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Understanding the Physical and Psychological Impairments and Associated Disability Characterising Individuals with Ankle symptoms and Osteoarthritis

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Abstract

Musculoskeletal conditions are prevalent worldwide and are associated with pain, disability and impaired quality of life (QoL). Osteoarthritis (OA) is a common, costly and disabling musculoskeletal condition. Lower limb OA research has focussed on the hip and knee and, as a consequence, impairments characterising ankle OA are not well understood. This thesis aims to advance our understanding of the physical, functional and psychological impairments and associated disability in individuals with persistent ankle symptoms and in those with radiographic evidence of ankle OA.

Study 1: A systematic literature review and meta-analysis was conducted to synthesise and appraise the quality of studies investigating physical impairments in ankle OA. The review identified eight studies, three of which were included in the meta-analyses. Meta-analyses revealed large impairments of ankle sagittal plane range of motion (ROM) on the affected compared to the unaffected side and less sagittal plane torque in ankle OA compared to controls. Evidence from single studies indicated deficits in frontal plane ROM and strength, talar translation and rotation, balance, electromyography of ankle muscles, abnormal bony alignments and greater fatty infiltrate in all calf muscle compartments in individuals with ankle OA. Critical appraisal of the literature revealed limitations surrounding assessor blinding, measurement validity, and lack of generalization.

Study 2: A cross-sectional laboratory study of 96 participants compared physical measures of function, strength, ROM and posture and patient-reported outcomes in 1) individuals with symptoms and radiographic evidence of ankle OA to asymptomatic individuals; and 2) asymptomatic individuals with and without radiographic evidence of ankle OA. Those with symptomatic OA reported greater pain, disability, instability, kinesiophobia, lower function and QoL, and exhibited significant deficits in muscle strength, ROM and ambulatory function compared to asymptomatic individuals. Most patient-reported and physical outcomes were similar between asymptomatic individuals with and without radiographic OA. Stair function times were significantly associated with QoL and self-reported function.

Study 3: A cross-sectional exploratory survey (n=394) was conducted to compare self-reported daily living and sports function, ankle pain and disability, physical activity, ankle instability, and QoL between individuals with and without persistent ankle pain and stiffness, and to explore factors associated with QoL. Individuals with ankle symptoms reported worse scores for all measures, except self-reported physical activity. Daily living function and age explained 66% of the variance in QoL.

Study 4: Individuals with and without persistent ankle pain and stiffness (n= 231) participated in an online survey to obtain data about pain severity, pain self-efficacy, anxiety, depression, kinesiophobia, pain catastrophizing, and function. Individuals with persistent ankle pain reported higher pain and depressive symptoms, and lower function than controls. Higher pain self-efficacy and lower levels of ankle pain and kinesiophobia were associated with a better function in the symptomatic group.

Study 5: Using the same sample in study 4, work limitation, function, and psychological features were compared between working individuals with and without persistent ankle symptoms and between working and non-working individuals with persistent ankle symptoms. Working individuals with ankle symptoms reported higher pain levels, work limitation, and lower function than working controls. Among the symptomatic group, individuals who remained in the workplace were significantly younger with less pain in the ankle and in other body sites, and at a lower risk of clinical catastrophising than individuals who were not working. Working individuals also reported higher function and pain self-efficacy compared to non-working symptomatic individuals. Total psychological stress, depression and catastrophizing were significantly lower among the working than non-working symptomatic individuals. Higher levels of depression and kinesiophobia and lower pain self-efficacy were associated with greater work limitation.

Study 6: Data on number of falls and associated injuries/hospitalization in the past 12 months, balance confidence, falls efficacy, function, and comorbidities associated with risk of falling were collected in individuals with and without persistent ankle pain and stiffness using an online survey (n=226). Individuals with persistent ankle pain and stiffness reported more falls, greater fear of falling, more fall-related injuries, lower function and balance confidence

when compared to controls. The number of falls was associated with fear of falling and severity of ankle pain.

This thesis has demonstrated that individuals with symptomatic ankle OA present with impairments in ambulation, ROM, muscle strength and endurance compared to asymptomatic individuals. Interestingly, there were minimal differences in these outcomes between individuals with and without radiographic OA who did not have ankle symptoms. This suggests the presence of ankle pain and stiffness has a greater influence on function and impairments than radiographic OA at the ankle. Further, our data indicate that persistent ankle pain and stiffness negatively impacts QoL and function and is associated with limitations at work, increased falls and psychological impairment. Further research is needed to better understand the mediators of the poorer physical impairments in ankle OA, psychological distress, and QoL in those with persistent ankle pain and stiffness. This would plausibly lead to more directed investigations of the effect of interventions for ankle OA.

Declaration by author

This thesis is composed of my original work and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Contributions by others to the thesis

Significant and substantial contributions were made by others to this research, work and writing represented and/or reported in this thesis.

- Dr. Michelle Smith played a major role in all aspects of this research. This included substantial input into the research design, recruitment, data collection processes, data analysis and interpretation, and provided critical revisions of written work.
- Professor Bill Vicenzino provided a core oversight of all aspects and processes of this research. This included but was not limited to the research question and study design, implementation, recruitment funding, analysis of the data and interpretation, drafting tables and figures, review, and guidance on data presentation and manuscripts/thesis chapters.
- Dr. David MacDonald, played a key role in the development of the research question, study design, the critique of literature for systematic reviews and manuscript preparation (including tables and figures) for all studies. Dr. MacDonald also provided guidance and feedback for presentations and revisions of written work.
- Dr. Rebecca Mellor played a key role in participant recruitment, management of testing venues, maintenance of laboratory testing devices, and coordination with radiography clinic.

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No works submitted towards another degree have been included in this thesis.

Research Involving Human or Animal Subjects

Ethical approval was gained from The University of Queensland's Human Research Ethics Committee A {approval number 2014001194} (Appendix 5), and all participants provided informed consent prior to participation (Appendix 6).

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List of Abbreviations used in the thesis

ANCOVA	Analysis of covariance
AOS	Ankle osteoarthritis scale
AQoL-6D	The Assessment of Quality of Life questionnaire-6D
BMI	Body mass index
CAIT	The Cumberland Ankle Instability Tool
CI	Confidence interval
COP	Centre of pressure
CPT	Cold pain threshold
DAH	Dorsal arch height
DAHDIFF	Dorsal arch height difference
DF	Dorsiflexion
EAI	Epidemiological Appraisal Instrument
EMG	Electromyography
EVER	Eversion
FAAM	Foot and Ankle Ability Measure
FMM	Foot Mobility Magnitude
FPI-6	Foot Posture Index (6-item)
HADS	Hospital Anxiety and Depression Scale
ICC	Intraclass Correlation Coefficient
INV	Inversion
IPAQ	The International Physical Activity Questionnaire
IQR	Inter-quartile Range
KL	Kellgren–Lawrence OA grading scale
MD	Mean difference

MDC	Minimal detectable change
MFW	Midfoot width
MFWDIFF	Mid-foot width difference
N/A	Not applicable
NRS	Numerical rating scale
OA	Osteoarthritis
PCS	Pain Catastrophizing Scale
PF	Plantarflexion
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSEQ-2	2-Item Short Pain Self-Efficacy Questionnaire
ROM	Range of motion
SD	Standard deviation
SEM	Standard error of measurement
SMD	Standardised mean difference
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TSK-11	Tampa Scale of Kinesiophobia
VAS	Visual analogue scale
WALS	Workplace Activity Limitations Scale
WHO	World Health Organisation

Chapter 1 Introduction

Musculoskeletal conditions represent the second leading cause of disability worldwide, affecting between one in three and one in five individuals [1]. Chronic musculoskeletal conditions at the ankle affect nearly 20% of Australian adults [2]. Other reported estimates for the prevalence of ankle pain range from 9%-15% of adults [3-5].

One of the most common and disabling musculoskeletal conditions is osteoarthritis (OA) [1]. Osteoarthritis is one of the most prevalent joint diseases [6] and is expected to become the fourth leading cause of disability worldwide by the year 2020 [7]. As per the international classification of disease (ICD-10) diagnosis Codes [8], OA is classified into primary, secondary and post-traumatic OA based on the underlying cause for the cartilage breakdown. Traumatic injuries to joints, which often occur in young adults, place the injured joint at risk for post-traumatic OA. Although OA is generally considered to be multifactorial in nature [9,10-12], it is agreed that OA at the ankle is associated with trauma to the joint such as ankle sprains [13,14] or fractures [15,16]. Over 80% of ankle OA is thought to be of post-traumatic origin [15]. Due to the post-traumatic origin of ankle OA, it affects a younger population than OA of other joints, which is most commonly primary, non-traumatic, in nature [15,17,18].

Pain and physical impairments related to musculoskeletal conditions are associated with negative impacts on social functioning, mental health, and quality of life (QoL) [7]. As such, assessment of impairment and disability is important to understand the overall impact of a health condition. The International Classification of Functioning, Disability, and Health (ICF) [19] is a biopsychosocial framework defined by the World Health Organization for classifying health and disability into three components: impairment, activity limitation and participation restriction. Osteoarthritis affects all of the components of the ICF. For example, joint stiffness and pain constitute impairments in body structure, mobility and gait limitation affect activity, and difficulty in maintaining social activities and work relates to restrictions on participation.

