing as the joint is mobilised.[36] In addition, the order effects further warranted analysis in the clinical situation as participants may experience more or less pain as the volume of walking increases as testing progresses. Participants were required to indicate that pain was back to pre-testing levels prior to

measurements in each ankle support. An assessment of perceived pain and difficulty by the order of testing was also conducted to investigate if they were indicators of an order-effect not eliminated with the experimental design.

5.3.2 Setting

The study took place from June 2012 to March 2013 in the orthopaedic trauma unit at the John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford, UK. The trauma unit is designated a Major Trauma Centre serving the Thames Valley region of the south of England.

5.3.3 Study Participants

Screening and recruitment

Participants were identified for screening by daily review of admission lists and consent was obtained for participation while they were inpatients or attending orthopaedic trauma clinics before or after surgery. A short eligibility check was made using a screening form based on the eligibility criteria (Appendix 8). Potential participants were given the opportunity to discuss the study with a member of the trauma research team and received a patient information sheet (Appendix 9) so they could consider taking part in the study and ask questions. Patients had at least 24 hours from the initial approach to consider taking part. Participants gave written informed consent (Appendix 10) prior to study registration and randomisation.

5.3.4 Eligibility criteria

Eligible participants were adults aged 18 years or over who had undergone ORIF surgery for an ankle fracture and who met the eligibility criteria below. Eligibility was assessed in two stages; at initial approach and then on the day of the planned study assessments immediately after the routine 6 week postoperative clinical review with the orthopaedic trauma surgical team (Appendix 11).

Inclusion Criteria

- Isolated ankle fracture
- Able to give informed consent
- Able to understand and respond appropriately to verbal instructions

On the day of gait analysis measurements:

- Permitted to remove ankle immobilising device for at least short time periods
- Allowed to fully weight bear as tolerated
- Able to walk a minimum of 10m since surgery

Exclusion Criteria

- Weber C type ankle fractures (requiring a screw across the distal tibiofibular joint, resulting in altered joint mechanics[242])
- Unable to walk outdoors unaided prior to fracture (as an indicator of baseline fitness required to test walking)
- Severe mental health disorder
- Dementia diagnosis (documented in medical records)
- Neurological disorder diagnosis (as this may limit symmetry of gait)
- Any previous severe lower limb fracture (as this may limit symmetry of gait and interpretation of the study)

On day of gait analysis measurements:

- Open wounds below the knee of the injured limb (which could affect application of the supports)
- Systemically unfit to undergo testing (e.g. nausea)
- Unable to safely walk without physical support from another person
- Uncontrolled respiratory disorder
- Uncontrolled epilepsy
- Cardiovascular instability (e.g. uncontrolled arrhythmias, syncope)

5.3.5 Interventions

The three ankle supports were Tubigrip, a stirrup brace and a walker boot, as described in sections 1.6, p.11 and 4.3.6, p.80. The supports were applied according to manufacturer guidelines by the lead investigator (an experienced musculoskeletal physiotherapist).

Following assessments the participants were able to select their preferred support and this was recorded as an outcome. The only circumstance where this was not the case was when the orthopaedic surgeon or lead investigator identified clinical reasons necessitating issue of a specific support only. Apart from the single session of gait assessments, the remainder of care was unaltered.

5.3.6 Overview of study procedures

The study procedures are outlined here prior to discussing the rationale and further detail below. After consent, participants underwent baseline assessments. The participant was then allowed a period of re-familiarisation to weight bearing gait under close supervision to ensure they were able to walk and bear at least some weight on the injured limb. Randomisation then took place, followed by gait analysis in each ankle support (Figure 36). The assessments were conducted approximately 1-2 hours after cast removal, for two main reasons 1) participants had not yet had the opportunity to start unrestricted weight bearing gait and 2) this is when assessment of weight bearing and the issuing of ankle supports usually occurs in clinical practice.

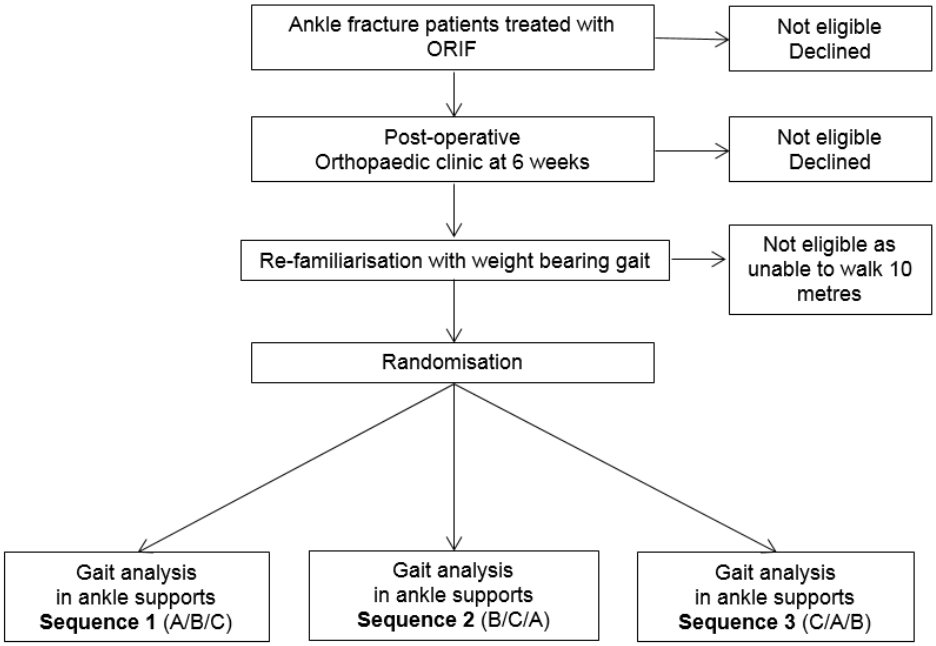


Figure 36: Overview of the stages of the study procedures.

5.3.7 Baseline assessments

A range of baseline data were obtained on the day of the gait measurements to describe the population of patients in the study (Appendix 12).[2] Data were collected on important participant demographics, medical history, injury characteristics and current signs and symptoms.

The baseline data collected were:

- Age (yrs) and gender were recorded to describe participant demographics.
- Charlson co-morbidity index (from 0, for no co-morbidity, higher scores indicating more severe disease, with a maximum of 29).[28] A measure of co-morbidity was included to give an indication as the severity of any adverse health states in the study population as co-morbidities could influence gait performance.[205]
- Injury characteristics (date of injury and surgery, Weber classification,[75] open/closed, number of malleoli injured).
- Questions were asked relating to balance since surgery as an indicator of current mobility performance prior to assessments of gait, including:
    - Walking aid used

    - Frequency of sensation of losing balance
    - Frequency of near falling episodes
    - Number of falls
- Method of ankle splinting since surgery (below-knee bivalved removable cast/non-removable cast).
- Questionnaires completed by the participants:
    - Lower Extremity Functional Scale questionnaire ([LEFS], 0-80, higher scores indicting higher lower limb function).[13, 127] Measurement properties for the LEFS are shown in Table 4, p.22.
    - Pain at rest in non-weight bearing visual analogue scale ([VAS]). The VAS was on a 10cm horizontal line and was measured as 0-100, 0=no pain and 100=worst pain imaginable. Pain VAS scores were used as a baseline descriptor and were also used as a reference during the data collection to monitor pain levels.
    - Health Utilities Index mark 3 (HUI3) questionnaire was completed by the participant to give an indicator of health state for the study participants. From the responses, a single-attribute health-related quality of life score was calculated for vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain, with 1.0 representing full health and 0 being the worst state.[93]

Baseline clinical assessment of ankle range of motion

Clinical assessments of ankle range of motion (active dorsiflexion and plantar flexion) were conducted with a goniometer.[32, 197] All participants were measured by the same assessor (the lead investigator) as studies have demonstrated moderate to excellent intra-rater reliability.[140] Participants were positioned on a plinth in long sitting, reclined to about 45˚. A support was placed under the upper part of the lower legs to flex the knee to 20-30˚, to reduce tension in the triceps surae muscle complex and to lift the heels off the surface of the plinth. Ankle range of motion was measured in degrees from the anatomical neutral position, otherwise known as plantar grade (Figure 37). Participants with insufficient dorsiflexion to move the ankle beyond neutral

were recorded as having a negative score. A goniometer was placed on the lateral aspect of the ankle; the axis of the goniometer was placed approximately 1.5cm inferior to the lateral malleolus; the stationary arm was placed parallel to the longitudinal axis of the fibula, lining up with the fibula head; the moveable arm was placed parallel to the longitudinal axis of the 5th metatarsal (Figure 38).

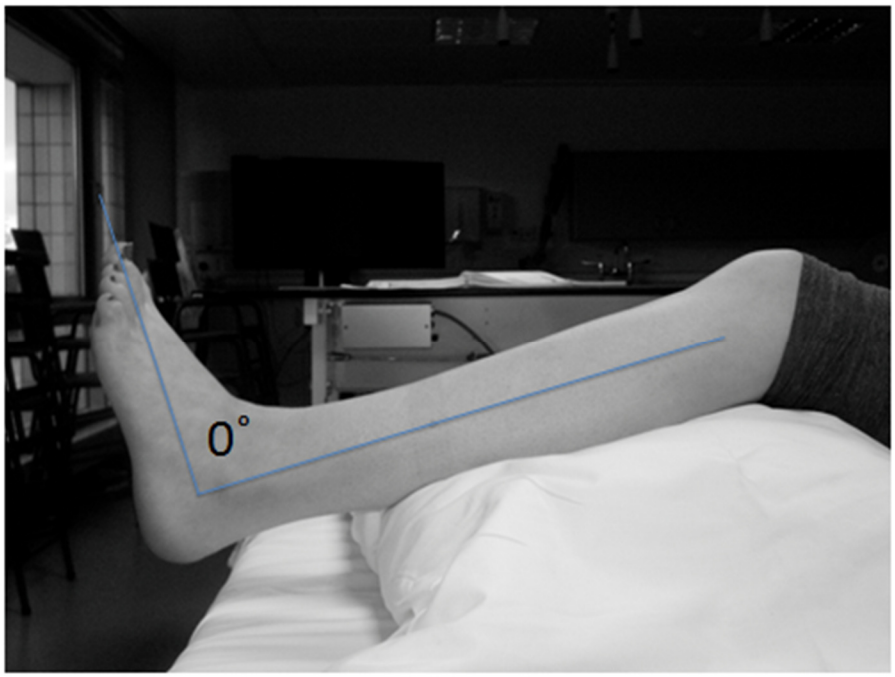


Figure 37: Lateral aspect of the lower leg with a line indicating plantargrade at the ankle.

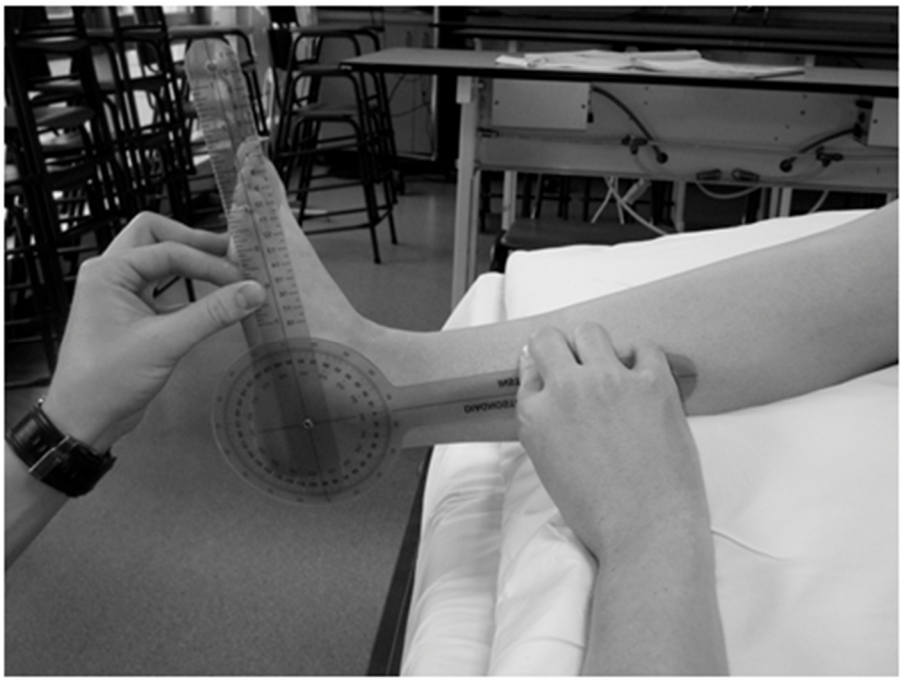


Figure 38: Positioning of the goniometer for the assessment of ankle dorsiflexion and plantar flexion range of motion.

5.3.8 Randomisation

Latin square randomisation and allocation concealment were conducted as per Chapter 4.

5.3.9 Blinding

It was not practical to blind the treatments as the support was applied by both the investigator and participant.

5.3.10 Re-familiarisation with weight bearing gait

Prior to measurements of gait, the participant was given gait re-education advice via verbal instruction and demonstration, reflecting clinical practice. This involved a preliminary trial of walking back and forth over the electronic walkway and was conducted at the patient's preferred walking speed. The purpose of the initial mobility assessment was to optimise safety and re-familiarise the participant to weight bearing gait technique. This also acclimatised the patient to the test conditions and determined whether they could walk the length of testing walkway and

transfer enough weight onto the limb to activate the walkway sensors. No further instructions were given upon the start of testing. Tubigrip was in situ throughout the initial mobility assessment. Walking aids were used if the subject was unable to mobilise safely without. The aid used was the minimum support required to enable safe mobilisation and was agreed by participant and investigator. The same walking aid was used in all subsequent testing, as variance of aids could be a significant confounder. For example, rollator use has been shown to prevent the identification of impairments that present when no aids are used.[208] If the participant was unable to complete the initial mobility assessment, the reason was documented.

5.3.11 Gait analysis procedures on the electronic walkway

The gait testing procedures were as per Chapter 4 (see section 4.3.16, p.84) with the exception that the testing was performed in a physiotherapy gymnasium. All test walks were closely supervised by the lead investigator, who walked in close proximity (approximately arms-length) but not touching. The investigator was positioned to the side and slightly behind the participant so as not to distract them or influence gait velocity during the test.

5.3.12 Primary outcome

Step length and single support time asymmetry at 6 weeks after surgery for ankle fracture

These 2 interdependent metrics are key indicators of asymmetry after ankle injury as discussed in detail in section 2.3.4, p.28.

5.3.13 Secondary outcome measures

Step width (cm)

Step width is the medial-lateral distance between the heels in double support.[114]

Walking velocity (m/s)

Walking velocity at slow, preferred and fast walking speeds.

As per Chapter 4, step length, single support time, step width and walking velocity were measured using the GAITRite® electronic walkway (CIR Symptoms, Havertown, PA, USA).

Self-reported pain and perceived difficulty walking ([VAS], 0-100)[264])

A VAS was used to quantify pain and perceived difficulty walking due to the simple and quick nature of this assessment.[77] Immediately after each ankle support was tested, participants were asked to make a mark on 100mm horizontal lines to indicate pain experienced and perceived difficulty while walking. The lines were marked as 'no pain' or 'no difficulty' and scored as zero at one end and 'worst pain possible' or 'impossible', scored as 100, at the other.

During the periods in between walking in each ankle support, the participant was also asked to indicate if the pain levels at rest in non-weight bearing were less than or equal to that prior to starting the gait analysis assessments. This was to minimise the risk of bias from a carry-over or order effect.

Peak isometric ankle dorsiflexion and plantar flexion muscle force (kg)

Strength tests were not conducted prior to gait assessments as the muscle fatigue and potential exacerbation of pain may have confounded the assessment of the effects of ankle supports on gait. Muscle strength was assessed using a hand-held dynamometer (Lafayette Manual Muscle Test System, Lafayette Instrument, IN, USA). The hand-held dynamometer resolution was 0.2kg. Hand-held dynamometry is an instrumented measure of peak force produced by a muscle. The 'gold standard' for quantifiable measures of muscle strength is isokinetic dynamometry.[221] Validation and reliability of hand-held dynamometry compared with isokinetic dynamometry was analysed in a systematic review that included 19 studies comparing the 2 methods.[221] There was overall moderate to good reliability and validity of hand-held dynamometer use in a range of muscle groups in clinical and healthy populations. Hand-held dynamometers are relatively inexpensive, unlike isokinetic dynamometers ($1,000 vs $40,000) and are highly portable. They

also take approximately the same time to operate as manual muscle testing, a routine clinical examination of muscle strength that is highly subjective and inaccurate.[221]

The participant was positioned in long sitting with the lower leg stabilised by the assessor. The dynamometer was placed on the foot (Figure 39) with a towel between the device and the dynamometer to protect the skin if required. The ankle was positioned in approximately 10° plantar flexion to accommodate the reduction in range of ankle dorsiflexion. The applicator attached to the device contours to the foot and is foam padded to aid comfort. Participants were asked to work up to a maximal contraction over a maximum of 5 seconds and without pushing into pain. The device was held steady by the investigator.[256] The participant was asked to maintain the isometric contraction, sometimes described as a 'make test' (as opposed to a 'break test' whereby the assessor applies force sufficient to overcome the participant's strength). Patients were measured 3 times and had 10 seconds rest between attempts. The peak force (kg) was recorded. A similar technique of hand-held dynamometry for ankle muscle strength has been shown to have good reliability in younger and older healthy adults.[220] One assessor undertook all assessments, overcoming the issues of poor inter-rater reliability with hand-held dynamometry of the ankle.[145]

i.

ii.

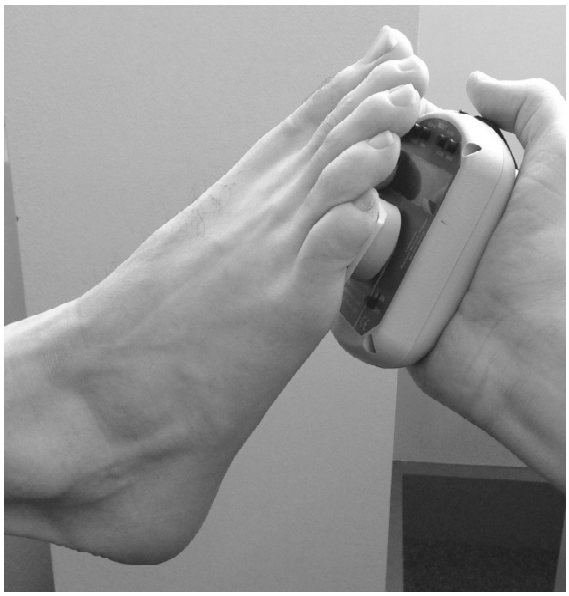


Figure 39: Lateral view of the positioning of the hand held dynamometer for i. dorsiflexion and ii. plantar flexion.

5.3.14 Adverse events

Some discomfort in the leg in the first 24 hours after testing was expected, as with normal physiotherapy. However, persisting and significant pain was considered an adverse event. Participants were asked to return an adverse event report form (Appendix 13) in a freepost envelope if pain after the assessments persisted longer than 48 hours or if pain severity was excessive, giving the example of significantly impaired sleep.

5.3.15 Sample size

Published estimates to inform the clinically important difference in temporo-spatial gait characteristics and effect size of ankle support use on the primary outcomes were not available. The effect size assumption was developed based on detecting a moderate to large effect size. The ankle supports had comparable purchase cost (£20 or less, excluding VAT) so differences in interventions would need to be moderate to large for the experiment to have an impact on clinical practice. Sample size was calculated using G*Power (v.3.1.3)[59] with a significance level (α) of 0.05, 90% power and effect size of *f* 0.4 (equivalent to Cohen's *d* standardised effect size of 0.8), assuming normal distribution. The sample size is based on variance explained in regression. As this was a cross-over study, the participants were their own controls, increasing the efficiency of the experimental design. A minimum of 15 participants were required to complete the series of gait assessments. It was anticipated that up to 20% of participants randomised would not complete the assessments in each support; therefore the target sample size for randomisation was 18.

5.3.16 Descriptive statistics

See section 4.3.18, p.85 for details on baseline data analysis and the computer software used.

As per Chapter 4 gait data were collected by the GAITRite® system. Each walking test was viewed with GAITRite® software. All contact from walking aids was manually or automatically removed before being accepted to ensure there was no interference.

5.3.17 Reliability

The 2 gait assessments at each of the 3 test speeds were subjected to a single analysis of reliability as per section 4.3.19, p.86.

5.3.18 Walking velocity

Analysis of walking velocity was conducted as per section 4.3.20, p.86**.**

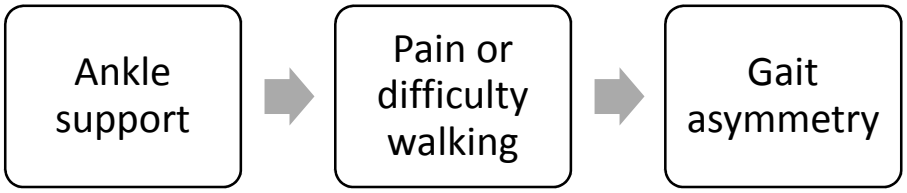
5.3.19 Analysis of primary endpoints

See Chapter 4 for a description of how step length, single support time symmetry indices and step width were analysed using multilevel modelling to improve estimates of the effects of ankle supports.

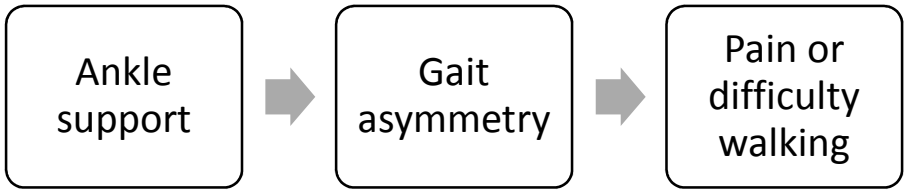
5.3.20 Pain and difficulty walking

Pain, difficulty walking and muscle strength outcomes were reported as medians, inter-quartile ranges and range as they were not normally distributed. Pain and difficulty walking in each ankle support were compared using Friedman's test. Pain and difficulty were also compared by the order of testing, to examine if there was a change over the 3 test periods. Post-test comparisons between different types of ankle support using the Wilcoxon matched-pairs signed-rank test was only conducted when the Friedman's test was statistically significant.

Pain and difficulty walking in each ankle support was not adjusted in the analysis of the effect of ankle supports on gait symmetry. Pain and difficulty walking were not considered to be valid confounder variables as they are on the causal pathway between the intervention (ankle supports) and the primary outcome (gait asymmetry), or are an outcome of changes in gait asymmetry (Figure 40). Intermediate variables that are theoretically on the causal pathway should not be adjusted for as this introduces bias into estimates of the effect of the intervention (exposure) on outcome.[146]



i.



ii.

Figure 40: Causal diagram where ankle support is the exposure, i. pain/difficulty walking in ankle support is the intermediate variable and gait asymmetry is the outcome, ii. gait asymmetry is the intermediate variable and pain/difficulty walking in ankle support is the outcome

5.3.21 Muscle strength

The reliability of the 3 repeated measures of ankle strength were analysed by intra-class correlation coefficients ($ICC_{1,1}$) from one-way analysis of variance (ANOVA), where all within-subject variability is treated as measurement error[79, 215]:

$$\text{ICC}\ (1,1) = \frac{\text{BMS} - \text{WMS}}{BMS + (k-1)WMS}$$

Where BMS is between-subject mean squares, WMS is within-subject mean squares and k is the number of measurements (in this instance 3).[195]

The mean of the 3 strength measurements was used for statistical comparisons between the injured and uninjured limbs. Strength between injured and uninjured ankles was compared using the Wilcoxon sign-rank test.

5.3.22 Correlation between gait velocity and asymmetry with ankle pain, range of motion and muscle strength asymmetry

An exploratory analysis was conducted to investigate the relationship between gait velocity at preferred walking speed and asymmetry with ankle pain, range of motion restrictions and muscle strength asymmetry. Muscle strength asymmetry was expressed as a symmetry index. An average of the 2 walk tests at preferred walking speed was selected to enable gait performance and physical impairment at the participants' natural speed. All of the repeated measures from all tests could not be used in this bivariate analysis of correlation that included non-normally distributed outcomes. Due to non-normal distributions, the correlation was analysed by Spearman's rank correlation coefficient.

5.3.23 Reporting

The study was reported based on recommendations from the CONSORT guidelines for randomised clinical trials.[155, 206]

5.3.24 Ethical approvals

This study was conducted according to Good Clinical Practice guidelines and approvals were obtained from the National Research Ethics Service South Central (Berkshire) (Ref: 12/SC/0146, Appendix 14) and the Research & Development department at Oxford University Hospitals NHS Trust (Appendix 15). Remuneration was not offered to participants. The risks involved with this study were expected to be within range of those in clinical practice and were low. Monitoring during the gait assessments, regular rest periods and the eligibility criteria for this study were designed to minimise risks and discomfort for participants.

5.4 Results

5.4.1 Participant characteristics

The flow of participants through the stages of the study is reported in a CONSORT diagram (Figure 41). Of the 105 patients screened for enrolment, 21 patients (20%) met the eligibility criteria. The main reason for not meeting the eligibility criteria were Weber C fracture classification or use of a syndesmosis screw (n=27). Eighteen participants were randomised and all completed gait analysis assessments in all 3 ankle supports and were included in the analysis. Three potential participants underwent initial mobility assessments but were not randomised because they were unable to tolerate weight bearing. Participants attended clinic at 6.2 (SD 0.7) weeks after surgery. Baseline characteristics of the randomised participants are shown in Table 19. Participants had an average age of 47 (SD 14) years and 10 were male and 8 were female. Of the domains assessed by the Health Utilities Index (HUI3), ambulation and pain had the worst scores.

Since surgery, 14 participants reported near falls, 11 of whom experienced multiple near falls. Three participants had experiences of at least one fall, but none were injurious. Prior to gait analysis, 1 participant had their ankle joint immobilised in a cast and 17 had removable forms of splinting to allow ankle exercises. Ankle range of motion was limited in the injured ankle compared with the uninjured side. All participants reported no change in ankle pain after 2 trial walks over the electronic walkway (20m in total) prior to randomisation.

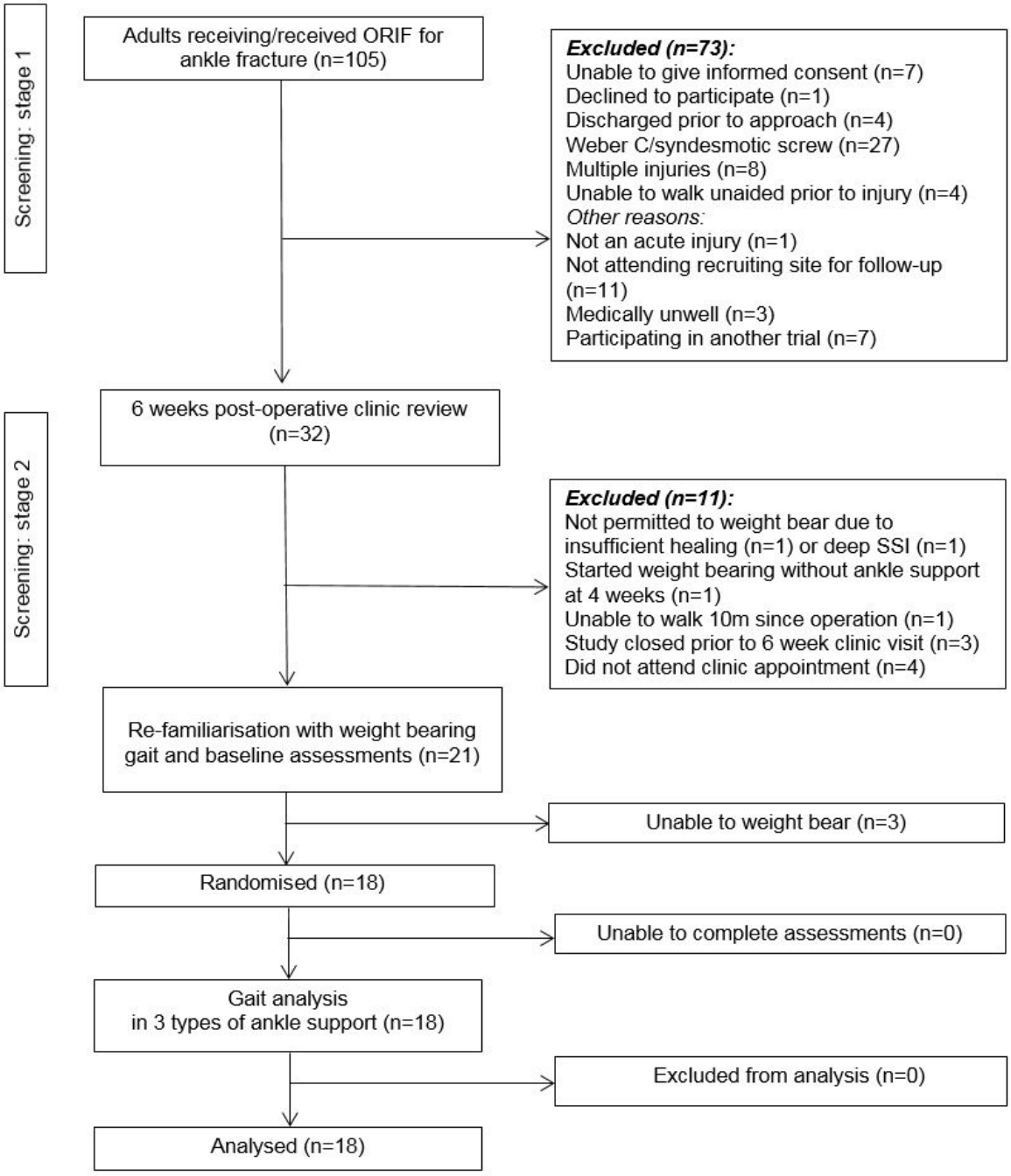


Figure 41: Flow chart of participants through the study.

Table 19: Baseline characteristics of participants (n=18).

Characteristics	
Age (yrs)	47 (SD 14, range 19-77)
Gender	
Male	10
Female	8
Body Mass Index (BMI)	27.5 (SD 4.3)
Charlson Comorbidity Index	0
HUI3 (Health Utility)	
Vision	0.94 (SD 0.11)
Hearing	0.98 (SD 0.05)
Speech	1.00 (SD 0)
Ambulation	0.62 (SD 0.27)
Dexterity	1.00 (SD 0)
Emotion	0.97 (SD 0.09)
Cognition	0.99 (SD 0.03)
Pain	0.88 (SD 0.15)
Lower Extremity Functional Scale (LEFS)	36 (SD 14.6)
Side of injury	
Left	7
Right	11
Weber classification	
A	1
B	17
Number of malleoli fractured	
Unimalleolar	4
Bimalleolar	5
Trimalleolar	9
Comminuted fracture	4
Open injury	1
Pain at rest (VAS, 0-100*)	7 (SD 11, range 0 to 47)
Walking aid used prior to testing	
Elbow crutches	15
Wheeled Zimmer frame	3

*0=no pain, 100=worst pain imaginable.
Data are mean (SD) or n unless otherwise stated.

Balance	
Losses of balance in last week	
Never	10
Often	6
Very often	2
Near miss for a fall since surgery	
None	4
Once	3
Less than once a week	8
More than once a week	3
Falls since surgery**	
None	15
One	1
Two	1
Three	1
Method of ankle splinting since surgery	
Bivalved removable cast	13
Non-removable cast	1
Walker boot	4
Range of movement(°)	
Ankle dorsiflexion	
Uninjured	12 (SD 5)
Injured	-2*** (SD 5)
Difference between sides	15 (SD 7)
Ankle plantar flexion	
Uninjured	53 (SD 8)
Injured	36 (SD 7)
Difference between sides	17 (SD 8)

**all were non-injurious
***degrees from reaching plantar grade
Data are mean (SD) or n unless otherwise stated.

5.4.2 Gait outcomes

The primary gait outcomes in each support at each walking test speed are shown in Table 20. Ten participants needed to use elbow crutches to ambulate and 8 participants did not require a walking aid.

Table 20: Gait outcomes in each ankle support and test condition (speeds slow, preferred and fast). Participants (n=18) were tested in 3 ankle supports at 3 different speeds.

	Tubigrip		**Stirrup**		**Walker**	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Velocity (m/s)						
Slow	0.42	(0.25)	0.39	(0.23)	0.40	(0.20)
Preferred	0.56	(0.34)	0.57	(0.31)	0.57	(0.30)
Fast	0.74	(0.36)	0.77	(0.38)	0.86	(0.37)
Step length symmetry index						
Slow	0.39	(0.25)	0.36	(0.26)	0.40	(0.25)
Preferred	0.37	(0.26)	0.36	(0.26)	0.37	(0.20)
Fast	0.30	(0.24)	0.31	(0.25)	0.29	(0.21)
Single support time symmetry index						
Slow	0.43	(0.22)	0.40	(0.24)	0.37	(0.20)
Preferred	0.42	(0.23)	0.36	(0.21)	0.38	(0.26)
Fast	0.35	(0.19)	0.34	(0.19)	0.26	(0.26)
Step width (cm)						
Slow	16.68	(3.62)	16.23	(3.72)	17.86	(4.14)
Preferred	16.45	(3.08)	16.19	(3.31)	17.62	(3.71)
Fast	15.97	(3.86)	15.61	(3.49)	16.92	(3.93)

5.4.3 Walking velocity

The reliability of the walking velocity in the 2 walking tests at each speed in each ankle support was excellent (Table 21).

Table 21: Intraclass correlation coefficients (ICC) and 95% confidence intervals (CI) for the two walks in each test condition. Participants (n=18) were tested in 3 ankle supports at 3 different speeds.

	Tubigrip		**Stirrup**		**Walker**	
	ICC	(95% CI)	ICC	(95% CI)	ICC	(95% CI)
Velocity (m/s)						
Slow	0.98	(0.96 to >0.99)	0.95	(0.91 to >0.99)	0.91	(0.83 to 0.99)
Preferred	0.98	(0.96 to >0.99)	0.97	(0.95 to >0.99)	0.96	(0.93 to >0.99)
Fast	0.84	(0.70 to 0.98)	0.99	(0.98 to >0.99)	0.97	(0.95 to >0.99)

Walking velocity at slow, preferred and fast speeds in all 3 supports are shown in Table 20 and Figure 42. Walking velocity was sequentially and statistically significantly faster at preferred (0.16 m/s, 95% CI 0.13 to 0.19, $P<0.001$) and fast (0.39 m/s, 95% CI 0.36 to 0.42, $P<0.001$) test speeds compared to the slow test. The variability in walking velocity increased in the fast speed tests compared with tests conducted at slow and preferred speeds (Table 20). Compared to Tubigrip, there was no evidence of an effect of stirrup brace use on walking velocity at any test speed (Table 22). Walking velocity was statistically significantly faster in the walker boot when compared with the Tubigrip but of a clinically unimportant difference across all test speeds of 0.04 m/s (95% CI 0.02 to 0.07, $P=0.021$).

A relationship between gait velocity and the other gait outcomes was evident, indicating these measures were speed-dependent. With increasing walking velocity, asymmetry between limbs lessened for step length (β=-0.23, 95% CI -0.28 to -0.18, $P<0.001$) and single support time (β=-0.23, 95% CI -0.29 to -0.18, $P<0.001$), and step width narrowed (β=-1.23cm, 95% CI -2.39 to -0.08, $P<0.036$).

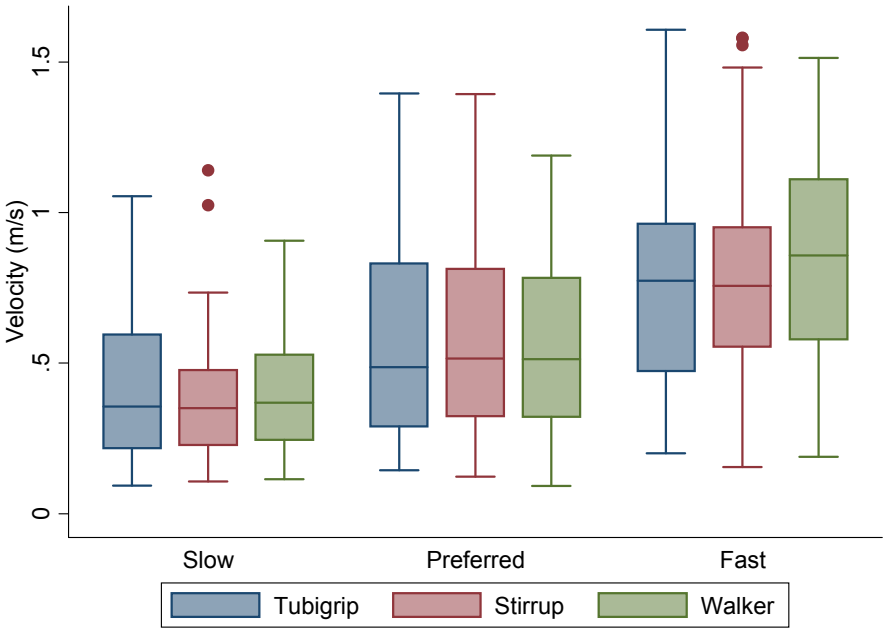


Figure 42: Box and whisker plot of velocity (m/s) of walking in each ankle support by test speed (n=18 participants with 18 observations each). The middle line of the box is the median, the top line is the upper quartile and the bottom line is the lower quartile. The error bars indicate the greatest and smallest values except outliers, which are represented by dots.

Table 22: Multilevel model for walking velocity in each ankle support compared with Tubigrip and test speed compared with slow speed (n=18).

Variable	β	95% CI		*P* value
Fixed effects				
Ankle support				
Tubigrip*	0.00			
Stirrup	-0.001	-0.03	0.03	0.96
Walker	0.04	0.01	0.07	0.021
Test speed				
Slow**	0.00			
Preferred	0.16	0.13	0.19	<0.001
Fast	0.39	0.36	0.42	<0.001
Constant (β_0)	0.39	0.26	0.52	<0.001
Random effects	Estimate			
Intercept SD	0.28	0.20	0.40	
Level 1 residuals SD	0.12	0.11	0.13	
Likelihood-ratio test[a]				

CI: Confidence Interval; SD: Standard Deviation.
*Ankle support reference category.
**Test speed reference category.
Random intercepts with fixed treatment and test speed effect at level 1.
$\beta < 0.0$ = velocity slower than reference category, $\beta > 0.0$ = velocity faster than reference category.

5.4.4 Step length asymmetry

Step length SI at each test speed by ankle support is shown in Figure 43. The step length SI by gait velocity by participant is shown in Figure 44. The high participant level variability in gait performance in each ankle support across the range of velocities necessitated the use of MLM to estimate the effect of the ankle supports.

Multilevel modelling: When compared with Tubigrip, there was no difference in step length asymmetry between limbs when walking in the walker boot or the stirrup brace (Table 23). There was an overall negative relationship between walking velocity and step length asymmetry. Step length asymmetry between limbs reduced 37% (-37%, 95% CI -54 to -19) for a 1m/s increase in velocity. Figure 45 shows limited differences in step length SI between the ankle supports and improvement in asymmetry as walking velocity increased. There was inaccuracy in the predicted step length symmetry indices for the fastest walking velocities. There were negative symmetry

indices at the highest walking velocities (Figure 45). These values are not valid scores as symmetry indices have a zero minimum. Therefore, although the model improved fit of the data compared to basic estimation methods there remained some uncertainty in the final model.

Random effect results: Allowing the intercept and slope for each participant to vary improved the fit of the model.

Sensitivity analyses: Walking aid use and the order in which the ankle support was tested were not statistically significant factors and had a negligible effect on the estimates when modelled in sensitivity analyses.

Model diagnostics: The diagnostic plots (Figure 46 and Figure 47) identified some limitations of the final model. Transformations did not substantially improve the model fit. Removing the observations of 1 participant who accounted for the largest residual did not alter the conclusions. Participant 9 (Figure 44) had asymmetry of more than 100% due to negative step length in the uninjured limb (failing to step the uninjured foot past the same point on the injured foot). Re-analysis with this participant's data removed did not alter the conclusions.

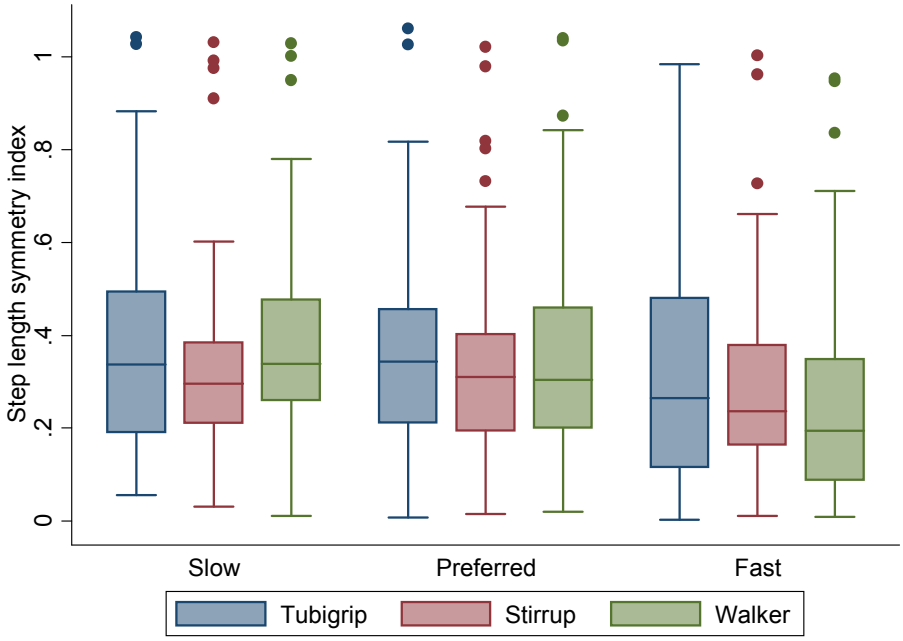


Figure 43: Box and whisker plot of step length symmetry index in each ankle support by test speed (n=18 participants with 18 observations each). The middle line of the box is the median, the top line is the upper quartile and the bottom line is the lower quartile. The error bars indicate the greatest and smallest values except outliers, which are represented by dots.

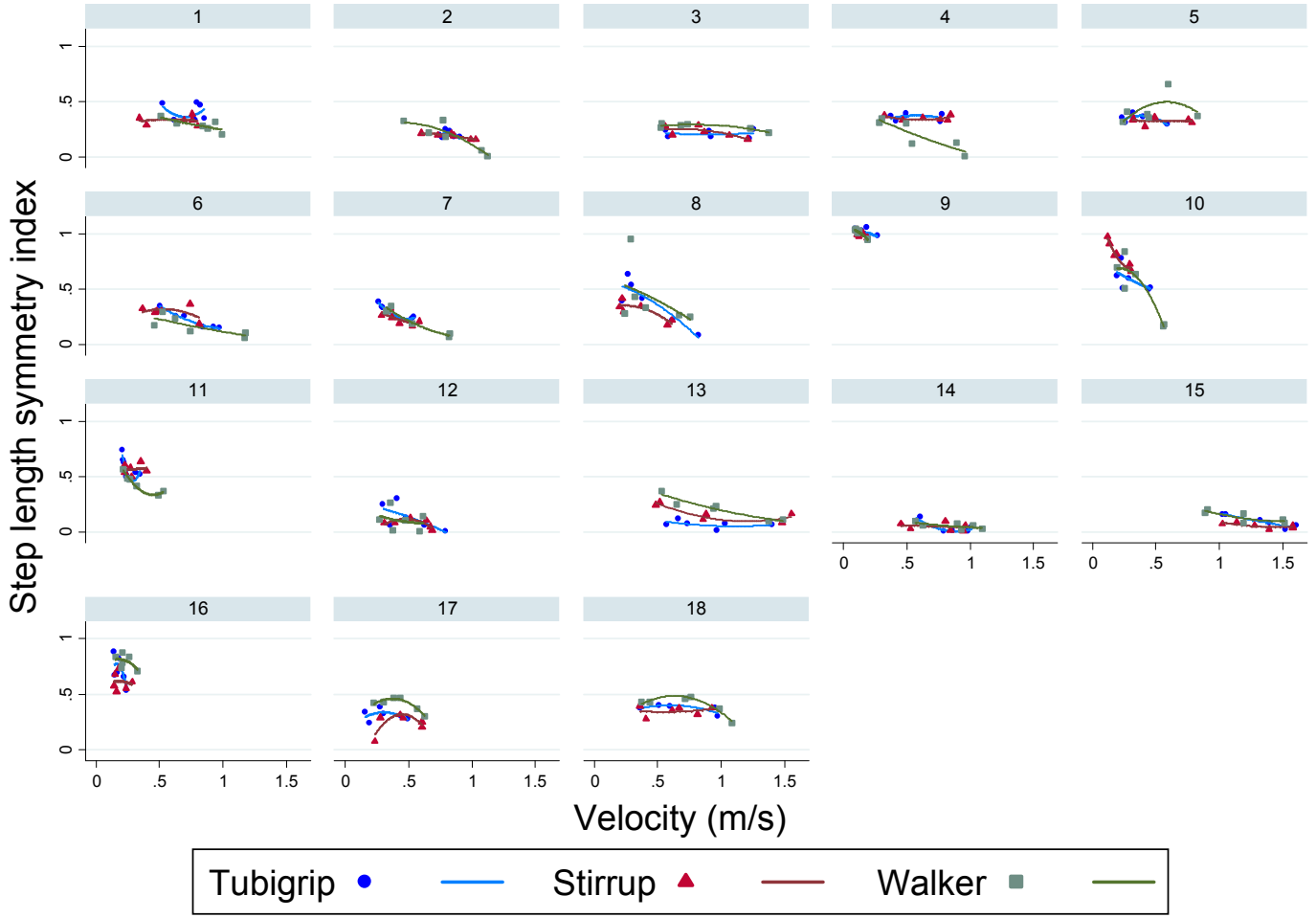


Figure 44: Two-way scatter plot with quadratic prediction plot of step length SI and walking velocity (m/s) (n=18 observations) by participant (n=18). There are 6 data points representing the 6 walking tests for each ankle support by participant. The quadratic prediction curve is plotted to fit these data points for each ankle support. The relationship between single support symmetry and velocity varies between participants and the support used.

Table 23: Multilevel modelling for step length symmetry index outcomes. Level 1 was the repeated measurement occasions (n=18) and level 2 was the participant (n=18).

Variable	**Model 0**[#]				**Model 1**[##]				**Model 2**[###]			
	β	95% CI		P value	β	95% CI		P value	β	95% CI		P value
Fixed effects												
Velocity	.	.	.	.	-0.23	-0.28	-0.18	<0.001	-0.37	-0.54	-0.19	<0.001
Velocity^2	.	.	.	.	.	.	.	.	.	.	.	.
Stirrup[*]	-0.01	-0.04	0.02	0.45	-0.01	-0.04	0.01	0.40	-0.02	-0.04	<0.01	0.07
Walker[*]	-0.01	-0.04	0.02	0.57	<0.01	-0.02	0.03	0.98	<0.01	-0.02	0.03	0.69
Constant (β_0)	0.35	0.25	0.46	<0.001	0.49	0.39	0.58	<0.001	0.51	0.38	0.63	<0.001
Random effects	Estimate				Estimate				Estimate			
Slope SD (velocity)	.	.	.		.	.	.		0.35	0.23	0.53	
Intercept SD	0.23	0.17	0.32		0.19	0.13	0.26		0.27	0.19	0.37	
Correlation (intercept and slope)	.	.	.		.	.	.		-0.91	-0.97	-0.72	
Level 1 residuals SD	0.10	0.10	0.11		0.09	0.09	0.10		0.08	0.08	0.09	
Likelihood-ratio test[a]					χ^2=66.99	*P*<0.001			χ^2=60.50	*P*<0.001		

CI: Confidence Interval; SD: Standard Deviation.
[*]Compared with Tubigrip (reference category).
[#] Random intercepts with fixed treatment effect at level 1.
[##] Added covariate (velocity) at Level 1.
[###] Random intercepts and slopes (as a function of velocity).
[a] vs. previous model.
β < 0.0 = step length SI better than reference category (Tubigrip), β > 0.0 = step length SI worse than reference category (Tubigrip).

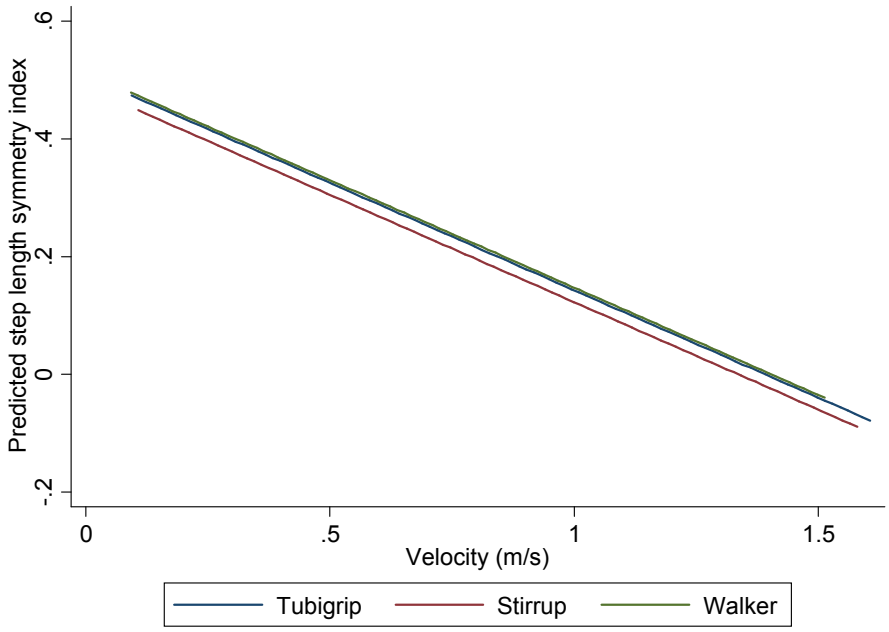


Figure 45: The final model predicted step length symmetry by walking velocity (m/s) in each type of ankle support. There was no statistically significant difference between the Tubigrip and the stirrup brace or walker boot.

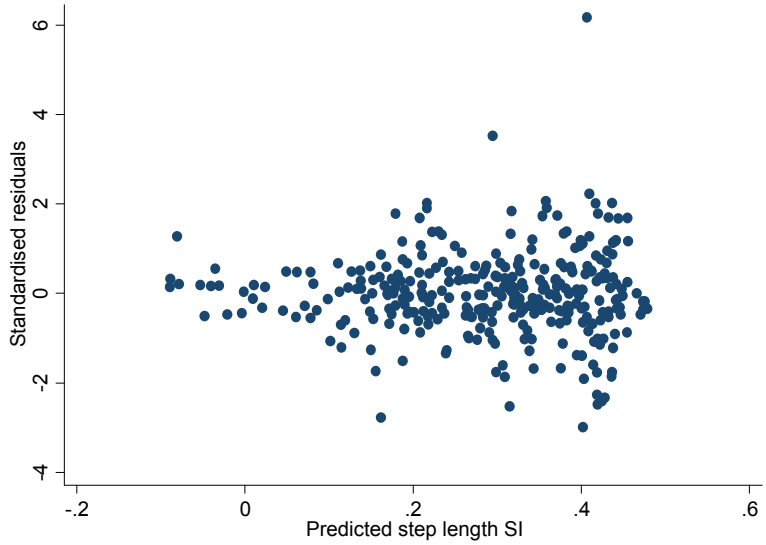


Figure 46: Scatterplot of standardised residuals and predicted values (Level 1) (n=324).

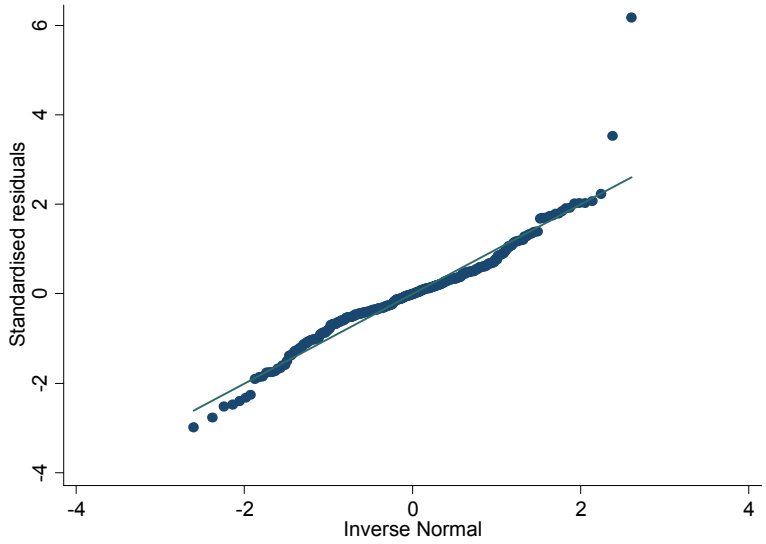


Figure 47: Q-Q plot of standardised residuals against normal distribution (level1) (n=324).

5.4.5 Single support time asymmetry

Single support time SI at each test speed by ankle support are shown in Figure 48. The single support time SI by gait velocity by participant is shown in Figure 49. The high participant level variability in gait performance in each ankle support across the range of velocities again highlighted the need for MLM to estimate the effect of the ankle supports.

Multilevel modelling: When compared with Tubigrip, asymmetry in single support time between limbs improved 3% in the stirrup brace (-3%, 95% CI -6 to 0, P=0.02) and 5% in the walker boot (-5%, 95% CI -7 to -2, P=0.001) (Table 24). There was an overall negative relationship between a participant's walking velocity and single support time SI. Single support time asymmetry between limbs reduced 27% (-27%, 95% CI -33 to -20, P<0.001) for a 1m/s increase in velocity. Figure 50 illustrates the improvement in single support asymmetry as walking velocity increased and also in the stirrup brace and walker boot compared to Tubigrip.

Random effect results: Allowing both the intercept and slope for each participant to vary improved the fit of the model.

Sensitivity analyses: Walking aid use was a statistically significant factor when added to the final model. Use of a walking aid was associated with 9% (95% CI 1 to 17, P=0.037) more asymmetry in single support time. Use of a walking aid changed the effect estimates for ankle supports by less than 1%. The order in which the ankle support was tested was not a statistically significant factor and had a negligible effect on the model estimates.

Model diagnostics: The diagnostic plots (Figure 51 and Figure 52) identified some limitations of the final model. Transformations did not substantially improve the model fit. Removing observations of level 1 residuals of more than 2 and less than -2 did not alter the estimates of the effect of the stirrup (-5%) and walker boot (-6%) to an important magnitude.

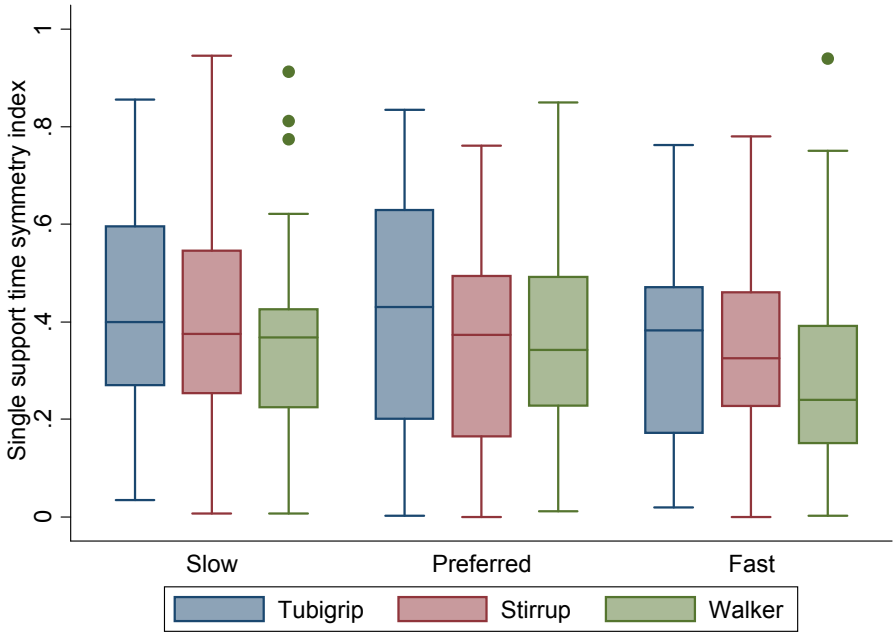


Figure 48: Box and whisker plot of single support time symmetry index in each ankle support by test speed (n=18 participants with 18 observations each). The middle line of the box is the median, the top line is the upper quartile and the bottom line is the lower quartile. The error bars indicate the greatest and smallest values except outliers, which are represented by dots.

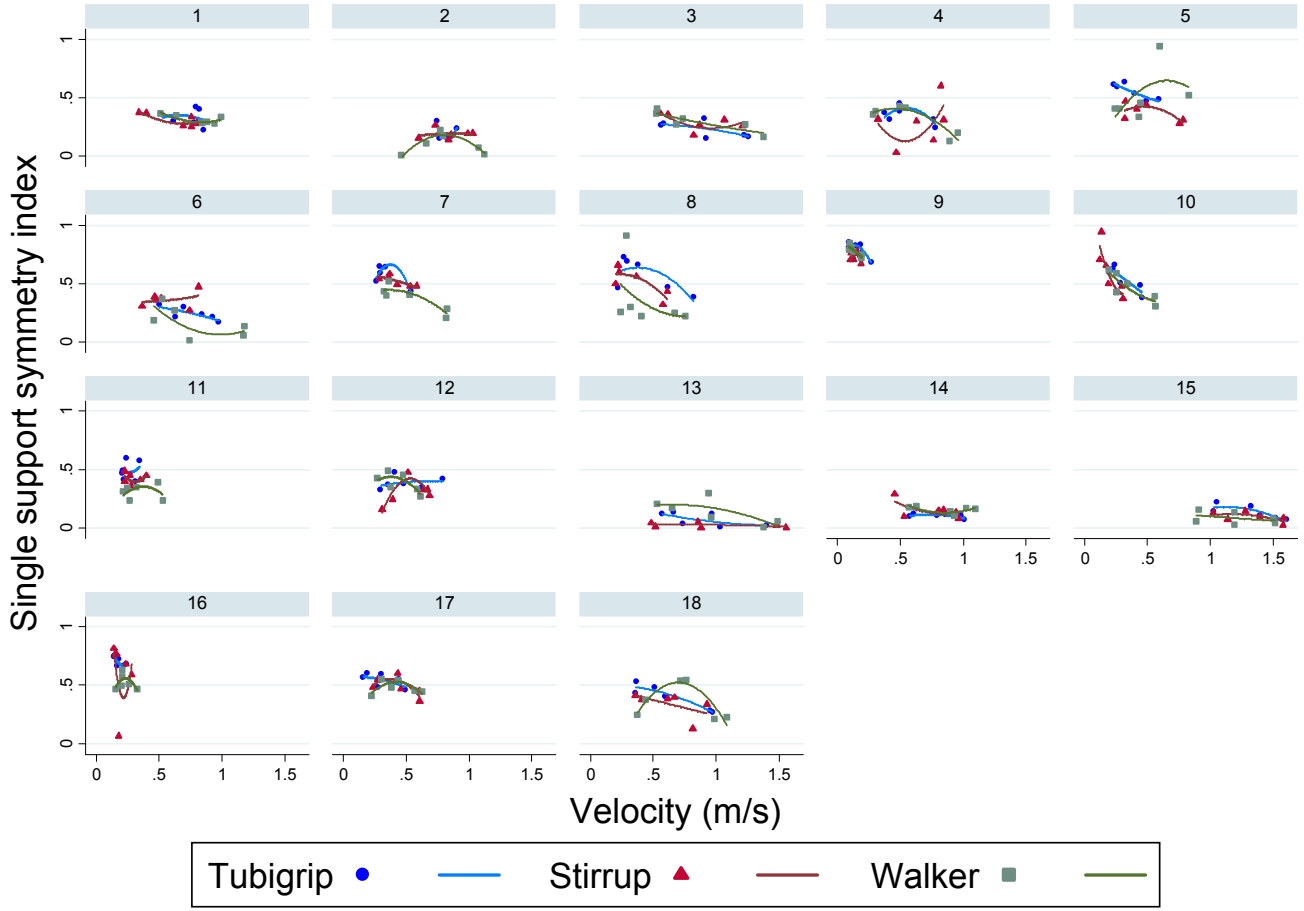


Figure 49: Two-way scatter plot with quadratic prediction plot of single support time SI and walking velocity (m/s) by participant (n=18). There are 6 data points representing the 6 walking tests for each ankle support by participant. The quadratic prediction curve is plotted to fit these data points for each ankle support. The relationship between single support symmetry and velocity varies between participants and the support used.

Table 24: Multilevel modelling for single support time symmetry index outcomes. Level 1 was the repeated measurement occasions (n=18) and level 2 was the participant (n=18).

Variable	**Model 0[#]**				**Model 1[##]**				**Model 2[###]**			
	β	95% CI		P value	β	95% CI		P value	β	95% CI		P value
Fixed effects												
Velocity	.	.	.	.	-0.22	-0.28	-0.17	<0.001	-0.27	-0.33	-0.20	<0.001
Velocity^2	.	.	.	.	.	.	.	.	.	.	.	.
Stirrup[*]	-0.03	-0.06	<0.01	0.04	-0.03	-0.06	<0.01	0.02	-0.03	-0.06	<0.01	0.02
Walker[*]	-0.06	-0.09	-0.03	<0.001	-0.05	-0.08	-0.02	<0.001	-0.05	-0.07	-0.02	0.001
Constant (β_0)	0.40	0.31	0.48	<0.001	0.53	0.46	0.59	<0.001	0.53	0.44	0.62	<0.001
Random effects	Estimate				Estimate				Estimate			
Slope SD (velocity)	.	.	.		.	.	.		0.10	0.06	0.17	
Intercept SD	0.18	0.13	0.25		0.12	0.09	0.17		0.17	0.12	0.25	
Level 1 residuals SD	0.11	0.10	0.12		0.10	0.10	0.11		0.10	0.09	0.11	
Likelihood-ratio test [a]					χ^2=53.24	*P*<0.001			χ^2=15.09	*P*=0.001		

CI: Confidence Interval; SD: Standard Deviation.
[*]Compared with Tubigrip (reference category).
[#] Random intercepts with fixed treatment effect at level 1.
[##] Added covariate (velocity) at Level 1.
[###] Random intercepts and slopes (as a function of velocity).
[a] vs. previous model.
β < 0.0 = single support time SI better than reference category (Tubigrip), β > 0.0 = single support time SI worse than reference category (Tubigrip).

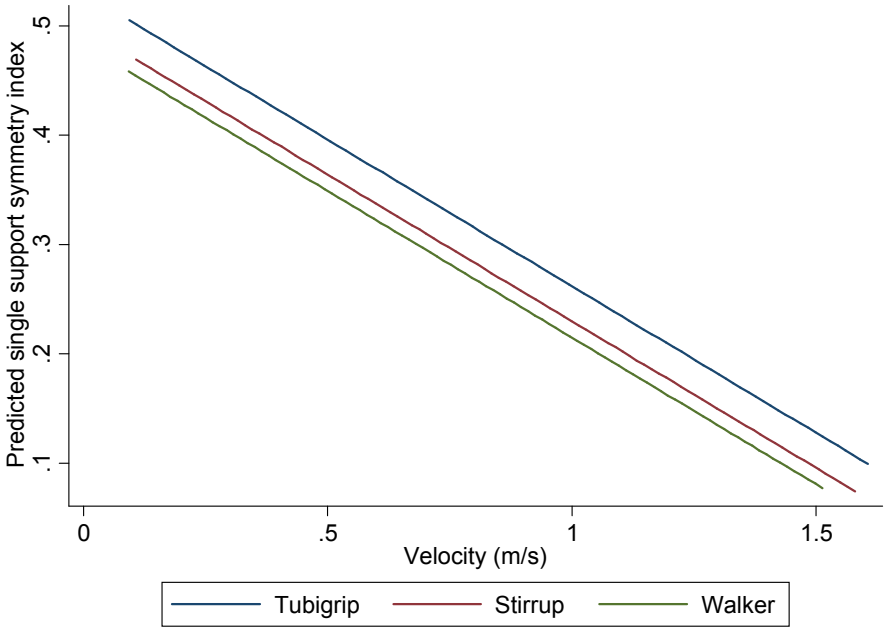


Figure 50: The final model predicted single support time symmetry by walking velocity (m/s) in each type of ankle support. There was a statistically significant difference in favour of the walker boot (P<0.00) compared with Tubigrip.

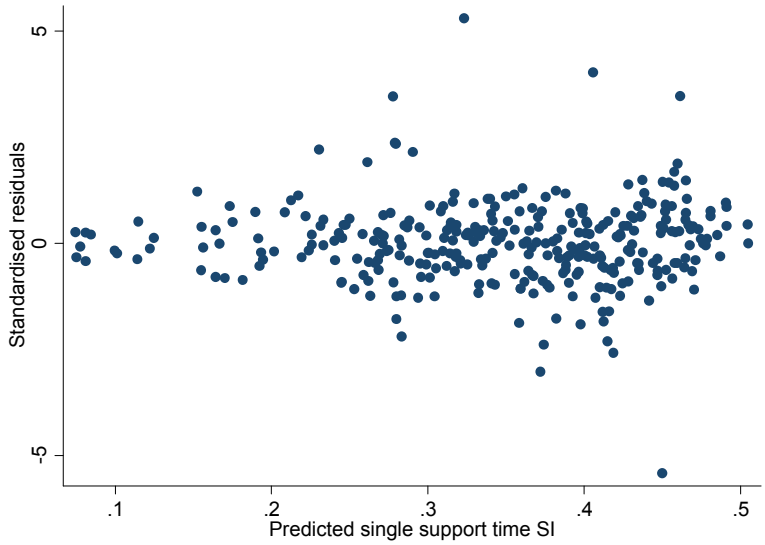


Figure 51: Scatterplot of standardised residuals and predicted values (Level 1) (n=324).

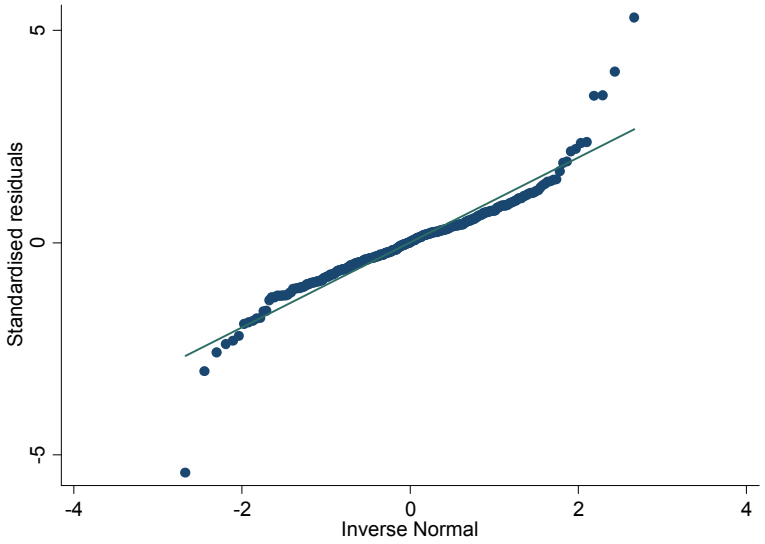


Figure 52: Q-Q plot of standardised residuals against normal distribution (level 1) (n=324).

5.4.6 Step width

Step width at each test speed by ankle support is shown in Figure 53. The step widths by gait velocity by participant are shown in Figure 54.

Multilevel modelling: When compared with Tubigrip, step width was 1.2cm (95% CI 0.6 to 1.7, $P<0.001$) wider when walking in the walker boot (Table 25). There was no difference in step width between Tubigrip and the stirrup brace. There was an overall negative relationship between a participant's walking velocity and step width. Step width was 1.5cm narrower (-1.5cm 95% CI -2.6 to -0.4) for a 1m/s increase in velocity. Figure 55 shows narrowing of step width as walking velocity increased and the wider step width in the walker boot compared with Tubigrip.

Random effect results: Allowing the intercepts for each participant to vary improved the fit of the model.

Sensitivity analyses: Walking aid use was a statistically significant factor when added to the final model. Use of a walking aid was associated with narrower step width (-3.3cm, 95% CI -5.9 to -0.7, $P=0.013$). Use of an aid altered the effect estimated for the ankle supports by <0.01cm. The order in which the ankle support was tested was not statistically significant and had a negligible effect on the model estimates.

Model diagnostics: The diagnostic plots (Figure 56 and Figure 57) identified some minor limitations of the final model for the most negative residuals. Overall the model for step width was a much better fit that than for the symmetry indices. Transformations did not substantially improve the model fit.

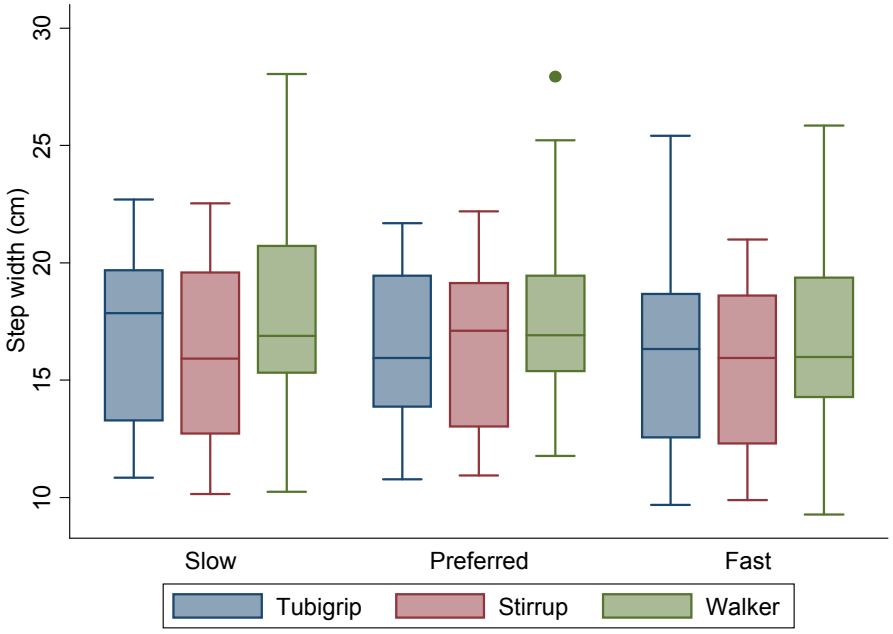


Figure 53: Box and whisker plot of step width (cm) in each ankle support by test speed (n=18 participants with 18 observations each). The middle line of the box is the median, the top line is the upper quartile and the bottom line is the lower quartile. The error bars indicate the greatest and smallest values except outliers, which are represented by dots.

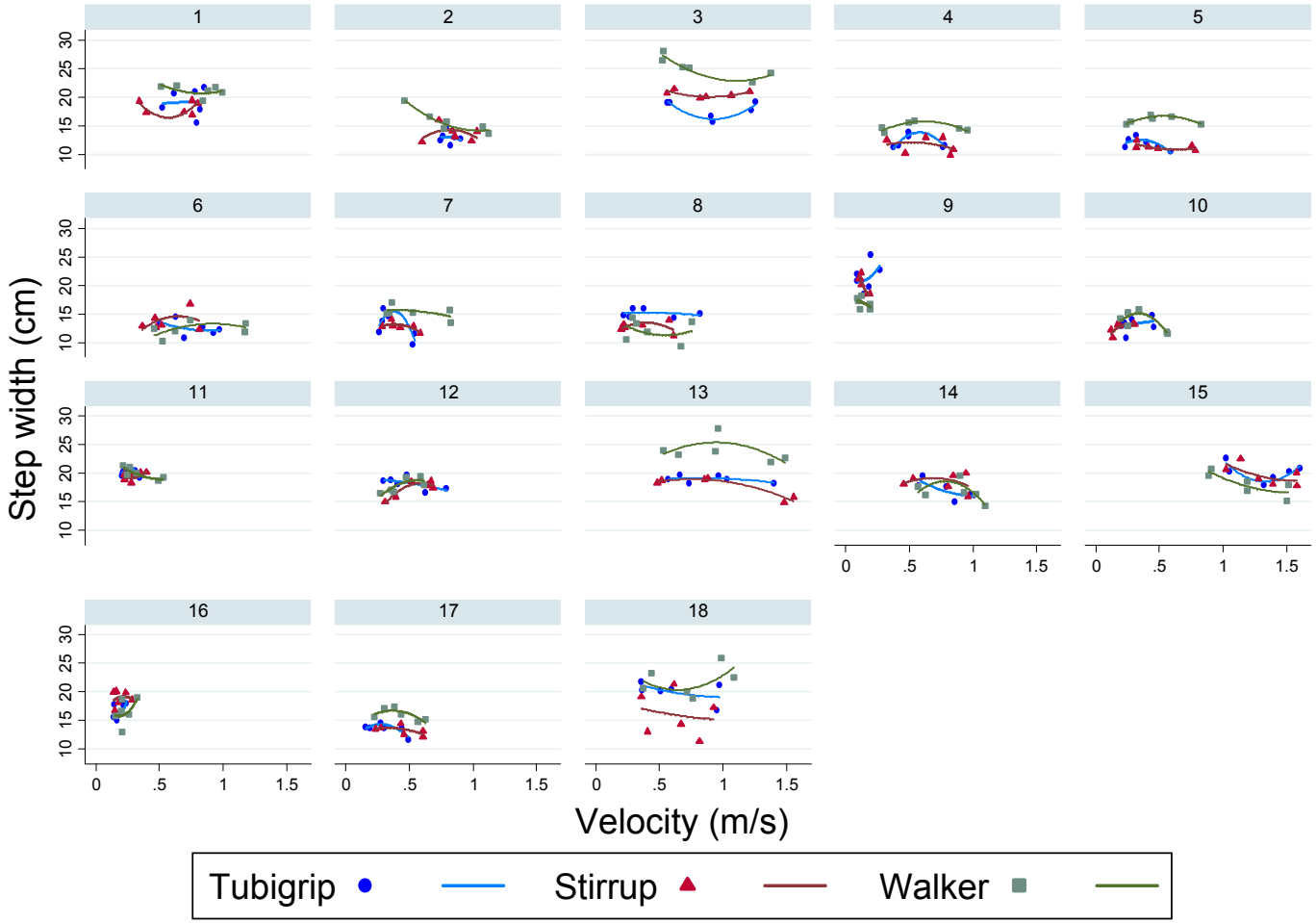


Figure 54: Two-way scatter plot with quadratic prediction plot of step width (cm) and walking velocity (m/s) (n=18 observations) by participant (n=18). There are 6 data points representing the 6 walking tests for each ankle support by participant. The quadratic prediction curve is plotted to fit these data points for each ankle support. The relationship between single support symmetry and velocity varies between participants and the support used.

Table 25: Multilevel modelling for step width (cm) outcomes. Level 1 was the repeated measurement occasions (n=18) and level 2 was the participant (n=18).

Variable	**Model 0[#]**				**Model 1[##]**			
	β	95% CI		P value	β	95% CI		P value
Fixed effects								
Velocity	.	.	.	.	-1.53	-2.64	-0.43	0.01
Velocity^2	.	.	.	.	.	.	.	.
Stirrup[*]	-0.35	-0.90	0.19	0.21	-0.36	-0.90	0.18	0.20
Walker[*]	1.10	0.55	1.65	<0.001	1.16	0.61	1.70	<0.001
Constant (β_0)	16.37	14.93	17.80	<0.001	17.25	15.61	18.88	<0.001
Random effects	Estimate				Estimate			
Slope SD (velocity)	.	.	.		.	.	.	
Intercept SD	2.99	2.14	4.18		3.15	2.25	4.41	
Level 1 residuals SD	2.05	1.90	2.22		2.02	1.87	2.19	
Likelihood-ratio test [a]					χ^2=7.2	*P*=0.007		

CI: Confidence Interval; SD: Standard Deviation.
[*]Compared with Tubigrip (reference category).
[#] Random intercepts with fixed treatment effect at level 1.
[##] Added covariate (velocity) at Level 1.
[a] vs. previous model.
β < 0.0 = step width narrower than reference category (Tubigrip), β > 0.0 = step width wider than reference category (Tubigrip).

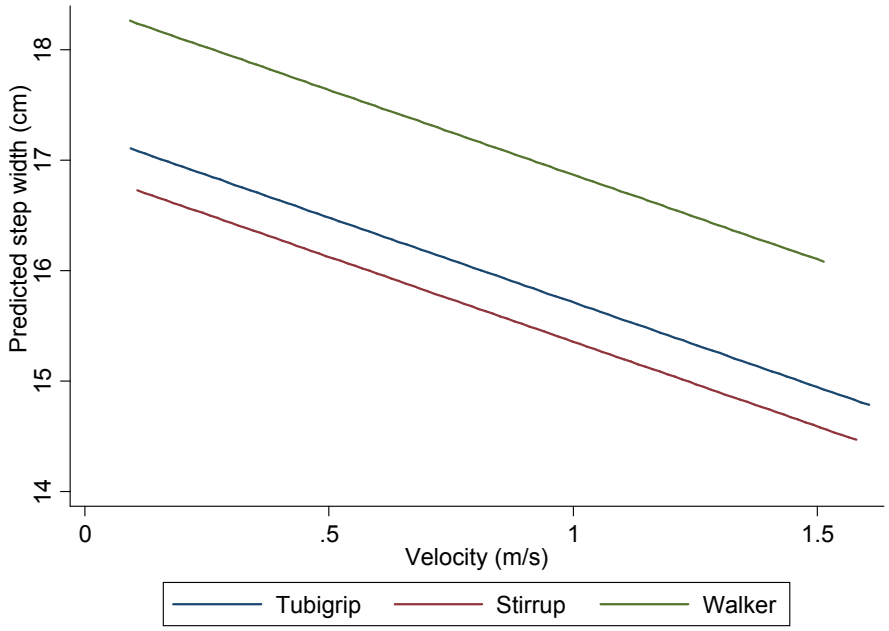


Figure 55: The final model predicted step width (cm) by walking velocity (m/s) in each type of ankle support. There was a statistically significant wider step width in the walker boot (P<0.001) compared with Tubigrip.

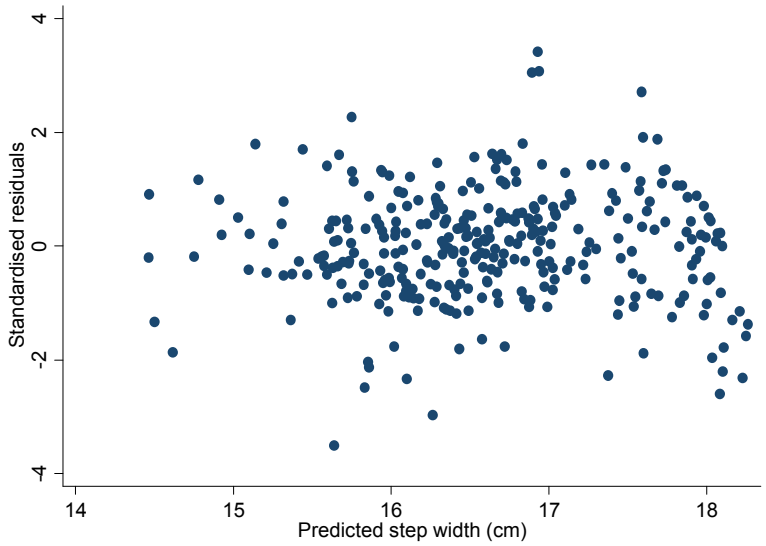


Figure 56: Scatterplot of standardised residuals and predicted values (Level 1) (n=324).

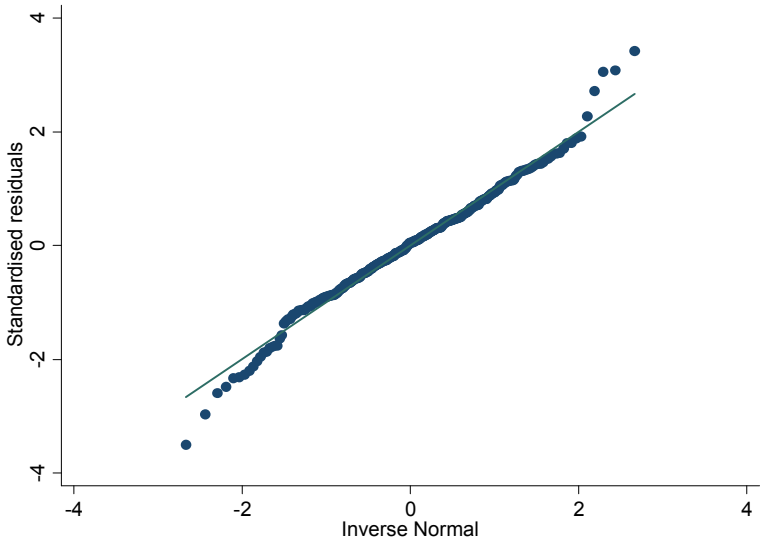


Figure 57: Q-Q plot of standardised residuals against normal distribution (level1) (n=324).

5.4.7 Pain and difficulty walking in different types of ankle support

The overall comparison of pain levels in the different ankle supports was statistically significantly different (*P*=0.03) therefore post-test comparisons between the supports were conducted using the Wilcoxon matched-pairs signed-rank test (Table 26 and Figure 58). Pain during walking was highest in the Tubigrip and was statistically significantly and substantially lower in the walker boot (*P*=0.011) and somewhat lower in the stirrup brace (*P*=0.014). Pain during walking was not statistically significantly different between the walker boot and the stirrup brace (*P*=0.20). There were no differences in difficulty walking between the types of ankle support (Figure 59).

Table 26: Self-rated pain and difficulty walking by ankle support (n=18).

Variable	**Median**	**IQR**	**Min, Max**	
Pain VAS				
Tubigrip	18	30	0, 76	
Stirrup	13	21	0, 72	
Walker	5	19	0, 52	
	Friedman's	7.0		*P*=0.03*
Difficulty VAS				
Tubigrip	14	28	0, 67	
Stirrup	4	29	0, 52	
Walker	16	29	0, 71	
	Friedman's	3.11		*P*=0.21

VAS 0-100, 0=no pain/difficulty, 100=worst pain possible/impossible

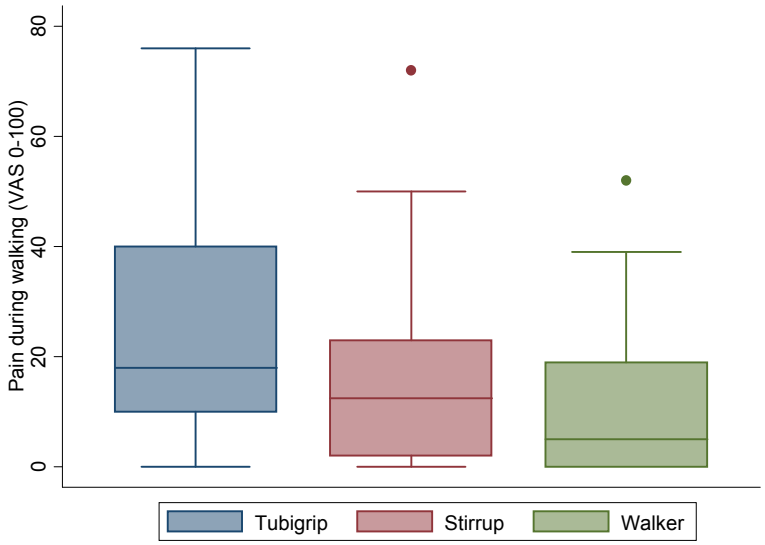


Figure 58: Box and whisker plot of self-rated pain walking in each ankle support (n=18, P=0.03). Pain was lower in the walker boot (P=0.011) and to a lesser extent in the stirrup brace (P=0.014) compared with Tubigrip. The middle line of the box is the median, the top line is the upper quartile and the bottom line is the lower quartile. The error bars indicate the greatest and smallest values except outliers, which are represented by dots.

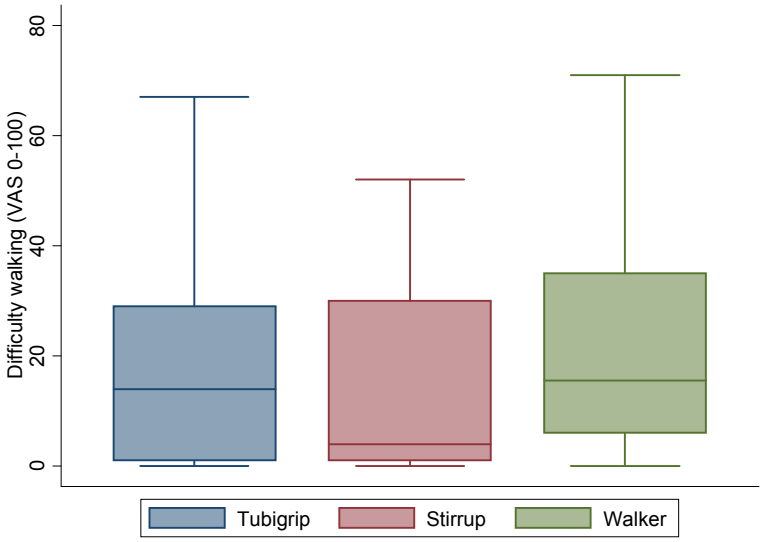


Figure 59: Box and whisker plot of self-rated difficulty walking in each ankle support (n=18, P=0.21). The middle line of the box is the median, the top line is the upper quartile and the bottom line is the lower quartile. The error bars indicate the greatest and smallest values except outliers, which are represented by dots.

5.4.8 Pain and difficulty walking by order of testing

There were no statistically significant differences in pain or difficulty between ankle supports tested first, second or third (Table 27; for pain see Figure 60 and for difficulty see Figure 61).

Table 27: Self-rated pain and difficulty walking by order of test (first/second/third) (n=18).

Variable	Median	IQR	Min, Max	
Pain				
Test 1	14	28	0, 72	
Test 2	12	19	0, 73	
Test 3	15	26	0, 76	
	Friedman's	1.58		*P*=0.45
Difficulty				
Test 1	13	34	0, 67	
Test 2	15	28	0, 52	
Test 3	9	27	0, 71	
	Friedman's	1.36		*P*=0.50

VAS 0-100, 0=no pain/difficulty, 100=worst pain possible/impossible

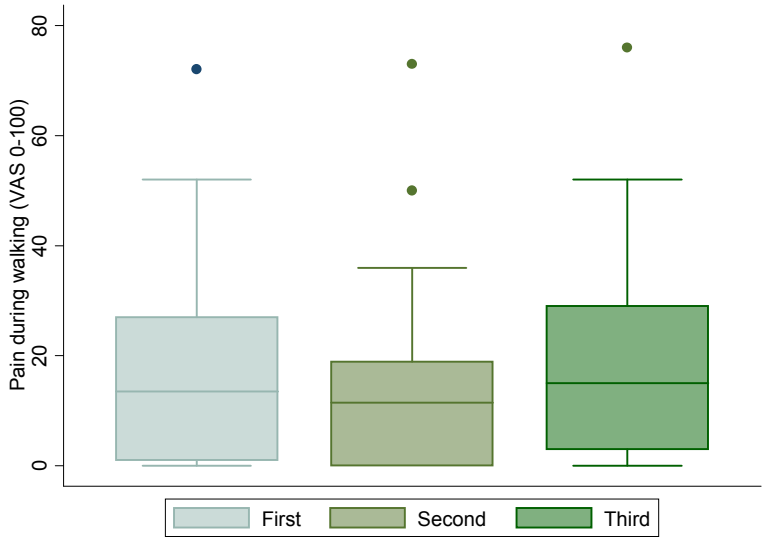


Figure 60: Box and whisker plot of self-rated pain by order of test (first/second/third) (n=18, P=0.45). The middle line of the box is the median, the top line is the upper quartile and the bottom line is the lower quartile. The error bars indicate the greatest and smallest values except outliers, which are represented by dots.

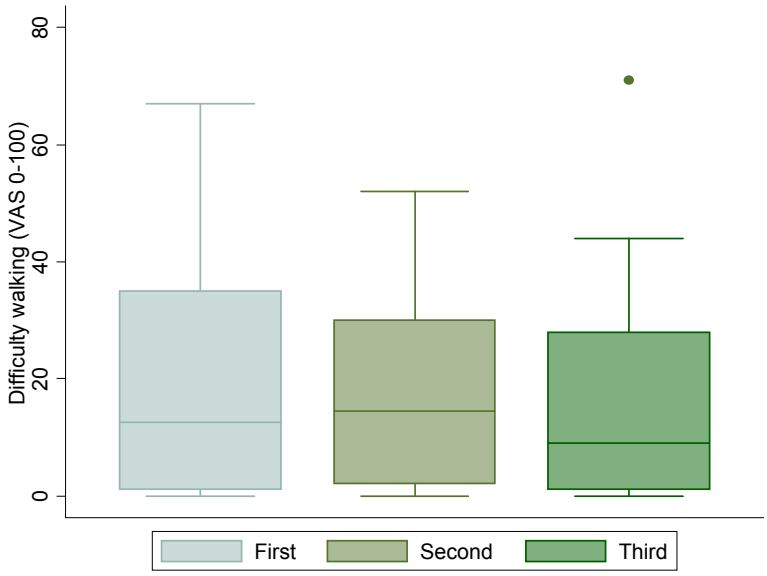


Figure 61: Box and whisker plot of self-rated difficulty walking by order of test (first/second/third) (n=18, P=0.50). The middle line of the box is the median, the top line is the upper quartile and the bottom line is the lower quartile. The error bars indicate the greatest and smallest values except outliers, which are represented by dots.

5.4.9 Ankle support issued after assessments

Thirteen participants chose Tubigrip as their preferred ankle support, 4 the stirrup brace, no participants wanted to use the walker boot as their primary support and one participant did not want to use ankle supports at all. However, of those whose primary support choice was Tubigrip, 5 also had a walker boot and 1 a stirrup brace for use outdoors. The main reason given for needing an additional support for outdoor use was for 'confidence' and in 2 cases it was advised by the orthopaedic surgeon and research physiotherapist as the participant was not sure which support they would want to use outside initially and asked for advice. No adverse events were reported by participants.

5.4.10 Peak isometric ankle muscle strength

Two participants declining undergoing muscle strength measurements after the walking assessments due to their own time limitations. For the 16 participants who underwent muscle strength measures there was moderate to excellent reliability (Table 28). The average muscle force measures for each participant for injured and uninjured ankles were compared (Figure 62). Differences in muscle force (kg) of injured and uninjured ankles for dorsiflexion and plantar flexion were statistically significant (Table 29). On average muscle strength in the injured limb compared with the uninjured limb was 37% weaker for dorsiflexion and 50% weaker for plantar flexion. Uninjured ankles were stronger than injured ankles by 7.9kg for dorsiflexion and 10.5kg for plantar flexion.

Table 28: Intraclass correlation coefficients (ICC) for three repeated ankle muscle strength measurements (n=16).

	Uninjured		**Injured**	
	ICC	95% CI	ICC	95% CI
Dorsiflexion	0.80	0.65 to 0.96	0.71	0.50 to 0.91
Plantar flexion	0.63	0.39 to 0.87	0.93	0.87 to 0.99

Table 29: Muscle strength (kg) of injured and uninjured ankle and difference for ankle dorsiflexion and plantar flexion (n=16).

Ankle movement	**Median**	**IQR**	**Min, Max**	***P****
Dorsiflexion				
Uninjured	17.6	9.7	10.6, 26.1	
Injured	11.4	5.5	3.1, 22.1	
Difference	7.9	5.5	-0.3, 16.0	0.0006
Plantar flexion				
Uninjured	25.0	4.0	16.5, 38.5	
Injured	11.2	9.4	2.3, 23.7	
Difference	10.5	10.8	1.3, 27.1	0.0004

* Wilcoxon sign-rank test (due to non-normal distribution).

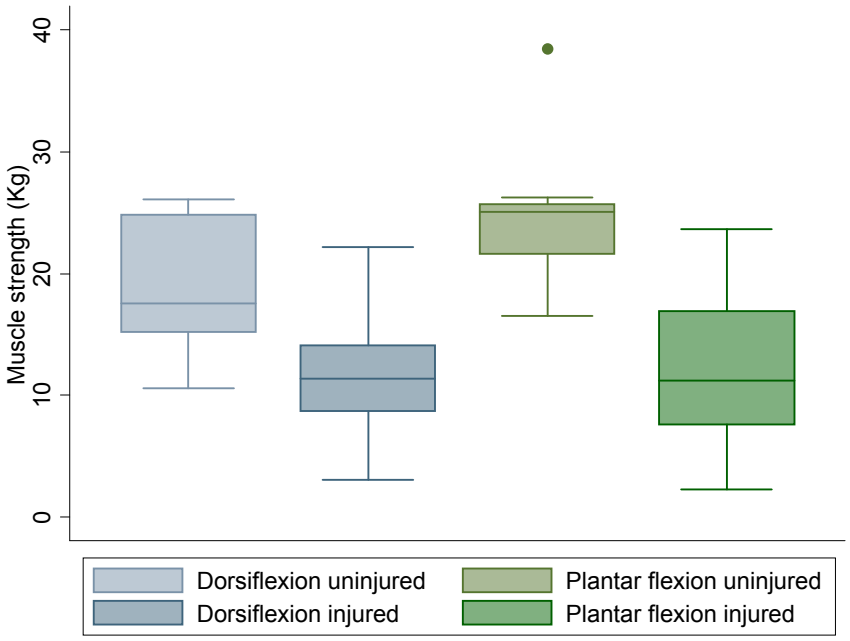


Figure 62: Box and whisker plot of muscle strength (kg) of injured and uninjured ankles (n=16) for dorsiflexion (P=0.0006) and plantar flexion (P=0.0004). The middle line of the box is the median, the top line is the upper quartile and the bottom line is the lower quartile. The error bars indicate the greatest and smallest values except outliers, which are represented by dots.

5.4.11 Relationship between gait velocity and asymmetry with ankle pain, range of motion and muscle strength

The results for the correlation analysis between gait outcomes at preferred walking speed and key physical impairments are shown in Table 30. There was a statistically significant correlation between most gait outcomes and restrictions in ankle dorsiflexion range of motion in all ankle supports. Larger restrictions in dorsiflexion were associated with greater asymmetry in step length and single support time, narrower step width and slower walking velocity. The relationships between gait outcomes and restrictions in plantar flexion were not statistically significant except for step width in the stirrup brace.

There were no statistically significant correlations between gait outcomes and the asymmetry in dorsiflexion muscle strength between limbs. There was a statistically significant positive

correlation between asymmetry in plantar flexion muscle strength and single support time asymmetry for the Tubigrip and stirrup brace. Higher pain scores during walking were statistically significantly associated with 1) greater single support time asymmetry and slower walking velocity in the walker boot and 2) narrower step width in Tubigrip.

Table 30: Correlation between gait velocity and asymmetry with ankle pain, range of motion and muscle strength asymmetry (n=18 unless otherwise stated)

Variables	Step length SI†			Single support SI†			Step width (cm)†			Velocity (m/s)†		
	T	S	W	T	S	W	T	S	W	T	S	W
Dorsiflexion ROM restriction	0.55* *P*=0.017	0.15 *P*=0.55	0.47* *P*=0.049	0.76* *P*=0.0003	0.72* *P*=0.0008	0.45 *P*=0.06	-0.55* *P*=0.019	-0.52* *P*=0.028	-0.73* *P*=0.0005	-0.67* *P*=0.0026	-0.65* *P*=0.0037	-0.64* *P*=0.0039
Plantar flexion ROM restriction	0.02 *P*=0.94	0.43 *P*=0.072	-0.28 *P*=0.26	0.24 *P*=0.34	0.094 *P*=0.71	-0.04 *P*=0.86	-0.30 *P*=0.23	-0.60* *P*=0.0081	-0.41 *P*=0.092	-0.11 *P*=0.67	-0.17 *P*=0.51	-0.10 *P*=0.70
Dorsiflexion muscle strength SI (n=16)	0.03 *P*=0.91	0.16 *P*=0.56	-0.13 *P*=0.64	0.28 *P*=0.29	0.39 *P*=0.13	-0.15 *P*=0.58	-0.10 *P*=0.73	-0.17 *P*=0.53	-0.35 *P*=0.18	-0.20 *P*=0.45	-0.43 *P*=0.094	-0.32 *P*=0.23
Plantar flexion muscle strength SI (n=16)	0.39 *P*=0.13	0.29 *P*=0.28	0.20 *P*=0.46	0.59* *P*=0.016	0.61* *P*=0.013	0.22 *P*=0.41	-0.065 *P*=0.81	-0.22 *P*=0.41	-0.40 *P*=0.12	-0.62* *P*=0.011	-0.64* *P*=0.0078	-0.60* *P*=0.015
Pain walking in support	0.05 *P*=0.84	0.12 *P*=0.63	0.41 *P*=0.095	0.23 *P*=0.35	0.32 *P*=0.20	0.67* *P*=0.0024	-0.56* *P*=0.0165	-0.46 *P*=0.054	-0.36 *P*=0.14	-0.071 *P*=0.78	-0.27 *P*=0.27	-0.53* *P*=0.024

Data are Spearman's rank correlation coefficient with *P*-value.
SI=symmetry index. T=Tubigrip, S=stirrup brace, W= walker boot. **P*<0.05. †mean of 2 walks at preferred walking speed.

5.5 Discussion

5.5.1 Summary of findings

Six weeks after ORIF surgery for ankle fracture, walking is highly asymmetric in terms of step length and single support time between limbs and walking velocity is slowed compared with that of healthy adults in Chapter 4. Deficits in ankle range of motion and muscle strength were found in the injured ankle when compared with the uninjured side. Larger restrictions in dorsiflexion were associated with greater asymmetry in step length and single support time, narrower step width and slower walking velocity across the ankle supports.