Research (mostly on hip and knee) has shown that OA is associated with pain, joint stiffness, reduced joint motion, joint malalignment, psychological distress, increased risk of fall, limited societal interaction, a decline in wellbeing and impaired work ability [20-23]. In light of the population affected by ankle OA, and the often long-lasting disability associated with

OA, ankle OA will likely be a major problem with the medical burden and the socioeconomic impact that extend to affect work participation and family commitments. Nonetheless, there is a scarcity of scientific data in the area of ankle OA. Much of the research focus on ankle OA is related to the technical and clinical success of ankle surgical intervention [24-29]. Further, most studies to date have focused on people during the latter stage of the OA.

In order to understand the specific impact of ankle OA on both the individual and society and optimize the management of this condition, an essential first step is to improve our understanding of the impairments associated with the condition in its clinical presentation. The aim of this thesis is to promote a better understanding of the physical and psychological impairments and associated disability of individuals with ankle pain and OA. The outcomes of this thesis may be used to inform management and identify therapeutic targets for people with ankle OA.

Chapter 2 Background

This chapter includes a synthesis of relevant background literature. In particular, the chapter explores the role of injury in the aetiology of ankle OA and introduces the International Classification of Functioning, Disability, and Health (ICF) as a conceptual framework to illustrate disability in OA. The gaps in the existing literature that will be addressed in this thesis are also highlighted. Finally, the specific aims and structure of this thesis are outlined.

2.1 Osteoarthritis

2.1.1 Magnitude of osteoarthritis

Osteoarthritis is a chronic pathology characterised by articular cartilage and subchondral bone degeneration. Osteoarthritis is one of the most prevalent joint diseases [6], affecting up to 9.6% and 18% of adult men and women respectively [6]. In 2012, approximately 33% of the English population over the age of 45 sought treatment related to OA [30], and 9.5% of Australian adults aged 35-64 years were diagnosed with OA [31].

Osteoarthritis has major personal, societal, psychological, and economic impacts including pain, stiffness, reduced joint motion, deformity, disability, loss of independence, limited societal interaction, and a decline in QoL [20,21]. It is the third-largest contributor to life-years lost due to disability in Australia [32]; and is expected by 2020 to become the fourth leading cause of disability worldwide [7]. Osteoarthritis is the second most common cause of missed work in developed countries [33]; and is associated with significant activity and work limitations [23,34-36]. In 2007, $2 billion of Australian health system funding was allocated for OA management [37].

Osteoarthritis is most common in weight-bearing joints of the lower limb [38]. The prevalence of radiographic hip and knee OA among adults in the United States has been reported at 27% and 27.8% respectively [39]. While there is limited data on ankle OA, conservative estimates report a prevalence of 1% of the world's adult population (approximately 7.6 million individuals worldwide) [40-42]. However, other data suggests that the actual prevalence is likely much higher. In 2013, it was reported that 7% of UK adults aged 45 years and over (approximately 1.77 million individuals) sought treatment for ankle or foot OA

[43]. Similarly, a recent community-based cohort study of 864 individuals identified the presence of radiographic ankle OA (defined as a Kellgren-Lawrence grade ≥ 2) in 7% of their study population [44]. Among cadaveric studies, degenerative changes at the ankle range between 2% and 18% [45-48]. Thus, data suggest the population with ankle OA is not trivial and warrants investigation.

2.1.2 Definition of OA

Osteoarthritis is diagnosed either radiographically or clinically [49]. Not all cases of radiographic OA is associated with clinical symptoms [50,51]. Previous research on the knee found only 15% of individuals who had evidence of radiographic knee OA presented with knee pain [50]. On the other hand, radiographic OA was found to occur more frequently in individuals with persistent knee joint pain >3 months in the past 12 months or >90 days in the past 6 months [52].

Plain radiographs (x-ray) are the most commonly used radiographic tool to define OA. The definition of radiographic joint degeneration is the presence of articular cartilage loss (inferred by joint-space narrowing), osteophytes and/or increased sub-chondral bone density and cysts [53]. A number of ankle radiographic grading systems exist with slightly variable criteria to determine the presence and severity of ankle OA. For example, The Morrey and Wiedeman [54] which is three-stage grading and the modified Takakura [55] a five-stage grading have similar early stage (1 and 2) OA (e.g., early sclerosis, minimum narrowing and osteophyte formation). The modified Takakura grading has an intermediate stage 3 OA that further differentiates the extent of joint space narrowing and subchondral bone contact. The advanced stage OA is similar in both classification (e.g., gross deformity, ankyloses, no joint space and bone contact). Other radiographic grading systems include the Kannus [56] and the venDijk [57] grading schemes, both consider the presence of cysts, subchondral sclerosis, osteophytes and joint space narrowing to determine OA severity.

The Kellgren-Lawrence (KL) grading scheme [58], which is extensively used for the diagnosis of OA in joints around the body, has good inter-observer reliability at the ankle and elsewhere [59]. In the ankle, mortise (an AP-view) and lateral radiographic views are used to determine the presence and grade of OA using the modified KL scale (Table 2.1) validated as a

tool for defining ankle OA severity [60]. It quantifies ankle OA into five grades (levels of severity) and similar to KL criteria used for the hip and knee, KL criteria for the ankle relies heavily on the presence of osteophytes as a discriminating factor between OA and non-OA.

Table 2.1: Radiographic grades of severity of ankle OA

KL Grade	Description
0	No radiographic findings of OA
1	Minute osteophytes of doubtful clinical significance
2	Definite osteophytes with mild joint space narrowing
3	Definite osteophytes with moderate joint space narrowing
4	Definite osteophytes with severe joint space narrowing

Osteoarthritis can also be diagnosed clinically. Clinically, OA is characterised by joint aching or pain, stiffness, reduced joint motion, crepitus, and variable levels of localised inflammation/effusion [7,53]. There is evidence from research on hip OA indicating a diagnostic accuracy of hip clinical examination in predicting the presence of radiographic hip OA [61]. Individuals are classified as having symptomatic OA if they have both radiographic signs of joint degeneration and clinical symptoms [62,63]. It is becoming apparent that radiographic evidence of OA does not correlate well with symptoms, or impairments, as symptoms appear to be the relevant determinant of impairments [64-66]. For example, previous research identified knee muscle weakness in individuals with knee pain but no radiographic knee OA, and no direct association between muscle strength and signs/severity of radiographic degeneration [67]. Further, individuals with chronic knee pain have been shown to have lower strength on the painful than the pain-free side, despite the same radiographic stage bilaterally [68]. Whether there is a relationship between radiographic evidence of OA and QoL is less clear, due to inconsistent research findings. Some studies have reported cross-sectional associations between radiographic OA and QoL [69,70]; whereas, other research on hip and knee pain reported strong associations between pain and QoL, but not radiographic OA [71]. The relation between radiographic evidence of OA, symptoms and impairments, and the clinical and radiographic OA assessments have not been investigated at the ankle.

2.1.3 Classification of OA

Osteoarthritis is classified based on the underlying mechanism for the cartilage breakdown. The International Statistical Classification of Diseases and Related Health Problems (ICD), is an international medical classification published by the World Health Organization (WHO) that is used to classify diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or disease [8]. In this classification (ICD-10 Diagnosis Codes), OA is classified as primary (M19.0), secondary (M19.2), and posttraumatic (M19.1). Primary OA features erosive cartilage changes in the absence of an identifiable cause or underlying abnormality and is most commonly associated with aging [45,72,73]. Secondary OA results from another disease or condition, such as obesity, congenital abnormalities, gout, rheumatoid arthritis (RA), or hormone disorders including diabetes. Finally, post-traumatic OA is a consequence of injury, repeated trauma or surgery to the joint [45]. Compared to the hip and knee joints, the ankle is nine times less susceptible to primary OA [47]. Valderrabano [45] undertook a large cohort study of 390 patients with ankle OA and found that 78% of the ankle OA cases were posttraumatic, 13% were secondary and only 9% were primary OA. This incidence is similar to the suggestion that 80% of ankle OA cases in the United States are thought to be post-traumatic, compared to only approximately 2% of the hip and 10% of the knee [15].

2.2 The Ankle joint

2.2.1 Anatomy and composition

Although the talo-crural joint is often considered “the ankle joint,” it is important to consider that the ankle comprises three articulations from a functional perspective: the talo-crural joint, the subtalar joint, and the distal tibiofibular syndesmosis [74].

The talo-crural joint also referred to as the tibiotalar joint or ankle mortise, is a uniaxial, modified hinge, synovial joint comprised of the tibia (tibial plafond and medial malleolus), fibular (lateral malleolus) and talus [75]. Together, the medial malleolus, which extends to the midpoint of the talus, and the lateral malleolus, which nearly extends to the level of the subtalar joint, form a mortise. The saddle shape of the talus allows it to remain in close contact with the articular surface of the mortise [76]. This intimate contact is thought to

be important for an even distribution of load at the ankle. The talo-crural joint is stabilized by the congruency of the bony articulation and the ligamentous complexes (the inferior tibiofibular complex and the collateral ligament complexes).

The subtalar joint is a synovial plane (condyloid) joint [77] made up of anterior, middle and posterior articulations [78]. The subtalar joint has congruent osseous anatomy and strong lateral ligamentous support from calcaneo-fibular, lateral talo-calcaneal, cervical and interosseous talocalcaneal ligaments [79]. The deltoid ligament medially also contributes to the stability to the posterior aspect of the subtalar joint.