This study suggests that ankle supports that limit ankle range of motion have 3 distinct immediate effects on temporo-spatial walking gait outcomes. Firstly, compared with Tubigrip, single support time was 3% and 5% less asymmetric in the stirrup brace and walker boot respectively. Secondly, step width was wider in the walker boot than in Tubigrip by a limited 1.2cm margin. Thirdly, self-reported pain was substantially lower in the walker boot and somewhat lower in the stirrup brace compared to Tubigrip. No differences in perceived difficulty walking in each ankle support were found. No differences were found in the effects of the supports on step length symmetry between the walker boot or stirrup brace compared with Tubigrip. There was also no difference in step width between the stirrup brace and Tubigrip. No participants wanted to use a walker boot as their primary ankle support after testing, but some indicated a preference for a walker boot as a secondary support for outdoor use.

5.5.2 Gait 6 weeks after ankle ORIF surgery

The reliability of temporo-spatial gait outcome measurements using the GAITRite® system in this population was excellent, as has been demonstrated in healthy adults.[12, 148] The walking assessments were tolerated well. Only 3/21 eligible participants that underwent the initial assessment of mobility were unable to weight bear. All 18 eligible participants that were able to weight bear were able to complete the walking assessments. This was higher than expected as the participants had to do 18 walks across the electronic walkway, covering at least 160.2m in total.

This is a considerable distance given that this was the first opportunity for the participants to perform unrestricted weight bearing after surgery. No participants reported significant or lasting pain after the assessments.

The average walking velocity in all ankle supports at all speeds (range 0.39 to 0.86 m/s) was well below similarly aged healthy adults under similar test conditions (range 0.88 to 1.58, Chapter 4) and accepted norms (1.2 to 1.6 m/s).[114] Walking velocity was statistically significantly faster at preferred and fast test speeds, so participants were able to vary their walking velocity even at this early stage of walking rehabilitation. The ability to vary walking velocity is an important aspect of normal gait performance that is used in day-to-day mobility.[178] However, the size of difference in walking velocity between slow test speed and the preferred and fast tests were less than half of that for healthy participants in Chapter 4. Walking velocity was statistically significantly faster in the walker boot when compared with the Tubigrip but of a clinically unimportant difference of 0.04 m/s. Similar to healthy participants in Chapter 4, walking velocity in the Tubigrip and stirrup brace were comparable at all 3 test speeds and there were no statistically significant differences.

5.5.3 Gait asymmetry after ankle ORIF compared with non-pathological gait

Compared with non-pathological gait (Chapter 4), mean step length asymmetry (Figure 63) and single support time asymmetry (Figure 64) were substantially worse, and step width was wider (Figure 65). The magnitude of differences between healthy adults and those 6 weeks after ankle ORIF is speed-dependent, with larger differences at slower walking velocities. Asymmetry in step length and single support time were substantially worse than velocity normalised values from similar test conditions previously reported in healthy older adults (3% step length and single support time),[88] people with hip osteoarthritis (7% step length and 9% single support time)[88] and people with hemiplegia after stroke (1% step length and 5% single support time)[87].

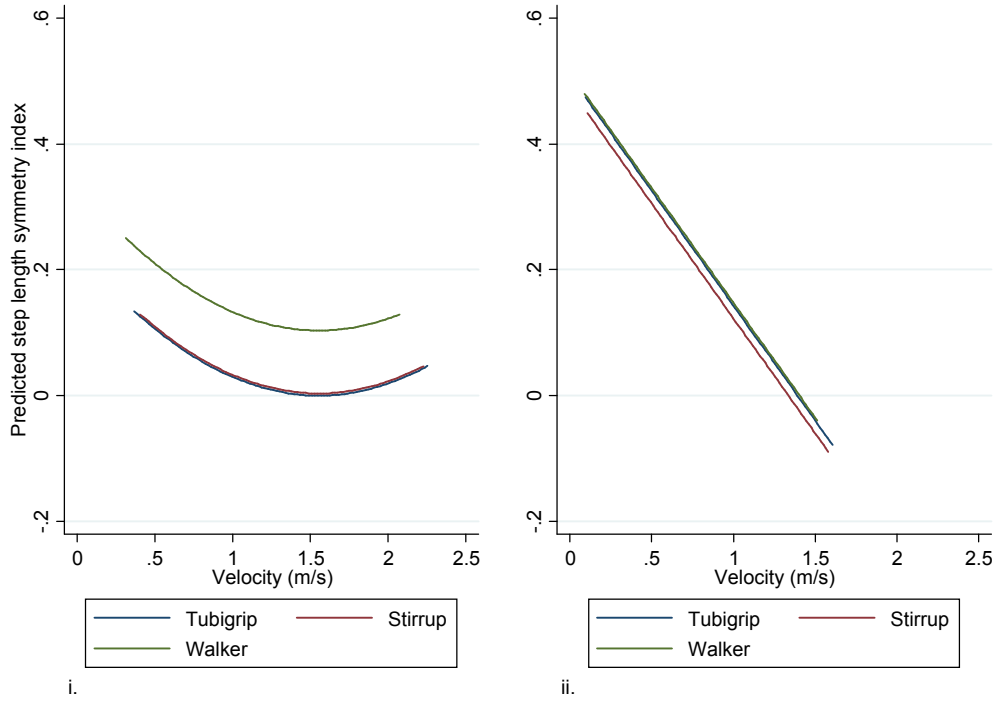


Figure 63: Predicted step length symmetry indices by walking velocity (m/s) in i. non-pathological gait (Chapter 4) and ii. 6 weeks after ankle ORIF surgery.

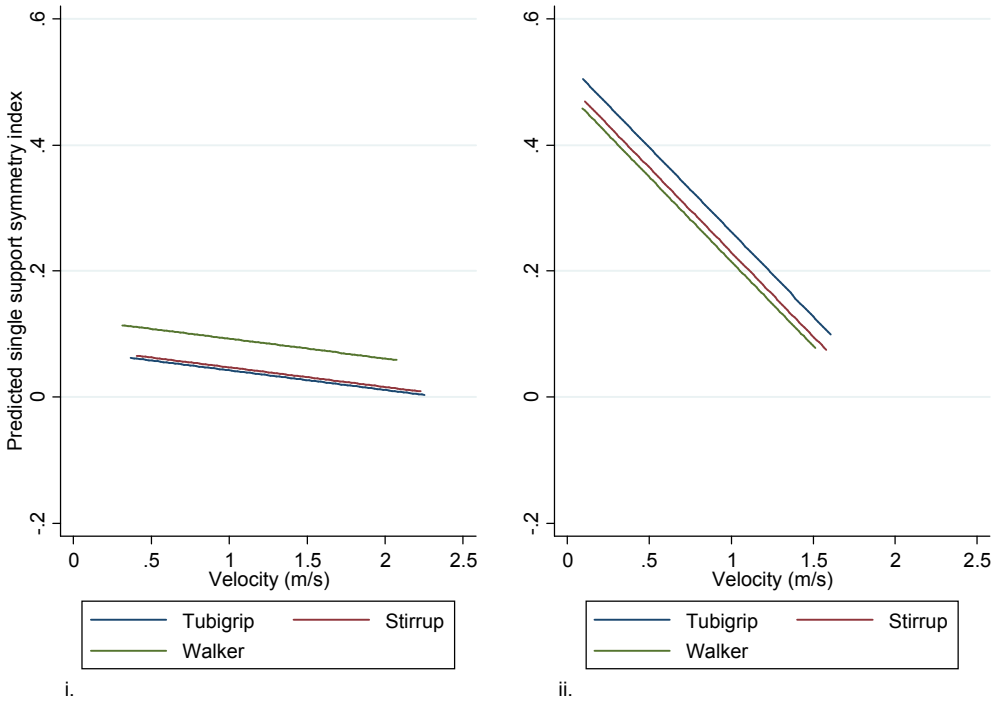


Figure 64: Predicted single support time symmetry indices by walking velocity (m/s) in i. non-pathological gait (Chapter 4) and ii. 6 weeks after ankle ORIF surgery.

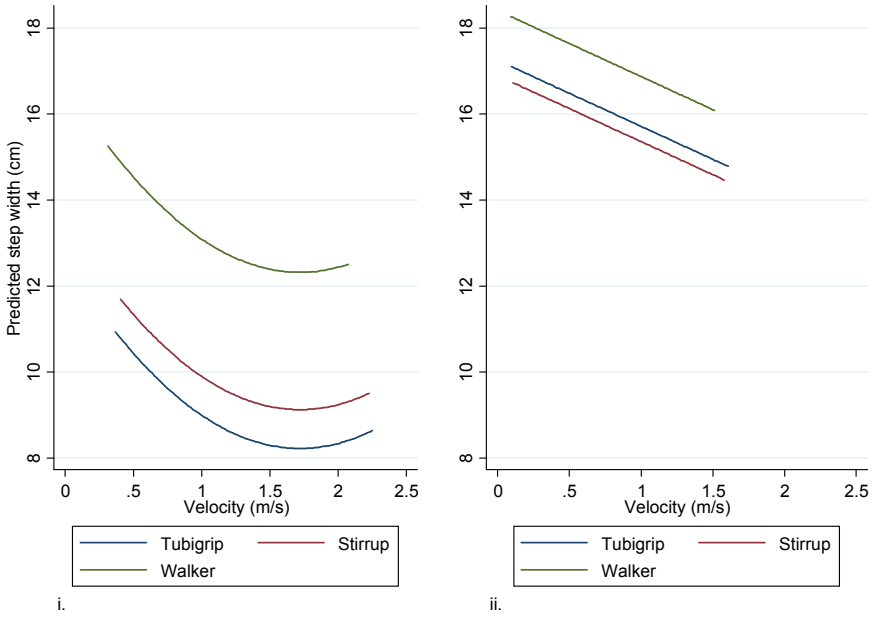


Figure 65: Predicted step width (cm) by walking velocity (m/s) in i. non-pathological gait (Chapter 4) and ii. 6 weeks after ankle ORIF surgery.

5.5.4 Comparison with other studies of gait after ankle ORIF surgery

The overall asymmetry in temporo-spatial characteristics of gait were consistent with the asymmetry in arthrokinematics at 9 weeks after ankle ORIF reported by Wolf et al.[273] in abstract form. Although reporting in the abstract was limited, the authors reported pain and gait asymmetry persisting at 6 months. Comparisons with other studies of gait after ankle ORIF are difficult because the timing of follow up is not sufficiently similar. A study at 1 year after surgery, using 3D motion analysis of 18 patients, found that injured ankle motion limitations were accompanied by shorter single support time and earlier foot off time in the gait cycle compared to the uninjured limb.[257] However, these temporal differences, as acknowledged by the authors, were of a very small and clinically unimportant magnitude at 1 year after surgery. Other studies of outcomes at 1 year report differences in the pattern of distribution of plantar pressure, which was attributed to compensatory re-distribution of pressure to reduce loads on the ankle and hind-foot.[9, 204] Although the degree of asymmetry in loading within the foot was evident in patients with and without good clinical outcomes, the implications are that asymmetries caused by local impairments can be

compensated for at surrounding joints over time to facilitate overall gait normalisation and return to function.

5.5.5 The effects of ankle supports 6 weeks after ankle ORIF surgery

The improvement in single support time asymmetry in the walker boot, and to a lesser extent the stirrup brace, suggests these supports increase tolerance of weight bearing and/or confer a mechanical advantage. The substantially reduced pain reported in the walker boot and the slightly improved pain in the stirrup brace may have allowed for a greater duration of single support time in the stance phase of gait for the injured limb. All participants had been non-weight bearing, or had the ankle immobilised during partial weight bearing, prior to the assessments. It is reasonable that walking in the walker boot and stirrup brace were less challenging for the ankle during loading compared to Tubigrip. Movement of the injured talocrural joint into dorsiflexion and plantar flexion and the closely related subtalar joint into inversion and eversion are challenging after a period of immobilisation due to active and passive joint stiffness.[30] Stirrup braces have been shown to limit subtalar inversion and eversion.[55] The study population had substantial limitations in active dorsiflexion and plantar flexion range of movement, possibly due to muscular insufficiency and/or a lack of compliance in the soft tissues around the ankle. It is hypothesised that the mechanical limitation of ankle motion offered by the walker boot with the rocker sole[48] could enable compensation for these ankle impairments through reducing the demand for ankle dorsiflexion during the single support phase of gait.[178]

The improvements in single support time asymmetry in the stirrup brace and walker boot were not accompanied by a decrease in step length asymmetry. As discussed in Chapter 2, in non-pathological gait these 2 gait parameters are usually proportional. The improvements in single support times may not be sufficient to enable step length asymmetry to significantly reduce.

The wider step width in the walker boot compared to Tubigrip may be due to the relative limb lengthening from the 4cm depth of the rocker sole. The greater step width and therefore wider

base of support in the walker boot may be desirable given the patient-reported issues with balance and falls identified in baseline assessments. A wider base of support may offer more stability, but the small difference is of questionable clinical importance. Furthermore, the 1.2cm difference is less than the spatial resolution accuracy of the GAITRite® walkway (1.27cm).

5.5.6 Range of ankle motion and pain

The restricted ankle dorsiflexion range of motion may have limited the gait symmetry that could be achieved. Larger restrictions in dorsiflexion were associated with greater asymmetry in step length and single support time, narrower step width and slower walking velocity across the ankle supports. Even though Tubigrip and stirrup braces are designed to allow sagittal plane motion, the participants could be limited in their ability to take advantage of the lack of mechanical limitation to ankle motion due to the restricted range of motion in the ankle joint itself following surgery. Abnormalities in joint motion may be due to the effects of injury, rather than the mechanical effects of the surgical implants, as biomechanical analysis before and after ankle ORIF in cadaver models have demonstrated restoration of joint kinematics after reduction and implant insertion.[149] Pain during gait after ankle ORIF surgery is also a factor that is likely to contribute to limitations in achieving more normal gait symmetry. Higher pain scores were statistically significantly associated with greater single support time asymmetry and slower walking velocity in the walker boot and narrower step width in Tubigrip.

5.5.7 Preferred ankle support after experiencing walking in each type

Participant preferences for use of Tubigrip suggest that pain relief may not be the deciding factor for choice of ankle support. A study of patient experiences after immobilisation suggests that the drive to get 'back to normal' and the relief of being able to start mobilising the ankle may have contributed to this preference.[270] Participants expressed preferences for a more substantial ankle support (stirrup brace or walker boot) for use outside. This preference for more ankle support for outdoor mobility may relate to the issues with balance and falls identified in the baseline

assessments. However, these choices may also relate to factors such as confidence. Further research using qualitative methods is recommended to gain a deeper understanding of the reasons for these treatment preferences.

5.5.8 Balance and falls

Despite the limited study sample (n=18), the incidental finding of balance impairments and falls in the baseline assessments for the study population is of clinical importance as the participants were a young age group to be reporting falls. Falls may contribute to risk of further injury and fear of falls may impede recovery.[203] Literature on falls and balance within the first 6 weeks after ankle ORIF is lacking, however the persisting balance impairments found at 14 months after ankle ORIF in 54 adults further indicates that this aspect of rehabilitation may warrant further investigation.[167] The extent of balance problems reported in the study population raise questions over walking aid technique and usage. The various challenges to balance at home and outside are different from the hospital environment where early postoperative gait training occurs.[112] Gait characteristics that are associated with lower risk of falls are a high degree of symmetry,[276] low variability[27] and adaptability.[261] Further study is needed to establish if there are benefits to additional gait training after surgery to address these issues, extending to home and outdoor environments to reduce issues with balance and falls in the postoperative period.

5.5.9 Muscle strength

Reliability of hand-held dynamometry measurements of isometric ankle muscle force was excellent for dorsiflexion in uninjured ankles and plantar flexion in injured ankles. Moderate levels of reliability were observed for dorsiflexion in injured ankles and plantar flexion in uninjured ankles. Given that this was the first formal test of muscle strength following immobilisation and limited weight bearing, the reliability of testing was acceptable. The levels of reliability were comparable to hand-held dynamometry in healthy adults using a similar 'make' test

of strength (ICC 95% CI 0.85-0.94 dorsiflexion and 0.76-0.94 plantar flexion)[220] and isokinetic dynamometry in after Achilles rupture (ICC 95% CI 0.65-0.98 plantar flexion).[29]

Asymmetry in muscle strength between the injured and uninjured ankle plantar flexors is likely to have contributed to the substantial gait asymmetry observed. Greater asymmetry in plantar flexion muscle strength was associated with greater single support time asymmetry for the Tubigrip and stirrup brace. Strength deficits in the dorsiflexors were not found to be associated with gait outcomes.

The 37% dorsiflexion and 50% plantar flexion deficits in peak muscle force in the injured limb compared to the uninjured offers further evidence of the deleterious effects of injury and immobilisation. The asymmetry far exceeds the 4.5% difference in ankle dorsiflexion strength between dominant and non-dominant limbs in healthy adults (aged 20-69).[182] The deficits in strength following ankle immobilisation after fracture are consistent with previous studies using other methods of assessment. Shaffer et al.[213] measured isometric peak plantar flexion torque 1 week after an 8 week immobilisation period following ankle ORIF surgery. The participants' (n=10) injured limbs had about half the strength of the uninjured and approximately a third of the strength of healthy age- and gender-matched controls. Christensen et al. also found plantar flexion strength was decreased by approximately 50% in the injured compared to uninjured limbs in conservatively managed ankle fracture patients (n=12). Deficits after 7 weeks immobilisation following ankle ORIF have also been studied. EMG measures of injured limbs (n=7) showed neural muscle activation was decreased by 42%, muscle cross-sectional area was reduced by 26% and plantar flexion torque was decreased by 75% compared to the uninjured side.[223] Psatha et al.[192] studied the loss of muscle volume during immobilisation in 18 adults with conservatively managed ankle fractures. There was 17-24% loss of cross-sectional area of the plantar flexors (triceps surae), twice that of the loss observed in the main dorsiflexor (tibialis anterior). They argued that this difference in proportional loss as a consequence of injury and immobilisation could be explained by the primary anti-gravity role of the triceps surae. However, a similar MRI study of

ankle ORIF patients (n=27) found no differences in anterior and posterior lower leg muscle atrophy.[224] As prior studies showed there is not a direct relationship between atrophy and power, the comparison with strength data from the current study requires caution.

All participants had a removable support to allow ankle exercises, except 1 participant who had full-time cast immobilisation, during the first 6 weeks following ORIF surgery. The substantial deficits in muscle strength in the injured limb compared with uninjured limb despite ankle exercise advice are consistent with animal studies demonstrating that muscle atrophy associated with immobilisation is not fully attenuated with brief periods of movement and exercise.[268] As identified in Chapter 3, there is also insufficient evidence in clinical trials to suggest that early ankle movements are effective in limiting loss of muscle strength after ankle ORIF surgery.

The deficits of strength compared with normative hand-held dynamometry values indicate that both uninjured and injured limbs had lower strength than healthy populations. Healthy adults have been shown to exceed 25.5kg (maximum measured) plantar flexion, and median dorsiflexion for women was 24kg and men exceeded 25.5kg.[243] An additional study found that dorsiflexion measures in healthy adults ranged from 23-25kg.[182] The impairments in strength may therefore not be isolated to the injured limb after ankle fracture surgery. The mechanisms for this loss of muscle function in muscles not immobilised may relate to the decline in overall physical activity after injury.[192] A limitation in comparing our study findings with other studies in healthy populations was that the restricted range of motion in the injured ankle meant that the isometric contraction performed during testing was in approximately 10° plantar flexion for injured and uninjured ankles, whereas in other studies the ankle was in a neutral position. This modification of ankle position for the testing was introduced in order to accommodate ankle range of motion restrictions.

5.5.10 Limitations

Although the within-subject cross-over design made efficient use of resources and time to answer the research question, there are concerns in this type of design that an order or carry-over effect

could bias the intervention effect estimates. The study benefitted from no drop-outs during the tests, which maintained the balance of the sequence of testing achieved through randomisation. Participant drop-outs would have been problematic, particularly if it was related to the effects of the supports, and would have made within-subject comparisons impossible.[151]

The effects of the order in which the supports were tested were formally assessed in sensitivity analyses. The order of testing did not influence the results for the main temporo-spatial gait outcomes. There were also no differences in self-reported pain and perceived difficulty walking in each ankle support when analysed by the order of testing. This experiment aimed to examine the effects of an externally applied ankle support and was undertaken over a short time period. Therefore, the assumption that removal of the ankle support was likely to remove the effect of the intervention should be taken into consideration when interpreting the results of this study. The alternative design to eliminate carry-over effects would have been a parallel randomised controlled trial. This design could have enabled a comparison of the effects of the ankle supports over time. However, this study design would have required resources beyond the scope of the current study and would also have required a much larger sample size due to the reduced statistical power of a between-subject design.

The one-off gait assessments in all three supports provided several clinically important findings. However, the study may have benefitted from the assessments being repeated at several intervals in the weeks following the first set of observations to see if the effects of the ankle supports are stable over time. These additional observations may have influenced the strength of conclusions that could be drawn. However, repeating the measurements would have been challenging due to the requirement for repeated clinic visits at a time when mobility is limited. In addition, the potential for loss to follow-up would have inflated the sample size and the influence of physiotherapy advice and intervention would have also been a potential confounding factor unless strictly standardised.

The findings of this study generalise well to the younger adult population with ankle fractures requiring ORIF surgery. The findings are not generalisable to those with a syndesmosis fixation as these patients were excluded due to the different ankle biomechanics in the patient group (see section 5.3.4, p.120). In addition, 3 eligible patients were not randomised as a result of an inability to weight bear, so inferences regarding the effects of ankle supports in this subgroup of participants are limited as they could not tolerate progression of gait training on the first day of permitted unrestricted weight bearing.

There are several limitations relating to the muscle strength assessments in this study. An important factor was the immediacy of the measurements as they were conducted after the gait assessments and so may have been influenced by muscle fatigue in either or both limbs. Muscle fatigue may have increased the variability observed. The strength assessments of the ankle would also have been enhanced by inclusion of assessment of the subtalar joint invertors and evertors crossing the ankle, which have an important role in limb stability. Persistent weakness in these muscle groups has been observed over 6 months after ankle ORIF surgery.[222]

5.6 Conclusion

The findings of this study highlight the substantial asymmetry in temporo-spatial gait characteristics, reduced walking velocity and ankle range of motion and muscle strength deficits following 6 weeks of limited weight bearing and immobilisation after ankle ORIF surgery. Pain and single support time asymmetry in a short distance and short-term walk are immediately improved with walker boot use and to a lesser extent by stirrup brace use. Step width also widens in a walker boot, which may confer some additional gait stability.

The findings of this study provide an evidence base for clinicians considering which ankle support to offer in order to support the transition to walking 6 weeks after ankle ORIF surgery. It is recommended that clinicians should consider the walker boot as a primary choice, and the stirrup brace as reasonable secondary choice, to reduce gait asymmetry and pain compared to Tubigrip at

the transition to rehabilitation of walking at 6 weeks after ankle ORIF surgery. Clinicians should be aware that these findings apply to short-term outcomes and also to adults with Weber type A/B ankle fractures, type C fractures were not included.

There are several additional findings that should be considered in selecting ankle supports at 6 weeks after ankle ORIF surgery. None of the participants preferred to use a walker boot as their primary ankle support, but some wanted to have one available for outdoor use. This indicates that improvements in pain and gait are not the deciding factor for ankle support selection for patients at this stage of recovery. Furthermore, the inter-relationship between physical ankle impairments and gait abnormalities after ankle ORIF surgery were highlighted in this study, especially restrictions in dorsiflexion, weakness of ankle planar flexor muscles and pain in the injured limb. Therefore, if the mechanical effects of the walker boot, such as the rocker sole, enable compensation for these physical impairments, then walker boot use could arguably be viewed as simply masking these important clinical issues. Whether using a walker boot could delay recovery by enabling compensation for physical impairments is an important area for future research.

The use of multilevel modelling can be applied to clinical populations to improve velocity-adjusted estimates of treatment effects for speed-dependent gait outcomes. Hand-held dynamometry is a practical measure of ankle dorsiflexion and plantar flexion strength with acceptable reliability 6 weeks after ankle ORIF surgery.

A parallel randomised controlled trial is now indicated to ascertain if these ankle supports have an effect on recovery over the subsequent months of rehabilitation on patient-reported ankle-related function/mobility outcomes, as well as on gait and other physical impairments. The incidental finding of balance problems in the postoperative period also warrants further exploration to establish whether further intervention is required to limit risk of falls and additional injury within the 6 weeks after surgery.

Chapter 6

6 The effects of ankle supports on recovery of mobility and return to usual sports or activities after severe ankle sprain in adults: an exploratory analysis using the Collaborative Ankle Support Trial (CAST) cohort.

In previous chapters, the effects of ankle supports have been studied at two stages of the recovery pathway after primary surgical management for ankle fracture, 1) the immediate postoperative recovery period in Chapter 3 and 2) the transition to rehabilitation and weight-bearing at 6 weeks in Chapter 5. The aim of this chapter is to explore the effects of different ankle supports applied for the primary management of severe ankle sprain. The effects of the ankle supports on a range of mobility outcomes and return to usual sports or activities in the short- and medium-term are investigated.

6.1 Background

The incidence of ankle sprain injuries resulting in hospital attendance in the USA has been estimated as 215 per 100,000 person-years, approximately half of these injuries occurring during sports.[259] In addition, it is reasonable to assume that many more individuals with ankle sprains will attend primary care facilities and sports clinics.[38] A high proportion of those attending emergency departments have sustained a severe sprain sufficient to cause difficulty weight bearing on the injured limb.[39] Weight bearing is difficult after ankle sprain due to ankle pain, swelling, lack of range of motion, instability, and deficits in balance and muscle strength.[24]

Difficulties weight bearing on the injured ankle impact on mobility. As discussed in Chapters 1 and 2, mobility includes purposeful weight bearing activities such as walking, ascending and descending stairs, squatting, jumping and running. Two important aims of early management after

severe ankle sprain are the recovery of mobility[34, 237] and the return to usual sports or activities.[109] An important early management decision after ankle sprain is whether to immobilise the ankle in an external support (e.g. cast or walker boot) or opt for early ankle movement. Early ankle movement is often supplemented with an external ankle support that is designed to allow a reasonable degree of ankle joint motion (e.g. elasticated tubular bandage or stirrup brace).[108] Recovery from ankle sprain can be slow. The average return to work is more than a week, which has substantial economic implications.[39] The approximate proportion of individuals who have not returned to sport within 6 weeks is 50% and within one year, 10%.[108]

6.1.1 The Collaborative Ankle Support Trial (CAST)

Due to the uncertainties of the effects of different ankle supports for the early management of ankle sprain, a multicentre pragmatic randomised controlled trial was funded by the NIHR Health Technology Assessment programme in the UK.[39, 117] Pragmatic trials aim to assess the effects of an intervention in the usual clinical circumstances in which it will be used, as opposed to explanatory trials that focus on assessing interventions in ideal and controlled conditions.[234] CAST focussed on severe ankle sprains, defined by the pragmatic clinical criterion of inability to weight bear on the injured limb. The primary outcome was overall self-reported ankle function recovery within the first 3 months. The trial compared ankle supports that allowed varying amounts of ankle movement with Tubigrip elasticated tubular bandage (Mölnlycke Health Care, Göteborg, Sweden), which does not offer mechanical limitations to movement. The ankle supports were:

- Below-knee cast for 10 days (applied as per routine local practice).
- Walker boot, which could be removed for ankle exercises (Bledsoe® boot, Bledsoe Boot Systems, Grand Prairie, TX).
- Ankle stirrup braces allowing ankle plantar flexion and dorsiflexion, but restraining inversion and eversion (Aircast® brace, DJO Incorporated, Vista, CA).

The duration of Tubigrip, stirrup brace and walker boot use was not set for a specific duration in the study, participants were advised to discontinue use when their ankle felt comfortable and they

felt confident to do so. The walker boots and stirrup braces were from different manufacturers than those used in Chapters 4 and 5. All of the interventions in CAST have been included in postoperative ankle fracture recovery, with the notable difference of the longer duration of 6 weeks cast immobilisation used after ankle ORIF surgery (Chapter 3).

In the short-term, at 4 weeks after injury, the below-knee cast was statistically significantly more beneficial in terms pain and quality of life subscales of the Foot and Ankle Outcome Score (FAOS)[199] and the SF-12 physical component score compared with Tubigrip. However, the sizes of the differences were small. In the medium-term, at 12 weeks after injury, the below-knee cast was statistically significantly more beneficial, with a moderate effect size, on the FAOS activities of daily living, sports and quality of life subscales. There was also a small benefit on the pain subscale. The ankle stirrup brace was also statistically significantly more beneficial than Tubigrip at 12 weeks post-injury, but in the FAOS quality of life subscale and SF-12 mental component scores only. The walker boot conferred no benefits compared with Tubigrip. In contrast, there were no differences between Functional Limitation Profile[144] (anglicised version of the Sickness Impact Profile) ambulatory subscale scores at any follow-up time point. In the longer term, at 9 months after injury, all groups had improved, but there were no differences between the interventions.

A noteworthy additional finding from CAST was that age and gender were both important predictors of outcome after ankle sprain. Increasing age was found to be an important determinant of recovery, both slowing and limiting recovery at the end of the trial follow-up at 9 months. Men also reported better outcome scores than women on average.

6.1.2 Response to the findings of CAST

The favourable effects of cast immobilisation were considered controversial at the time of initial publication (2009) due to the contrast with recommended practices of early ankle movement in the preceding decades[82] and this provoked criticism.[110, 186, 246] There has been limited incorporation of

the findings of CAST into clinical guidelines despite it being the largest well-designed pragmatic trial comparing immobilisation and early ankle movement.

A 2010 review highlighted that CAST contradicted previous literature reviews and current practice but argued that due to perceived limitations of the trial, *'functional support rather than immobilization for most ankle sprains should remain in place'*.[123] An interpretation of the findings in an 'evidence-based algorithm' based on expert opinion in 2012 commented that CAST: *'...failed to compare the different methods of immobilization with the current gold standard* [early ankle movement]. *Therefore, this trial does not contribute to the ongoing debate about the best treatment for acutely sprained ankles'*.[187] The authors go further to indicate that immobilisation necessitates thrombo-prophylaxis, results in muscle atrophy, which could limit return to sports, and is more expensive than early ankle movement.

Based on published data from CAST, these criticisms are questionable.[39] Firstly, the Tubigrip, walker boot and stirrup brace interventions were accompanied with standardised ankle exercise instruction, reflecting accepted definitions of early ankle movement in the related Cochrane review.[108] As CAST was a pragmatic trial, participants could also access physiotherapy to promote ankle movement recovery. Secondly, five thrombosis events were reported, two events each in the Tubigrip and stirrup brace groups and one in the cast group. Therefore the rationale for thrombo-prophylaxis may not be a consideration limited to short-term immobilisation interventions. Thirdly, muscle atrophy and return to sport are two different outcomes, and the CAST Trial found that the FAOS sports subscale was better in the cast immobilisation group. However, it is noted that the FOAS sports subscale is a self-reported measure of overall functional performance that does not specifically state whether participants have returned to sport. Fourthly, a thorough analysis of cost-effectiveness was conducted as part of CAST. The cost-utility analysis found that the stirrup brace was £301 per Quality-Adjusted Life Year (QALY), similar to the below-knee cast at £339 per QALY, and £2116 per QALY for the walker boot.

Subsequent randomised controlled trials investigating different types of early ankle movement have been reported since CAST. A trial reported in 2012 included participants with severe sprains and compared taping with the stirrup brace.[119] A further trial, currently underway in the Netherlands, includes ankle sprains of all severities and comparing no support with taping or a stirrup brace.[272] Additional reviews have acknowledged the findings of CAST but indicate preferences for early ankle movement.[109, 123] All these studies mention the recommendation for early ankle movement based on the 2002 Cochrane review.

In contrast to the criticisms of CAST, a short period of cast immobilisation for severe ankle sprains has been recommended in more recent systematic reviews[180, 209] and in clinical guidelines by the Orthopaedic Section of the American Physical Therapy Association, published in 2013.[138] However, the advice to clinicians in the NHS remains generic regarding severe sprains - that joints should be immobilised for a few days only.[165]

6.1.3 Barriers to the implementation of the findings of CAST

A barrier to implementation of the findings of CAST into clinical practice and the broader ankle sprain literature may relate to the lack of information on the effects of the different ankle supports on specific mobility tasks and whether there was an earlier return to usual sports or activities. The FAOS function and sport sub-scales and SF-12 Physical Component Scale are a composite of many contrasting tasks and symptoms. As highlighted in section 2.2, p.19, the activities of daily living subscale includes diverse questions relating to climbing stairs, walking, shopping, bed mobility and domestic duties.

There is also some basis for concern that while short-term immobilisation in a below-knee cast may lead to positive effects on recovery of lower level functional tasks overall, it may be detrimental to tasks requiring a larger range of ankle motion or level of muscle control. After removal of the cast, tasks such as squatting, descending stairs, jumping and running require larger ranges of ankle range of motion and muscle control than, for example, walking tasks.[64, 172, 191, 198]

Diminished joint range of motion and muscle strength are well established consequences of a period of immobilisation[103, 162] and therefore, may well have different effects on different types of mobility tasks and return to sports. Additional information on recovery of specific mobility tasks and rates of return to usual sports or activities would be informative to clinicians and researchers.

This secondary analysis aims to explore the effects of ankle supports on different types of mobility tasks and return to sport outcomes to aid clinical interpretation and facilitate implementation of the findings of CAST, as well as generate questions to direct future research.

6.2 Objectives

Primary objective:

- To determine the effects of different types of ankle support on short- and medium-term recovery of mobility after severe ankle sprain.

Secondary objectives:

- To analyse the effects of different types of ankle support on return to sport and usual activities.
- To explore the effect of age and gender on the effects of ankle support.
- To investigate the relationship between age and pain as a potential mechanism for explaining the influence of age on mobility outcomes.

6.3 Methods

6.3.1 Design

This secondary exploratory analysis was undertaken after the original trial results were analysed and reported. The CAST Trial protocol is described in detail elsewhere[118] and key features relevant to this analysis are detailed below. A summary of the study design is shown in Figure 66.

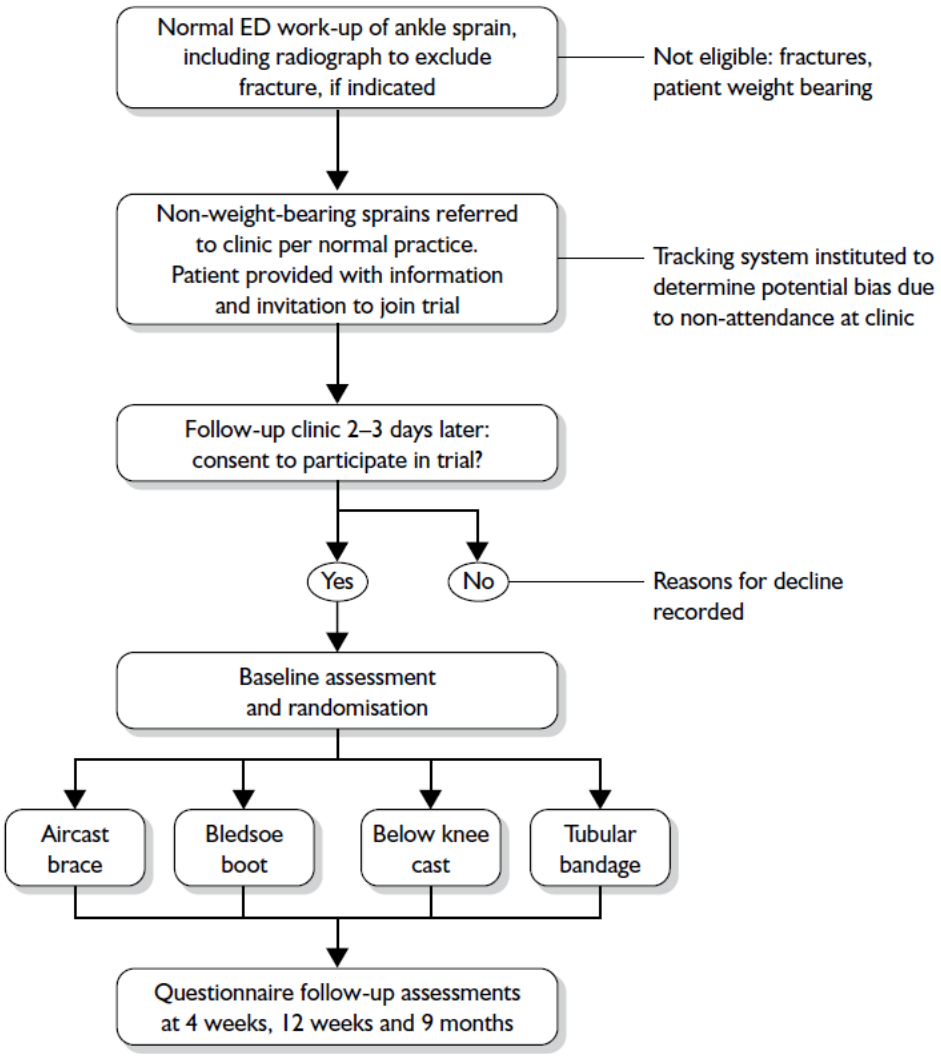


Figure 66: Flow diagram of participants through the CAST study. ED, emergency department. This figure was published in Cooke et al.[39], Health Technology Assessment (HTA), NIHR Journals Library (2009).

6.3.2 Setting

Eight emergency departments in National Health Service (NHS) England, UK.

6.3.3 Participants

Participants were from a pragmatic multicentre individually randomised controlled trial (n=584). Participants had attended an emergency department with a severe ankle ligament sprain. The severe nature of the sprain was inferred by an inability to weight bear at initial presentation and also at a trial clinic review 2-3 days later, consistent with a grade II and III ligament sprain (Table 2, p.6). The pragmatic clinical criteria of weight bearing ability to assess ankle sprain severity was selected to reflect emergency department practice in the UK.[38] It was not reflective of clinical practice in the UK to wait 5 days to conduct a full physical examination to assess injury severity, even though there is some evidence that delayed examination gives higher diagnostic sensitivity and specificity than examination at 2 days.[244] All participants had radiographs of the ankle as the Ottawa ankle rules indicate that inability to weight bear, along with pain in the malleolar region, requires imaging to rule out fracture.[4] The eligibility criteria for CAST are shown in Table 31.

Table 31: The CAST Trial eligibility criteria.

Inclusion criteria	Exclusion criteria
• Patients attending emergency departments with sprain of the ankle and an inability to weight bear at the time of presentation to the emergency department and their review clinic appointment. • Age 16 years and older. • Able to give informed consent.	• Age less than 16 years (because of the possibility of confusion with epiphyseal injuries). • Ankle fracture (except flake fractures of less than 2 mm as these are normally treated as soft-tissue injuries). • Any other recent fracture. • Any contraindication to any of the four arms of the trial (e.g. high risk of deep-vein thrombosis). • Poor skin viability preventing splinting or casting. • Injury more than 7 days previously.

6.3.4 Baseline assessments

Prior to randomisation a range of baseline assessments were conducted, including:

- Demographics: age (yrs), gender, Body Mass Index ([BMI], kg/m^2) was calculated from patient-reported height and weight.
- Injury characteristics: previous instability, pain measured at rest and when attempting to weight bear, using a visual analogue scale ([VAS], 0-100, 0=no pain and 100=worst pain imaginable).

6.3.5 Interventions

Three different types of mechanical ankle support designed to limit ankle range of motion were compared with Tubigrip (Mölnlycke Health Care, Göteborg, Sweden). Tubigrip is an elasticated tubular bandage that does not provide mechanical ankle support. Tubigrip was applied in a double layer from the tibial tuberosity to the metatarsal heads. The three types of ankle supports were:

- *Below-knee cast:* applied from the tibial tuberosity to the metatarsal heads. The cast consisted of an under-layer of Tubinette® (Mölnlycke Health Care, Göteborg, Sweden), a mid-layer of padding and then an outer complete synthetic rigid cast.
- *Ankle stirrup brace:* The Aircast® brace (DJO Incorporated, Vista, CA, USA). This stirrup brace offers compression around the malleolar region and is formed by two external semi-rigid struts medially and laterally, with a pneumatic cushion on the inside. The support restricts ankle motion in the frontal plane but allows motion in the sagittal plane.
- *Walker boot:* The Bledsoe® boot (Bledsoe Boot Systems, Grand Prairie, TX, USA) is a type of removable boot with fixed vertical struts attached to a foot-plate to restrict ankle range of movement in all planes.

Interventions were applied in the emergency department within 7 days of injury and a few hours after randomisation. The cast was applied for 10 days, the duration of Tubigrip, stirrup brace and walker boot use was not set for a specific duration in the study. Participants were advised to discontinue use when their ankle felt comfortable and they felt confident to do so. Depending on the hospital, interventions were applied by plaster technicians, physiotherapists or nurses. Standardised training was provided as part of the trial. The interventions in the trial were all described to participants prior to consent and randomisation. Participants refusing their randomised intervention were offered Tubigrip by default. Standardised written and verbal instructions were given to participants. The advice included information on the management of swelling, pain control, application of ice, progression of walking, when to remove and stop using

the ankle support, simple ankle exercises and how to wash the support in accordance with manufacturers' guidance. Walking aids were issued to all participants. Physiotherapy referral was permitted if deemed appropriate at follow-up. Randomisation was stratified by centre and was conducted centrally by an independent unit.

6.3.6 Outcomes

Outcomes were obtained via postal questionnaires with reminders and telephone calls to improve response rates.[161] The follow-up time points of 4 and 12 weeks are included in this analysis. The 9 month follow-up time point was not included as there is no evidence that ankle immobilisation has an effect on longer term ankle related-function/mobility outcomes after severe ankle injury (at one year following ankle ORIF in Chapter 3 and at 9 months in original CAST trial analysis). The focus of this study was to explore the effects of immobilisation in the earlier phases of recovery to build understanding of the effects of ankle supports on a range of mobility outcomes.

6.3.7 Mobility outcomes

Indicators of ongoing problems with a range of weight bearing mobility tasks were taken from the EQ-5D[56] and Foot and Ankle Outcome Score (FAOS; see section 2.2, p.19 for further details)[199] questionnaires used in CAST. This enabled the following outcomes to be investigated:

i. *General mobility problems:* the overall self-reported outcome of difficulties with general mobility was taken from the EQ-5D mobility question. The original question was a 3-point scale of no problem walking, some problems or confined to bed. This was converted to a binary outcome 'no problems' or 'problems' with mobility. This outcome was deemed useful clinically in two ways. Firstly, there is often an interest in which treatment will offer the quickest overall mobility recovery. Secondly, the EQ-5D is now used as a routine outcome measure in therapy departments in the UK, as promoted by the Chartered Society of Physiotherapy,[43] and so is broadly an outcome of interest to clinicians.

ii. *Difficulty with walking on a flat surface, ascending stairs, descending stairs, squatting, jumping and running:* separate subscales of the FAOS contain questions relating to a range of weight bearing mobility tasks. Each question allows responses on 5-point Likert scale; 'none', 'mild', 'moderate', 'severe', and 'extreme' difficulty. To assess the probability of ongoing difficulty with the mobility task, this was converted to a binary outcome with a cut off between 'none' and the other responses. Alternative options would have been to assess this as an ordinal outcome, but this has limitations. Likelihood of a binary outcome occurring, between no difficulty and difficulty with a functional activity, is simpler to interpret and therefore apply in the clinical context. In contrast, interpreting mild, moderate and severe difficulty is subjective and multiple likelihoods are more challenging to explain to patients and are more difficult to understand.

iii. *Return to usual sports or activities:* each participant was asked if they had returned to their usual sports or activities at each follow-up. A binary outcome between not returned and returned partly or fully was analysed.

6.3.8 Potential confounder and interaction variables

Age and gender are included in the analysis for two reasons. Firstly, the original CAST analysis already indicated age and gender as important covariates to consider.[39] Secondly, age and gender could also be important effect modifiers and so investigating interactions is an important step in investigating the effect of ankle supports on mobility outcomes.

An additional analysis was undertaken to explore whether pain was associated with age. Pain on weight bearing was reported on a visual analogue scale ([VAS], 0-100, 0=no pain and 100=worst pain imaginable).

6.3.9 Adherence

The levels of adherence with each ankle support were also reported as this is a key part of clinical interpretation of the results regarding the effects of different ankle supports on mobility outcomes.

6.3.10 Analysis

Baseline characteristics of participants and all primary and secondary outcome data were summarised as counts (%), means (SD) and range, as appropriate. Outcome data by ankle support and at each follow-up time point are summarised. A CONSORT flow diagram was used to illustrate the flow of participants through the study and analyses.[155]

The analysis was by intention-to-treat. Consistent with the design of the CAST Trial, intention-to-treat is required for pragmatic studies. An intention–to-treat analysis is where all participants of the trial are analysed according to their allocated intervention, regardless of what treatment they actually received.[97] The alternative is a per protocol analysis, where only participants who adhered to the study protocol, including adhering to treatment allocation, are included in the analysis.[97] The intention-to-treat approach provides clinicians with estimates of the effect of the treatment approaches within the realities of clinical practice rather than the effects for patients for whom the treatment adherence is absolute.[91] The original CAST Trial analysis found that overall results were consistent between the intention-to-treat analysis and sensitivity analyses exploring the influence of treatment uptake.[39]

Dealing with missing data

The baseline characteristics of those for whom data were or were not available for analysis were summarised and compared using parametric or non-parametric statistical comparisons, as appropriate. A complete case analysis was subsequently undertaken. In a complete case analysis, only participants with data on all variables are used in the analysis.[265] It was deemed reasonable to use this approach as the original trial underwent extensive imputation in sensitivity analyses, which indicated the findings were not sensitive to missing data.[39]

Logistic regression

The effect of ankle supports was estimated using logistic regression. The ankle supports (cast, stirrup brace and walker boot) were compared with Tubigrip, the reference category. The models were built in stages.

- Model 1: unadjusted model with the treatment groups as predictor variables.
- Model 2: adjusted model including variables for age and gender.
- Model 3: interaction model including interaction terms for treatment and gender, and treatment and age.

To determine if the model fit was improved by adjustment, the unadjusted and adjusted models were compared using the likelihood ratio test.[113, 130] The likelihood ratio test is a test statistic to compare the fit of a model with the previous one, to see whether adding the parameters improved the model fit. If it was not statistically significant (P<0.05), it indicated the additional terms did not improve the fit of the model. To test the null hypothesis of no interaction, the models with and without the interaction terms were compared using the likelihood ratio test.[113] The results of the interaction were only reported if the likelihood ratio test was statistically significant.

The odds ratios (OR) and 95% confidence intervals (CI) were calculated for each variable in each model. The OR is compared to the reference category of Tubigrip (OR set at 1.0). If the OR was >1.0 then the outcome was more likely in the comparator group, if OR<1 then the outcome was less likely in the comparator group. No adjustments were included for baseline scores as these were balanced between treatment groups.

Post-estimation analysis

Predicted probabilities with 95% CI for each logistic regression outcome were calculated and plotted by age (5 year increments from 20 to 60) for each ankle support. Goodness of fit was assessed using the Hosmer-Lemeshow Test. In the test, subjects were grouped into deciles of

predicted probabilities unless this resulted in substantially uneven group sizes, in which case the number of groups was reduced for the test.[94] A P-value of >0.05 was used as a cut off, indicating the model was well-fitting by failing to reject the null hypothesis of no difference between the observed and predicted values.

A statistical adjustment for multiple comparisons was not conducted due to recommendations that, on balance, this would introduce several other issues.[177] For example, adjustment for multiple comparisons increases type II error likelihood. Furthermore, each individual outcome was of interest in this exploratory study, not a universal null hypothesis, which is the basis for statistical adjustment.[177] Risk of type I error from multiple hypothesis testing was protected against by 1) specifying the number of analyses prior to conducting further analysis on the data and 2) by reporting 95% confidence intervals in addition to P-values - illustrating the range of likely effect estimates as well as the statistical significance.[160]

The relationship between age and pain outcomes

To explore if the influence of age on mobility and return to usual sports or activities was associated with pain, a linear regression plot with 95% CI of age with pain was conducted.

The analyses were conducted using STATA version 12 (StataCorp, College Station, TX, USA).

6.3.11 Sample size

As a study of an existing dataset, the sample size was pre-determined. However, to establish if there was sufficient power for the analytical approach described above, power analysis was conducted. To detect a 10% difference in probability of still having problems, between probabilities 0.3 and 0.2, with an alpha of 0.05, and strong correlation between predictor variables (0.6), 319 observations were required for 80% power and 436 observations were required for 90% power. Shifting the probability distribution to between 0.6 and 0.5 resulted in the requirement for 379 and 521 observations for 80% and 90% power respectively. The size of the CAST cohort was

therefore adequately powered to explore a reasonable effect size under this range of assumptions. The number of predictors was also well within the conservative recommendation for logistic regression of 10 events per predictor.[252]

6.4 Results

6.4.1 Participants

1522 patients with ankle sprain were seen in emergency departments, of whom 1192 attended the CAST clinic 3 days later. 512 patients did not meet the inclusion criteria, 17 declined and 17 did not participate for other reasons. 584 patients were eligible and consented to participation in the trial and were randomised (Figure 67). Baseline characteristics by randomisation group were well balanced (Table 32). The median number of days from injury to application of the ankle support was 3 (IQR 2). Follow-up for the trial was good at 4 weeks 486/584 (83%) and at 12 weeks 481/584 (82%). Item-level missing data for the different outcomes in the analysis were also favourable. At 4 weeks, data were available for the outcomes in this study ranged from 447/584 (77%) to 459/584 (79%) participants. At 12 weeks data was from 389/584 (67%) to 398/584 (68%) participants. Comparisons of baseline characteristics of those for whom data were or were not obtained were similar for the mobility outcome at 4 weeks (Table 33) and 12 weeks (Table 34). Several baseline characteristics were statistically significant different between participants who did and did not provide data. The size of the differences between participant baseline characteristics were not clinically important. The exception was a difference between genders at 12 weeks (Table 34), with a higher tendency for males not to respond.

6.4.2 Interventions

29/584 of participants (5%) refused to accept the randomised treatment; one participant each for the stirrup and walker boot groups (1%), 4 participants in the Tubigrip group (3%) and 23 participants in the cast group (16%). In the cast group the main reason for refusal was unwillingness to be put in a cast (n=8).

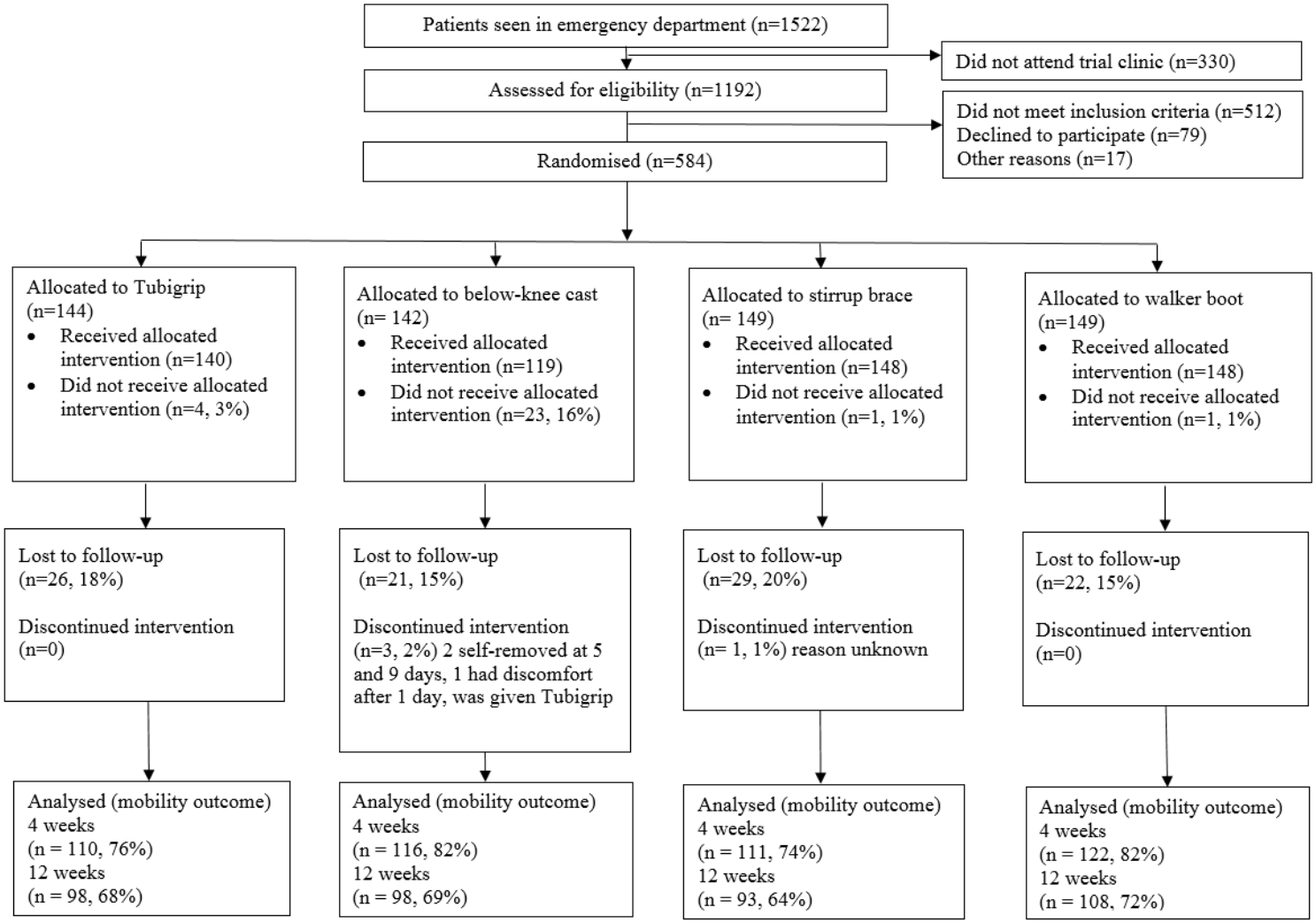


Figure 67: Flow diagram of participant progress through the trial and analysis.

Table 32: Baseline characteristics of study participants.

	Tubigrip	Below-knee cast	Stirrup brace	Walker boot	*P*-value
n	144	142	149	149	
Age (yrs), mean (SD)	31.2 (11.1)	29.5 (10.5)	29.2 (10.7)	29.7 (10.7)	0.36
Gender					0.69
Female	64 (44%)	54 (38%)	65 (44%)	64 (43%)	
Male	80 (56%)	88 (62%)	84 (56%)	85 (57%)	
Body Mass Index (kg/m^2), mean (SD)	26.5 (5.0)	27.0 (4.8)	26.1 (5.8)	25.8 (5.0)	0.30
Previous instability					0.67
Yes	30 (20.8%)	23 (16.2%)	26 (17.4%)	31 (20.8%)	
No	106 (73.6%)	111 (78.2%)	116 (77.9%)	112 (75.2%)	
Missing	8 (5.6%)	8 (5.6%)	7 (4.7%)	6 (4.0%)	
Pain at rest VAS, median (IQR)	32 (18, 55)	38.5 (19.5, 51.5)	40 (21.5, 55)	32 (18, 54.5)	0.68
Pain attempting weight bearing VAS, median (IQR)	78 (65, 90)	77 (67, 93)	80 (71, 90)	77 (61, 90)	0.30
SF-12 physical score[258], median (IQR)	35.8(27.0, 43.2)	37.7 (28.9, 43.1)	32.3 (27.5, 41.3)	34.2 (27.4, 43.4)	0.20
Mobility problems at baseline					0.71
No problems	7 (5%)	5 (4%)	4 (3%)	4 (2.7%)	
Problems	137 (95%)	136 (96%)	145 (97%)	145 (97.3%)	
Missing	0	1 (1%)	0	0	
Difficulty walking on a flat surface at baseline					0.80
No problems	1 (1%)	1 (1%)	0	1 (1%)	
Problems	138 (96%)	137 (97%)	143 (96%)	145 (97%)	
Missing	5 (4%)	4 (3%)	6 (4%)	3 (2%)	
Difficulty ascending stairs at baseline					0.38
No problems	1 (1%)	0	0	0	
Problems	137 (95 %)	137 (97%)	143 (96%)	146 (98%)	
Missing	6 (4%)	5 (4%)	6 (4%)	3 (2%)	
Difficulty descending stairs at baseline					0.38
No problems	1 (1%)	0	0	0	
Problems	137 (95%)	137 (97%)	142 (95%)	146 (98%)	
Missing	6 (4%)	5 (4%)	7 (5%)	3 (2%)	
Difficulty squatting at baseline					0.83
No problems	4 (3%)	4 (3%)	2 (1%)	4 (3%)	
Problems	133 (92%)	132 (93%)	136 (91%)	140 (94%)	
Missing	7 (5%)	6 (4%)	11 (7%)	5 (3%)	
Difficulty squatting at baseline					0.64
No problems	6 (4%)	4 (3%)	3 (2%)	3 (2%)	
Problems	130 (90%)	132 (93%)	135 (91%)	140 (94%)	
Missing	8 (6%)	6 (4%)	11 (7%)	6 (4%)	
Difficulty running at baseline					0.40
No problems	5 (4%)	4 (3%)	3 (2%)	1 (1%)	
Problems	131 (91%)	132 (93%)	135 (91%)	142 (95%)	
Missing	8 (6%)	6 (4%)	11 (7%)	6 (4%)	

Data are mean (SD) or n (%)

Table 33: Baseline characteristics of participants who did and did not provide data at 4 weeks after injury.

Factor	No data	Data obtained	*P*-value
n	125	459	
Randomisation Group			0.30
Tubigrip	34 (27%)	110 (24%)	
Below-knee cast	26 (21%)	116 (25%)	
Stirrup brace	38 (30%)	111 (24%)	
Walker boot	27 (22%)	122 (27%)	
Age (yrs), median (IQR)	25 (20, 36)	28 (21, 38)	0.077
Gender			0.23
Female	47 (38%)	200 (44%)	
Male	78 (62%)	259 (56%)	
Body Mass Index (kg/m^2), median (IQR)	24.7 (22.1, 28.6)	25.2 (23.0, 29.4)	0.24
Previous instability			0.096
Yes	30 (24%)	80 (17%)	
No	89 (71%)	356 (78%)	
Missing	6 (5%)	23 (5%)	
Pain at rest VAS (baseline), median (IQR)	35.5 (22.5, 51.5)	36 (18, 54.5)	0.67
Pain attempting weight bearing VAS (baseline), median (IQR)	80 (70, 90)	78 (65, 90)	0.17
SF12 physical score (baseline), median (IQR)	34.2 (28.1, 41.2)	34.7 (27.5, 43.1)	0.79
Mobility problems at baseline			0.21
No problems	2 (2%)	18 (4%)	
Problems	122 (98%)	441 (96%)	
Missing	1 (1%)	0	
Difficulty walking on a flat surface at baseline			0.36
No problems	0	3 (1%)	
Problems	122 (98%)	441 (96%)	
Missing	3 (2%)	15 (3%)	
Difficulty ascending stairs at baseline			0.057
No problems	1 (1%)	0	
Problems	121 (97%)	442 (96%)	
Missing	3 (2%)	17 (4%)	
Difficulty descending stairs at baseline			0.057
No problems	1 (1%)	0	
Problems	121 (97%)	441 (96%)	
Missing	3 (2%)	18 (4%)	
Difficulty squatting at baseline			0.51
No problems	4 (3%)	10 (2%)	
Problems	115 (92%)	426 (93%)	
Missing	6 (5%)	23 (5%)	
Difficulty jumping at baseline			0.028
No problems	7 (6%)	9 (2%)	
Problems	112 (90%)	425 (93%)	
Missing	6 (5%)	25 (5%)	
Difficulty running at baseline			0.13
No problems	5 (4%)	8 (2%)	
Problems	114 (91%)	426 (93%)	
Missing	6 (5%)	25 (5%)	

Data are median (IQR) or n (%)

Table 34: Baseline characteristics of participants who did and did not provide data at 12 weeks after injury.

Factor	Non-responder	Responder	*P*-value
n	187	397	
Randomisation Group			0.31
Tubigrip	46 (25%)	98 (25%)	
Below-knee cast	44 (24%)	98 (25%)	
Stirrup brace	56 (30%)	93 (23%)	
Walker boot	41 (22%)	108 (27%)	
Age (yrs), median (IQR)	26 (21, 35)	28 (21, 38)	0.065
Gender			0.019
Female	66 (35%)	181 (46%)	
Male	121 (65%)	216 (54%)	
Body Mass Index (kg/m^2), median (IQR)	24.7 (22.1, 29.4)	25.3 (23.1, 29.2)	0.27
Previous instability			0.28
Yes	40 (21%)	70 (18%)	
No	138 (74%)	307 (77%)	
Missing	9 (5%)	20 (5%)	
Pain at rest VAS (baseline), median (IQR)	40.5 (22, 55)	35 (18, 53)	0.15
Pain attempting weight bearing VAS (baseline), median (IQR)	80 (71, 91)	76 (64, 90)	0.004
SF12 physical score (baseline), median (IQR)	34.9 (27.9, 42.5)	34.1 (27.5, 43.1)	0.83
Mobility problems at baseline			0.50
No problems	5 (3%)	15 (4%)	
Problems	181 (97%)	382 (96%)	
Missing	1 (1%)	0	
Difficulty walking on a flat surface at baseline			0.96
No problems	1 (1%)	2 (1%)	
Problems	180 (96%)	383 (97%)	
Missing	6 (3%)	12 (3%)	
Difficulty ascending stairs at baseline			0.15
No problems	1 (1%)	0	
Problems	180 (96%)	383 (97%)	
Missing	6 (3%)	14 (4%)	
Difficulty descending stairs at baseline			0.15
No problems	1 (1%)	0	
Problems	180 (96%)	382 (96%)	
Missing	6 (3%)	15 (4%)	
Difficulty squatting at baseline			0.040
No problems	8 (4%)	6 (2%)	
Problems	169 (90%)	372 (94%)	
Missing	10 (5%)	19 (5%)	
Difficulty jumping at baseline			0.008
No problems	10 (5%)	6 (1.5%)	
Problems	166 (89%)	371 (94%)	
Missing	11 (6%)	20 (5%)	
Difficulty running at baseline			0.085
No problems	7 (4%)	6 (2%)	
Problems	169 (90%)	371 (94%)	
Missing	11 (6%)	20 (5%)	

Data are median (IQR) or n (%)

6.4.3 Mobility outcomes

Problems with general mobility (from EQ-5D)

At 4 and 12 weeks after injury, 49% and 29% of participants respectively reported problems with general mobility (Table 35). At 4 weeks 10-day cast immobilisation was associated with lower rates of participants reporting mobility problems (46/116 participants, 40%) compared with Tubigrip (59/110 participants, 54%), the difference was statistically significant in unadjusted analysis only (Table 36). At 12 weeks participants in the cast group (26/98 participants, 27%) and the walker boot group (23/108 participants, 21%) had better general mobility than those in the Tubigrip group (39/98 participants, 40%), indicating some benefit to immobilising the ankle after injury. However, only the results for the walker boot were statistically significantly different to Tubigrip after adjusting for age and gender (OR 0.45, 95% CI 0.24 to 0.85, *P*=0.011) (Table 36). Therefore, compared to the Tubigrip group, the odds of having problems with mobility at 12 weeks were reduced by 55% (95% CI 15 to 76) for the walker boot group. Predicted probabilities of mobility problems by age for different ankle supports after injury are shown for 4 weeks in Figure 68 and for 12 weeks in Figure 69. The probability of recovery favouring the below-knee cast at 4 weeks and the walker boot at 12 weeks can be observed. There was decreasing difference in the effects of ankle supports and a worsening outcome as age increased.

Table 35: Participant reported problems with general mobility at 4 and 12 weeks after injury.

Mobility	Tubigrip	Below-knee cast	Stirrup brace	Walker boot	Total
4 weeks					
No problems	51	70	53	58	232
Problems	59 (54%)	46 (40%)	58 (52%)	64 (52%)	227 (49%)
12weeks					
No problems	59	72	65	85	281
Problems	39 (40%)	26 (27%)	28 (30%)	23 (21%)	116 (29%)
Data are n (%)					

Table 36: Unadjusted and adjusted odds ratios (OR) with 95% CI for the effects of different types of ankle supports compared to Tubigrip on problems with general mobility at 4 and 12 weeks.

Mobility	Unadjusted			Adjusted		
Outcome	OR	95% CI	P	OR	95% CI	*P*
4 weeks (n=459)						
Tubigrip[a]	1.0	.		1.0	.	
Cast	0.57	0.34, 0.96	0.036	0.66	0.37, 1.15	0.14
Stirrup	0.95	0.56, 1.60	0.84	1.05	0.60, 1.84	0.86
Walker	0.95	0.57, 1.60	0.86	1.12	0.65, 1.93	0.70
Gender[b]	.	.	.	1.67	1.13, 2.49	0.011
Age	.	.	.	1.06	1.04, 1.08	<0.001
*LR test χ^2 (2)=47.30 *P*<0.001						
12 weeks (n=397)						
Tubigrip	1.0	.		1.0	.	
Cast	0.55	0.30, 0.99	0.05	0.60	0.32, 1.13	0.11
Stirrup	0.65	0.36, 1.19	0.16	0.73	0.39, 1.37	0.33
Walker	0.41	0.22, 0.76	0.004	0.45	0.24, 0.85	0.014
Gender[b]	.	.	.	1.73	1.09, 2.74	0.02
Age	.	.	.	1.04	1.02, 1.06	<0.001
*LR test χ^2 (2)=26.86 *P*<0.001						

[a]reference category. [b]coded 0=male. 1=female, LR=Likelihood Ratio. *unadjusted vs. adjusted model. OR<1=favours ankle support compared to Tubigrip, OR>1=favours Tubigrip over ankle support.

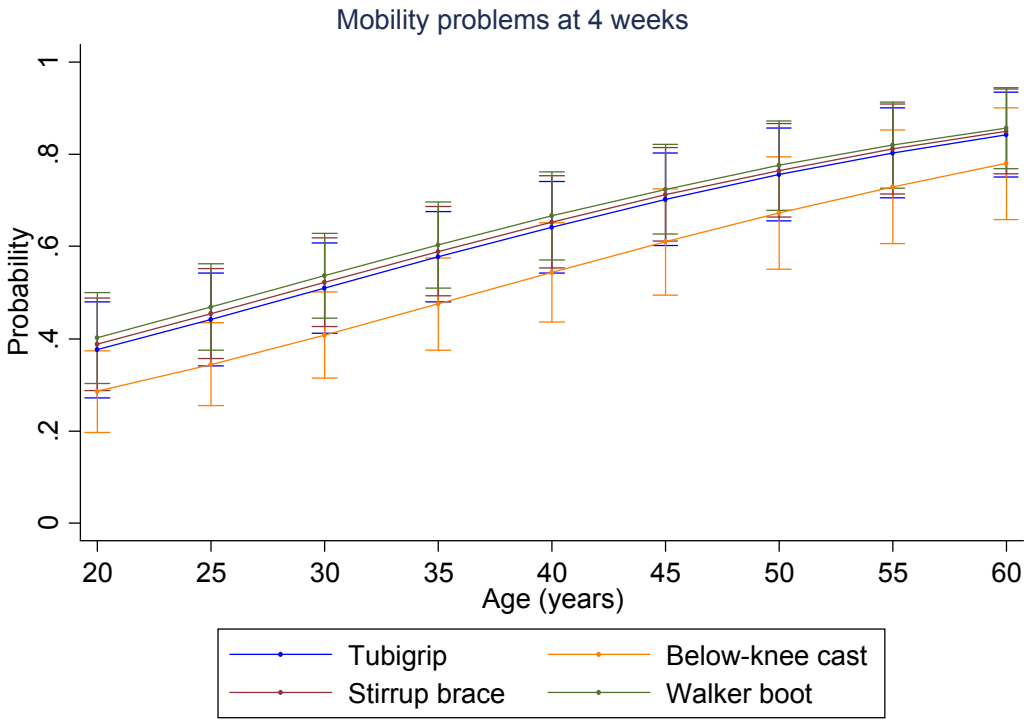


Figure 68: Predicted probability (95% CI error bar) of general mobility problems by age (years) for different ankle supports at 4 weeks after injury.

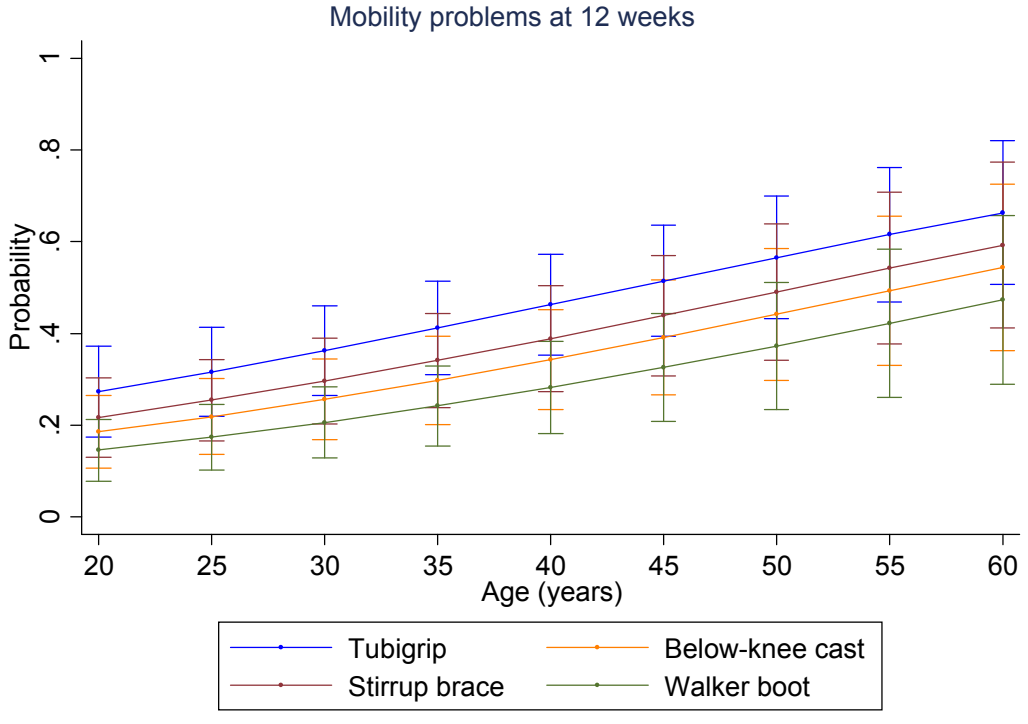


Figure 69: Predicted probability (95% CI error bar) of general mobility problems by age (years) for different ankle supports at 12 weeks after injury.

Difficulty walking on a flat surface

At 4 weeks and 12 weeks after injury, 55% and 34% of participants respectively reported difficulty walking on a flat surface (Table 37). At 4 weeks after injury there were lower rates of difficulty walking in the cast group (49/114 participants, 43%), compared with 58% to 61% in the other groups. There was a statistically significant difference in favour of the below-knee cast group compared with the Tubigrip group in both unadjusted and adjusted analyses (OR 0.55, 95% CI 0.31 to 0.96, *P*=0.035) (Table 38). Therefore, compared to the Tubigrip group, the odds of difficulty walking on a flat surface at 4 weeks were reduced by 45% (95% CI 4 to 69) for the 10-day cast immobilisation group. There were no differences in difficulty walking on a flat surface between the groups at 12 weeks. Predicted probabilities for difficulty walking by age and by ankle support are shown at 4 weeks in Figure 70 and at 12 weeks in Figure 71. The probability of recovery favouring the below-knee cast at 4 weeks can be observed, as can the narrower difference in effect of the supports and a worsening overall outcome as age increases.

Table 37: Participant reported difficulty walking on a flat surface reported at 4 and 12 weeks after injury.

Walking	Tubigrip	Below-knee cast	Stirrup brace	Walker boot	Total
4 weeks					
No problems	43	65	47	51	206
Problems	68 (61%)	49 (43%)	65 (58%)	70 (58%)	252 (55%)
12weeks					
No problems	60	71	58	74	263
Problems	40 (40%)	26 (27%)	35 (38%)	34 (31%)	135 (34%)
Data are n (%)					

Table 38: Unadjusted and adjusted odds ratios (OR) with 95% CI for the effects of different types of ankle supports compared to Tubigrip on difficulty walking on a flat surface at 4 and 12 weeks.

Walking	Unadjusted			Adjusted		
Outcome	OR	95% CI	P	OR	95% CI	*P*
4 weeks (n=458)						
Tubigrip[a]	1.0	.		1.0	.	
Cast	0.48	0.30, 0.94	0.03	0.55	0.31, 0.96	0.035
Stirrup	0.87	0.52, 1.66	0.81	0.96	0.54, 1.68	0.88
Walker	0.87	0.56, 1.74	0.97	1.02	0.59, 1.78	0.94
Gender[b]	.	.	.	1.93	1.30, 2.88	0.001
Age	.	.	.	1.05	1.03, 1.07	<0.001
*LR test χ^2 (2)=45.33 *P*<0.001						
12 weeks (n=398)						
Tubigrip[a]	1.0	.		1.0	.	.
Cast	0.55	0.30, 1.00	0.051	0.60	0.32, 1.13	0.11
Stirrup	0.91	0.51, 1.62	0.74	1.04	0.57, 1.90	0.91
Walker	0.69	0.39, 1.22	0.20	0.79	0.43, 1.42	0.43
Gender[a]	.	.	.	1.70	1.03, 2.63	0.02
Age	.	.	.	1.04	1.02, 1.06	<0.001
*LR test χ^2 (2)=26.73 *P*<0.001						

[a]reference category, [b]coded 0=male, 1=female, LR=Likelihood Ratio. *unadjusted vs. adjusted model. OR<1=favours ankle support compared to Tubigrip, OR>1=favours Tubigrip over ankle support.

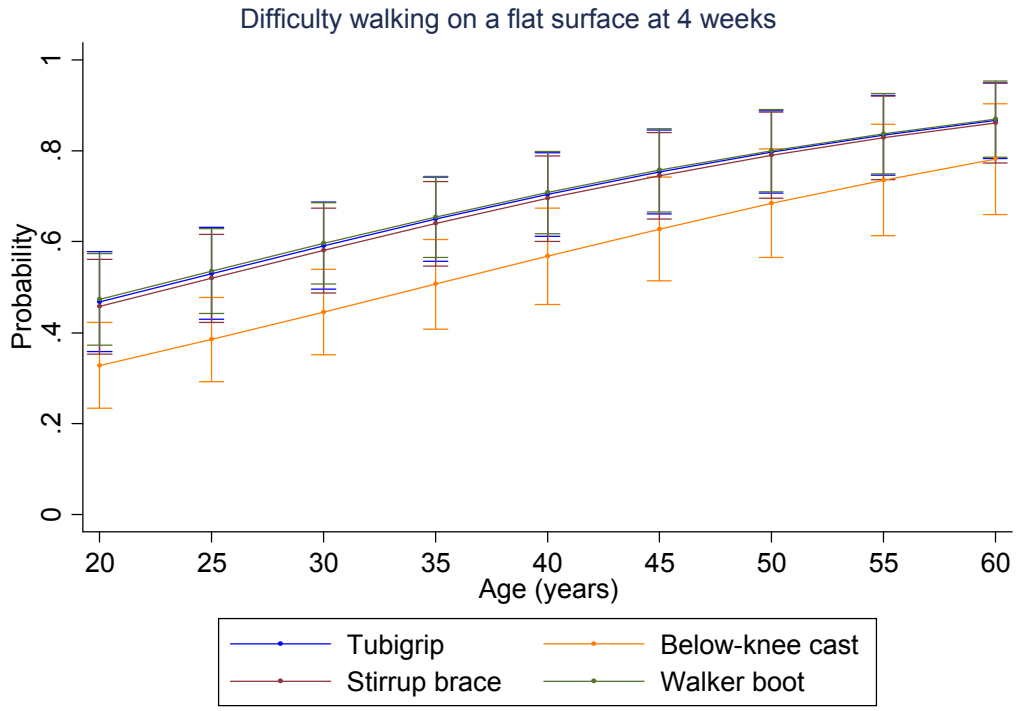


Figure 70: Predicted probability (95% CI error bar) of difficulty walking on a flat surface by age (years) for different ankle supports at 4 weeks after injury.

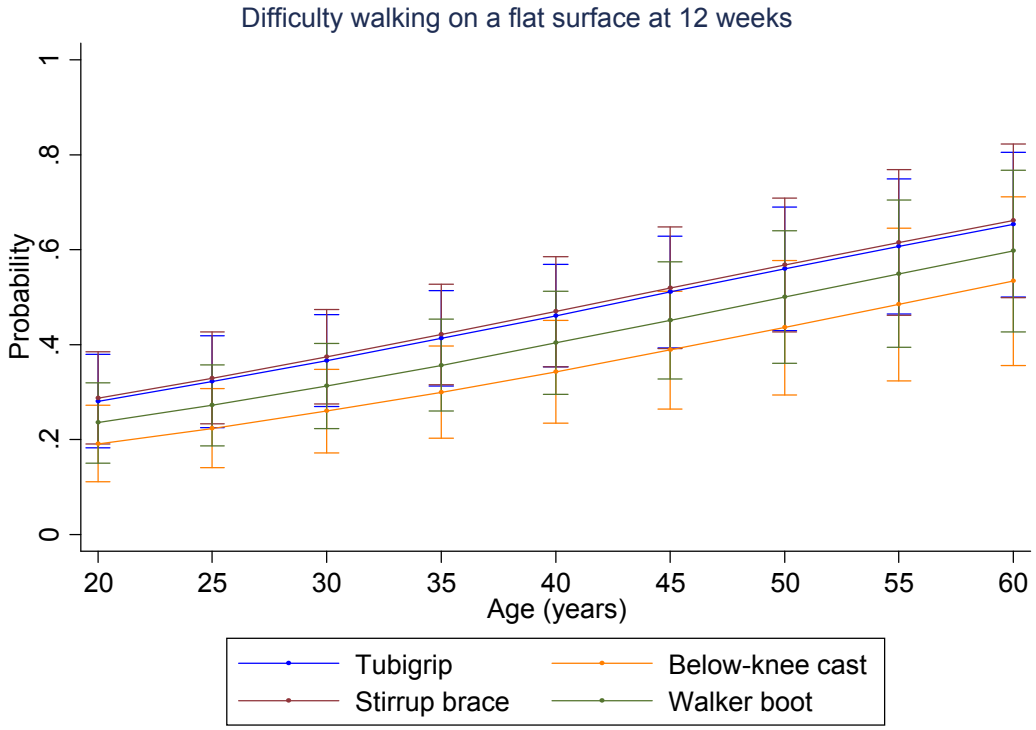


Figure 71: Predicted probability (95% CI error bar) of difficulty walking on a flat surface by age (years) for different ankle supports at 12 weeks after injury.

Difficulty ascending and descending stairs

At 4 weeks and 12 weeks after injury, 66% and 42% of participants respectively reported difficulty ascending stairs (Table 39) and 68% and 44% respectively reported difficulty descending stairs (Table 41). At 4 weeks after injury there were lower rates of difficulty negotiating stairs in the cast group (ascending 63/115 participants, 55% and descending 67/115 participants, 58%), compared with 69% to 72% in the other groups. The difference between the cast and Tubigrip groups was only statistically significant in unadjusted analysis (Table 40 and Table 42). There were no differences between groups at 12 weeks. Predicted probabilities for difficulty negotiating stairs by age and by ankle support are shown at 4 weeks in Figure 72 and Figure 74, and at 12 weeks in Figure 73 and Figure 75. The probability of recovery favouring the below-knee cast at 4 weeks can be observed, as can the narrower difference in effect between ankle supports and worsening overall outcome as age increases.

Table 39: Participant reported difficulty ascending stairs reported at 4 and 12 weeks after injury.

Ascend	Tubigrip	Below-knee cast	Stirrup brace	Walker boot	Total
4 weeks					
No problems	33	52	34	37	156
Problems	77 (70%)	63 (55%)	78 (70%)	84 (69%)	302 (66%)
12weeks					
No problems	54	62	45	68	229
Problems	45 (45%)	34 (35%)	48 (52%)	41 (38%)	168 (42%)
Data are n (%)					

Table 40: Unadjusted and adjusted odds ratios (OR) with 95% CI for the effects of different types of ankle supports compared to Tubigrip on difficulty ascending stairs at 4 and 12 weeks.

Ascend stairs	Unadjusted			Adjusted		
Outcome [a]	OR	95% CI	P	OR	95% CI	*P*
4 weeks (n=458)						
Tubigrip[a]	1.0	.		1.0	.	
Cast	0.52	0.30, 0.90	0.019	0.58	0.33, 1.03	0.062
Stirrup	0.98	0.55, 1.74	0.95	1.07	0.59, 1.93	0.83
Walker	0.97	0.55, 1.71	0.92	1.11	0.62, 1.99	0.73
Gender[b]	.	.	.	1.38	0.91, 2.09	0.13
Age	.	.	.	1.05	1.03, 1.07	<0.001
*LR test χ^2 (2)=30.01 *P*<0.001						
12 weeks (n=397)						
Tubigrip[a]	1.0	.		1.0	.	
Cast	0.66	0.37, 1.17	0.15	0.72	0.39, 1.30	0.27
Stirrup	1.28	0.73, 2.26	0.39	1.48	0.82, 2.67	0.19
Walker	0.72	0.42, 1.26	0.25	0.82	0.46, 1.45	0.49
Gender[a]	.	.	.	0.98	0.64, 1.50	0.93
Age	.	.	.	1.05	1.03, 1.07	<0.001
*LR test χ^2 (2)=25.15 *P*<0.001						

[a]reference category. [b]coded 0=male, 1=female. LR=Likelihood Ratio. *unadjusted vs. adjusted model. OR<1=favours ankle support compared to Tubigrip, OR>1=favours Tubigrip over ankle support.

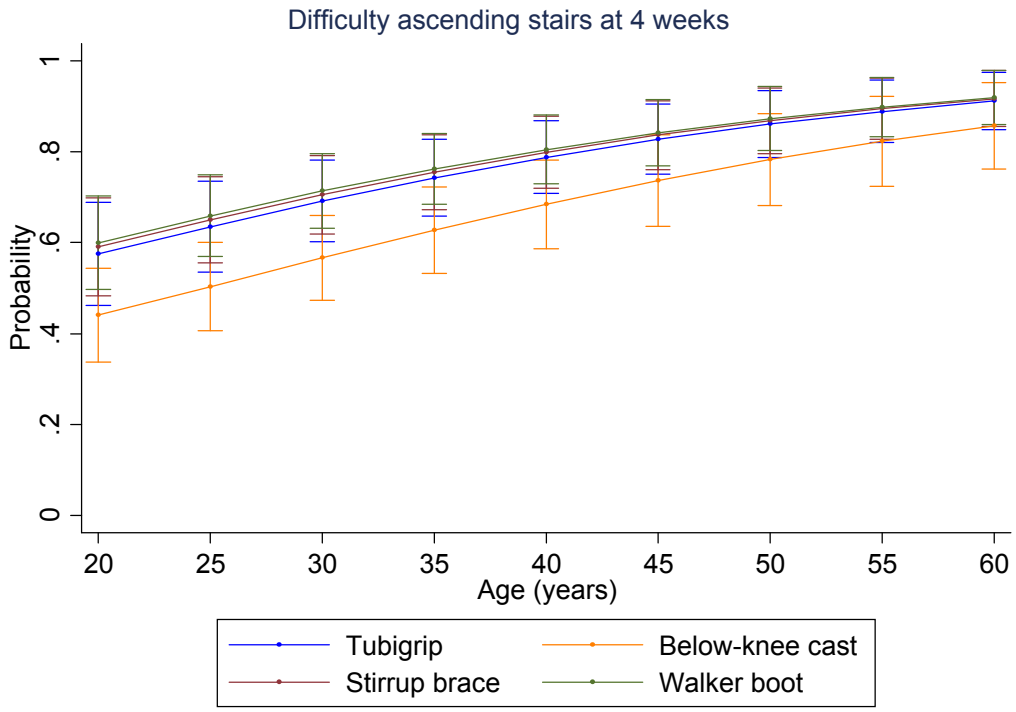


Figure 72: Predicted probability (95% CI error bar) of difficulty ascending stairs by age (years) for different ankle supports at 4 weeks after injury.

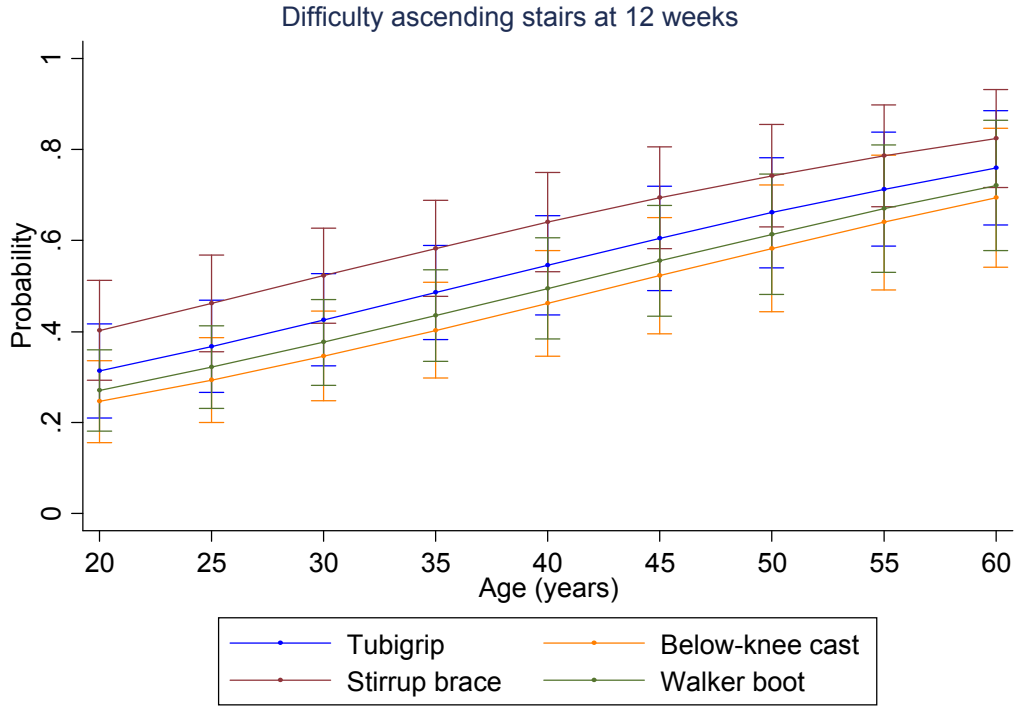


Figure 73: Predicted probability (95% CI error bar) of difficulty ascending stairs by age (years) for different ankle supports at 12 weeks after injury.

Table 41: Participant reported difficulty descending stairs reported at 4 and 12 weeks after injury.

Descend	Tubigrip	Below-knee cast	Stirrup brace	Walker boot	Total
4 weeks					
No problems	31	48	32	36	147
Problems	79 (72%)	67 (58%)	80 (71%)	85 (70%)	311 (68%)
12weeks					
No problems	50	61	46	66	223
Problems	49 (49%)	35 (36%)	47 (51%)	43 (39%)	174 (44%)
Data are n (%)					

Table 42: Unadjusted and adjusted odds ratios (OR) with 95% CI for the effects of different types of ankle supports compared to Tubigrip on difficulty descending stairs at 4 and 12 weeks.

Descend stairs	Unadjusted			Adjusted		
Outcome[a]	OR	95% CI	P	OR	95% CI	*P*
4 weeks (n=458)						
Tubigrip[a]	1.0	.		1.0	.	
Cast	0.55	0.31, 0.96	0.034	0.62	0.35, 1.10	0.10
Stirrup	0.98	0.55, 1.76	0.95	1.06	0.58, 1.94	0.84
Walker	0.93	0.52, 1.64	0.73	1.06	0.58, 1.90	0.86
Gender[b]	.	.	.	1.41	0.92, 2.15	0.11
Age	.	.	.	1.05	1.03, 1.08	<0.001
*LR test χ^2 (2)=29.57 *P*<0.001						
12 weeks (n=397)						
Tubigrip[a]	1.0	.		1.0	.	
Cast	0.59	0.33, 1.04	0.067	0.64	0.35, 1.17	0.15
Stirrup	1.04	0.59, 1.84	0.89	1.23	0.67, 2.23	0.50
Walker	0.66	0.38, 1.15	0.15	0.76	0.43, 1.36	0.36
Gender[a]	.	.	.	1.09	0.71, 1.67	0.69
Age	.	.	.	1.06	1.03, 1.08	<0.001
*LR test χ^2 (2)=37.93 *P*<0.001						

[a]reference category. [b]coded 0=male, 1=female. LR=Likelihood Ratio. *unadjusted vs. adjusted model. OR<1=favours ankle support compared to Tubigrip, OR>1=favours Tubigrip over ankle support.

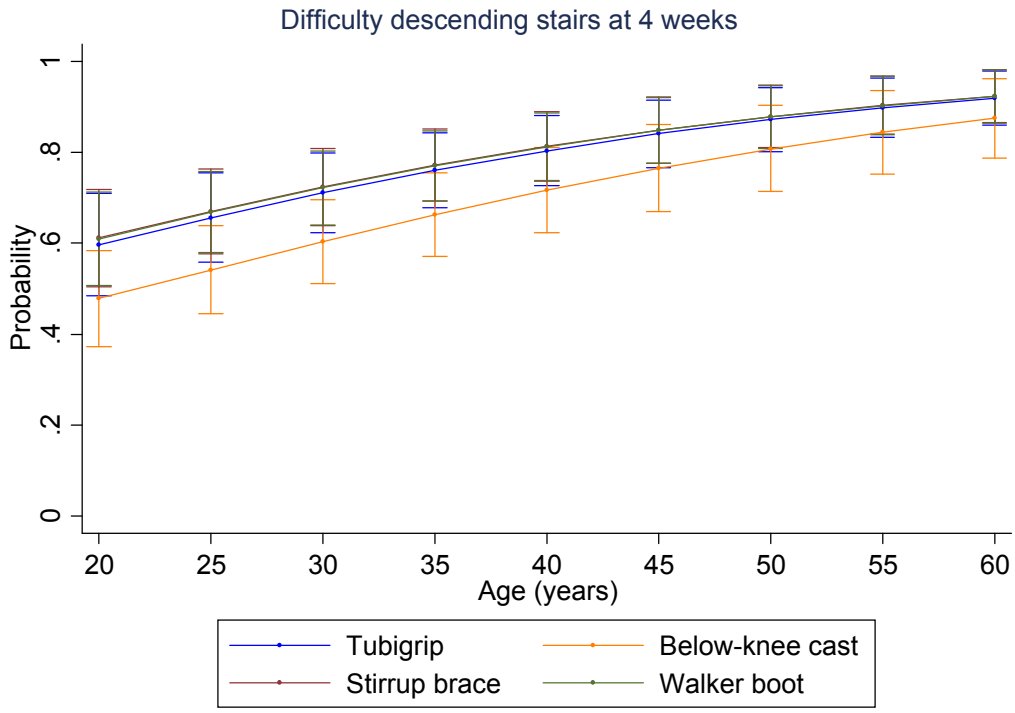


Figure 74: Predicted probability (95% CI error bar) of difficulty descending stairs by age (years) for different ankle supports at 4 weeks after injury.

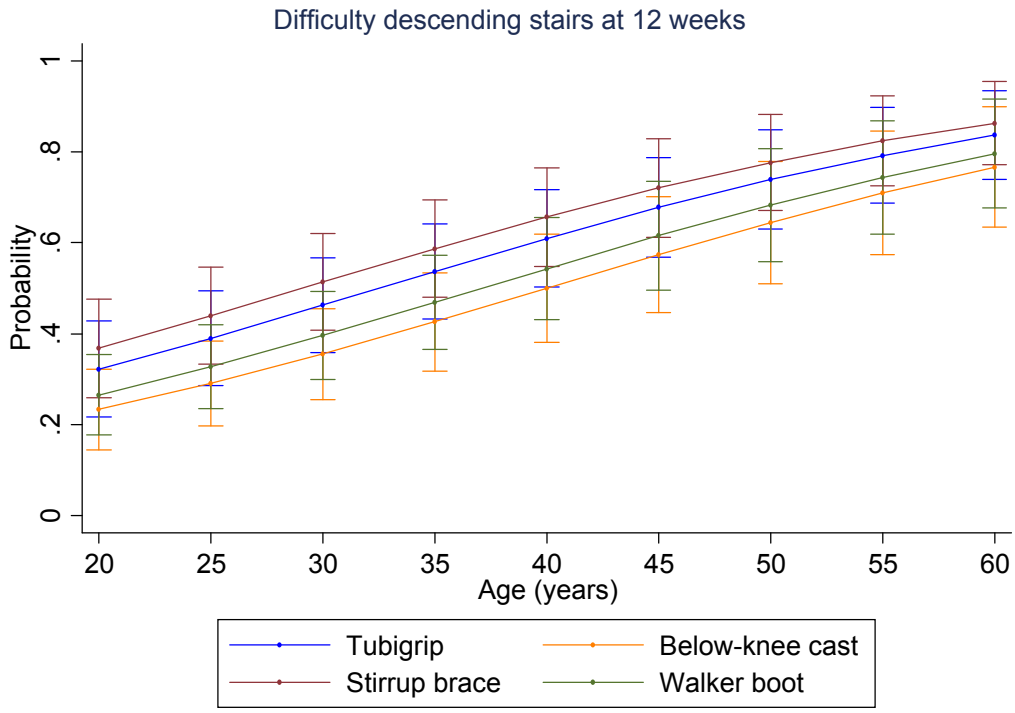


Figure 75: Predicted probability (95% CI error bar) of difficulty descending stairs by age (years) for different ankle supports at 12 weeks after injury

Difficulty squatting

At 4 and 12 weeks after injury, 80% and 63% of participants respectively reported difficulties squatting (Table 43). At 4 weeks there were no differences between the groups using different ankle supports (Table 44). At 12 weeks the 10-days of cast was (55/106 participants, 57%) was more beneficial than Tubigrip (69/97 participants, 71%). This finding was only statistically significant in unadjusted analysis. Predicted probabilities of difficulties squatting by age and by ankle support are shown at 4 weeks in Figure 76 and at 12 weeks in Figure 77. The probability of recovery favouring the below-knee cast group at 12 weeks, can be observed. The differences between the below-knee cast and other supports was narrower as age increases. A worsening overall outcome with increasing age is again observed.

Table 43: Participant reported difficulty squatting reported at 4 and 12 weeks after injury.

Squatting	Tubigrip	Below-knee cast	Stirrup brace	Walker boot	Total
4 weeks					
No problems	23	27	18	22	90
Problems	83 (78%)	88 (77%)	92 (84%)	96 (81%)	359 (80%)
12weeks					
No problems	28	41	32	42	143
Problems	69 (71%)	55 (57%)	61 (66%)	63 (60%)	248 (63%)
Data are n (%)					

Table 44: Unadjusted and adjusted odds ratios (OR) with 95% CI for the effects of different types of ankle supports compared to Tubigrip on difficulty squatting at 4 and 12 weeks.

Squatting	Unadjusted			Adjusted		
Outcome[a]	OR	95% CI	P	OR	95% CI	*P*
4 weeks (n=449)						
Tubigrip[a]	1.0	.		1.0	.	
Cast	0.90	0.48, 1.70	0.75	0.99	0.52, 1.90	0.99
Stirrup	1.42	0.71, 2.81	0.32	1.49	0.75, 2.99	0.56
Walker	1.2	0.63, 2.33	0.57	1.33	0.68, 2.59	0.40
Gender[b]	.	.	.	1.37	0.84, 2.25	0.21
Age	.	.	.	1.03	1.01, 1.07	0.003
*LR test χ^2 (2)=12.83 *P*=0.002						
12 weeks (n=391)						
Tubigrip[a]	1.0	.		1.0	.	
Cast	0.54	0.30, 0.99	0.046	0.58	0.32, 1.06	0.077
Stirrup	0.77	0.42, 1.43	0.41	0.83	0.44, 1.54	0.55
Walker	0.61	0.34, 1.10	0.098	0.65	0.36, 1.18	0.16
Gender[a]	.	.	.	1.20	0.78, 1.85	0.40
Age	.	.	.	1.03	1.01, 1.06	0.002
*LR test χ^2 (2)=12.42 *P*<0.001						

[a]reference category. [b]coded 0=male, 1=female. LR=Likelihood Ratio. *unadjusted vs. adjusted model. OR<1=favours ankle support compared to Tubigrip, OR>1=favours Tubigrip over ankle support.