The inferior tibiofibular joint, also known as the tibiofibular syndesmosis, is a syndesmotic joint formed by the convex facet of the fibula and the concave facet of the tibia. The fibular part of the joint is congruent with its tibial counterpart. The joint is stabilised by the distal anterior and posterior tibiofibular ligaments, the transverse ligament and the interosseous ligament [80]. The inferior tibiofibular joint is important for the stability of the mortise of the talo-crural joint.

2.2.2 Cartilage characteristics of the ankle

To comprehend ankle OA, this section briefly reviews the basics of ankle articular cartilage owing to its importance in the development of OA. The degeneration of articular cartilage is a hallmark of OA. Adult articular cartilage (hyaline) is an avascular, aneural and alymphatic connective tissue that is 2 to 4 mm thick [81,82]. The thickness of articular cartilage varies depending on the joint congruency [83]. The principal functions of articular cartilage are to provide a low-friction gliding surface for joint articulation, act as a shock absorber and to facilitate the load transmission to subchondral bones.

The articular cartilage at the ankle is different from that of other synovial weight-bearing joints. It is thought that differences in ankle joint anatomy and cartilage properties may protect the ankle from primary degenerative changes [62,84]. Ankle articular cartilage has been shown to be thinner than that of the hip and knee [83,85] but also stiffer and more resistant to indentation [86]. The contact area of the ankle joint is smaller than that of the hip or knee [87] which means that a greater compressive force per unit area is exhibited over the

ankle joint cartilage [87]. Nonetheless, the joint congruity at the ankle is thought to protect the articular cartilage from high stress and secondary degeneration [83,88].

Further, the bio-molecular composition of talar articular cartilage is denser and has a higher turnover of matrix material in response to stress than tibiofemoral joint articular cartilage [89,90]. The varying capabilities of articular cartilage to react to stimuli was further confirmed when same injurious compression protocol applied to the tibiofemoral and ankle cartilage induced damage to 6% of ankle cartilage disk compared to 46 % of the knee cartilage disk with similar peak stresses [91]. Altogether, these unique features of ankle articular cartilage and the congruity of the ankle joint may explain the reduced prevalence of primary ankle OA (compared to hip and knee), which in turn is likely why ankle OA has received so little attention compared to hip and knee OA.

2.3 Aetiology of ankle OA

The aetiology of OA at the ankle, like that at other joints, is multifactorial. However, there is a consensus in the literature that ankle OA is predominantly a result of previous injury or trauma [13-15,17,44], such as ligament injury or fracture. Other factors associated with ankle OA include age [44], female sex [92], malalignment [13], malalignment with ligament insufficiency [93], age 30 years or older at the time of injury [91], and increased body mass index (BMI) [44,94].

2.3.1 Ankle sprains and instability

While an ankle sprain is often perceived as a minor injury, both mild and severe sprains increase the risk of ankle OA. In a large cohort study (n=247), Valderrabano [13] found that 55% of ankle OA cases were associated with previous ligamentous injury, with 85% of those cases associated with a lateral ankle sprain. Consistent with those observations, an anatomic study of elderly cadavers found degenerative changes in the talo-crural joint cartilage in 79% of ankles with previous talofibular ligament injuries [14]. The time between the development of ankle OA and initial injury is thought to be related to the severity of cartilage trauma [95,96]. As such, a severe ankle sprain is associated with a reduced time from the injury until the development of symptomatic end-stage ankle OA compared to recurrent sprains of less severity (25.7 vs 38.0 years) [13].

Chronic ankle instability (CAI), which is a common sequella of ankle sprains characterised by recurrent sprains, giving way and instability at the ankle [97,98], is also associated with ankle OA [18,99,100]. Arthroscopic findings suggest that 55% of individuals with CAI have cartilage lesions to the talus [101], and pre-surgical assessments have found talar cartilage fibrillation and cartilage defect in 25% and 14% of CAI patients, respectively [102]. In addition to probable cartilage damage at the time of the sprain(s), it has been suggested that altered load distribution at the ankle joint may also contribute to ankle OA development in this population [18,103,104].

2.3.2 Ankle fractures

Ankle fractures are an increasingly prevalent health care problem [105,106]. It is estimated that 62% of ankle OA occurs subsequent to an ankle fracture [45]. Malleolar, tibial plafond [95] and talar fractures [107,108] are frequently associated with the development of post-traumatic ankle OA [95].

The type and severity of ankle fracture, associated articular surface incongruity/mal-alignment, instability and healing complications are reported to correlate with post-traumatic ankle OA. The prevalence of posttraumatic OA increased with the increasing severity of fracture and pattern for example; fractures that resulted in malleolar fragments were considered a severe pattern of fracture and correlated with a higher prevalence of OA [92,109]. In high-energy injuries, such as skiing and motor vehicle accidents, acute loading can result in overwhelming injury to the articular cartilage and joint degeneration can occur relatively rapidly. Within two years of an ankle fracture or joint injury, post-trauma radiographs can show evidence of degenerative joint changes [92,110,111]. Joint incongruency reduces the joint contact area which could lead to mechanical loading that exceeds the capacity of the articular cartilage cells and matrix to repair [112,113]. Individuals with complications during fracture healing (e.g. osseous disturbance, infections, osteomyelitis, osteonecrosis, development of arthrofibrosis, and complex regional pain syndrome) have been shown to develop ankle OA earlier than those with uncomplicated fracture-healing [114,115].

2.3.3 Hindfoot malalignment

Individuals with ankle OA often present with concomitant hindfoot deformity, most commonly a varus deformity [55,116]. Varus or valgus angulation is defined by the angle between the anatomical axis of the tibia and a line perpendicular to the articular surface of the talar dome [117-119]. An angle of <10° varus or valgus is considered a neutral ankle alignment, while an angle of ≥10° is considered to be varus or valgus malalignment deformity [118].

Valgus and varus hindfoot malalignment can be caused by neurological conditions, trauma (such as tibial fractures [120]), genetics and other unknown factors [121]. A longitudinal prospective study of individuals with malalignment following a tibial fracture found a direct correlation between the degree of tibial malalignment and ankle joint degeneration [120]. Deviations from normal hindfoot or tibial alignment are thought to reduce the ankle joint contact area [122,123] and tibiotalar force transmission [121]. Any shift from neutral joint alignment moves the normal load-bearing regions of the ankle joint to areas less well adapted to withstand load and asymmetrical load distribution across the joint. This subsequently predisposes the joint to asymmetric ankle OA.

2.4 A possible increasing risk of ankle OA

In light of increases in sports participation and injuries, it is likely that the incidence of ankle OA is also on the rise. Over the past decade, the number of individuals who participate in sports has increased. For instance, in the United Kingdom, the number of individuals participating in a sporting activity at least once a week rose by 750,000 from 2011 to 2012 [124]. Perhaps unsurprisingly, the incidence of sports-related injuries, particularly to the lower limbs has also increased [125,126]. The ankle joint is among the most commonly injured joints [127]. Research has shown that acute ankle injury was the second most common career ending acute injury after the knee among 185 retired English professional soccer players [128]. Ankle sprains are the most common injury seen in US emergency departments [129], with over 3.1 million sprains occurring between 2002 and 2006 [129], 50% of which were due to sport-related injuries [129,130].

Ankle sprains are most common among individuals in the second to third decade of life [131]. As the majority of ankle OA is post-traumatic in nature and ankle sprains are

associated with the development of OA in 25.7 to 38.0 years [13], it is likely that ankle OA is or will be affecting individuals of a relatively young age. This is consistent with data suggesting that ankle OA occurs earlier in life than that of other joints[15,17,18]. The onset of ankle OA at a time of life where individuals have high work and family demands and are typically active in sporting and recreational pursuits will likely have a significant impact on QoL. Further, the impact of OA will be felt for a longer period of time than individuals of more advanced age.

2.5 Impairments and disability

2.5.1 The International Classification of Functioning, Disability and Health (ICF)

The World Health Organization (WHO) International Classification of Functioning, Disability, and Health (ICF) has been used to systematically describe the impairments and limitations in functioning (disability) encountered by individuals with a health condition. The ICF is a biopsychosocial model that considers biological, environmental and social perspectives and interactions [19]. Information in the ICF model are arranged into two different domains, 1) *functioning and disability* and 2) *contextual factors*. The ICF domain of *functioning and disability* is composed of three parts 1) body function and structures, and 2) activities and 3) participation.

Impairments are part of the "disease process" and refer to problems of body functions and structures associated with a health condition. Body function and structures refer to the physiological aspects of the affected anatomical body part or system; and describes the impairment experienced at the physical level as a consequence of a health condition/disease process. Activities refer to the consequences of impairments of body function and structures that affect the execution and performance of particular functional tasks, such as walking or stair negotiation. A bidirectional relationship exists between body function and structures and activities, in that a limitation in one domain contributes to a limitation in the other. Participation is involvement in an activity with individual meaning and relevance, such as sports, employment or shopping. The relationship between activities and participation is also bidirectional; limitation in activities affects participation and vice versa. Disability is a collective term that encompasses impairments, activity limitations and participation

restrictions [132] that limit an individual's ability to perform or undertake a task in the same way as a non-disabled person [132,133].

The *contextual factors* domain of the ICF includes the two contexts, environmental (physical and social) and personal (such as age, sex, social status, coping and behaviour patterns), that either facilitate or hinder an individual's functioning within the context of the health condition.