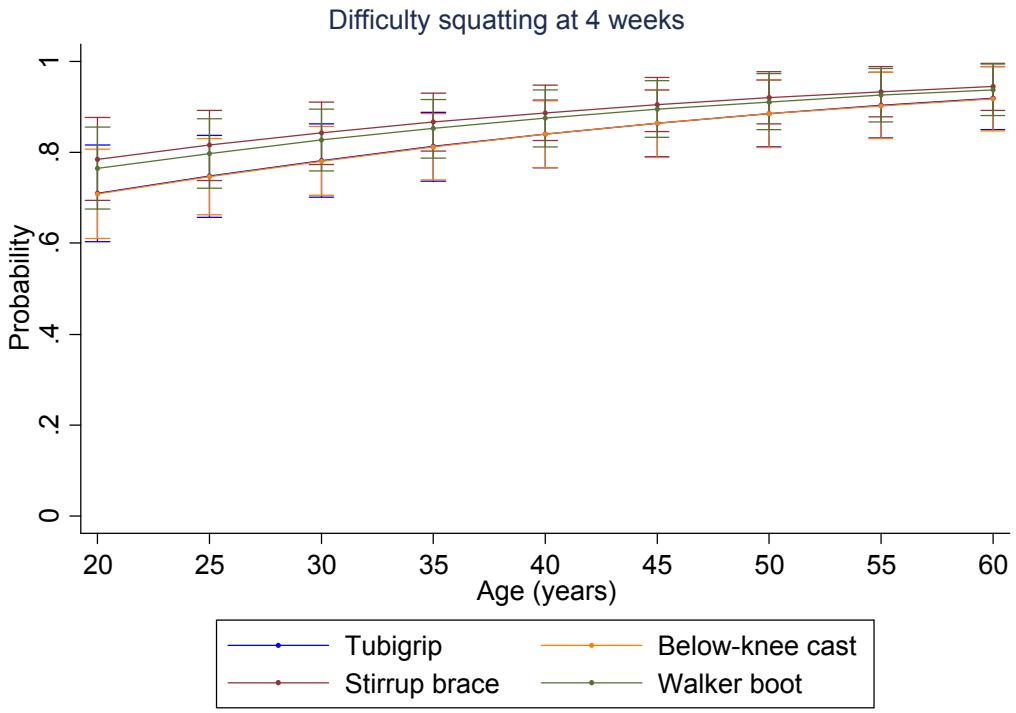


Figure 76: Predicted probability (95% CI error bar) of difficulty squatting by age (years) for different ankle supports at 4 weeks after injury.

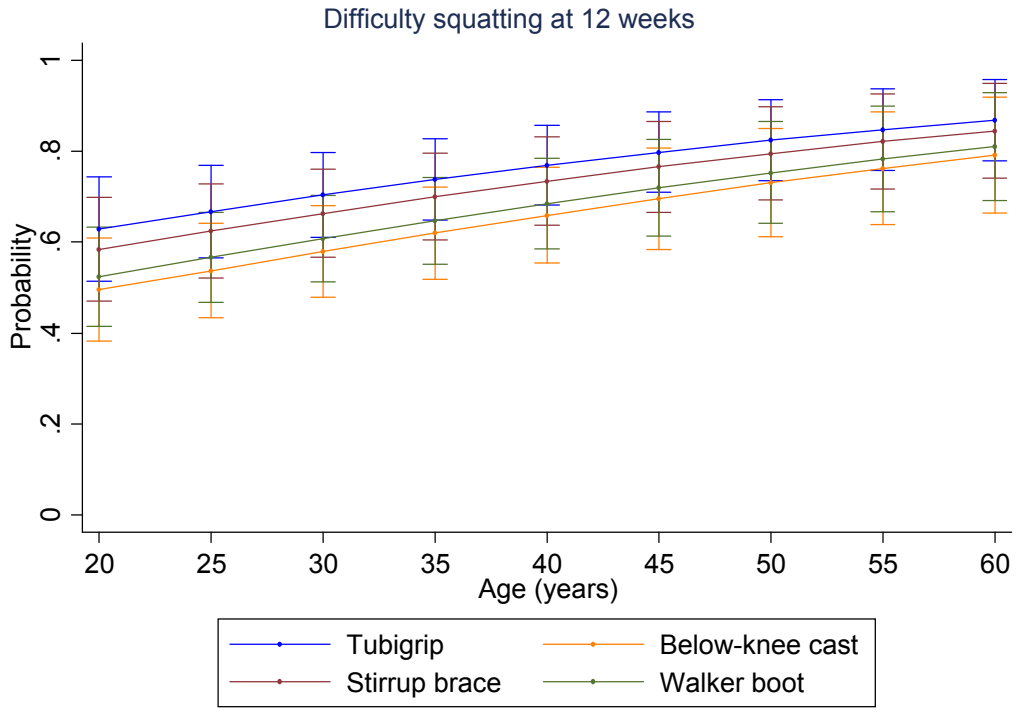


Figure 77: Predicted probability (95% CI error bar) of difficulty squatting by age (years) for different ankle supports at 12 weeks after injury.

Difficulty jumping

At 4 and 12 weeks after injury, 91% and 74% of participants respectively reported difficulties jumping (Table 45). At 4 weeks there was a statistically significant effect in favour of the cast and stirrup brace in the interaction model only (Table 46). The cast and stirrup brace offered more benefit to those aged less than 25 years (Figure 78). The observed improvements in outcome for older participants in the Tubigrip group are to be interpreted with caution due to wide confidence intervals for the estimates of effect in the age groups over 50 years. At 12 weeks there were statistically significant differences in unadjusted analyses in favour of the cast (63/95 participants, 66%), and to a lesser amount the walker boot (74/104 participants, 70%), when compared with Tubigrip (81/97 participants, 84%). This was not statistically significant when adjusted for age and gender. Predicted probabilities plotted by ankle support show a reducing treatment effect as age increases (Figure 79).

Table 45: Participant reported difficulty jumping reported at 4 and 12 weeks after injury.

Jumping	Tubigrip	Below-knee cast	Stirrup brace	Walker boot	Total
4 weeks					
No problems	8	15	10	9	42
Problems	98 (92%)	99 (87%)	100 (91%)	108 (92%)	405 (91%)
12 weeks					
No problems	16	32	23	31	102
Problems	81 (84%)	63 (66%)	70 (75%)	73 (70%)	287 (74%)
Data are n (%)					

Table 46: Unadjusted and adjusted odds ratios (OR) with 95% CI for the effects of different types of ankle supports compared to Tubigrip on difficulty jumping at 4 and 12 weeks.

Jumping	Unadjusted			Adjusted			Interaction		
Outcome	OR	95% CI	P	OR	95% CI	*P*	OR	95% CI	*P*
4 weeks (n=447)									
Tubigrip[a]	1.0	.		1.0	.		1.0	.	
Cast	0.54	0.22, 1.33	0.18	0.57	0.23, 1.41	0.22	0.004	<0.001, 0.10	0.001
Stirrup	0.82	0.31, 2.15	0.68	0.86	0.32, 2.28	0.76	0.03	0.001, 0.67	0.028
Walker	0.98	0.36, 2.64	0.97	1.05	0.39, 2.83	0.93	0.08	0.003, 1.8	0.11
Gender[b]	.	.	.	0.87	0.45, 1.67	0.67	1.14	0.26, 5.11	0.86
Age	.	.	.	1.04	1.00, 1.08	0.04	0.95	0.89, 1.01	0.11
Gender.Cast	.	.	.	.	.	.	0.76	0.11, 5.21	0.78
Gender.Stirrup	.	.	.	.	.	.	0.74	0.10, 5.46	0.77
Gender.Walker	.	.	.	.	.	.	0.66	0.89, 5.06	0.69
Age.Cast	.	.	.	.	.	.	1.20	1.07, 1.34	0.002
Age.Stirrup	.	.	.	.	.	.	1.13	1.01, 1.25	0.024
Age.Walker	.	.	.	.	.	.	1.09	0.99, 1.20	0.078
*LR test χ^2 (2)=4.85 *P*=0.089; **LR test χ^2 (8)=17.86 *P*=0.022									
12 weeks (n=389)									
Tubigrip[a]	1.0	.		1.0	.	.	.	.	
Cast	0.39	0.20, 0.77	.007	0.41	0.21, 0.82	0.012	.	.	.
Stirrup	0.60	0.29, 1.23	0.162	0.64	0.31, 1.31	0.22	.	.	.
Walker	0.47	0.24, 0.92	0.028	0.49	0.25, 0.98	0.043	.	.	.
Gender[a]	.	.	.	1.06	0.67, 1.70	0.79	.	.	.
Age	.	.	.	1.03	1.01, 1.05	0.014	.	.	.
*LR test χ^2 (2)=6.85 *P*=0.033									

[a]reference category. [b]Coded 0=male, 1=female. LR=Likelihood Ratio. *unadjusted vs. adjusted model, **unadjusted model vs. interaction model.
OR<1=favours ankle support compared to Tubigrip, OR>1=favours Tubigrip over ankle support.

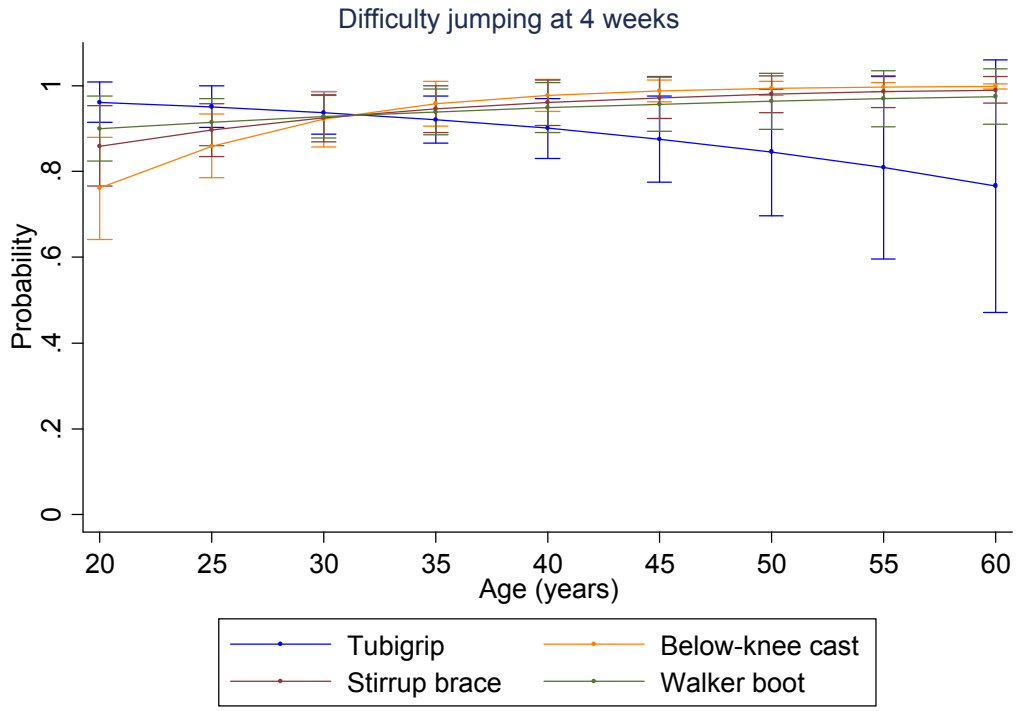


Figure 78: Predicted probability including age by treatment interaction (95% CI error bar) of difficulty jumping by age (years) for different ankle supports at 4 weeks after injury.

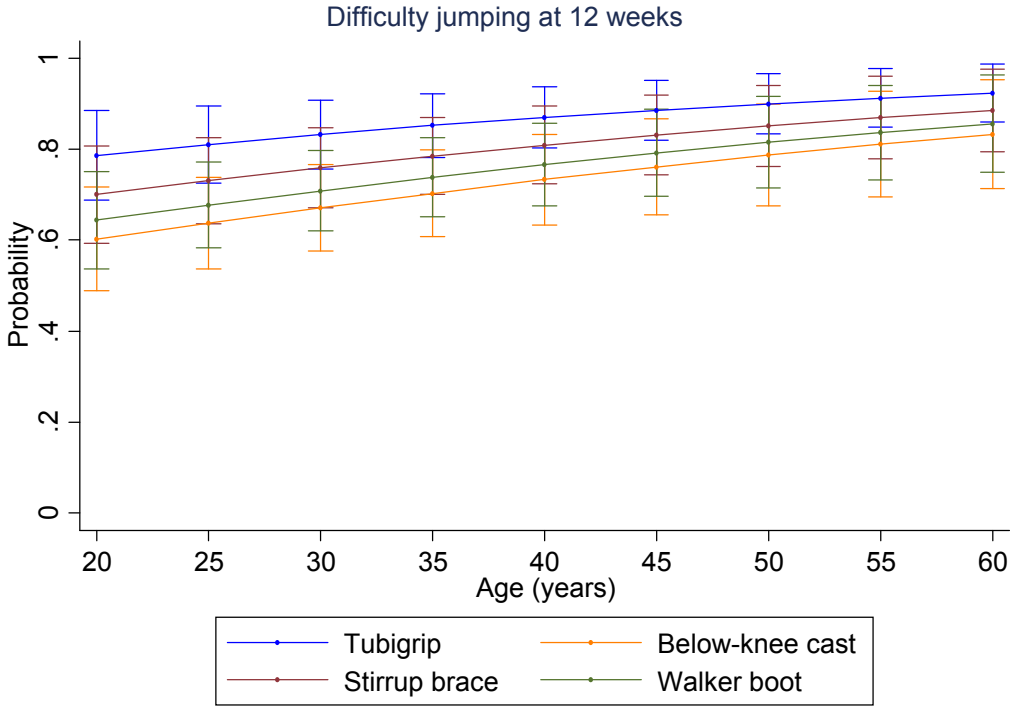


Figure 79: Predicted probability (95% CI error bar) of difficulty jumping by age (years) for different ankle supports at 12 weeks after injury.

Difficulty running

At 4 and 12 weeks after injury, 91% and 74% of participants respectively reported difficulties running (Table 47). Similar to jumping outcomes, at 4 weeks there was a statistically significant effect in favour of the cast and stirrup brace in the interaction model only (Table 48). The cast and stirrup brace offered more benefit to those aged less than 25 years (Figure 80). The observed improvements in outcome for older participants in the Tubigrip group are to be interpreted with caution due to wide confidence intervals for the estimates of effect in the age groups over 50 years. There were no differences between supports at 12 weeks. Predicted probabilities plotted by support again show the reducing treatment effect differences between supports as age increases (Figure 81).

Table 47: Participant reported difficulty running reported at 4 and 12 weeks after injury.

Running	Tubigrip	Below-knee cast	Stirrup brace	Walker boot	Total
4 weeks					
No problems	8	15	9	8	40
Problems	99 (93%)	99 (87%)	101 (92%)	110 (93%)	409 (91%)
12weeks					
No problems	20	30	24	28	102
Problems	77 (79%)	65 (68%)	69 (74%)	76 (73%)	287 (74%)
Data are n (%)					

Table 48: Unadjusted and adjusted odds ratios (OR) with 95% CI for the effects of different types of ankle supports compared to Tubigrip on difficulty running at 4 and 12 weeks.

Running	Unadjusted			Adjusted			Interaction		
Outcome	OR	95% CI	P	OR	95% CI	*P*	OR	95% CI	*P*
	4 weeks (n=449)								
Tubigrip[a]	1.0	.		1.0	.		1.0	.	
Cast	0.53	0.22, 1.31	0.17	0.57	0.23, 1.43	0.23	0.01	<0.001, 0.28	0.006
Stirrup	0.91	0.34, 2.45	0.85	0.93	0.35, 2.53	0.89	0.01	<0.001, 0.31	0.010
Walker	1.11	0.40, 3.07	0.84	1.19	0.43, 3.30	0.74	0.91	<0.35, 23.26	0.95
Gender[b]	.	.	.	1.28	0.64, 2.56	0.49	1.86	0.40, 8.67	0.43
Age	.	.	.	1.03	0.99, 1.06	0.14	0.96	0.90, 1.02	0.20
Gender.Cast	.	.	.	.	.	.	0.34	0.05, 2.32	0.27
Gender.Stirrup	.	.	.	.	.	.	1.04	0.12, 8.84	0.97
Gender.Walker	.	.	.	.	.	.	1.55	0.15, 16.19	0.72
Age.Cast	.	.	.	.	.	.	1.16	1.04, 1.29	0.006
Age.Stirrup	.	.	.	.	.	.	1.19	1.04, 1.37	0.012
Age.Walker	.	.	.	.	.	.	1.00	0.91, 1.10	0.99
*LR test χ^2 (2)=3.29 *P*=0.19; **LR test χ^2 (8)=20.79 *P*=0.0077									
	12 weeks (n=389)								
Tubigrip[a]	1.0	.		1.0	.		.	.	
Cast	0.56	0.29, 1.08	0.085	0.60	0.31, 1.15	0.12	.	.	.
Stirrup	0.75	0.38, 1.47	0.40	0.78	0.40, 1.55	0.48	.	.	.
Walker	0.71	0.37, 1.36	0.30	0.74	0.38, 1.44	0.38	.	.	.
Gender[a]	.	.	.	1.30	0.81, 2.08	0.27	.	.	.
Age	.	.	.	1.02	0.99, 1.05	0.07	.	.	.
*LR test χ^2 (2)=5.29 *P*=0.071									

[a]reference category. [b]coded 0=male, 1=female. LR=Likelihood Ratio. *unadjusted vs. adjusted model, **unadjusted model vs. interaction model.
OR<1=favours ankle support compared to Tubigrip, OR>1=favours Tubigrip over ankle support.

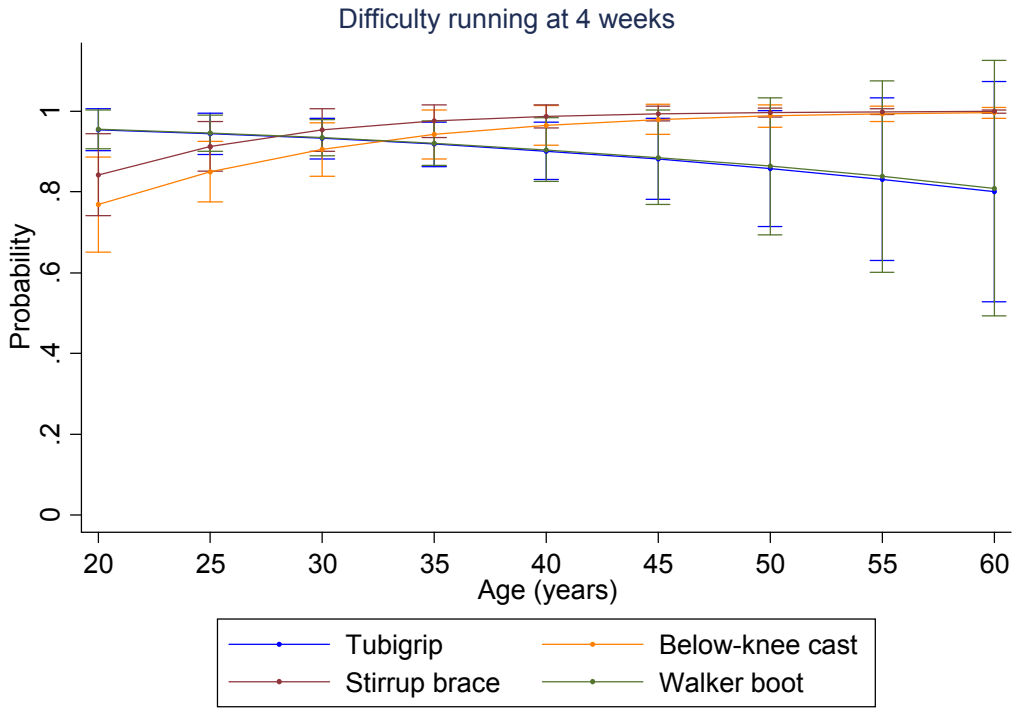


Figure 80: Predicted probability including age by treatment interaction (95% CI error bar) of difficulty running by age (years) for different ankle supports at 4 weeks after injury.

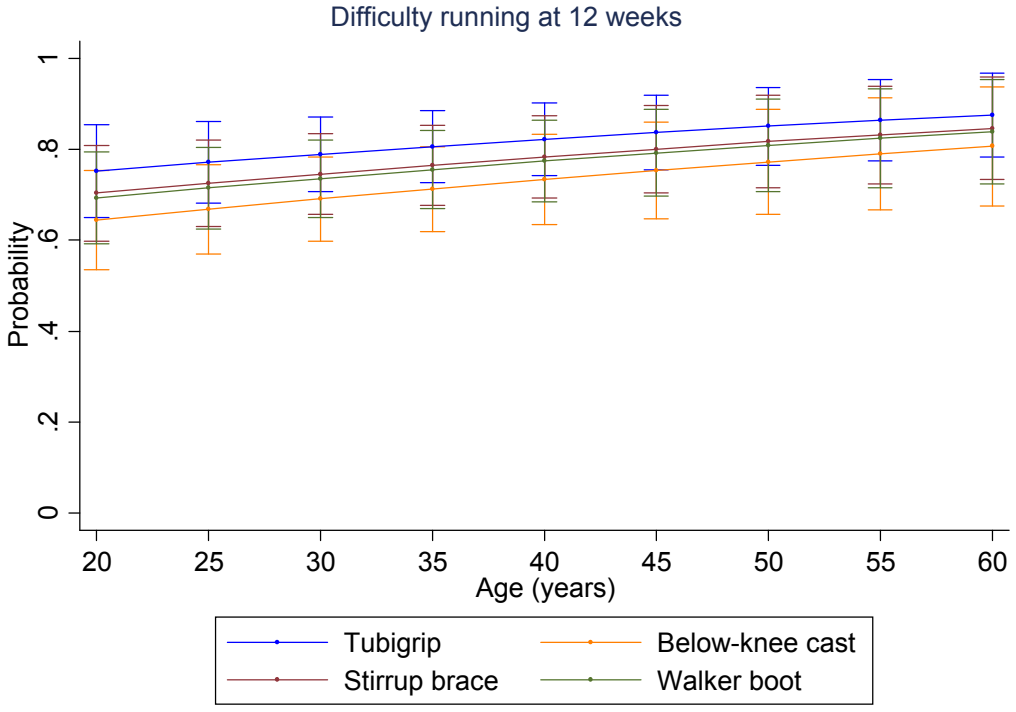
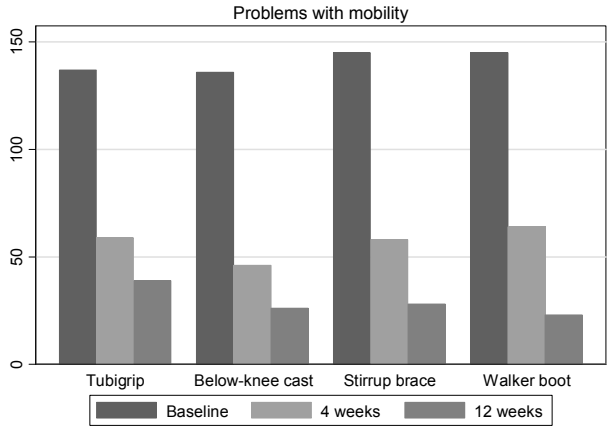


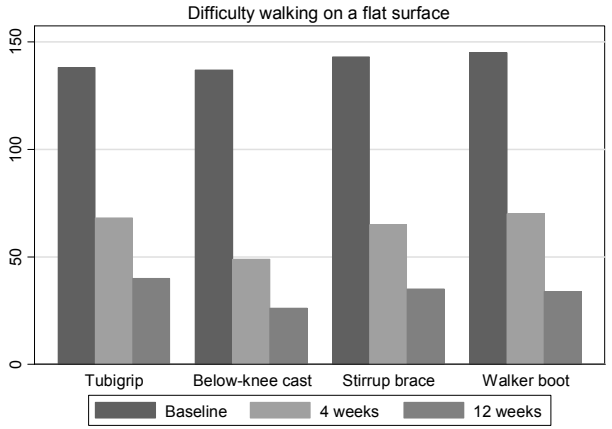
Figure 81: Predicted probability (95% CI error bar) of difficulty running by age (years) for different ankle supports at 12 weeks after injury.

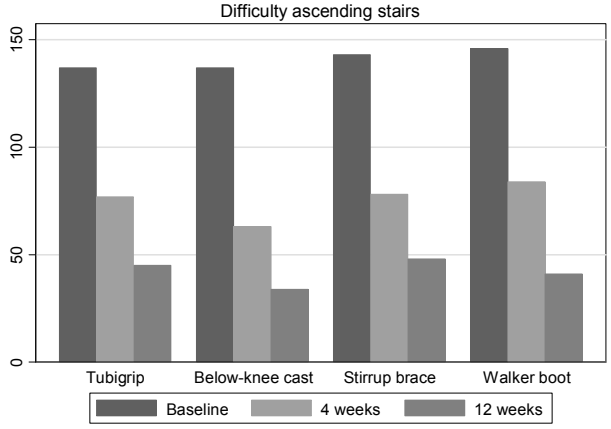
6.4.4 Comparison of different types of mobility outcomes

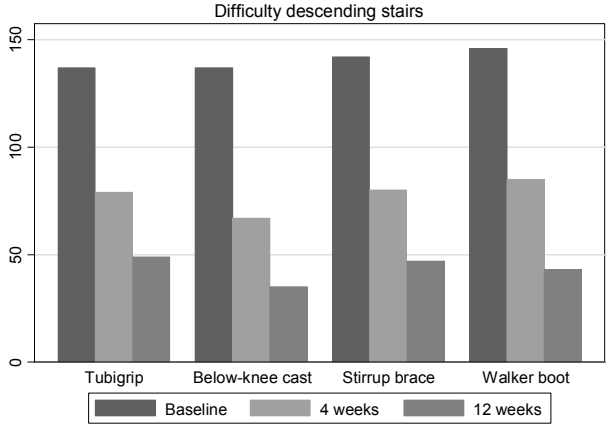
The recovery of different mobility tasks from baseline through to 4 and 12 weeks had a steep rate of improvement between baseline and 4 weeks compared with the improvement between 4 and 12 weeks, as shown in Figure 82.

When the effects for each ankle support on functional outcomes are compared with Tubigrip, at 4 weeks (Figure 83) and 12 weeks (Figure 84), an overall pattern emerges. At 4 weeks, outcomes appear to favour cast immobilisation and at 12 weeks the other supports, particularly the walker boot, have also improved for most outcomes compared with Tubigrip. It is also notable that although odds ratios are reasonably consistent, 95% confidence intervals are consistent with no difference in the majority of outcomes.


Problems with mobility
0
50
100
150
Tubigrip
Below-knee cast
Stirrup brace
Walker boot
Baseline
4 weeks
12 weeks


Difficulty walking on a flat surface
0
50
100
150
Tubigrip
Below-knee cast
Stirrup brace
Walker boot
Baseline
4 weeks
12 weeks


Difficulty ascending stairs
0
50
100
150
Tubigrip
Below-knee cast
Stirrup brace
Walker boot
Baseline
4 weeks
12 weeks


Difficulty descending stairs
0
50
100
150
Tubigrip
Below-knee cast
Stirrup brace
Walker boot
Baseline
4 weeks
12 weeks

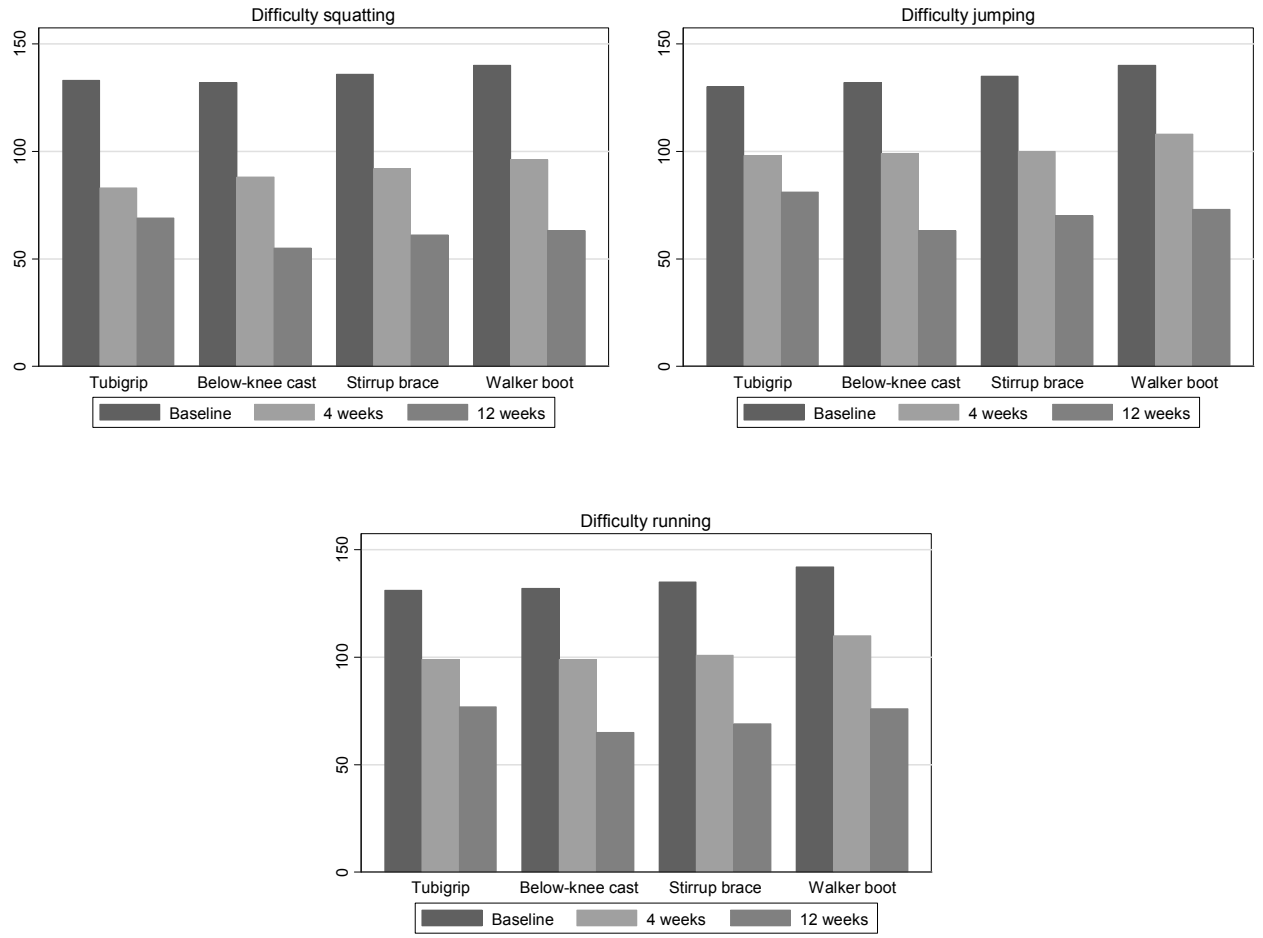


Figure 82: Bar charts showing the number of participants (y-axis) with problems with general mobility or difficulty with specific mobility tasks at baseline, 4 weeks and 12 weeks by ankle support.

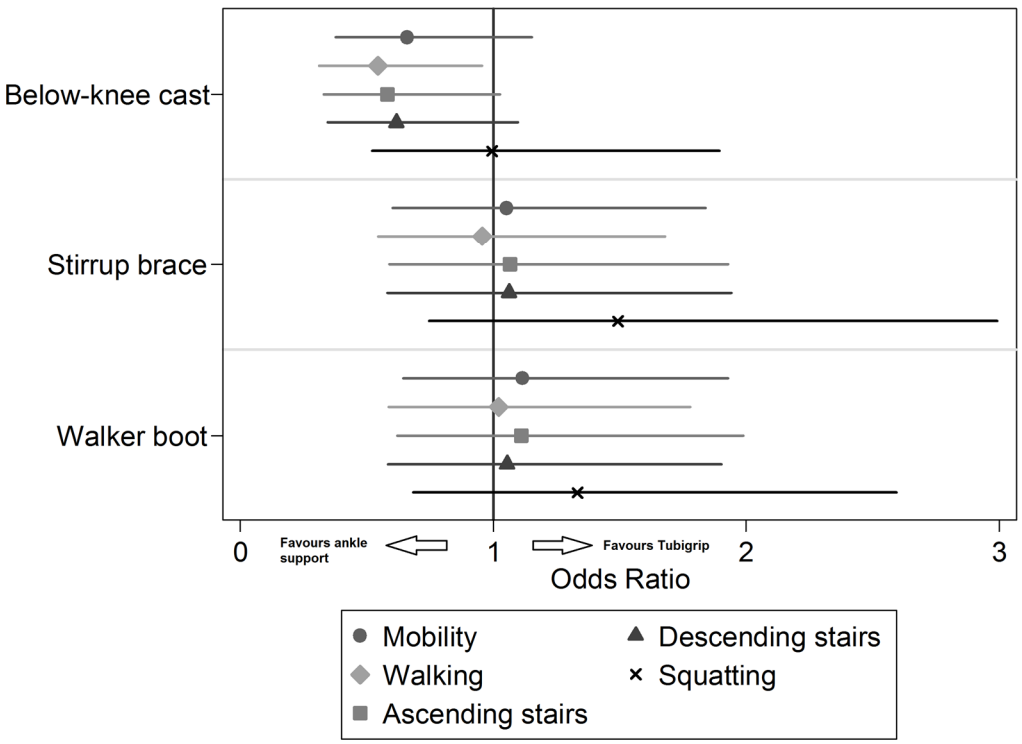


Figure 83: Odds Ratio with 95% CI of difficulties for mobility outcomes compared to Tubigrip at 4 weeks by ankle support. Note: jumping and running outcomes are omitted due to interaction effect with age. Reference line on x-axis denotes odds ratio 1.0 (no difference).

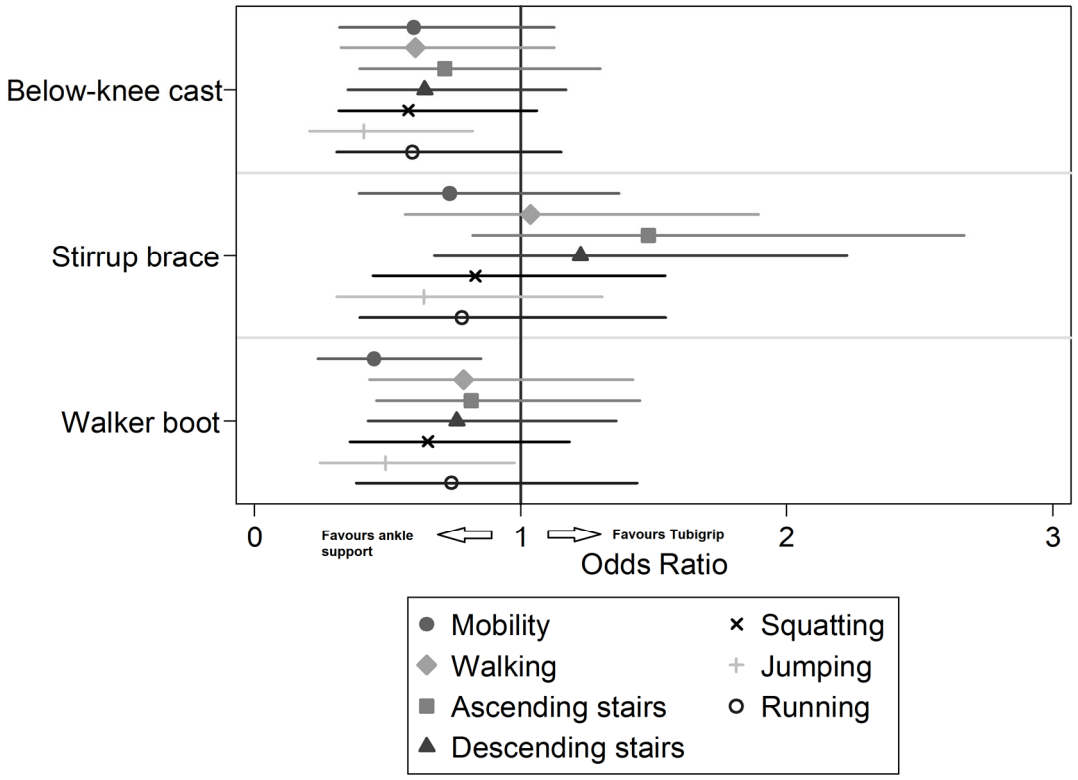


Figure 84: Odds Ratio with 95% CI of difficulties for mobility outcomes compared with Tubigrip at 12 weeks by ankle support. Reference line on x-axis denotes odds ratio 1.0 (no difference).

6.4.5 Return to usual sports and activities

Overall, approximately half of participants had returned to sports or activities at 4 weeks and three-quarters had returned by 12 weeks. At 4 weeks post injury, 60% of patients in the cast group, 57% in the stirrup brace group and 54% in the walker boot group had returned to sport, compared with 47% in the Tubigrip group (Table 49). The differences between groups were not statistically significant (Table 50). At 12 weeks there were no differences between groups, with return to sports being 72% for Tubigrip, 73% for the cast, 76% for the stirrup brace and 77% for the walker boot. The probability of recovery favouring the cast can be observed at 4 weeks (Figure 85). At 12 weeks the effects of the supports are similar (Figure 86).

Table 49: Participant reported return to usual sports and activities at 4 and 12 weeks after injury.

Sports	Tubigrip	Below-knee cast	Stirrup brace	Walker boot	Total
4 weeks					
Not returned	59	46	50	56	211
Returned	53 (47%)	69 (60%)	65 (57%)	65 (54%)	252 (54%)
12weeks					
Not returned	33	30	29	27	119
Returned	84 (72%)	83 (73%)	90 (76%)	92 (77%)	349 (75%)
Data are n (%)					

Table 50: Unadjusted and adjusted odds ratios (OR) with 95% CI for the effects of different types of ankle supports compared to Tubigrip on return to usual sports and activities at 4 and 12 weeks.

Sports	Unadjusted			Adjusted		
Outcome	OR	95% CI	P	OR	95% CI	*P*
4 weeks (n=463)						
Tubigrip[a]	1.0	.		1.0	.	
Cast	1.67	0.99, 2.83	0.056	1.69	0.99, 2.89	0.056
Stirrup	1.45	0.86, 2.44	0.17	1.39	0.81, 2.36	0.23
Walker	1.29	0.77, 2.16	0.33	1.27	0.75, 2.15	0.37
Gender[b]	.	.	.	1.70	1.13, 2.49	0.008
Age	.	.	.	0.97	1.04, 1.08	0.001
*LR test χ^2 (2)=16.44 *P*<0.001						
12 weeks (n=468)						
Tubigrip	1.0	.		1.0	.	
Cast	1.09	0.61, 1.94	0.78	1.01	0.56, 1.83	0.97
Stirrup	1.22	0.68, 2.18	0.50	1.13	0.63, 2.04	0.70
Walker	1.34	0.22, 2.41	0.33	1.26	0.69, 2.29	0.45
Gender[b]	.	.	.	1.28	0.82, 2.00	0.27
Age	.	.	.	0.96	0.94, 0.98	<0.001
*LR test χ^2 (2)=14.80 *P*<0.001						

[a]reference category. [b]coded 0=male, 1=female. LR=Likelihood Ratio. *unadjusted vs. adjusted model. OR<1=favours Tubigrip over ankle support, OR>1= favours ankle support compared to Tubigrip.

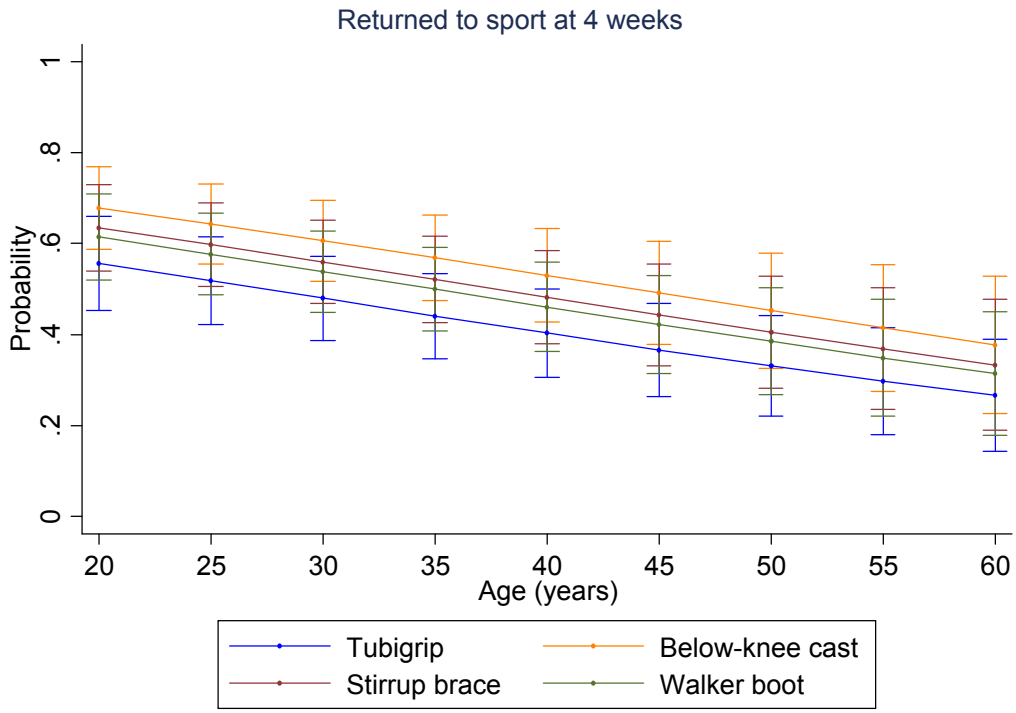


Figure 85: Predicted probability (95% CI error bar) of return to usual sports or activities by age (years) for different ankle supports at 4 weeks after injury.

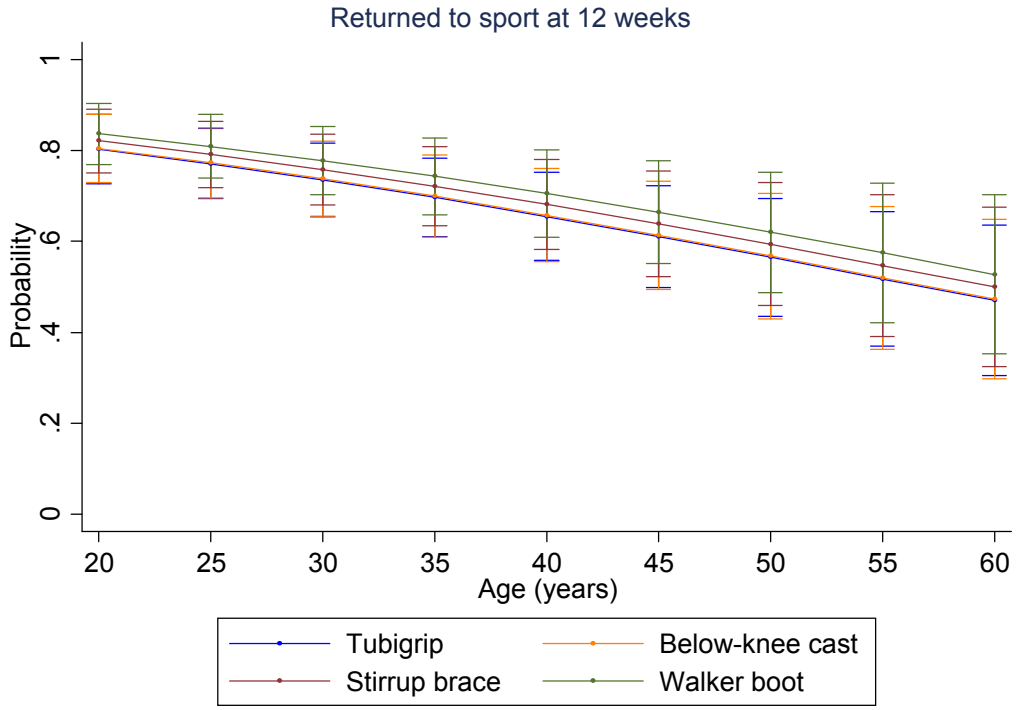


Figure 86: Predicted probability (95% CI error bar) of return to usual sports or activities by age (years) for different ankle supports at 12 weeks after injury.

6.4.6 Influence of age and gender on outcomes

Age was a statistically significant predictor for every outcome. Across all outcomes there was a consistent worsening of outcome as age increased. Furthermore, as age increased, the difference in the effect between the ankle supports tended to reduce. Gender was a less important factor. Gender was a statistically significant predictor indicating worse outcomes for females in only two outcomes, namely problems with mobility and difficulty walking on a flat surface at both 4 and 12 weeks.

6.4.7 Relationship between age and pain

There was a positive correlation between age (yrs) and pain scores (VAS 0-100) on weight bearing and this was consistent at 4 weeks (β 0.71, 95% CI 0.49 to 0.93, P<0.001, Figure 87) and 12 weeks (β 0.53, 95% CI 0.32 to 0.74, P<0.001, Figure 88).

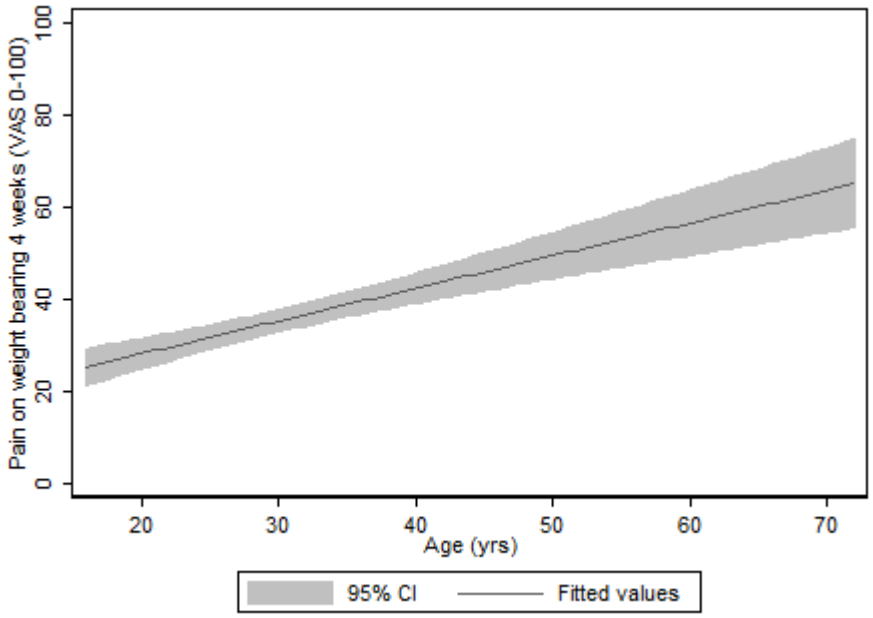


Figure 87: Linear regression plot with 95% CI showing positive relationship between age (yrs) and pain on weight bearing (VAS 0=no pain, 100=worst pain imaginable) at 4 weeks (n=461).

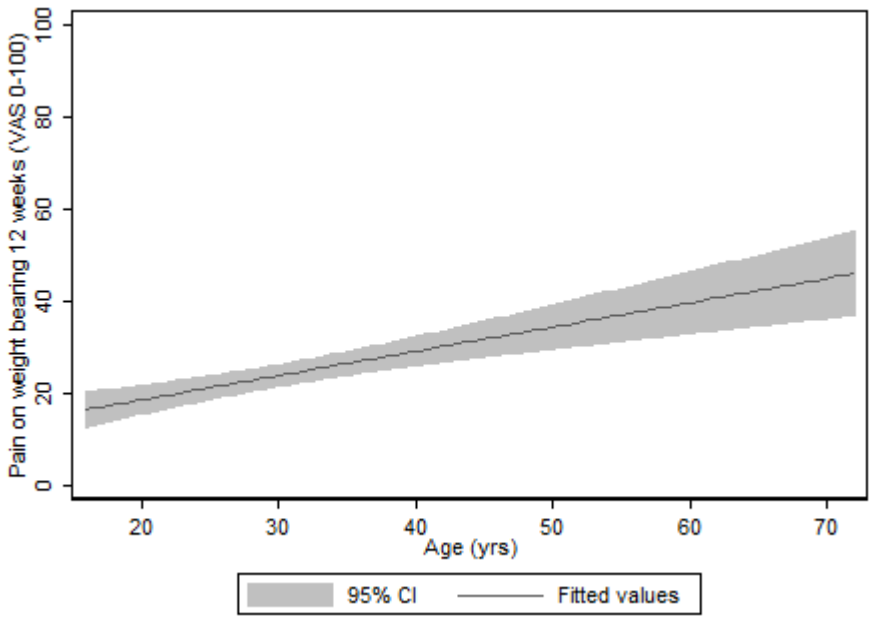


Figure 88: Linear regression plot with 95% CI showing positive relationship between age (yrs) and pain on weight bearing (VAS 0=no pain, 100=worst pain imaginable) at 12 weeks (n=460).

6.4.8 Model diagnostics

The Hosmer-Lemeshow Test was not significant for any of the logistic regression models, indicating that the models were not significantly different from the observed values. There were no consistent outliers across outcomes, nor a clinical rationale for excluding any of the participants to improve the model fit.

6.5 Discussion

6.5.1 Summary of findings

When the effects for each ankle support were compared with Tubigrip at 4 weeks and 12 weeks there was an overall modest improvement in recovery at 4 weeks favouring 10-day cast immobilisation across all mobility outcomes, and at 12 weeks results for participants using the other supports have also improved for most outcomes compared with Tubigrip. However, there is some uncertainty in the estimates of effect for the majority of mobility outcomes.

The odds of difficulty walking at 4 weeks were moderately lower in the 10-day cast immobilisation group compared with the Tubigrip group. For general mobility problems and difficulties with stair ascent and descent there were benefits for the cast immobilisation group compared with Tubigrip, but these were not statistically significant after adjustment for age and gender. When compared with Tubigrip, the cast and stirrup brace offered benefit for those aged less than 25 years in terms of recovery of jumping and running at 4 weeks after injury.

At 12 weeks the odds of general mobility problems were moderately lower for participants using the walker boot compared with Tubigrip. When compared with Tubigrip, reported difficulties squatting favoured the cast group, whereas jumping favoured casting and walker boot groups, but in unadjusted analyses only. The importance of age as a predictor of recovery after sprain was statistically significant across all outcomes and had an important influence on treatment effect sizes, with differences narrowing as age increased. Increasing age was positively associated with higher pain scores on weight bearing at 4 and 12 weeks. There were no differences in return to usual sports or activities for any intervention group.

The recovery of different mobility tasks from baseline through to 4 and 12 weeks had a steeper rate of improvement between baseline and 4 weeks than between 4 and 12 weeks. Approximately half of participants reported general problems with mobility at 4 weeks and about a third at 12 weeks.

Higher level mobility tasks had much higher levels of limitation. Difficulties with jumping and running were 91% at 4 weeks. Interestingly this was lower than the rates of return to sport, half of participants returning at 4 weeks, indicating patients are willing to return to usual sports or activities before full recovery of higher level mobility tasks.

6.5.2 Interpretation of findings

The overall findings that the cast offered most benefit early after severe ankle sprain is consistent with the conclusions of the original CAST analysis. However, in contrast to the original findings, this study finds the benefits of cast immobilisation for mobility outcomes are generally at 4 weeks, not at 12 weeks. CAST found small differences in favour of the cast group at 4 weeks in the pain and quality of life subscales of the FAOS and the physical component of the SF-12. However, the beneficial effects of the cast in the original CAST analysis were larger for activities of daily living, sports and quality of life FAOS subscales at 12 weeks.

The original CAST analysis also found that the ankle stirrup brace was found to be statistically significantly more beneficial than Tubigrip at 12 weeks in the quality of life subscale only. The analysis presented here found benefits for the stirrup brace in the recovery of jumping and running for adults under 25 years at 4 weeks only. The walker boot conferred no benefits compared with Tubigrip in the outcomes in the original CAST study. This study found that there are fewer reports of general mobility problems at 12 weeks for participants using the walker boot.

The differences between the original CAST analysis and the one presented here are likely to be due to two main reasons. Firstly, not all of the overall treatment effect was driven by mobility. Secondly, there may be some loss of precision in the analysis. The original sample size was powered for a continuous outcome based on a FAOS subscale (0-100), with each subscale containing between 4 and 17 items. The use of single dichotomised outcome for specific mobility tasks is a less efficient statistical design for the given sample size. These statistical efficiency issues may also account for some of the inconsistencies across mobility outcomes.

The finding of no differences in return to usual sports or activities between ankle supports contradicts the suggestion that cast immobilisation would impact on muscle function to an extent that return to sports would be more limited compared with supports that enable the ankle to mobilise.[123]

Comparison with other studies

The contrast in findings of the original CAST trial with the 2002 Cochrane review was discussed in the introduction section to this chapter. The relatively short immobilisation period of 10-days may be an important factor in the benefits of the cast found in the CAST cohort. In the Cochrane review there were 21 trials, which had immobilisation periods ranging between 1 and 6 weeks. The findings favoured early ankle movement over immobilisation across most outcomes assessed, but there were limited differences between early ankle movement and immobilisation when excluding studies at high risk of bias. The ongoing influence of the Cochrane review[109] is problematic, not only by the fact it has not been updated in over a decade, but also by the pooling of heterogeneous clinical populations without accounting for important differences. There was a lack of stratification of treatment estimates by duration of immobilisation or severity of injury, limiting direct comparisons with the CAST cohort. Severity of injury is related to clinical outcome[173] and longer periods of immobilisation have been found to be progressively more detrimental to cellular activity in ligaments.[255]

Several randomised controlled trials comparing ankle supports for the management of ankle sprain have been published since the Cochrane review. A pilot study conducted in the UK included 36 participants with ankle sprains, with severe injuries classified as a loss of weight bearing ability.[228] That study did not include an ankle support designed to limit movement, Tubigrip was compared with elastic stockings. They found indicators of improved SF-12, functional scores and measures of ankle swelling and range of motion in the elastic stocking group. These findings need substantiating in an adequately powered trial before clinical inferences are made. However, the

role of compression in combination with ankle supports for ankle sprain management may warrant further investigation in severe injuries as this could feasibly reduce the risk of deep vein thrombosis.

Boyce et al.[20] conducted a trial in the UK, randomising 50 people with grade II or III sprains within 24 hours of injury to either a stirrup brace or elasticated support bandage (presumably Tubigrip or equivalent). They found patient-reported function/mobility improved more in the brace group at 10 days and 8 weeks but no differences were found in pain scores. Lardenoye et al.[119] conducted a trial in the Netherlands including 100 people with grade II or III ankle sprains. Participants were randomised at 1 week after injury to stirrup brace or taping, both 4 weeks in duration. No differences in self-reported function, return to work or sports and range of ankle movement were found. However, 60% of the taping group had skin complications from the tape. An additional trial is underway in the Netherlands comparing Tubigrip plus taping versus Tubigrip plus a stirrup brace versus no support.[272] It is of note that none of these trials including severe (grade III) sprains have incorporated an immobilisation intervention arm, reflecting trends in the literature favouring early ankle movement.

Beynnon et al.[11] conducted a trial in Sweden, including 212 adults with ankle sprains, 32 of these being grade III injuries (15%). The three different grades of severity for ankle sprain were given different interventions and comparators. The grade III sprains were given 10 days of cast immobilisation or a stirrup brace. No differences between groups were found in the patient-reported time to return to normal walking and stair climbing. The main limitation of the trial was the limited sample size for severe injuries in particular, leading to risk of a type II error as a result of limited statistical power to detect differences between groups. This trial highlights the concept of stratifying the level of mechanical ankle support offered according to clinical classification of sprain severity, an approach that warrants further investigation.

A 2014 randomised trial by Naeem et al.[159] conducted in Pakistan compared cast immobilisation with early ankle movement. In contrast to CAST, the study population had sustained a grade I or II sprain. Participants were followed-up at 2 and 6 weeks. There was no difference in function scores at 2 weeks, but at 6 weeks there was difference in favour of early ankle movement. There are limitations to the trial, as the estimates were not adjusted for baseline imbalance in gender between the two groups and a lack of blinding of outcome assessors. The duration of cast immobilisation and the details of what the early ankle movement intervention entailed were not reported either. The lead author was contacted to obtain this information but no response was received. Due to the limitations in reporting it is difficult to draw conclusions as to whether the duration of cast immobilisation, grade of ankle sprain or risk of bias contribute to the differences in findings in this study compared with the CAST cohort.

A randomised trial conducted in Brazil included 186 participants with severe (grade III confirmed on MRI) ankle sprains.[190] The trial compared 3 weeks in a walker boot followed by 3 weeks in a stirrup brace versus 6 weeks in a stirrup brace. The AOFAS score outcomes favoured the stirrup brace at 6 weeks, not at weeks 1, 3 or 12. There were no other differences between the groups. However, the Brazilian trial manuscript did not report on sequence generation, allocation concealment or blinding of outcome assessors, so the risk of bias assessment is unclear. The limited differences between the effects of the walker boot and stirrup brace are in concordance with findings in the CAST cohort.

The systematic MRI of all severe ankle sprains enrolled in the Brazilian trial perhaps give some indication as to the complex nature of ankle ligament injury. It was reported that 44% of injured ankles were found to have a talar bone bruise, none had an osteochondral lesion (defect in the subchondral bone or cartilage). Previous studies reported in a 2013 systematic review, including 9 case series, found rates of bone bruises to be up to 40% after ankle ligament injury.[131] It has been suggested that osteochondral injuries should be restricted to non-weight bearing for 4 to 6 weeks to allow the area to heal effectively[143], an approach that contrasts with early ankle movement. The

involvement of osteochondral injury has led some to recommend a period of immobilisation for more severe ankle sprains.[274] The immobilisation of the ankle should theoretically have two mechanical effects. Firstly, holding the ankle in neutral should maintain higher pressure contact on the talus to the central articular surface, away from the areas that are likely to be injured in inversion and eversion.[170] Secondly, there may be a reduction of the compressive forces that occur during normal walking due to restricted triceps surae muscle activity. The compression forces from triceps surae are up to 5 times body weight in unrestricted gait.[170] MRI of the injured ankle was not conducted as part of the CAST study so the rate of bone bruising is not known, but it is reasonable to assume that the rate would have been higher than in lower severity ankle sprain populations. The benefits of immobilisation specifically in more severe ankle sprains in the CAST cohort were in the short- and medium-term, not at 9 month follow-up. Therefore the benefits of 10-day cast immobilisation do not appear to affect ankle function in the longer-term, regardless of whether osteochondral injuries were present in the study population.

6.5.3 The role of immobilisation in the management of severe ankle injury

The mechanism by which a brief period of immobilisation may result in improved mobility at 4 weeks and wider outcomes at 12 weeks may relate to the severity of injury and the healing of ligament tissue. The 10-day immobilisation period appears to be consistent with the phases of soft-tissue healing. By day 10 after injury the acute inflammatory phase should have just subsided and the proliferative phase, where new collagen is produced, is underway.[103] A short period of immobilisation is consistent with the principles of resting a soft tissue injury in the acute phase[17] and this is what was proposed after CAST. There is a risk that starting movement of the ankle straight away or excessively in the acute phase could disrupt the injured ligament. The rationale for using immobilisation after severe injury is sound given the larger extent of ligamentous disruption and the importance of allowing new collagen to start forming between the ends of the torn ligament before starting to mobilise the ankle joint. Pain and swelling also need to be controlled in the early phase after a severe sprain. Immobilisation can aid this by limiting

mechanical stimuli to nociceptors in the injured tissues and also to other afferent receptors in the area of injury that become centrally sensitised as part of the inflammatory response after trauma.[245]

As highlighted by Hertel,[82] the management of severe ligament injuries of the ankle with early ankle movement is at odds with those of the glenohumeral joint, which are typically immobilised in the acute phase.[73] However, controversies exist in other severe lower limb ligament injuries such as the medial collateral ligament of the knee. This is due to basic research evidence on the negative effects of immobilisation and the beneficial effects of movement on healing of ligaments, and also inconsistencies in clinical study outcomes.[135]

One of the issues relating to the cast intervention in the CAST study was compliance with the intervention. The 6% of participants who were randomised to casting and then were unwilling to have a cast applied, and the 2 participants that self-removed their casts, are indicators that patients have lower preferences for the cast. However, the analysis by intention-to-treat provides an estimate of the outcomes that could be expected in patients offered this treatment. Compliance may also be low in the other ankle supports as these were all easily removable, but adherence could not be easily measured. What is clear from a qualitative study of patients' experiences in a cast is that the difficulties of wearing a cast are wide ranging, but tolerated, on the basis of necessity for recovery and lack of other options to manage an injury.[270]

6.5.4 The influence of age on recovery

Worsening mobility outcomes with increasing age were as expected. A previous prognostic study of 85 randomised controlled trial participants with acute ankle sprains found that age and weight bearing status at baseline were statistically significant predictors of functional status at 4 weeks and 4 months after injury.[173]

The finding of increased pain with advancing age may partly explain why age is an important factor in recovery from ankle sprain. The mechanism of pain in ageing is a rapidly developing

field.[35, 68] However, other factors are likely to be involved in the worsening outcomes with increasing age. Sarcopenia, the ageing-related loss of muscle mass and strength, begins at the age of 30 and continues at 1-2% each year.[1] The physiological response to short-periods of immobilisation may result in more profound muscle loss and slower or incomplete recovery in older adults.[254] Furthermore, ageing is also associated with vascular and compositional changes in ligaments, detrimentally influencing mechanotransduction (cellular response to load), capacity to heal and biomechanical properties.[142] In addition to musculoskeletal considerations, the increasing frequency of comorbidities in older age may also reduce resilience to injury.[6, 33]

6.5.5 Strengths and limitations of the study

The main strength of this study is its utilisation of data from the largest well-designed clinical trial comparing ankle supports. The pragmatic design of the original CAST study and the fact that it was conducted across emergency departments in the NHS across England also increases generalisability. However, the findings are restricted to those with severe ankle sprains.

The large sample size enabled an investigation into the proposed aims of this chapter. The utilisation of a large cohort to explore new questions is advantageous when considering the resources required to conduct a clinical study of this size. This multicentre clinical study required a large team of clinical researchers, substantial funding and took several years to conduct. However, as discussed in section 6.5.2, the loss of precision by using a dichotomous instead of a continuous outcome is a limitation of the study.

Attrition bias may have been introduced by the loss of approximately 20% of participants at follow-up. However, rates of loss to follow-up were comparable across intervention groups, as were the baseline characteristics of responders and non-responders. A 20% loss to follow-up is also comparable with other clinical trial cohorts with musculoskeletal injury attending emergency departments in the UK.[116]

Issues of multiplicity were managed by careful pre-planning of analyses and selection of outcomes.[37] Besides, multiplicity is less of an issue in larger datasets.[185] Careful reporting of all comparisons allows the reader to interpret the findings in the context of all comparisons, whether they were statistically significant or not.

The outcomes were pre-defined by data collected from the original trial. The inclusion of physical performance tests would have verified the level of mobility status. For example, gait analysis in a sub-study could have provided a detailed quantitative estimate of the impact of different supports on weight bearing gait and would have required fewer participants, as utilised in Chapters 4 and 5.

6.5.6 Clinical and research implications

This study adds evidence of potential benefits of a short period of cast immobilisation after severe ankle sprains in adults attending emergency departments. An updated systematic review and meta-analysis of all trials comparing immobilisation and early ankle movement for ankle sprain is now indicated, taking care to stratify estimates by injury severity and duration of immobilisation. Additional studies would be required to determine whether a short period of immobilisation is also effective for other severe soft tissue injuries, such as the collateral ligaments of the knee.

Age is an important predictor of recovery from severe ankle sprain. Research is required to establish why older adults experience more pain and to identify other contributing factors for poor outcome. There is a case for developing a prognostic tool to identify those at risk of poor outcomes. This may lead to stratified rehabilitation, an approach that has led to improvement in outcomes in other musculoskeletal conditions.[84]

6.6 Conclusion

The use of 10-day cast immobilisation in the management of severe ankle sprains offers most benefit overall in short-term mobility. In the medium-term, the benefits for a single support for

mobility outcomes are less clear. Overall recovery in the short- and medium-term worsens with increasing age. Additional studies are indicated to improve mobility outcomes in older adults who experience more pain after severe ankle sprain.

6.7 Funding

The original trial was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme. The views and opinions expressed therein are those of the author and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.

Chapter 7

7 Final discussion

This chapter revisits the thesis aims and summarises key findings and limitations. Drawing from the evidence generated, cross-cutting themes and clinical and research implications from this thesis are discussed.

7.1 Aims of the thesis

The main aims of this thesis were:

- To investigate the effects of ankle immobilisation compared with ankle movement on a range of mobility outcomes after severe ankle injury (ligament sprain and fracture).
- To develop experimental and analytical techniques to estimate the effects of different types of ankle support on walking gait.
- To make recommendations on ankle immobilisation interventions for research and clinical practice.

This research was important for two main reasons 1) mobility recovery from severe ankle injury is often poor[45, 169, 173, 189], and 2) evidence concerning optimal management of severe ankle injuries needs to be developed to better inform clinical decision making and direct future research.[108, 122]

7.2 The contribution of this thesis to clinical and research knowledge

This thesis has contributed evidence that ankle immobilisation confers several clinical benefits when compared with allowing joint motion following severe ankle injury. In Chapter 3, a systematic review and meta-analysis showed that in the 6 weeks of recovery following ankle ORIF surgery, there is insufficient clinical trial evidence that early ankle movements offer a benefit in

term of mobility recovery. Early ankle movements compared with immobilisation reduced risk of thrombosis. However, compared with cast immobilisation, risk of deep and superficial surgical site infection and fixation-related complications were higher when ankle movements were permitted.

Chapter 4 employed gait analysis techniques to show that a walker boot, designed to limit ankle range of motion during locomotion, when compared with Tubigrip, induced gait abnormalities in non-pathological gait. The clinical study in Chapter 5 including participants at the transition to unrestricted weight-bearing and rehabilitation of walking at 6 weeks after ankle ORIF showed that, when compared with Tubigrip, a walker boot and to a lesser extent a stirrup brace offered improvements in gait symmetry and reductions in pain. The analytical approach developed in Chapters 4 and 5 provide a novel step toward overcoming some of the barriers in analysing speed-dependent gait outcomes. By accounting for the effect of walking velocity using multilevel modelling, participants could be assessed in real world conditions while also adjusting estimates for important confounding variables.

Finally, an exploratory analysis using the CAST Trial cohort was conducted in Chapter 6. It was shown that 10 days of cast immobilisation compared with Tubigrip, in the acute management of severe ankle sprains, offered improved recovery of a wide range of mobility outcomes at 4 weeks after injury, especially walking. There was no evidence of a detrimental effect from cast immobilisation on higher level mobility activities, such as stair climbing, jumping and running, at 4 or 12 weeks after severe sprain.

7.3 Implications of findings in this thesis

Overall, these findings are contrary to the general shift in clinical practice recommendations in promoting early movement to accelerate recovery of mobility following acute ligament injury[109, 187] and after ORIF surgery.[122] Based on the findings of this thesis, the overall recommendation is that externally applied ankle immobilisation has several advantages over allowing ankle movement in

the recovery and early rehabilitation phases after severe ankle injury. Detailed analyses of individual study findings are found in the individual chapters. However, several themes have emerged through the research reported in this thesis and these are discussed in the following sections.

7.3.1 Limitations in animal models as a basis for clinical practice and research

The theoretical rationale underpinning the recommendation for ankle motion appears justified based on basic research on the deleterious effects of immobilisation overviewed in Chapter 1. The overall benefits of load for musculoskeletal tissues have been well established through basic research and the mechanisms are being increasingly understood.[76, 111] The discord between the basic research and the clinical findings of this thesis may be a result of the challenges of transferring results from basic research into the specific clinical situation of acute severe ankle injury. The limitations of animal models as a basis for clinical practice and research have been criticised recently in the *British Medical Journal* by Pound and Bracken.[188] They argue that there is limited evidence of transferability from animals to clinical research, which may be due to methodological shortcomings, under- or poor reporting of experiments and unestablished validity of animal models.

In the context of soft tissue healing research there are many complex factors influencing healing that are not considered in animal studies. One of the main differences is that much of the research on the effects of immobilisation and exercise after limb injury is based on the quadrupedal gait of animals rather than the bipedal gait of humans, a fundamental difference in lower limb loading between species. There are also broader psychosocial and environmental factors in the human experience of injury,[267] which complicates transferability of animal research to human functioning. These issues highlight the value of applied clinical research to translate and evaluate basic research findings before changes in practice are advised.

7.3.2 Severity of injury

Severity of injury is an important clinical factor when considering the benefits and risk of harms with the use of immobilisation versus movement following injury. One of the proposed benefits of ORIF surgery is that the stabilisation of the fracture facilitates earlier movement of the injured joint, minimising the deleterious effects of immobilisation.[200, 262] However, this approach is complicated by the conflicting need to protect surgical wounds and surgical implants in the acute phase. As shown in Chapter 3, there is clinical trial evidence of an increased risk of harms such as deep and superficial surgical site infection with use of early ankle movement when compared with immobilisation after ORIF surgery.

Following severe ligamentous injury, which occurs in isolation or in combination with fracture, early movement could potentially disturb the healing tissue and cause further bleeding (Chapter 1). Therefore, the risk of disturbing healing of a ruptured ligament presents a different scenario to milder grade sprains where there is less tissue damage and response is favourable to early movement.[19, 173] The severity of soft tissue injury is therefore an important factor to consider when examining clinical trial evidence on the effects of immobilisation.

7.3.3 Duration of immobilisation

The duration of immobilisation may be an important factor in terms of treatment effect. Severe sprains treated with the relatively brief period of 10 days of cast immobilisation (Chapter 6) had better mobility outcomes than Tubigrip. One factor that may have contributed to the differences in the CAST study and previous clinical trials comparing immobilisation and early movement after sprain is that the duration of immobilisation in previous studies has varied from 1 to 6 weeks.[108]

There was no clinical trial evidence of benefit in patient-reported functional/mobility recovery in the short or longer term between 6 weeks of cast immobilisation and early ankle movement after ORIF surgery for ankle fracture (Chapter 3). However, Van Schie-Van der Weert et al.[248] found the duration of immobilisation in a cast to be a statistically significant determinant of functional

outcome at approximately 4 years after Weber B ankle fracture in a multivariable analysis of a cohort study.

It is hypothesised that the duration of immobilisation after ankle ORIF surgery could be reduced from 6 weeks to around 2 weeks. The reduction in duration of immobilisation may introduce some of the benefits in terms of soft tissue injury recovery from a shorter period of immobilisation demonstrated in Chapter 6. Two weeks of immobilisation would also allow a reasonable duration of protection for the surgical wounds with the aim of reducing risk of complications such as surgical site infection. Before being considered in wider clinical practice this hypothesis needs evaluation in a clinical trial, comparing 2 versus 6 weeks of cast immobilisation following ankle ORIF surgery.

In such a trial, the increased risk of thrombosis with immobilisation after ORIF surgery could be reduced with modern thrombo-prophylaxis.[7] National Institute for Health and Care Excellence (NICE) guidance from 2010 indicates that thrombo-prophylaxis is recommended for most patients undergoing ORIF surgery due to reduced mobility after ankle fracture and admission to hospital.[164] However, authors of a recent prospective, multicentre, cohort study from Canada have questioned the value of thrombo-prophylaxis in this patient group. They studied 1,200 patients who were immobilised after lower limb trauma and not offered thrombo-prophylaxis and found a thrombus/thromboembolism rate of 0.6%. (95% CI 0.2 to 1.2).[210] Given the low event rates of thrombus/thromboembolism, a very large RCT would be needed to determine the clinical and cost effectiveness of thrombo-prophylaxis. A call for further trials was made in the NICE guidelines and was also highlighted in a recent RCT discussed below.

A RCT published in August 2014[229] compared Tubigrip with ankle injury stockings, both worn with a walker boot to immobilise the ankle for 6 weeks, in the management of ankle fractures. The trial included fractures that were stable and conservatively managed or unstable and managed with ORIF surgery. The compression from the stockings aimed to reduce thrombotic events and reduce

swelling to improve recovery. The severe ankle fractures that underwent ORIF surgery were also given heparin as a thrombo-prophylactic. Compared with Tubigrip, the group using the compression stocking had substantially better patient-reported function and reduced ankle circumference in the injured leg compared with the uninjured at 4, 8, 12 weeks and 6 months. The authors acknowledged that the study was not powered to determine a difference in thrombotic event rates (n=90). The main limitation when interpreting the results of this study were that despite the use of minimisation, 7% more participants in the Tubigrip group had undergone ORIF surgery and there were no reports of a statistical adjustment or stratification of the analysis for this important prognostic factor difference between groups. However, the implications of this study are that the addition of compression therapy may contribute to reductions in swelling, reduce some of the deleterious effects of ankle immobilisation and hypothetically aid in thrombo-prophylaxis. A fully powered RCT would be required to investigate this hypothesis. A trial that focussed on severe ankle fractures that have undergone ORIF surgery would be recommended, reducing clinical heterogeneity in the study population and focussing on those most at risk of worse function outcomes and higher rates of thrombosis.

Whether a shorter period of immobilisation would balance the benefits and harms of immobilisation after ORIF surgery is uncertain as most of the negative effects of immobilisation relating to muscle atrophy occur in the first few days.[104] As most severe ankle injuries are immobilised for the first few days before definitive management, it may explain why there are limited differences in the effects of early ankle movement protocols. It is also noted that long-term differences in mobility were not evident in clinical trials following ankle ORIF surgery (Chapter 3) and at 9 months after severe ankle sprain in the CAST Trial.[117] Longitudinal studies of ankle impairments (range of motion, pain, neuromuscular function and gait) embedded within future RCTs in this area may provide a greater insight into the mechanisms relating to immobilisation versus ankle movement after severe injury.

7.3.4 Analysis of gait in different ankle supports

The immediate effects of ankle supports on gait were estimated using a novel approach to analysis. To the best of the author's knowledge this has provided the first data comparing common ankle supports used in the management of severe ankle injury. The data in Chapter 4 indicated that for healthy adults, with no ankle impairments, the walker boot induced gait abnormality. In Chapter 5, the walker boot and to a lesser extent the stirrup brace improved gait asymmetry and reduced pain in participants 6 weeks after ankle ORIF surgery. The implications of the findings of these two studies is that as recovery and rehabilitation progresses and ankle impairments resolve, persistent use of a walker boot may transition from facilitating reduced gait asymmetry to maintaining a level of gait asymmetry. This highlights the need for a planned weaning of walker boot use to ensure the transition to gait with no ankle support is timely. Precisely when and how to best achieve this transition to unsupported gait after ankle ORIF surgery is a subject for future studies.

7.3.5 Exercise therapy

A question raised by the studies in Chapters 3 and 5 is whether the exercises in the ankle movement intervention groups were sufficiently challenging or adhered to in order to maximise their effect on ankle impairments and mobility recovery. In Chapter 3 the early ankle movement interventions were limited in reporting and there were no details on exercise adherence. Future trials including an exercise component need to follow guidelines on describing complex interventions to facilitate evaluation.[89]

7.4 Limitations of this thesis and directions for future research

The limitations for each study within this thesis are considered in their respective chapters. However, limitations of the thesis more broadly are considered below. In addition, directions for future research are discussed.

The studies in this thesis generalise well to adults with severe ankle injury, but within the studies there are limited numbers of older aged adults, those over 60 years old. As established in Chapter 6, for ankle sprain, and in the author's previous work in ankle fracture recovery,[107] older aged individuals are at risk of poorer mobility outcomes after severe ankle injury. The findings in Chapter 6 indicate that differences in the effects of different ankle supports are smaller in older adults after severe ankle sprain. The CAST cohort could provide a basis for investigating prognosis to explore factors other than age that affect outcomes following severe ankle sprain. This may help identify why older adults have worse outcomes and give direction for future rehabilitation strategies.

The initial management between ORIF surgery and cast immobilisation is currently being investigated in older adults in a multicentre RCT, for which the author is part of the management team.[269] The results of this trial will inform early ankle fracture management in older adults, but it will also be the largest cohort of older ankle fracture patients. The data from the trial will be used to investigate prognostic factors for recovery following ankle fracture.

This thesis focussed on physical impairments and mobility following severe ankle injury. Although physical impairments are the main outcomes that present clinically following severe ankle injury, as discussed in Chapter 1, there are other factors that may influence mobility outcomes. As indicated in the ICF model of disability in Figure 5 in Chapter 1, personal factors (e.g. psychological issues and coping styles) and environmental factors (e.g. social support, relationships and health and social services and policy) also play a role in activity limitation after injury. These wider factors have been explored following ankle fracture in a qualitative study with patients and clinicians. The study findings highlighted the focus on the physical and occupational aspects of ankle fracture recovery by clinicians and patients. However, patients were also concerned with the wider impact of the injury on finances, psychological status, social activity and aesthetics of physical appearance.[147] The complex nature of activity limitations after severe ankle

injury need to be considered in further research into broader rehabilitation approaches, both during and after use of immobilisation.

7.5 Research recommendations

The research findings from this thesis would be developed further with additional clinical research. There is a need to ensure future trials have a low risk of bias, as design and reporting of trials in this area are generally poor, as discussed in Chapters 3 and 6. As a minimum, the clinical trials in the field need to have adequate randomisation sequence generation, allocation concealment, blinded outcome assessors and be adequately powered and reported according to CONSORT standards.[206]

Many areas for future clinical research have been suggested by the data in this thesis, of which there are overall priorities. Firstly, a parallel RCT comparing 2 weeks immobilisation versus 6 weeks immobilisation after ankle ORIF surgery is proposed, as outlined above. Secondly, a parallel RCT comparing ankle supports issued at the transition to rehabilitation of walking at 6 weeks after ankle ORIF surgery, to assess the effect of these interventions over time. The second trial could be a second stage of randomisation after the first trial. The rationale for conducting further research on ankle supports issued to facilitate normal gait after ankle ORIF surgery is that a longer duration of ankle support use may have different effects to the immediate effects observed in Chapter 5. It is of note that this trial would require substantial resources. To detect a clinically important difference in a the Lower Extremity Functional Scale (9 points),[13] with previously published standard deviations of 15 points,[8] alpha 0.05 and power 0.8, 44 participants would be required for each group (calculated on STATA, assuming normal distribution of outcomes and using a *t-test* to compare groups). Further inflation of the sample size due to expected loss to follow up would also need to be factored into the final sample size target.

It was established in Chapter 6 that the 2002 Cochrane review,[108] comparing ankle immobilisation with movement in the acute management of ankle sprains, needs to be updated. This is due to its

ongoing prominence in the literature, despite not including many subsequent RCTs, including the CAST study. The author and colleagues have applied to the Cochrane Bone, Joint and Muscle Trauma Group and have now registered to conduct this updated systematic review and meta-analysis. We plan a subgroup analysis for injury severity and duration of immobilisation.

Further use of multilevel modelling to adjust for walking velocity in the assessment of speed-dependent gait outcomes is also warranted. The techniques and programming have now been developed and could be employed to investigate the effects of other rehabilitation interventions, for example, verbal instructions used in gait re-education and pain-relieving modalities.

7.6 Conclusion

This thesis has contributed clinical evidence favouring a role for ankle immobilisation in the pathway of recovery and rehabilitation following severe ankle injury to optimise mobility recovery. In the 6 week recovery period after ankle ORIF surgery there is insufficient clinical trial evidence that early ankle movements offer a benefit in terms of mobility recovery. Compared with cast immobilisation, risk of deep and superficial surgical site infection and fixation-related complications were higher when ankle movements were permitted. Clinicians should be aware of the benefits and risk of harms outlined, as well as the limitations in the current evidence base. Gait analysis techniques showed that a walker boot, designed to limit ankle range of motion during locomotion, when compared with Tubigrip, induced gait abnormalities in non-pathological gait. Novel analytical techniques have been developed within this thesis to adjust for walking velocity when measuring speed-dependent gait outcomes. These techniques should prove useful to wider gait analysis applications.

At the transition to unrestricted weight-bearing and rehabilitation of walking at 6 weeks after ankle ORIF, a walker boot and to a lesser extent a stirrup brace offered improvements in gait symmetry and reductions in pain when compared with Tubigrip. An exploratory analysis showed that 10 days of cast immobilisation compared with Tubigrip, in the acute management of severe ankle

ligament sprains, offered improved recovery of a wide range of mobility outcomes at 4 weeks after injury, especially walking.

This thesis has generated hypotheses and made suggestions on the direction of future clinical research. There is a need for additional well-designed and well-reported studies to further the evaluation of the role of immobilisation following ankle ORIF surgery and severe ankle ligament sprains.

References

1. Ali S, Garcia JM. Sarcopenia, cachexia and aging: diagnosis, mechanisms and therapeutic options - a mini-review. *Gerontology.* 2014;60(4):294-305.

2. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet.* 2000;355(9209):1064-1069.

3. Astephen Wilson JL. Challenges in dealing with walking speed in knee osteoarthritis gait analyses. *Clin Biomech (Bristol, Avon).* 2012;27(3):210-112.

4. Bachmann LM, Kolb E, Koller MT, Steurer J, ter Riet G. Accuracy of Ottawa ankle rules to exclude fractures of the ankle and mid-foot: systematic review. *BMJ.* 2003;326(7386):417.

5. Baker J, Fraser-Thomas J, Dionigi R, Horton S. Sport participation and positive development in older persons. *Eur Rev Aging Phys Act.* 2010;7(1):3-12.

6. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet.* 2012;380(9836):37-43.

7. Barrera LM, Perel P, Ker K, Cirocchi R, Farinella E, Morales Uribe CH. Thromboprophylaxis for trauma patients. *Cochrane Database Syst Rev.* 2013(3):CD008303.

8. Beckenkamp P, Lin CW, Herbert R, et al. EXACT: EXercise or Advice after ankle fraCTure. Design of a randomised controlled trial. *BMC Musculoskelet Disord.* 2011;12(1):148.

9. Becker HP, Rosenbaum D, Kriese T, Gerngross H, Claes L. Gait asymmetry following successful surgical treatment of ankle fractures in young adults. *Clin Orthop Relat Res.* 1995(311):262-269.

10. Besch L, Radke B, Mueller M, et al. Dynamic and functional gait analysis of severely displaced intra-articular calcaneus fractures treated with a hinged external fixator or internal stabilization. *J Foot Ankle Surg.* 2008;47(1):19-25.

11. Beynnon BD, Renstrom PA, Haugh L, Uh BS, Barker H. A prospective, randomized clinical investigation of the treatment of first-time ankle sprains. *Am J Sports Med.* 2006;34(9):1401-1412.

12. Bilney B, Morris M, Webster K. Concurrent related validity of the GAITRite walkway system for quantification of the spatial and temporal parameters of gait. *Gait Posture.* 2003;17(1):68-74.

13. Binkley JM, Stratford PW, Lott SA, Riddle DL. The Lower Extremity Functional Scale (LEFS): scale development, measurement properties, and clinical application. North American Orthopaedic Rehabilitation Research Network. *Phys Ther.* 1999;79(4):371-383.

14. Black JDJ, Bhavikatti M, Al-Hadithy N, Hakmi A, Kitson J. Early weight-bearing in operatively fixed ankle fractures: a systematic review. *Foot (Edinb).* 2013;23(2-3):78-85.

15. Black N. Patient reported outcome measures could help transform healthcare. *BMJ.* 2013;346:f167.

16. Bleakley CM, Glasgow P, MacAuley DC. PRICE needs updating, should we call the POLICE? *Br J Sports Med.* 2012;46(4):220-221.

17. Bleakley CM, GLasgow PD, Phillips N, et al. *Management of acute soft tissue injury using Protection, Rest, Ice, Compression and Elevation (PRICE): recommendations from the Association of Chartered Physiotherapists in Sports and Exercise Medicine (ACPSM)*. UK: ACPSM; 2010.

18. Bleakley CM, McDonough SM, MacAuley DC. Some conservative strategies are effective when added to controlled mobilisation with external support after acute ankle sprain: a systematic review. *Aust J Physiother.* 2008;54(1):7-20.
19. Bleakley CM, O'Connor SR, Tully MA, et al. Effect of accelerated rehabilitation on function after ankle sprain: randomised controlled trial. *BMJ.* 2010;340:c1964.
20. Boyce SH, Quigley MA, Campbell S. Management of ankle sprains: a randomised controlled trial of the treatment of inversion injuries using an elastic support bandage or an Aircast ankle brace. *Br J Sports Med.* 2005;39(2):91-96.
21. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med.* 2007;26(1):53-77.
22. Brown OL, Dirschl DR, Obremskey WT. Incidence of hardware-related pain and its effect on functional outcomes after open reduction and internal fixation of ankle fractures. *J Orthop Trauma.* 2001;15(4):271-274.
23. Brown TD, Johnston RC, Saltzman CL, Marsh JL, Buckwalter JA. Posttraumatic osteoarthritis: a first estimate of incidence, prevalence, and burden of disease. *J Orthop Trauma.* 2006;20(10):739-744.
24. Brukner P, Khan K. *Clinical sports medicine*. 3rd ed. London: McGraw-Hill; 2007.
25. Burdett RG, Borello-France D, Blatchly C, Potter C. Gait comparison of subjects with hemiplegia walking unbraced, with ankle-foot orthosis, and with Air-Stirrup brace. *Phys Ther.* 1988;68(8):1197-1203.
26. Bus SA, Valk GD, van Deursen RW, et al. The effectiveness of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in diabetes: a systematic review. *Diabetes Metab Res Rev.* 2008;24 (Suppl 1):S162-180.
27. Callisaya ML, Blizzard L, Schmidt MD, et al. Gait, gait variability and the risk of multiple incident falls in older people: a population-based study. *Age Ageing.* 2011;40(4):481-487.
28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.
29. Chester R, Costa ML, Shepstone L, Donell ST. Reliability of isokinetic dynamometry in assessing plantarflexion torque following Achilles tendon rupture. *Foot Ankle Int.* 2003;24(12):909-915.
30. Chesworth BM, Vandervoort AA. Comparison of passive stiffness variables and range of motion in uninvolved and involved ankle joints of patients following ankle fractures. *Phys Ther.* 1995;75(4):253-261.
31. Cimino W, Ichtertz D, Slabaugh P. Early mobilization of ankle fractures after open reduction and internal fixation. *Clin Orthop Relat Res.* 1991(267):152-156.
32. Clarkson HM. *Musculoskeletal assessment: joint range of motion and manual muscle strength*. 2nd ed. Philadelphia ; London: Lippincott Williams & Wilkins; 2000.
33. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet.* 2013;381(9868):752-762.
34. Cleland JA, Mintken PE, McDevitt A, et al. Manual physical therapy and exercise versus supervised home exercise in the management of patients with inversion ankle sprain: a multicenter randomized clinical trial. *J Orthop Sports Phys Ther.* 2013;43(7):443-455.

35. Cole LJ, Farrell MJ, Gibson SJ, Egan GF. Age-related differences in pain sensitivity and regional brain activity evoked by noxious pressure. *Neurobiol Aging.* 2010;31(3):494-503.
36. Collins N, Teys P, Vicenzino B. The initial effects of a Mulligan's mobilization with movement technique on dorsiflexion and pain in subacute ankle sprains. *Man Ther.* 2004;9(2):77-82.
37. Cook RJ, Farewell VT. Multiplicity considerations in the design and analysis of clinical trials. *J R Stat Soc Ser A Stat Soc.* 1996;159(1):93-110.
38. Cooke MW, Lamb SE, Marsh J, Dale J. A survey of current consultant practice of treatment of severe ankle sprains in emergency departments in the United Kingdom. *Emerg Med J.* 2003;20(6):505-507.
39. Cooke MW, Marsh JL, Clark M, et al. Treatment of severe ankle sprain: a pragmatic randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial. *Health Technol Assess.* 2009;13(13):144.
40. Court-Brown CM, Caesar B. Epidemiology of adult fractures: a review. *Injury.* 2006;37(8):691-697.
41. Crompton RH, Vereecke EE, Thorpe SKS. Locomotion and posture from the common hominoid ancestor to fully modern hominins, with special reference to the last common panin/hominin ancestor. *J Anat.* 2008;212(4):501-543.
42. Crosbie J, Green T, Refshauge K. Effects of reduced ankle dorsiflexion following lateral ligament sprain on temporal and spatial gait parameters. *Gait Posture.* 1999;9(3):167-172.
43. CSP. *EQ-5D-5L - Measuring change in musculoskeletal physiotherapy outpatient services*. London: Chartered Society of Physiotherapy; 2010.
44. Cummings SR, Kohn MA, Hulley SB. Designing questionnaires, interviews and online surveys. In: Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB, eds. *Designing Clinical Research*. 4th ed. ed. PA, USA: Lippincott Williams & Wilkins; 2013.
45. Del Buono A, Smith R, Coco M, Woolley L, Denaro V, Maffulli N. Return to sports after ankle fractures: a systematic review. *Br Med Bull.* 2013;106:179-191.
46. DeMaio M, McHale K, Lenhart M, Garland J, McIlvaine C, Rhode M. Plaster: our orthopaedic heritage: AAOS exhibit selection. *J Bone Joint Surg Am.* 2012;94(20):e152.
47. Devlin N, Appleby J. *Getting the most out of proms: putting health outcomes at the heart of NHS decision-making*. London: The King's Fund; 2010.
48. DiLiberto FE, Baumhauer JF, Wilding GE, Nawoczenski DA. Alterations in plantar pressure with different walking boot designs. *Foot Ankle Int.* 2007;28(1):55-60.
49. Dirschl DR, Marsh JL, Buckwalter JA, et al. Articular fractures. *J Am Acad Orthop Surg.* 2004;12(6):416-423.
50. DiStasio AJ, Jaggears FR, DePasquale LV, Frassica FJ, Turen CH. Protected early motion versus cast immobilization in postoperative management of ankle fractures. *Contemp Orthop.* 1994;29(4):273-277.
51. Dogra AS, Rangan A. A prospective randomised control study comparing early mobilisation versus immobilisation of surgically treated ankle fractures [abstract]. *J Bone Joint Surg Br.* 1997;79:367-368.
52. Dogra AS, Rangan A. Early mobilisation versus immobilisation of surgically treated ankle fractures. Prospective randomised control trial. *Injury.* 1999;30(6):417-419.

53. Egol KA, Dolan R, Koval KJ. Functional outcome of surgery for fractures of the ankle. *J Bone Joint Surg Br.* 2000;82(2):246-249.
54. Egol KA, Koval KJ. Functional outcome following ankle fracture surgery: a prospective, randomized comparison of two treatment protocols [abstract]. Paper presented at: Orthopaedic Trauma Association Annual Meeting; Oct 8-10, 1998.
55. Eils E, Demming C, Kollmeier G, Thorwesten L, Volker K, Rosenbaum D. Comprehensive testing of 10 different ankle braces. Evaluation of passive and rapidly induced stability in subjects with chronic ankle instability. *Clin Biomech (Bristol, Avon).* 2002;17(7):526-535.
56. EuroQol-Group. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16:199-208.
57. Everhart J, Best T, Flanigan D. Psychological predictors of anterior cruciate ligament reconstruction outcomes: a systematic review. *Knee Surg Sports Traumatol Arthrosc.* 2013:1-11.
58. Eyckmans J, Boudou T, Yu X, Chen Christopher S. A hitchhiker's guide to mechanobiology. *Dev Cell.* 2011;21(1):35-47.
59. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods.* 2007;39(2):175-191.
60. Field AP. *Discovering statistics using SPSS*. 3rd ed. London: Sage; 2009.
61. Field AP, Hole G. *How to design and report experiments*. London: Sage; 2003.
62. Finsen V, Benum P. Osteopenia after ankle fractures. The influence of early weight bearing and muscle activity. *Clin Orthop.* 1989;245:261-268.
63. Finsen V, Saetermo R, Kibsgaard L, et al. Early postoperative weight-bearing and muscle activity in patients who have a fracture of the ankle. *J Bone Joint Surg Am.* 1989;71(1):23-27.
64. Fong CM, Blackburn JT, Norcross MF, McGrath M, Padua DA. Ankle-dorsiflexion range of motion and landing biomechanics. *J Athl Train.* 2011;46(1):5-10.
65. Franke J, Goldhahn S, Audige L, Kohler H, Wentzensen A. The dynamic vacuum orthosis: a functional and economical benefit? *Int Orthop.* 2008;32(2):153-158.
66. Fritz S, Lusardi M. White paper: “walking speed: the sixth vital sign”. *J Geriatr Phys Ther.* 2009;32(2):2-5.
67. Furman BD, Olson SA, Guilak F. The development of posttraumatic arthritis after articular fracture. *J Orthop Trauma.* 2006;20(10):719-725.
68. Gagliese L. Pain and aging: the emergence of a new subfield of pain research. *J Pain.* 2009;10(4):343-353.
69. Galanaud JP, Laroche JP, Righini M. The history and historical treatments of deep vein thrombosis. *J Thromb Haemost.* 2013;11(3):402-411.
70. Gardner MJ, Demetrakopoulos D, Briggs SM, Helfet DL, Lorich DG. The ability of the Lauge-Hansen classification to predict ligament injury and mechanism in ankle fractures: an MRI study. *J Orthop Trauma.* 2006;20(4):267-272.
71. Glazebrook M, Daniels T, Younger A, et al. Comparison of health-related quality of life between patients with end-stage ankle and hip arthrosis. *J Bone Joint Surg Am.* 2008;90(3):499-505.
72. Goldberg AJ, MacGregor A, Dawson J, et al. The demand incidence of symptomatic ankle osteoarthritis presenting to foot & ankle surgeons in the United Kingdom. *Foot (Edinb).* 2012;22(3):163-166.

73. Hanchard N, C. A., Goodchild L, M., Kottam L. Conservative management following closed reduction of traumatic anterior dislocation of the shoulder. *Cochrane Database Syst Rev.* 2014(4):CD004962.
74. Hancock MJ, Herbert RD, Stewart M. Prediction of outcome after ankle fracture. *J Orthop Sports Phys Ther.* 2005;35(12):786-792.
75. Handley R, Gandhe A. Ankle fractures. In: Bulstrode CJK, ed. *Oxford textbook of trauma and orthopaedics*. 2nd ed. Oxford: Oxford University Press; 2011.
76. Hart DA, Scott A. Getting the dose right when prescribing exercise for connective tissue conditions: the Yin and the Yang of tissue homeostasis. *Br J Sports Med.* 2012;46(10):696-698.
77. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken).* 2011;63(S11):S240-S252.
78. Hedström M, Ahl T, Dalén N. Early postoperative ankle exercise. A study of postoperative lateral malleolar fractures. *Clin Orthop.* 1994(300):193-196.
79. Helbostad JL, Askim T, Moe-Nilssen R. Short-term repeatability of body sway during quiet standing in people with hemiparesis and in frail older adults. *Arch Phys Med Rehabil.* 2004;85(6):993-999.
80. Helbostad JL, Moe-Nilssen R. The effect of gait speed on lateral balance control during walking in healthy elderly. *Gait Posture.* 2003;18(2):27-36.
81. Hendy AM, Spittle M, Kidgell DJ. Cross education and immobilisation: mechanisms and implications for injury rehabilitation. *J Sci Med Sport.* 2012;15(2):94-101.
82. Hertel J. Immobilisation for acute severe ankle sprain. *Lancet.* 2009;373(9663):524-526.
83. Higgins J, Green S, Cochrane Collaboration. *Cochrane handbook for systematic reviews of interventions*. Chichester, England ; Hoboken, NJ: Wiley-Blackwell; 2008.
84. Hill JC, Whitehurst DGT, Lewis M, et al. Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial. *Lancet.* 2011;378(9802):1560-1571.
85. Hiller CE, Nightingale EJ, Raymond J, et al. Prevalence and impact of chronic musculoskeletal ankle disorders in the community. *Arch Phys Med Rehabil.* 2012;93(10):1801-1807.
86. Hodt-Billington C. *Measures of symmetry in gait: methodological principles and clinical choices*. Bergen: Department of Public Health and Primary Health Care, University of Bergen; 2011.
87. Hodt-Billington C, Helbostad JL, Moe-Nilssen R. Should trunk movement or footfall parameters quantify gait asymmetry in chronic stroke patients? *Gait Posture.* 2008;27(4):552-558.
88. Hodt-Billington C, Helbostad JL, Vervaat W, Rognsvag T, Moe-Nilssen R. Criteria of gait asymmetry in patients with hip osteoarthritis. *Physiother Theory Pract.* 2012;28(2):134-141.
89. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ.* 2014;348:g1687.

90. Holden JE, Kelley K, Agarwal R. Analyzing change: a primer on multilevel models with applications to nephrology. *Am J Nephrol.* 2008;28(5):792-801.
91. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ.* 1999;319(7211):670-674.
92. Horisberger M, Valderrabano V, Hintermann B. Posttraumatic ankle osteoarthritis after ankle-related fractures. *J Orthop Trauma.* 2009;23(1):60-67.
93. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI): concepts, measurement properties and applications. *Health Qual Life Outcomes.* 2003;1(1):54.
94. Hosmer DW, Lemeshow S, Sturdivant RX. *Applied logistic regression*. 3rd ed. Hoboken, New Jersey: Wiley; 2013.
95. HSCIC. Hospital Episodes Statistics - Accident and Emergency attendances in England 2012-13. London: Health and Social Care Information Centre; 2014.
96. Hubbard TJ, Hicks-Little CA. Ankle ligament healing after an acute ankle sprain: an evidence-based approach. *J Athl Train.* 2008;43(5):523-529.
97. Hulley SB, Cummings SR, Browner WS, Grady D, Newman TB. *Designing clinical research*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2013.
98. Hunt KJ, Hurwit D. Use of patient-reported outcome measures in foot and ankle research. *J Bone Joint Surg Am.* 2013;95(16):e118.
99. Hupperets MDW, Verhagen EALM, van Mechelen W. Effect of unsupervised home based proprioceptive training on recurrences of ankle sprain: randomised controlled trial. *BMJ.* 2009;339:b2684.
100. Hurschler C, Provenzano PP, Vanderby Jr. R. Scanning electron microscopic characterization of healing and normal rat ligament microstructure under slack and loaded conditions. *Connect Tissue Res.* 2003;44(2):59-68.
101. Hutchins S, Bowker P, Geary N, Richards J. The biomechanics and clinical efficacy of footwear adapted with rocker profiles - evidence in the literature. *Foot (Edinb).* 2009;19(3):165-170.
102. Kannus P, Palvanen M, Niemi S, Parkkari J, Jarvinen M. Stabilizing incidence of low-trauma ankle fractures in elderly people Finnish statistics in 1970-2006 and prediction for the future. *Bone.* 2008;43(2):340-342.
103. Kannus P, Parkkari J, Jarvinen TL, Jarvinen TA, Jarvinen M. Basic science and clinical studies coincide: active treatment approach is needed after a sports injury. *Scand J Med Sci Sports.* 2003;13(3):150-154.
104. Kannus R, Jòzsa L, Renström R, et al. The effects of training, immobilization and remobilization on musculoskeletal tissue. *Scand J Med Sci Sports.* 1992;2(3):100-118.
105. Karlsson J. Acute ankle injuries. In: Brukner P, Khan K, eds. *Clinical Sports Medicine*. 3rd ed. North Ryde: McGraw Hill Australia; 2007.
106. Katz MH. *Study design and statistical analysis: a practical guide for clinicians*. Cambridge: Cambridge University Press; 2006.
107. Keene D, James G, Lamb SE, et al. Factors associated with mobility outcomes in older people post-ankle fracture: an observational cohort study focussing on peripheral vessel function. *Injury.* 2013;44(7):987-993.
108. Kerkhoffs G, Rowe B, Assendelft W, Kelly K, Struijs P, van Dijk C. Immobilisation and functional treatment for acute lateral ankle ligament injuries in adults. *Cochrane Database Syst Rev.* 2002(3):CD003762.
109. Kerkhoffs GM, van den Bekerom M, Elders LAM, et al. Diagnosis, treatment and prevention of ankle sprains: an evidence-based clinical guideline. *Br J Sports Med.* 2012;46(12):854-860.