Interactions between the different domains of the ICF have the potential to influence an individual's QoL [134] (Figure 2.1). Thus, understanding impairments at the level of body function and structure, activities and participation, with consideration of environmental and personal factors, is important to understand the influence of a health condition on QoL.

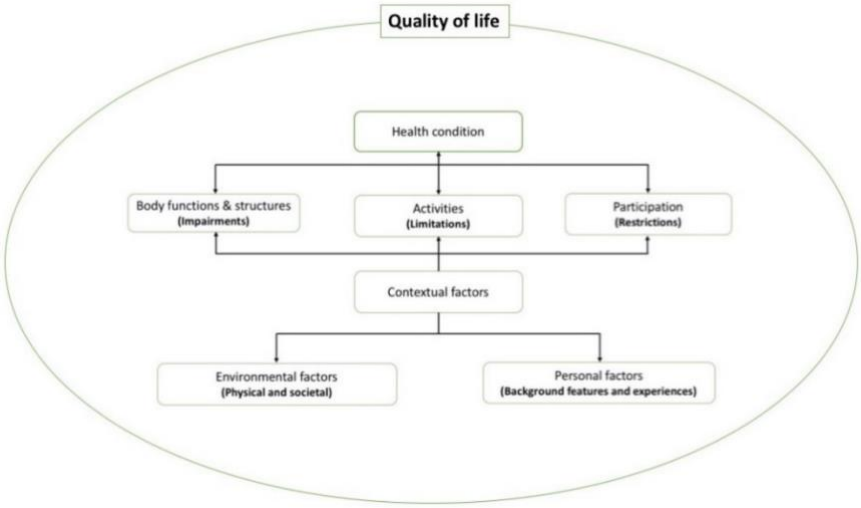

Figure 2. 1: Illustrative interaction between the different components of ICF

2.6 Impairments and disability in OA

Research on impairments and disability in ankle OA is limited and existing studies often do not compare findings to healthy controls [135,136], or combined the results for ankle OA and rheumatoid arthritis (RA) [137-144]. The few studies that have considered ankle OA separately have used modest sample sizes, which raise questions about their power and generalizability [145-148]. These methodological considerations limit the interpretation of existing data. The following section will use elements of the ICF model to describe impairments

associated with ankle OA. Characteristic impairments that warrant consideration during OA assessment, development and application of management plans and outcomes assessment will be highlighted. In light of the limited research in ankle OA population, studies on the characteristic impairments in OA of other weight-bearing joints (i.e. the hip and knee) will also be presented.

2.6.1 Body function and structure in OA

The body structure and function component of OA relates to both degeneration of articular cartilage and subchondral bone, and impairments such as pain, muscle weakness, and deficits in range of motion (ROM). While damage to cartilage and subchondral bone may be non-modifiable in management, other impairments may be able to be addressed with targeted treatment.

Musculoskeletal pain is the main reason for seeking medical care [149]. Pain is a cardinal symptom [150] and a key determinant of disability in individuals with musculoskeletal conditions and OA [151]. Research on retired soccer players showed that ankle joint pain on daily activities was reported by 17.2% of retired players while 9% reported pain on walking [128]. Pain also has a detrimental effect on QoL [152]. Research on a small sample of individuals with ankle OA (n=5) and healthy controls (n=5) showed that those with OA group presented with significantly higher pain scores 26 ± 7.6 on the Short Form health survey (SF-36; 54.2 ± 3.7 vs 87.6 ± 17.2) and Ankle Osteoarthritis Scale (AOS; 26 ± 7.6 vs 1.8 ± 4) [153]. Both of these tools (i.e. SF-36 and AOS) have pain sub-scales commonly used to evaluate pain in clinical and general populations.

Muscle weakness is a common impairment in individuals with OA in weight-bearing joints [154]. There is some evidence from small studies of ankle muscle weakness in ankle OA compared to controls [145,146,155]. Similarly, hip and knee muscle weakness has been identified in individuals with hip [156] and knee OA [157-159] compared to controls.

Reduced joint mobility and stiffness are common clinical features of OA. Individuals with ankle OA have reduced total ankle dorsiflexion-plantarflexion ROM [160,161,162-164]. This is important because reduced ankle dorsiflexion has been associated with compromised balance and function [165,166-169]. However, it is not clear whether the limitation is in

dorsiflexion, plantarflexion or both. There is also evidence of decreased inversion-eversion ROM from one study [145]. Most participants in studies that have investigated ankle ROM have been awaiting surgery with end-stage ankle, which limits the generalisability of findings. Reduced hip and knee joint mobility has been reported in hip and knee OA [22].

2.6.2 Activities and participation in OA

The impact of OA on activities and participation can be measured using self-report or performance-based measures. Osteoarthritis has been linked with a progressive deterioration in function [112,170]. In 2009, 592,000 Australians reported having a disability related to arthritis [171]. The WHO estimates that 80% of individuals with OA present with movement limitation and 25% are unable to perform major daily activities [172].

There has been limited research on functional limitations in ankle OA. A small pilot study (with five participants per group) found that individuals with ankle OA reported higher disability compared to age-matched controls [147]. Comparisons between the end-stage ankle and hip OA showed similar levels of physical disability between groups [173]. However, as both the ankle and hip OA groups had end-stage OA and were awaiting surgery, a poor function would be expected. Research exploring function in earlier stages of ankle OA is warranted.

Pain can influence participation in meaningful activities, as such, it can initiate avoidance as cognitive (avoiding painful experience) or behavioural (avoiding activities) [174] reaction which can, in turn, lead to a range of consequences including activity restriction, muscle deconditioning, impaired balance, more pain, limited participation and disability [175,176]. While participation in meaningful activities such as work and recreation has not specifically been investigated in ankle OA, research on individuals with arthritis (OA, rheumatoid arthritis, gout, lupus, or fibromyalgia) indicate that they do not meet the recommended level of activity for arthritis [177,178] (30 minutes of moderate-intensity physical activity at least 3 days per week) [179]. There is evidence that OA limits work participation [23,34-36] and those limitations are reported to be 3-5 times higher in individuals with OA compared to individuals without OA [180,181].

Participation in meaningful activities can be influenced by fear of fall and falling. Research suggests that individuals with OA have an increased risk of falls [182-184]. Pain is also

associated with fear of falling [185] which has been linked to restriction of activities [186]. Granting that OA related impairments including pain, decreased muscle strength and reduced joint motion, have been suggested to increase the risk of falls in older adults [168,187-191], it is possible that individuals with ankle OA may be at risk of falls which warrant investigation.

2.6.3 Contextual factors in OA

Considering OA from other areas of the body, due to lack of research at the ankle, sex, age, BMI, cognitive factors such as pain beliefs, self-efficacy, fear of movement and psychological distress (anxiety and depression) are contextual factors that have been shown to relate to functioning and disability in OA. Women with OA experience higher disability and functional decline than men with OA [192-194]. Psychological distress is greater in younger, compared to older, individuals with OA [195]. In light of ankle OA affecting a younger population than that of other joints, this may be a concern in ankle OA [15,17,18]. High BMI is a key determinant of disability in knee OA [64].

There are many psychosocial considerations that are likely to affects the functioning in chronic pain and OA. Research has reported that 20% of individuals with OA experience symptoms of depression and anxiety [196], and that depression is associated with decreased physical activity participation [197,198]. Higher fear of movement, anxiety, depression, catastrophizing [199] and lower pain self-efficacy [200] are all associated with pain [201], and related to disability [200,202]. Low levels of self-efficacy have been linked to higher disability in individuals with OA of the knee and hip [203]. It remains unclear whether these findings extend to individuals with ankle OA.

2.6.4 Health-related QoL in OA

Quality of life is a product of the interaction between the *functioning/disability* and *contextual factors* components of the ICF and is an important goal of the management of health conditions. Individuals with musculoskeletal disorders report lower QoL compared to individuals without musculoskeletal disorders [204], and those with OA report poorer QoL than healthy individuals [205]. According to the 2014–15 National Health Survey [206], Australians aged 18 and over with OA were 4.3 times more likely to report very severe pain, and 2.3 times more likely to report poor health status as compared with those without OA.

The majority of research investigating QoL in OA involves the hip and knee joints. Studies have shown that hip and knee OA has a negative effect on QoL [207-209] and psychological health [210-213]. However, comparatively little is known about the experience of individuals with ankle OA. Saltzman et al [214] used the SF-36 to compare the physical and mental component summary scores between individuals with ankle OA and controls and found mental component scores in ankle OA significantly lower than that of the controls. Further, the physical component scores in individuals with ankle OA were similar to populations with severely disabling medical conditions such as end-stage renal disease, radiculopathy and congestive heart failure [214].

2.7 What is missing?

In the previous section, the ICF served as a system to describe OA across the different domains of health. While there is evidence of the impact of hip and knee OA on disability [207-209], participation in daily living activities (ADL) [215] and QoL [204], little is known about the impact of ankle OA on these and other elements of activities, participation, and QoL. Further, the few studies that investigated impairments in body structure and function in ankle OA have used small sample sizes and/or populations with end-stage OA awaiting surgery. Thus, impairment characteristics of the early stage of ankle OA are not known. Furthermore, no study has focused on examining the extent to which age, ankle pain, self-efficacy or anxiety contribute to disability in individuals with ankle OA.

Since little is known about the key impairments to body structure and function, or the impact of ankle OA on activities, participation and QoL, it is difficult to design and appropriately assess the impact of treatment programs for individuals with ankle OA. It is therefore important to identify specific impairments associated with ankle OA to guide management of this condition. Understanding disability and factors related to the disability in ankle OA will help identify key outcomes to determine the impact of an intervention which will, in turn, guide the development of evidence-based practice guidelines in the management of ankle OA.

2.8 Thesis aims and objectives

The aim of this thesis is to promote a better understanding of the physical impairments and associated disability of individuals with ankle pain and OA. The studies in this thesis include a systematic review to synthesise the existing literature on physical impairments in ankle OA, a cross-sectional laboratory study to assess physical and functional impairments in ankle OA, and cross-sectional online surveys to explore the impact of ankle symptoms on pain, disability, physical activity, psychosocial factors, falls, work ability and QoL.

Specific objectives of this thesis were to:

1. Systematically review available evidence of physical impairments in individuals with ankle OA (Chapter 3);
2. Compare physical measures (ambulatory function, ankle muscle strength and endurance, ROM, ankle-subtalar joint laxity, foot mobility and posture) and patient-reported outcomes (QoL, perceived function, pain, disability, kinesiophobia and physical activity) between 1) individuals with symptomatic ankle OA and asymptomatic controls, and between 2) asymptomatic individuals with and without evidence of ankle OA, and to explore the relation between QoL, patient-reported outcomes and physical impairments (Chapter 5);
3. Compare pain, stiffness and patient-reported outcomes (QoL, perceived function, disability, kinesiophobia and physical activity) between individuals with persistent ankle symptoms and asymptomatic controls (Chapter 6);
4. Identify whether the psychological characteristics of individuals with ankle symptoms differ from that of asymptomatic controls, and to assess the association between psychological characteristics and 1) pain, and 2) self-reported function (Chapter 7);
5. Assess work limitations experienced by individuals with and without ankle symptoms, compare function and psychological features between working and non-working individuals with ankle symptoms, and to explore factors associated with work limitation in the symptomatic group (Chapter 8);

6. Compare the self-reported history of falls, balance confidence and falls self-efficacy between individuals with ankle symptoms and asymptomatic controls, and to identify factors associated with the frequency of falls in individuals with ankle symptoms (Chapter 9).

2.9 Overview of thesis structure

This thesis is presented with a series of chapters to address the thesis objectives identified above. Traditional thesis format was selected for The Background (Chapter 2), The Methodology (Chapter 4), and the Discussion and Conclusion (Chapter 10). These three chapters indorse the thesis context with supplementary details not provided in other chapters prepared for publication in peer review journals.

Publication incorporated as Chapter 3

Al-Mahrouqi MM, MacDonald DA, Vicenzino B, Smith MD. Physical impairments in adults with ankle osteoarthritis: A systematic review and meta-analysis. Journal of Orthopaedic & Sports Physical Therapy. 2018; 48(6):449-459.

Contributor	Statement of contribution
Munira Al Mahrouqi (Candidate)	Conception and study design (25%) Literature searches (100%) Quality appraisal (50%) Data extraction and analysis (100%) Drafting the manuscript (100%)
Michelle Smith (Principal advisor)	Conception and study design (25%) Critical revision of manuscript (40%)
David MacDonald (Associate advisor)	Conception and study design (25%) Quality appraisal (50%) Critical revision of manuscript (20%)
Bill Vicenzino (Associate advisor)	Conception and study design (25%) Critical revision of manuscript (40%)

Chapter 3 Physical impairments in adults with ankle osteoarthritis: A systematic review and meta-analysis.

3.1 Introduction

Osteoarthritis is one of the most prevalent and costly [216,217] health conditions and causes of disability [15,16,95]. The World Health Organisation estimates that 80% of people with OA are limited in their movement, and 25% are unable to perform many daily activities [218]. Ankle OA affects approximately 70 million people worldwide [217]. It is predominantly associated with previous ankle trauma, including ankle sprains [14,] and fractures[15,17,18]. Given that ankle sprains are the most common injury among sportspeople [129,130] and the most common injury seen in US emergency departments [131], the incidence of ankle OA is a considerable health concern. There is evidence that individuals with post-traumatic ankle OA report higher levels of disability, measured by the ankle osteoarthritis scale relative to age-matched controls [147]. Studies investigating the QoL indicate that mental and physical disability associated with ankle OA is similar to that of individuals with end-stage hip OA [173], renal disease, radiculopathy and congestive heart failure [214]. Due to the post-traumatic origin of ankle OA, it affects a younger population than OA of other joints [15,17]. The disability associated with ankle OA may negatively impact earning potential and the ability to meet familial obligations.

In contrast to hip and knee OA, management options for ankle OA are limited with lower success rates and less favorable long-term outcomes following surgical intervention [219-222,236]. Physical therapy is frequently used to manage pain and disability associated with OA [223]. The goals of intervention are often achieved by addressing physical impairments, such as low muscle strength/ endurance, limited range of motion (ROM) and poor balance [224-226], which improve pain and function [224,227,228]. Recent International Ankle Consortium recommendations highlighted the need to address and raise awareness and understanding of the consequence of lateral ankle sprain [229], of which ankle OA is one. At the moment, it is challenging to determine which impairment(s) should take priority as a therapeutic target(s) for patients with ankle OA. Consistent with International Ankle Consortium recommendations, an improved understanding of the scope and extent of physical

impairments in individuals with ankle OA is required. Further, understanding key impairments in ankle OA will inform the selection of outcomes measures, and development of non-surgical interventions for studies investigating disease management. This systematic review aimed to document reported physical impairments in adults with ankle OA by comparing affected and unaffected sides in adults with unilateral ankle OA and healthy controls.

3.2 Methods

3.2.1 Design

The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42016036720). The following variations from the protocol were implemented: (a) gait-related outcomes were excluded from this review as they were deemed of sufficient quantum to warrant a separate review; and (b) the I^2 statistic was used as the indicator of statistical homogeneity instead of chi-square statistic. Reporting was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria [230] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [231,232].

3.2.2 Search Strategy

A comprehensive search strategy was devised in collaboration with a medical librarian. Three sets of entry strings were combined with AND. The first set of terms included synonyms for ankle OA and the second set specified anatomical location. The terms in each set were combined using OR. Those two sets of search strings were combined using AND to a third search string consisting of physical outcomes and synonyms (range of motion, muscle strength, balance, and proprioception). Finally, a set of NOT terms (searched in titles and abstracts) was used to exclude animal, cadaveric and pediatric studies, and papers investigating unrelated health conditions, such as anterior cruciate ligament injury, patellofemoral pain or hallux valgus. PubMed, EMBASE, CINAHL, Web of Science, and SPORTDiscus databases were searched with no language or date restriction. The detailed search algorithm for different databases is presented in Appendix 1.

3.2.3 Eligibility Criteria

Retrieved titles and abstracts were screened for eligibility using the following criteria: 1) the study investigated physical impairments associated with ankle OA, and 2) the study compared physical impairments between individuals with and without ankle OA or compared the affected and unaffected side in individuals with ankle OA. Intervention studies were eligible for inclusion if pre-intervention measures were compared to individuals without ankle OA or to the unaffected side. Studies of different types of arthritis (e.g. rheumatoid arthritis, septic arthritis) were only included if data for ankle OA were reported separately. Abstracts from scientific meetings, case reports, and descriptions of surgical techniques were excluded.

3.2.4 Study Selection

One author (MM) screened all articles identified in the literature search using the pre-defined inclusion and exclusion criteria. A second author (MDS) screened a randomly selected 5% of the total studies. Full articles were retrieved and screened when inclusion could not be determined by reading the title and abstract. Translations were sought to determine the eligibility of five non-English publications (three French, one German and one Korean), one of which was eligible. Reference lists of all eligible studies were manually screened for potential studies not found by the electronic database search. The final eligibility of selected publications was determined by consensus with all authors.

3.2.5 Assessment of Study Quality and Risk of Bias

Quality assessment of all eligible studies was completed using the Epidemiological Appraisal Instrument (EAI) [233]. The EAI has demonstrated good/excellent validity, and (intra and inter-rater) reliability [233]. Ten of the original EAI items (related to intervention, randomisation, and follow-up) were not used, because they did not apply to cross-sectional and case-control study designs. Two reviewers (MM) and (DM) independently rated each article after de-identification by removal of author, journal, and title. Scores were compared for consensus and disagreements were resolved by a third investigator (although this was not necessary). The overall score was recorded as an average of the scores from all applicable items (range 0-1).

3.2.6 Data Extraction

Data from eligible studies were extracted into a pre-designed evidence table by one reviewer (MM) and verified by a second (DAM). The following data were extracted from eligible studies: authors, publication year, country, study objectives as stated by the authors, study design, OA definition/diagnosis, population characteristics, comparisons made, outcome measures, measurement tools used and study findings (values expressed as mean and SD).

3.2.7 Data Analysis

Kappa statistics were used to report the inter-rater reliability between the two assessors for study selection and quality assessment. Inter-rater reliability was categorized as poor (<0.00), slight (0.00–0.2), fair (0.21–0.4), moderate (0.41–0.6), substantial (0.61–0.8) or almost perfect (0.81– 1.0) [234]. Data were analysed using SPSS V.25 software (SPSS Inc., Chicago, USA).