110. Kerkhoffs GM, van den Bekerom MP, Struijs PA, van Dijk CN. 10-day below-knee cast for management of severe ankle sprains. *Lancet.* 2009;373(9675):1601.
111. Khan KM, Scott A. Mechanotherapy: how physical therapists' prescription of exercise promotes tissue repair. *Br J Sports Med.* 2009;43(4):247-252.
112. Kimmel LA, Edwards ER, Liew SM, Oldmeadow LB, Webb MJ, Holland AE. Rest easy? Is bed rest really necessary after surgical repair of an ankle fracture? *Injury.* 2012;43(6):766-771.
113. Kirkwood BR, Sterne JAC, Kirkwood BR. *Essential medical statistics*. 2nd ed. Oxford: Blackwell Science; 2003.
114. Kirtley C. *Clinical gait analysis: theory and practice*. Edinburgh: Elsevier Churchill Livingstone; 2006.
115. Kressig RW, Beauchet O, European GNG. Guidelines for clinical applications of spatio-temporal gait analysis in older adults. *Aging Clin Exp Res.* 2006;18(2):174-176.
116. Lamb SE, Gates S, Williams MA, et al. Emergency department treatments and physiotherapy for acute whiplash: a pragmatic, two-step, randomised controlled trial. *Lancet.* 2013;381(9866):546-556.
117. Lamb SE, Marsh JL, Hutton JL, Nakash R, Cooke MW. Mechanical supports for acute, severe ankle sprain: a pragmatic, multicentre, randomised controlled trial. *Lancet.* 2009;373(9663):575-581.
118. Lamb SE, Nakash RA, Withers EJ, et al. Clinical and cost effectiveness of mechanical support for severe ankle sprains: design of a randomised controlled trial in the emergency department. *BMC Musculoskelet Disord.* 2005;6:1.
119. Lardenoye S, Theunissen E, Cleffken B, Brink PR, de Bie RA, Poeze M. The effect of taping versus semi-rigid bracing on patient outcome and satisfaction in ankle sprains: a prospective, randomized controlled trial. *BMC Musculoskelet Disord.* 2012;13:81.
120. Lee KM, Chung CY, Kwon SS, et al. Ankle fractures have features of an osteoporotic fracture. *Osteoporos Int.* 2013:1-7.
121. Lehtonen H, Järvinen TLN, Honkonen S, Nyman M, Vihtonen K, Järvinen M. Use of a cast compared with a functional ankle brace after operative treatment of an ankle fracture. *J Bone Joint Surg Am.* 2003;85(2):205-211.
122. Lin CW, Donkers NA, Refshauge KM, Beckenkamp PR, Khera K, Moseley AM. Rehabilitation for ankle fractures in adults. *Cochrane Database Syst Rev.* 2012(11):CD005595.
123. Lin CW, Hiller CE, de Bie RA. Evidence-based treatment for ankle injuries: a clinical perspective. *J Man Manip Ther.* 2010;18(1):22-28.
124. Lin CW, Moseley AM, Haas M, Refshauge KM, Herbert RD. Manual therapy in addition to physiotherapy does not improve clinical or economic outcomes after ankle fracture. *J Rehabil Med.* 2008;40(6):433-439.
125. Lin CW, Moseley AM, Herbert RD, Refshauge KM. Pain and dorsiflexion range of motion predict short- and medium-term activity limitation in people receiving physiotherapy intervention after ankle fracture: an observational study. *Aust J Physiother.* 2009;55(1):31-37.
126. Lin CW, Moseley AM, Refshauge KM. Rehabilitation for ankle fractures in adults. *Cochrane Database Syst Rev.* 2008(3):CD005595.
127. Lin CW, Moseley AM, Refshauge KM, Bundy AC. The Lower Extremity Functional Scale has good clinimetric properties in people with ankle fracture. *Phys Ther.* 2009;89(6):580-588.

128. Lin TW, Cardenas L, Soslowsky LJ. Biomechanics of tendon injury and repair. *J Biomech.* 2004;37(6):865-877.
129. Lindemann U, Najafi B, Zijlstra W, et al. Distance to achieve steady state walking speed in frail elderly persons. *Gait Posture.* 2008;27(1):91-96.
130. Long JS, Freese J. *Regression models for categorical dependent variables using Stata*. 2nd ed. College Station, Texas: StataCorp LP; 2006.
131. Longo U, Loppini M, Romeo G, van Dijk CN, Maffulli N, Denaro V. Bone bruises associated with acute ankle ligament injury: do they need treatment? *Knee Surg Sports Traumatol Arthrosc.* 2013;21(6):1261-1268.
132. Losch A, Meybohm P, Schmalz T, et al. Functional results of dynamical gait analysis after 1 year of hobby-athletes with a surgically treated ankle fracture. *Sportverletz Sportschaden.* 2002;16(3):101-107.
133. Losch A, Meybohm P, Schmalz T, et al. Prospective randomised study on the cost/benefit analysis of early functional after-treatment in operatively treated ankle joint fractures. *Hefte zu der Unfallchirurg.* 2002;284:232-233.
134. Magee DJ, Zachazewski JE, Quillen WS. *Scientific foundations and principles of practice in musculoskeletal rehabilitation*. St. Louis, Mo.: Saunders Elsevier; 2007.
135. Marchant MH, Jr., Tibor LM, Sekiya JK, Hardaker WT, Jr., Garrett WE, Jr., Taylor DC. Management of medial-sided knee injuries, part 1: medial collateral ligament. *Am J Sports Med.* 2011;39(5):1102-1113.
136. Marqueen T, Owen J, Nicandri G, Wayne J, Carr J. Comparison of the syndesmotic staple to the transsyndesmotic screw: a biomechanical study. *Foot Ankle Int.* 2005;26(3):224-230.
137. Marsh JL, Buckwalter J, Gelberman R, et al. Articular fractures: does an anatomic reduction really change the result? *J Bone Joint Surg Am.* 2002;84(7):1259-1271.
138. Martin RL, Davenport TE, Paulseth S, Wukich DK, Godges JJ, Orthopaedic Section American Physical Therapy A. Ankle stability and movement coordination impairments: ankle ligament sprains. *J Orthop Sports Phys Ther.* 2013;43(9):A1-40.
139. Martin RL, Irrgang JJ. A survey of self-reported outcome instruments for the foot and ankle. *J Orthop Sports Phys Ther.* 2007;37(2):72-84.
140. Martin RL, McPoil TG. Reliability of ankle goniometric measurements. *J Am Podiatr Med Assoc.* 2005;95(6):564-572.
141. Mazur JM, Schwartz E, Simon SR. Ankle arthrodesis. Long-term follow-up with gait analysis. *J Bone Joint Surg Am.* 1979;61(7):964-975.
142. McCarthy MM, Hannafin JA. The mature athlete: aging tendon and ligament. *Sports Health.* 2014;6(1):41-48.
143. McCollum GA, Calder JDF, Longo UG, et al. Talus osteochondral bruises and defects: diagnosis and differentiation. *Foot Ankle Clin.* 2013;18(1):35-47.
144. McDowell I. *Measuring health: a guide to rating scales and questionnaires*. 3rd ed. New York ; Oxford: Oxford University Press; 2006.
145. McMahon LM, Burdett R, Whitney SL. Effects of muscle group and placement site on reliability of hand-held dynamometry strength measurements. *J Orthop Sports Phys Ther.* 1992;15(5):236-242.
146. McNamee R. Confounding and confounders. *Occup Environ Med.* 2003;60(3):227-234.
147. McPhail S, Dunstan J, Canning J, Haines T. Life impact of ankle fractures: qualitative analysis of patient and clinician experiences. *BMC Musculoskelet Disord.* 2012;13(1):224.

148. Menz HB, Latt MD, Tiedemann A, Mun San Kwan M, Lord SR. Reliability of the GAITRite walkway system for the quantification of temporo-spatial parameters of gait in young and older people. *Gait Posture.* 2004;20(1):20-25.
149. Michelson JD, Hamel AJ, Buczek FL, Sharkey NA. Kinematic behavior of the ankle following malleolar fracture repair in a high-fidelity cadaver model. *J Bone Joint Surg Am.* 2002;84(11):2029-2038.
150. Mieras JN, Singleton TJ, Barrett SL. Contralateral peak plantar pressures with a postoperative boot: a preliminary study. *J Am Podiatr Med Assoc.* 2011;101(2):127-132.
151. Mills EJ, Chan AW, Wu P, Vail A, Guyatt GH, Altman DG. Design, analysis, and presentation of crossover trials. *Trials.* 2009;10:27.
152. Mills K, Hettinga BA, Pohl MB, Ferber R. Between-limb kinematic asymmetry during gait in unilateral and bilateral mild to moderate knee osteoarthritis. *Arch Phys Med Rehabil.* 2013;94(11):2241-2247.
153. Mitchell MN. *A visual guide to Stata graphics*. 3rd ed. College Station, Tex.: Stata Press; 2012.
154. Moe-Nilssen R. A method for reliability analysis of speed-related repeated measures gait data. *Gait Posture.* 2011;33(2):297-299.
155. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ.* 2010;340:c869.
156. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339:b2535.
157. Murray AM, McDonald SE, Archbold P, Crealey GE. Cost description of inpatient treatment for ankle fracture. *Injury.* 2011;42(11):1226-1229.
158. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2197-2223.
159. Naeem M, Rahimnajjad MK, Rahimnajjad NA, Idrees Z, Shah GA, Abbas G. Assessment of functional treatment versus plaster of Paris in the treatment of grade 1 and 2 lateral ankle sprains. *J Orthop Traumatol.* 2014;[In Press].
160. Nakagawa S, Cuthill IC. Effect size, confidence interval and statistical significance: a practical guide for biologists. *Biol Rev Camb Philos Soc.* 2007;82(4):591-605.
161. Nakash RA, Hutton, J.L., Jorstad-Stein, E.C., Gates, S., Lamb, S.E. Maximising response to postal questionnaires - a systematic review of randomised trials in health research. *BMC Med Res Methodol.* 2006;6:2.
162. Nash CE, Mickan SM, Del Mar CB, Glasziou PP. Resting injured limbs delays recovery: a systematic review. *J Fam Pract.* 2004;53(9):706-712.
163. Neumann DA. *Kinesiology of the musculoskeletal system: foundations for physical rehabilitation*. St. Louis ; London: Mosby; 2002.
164. NICE. *Venous thromboembolism: reducing the risk: Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital*. Manchester: National Institute for Health and Care Excellence; 2010.
165. NICE. Sprains and strains (Clinical Knowledge Summaries). *National Institute for Health and Care Excellence*. Available at: http://cks.nice.org.uk/sprains-and-strains#!topicsummary. Accessed 22.5.2014.

166. Nightingale EJ, Moseley AM, Herbert RD. Passive dorsiflexion flexibility after cast immobilization for ankle fracture. *Clin Orthop.* 2007;456:65-69.
167. Nilsson G, Ageberg E, Ekdahl C, Eneroth M. Balance in single-limb stance after surgically treated ankle fractures: a 14-month follow-up. *BMC Musculoskelet Disord.* 2006;7(1):35.
168. Nilsson G, Nyberg P, Ekdahl C, Eneroth M. Performance after surgical treatment of patients with ankle fractures - 14-month follow-up. *Physiother Res Int.* 2003;8(2):69-82.
169. Nilsson GM, Jonsson K, Ekdahl CS, Eneroth M. Unsatisfactory outcome following surgical intervention of ankle fractures. *Foot Ankle Surg.* 2005;11(1):11-16.
170. Nordin M, Frankel VH. *Basic biomechanics of the musculoskeletal system*. 4th ed. Philadelphia ; London: Wolters Kluwer/Lippincott Williams & Wilkins; 2011.
171. North K, Potter MQ, Kubiak EN, Bamberg SJ, Hitchcock RW. The effect of partial weight bearing in a walking boot on plantar pressure distribution and center of pressure. *Gait Posture.* 2012;36(3):646-649.
172. Novacheck TF. The biomechanics of running. *Gait Posture.* 1998;7(1):77-95.
173. O'Connor SR, Bleakley CM, Tully MA, McDonough SM. Predicting functional recovery after acute ankle sprain. *PLoS One.* 2013;8(8):e72124.
174. Olerud C, Molander H. A scoring scale for symptom evaluation after ankle fracture. *Arch Orthop Trauma Surg.* 1984;103(3):190-194.
175. Omori G, Kawakami K, Sakamoto M, Hara T, Koga Y. The effect of an ankle brace on the 3-dimensional kinematics and tibio-talar contact condition for lateral ankle sprains. *Knee Surg Sports Traumatol Arthrosc.* 2004;12(5):457-462.
176. Ozcivici E, Luu YK, Adler B, et al. Mechanical signals as anabolic agents in bone. *Nat Rev Rheumatol.* 2010;6(1):50-59.
177. Perneger TV. What's wrong with Bonferroni adjustments. *BMJ.* 1998;316(7139):1236-1238.
178. Perry J, Burnfield JM. *Gait analysis: normal and pathological function*. 2nd ed. Thorofare, NJ: SLACK; 2010.
179. Perttunen JR, Nieminen H, Tukiainen E, Kuokkanen H, Asko-Seljavaara S, Komi PV. Asymmetry of gait after free flap reconstruction of severe tibial fractures with extensive soft-tissue damage. *Scand J Plast Reconstr Surg Hand Surg.* 2000;34(3):237-243.
180. Petersen W, Rembitzki IV, Koppenburg AG, et al. Treatment of acute ankle ligament injuries: a systematic review. *Arch Orthop Trauma Surg.* 2013;133(8):1129-1141.
181. Petty NJ. *Principles of neuromusculoskeletal treatment and management : a guide for therapists*. 2nd ed. Edinburgh: Churchill Livingstone; 2011.
182. Phillips BA, Lo SK, Mastaglia FL. Muscle force measured using “break” testing with a hand-held myometer in normal subjects aged 20 to 69 years. *Arch Phys Med Rehabil.* 2000;81(5):653-661.
183. Pihlajamaki H, Hietaniemi K, Paavola M, Visuri T, Mattila VM. Surgical versus functional treatment for acute ruptures of the lateral ligament complex of the ankle in young men: a randomized controlled trial. *J Bone Joint Surg Am.* 2010;92(14):2367-2374.
184. Pocock SJ. *Clinical trials: a practical approach*. Chichester: Wiley; 1983.
185. Pocock SJ. Clinical trials with multiple outcomes: a statistical perspective on their design, analysis, and interpretation. *Control Clin Trials.* 1997;18(6):530-545.
186. Polzer H. 10-day below-knee cast for management of severe ankle sprains. *Lancet.* 2009;373(9675):1602.

187. Polzer H, Kanz KG, Prall WC, et al. Diagnosis and treatment of acute ankle injuries: development of an evidence-based algorithm. *Orthop Rev (Pavia).* 2012;4(1):e5.
188. Pound P, Bracken MB. Is animal research sufficiently evidence based to be a cornerstone of biomedical research? *BMJ.* 2014;348:g3387.
189. Pourkazemi F, Hiller CE, Raymond J, Nightingale EJ, Refshauge KM. Predictors of chronic ankle instability after an index lateral ankle sprain: a systematic review. *J Sci Med Sport.* 2014;[In press].
190. Prado MP, Mendes AA, Amodio DT, Camanho GL, Smyth NA, Fernandes TD. A comparative, prospective, and randomized study of two conservative treatment protocols for first-episode lateral ankle ligament injuries. *Foot Ankle Int.* 2014;35(3):201-206.
191. Protopapadaki A, Drechsler WI, Cramp MC, Coutts FJ, Scott OM. Hip, knee, ankle kinematics and kinetics during stair ascent and descent in healthy young individuals. *Clin Biomech (Bristol, Avon).* 2007;22(2):203-210.
192. Psatha M, Wu Z, Gammie FM, et al. A longitudinal MRI study of muscle atrophy during lower leg immobilization following ankle fracture. *J Magn Reson Imaging.* 2012;35(3):686-695.
193. Punt IM, Ziltener J-L, Laidet M, Armand S, Allet L. Gait and physical impairments in acute ankle sprain patients receiving no physical therapy. *PM R.* 2014;[In press].
194. Rabe-Hesketh S, Skrondal A. *Multilevel and longitudinal modeling using Stata*. 3rd ed. College Station, Tex.: Stata Press Publication; 2012.
195. Rankin G, Stokes M. Reliability of assessment tools in rehabilitation: an illustration of appropriate statistical analyses. *Clin Rehabil.* 1998;12(3):187-199.
196. Rasmussen S, Sperling KP, Jensen PK. Aircast pneumatic walker reduces pain and enhances rehabilitation after supination-eversion type 4 fractures [abstract] *Danish Orthopaedic Society Meeting.* 2000.
197. Reese NB, Bandy WD. *Joint range of motion and muscle length testing*. Philadelphia ; London: Saunders; 2002.
198. Riener R, Rabuffetti M, Frigo C. Stair ascent and descent at different inclinations. *Gait Posture.* 2002;15(1):32-44.
199. Roos EM, Brandsson S, Karlsson J. Validation of the foot and ankle outcome score for ankle ligament reconstruction. *Foot Ankle Int* 2001;22(10):788-794.
200. Ruedi TP, Murphy WM. *AO principles of fracture management*. Stuttgart ; New York: Thieme; 2000.
201. Sadeghi H. Local or global asymmetry in gait of people without impairments. *Gait Posture.* 2003;17(3):197-204.
202. Savovic J, Weeks L, Sterne J, et al. Evaluation of the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials: focus groups, online survey, proposed recommendations and their implementation. *Syst Rev.* 2014;3(1):37.
203. Scheffer AC, Schuurmans MJ, van Dijk N, van der Hooft T, de Rooij SE. Fear of falling: measurement strategy, prevalence, risk factors and consequences among older persons. *Age Ageing.* 2008;37(1):19-24.
204. Schmidt R, Meyer-Wolbert B, Roderer M, et al. Dynamic gait analysis. Means for quality assurance after surgically treated ankle joint fractures. *Unfallchirurg.* 1999;102(2):110-114.
205. Schoon Y, Bongers K, Van Kempen J, Melis R, Olde Rikkert M. Gait speed as a test for monitoring frailty in community-dwelling older people has the highest diagnostic value compared to step length and chair rise time. *Eur J Phys Rehabil Med.* 2014;[In press].

206. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ.* 2010;340:c332.
207. Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet.* 2002;359(9306):614-618.
208. Schwenk M, Schmidt M, Pfisterer M, Oster P, Hauer K. Rollator use adversely impacts on assessment of gait and mobility during geriatric rehabilitation. *J Rehabil Med Suppl.* 2011;43(5):424-429.
209. Seah R, Mani-Babu S. Managing ankle sprains in primary care: what is best practice? A systematic review of the last 10 years of evidence. *Br Med Bull.* 2011;97(1):105-135.
210. Selby R, Geerts WH, Kreder HJ, Crowther MA, Kaus L, Sealey F. Symptomatic venous thromboembolism uncommon without thromboprophylaxis after isolated lower-limb fracture. *J Bone Joint Surg Am.* 2014;96(10):e83.
211. Senn S. Cross-over trials, carry-over effects and the art of self-delusion. *Stat Med.* 1988;7(10):1099-1101.
212. Senn S. *Cross-over trials in clinical research*. 2nd ed. Chichester: Wiley; 2002.
213. Shaffer MA, Okereke E, Esterhai JL, et al. Effects of immobilization on plantar-flexion torque, fatigue resistance, and functional ability following an ankle fracture. *Phys Ther.* 2000(8):769-780.
214. Shah NH, Sundaram RO, Velusamy A, Braithwaite IJ. Five-year functional outcome analysis of ankle fracture fixation. *Injury.* 2007;38(11):1308-1312.
215. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull.* 1979;86(2):420-428.
216. Simera I, Moher D, Hirst A, Hoey J, Schulz KF, Altman DG. Transparent and accurate reporting increases reliability, utility, and impact of your research: reporting guidelines and the EQUATOR Network. *BMC Med.* 2010;8:24.
217. Smith GE. The most ancient splints. *BMJ.* 1908;1(2465):732-736.732.
218. Sondenaa K, Alho A, Hoigaard U, Smith D. The effect of immobilization in a plaster cast on ankle fractures after stable osteosynthesis. A randomized trial [abstract]. *Acta Orthop Scand.* 1982:710.
219. Sondenaa K, Hoigaard U, Smith D, Alho A. Immobilization of operated ankle fractures. *Acta Orthop Scand.* 1986;57(1):59-61.
220. Spink MJ, Fotoohabadi MR, Menz HB. Foot and ankle strength assessment using hand-held dynamometry: reliability and age-related differences. *Gerontology.* 2010;56(6):525-532.
221. Stark T, Walker B, Phillips JK, Fejer R, Beck R. Hand-held dynamometry correlation with the gold standard isokinetic dynamometry: a systematic review. *PM R.* 2011;3(5):472-479.
222. Steinfeld Y, Shabat S, Nyska M, Peretz C, Dvir Z. Ankle rotators strength and functional indices following operative intervention for ankle fractures. *Isokinet Exerc Sci.* 2012;20(3):173-179.
223. Stevens JE, Pathare NC, Tillman SM, et al. Relative contributions of muscle activation and muscle size to plantarflexor torque during rehabilitation after immobilization. *J Orthop Res.* 2006;24(8):1729-1736.
224. Stevens JE, Walter GA, Okereke E, et al. Muscle adaptations with immobilization and rehabilitation after ankle fracture. *Med Sci Sports Exerc.* 2004;36(10):1695-1701.
225. Stockle U, Konig B, Tempka A, Sudkamp NP. Cast immobilization versus vacuum stabilizing system. Early functional results after osteosynthesis of ankle joint fractures. [German]. *Unfallchirurg.* 2000;103(3):215-219.

226. Streiner DL, Norman GR. *Health measurement scales: a practical guide to their development and use*. 4th ed. Oxford: Oxford University Press; 2008.
227. Studenski S. Bradypedia: is gait speed ready for clinical use? *J Nutr Health Aging.* 2009;13(10):878-880.
228. Sultan MJ, McKeown A, McLaughlin I, Kurdy N, McCollum CN. Elastic stockings or Tubigrip for ankle sprain: a randomised clinical trial. *Injury.* 2012;43(7):1079-1083.
229. Sultan MJ, Zhing T, Morris J, Kurdy N, McCollum CN. Compression stockings in the management of fractures of the ankle: a randomised controlled trial. *Bone Joint J.* 2014;96(8):1062-1069.
230. Terada M, Pietrosimone BG, Gribble PA. Therapeutic interventions for increasing ankle dorsiflexion after ankle sprain: a systematic review. *J Athl Train.* 2013;48(5):696-709.
231. Terrier P, Deriaz O, Meichtry A, Luthi F. Prescription footwear for severe injuries of foot and ankle: effect on regularity and symmetry of the gait assessed by trunk accelerometry. *Gait Posture.* 2009;30(4):492-496.
232. Thakore RV, Hooe BS, Considine P, et al. Ankle fractures and employment: a life-changing event for patients. *Disabil Rehabil.* 2014;[In press].
233. Thomas G, Whalley H, Modi C. Early mobilization of operatively fixed ankle fractures: a systematic review. *Foot Ankle Int.* 2009;30(7):666-674.
234. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol.* 2009;62(5):464-475.
235. Thur CK, Edgren G, Jansson KA, Wretenberg P. Epidemiology of adult ankle fractures in Sweden between 1987 and 2004: a population-based study of 91,410 Swedish inpatients. *Acta Orthop.* 2012;83(3):276-281.
236. Tropp H, Norlin R. Ankle performance after ankle fracture: a randomized study of early mobilization. *Foot Ankle Int.* 1995;16(2):79-83.
237. Tully MA, Bleakley CM, O'Connor SR, McDonough SM. Functional management of ankle sprains: what volume and intensity of walking is undertaken in the first week postinjury. *Br J Sports Med.* 2012;46(12):877-882.
238. Turner AS. Research in Orthopedic Surgery. In: Souba WW, Wilmore DW, eds. *Surgical Research*. Waltham, MA: Academic Press; 2001:1137-1200.
239. Twisk JWR. *Applied multilevel analysis: a practical guide*. Cambridge: Cambridge University Press; 2006.
240. Usherwood JR, Channon AJ, Myatt JP, Rankin JW, Hubel TY. The human foot and heel–sole–toe walking strategy: a mechanism enabling an inverted pendular gait with low isometric muscle force? *J R Soc Interface.* 2012.
241. Valderrabano V, Horisberger M, Russell I, Dougall H, Hintermann B. Etiology of Ankle Osteoarthritis. *Clin Orthop Relat Res.* 2009;467(7):1800-1806.
242. van den Bekerom MPJ, Hogervorst M, Bolhuis HW, van Dijk CN. Operative aspects of the syndesmotic screw: review of current concepts. *Injury.* 2008;39(4):491-498.
243. van der Ploeg RJ, Fidler V, Oosterhuis HJ. Hand-held myometry: reference values. *J Neurol Neurosurg Psychiatry.* 1991;54(3):244-247.
244. van Dijk CN, Lim LS, Bossuyt PM, Marti RK. Physical examination is sufficient for the diagnosis of sprained ankles. *J Bone Joint Surg Br.* 1996;78(6):958-962.
245. van Griensven H, Barker S, Galindo H. *Pain in practice: theory and treatment strategies for manual therapists*. Edinburgh: Butterworth Heinemann ELsevier; 2005.

246. van Rijn RM, van Middelkoop M. 10-day below-knee cast for management of severe ankle sprains. *Lancet.* 2009;373(9675):1601.
247. van Rijn RM, van Os AG, Bernsen RM, Luijsterburg PA, Koes BW, Bierma-Zeinstra SM. What is the clinical course of acute ankle sprains? A systematic literature review. *Am J Med.* 2008;121(4):324-331 e326.
248. van Schie-Van der Weert EM, van Lieshout EM, De Vries MR, van der Elst M, Schepers T. Determinants of outcome in operatively and non-operatively treated Weber-B ankle fractures. *Arch Orthop Trauma Surg.* 2012;132(2):257-263.
249. Venesmaa P, Arokoski J, Airaksinen O, Eskelinen J, Suomalainen O, Kroger H. Comparing postoperative immobilisation of ankle fractures with aircast or standard cast: a randomised prospective study [abstract]. *J Bone Joint Surg Br* 2004;86(Suppl 3):S255-256.
250. Vioreanu M, Dudeney S, Hurson B, Kelly E, Orourke K, Quinlan W. Early mobilization in a removable cast compared with immobilization in a cast after operative treatment of ankle fractures: A prospective randomized study. *Foot Ankle Int.* 2007;28(1):13-19.
251. Vioreanu M, O'Briain D, Dudeney S, et al. Early exercising in removable cast compared with immobilisation in cast after operative treatment of ankle fractures. A prospective randomised study [abstract]. *J Bone Joint Surg Br.* 2006:280.
252. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and cox regression. *Am J Epidemiol.* 2007;165(6):710-718.
253. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2163-2196.
254. Wall BT, Dirks ML, van Loon LJ. Skeletal muscle atrophy during short-term disuse: implications for age-related sarcopenia. *Ageing Res Rev.* 2013;12(4):898-906.
255. Walsh S, Frank C, Hart D. Immobilization alters cell-metabolism in an immature ligament. *Clin Orthop Relat Res.* 1992(277):277-288.
256. Wang C-Y, Olson SL, Protas EJ. Test-retest strength reliability: hand-held dynamometry in community-dwelling elderly fallers. *Arch Phys Med Rehabil.* 2002;83(6):811-815.
257. Wang R, Thur CK, Gutierrez-Farewik EM, Wretenberg P, Brostrom E. One year follow-up after operative ankle fractures: a prospective gait analysis study with a multi-segment foot model. *Gait Posture.* 2010;31(2):234-240.
258. Ware JJ, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Medical Care.* 1996;34(3):220-233.
259. Waterman BR, Owens BD, Davey S, Zacchilli MA, Belmont PJ, Jr. The epidemiology of ankle sprains in the United States. *J Bone Joint Surg Am.* 2010;92(13):2279-2284.
260. Webster KE, Wittwer JE, Feller JA. Validity of the GAITRite walkway system for the measurement of averaged and individual step parameters of gait. *Gait Posture.* 2005;22(4):317-321.
261. Weerdesteyn V, Rijken H, Geurts AC, Smits-Engelsman BC, Mulder T, Duysens J. A five-week exercise program can reduce falls and improve obstacle avoidance in the elderly. *Gerontology.* 2006;52(3):131-141.
262. Westerman RW, Porter K. Ankle fractures in adults: an overview. *Trauma.* 2007;9(4):267-272.

263. Wetzler MJ, Whitelaw GP, Lee PC. The post-operative management of ankle fractures with pneumatic braces versus short leg cast [abstract]. *Orthop Trans.* 1991;15:719.
264. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. *Res Nurs Health.* 1990;13(4):227-236.
265. White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. *Stat Med.* 2010;29(28):2920-2931.
266. Whittle M, Levine D, Richards J, Whittle M. *Whittle's gait analysis*. 5th ed. Edinburgh: Churchill Livingston; 2012.
267. WHO. *International Classification of Functioning, Disability and Health (ICF)*. Geneva, Switzerland: World Health Organization; 2001.
268. Widrick JJ, Fitts RH. Peak force and maximal shortening velocity of soleus fibers after non-weight-bearing and resistance exercise. *J Appl Physiol.* 1997;82(1):189-195.
269. Willett K, Keene DJ, Morgan L, et al. Ankle Injury Management (AIM): design of a pragmatic multi-centre equivalence randomised controlled trial comparing Close Contact Casting (CCC) to Open surgical Reduction and Internal Fixation (ORIF) in the treatment of unstable ankle fractures in patients over 60 years. *BMC Musculoskelet Disord.* 2014;15(1):79.
270. Williams M. The patient's experience in a plaster cast. *Int J Orthop Trauma Nurs.* 2010;14(3):132-141.
271. Wilson AJ. Ankle fractures: understanding the mechanism of injury is the key to analyzing the radiographs. *Emerg Radiol.* 1998;5(1):49-60.
272. Witjes S, Gresnigt F, van den Bekerom MP, Olsman JG, van Dijk NC. The ANKLE TRIAL (ankle treatment after injuries of the ankle ligaments): what is the benefit of external support devices in the functional treatment of acute ankle sprain? A randomised controlled trial. *BMC Musculoskelet Disord.* 2012;13:21.
273. Wolf SI, Lessl E, Müller S, Schmidmaier G, Dreher T. Persistent diminished joint function following ankle fracture - a risk factor for posttraumatic osteoarthritis? [abstract]. *Gait Posture.* 2013;38 (Suppl 1):S101-102.
274. Yammine K, Fathi Y. Ankle "sprains" during sport activities with normal radiographs: Incidence of associated bone and tendon injuries on MRI findings and its clinical impact. *Foot (Edinb).* 2011;21(4):176-178.
275. Yogev G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord.* 2008;23(3):329-342.
276. Yogev G, Plotnik M, Peretz C, Giladi N, Hausdorff J. Gait asymmetry in patients with Parkinson's disease and elderly fallers: when does the bilateral coordination of gait require attention? *Exp Brain Res.* 2007;177(3):336-346.
277. Zaghloul A, Haddad B, Barksfield R, Davis B. Early complications of surgery in operative treatment of ankle fractures in those over 60: a review of 186 cases. *Injury.* 2014;45(4):780-783.

Appendices

Appendix 1 - Search strategies

EMBASE via Ovid

1: (distal and (fibula* or tibia*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

2: (ankle* or malleol* or unimalleol* or bimalleol* or trimalleol* or potts or weber or lauge-hansen).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

3: fracture*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

4: exp ankle fracture/ or exp ankle dislocation/ or exp malleolus fracture/

5: (1 or 2) and 3

6: 4 or 5

7: limit 6 to (clinical trial or randomized controlled trial or controlled clinical trial)

8: limit 7 to yr="1982 - 2012"

Cochrane Library

1: MeSH descriptor Ankle Joint explode all trees 2: MeSH descriptor Ankle explode all trees 3: MeSH descriptor Ankle Injuries explode all trees 4: (distal near tibia* near fracture*) or (distal near fibula* near fracture*) or (low* near tibia* near fracture*) or (low* near fibula* near fracture*) 5: (ankle or malleol*) near fracture* or (ankle or unimalleol*) near fracture* or (ankle or bimalleol*) near fracture* or (ankle or trimalleol*) near fracture* 6: (weber or lauge-hansen or potts) and ankle 7: fracture* 8: MeSH descriptor Fractures, Bone explode all trees 9: (#7 OR #8) 10: (#1 OR #2 OR #3 OR #6) 11: (#9 AND #10) 12: (#4 OR #5 OR #11)

AMED via OVID

1: (distal and (fibula* or tibia*)).mp. [mp=abstract, heading words, title]

2: (ankle* or malleol* or unimalleol* or bimalleol* or trimalleol* or potts or weber or lauge-hansen).mp. [mp=abstract, heading words, title]

3: fracture*.mp. [mp=abstract, heading words, title]

4: (1 or 2) and 3

5: exp Ankle Injuries/

6: exp Fractures, Bone/

7: 5 and 6

8: 4 or 7

9: limit 8 to yr="1982 - 2012"

CINAHL via EBSCO

S11: S6 AND S10

S10: S7 OR S8 or S9

S9: random* AND (allocat* OR assign* OR basis OR order*)

S8: ((MH "Comparative Studies") OR (MH "Prospective Studies") OR (MH "Experimental Studies")) OR Evaluation research

S7: (MH "Clinical Trials+") OR (MH "Randomized Controlled Trials")

S6: S1 OR S5

S5: (fracture*) AND (S2 or S3)

S4: fracture*

S3: (ankle* or malleol* or unimalleol* or bimalleol* or trimalleol* or potts or weber or lauge-hansen)

S2: (distal and (fibula* or tibia*))

S1: (MM "Ankle Fractures") OR (MH "Ankle Dislocation")

SPORTDiscuss via EBSCO

S8: S7 AND S6

S7: S4 OR S5

S6: random* AND (allocat* OR assign* OR basis OR order*)

S5: DE "ANKLE -- Fractures"

S4: (fracture*) AND (S1 or S2)

S3: fracture*

S2: (ankle* or malleol* or unimalleol* or bimalleol* or trimalleol* or potts or weber or lauge-hansen)

S1: (distal and (fibula* or tibia*))

PEDro

Abstract & Title: fracture

Subdiscipline: Orthopaedics

Body Part: Foot and ankle

Appendix 2 - Systematic review data extraction form.

Data extraction form – to be completed on word processor.
Study Selection

FIRST THREE AUTHORS	
YEAR	

Reports / citations for study.

Code each paper	Author(s)	Report type: Journal/Conference Proceedings etc.	Year
A			
B			
C			

Reviewer Id (initials):
Date form started: / /…
Please highlight any info indicated not reported (NR) or unclear (UC) where you think information from authors would be of high value to the review
If referring to information in the paper please reference location (e.g. Table 1, page 6 paragraph 3 etc.).

Trial characteristics	**Enter details or <u>underline</u> or bold correct entry**
Trial design	parallel / cross-over / cluster / factorial / other:…….
Number of centres (number of Principle Investigator led recruiting centres; include non-recruiting)	
Country / Countries of the centres	
Dates of recruitment (start and end dates; month/year)	

Funding source	Industry (manufacturer) / Public / Mixed / NR / Other …….. Is there a vested interest / conflict of interest: Y / N / NR / UC Professional group(s) of study team: orthopaedic surgery / Physiotherapy / other: UC……..
Power/sample size calculation	*A priori* Sample size calculation: Y / NR / UC Value: …….. Expected clinically important difference on primary outcome? Y / NR / UC Value:……
Statistical analysis	Primary (state method and if seems appropriate) Secondary (state method and if seems appropriate) Intention-to-treat? Y / N / UC Statistical method for dealing with confounders (a priori or post-hoc statistical adjustment?)
Method for dealing with incomplete outcome data	

Participant characteristics	**Enter details below (if more than 2 groups split columns as required)**	
Inclusion criteria		
Exclusion criteria		
Age (mean, standard deviation, range)	Intervention	Control/standard care
Sex of participants (numbers / % in whole numbers)	Intervention	Control/standard care
Fracture type / classification (numbers / % in whole numbers)	Intervention	Control/standard care
Comorbidities (All reported)	Intervention	Control/standard care
Smoking (current/ex-smoker: cigarettes per day: years)	Intervention	Control/standard care
Diabetes (type 1 or 2: years since diagnosis)	Intervention	Control/standard care
Current alcohol intake (units per week)	Intervention	Control/standard care
How many people were randomised?		
Number of participants in each intervention group	Intervention	Control/standard care

Number of participants who received intended treatment (include reasons for not receiving intervention)	Intervention	Control/standard care
Length of follow-up reported – Primary / longest duration (mean weeks, months or years / SD / range)		
Number and % of participants lost to follow-up (at each time-point) Are reasons given?	Intervention	Control/standard care
Number and % of participants who were included in the analysis (at each time-point) (include reasons for exclusions e.g. missing data, technical issues)	Intervention	Control/standard care
Intervention characteristics	**Enter details below (if more than 2 groups split columns as required)**	
Specific intervention(s) Types and durations of immobilisation and details of all other components of interventions (surgery/exercise/advice/ weight-bearing strategies etc.)	Method of immobilisation ***Intervention –*** *Specific technique:* *Materials:* *Device (including manufacturer):* *Removable?:* *Joints immobilised: ankle / knee / forefoot / full foot* *Position of immobilization:* *Anaesthesia during application? (type):* *Duration:* *Weight-bearing:* *Other aspects of care specific to intervention (e.g. wound care, advice, exercise):* How often were participants seen (trial and clinical):	Method of immobilisation ***Control/standard care –*** *Specific technique:* *Materials:* *Device (including manufacturer):* *Removable?:* *Joints immobilised: ankle / knee / forefoot / full foot* *Position of immobilization:* *Anaesthesia during application? (type):* *Duration:* *Weight-bearing:* *Other aspects of care specific to intervention (e.g. wound care, advice, exercise):* How often were participants seen (trial and clinical):

When was the intervention delivered (from injury)	
Standardisation of other aspects of care common to all groups	
Methods used to standardise interventions and other aspects of care including study-specific training/manuals	
Who delivers the intervention (expertise/profession/experience of intervention/managing condition)	
In what setting is the intervention delivered e.g. specialised/non-specialised units, clinics or in theatre	
Procedure for tailoring the intervention for individuals (including comorbidity, tolerance and clinical circumstances)	

D*ata Extraction*

Outcomes relevant to review		**How measured** (tool/subset of tool reported/method and if face-to-face, postal, blinded)	Unit of measurement (state units or enter 'events')	Time-point (add rows to add data for multiple time-pints)	Intervention group			Control group			Estimate of effect
	Reported in paper (**bold**)				n	missing	Mean (SD) or no of participants with event	n	missing	Mean (SD) or no of participants with event	(e.g. estimate; Confidence Interval; p-value)
Physical function: condition specific questionnaires (e.g. Olerud Molander Ankle Score and the Lower Extremity Functional Scale) and relevant components of health scales (e.g. SF-12) or other method (specify).	Yes / No / UC / NR										
Pain (e.g. Visual Analogue Scale)	Yes / No / UC / NR										
Adverse events: all complications related to treatment; pressure sore, wound infection, post-traumatic thromboembolism, Complex Regional Pain Syndrome (CPRS 1), peripheral nerve injury or treatment failure (requiring surgery or further surgery or alternative definitive treatment) etc.	Yes / No / UC / NR										
Patient satisfaction/experience of intervention (patient-reported)	Yes / No / UC / NR										
Compliance / adherence to the intervention	Yes / No / UC / NR										
Reasons for deviations from intervention protocol (e.g. treatment failure, complication)	Yes / No / UC / NR										
Stiffness (patient-reported)	Yes / No / UC / NR										

Swelling (patient reported and clinical measurement)	Yes / No / UC / NR										
Range of ankle motion (clinical measurement)	Yes / No / UC / NR										
Muscle function (strength and endurance)	Yes / No / UC / NR										
Walking, balance and stair climbing performance	Yes / No / UC / NR										
Time to hospital discharge, return to work and leisure activities	Yes / No / UC / NR										
Malunion and non-union (if reported, how are these defined and quantified)	Yes / No / UC / NR										
Quality of life	Yes / No / UC / NR										
Economic outcomes (individual and wider health resource use and costs	Yes / No / UC / NR										
Other relevant (state what and where found – don't extract data)											

Additional comments / data - Other information which you feel is relevant to the results Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review.

References to other trials

Did this report include any references to **published reports** of potentially eligible trials not already identified for this review?		
First author	Journal / Conference	Year of publication
Did this report include any references to **unpublished data** from potentially eligible trials not already identified for this review? If yes, please give author name and details		

Correspondence required? Yes / no

Appendix 3 - Risk of bias assessment form

DOMAIN	Description (quotes from text in inverted commas)	Risk of bias judgement (use criteria)			Comments
		'low risk'	'high risk'	'unclear risk'	
Sequence generation Was the allocation sequence adequately generated?.					
Allocation concealment. Was allocation adequately concealed?					
Blinding of participants, personnel and outcome assessors Was knowledge of the allocated intervention adequately prevented during the study?	*Primary outcome: Subjective*				
	Objective				
	Secondary outcome(s) Subjective				
	Objective				
Incomplete outcome data Were incomplete outcome data adequately addressed?	*Primary outcome: Subjective*				
	Objective				
	Secondary outcome(s) Subjective				

	Objective				
Reporting bias. Selective reporting. Are reports of the study free of suggestion of selective outcome reporting?					
Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?					

Appendix 4 - Participant recruitment poster

Ethics Reference: MSD/IDREC/C1/2012/17

Effects of Ankle Supports on Walking

Participants needed for research project

Why do we want to do this study?

We are investigating the effects of different ankle supports on walking quality. Measuring how walking is effected by ankle supports in a healthy population will help us to understand how ankle supports influence walking after injury.

What does the research involve?

We are looking for 18 healthy volunteers. The study involves a short questionnaire and measurements of walking quality in 3 different ankle supports. Walking will be measured by walking across a mat that picks up pressure from your footsteps. Your involvement would be approximately 30 minutes in total.

If you are over 18 year of age and would be interested in participating in this study, please contact David Keene on 01865 740389 or email david.keene@ndorms.ox.ac.uk

Walking in different ankle supports
David Keene: 01865 740389
david.keene@ndorms.ox.ac.uk

Walking in different ankle supports
David Keene: 01865 740389
david.keene@ndorms.ox.ac.uk

Walking in different ankle supports
David Keene: 01865 740389
david.keene@ndorms.ox.ac.uk

Walking in different ankle supports
David Keene: 01865 740389
david.keene@ndorms.ox.ac.uk

Walking in different ankle supports
David Keene: 01865 740389
david.keene@ndorms.ox.ac.uk

Walking in different ankle supports
David Keene: 01865 740389
david.keene@ndorms.ox.ac.uk

Walking in different ankle supports
David Keene: 01865 740389
david.keene@ndorms.ox.ac.uk

Walking in different ankle supports
David Keene: 01865 740389
david.keene@ndorms.ox.ac.uk

Walking in different ankle supports
David Keene: 01865 740389
david.keene@ndorms.ox.ac.uk

Walking in different ankle supports
David Keene: 01865 740389
david.keene@ndorms.ox.ac.uk

Walking in different ankle supports
David Keene: 01865 740389
david.keene@ndorms.ox.ac.uk

Appendix 5 - Patient information sheet (healthy participants)

Lead Investigator:

David Keene
Research Physiotherapist
Kadoorie Trauma Research Centre
John Radcliffe Hospital
Oxford
OX3 9DU
Tel: 01865 740328
Fax: 01865 857611
david.keene@ndorms.ox.ac.uk

Co- Investigators / project supervisors:

Professor Sallie Lamb
(Kadoorie Professor of Trauma Rehabilitation, University of Oxford; Director of the Warwick Clinical Trials Unit, University of Warwick)
Professor Keith Willett
(National Clinical Director for Trauma Care; Professor of Orthopaedic Trauma Surgery, University of Oxford)

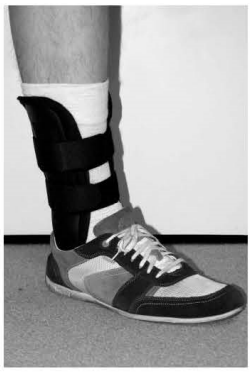
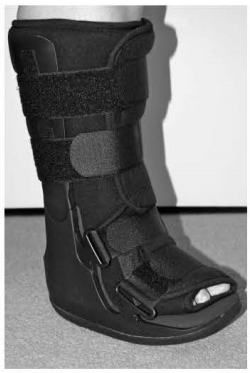
PARTICIPANT INFORMATION SHEET

Effects of Ankle Support Interventions on Normal Gait

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and take your time to decide whether or not you wish to take part.

What is the purpose of the study?

In health care we can offer a variety of supports which aim to improve walking including a tubular elasticated bandage, an ankle stirrup splint or a walking boot (see below). The supports are all used in current standard care. We do not know which of these supports is most helpful for walking. The purpose of this research is to look at the ease and quality of walking in each of these supports in healthy adults.

		
Elasticated tubular bandage	**Ankle Stirrup splint**	**Walker boot**

Why have I been invited and do I have to take part?

You have been asked to consider taking part in this study because you are a healthy adult (over 18 years old). We need to study the effects ankle supports have on normal walking so we can get a better understanding of how they influence walking after injury. We will be asking 18 healthy adults to volunteer for this study. If you are interested in participating, you can ask questions and discuss the study further with the lead investigator. You can take plenty of time to think about it and discuss with friends or family if you wish. You are free to withdraw at any time, without giving a reason.

What will happen if I take part?

If you choose to be in this study the first thing we will do is arrange an appointment at the Kadoorie Centre in the John Radcliffe Hospital. You will be able to see the equipment and the ankle supports. We will ask some questions about your general health to ensure it is appropriate for you take part in the study. If you are happy to be involved in the study we will ask you to sign a consent form.

The walking measurements should take approximately 30 minutes and will be conducted by a qualified senior physiotherapist. We will measure your walking using an electronic system, and ask you to walk over a mat of about 16 feet length (see picture below). The walkway measures each of your foot prints as you walk. You will be asked to walk at a range of speeds in each ankle support. We will ask you to walk down the walkway a few times, but you will be able to rest between each test if needed.

The electronic walkway

What are the possible risks and benefits of taking part?

The walking assessments are not expected to cause any discomfort. Some people may feel tired after the walking measurements but this should not be significant and settle within a short period.

The study is unlikely to help you directly, but the information we get from this study will help improve the treatment of people with ankle injuries in the future. Before participating you should consider if this will affect any health insurance you have and seek advice if necessary.

Would my taking part in this study be kept confidential?

All information collected about you will be kept strictly confidential. How it is collected, handled, stored and destroyed will comply with the Data Protection Act 1998. Any information included in any reports will have your name and address removed so that you cannot be recognised from it.

We will also ask your permission for access to your data by responsible individuals involved in the organising or regulating research when or if it is required. Their role is to check the study is being carried out correctly.

Information collected in studies such as this is kept securely for at least 5 years from the end of the study. We do not use this data for any other purpose without further permission from the Research Ethics Committee and you.

What happens if I have any questions, concerns or complaints about the study?

If you have a concern about any aspect of this project, please speak to the researcher concerned (David Keene, EASING study Lead Investigator, Tel. 01865 740328) who will do his best to answer your query. If you remain unhappy and wish to make a formal complaint, please contact the Research Ethics Committee at the University of Oxford (ethics@medsci.ox.ac.uk; Medical Sciences Inter-Divisional Research Ethics Committee, Medical Sciences Divisional Office, Level 3 John Radcliffe Hospital, Oxford, OX3 9DU, UK).

What will happen to the results of the research study?

The information will be presented at national and international research meetings and in research journals. If you wish to be told about what we learn from the study, we can contact you once the findings are made public.

The research will also be written up as a thesis (a detailed report). On successful submission of the thesis, it will be deposited both in print and online in the University archives, to facilitate its use in future research.

Who is organising and funding the research?