Studies with similar outcome measures and methods were considered for meta-analyses using RevMan 5 (Copenhagen, Denmark, The Nordic Cochrane Centre, 2006). Heterogeneity was assessed by inspecting the I^2 statistic and was considered unacceptably high for values greater than 75% [235]. When homogeneity was less than or equal to 75%, data were pooled in a statistical meta-analysis with random effects.

Data representing point estimates of effect are presented as standardized mean differences (SMDs) and their confidence intervals (CI) in tabular format and in forest plots where appropriate. The SMD was calculated as the difference between ankle OA and control group means divided by the pooled standard deviation (SD) for all outcomes. For studies in which the SD was not available, it was calculated as the product of the standard error of the mean and the square root of the sample size [236]. Differences in outcomes between the affected side in individuals with ankle OA and controls were calculated such that negative differences indicated that the measure for ankle OA was lower relative to controls, and positive differences indicated the opposite. Between-group differences were considered significant if the 95% CI did not contain zero. Effect sizes were interpreted as small (SMD>0.2),

medium (>0.5) and large (>0.8) [237]. SMD [CI] is reported throughout the text to provide a point estimate of effect for comparisons between measures with different units.

3.3 RESULTS

3.3.1 Study Selection

The search identified 4565 results, with 3439 unique studies remaining after removal of duplicates. After screening titles and abstracts, it was decided to exclude gait-related measures from this review due to the quantum of papers, which warrants a separate review. This left 28 full-text articles that were then assessed for eligibility. Corresponding authors were contacted when information unavailable in the paper was needed to determine eligibility [145,147]. Eight studies met the eligibility criteria (Figure 3.1). There were no disagreements between the two reviewers in the eligibility assessment (undertaken on a random 5% (172) of the studies identified). A subsequent manual reference list search of included studies did not reveal any additional studies.

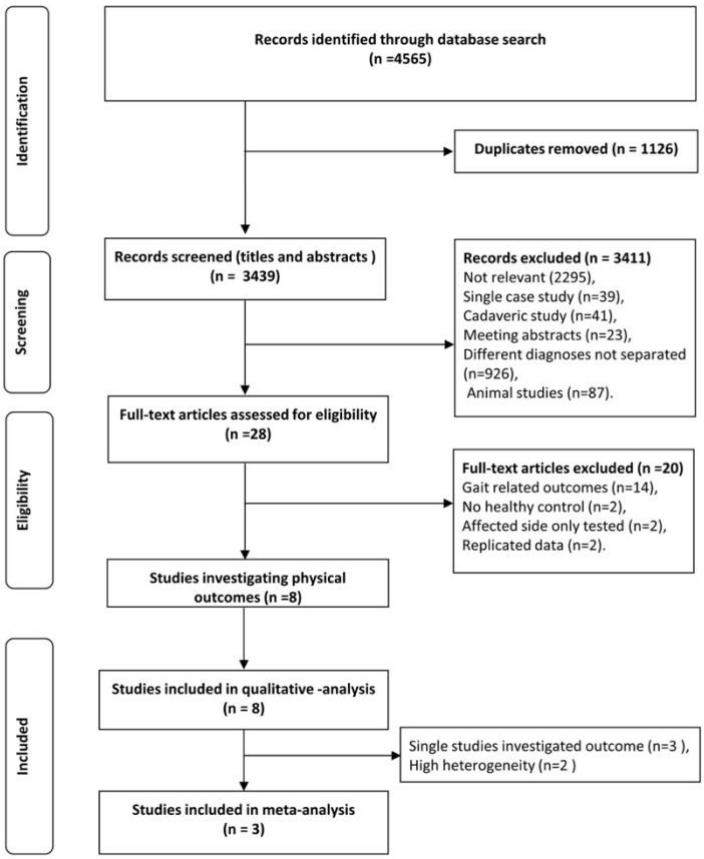

FIGURE 3. 1: PRISMA 2009 flow chart for the selection process

3.3.2 Assessment of Study Quality and Risk of Bias

There were no disagreements between the two raters among the 264 quality assessment items rated (κ=1.000 ($p<0.01$)). The EAI quality assessment demonstrated a median score of 0.36 out of 1 (range: 0.30-0.56; Appendix 2). Descriptions of the research objectives [145-147,155,238-241], study design [145-147,155,238-241], main outcomes [145,146,155,238,239,241], standardized assessment of outcomes [145,146,155,238,239,241],and key findings [145-147,155,238-241] were addressed in most studies. The items which were not well addressed were *a priori* sample size calculation [239], missing data and dropouts [238], and assessor blinding [146]. Three studies [145,146,239] collected prior history of ankle injuries as a contributing factor to OA development, but only one study [145] included this information in the analysis. No study reported the results by age or sex. Only two studies reported the validity of their main measures [155,239], and two provided information about the psychometric properties of the physical impairment measures [145,240].

3.3.3 Study Characteristics

All studies were published between 2006 and 2013 and conducted in the following geographical locations: Switzerland (n=2) [155,239], Korea (n=2) [240,241], Japan (n=1) [238], USA (n=2) [147,146], and Canada (n=1) [145], There were a total of 343 ankle OA and 220 control participants across studies. Individual study sample sizes ranged from 10 (5 ankle OA and 5 controls) [147] participants to 154 (104 ankle OA and 50 controls) [240]. Seven studies compared data between individuals with ankle OA and controls [145-147,155,238,240,241], and 4 studies compared the affected and unaffected ankles in individuals with ankle OA [145,146,155,239] (with 3 studies reporting both comparisons [146,145,155]). Characteristics of studies included in the review are presented in Table 3.1.

Table 3.1: Characteristics of studies included in the review

Author Year	Country	EAI score	OA cases	Control cases	Outcomes investigated	Results
Wiewiorski et al. (2012)	Switzerland	0.41	21 (10 M, 11 F) Age (35–76 y)	Unaffected side	▪ Total DF/PF ROM ▪ Calf circumference ▪ Muscle CSA ▪ Muscle fatty infiltration	▪ Less total DF/PF ROM and lower calf circumference on the affected side compared to the unaffected side ▪ Greater Fatty infiltration and smaller overall anatomical CSA in all compartments and muscles on the affected compared to unaffected side in individuals with ankle OA. ▪ Smaller CSA for Soleus and the deep posterior muscles on the affected compared to the unaffected side.
Valderrabano et al. (2006)	Canada	0.36	15 (6M, 9F) Age 53.3(33- 74 y)	15 (6M, 9F) Age 52.9 (27-65y)	▪ Total DF/PF ROM ▪ Calf circumference ▪ DF-PF torque ▪ Surface EMG amplitude and frequency during muscle MVC	▪ Less total DF/PF ROM on the affected side compared to the unaffected side. ▪ No difference in calf circumference on the affected side compared to the unaffected side and controls. ▪ Significant DF/PF weakness on the affected side compared to unaffected and control. ▪ No difference in calcaneal alignment between moderate-advanced OA and controls or between sides in individuals with OA. ▪ Mean EMG frequency was lower for all tested muscles on the affected compared to unaffected side in ankle OA ▪ Lower Anterior tibial and medial gastrocnemius EMG frequencies in ankle OA compared to controls ▪ Lower Medial gastrocnemius but not anterior tibial, peroneus longus or soleus EMG amplitude in ankle OA compared to controls
Nüesch et al. (2012)	Switzerland	0.35	12 (6M+ 6F) Age 56.60 y	12 (7M, 5F) Age 48.41	▪ Calf circumference ▪ DF-PF torque	▪ No difference in calf circumference on the affected side compared to the unaffected side and controls. ▪ Significant DF/PF weakness on the affected side compared to control.
Hayashi et al. (2008)	Japan	0.56	80 (15M, 65F) Age 64 (32 -85 y)	50 (10 M, 40F) Age 39 (13- 86 y)	▪ Radiographic bony alignment	▪ Progressive increase TPC angle from mild OA to moderate OA, then decreased in advanced OA compared to controls ▪ Less TTS and TAS angles in all stages of ankle OA compared to controls

						▪ Smaller TAS and TLS angles in ankle OA compared to controls ▪ Greater TMM angle in advanced OA and less TTS angle for moderate and advanced ankle OA compared to controls
Hubbard et al. (2009)	USA	0.33	(4M, 4F) Age (51.8±11.41y)	(4M, 4F) Age (51.5±11.2y)	▪ Mechanical stability ▪ DF-PF and INV-EV torque ▪ Static balance	▪ Less anterior displacement on the affected ankle compared to the unaffected ankle in ankle OA and controls. ▪ Less inversion and eversion on the affected compared to the unaffected ankle in individuals with ankle OA and controls. ▪ No difference in posterior displacement between sides or groups. ▪ Greater total COP displacement and total velocity. ▪ Greater ML velocity and AP sway in OA compared to controls. ▪ Weaker DF, PF, INV, and EV on the affected ankle compared to the unaf-fected ankle in individuals with ankle OA and controls.
Lee et al. (2011)	Korea	0.39	98 (47M, 51F) Age 58.2 (43 -78y)	80 (57M, 23F) Age 23.4 (18 – 25y)	▪ Radiographic bony alignment	▪ Greater talar tilt angle on the affected ankle than controls. ▪ Smaller TAS and TLS angles and an increase in TMM angle as the stage of OA progressed compared to controls.
Lee et al. (2013)	Korea	0.36	104 (72M,32 F) Age 62 (22-77 y)	50	▪ Radiographic bony alignment	▪ Smaller tibio-talar ratio in individuals with ankle OA than controls.
Wikstrom & Anderson. (2013)	USA	0.30	5 Age (63.4±11.3y)	5 Age (60.0±3.0y)	▪ Standing balance	▪ Greater anteroposterior sway in OA compared to controls.

Abbreviations: F, female; M, male; Y, years; PF, plantar flexion; DF, dorsiflexion; INV, inversion; EV, eversion; MVC, maximum voluntary contraction; COP, centre of pressure; AP, Anteroposterior; ML, Medial-lateral; TMM (◦), The angle between the distal third of the tibial shaft and the medial malleolar joint surface; TTS (◦), The angles between the tibial shaft the articular surface of the talar dome; TPC (◦), The angle between the tibial shaft axis and the articular surface of the posterior facet of the calcaneus; TAS (◦), The angle between the tibial shaft and tibial articular surface in the frontal plane on weight-bearing x-ray; TLS (◦), The angle between the tibial shaft axis and the articular surface of the tibial shaft in the sagittal plane on weight-bearing x-ray; SIA, angle between the articular surface of the talar dome and the posterior facet of the calcaneus; Tibiotalar ratio, ratio into which the mid-longitudinal axis of the tibial shaft divides the longitudinal talar length; CSA, cross sectional area; EMG, electromyography; ±, standard deviation.

3.3.4 OA Diagnosis

The majority of studies used radiographic imaging to establish the presence of OA (n=7) [147,238,239,146,240,145,241]. One study did not specify the method of establishing OA diagnosis [155]. Four studies [238,145,239,241] reported radiographic classification criteria used to establish a diagnosis of ankle OA; whereas, three studies did not specify how the radiographs were evaluated [147,146,240]. No study provided information on the reliability of the radiographic classification system.

The radiographic classifications used were the three-stage Morrey and Wiedeman classification [54] (n=2) [145,239] and the modified five-stage Takakura classification [55] (n=2) [238,241]. The Morrey and Wiedeman and the modified Takakura classification systems have similar early stage (1and 2) OA definitions (e.g., early sclerosis, minimum narrowing, and osteophyte formation). The modified Takakura classification includes an intermediate stage 3 OA classification that further differentiates the extent of joint space narrowing and subchondral bone contact. The advanced stage OA is similar in both classifications (e.g., gross deformity, ankyloses, no joint space and bone contact). For this systematic review, ankle OA radiographic severity was collapsed to three categories incorporating both classifications: mild (stage 1), moderate (stage 2) and advanced OA (stages 3-4; Appendix 3).

3.3.5 Meta-analyses

Three studies contributed data to the meta-analyses of total sagittal plane ROM, calf circumference, and maximal voluntary isometric dorsiflexion (DF) and plantar flexion (PF) strength. Data (SMD and CI) are presented in forest plots (Figures 3.2 and 3.3). Large effects were identified for sagittal plane ROM (two studies [145,239]) and maximal voluntary isometric strength (two studies [145,155]). Pooled data indicate less sagittal plane ROM on the affected compared to unaffected side in individuals with ankle OA, and lower maximum ankle DF and PF torque on the affected side in individuals with ankle OA compared to controls.

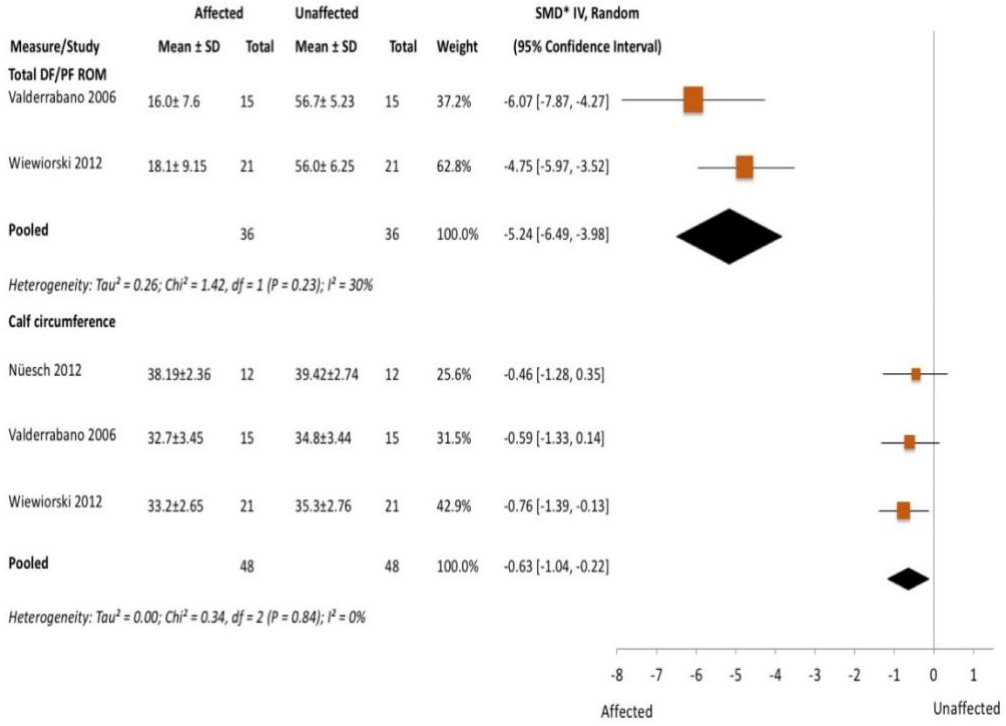

FIGURE 3. 2: Range of movement and calf circumference differences between sides in ankle OA

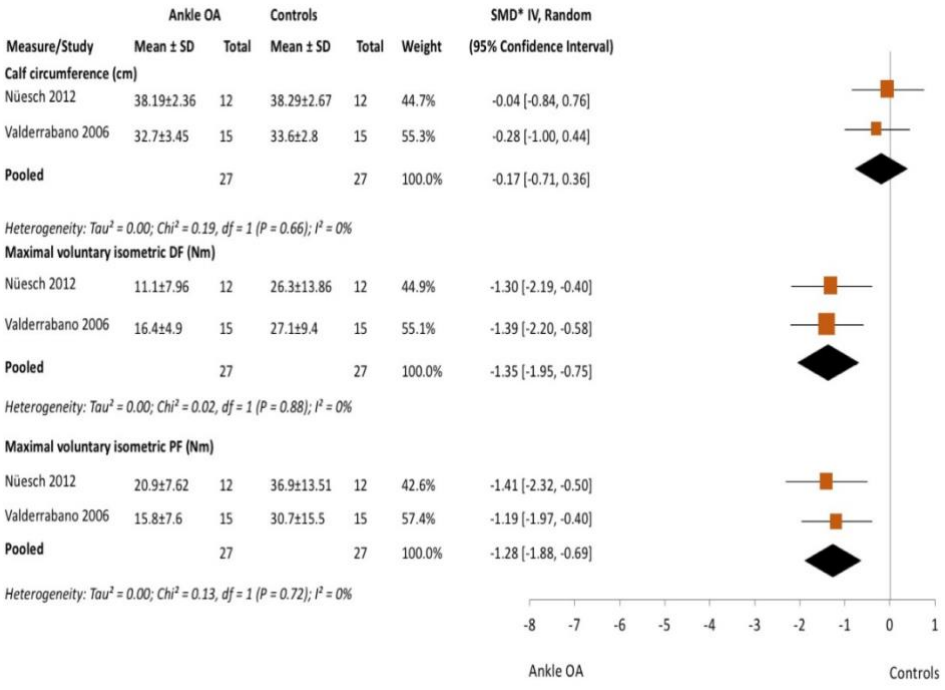

FIGURE 3. 3: Calf circumference and muscle strength differences between groups

3.3.6 Outcomes from Single Studies

Single studies assessed ROM, torque, calf circumference, ankle arthrometry, bony alignment, muscle electromyography (EMG), calf cross-sectional area (CSA) and fatty infiltration in calf muscles in individuals with ankle OA compared to controls or the individual's unaffected side. Pooling of data was not possible due to differences in reported outcomes or methods of measurement, or high heterogeneity. All data pertaining to effect sizes for outcomes are presented in (APPENDIX 4) and outcomes with large effect sizes are reported below.

3.3.6.1 Range of Movement (ROM)

One study compared total ankle DF and PF (sagittal) ROM and inversion and eversion (frontal) ROM between individuals with ankle OA and controls, with frontal plane ROM also compared between sides in individuals with ankle OA [145] (sagittal plane ROM reported in the meta-analysis, Figure 3. 2). Large effects were found for less frontal and sagittal plane ROM in individuals with ankle OA compared to controls, and less frontal plane ROM in individuals with ankle OA compared to the contralateral side [145].

3.3.6.2 Ankle Arthrometry

One study [146] used a portable ankle arthrometer (Blue Bay Research, Navarre FL) to measure anterior-posterior displacement and inversion-eversion rotation. Large SMDs indicated less anterior displacement and inversion and eversion rotation on the affected ankle in individuals with OA compared to the unaffected ankle and controls. Eversion rotation was also less on the unaffected side in ankle OA than in controls.