The organisation funding this research is the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences. It is a department of the Medical Sciences Division within the University of Oxford which researches conditions relating to the bones, joints and muscles. The study will be managed through the Kadoorie Centre for Critical Care Research and Education based at the John Radcliffe Hospital.

The researchers involved in this study do not receive any payment other than what is required to cover the necessary expenses. The study is independent of any commercial organisation. We will not be reimbursing participants expenses or offering fees for involvement in the study.

Who has reviewed the study?

This study has been looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the Central Oxford University Research Ethics Committee.

Thank you for considering participation in this study and for taking time to read this information sheet

Appendix 6 - Case Report Form (healthy participants)

Participant details	Participant no:			Participant initials:			

UNIVERSITY OF OXFORD

EASING

Effects of Ankle Support Intervention on Normal Gait

Case Report Forms

STUDY SITE/UNIT:	Kadoorie Centre
LEAD INVESTIGATOR:	David Keene Research Physiotherapist

Participant details	Participant no:			Participant initials:		

ELIGIBILITY SCREENING

Inclusion Criteria	**Yes**	**No***
1 Aged 18 years or over?		
2 Able to give informed consent?		
3 Able to understand and respond appropriately to verbal instructions?		
4 Able to walk minimum or 10m (with or without aid)?		
5 Able to walk minimum or 10m (with or without aid)?		

*If any inclusion criteria are ticked no then the patient is not eligible for the study.

Exclusion Criteria	**Yes***	**No**
1 Open wounds below the knee of the injured limb (to allow application of the supports)		
2 Neurological disorder (as this may limit symmetry of gait possible)		
3 Previous major lower limb fracture (as this may limit symmetry of gait possible)		
4 Systemically unfit to undergo testing (i.e. nausea, fever, active infection requiring antibiotics)		
5 Unable to safely walk without physical support from another person		
6 Uncontrolled health disorder (respiratory, cardiovascular, epilepsy, blood pressure)		

* If any exclusion criteria are ticked yes then the patient is not eligible for the study.

Participant details	Participant no:			Participant initials:			

Do you want to be informed of the results of this study? Yes ☐ No ☐

If yes, please complete patient contact details sheet

BASELINE

Allergies (note: especially to materials in supports)

Known allergies ☐ Yes ☐ No

Type ……

Age: ☐☐

Male ☐ **Female** ☐

Participant details	Participant no:			Participant initials:			

Lower Extremity Functional Scale:

We are interested in knowing whether you are having any difficulty at all with the activities listed below because of your lower limb problem for which you are currently seeking attention. Please provide an answer for each activity.

Today, do you or would you have any difficulty at all with:

(Circle one number on each line)

Activities	**Extreme Difficulty Or Unable to Perform Activity**	**Quite a Bit of Difficulty**	**Moderate Difficulty**	**A Little Bit of Difficulty**	**No Difficulty**
Any of your usual work, household, or school activities	0	1	2	3	4
Your usual hobbies, recreational or sporting activities	0	1	2	3	4
Getting into or out of the bath	0	1	2	3	4
Walking between rooms	0	1	2	3	4
Putting on your shoes or socks	0	1	2	3	4
Squatting	0	1	2	3	4
Lifting an object, like a bag of groceries from the floor	0	1	2	3	4
Performing light activities around your Home	0	1	2	3	4
Performing heavy activities around your Home	0	1	2	3	4
Getting into or out of a car	0	1	2	3	4
Walking 2 blocks	0	1	2	3	4
Walking a mile	0	1	2	3	4
Going up or down 10 stairs (about 1 flight of stairs)	0	1	2	3	4
Standing for 1 hour	0	1	2	3	4
Sitting for 1 hour	0	1	2	3	4
Running on even ground	0	1	2	3	4

Continued on next page

Participant details	Participant no:			Participant initials:		

Running on uneven ground	0	1	2	3	4
Making sharp turns while running fast	0	1	2	3	4
Hopping	0	1	2	3	4
Rolling over in bed	0	1	2	3	4

Walking aid used normally?

None ☐

One crutch ☐

Two crutches ☐

One stick ☐

Two sticks ☐

Frame / Rollator ☐

Participant details	Participant no:			Participant initials:			

Trial walk over the electronic walkway

Proceeding to randomisation?

No...

...unable to exert enough weight on the limb to activate the walkway sensors ☐

...due to pain ☐

...due to fatigue that does not settle after rest period ☐

...due to balance (needs external assistance) ☐

Yes ☐

Other

Details:

6

Participant details	Participant no:				Participant initials:			

RANDOMISATION

Researcher instruction: Take the next numbered unused sealed envelope and write the patients study number and todays date on the front. After all details have been written onto the front open the envelope to reveal the allocation and cross the box below:

Sequence 1: A, B, C ☐

Sequence 2: B, C, A ☐

Sequence 3: C, A, B ☐

Key:

A=elasticated tubular bandage

B=stirrup splint

C=walker boot

Now tick the boxes below to indicate the support to be assessed first, second and third.

Place the allocation back in the envelope and place envelope in x for pick up by researcher (these need to be retained as proof of allocation)

Participant details	Participant no:			Participant initials:		

WALKING ASSESSMENT

First Support A ☐ B ☐ C ☐

Comment on walking technique:

Second Support A ☐ B ☐ C ☐

Comment on walking technique:

Third Support A ☐ B ☐ C ☐

Comment on walking technique:

Participant details	Participant no:				Participant initials:			

If walking assessments are discontinued at any point, please state at what stage and the reason below:

Pain ☐

Fatigue ☐

Other ☐

Details (including the stage of assessments procedures were halted):

Researcher declaration:

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the study was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the study.

Investigator's Signature: ----------

Date of signature:

D	d	m	m	m	y	y	y	y

Participant details	Participant no:			Participant initials:			

Adverse Events

Has the patient experienced any Adverse Events since signing the Informed Consent? ☐ Yes, specify below ☐ No

AE no.	Adverse Event	Start Date dd/mmm/yyyy	Stop Date dd/mmm/yyyy	Outcome 1=Recovered 2=Recovered with sequelae 3=Continuing 4=Patient Died 5=Change in AE 6=unknown	Severity 1=Mild 2=Moderate 3=Severe	Plausible relationship to Study Proceedures	Withdrawn due to AE?	Serious AE (SAE)?	If SAE does it require immediate reporting? (see Protocol)?
		/ / :	/ / :			☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
		/ / :	/ / :			☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
		/ / :	/ / :			☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

Participant details	Participant no:			Participant initials:			

Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- Results in death during or within 30 minutes of testing
- Is life-threatening

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation directly as a result of the study assessments
- Results in persistent or significant disability/incapacity as a result of the study assessments
- Results in further surgery directly as a result of an event during the study assessment
- Results in medical attention as a result of an event during or within 30 minutes of testing (includes injurious fall)

Appendix 7 - CUREC ethics approval

University of Oxford

Medical Sciences Office
John Radcliffe Hospital, Headington, Oxford OX3 9DU

From Samantha Hatzis

CONFIDENTIAL
Mr David Keene
NDORMS

Ref. MSD/IDREC/C1/2012/17

21 February 2012

Dear Mr Keene

CUREC checklist

I am writing to acknowledge receipt of your CUREC/1 form for your project:

EASING: Effects of ankle support intervention on normal gait.

On the basis of the information you have provided this has now been approved by the Medical Sciences IDREC.

The reference number for this project is MSD/IDREC/C1/2012/17 and may I remind you that your project may be reviewed at some stage during an annual audit of projects.

Amendments
Should you at some stage alter some of the techniques or procedures then you should first undertake a checklist (CUREC/1) to see whether these changes alter the ethics of the research. If these remain the same then the committee will require notification of the changes to lodge with the project. If they do not remain the same then you may need to complete a CUREC/2 form and undergo further scrutiny by the committee.

Please do not hesitate to contact me if you have any queries about this.

Yours sincerely,

Samantha Hatzis (Mrs)
Secretary to the MSD IDREC

E-Mail: ethics@medsci.ox.ac.uk

Appendix 8 - Screening form part 1

S	C					

Screening Number

Check **Participant Log** for next available screening number

Screening Form
Part 1 – First eligibility assessment

To be completed by the designated person: complete one screening form for each patient who is: over 18 years of age, has an isolated ankle fracture and had/will have Open Reduction Internal Fixation

Please work through the questions in the order they appear on the form

Please place a cross through correct responses ☒

Date of birth: D D M M Y Y Y Y

Gender: ☐ Male ☐ Female

Initials: ☐☐☐

Date of injury: D D M M Y Y Y Y

Date of screening: D D M M Y Y Y Y

If patient later randomised, enter Study Number here: ☐☐☐☐☐

Please place ☒ a cross through correct responses

Inclusion criteria:

1.	Patient over 18 years of age	☐ Yes	☐ No
2.	Patient has isolated ankle fracture	☐ Yes	☐ No
3.	Had/will have Open Reduction and Internal Fixation.....	☐ Yes	☐ No
4.	Able to understand & respond appropriately to verbal instructions...	☐ Yes	☐ No
5.	Able to give informed consent...	☐ Yes	☐ No

If **any** '**No'** response above (Q1-5), the patient **cannot** be entered into the study, **go directly to Q25** at end of form.
If **'Yes'** to **all** Q1-5 above, **continue to Q6.**

Exclusion criteria:

6.	Weber C type ankle fracture.....	☐ Yes	☐ No
7.	Unable to walk outdoors unaided before injury.....	☐ Yes	☐ No
8.	Diagnosed dementia	☐ Yes	☐ No
9.	Unable to adhere to study protocol or assessments (e.g. for mental health reasons).....	☐ Yes	☐ No
10.	Neurological disorder	☐ Yes	☐ No
11.	Previous major lower limb fracture.....	☐ Yes	☐ No

Other reason excluded:

12.	Multiple injuries (bilateral ankle fractures or other significant injury)	☐ Yes	☐ No
13.	Participant entered into another research study (during this admission to hospital)	☐ Yes	☐ No
14.	Other reason patient not suitable for study *(please specify)*	☐ Yes	☐ No

If **any** '**Yes'** response above (Q6-14), the patient **cannot** be entered into the study, **go directly to Q25** at the end of form.
If **'No'** to **all** Q6-14, **continue.**

CONSENT. Indicate outcome of informed consent process below:

15. Patient willing to give informed consent? ☐ Yes ☐ No, declined
(please give reason below if stated)

If **'No'** indicated above (Q15), the patient **cannot** be entered into the study, **go directly to Q25.**

If **'Yes'** in Q15, obtain consent and go to Q16.

16. Confirm signed consent obtained: ☐ Complete the information in Q17 onwards.

ANKLE:

17. Affected side ☐ Left ☐ Right

18. Comminution ☐ Yes ☐ No

19. Weber classification ☐ A ☐ B NB: Type C excluded

20. Number of malleoli involved? ☐ Uni-malleolar ☐Bi-malleolar ☐Tri malleolar

21. Open fracture ☐ Yes ☐ No

ACTIONS REQUIRED

Cross ☒ when carried out

22. Please check all questions have been completed. ☐

23. Sign and date bottom of form. ☐

24. **Once consent is obtained, screening stage 2 and baseline information should be collected *prior to* randomisation**; see documentation pack 'Day of study assessments'. ☐

25. **All patients screened**:
If patient is **not** suitable for the study: Sign and date below and return to Trauma trial office to be filed.

Update *unsuitable/declined column* on 'Participant Log'. ☐

OR:

If patient **is suitable** for study: Update consented dates on 'Participant Log'. Transcribe relevant information from this Screening Form onto the Randomisation Form. ☐

Researcher signature: _____ Date:_____

Trauma Clinical Trials Office, Kadoorie Centre, John Radcliffe Hospital, Oxford OX3 9DU. Email: david.keene@ndorms.ox.ac.uk

Appendix 9 - Patient information sheet (clinical study)

Lead Investigator:

David Keene
Research Physiotherapist
Kadoorie Trauma Research Centre
John Radcliffe Hospital
Oxford
OX3 9DU
Tel: 01865 740328
Fax: 01865 857611

Co- Investigators / project supervisors:

Professor Sallie Lamb
(Kadoorie Professor of Trauma Rehabilitation, University of Oxford; Director of the Warwick Clinical Trials Unit, University of Warwick)
Professor Keith Willett
(National Clinical Director for Trauma Care; Professor of Orthopaedic Trauma Surgery, University of Oxford)

PATIENT INFORMATION SHEET

Supports for Ankle Fractures in Early Rehabilitation (SAFER)

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve.

Please take time to read the following information carefully.

One of our team will go through the information sheet with you and answer any questions you have. We'd suggest this should take about 20 minutes.

- **Part 1** tells you the purpose of this study and what will happen to you if you take part.
- **Part 2** gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information.

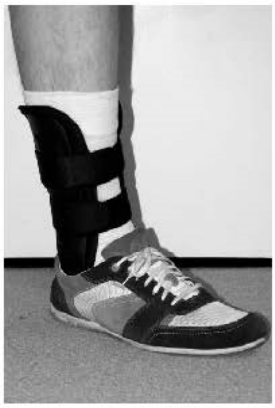
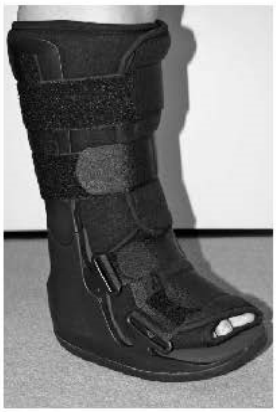
Take your time to decide whether or not you wish to take part.

PART 1

What is the purpose of the study?

After surgery for a broken ankle, the lower leg and foot are set in a cast for several weeks. Once the surgeon is happy for weight to be put onto the injured leg without the cast on, we often provide an ankle support to help with walking.

We can offer a variety of supports which aim to improve walking including a tubular elasticated bandage, an ankle stirrup splint or a walking boot. These can all be removed at home for washing and sleeping etc (see pictures below). The supports are all used in current standard care. We do not know which of these supports is most helpful.

		
Elasticated tubular bandage	**Ankle Stirrup splint**	**Walker boot**

The purpose of this research is to look at the ease and quality of walking in each of these supports.

Why have I been invited and do I have to take part?

You have been asked to consider taking part in this study because you have a broken ankle. We will be asking 18 patients to participate, and you have been asked because your break is one of the commonest types we see and you will be having the surgery most injuries like this receive.

Do I have to take part?

You do not have to take part in this study. If you decide not to take part, your medical care will not be affected in anyway. If you are interested in participating, we will describe the study in more detail, giving you plenty of time to think about it and discuss with friends or family if you wish. You are free to withdraw at any time, without giving a reason. This

would not affect the standard of care you receive. If you choose to be in this study the first thing we will ask you to do is sign a consent form, you will get a copy to keep.

What will happen if I take part?

As part of your routine care after surgery you will be asked to attend appointments at the Trauma Outpatient Clinic at the hospital, where one of the surgeons will review your progress. When your break is sufficiently healed, the cast will be removed, and you will be taught how to put weight through the leg. You will be given an ankle support. If you want to take part in the research, we will make sure that you are fit and well enough to do so and then measure your walking in different supports during this clinic visit. Participating in the research will extend the length of this appointment by about one hour but there are no additional appointments to attend. You will be given the contact details of the researcher in case you want to discuss anything about the study.

The walking measurements should take approximately 1 hour and will be conducted by a qualified senior physiotherapist in the physiotherapy gym near the Trauma Fracture Clinic. We will measure your walking using an electronic system, and ask you to walk over a mat of about 16 feet long (see picture below). You will be able to use your usual walking aid, and walk at a range of speeds you are happy with. We will ask you to walk down the walkway a few times, but you will be able to rest between each test. The mat measures each of your foot prints as you walk. All the information is sent to a computer and recorded. We will also ask some questions about your ankle break, how well you feel you are walking, and whether you are experiencing any discomfort whilst walking.

The electronic walkway

No aspect of normal treatment is withheld because you are in the study. You will be able to choose the support that you use for the first few weeks of your rehabilitation, unless your surgeon or the researcher (a senior physiotherapist) indicates there are clinical reasons for you to use a specific device.

The table below explains when we would like to collect information about you:

Time	Place	Information
Information about the study	Hospital ward/orthopaedic clinic	• We will get information from medical notes and clinicians to ensure it is appropriate for you to take part in the study • Consent form
Baseline: before you have your walking measured	Trauma Outpatient department	• Consent form (if not already completed) • Questionnaire about your general health, social situation and mobility completed with you and from information from the medical notes
Walking measurements when your surgeon is happy for you to walk on the injured leg without a cast	Trauma Outpatient department (usually about 6 weeks after surgery when you come to the clinic to see the surgeon)	• Measurement of walking • Self-assessment of walking quality and comfort after each support is used • Strength of the ankle measured if you feel up to it on the day

What are the possible risks and benefits of taking part?

The walking assessments are not expected to cause any additional long-term problems or discomfort compared with patients who are not involved in the research as all patients will starting to increase their walking at this stage of recovery. Some people can find the early stages of walking on the injured ankle to be uncomfortable and it may be tiring. The ankle can also become swollen when you come out of the cast. These symptoms are all common and expected when you start to walk on the ankle again for the first time out of the cast.

We cannot promise the study will help you, but the information we get from this study will help improve the treatment of people with ankle fractures in the future. Before participating you should consider if this will affect any insurance you have and seek advice if necessary.

Would my taking part in this study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

What happens if I have any questions, concerns or complaints about the study? What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

This completes Part 1 of the information sheet

If the information has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision

PART 2

What if relevant new information becomes available?

Sometimes we get new information about the treatments being studied before we have recruited all the patients we had planned to. If this does happen the trial would be stopped early as it would have achieved its aim of showing us which is the better treatment.

What happens if I don't want to carry on with the study?

You are free to withdraw from the study at any time without giving a reason. This decision would not impact your normal care. If you are happy to give a reason, this can help us in designing future research. Some people decide that they do not want to continue but do not mind us using the data we have already collected. Others would like all their information removed from the database.

What if there is a problem?

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact David Keene, SAFER study Chief Investigator, Tel. 01865 740328 email: david.keene@ndorms.ox.ac.uk or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or the head of CTRG, email heather.house@admin.ox.ac.uk

If you remain unhappy and want independent help or wish to complain formally, you can contact the Patient Advice and Liaison Service (PALS) Tel. 01865 221473 / 740868.

NHS indemnity operates in respect of the clinical treatment with which you are provided. In addition, the University of Oxford has appropriate insurance related arrangements in place in respect of the University's role as Research Sponsor of this study.

Would my taking part in this study be kept confidential?

All information collected about you, either from you personally or from your medical records or x-rays, will be kept strictly confidential. How it is collected, handled, stored and destroyed will comply with the Data Protection Act 1998. Any information about you that leaves the hospital or is included in any reports will have your name and address removed so that you cannot be recognised from it.

The only person who may be given your details will be your doctors. We will ask your permission to tell them that you have agreed to take part in the study and what treatment you have been given. Responsible members of the University of Oxford or the Oxford University Hospitals NHS Trust may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations.

Information collected in studies such as this is kept as part of your confidential medical records. Anonymised data is kept for at least 5 years from the end of the study by the trials unit both as a paper copy and on a secure database. We do not use this data for any other purpose without further permission from the Research Ethics Committee and you.

What will happen to the results of the research study?

The research will be used by surgeons and physiotherapists to help them decide the best ankle support for patients with the same type of injury as you have. The information will be presented at national and international medical meetings and in research journals. If you wish to be told about what we learn from the study, we can contact you once the findings are made public.

This study is an educational study and fulfils part of the requirements for the award of a DPhil from the University of Oxford. If you agree to participate in this project, the research will be written up as a thesis (detailed report). On successful submission of the thesis, it will be deposited both in print and online in the University archives, to facilitate its use in future research.

Who is organising and funding the research?

The organisation funding this research is the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences. It is a department of the Medical Sciences Division within the University of Oxford which researches conditions relating to the bones, joints and muscles. The study will be managed through the Kadoorie Centre for Critical Care Research and Education based at the John Radcliffe Hospital.

The doctors and research staff involved in this study do not receive any payment other than what is required to cover the necessary expenses. The study is independent of any commercial organisation. We will not be offering payment for participants in the study. We will not be offering expenses for participants as these should be minimal because the assessments take place at the same time as a routine appointment as part of normal care.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the Berkshire Research Ethics Committee.

Further information about research

Further information about medical research is available through the NHS Choices website: http://www.nhs.uk/Conditions/Clinical-trials/Pages/Introduction.aspx

Thank you for considering participation in this study and for taking time to read this sheet

Appendix 10 - Consent form

UNIVERSITY OF OXFORD

Oxford University Hospitals NHS
NHS Trust

Ethics Reference: 12/SC/0146

CONSENT FORM

Title of Project: **Supports for Ankle Fractures in Early Rehabilitation (SAFER)**

Name of Researcher: **David Keene**

Patient Study Number: ……

		Please initial boxes
1.	I confirm that I have read and understand the information sheet dated 02.04.12 (version 3.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3.	I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from regulatory authorities, the University of Oxford or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4.	I understand that appropriate personal identifying information will be collected, stored and used by the study office to enable follow up of my health status. This is on the understanding that any information will be treated with the strictest security and confidentiality.	☐
5.	I agree to my hospital doctors being informed of my participation in the study.	☐
6.	I agree to take part in the above study.	☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed: 1 for patient; 1 for researcher site file (original); 1 to be kept in medical notes

Appendix 11 - Screening form part 2

S	C					

Screening Number

Check **Participant Log** for next available screening number

Screening Form
Part 2 - Day of cast removal

To be completed by the designated person: complete one screening form for each patient who has been approached about study, passed screening part 1 and is having/had their cast removed in clinic:

Please work through the questions in the order they appear on the form

Please place a cross through correct responses ☒

Date of birth: D D M M Y Y Y Y

Gender: ☐ Male ☐ Female

Initials: ☐☐☐

If patient later randomised, enter Study Number here: ☐☐☐☐☐

Date of screening part 1: D D M M Y Y Y Y

Date of surgery: D D M M Y Y Y Y

Please place a cross through correct responses ☒

Inclusion criteria:

1. No longer essential to wear ankle immobilising cast or device (seek confirmation by patients surgeon) ..... ☐ Yes ☐ No
2. Allowed to fully weight-bear as tolerated ..... ☐ Yes ☐ No
3. Able to walk minimum of 10 metres (with/without aid) since surgery ☐ Yes ☐ No

If **any** '**No**' response above (Q1-3), the patient **cannot** be entered into the study, **go directly to Q16** at end of form.
If '**Yes**' to **all** Q1-3 above, **continue to Q4.**

Exclusion criteria:

4. Open wounds below the knee of the injured limb..... ☐ Yes ☐ No
5. Systemically unfit to undergo walking assessments (i.e. nausea, fever) ☐ Yes ☐ No
6. Uncontrolled respiratory disorder..... ☐ Yes ☐ No
7. Uncontrolled epilepsy ..... ☐ Yes ☐ No
8. Cardiovascular instability (e.g. uncontrolled arrhythmias, syncope) ☐ Yes ☐ No

Other reason excluded:

9. Did not receive ORIF ☐ Yes ☐ No
10. Other reason patient not suitable for study ☐ Yes ☐ No
    (please specify)

.....

If **any** '**Yes**' response above (Q4-10), the patient **cannot** be entered into the study, **go directly to Q15** at the end of form.
If '**No**' to **all** Q4-10, **continue.**

CONSENT.

11. Patient willing to proceed with study? ☐ Yes ☐ No, declined
(please give reason below if stated)

If **'No'** indicated above (Q11), the patient **cannot** be entered into the study, **go directly to Q16.**

If **'Yes'** in Q11, obtain consent and go to Q12.

12. Confirm signed consent obtained: ☐ Complete the information in Q13 onwards.

ACTIONS REQUIRED

Cross when carried out ☒

13. Please check all questions have been completed. ☐

14. Sign and date bottom of form. ☐

15. **Baseline information and initial mobility assessment should be conducted *prior to* randomisation**; see CRF.

16. **All patients screened**:
If patient is **not** suitable for the study: Sign and date below and return to Trauma trial office to be filed.

Update *unsuitable/declined column* on 'Participant Log'. ☐

OR:

If patient **is suitable** for study: Update dates on 'Participant Log'. ☐

Researcher signature: _____ Date:_____

Trauma Clinical Trials Office, Kadoorie Centre, John Radcliffe Hospital,
Oxford OX3 9DU. Email: david.keene@ndorms.ox.ac.uk

Appendix 12 - Case report form (clinical study)

Participant details	Participant no:			Participant initials:		

Oxford University Hospitals NHS
NHS Trust

SAFER

Supports for Ankle Fractures in Early Rehabilitation

Case Report Forms

CLINICAL TRIAL SITE/UNIT:	Oxford Trauma Unit, John Radcliffe Hospital
PRINCIPAL INVESTIGATOR:	David Keene Research Physiotherapist

Participant details	Participant no:		Participant initials:	

Do you want to be informed of the results of this study? Yes ☐ No ☐

Height:.....

Weight:.....

BASELINE

General Health

Charlson Comorbidity Index (Apply 1 point to each unless otherwise noted, mark as 0 if not applicable)

Myocardial Infarction..... ☐

Congestive Heart Failure..... ☐

Peripheral Vascular Disease..... ☐

Cerebrovascular Disease..... ☐

Dementia (exclusion criteria)..... ☐

Chronic Obstructive Pulmonary Disease (COPD)..... ☐

Connective Tissue Disease..... ☐

Peptic Ulcer Disease..... ☐

Diabetes Mellitus (1 point uncomplicated, 2 points if end-organ damage)..... ☐

Moderate to Severe Chronic Kidney Disease (2 points)..... ☐

Hemiplegia (2 points)..... ☐

Leukaemia (2 points)..... ☐

Lymphoma (2 points)..... ☐

Solid Tumour (2 points, 6 points if metastatic)..... ☐

Liver Disease (1 point mild, 3 points if moderate to severe)..... ☐

AIDS (6 points)..... ☐

Other relevant existing or past medical problems:

.....

Participant details	Participant no:		Participant initials:	

Allergies

Known allergies ☐ Yes ☐ No

Type ……

Participant details	Participant no:		Participant initials:	

HU13 Multi-Attribute Health Status Classification System

Please work down the list of statements for each attribute. Circle the level of statement that best describes your health state in the last week:

Attribute	Level (circle)	Description
Vision	1	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.
	2	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, but with glasses.
	3	Able to read ordinary newsprint with or without glasses but unable to recognize a friend on the other side of the street, even with glasses.
	4	Able to recognize a friend on the other side of the street with or without glasses but unable to read ordinary newsprint, even with glasses.
	5	Unable to read ordinary newsprint and unable to recognize a friend on the other side of the street, even with glasses.
	6	Unable to see at all.
Hearing	1	Able to hear what is said in a group conversation with at least three other people, without a hearing aid.
	2	Able to hear what is said in a conversation with one other person in a quiet room without a hearing aid, but requires a hearing aid to hear what is said in a group conversation with at least three other people.

Participant details	Participant no:	Participant initials:

	3	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid, and able to hear what is said in a group conversation with at least three other people, with a hearing aid.
	4	Able to hear what is said in a conversation with one other person in a quiet room, without a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid.
	5	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid.
	6	Unable to hear at all.
Speech	1	Able to be understood completely when speaking with strangers or people who know me well.
	2	Able to be understood partially when speaking with strangers but able to be understood completely when speaking with people who know me well.
	3	Able to be understood partially when speaking with strangers or people who know me well.
	4	Unable to be understood when speaking with strangers but able to be understood partially by people who know me well.
	5	Unable to be understood when speaking to other people (or unable to speak at all).

5

Participant details	Participant no:		Participant initials:	

Ambulation	1	Able to walk around the neighbourhood without difficulty, and without walking equipment.
	2	Able to walk around the neighbourhood with difficulty, but does not require walking equipment or the help of another person.
	3	Able to walk around the neighbourhood with walking equipment, but without the help of another person.
	4	Able to walk only short distances with walking equipment, and requires a wheelchair to get around the neighbourhood.
	5	Unable to walk alone, even with walking equipment. Able to walk short distances with the help of another person, and requires a wheelchair to get around the neighbourhood.
	6	Cannot walk at all.
Dexterity	1	Full use of two hands and ten fingers
	2	Limitations in the use of hands or fingers, but does not require special tools or help of another person.
	3	Limitations in the use of hands or fingers, is independent with use of special tools (does not require the help of another person).
	4	Limitations in the use of hands or fingers, requires the help of another person for some tasks (not independent even with the use of special tools).
	5	Limitations in the use of hands or fingers, requires the help of another person for most tasks (not independent even with the use of special tools).

6

Participant details	Participant no:	Participant initials:

	6	Limitations in the use of hands or finders, requires the help of another person for all tasks (not independent even with the use of special tools).
Emotion	1	Happy and interested in life.
	2	Somewhat happy.
	3	Somewhat unhappy.
	4	Very unhappy.
	5	So unhappy that life is not worthwhile.
Cognition	1	Able to remember most things, think clearly and solve day to day problems.
	2	Able to remember most things, but have a little difficulty when trying to think and solve day to day problems.
	3	Somewhat forgetful, but able to think clearly and solve day to day problems.
	4	Somewhat forgetful, and have a little difficulty when trying to think or solve day to day problems.
	5	Very forgetful, and have great difficulty when trying to think or solve day to day problems.
	6	Unable to remember anything at all, and unable to think or solve day to day problems.

Participant details	Participant no:		Participant initials:	

Pain	1	Free of pain and discomfort.
	2	Mild to moderate pain that prevents no activities.
	3	Moderate pain that prevents a few activities.
	4	Moderate to severe pain that prevents some activities.
	5	Severe pain that prevents most activities.

Participant details	Participant no:			Participant initials:		

Lower Extremity Functional Scale:

We are interested in knowing whether you are having any difficulty at all with the activities listed below <u>because of your lower limb</u> problem for which you are currently seeking attention. Please provide an answer for each activity.

Today, <u>do you</u> or <u>would you</u> have any difficulty at all with:

(Circle one number on each line)

Activities	**Extreme Difficulty Or Unable to Perform Activity**	**Quite a Bit of Difficulty**	**Moderate Difficulty**	**A Little Bit of Difficulty**	**No Difficulty**
Any of your usual work, household, or school activities	0	1	2	3	4
Your usual hobbies, recreational or sporting activities	0	1	2	3	4
Getting into or out of the bath	0	1	2	3	4
Walking between rooms	0	1	2	3	4
Putting on your shoes or socks	0	1	2	3	4
Squatting	0	1	2	3	4
Lifting an object, like a bag of groceries from the floor	0	1	2	3	4
Performing light activities around your Home	0	1	2	3	4
Performing heavy activities around your Home	0	1	2	3	4
Getting into or out of a car	0	1	2	3	4
Walking 2 blocks	0	1	2	3	4
Walking a mile	0	1	2	3	4
Going up or down 10 stairs (about 1 flight of stairs)	0	1	2	3	4
Standing for 1 hour	0	1	2	3	4
Sitting for 1 hour	0	1	2	3	4
Running on even ground	0	1	2	3	4

<u>Continued on next page</u>

Participant details	Participant no:		Participant initials:	

Activities	Extreme Difficulty Or Unable to Perform Activity	Quite a Bit of Difficulty	Moderate Difficulty	A Little Bit of Difficulty	No Difficulty
Running on uneven ground	0	1	2	3	4
Making sharp turns while running fast	0	1	2	3	4
Hopping	0	1	2	3	4
Rolling over in bed	0	1	2	3	4

What has been limiting your mobility in the last week?

Pain ☐

Breathlessness ☐

Other ☐

Details:

Date weight-bearing commenced:

D d m m m y y y y

Participant details	Participant no:		Participant initials:	

Walking Aids prior to this ankle injury

None ☐

One crutch ☐

Two crutches ☐

One stick ☐

Two sticks ☐

Frame / Rollator ☐

Walking aid used prior to cast removal

None ☐

One crutch ☐

Two crutches ☐

One stick ☐

Two sticks ☐

Frame / Rollator ☐

Method of immobilisation prior to today

None ☐

Walker boot ☐

Stirrup ☐

Tubigrip ☐

Cast ☐ Removable ☐

Other: ……

Were ankle exercises started prior to today's appointment?

Yes ☐ No ☐

Participant details	Participant no:		Participant initials:	

Balance and falls:

Have you have difficulties balancing whilst walking on a level surface in the last week?

Please indicate which statement below best describes your situation

Never ☐

Often ☐

Very Often ☐

Always ☐

Since your discharge from hospital after ankle surgery, have you had any 'near' misses, where you had to grab or reach for something or someone to prevent falling over?

Please indicate which statement below best describes your situation

No ☐

Once ☐

Less than once a week ☐

More than once a week ☐

At least once a day ☐

Since your discharge from hospital after ankle surgery, have you had a fall, including a slip or trip, in which you lost your balance and landed on the floor or ground or lower level?

No ☐

Yes ☐

If yes, number of falls ☐☐☐

Participant details	Participant no:			Participant initials:		

Have you had any broken bones apart from your ankle in the last 12 months as a result of falling?

No ☐

Yes ☐

If yes, details:

Participant details	Participant no:		Participant initials:	

Social Circumstances

Current residence

Own home ☐

Home care package ☐

Warden accommodation ☐

Residential home ☐

Nursing home ☐

Rehabilitation ☐

Acute hospital ☐

Community hospital ☐

Temporary residence ☐

Participant details	Participant no:			Participant initials:			

Pain assessment

How severe is your pain now at rest?

Place a vertical mark on the line below to indicate how your pain feels.

No Pain ——————————— Worst pain possible

Participant details	Participant no:		Participant initials:	

Range of movement assessment

	Uninjured ankle	**Injured ankle**
Angle of ankle dorsiflexion (in degrees)		
Angle of ankle plantarflexion (in degrees)		

Participant details	Participant no:		Participant initials:	

Initial mobility assessment prior to randomisation:

Walking aid:

None ☐

One crutch ☐

Two crutches ☐

One stick ☐

Two sticks ☐

Frame / Rollator ☐

Describe technique (i.e. reciprocal, step-to pattern, 4 point tec.):

Participant details	Participant no:		Participant initials:	

Trial walk over the electronic walkway

How severe was your pain when walking?

Place a vertical mark on the line below to indicate how your pain felt.

No Pain ——————————— Worst pain possible

How severe is your pain now at rest?

Place a vertical mark on the line below to indicate how your pain feels.

No Pain ——————————— Worst pain possible

Proceeding to randomisation?

No…

…unable to exert enough weight on the limb to activate the walkway sensors ☐

…due to an increase in resting pain ☐

…due to fatigue that does not settle after rest period ☐

…due to balance (needs external assistance) ☐

Yes ☐

Other

Details:

Participant details	Participant no:		Participant initials:	

RANDOMISATION

Researcher instruction: Take the next numbered unused sealed envelope and write the patients study number and todays date on the front. After all details have been written onto the front open the envelope to reveal the allocation and cross the box below:

Sequence 1: A, B, C ☐

Sequence 2: B, C, A ☐

Sequence 3: C, A, B ☐

Key:

A=elasticated tubular bandage

B=stirrup splint

C=walker boot

Now tick the boxes below to indicate the support to be assessed first, second and third.

Place the allocation back in the envelope and place envelope in x for pick up by researcher (these need to be retained as proof of allocation)

Participant details	Participant no:		Participant initials:	

WALKING ASSESSMENT

First Support A ☐ B ☐ C ☐

Comment on walking technique:

How severe was your pain when walking? (completed by the participant)

Place a vertical mark on the line below to indicate how your pain felt.

No Pain ——————————— Worst pain possible

How difficult was it to walk?

Place a vertical mark on the line below to indicate how difficult it was to walk.

No difficulty ——————————— Impossible

How severe is your pain now at rest?

Place a vertical mark on the line below to indicate how your pain feels.

No Pain ——————————— Worst pain possible

Participant details	Participant no:		Participant initials:	

Second Support A ☐ B ☐ C ☐

Comment on walking technique:

How severe was your pain when walking?

Place a vertical mark on the line below to indicate how your pain felt.

No Pain ——— Worst pain possible

How difficult was it to walk?

Place a vertical mark on the line below to indicate how difficult it was to walk.

No difficulty ——— Impossible

How severe is your pain now at rest?

Place a vertical mark on the line below to indicate how your pain feels.

No Pain ——— Worst pain possible

Participant details	Participant no:			Participant initials:			

Third Support A ☐ B ☐ C ☐

Comment on walking technique:

How severe was your pain when walking?

Place a vertical mark on the line below to indicate how your pain felt.

No Pain ——— Worst pain possible

How difficult was it to walk?

Place a vertical mark on the line below to indicate how difficult it was to walk.

No difficulty ——— Impossible

How severe is your pain now at rest?

Place a vertical mark on the line below to indicate how your pain feels.

No Pain ——— Worst pain possible

Participant details	Participant no:		Participant initials:	

If walking assessments are discontinued at any point, please state at what stage and the reason below:

Pain ☐

Fatigue ☐

Other ☐

Details (including the stage of assessments procedures were halted):

Is the participant a candidate to proceed with muscle strength assessment?

Yes ☐

No (reason)

Declines ☐

Pain increase ☐

Fatigue ☐

Other ☐

Details……

Participant details	Participant no:		Participant initials:	

Muscle strength assessment

Uninjured ankle

Movement	attempt 1		attempt 2		attempt 3	
	Peak force (kg)	Peak time (s)	Peak force (kg)	Peak time (s)	Peak force (kg)	Peak time (s)
Ankle dorsiflexion						
Ankle plantarflexion						

Injured ankle

Movement	attempt 1		attempt 2		attempt 3	
	Peak force (kg)	Peak time (s)	Peak force (kg)	Peak time (s)	Peak force (kg)	Peak time (s)
Ankle dorsiflexion						
Ankle plantarflexion						

Participant details	Participant no:		Participant initials:	

Walking aid issued:

None ☐

One crutch ☐

Two crutches ☐

One stick ☐

Two sticks ☐

Frame / Rollator ☐

Ankle support issued (with advice to wean with physiotherapist)

None ☐

Tubigrip ☐

Stirrup splint ☐

Walker boot ☐

Other (specify) ☐ .....

Reason for selection

Patient preference ☐ Why?.....

Surgeon decision ☐ Why?.....

Physiotherapist decision ☐ Why?.....

Letter to consultant into medical notes ☐

Participant details	Participant no:		Participant initials:	

Researcher declaration:

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the study was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the study.

Investigator's Signature: ----------

Date of signature: | | | | | | | | | |

D d m m m y y y y

Participant details	Participant no:		Participant initials:	

Adverse Events

Has the patient experienced any Adverse Events since signing the Informed Consent? ☐ Yes, specify below ☐ No

AE no.	Adverse Event	Start Date dd/mm/yyyy	Stop Date dd/mm/yyyy	Outcome 1=Recovered 2=Recovered with sequelae 3=Continuing 4=Patient Died 5=Change in AE 6=unknown	Severity 1=Mild 2=Moderate 3=Severe	Plausible relationship to Study Proceedures	Withdrawn due to AE?	Serious AE (SAE)?	If SAE does it require immediate reporting? (see Protocol)?
		/ / :	/ / :			☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
		/ / :	/ / :			☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
		/ / :	/ / :			☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

27

Participant details	Participant no:		Participant initials:	

Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- Results in death during or within 30 minutes of testing
- Is life-threatening

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation directly as a result of the study assessments
- Results in persistent or significant disability/incapacity as a result of the study assessments
- Results in further surgery directly as a result of an event during the study assessment
- Results in medical attention as a result of an event during or within 30 minutes of testing (includes injurious fall)

There may be some discomfort in the leg in the first 24 hours after testing, just as with normal physiotherapy, but that this should not last longer than 48 hours nor be excessive (for example significantly impairing sleep). We will ask participants to report pain levels after the testing procedure, and to contact us if discomfort persists or significant levels of pain develop. Persisting and significant pain will be considered an adverse event.

28

Appendix 13 - Adverse event reporting form

UNIVERSITY OF OXFORD

Oxford University Hospitals NHS
NHS Trust

PARTICIPANT REPORTING PROBLEMS SHEET

Your study Number: ☐☐☐☐☐

We have made every effort to ensure your involvement in the study is safe. However if you experience any of the any unexpected problems listed below please could you complete and return this form to the study office in the freepost envelope provided.

Please note there may be some discomfort in the leg in the first 24 hours after the study assessments, just as with normal physiotherapy, but that this should not last longer than 48 hours nor be excessive (for example significantly impairing sleep).

Please return this reporting sheet to us here in the study office if you have these problems:

Please mark a cross in the box

Pain lasted more than 48 hours after study assessments ☐

Pain was significantly disturbed your sleep after the study assessment ☐

Other problem you want to report – please give details below ☐

Date: _____

SAFER Study, Trauma Clinical Trials Office, Kadoorie Centre, John Radcliffe Hospital, Oxford OX3 9DU. Telephone: 01865 740328

Appendix 14 - NHS Research Ethics Committee (REC) approval letter

NHS
National Research Ethics Service

NRES Committee South Central - Berkshire
Bristol REC Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 3421389
Facsimile: 0117 3420445

29 March 2012

Mr David Keene
Kadoorie Centre
John Radcliffe Hospital
Oxford
OX3 9DU

Dear Mr Keene,

Study title:	**SAFER: Supports for Ankle Fractures in Early Rehabilitation:The effects of different ankle supports on gait during the initial period of unrestricted weight-bearing after operatively treated ankle fractures in adults.**
REC reference:	**12/SC/0146**
Protocol number:	**3.0**

The Research Ethics Committee reviewed the above application at the meeting held on 20 March 2012. Thank you for attending to discuss the study. The Committee appreciated this very well designed study.

Ethical opinion

After the Committee's initial discussions you were invited to join the meeting to clarify the following issues:

1. The Committee requested clarification on the recruitment procedure.

   You replied that the research team would be included in the morning meeting with the physicians, surgeons, physiotherapists and nurses. This would allow communication between all parties. The surgeons, physicians and physiotherapists would ask potential participants if they would be interested in taking part in the study. The Committee queried when the screening process would take place. You answered that this would occur after referral and that the surgeon will inform the research team if participants were not appropriate. When the surgeons asked if potential participants were interested the second informal screening would take place; when participants medical notes were checked. The research team would be included in some of the screening but most would be done by the care team. The Committee was content with this thorough answer.

2. The Committee asked if the physician was allowed an input in choice of support for the participant. You confirmed that the physician/surgeon was involved, but the choice of `support was up to the participant. If not suitable, for clinical reasons, the physician and/or physiotherapist would inform the participant. It was clear that in the

vast majority of cases the choice of support was arbitrary

3. The Committee requested clarification of the randomisation strategy. It was unsure how the first sequence would be chosen.

   You informed the Committee that after the patients walking was assessed the research team would draw a random card. This card would be one of three sequences – created to avoid bias. The classic concealment method of randomisation would be utilised; the sequence covered by three layers of tinfoil and inside an envelope. An envelope would randomly be chosen for each participant, and the envelope number written on the patient card. The Committee was content with this answer.

4. The Committee commented on the testing of ankle strength. It noted that this test was optional.

   You replied that some participants may feel tired and/or sore and may not want to undergo the procedure. The research team would monitor participants and if in pain etc. they would not do muscle testing procedure.

5. The Committee queried if the researcher would be collecting enough pre variables; such as weight, height, age etc.

   You answered that it was extremely difficult to test these variables between patients. In this study the patient would act as their own control so there was no need to take account of these between-patient variables.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study:

1. Please remove mention of the GP from the Consent Form. It is unnecessary to inform patients' GPs about their participation.
2. Please add the following sentence to PIS part 1 'this study is an educational study and fulfils part of the requirements for the award of a DPhil from the University of Oxford'.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering Letter		28 February 2012
Evidence of insurance or indemnity	AON: Period 01/08/2011 to 01/08/2012	22 July 2011
GP/Consultant Information Sheets	1.0	12 January 2012
Investigator CV	Keith Willett	
Investigator CV	Sarah Lamb	
Investigator CV	David Keene	30 January 2012
Letter from Sponsor		28 February 2012
Participant Consent Form	1.0	23 January 2012
Participant Information Sheet	2.0	11 February 2012
Protocol	3.0	22 February 2012
REC application		28 February 2012
Referees or other scientific critique report		16 February 2012

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

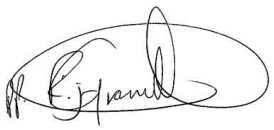
You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/SC/0146	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely,



Mr David Carpenter
Chair

Email: scsha.berksrec@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
After ethical review – guidance for researchers

Copy to: *Ms Heather House, University of Oxford*
Ms Heather House, Oxford University Hospitals NHS Trust

David Keene
Research Physiotherapist
Kadoorie Trauma Research Centre
John Radcliffe Hospital
Oxford
OX3 9DU
Tel: 01865 740328
Fax: 01865 857611

david.keene@ndorms.ox.ac.uk

2nd April 2012

Re: SAFER: Supports for Ankle Fractures in Early Rehabilitation (REC ref. 12/SC/0146)

Dear Mr David Carpenter (Berkshire REC),

Further to my recent letter indicating favourable ethical approval, subject to conditions, I am pleased to enclose the following updated document:

- Patient information sheet v3.0 (02/04/2012)

Please note that on the consent form I have not asked for permission to inform the patients GP about their participation but their hospital doctor (who would need to know what ankle support has been issued). I hope this is satisfactory and have therefore not amended this document.

I valued the feedback from the panel and in light of this will be asking participants for their heath and weight as suggested. On reflection, this will be a valuable variable when interpreting the strength measures.

I would be very grateful if you could confirm receipt of this letter indicating if you are satisfied I have met the conditions of my approval. Do not hesitate to contact me should you require any further information.

Yours sincerely,

Mr David Keene
Research Physiotherapist

NHS
National Research Ethics Service

NRES Committee South Central - Berkshire
Bristol REC Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 3421389
Facsimile: 0117 3420445

10 April 2012

Mr David Keene
Kadoorie Centre
John Radcliffe Hospital
Oxford
OX3 9DU

Dear Mr Keene,

Full title of study:	**SAFER: Supports for Ankle Fractures in Early Rehabilitation:The effects of different ankle supports on gait during the initial period of unrestricted weight-bearing after operatively treated ankle fractures in adults.**
REC reference number:	**12/SC/0146**
Protocol number:	**3.0**
EudraCT number:	

Thank you for your letter of 02 April 2012. I can confirm the REC has received the documents listed below as evidence of compliance with the approval conditions detailed in our letter dated 20 March 2012. Please note these documents are for information only and have not been reviewed by the committee.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Covering Letter		02 April 2012
Participant Information Sheet	3.0	05 April 2012

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

12/SC/0146	Please quote this number on all correspondence

Yours sincerely,

Ms Rae Granville
Committee Co-ordinator

E-mail: scsha.berksrec@nhs.net

Copy to: *Ms Heather House,*
Ms Heather House, Oxford University Hospitals NHS Trust

Appendix 15 - Oxford University Hospitals NHS Trust R & D approval letter

Oxford University Hospitals NHS
NHS Trust

SH/TG/AA/10091

Mr David Keene
Research Physiotherapist
Kadoorie Centre
Level 3 , John Radcliffe Hospital
Oxford University Hospitals Trust
Headington, Oxford
OX3 9DU

From the R & D Lead
OUH Research & Development
Joint Research Office
Block 60, Churchill Hospital
Old Road, Headington
Oxford OX3 7LE

Tel: (01865) 572239
Fax: (01865) 572242
Adeeba.asif@ouh.nhs.uk

Friday, 25 May 2012

Dear Mr Keene

Re: The effects of different ankle supports on gait during the initial period of unrestricted weight bearing after operatively treated ankle fractures in adults.
Research and Development Reference: 10091
Research Ethics Committee Reference: 12/SC/0146

Confirmation of Trust Management Approval

On behalf of the Oxford University Hospitals NHS Trust, I am pleased to confirm Trust Management Approval and Indemnity for the above research on the basis described in the application, protocol and other supporting documents.

Conditions of Approval

Your attention is drawn to the attached conditions of approval. Breach of these conditions may result in Trust Management Approval being revoked.

Ethics Correspondence

In order to facilitate good communications and avoid unnecessary delays please copy all correspondence with the Research Ethics Committee (REC) to R&D, providing copies of all relevant documents.

Research Sponsorship

It is noted that University of Oxford has agreed to Sponsor this trial.

Site Specific Assessment

This Trust Management Approval letter also incorporates site specific assessment for the Oxford University Hospitals NHS Trust site

Approved Documents

Document Type	Version	Date
Protocol	3.0	22 February 2012
Participant Information Sheet	3.0	02 April 2012
Participant Consent Form	1.0	23 January 2012
Consultant Letter	1.0	12 January 2012
Investigator's CV	Keith Willet	
Investigator's CV	Sarah Lamb	
Investigator's CV	David Keene	
Referees or other scientific critique report		16 February 2012
Letter from Sponsor		28 February 2012
Insurance Certificate		Expires Aug 2012
REC Favourable Opinion		29 March 2012
NHS R&D Form		
NHS SSI Form	OUH NHS Trust	

I wish you every success with the study.

Yours sincerely,

Shahista Hussain
Research Support Services Manager

Copy to:	Sponsor contact: Karl Shepherd	Karl.shepherd@admin.ox.ac.uk