3.3.6.3 Calf cross Sectional Area (CSA) and Fatty Infiltration

One MRI study [239] quantified CSA and fatty infiltration in the medial and lateral gastrocnemius and soleus muscles, and the anterior, lateral and deep posterior compartments of the calf in individuals with ankle OA. Large effects indicated smaller soleus CSA, smaller overall anatomical calf CSA, and greater fatty infiltration in all muscles/compartments in the affected compared to the unaffected side in individuals with ankle OA.

3.3.6.4 Joint Torque

Comparison of DF and PF torque between sides in individuals with ankle OA indicated lower torque on the affected than on the unaffected side [145]. Ankle DF, PF, inversion and eversion torque normalised to body weight was less on the affected and unaffected ankles in individuals with OA compared to controls [146]. There were also large deficit effects for normalised eversion and inversion torque on the affected compared to the unaffected side in individuals with ankle OA.

3.3.6.5 Muscle Electromyography (EMG)

Large SMDs from one study indicated lower medial gastrocnemius EMG amplitude and lower anterior tibial and medial gastrocnemius muscle EMG frequencies on the affected side in individuals with ankle OA compared to controls [145]. EMG frequency on the affected side was also lower for the medial gastrocnemius, soleus and peroneus longus compared to the unaffected side.

3.3.6.6 Standing Balance

Balance during double leg stance was assessed in two studies using different testing methodology and outcomes [147,146]. Data indicated a greater total centre of pressure (COP) displacement and velocity [146], mediolateral velocity [146] and anteroposterior sway [147] in individuals with ankle OA compared to controls.

3.3.6.7 Bony Alignment

Alignment data were identified in four studies using radiographic [238,240,241], or goniometric measures [145]. The angle between the distal third of the tibial shaft and the joint surface of the medial malleolus (TMM) was greater in those with advanced OA [238,241], and the angle between the tibial shaft and the articular surface of the talar dome (TTS) was less for those with moderate and advanced ankle OA compared to controls, both measures indicating greater varus in those with ankle OA. Individuals with moderate and advanced ankle OA also had a greater angle between the articular surface of the talar dome and the posterior facet of the calcaneus (SIA) than did controls [238]. The angles between the tibial shaft and tibial articular surface in the frontal (TAS) and sagittal (TLS) planes were assessed in two studies [238,241], which could not be pooled due to high heterogeneity (I^2 values>75%). Large effects

indicated that TAS (two studies [238,241]) and TLS (one study [241]) was smaller for individuals with moderate and advanced ankle OA compared to controls. The tibio-talar ratio (the mid-longitudinal axis of the tibial shaft divided into that of the talus) [240] was smaller in individuals with advanced ankle OA than controls. SMDs for talar tilt angle (the angle between talo-crural joint surfaces with the ankle in supination [242]) could not be calculated due to a standard deviation of zero in the control group [241].

3.4 Discussion

This systematic review synthesised data from eight studies investigating physical impairments in individuals with ankle OA compared to controls or the unaffected side. The quality appraisal highlighted a general lack of reporting missing data, assessor blinding and measurement validity. Meta-analyses of three studies provided evidence of less sagittal plane ROM and smaller calf circumference on the affected compared to unaffected side in individuals with ankle OA and lower ankle torque production in individuals with ankle OA compared to controls. Evidence from single studies reported less total frontal plane ROM, lower frontal plane torque production, and less talar translation and rotation on arthrometry on the affected compared to the unaffected side in individuals with ankle OA and controls. Single studies also reported more fatty infiltration, smaller muscle CSA and a shift towards lower EMG frequencies for some muscles that influence ankle movements on the affected compared to the unaffected side with differences in bony alignment on the affected ankle compared to controls.

Ankle OA impairments are likely to present as elements of a complex patho-etiologic paradigm. Limited joint mobility is one of the clinical signs of OA [243,151,244,245] and is commonly present after an ankle sprain [246,247]. Large ROM differences are present between affected and unaffected ankles in individuals with ankle OA [145,239] and between the affected ankle in individuals with ankle OA and controls [145]. The limited joint mobility may be due to factors such as shortened musculotendinous structures (i.e. shortened gastrocnemius-soleus complex) [248,249], limited accessory or physiological joint motions (i.e. limited talar glide) [250-252] due to degeneration or capsular restriction [253], or chronic inflammation or pain [254]. Consistent with restricted ankle ROM, individuals with ankle OA have less anterior talar translation and inversion and eversion rotation on arthrometry compared to controls. These findings suggest

that ROM deficits in individuals with ankle OA are related to joint restriction, in addition to potentially shortened musculotendinous structures. Because only total ankle ROM is reported, it is unclear whether ROM deficits at the ankle are due to PF restriction, DF restriction, or both. This is important because reduced ankle DF has been associated with impaired gait, and compromised balance and function [169,165-167,168]. An improved understanding of the underlying mechanisms of movement restriction could lead to improved patient management.

Large differences in isometric PF, DF, inversion, and eversion torque production were found between the affected side in individuals with ankle OA and controls. Lower PF torque production is consistent with findings of lower medial gastrocnemius EMG amplitude and frequency in individuals with ankle OA (affected side) compared to controls. The relationship between lower torque production in other directions of ankle movement and EMG amplitude/frequency of relevant muscles was not readily apparent, and the interpretation of altered EMG findings is unclear. Lower EMG amplitude and muscle strength may be due to an inability of the central nervous system to fully activate the muscle [255] (arthrogenous muscle inhibition) which has been shown in knee OA [256,257], post-knee trauma [258], acute ankle sprains [259] and functional ankle instability [260]. OA-related muscle inhibition is thought to occur due to pain [167, 257,261], joint immobilization [145] and altered sensory output accompanying articular cartilage structural changes [262,263].

Weaker muscles and lower muscle activation may contribute to, or be a consequence of, muscle atrophy. Calf circumference was smaller on the affected compared to the unaffected side in individuals with ankle OA, but not between individuals with ankle OA and controls. The difference in calf circumference between the affected and unaffected sides in individuals with ankle OA [145,239,155] was driven by the findings of Wiewiorski et al [239]. Greater fatty infiltration and smaller posterior muscle size [239] may contribute to smaller calf circumference and muscle weakness on the affected side in individuals with ankle OA. The hypertrophy/increased muscle CSA on the unaffected side in ankle OA may be an adaptation related to increased use of the unaffected side in individuals with unilateral ankle OA.

Although only investigated in studies with small sample sizes [147,146], the standing balance was impaired in individuals with ankle OA compared to controls. Standing balance

[264,265] and proprioception [266-268] deficits are also observed in ankle sprains. Reduced joint motion [168,189], weak muscles [187] and pain [269] could contribute to compromised balance in ankle OA. As impaired balance is linked with falls [187;191,270], this may suggest an increased risk of falls in this population. Further research to understand specific elements of balance impairment and evaluate the incidence of falls in people with ankle OA is needed.

Individuals with ankle OA commonly present with concomitant varus hindfoot [55,116]. This shift in alignment alters the normal load bearing across the ankle joint resulting in asymmetrical load distribution. A direct correlation between the extent of malalignment and amount of degenerative changes at the ankle has been reported [120]. Key findings from data on tibio-calcaneal and tibio-talar angles suggest that the progressive subtalar joint valgus inclination is an attempt to compensate for tibial varus. It is unclear whether the malalignment was pre-existing and possibly contributed to ankle OA or was a consequence of ankle OA. In individuals with knee joint OA, malalignment predicts a decline in physical function [271], but the effect of alignment on physical function in individuals with ankle OA is yet to be explored.

A number of factors must be considered when interpreting the findings from this systematic review. First, many studies used a convenience sample of individuals with end-stage OA awaiting surgical intervention [238,239,240]. These participants likely have the most severe symptoms and impairments related to ankle OA, which may not represent the broader ankle OA population and limits the generalizability of data. Further research investigating impairments present in the earlier stages of ankle OA is warranted. Second, pooling data and comparison between studies was limited by the populations, comparisons made, and single studies that assessed many measures (e.g., weighted muscle torque [146], calf CSA [239], balance [146], muscle EMG [145,239] and mechanical instability [146]). Third, some studies compared individuals with ankle OA to controls whereas others compared data between affected and unaffected sides in individuals with ankle OA. Evidence from other musculoskeletal conditions of bilateral impairments in individuals with unilateral problems [272, 273-275] suggests that comparison to the unaffected side may not be the most appropriate approach to study impairments in individuals with ankle OA.

Fourth, while there were methodological limitations in the research of physical impairments in individuals with ankle OA, the included studies offered insight into OA related impairments that should be explored by further research. The assessment of study quality highlights the need for future studies to specify validity of outcome measures, include a control (unaffected) group, recruit individuals with ankle OA from the general population, and consider demographics and stage of OA in analyses; to optimize generalizability of findings. Investigation of direction-specific ROM deficits and performance of functional tasks (such as walking and stairs) is needed. Further, longitudinal study designs are necessary to understand the development and progression of physical impairments in individuals with different stages of ankle OA. Finally, to our knowledge this review is the first to study impairments in ankle OA, it has employed a comprehensive strategy with terms that cast a broad net over the literature. However, it may have missed relevant articles with different keywords, an unclear or covert title or abstract, or studies not indexed in the specified databases.

3.5 CONCLUSION

This systematic review assessed the literature and identified issues with the methodological quality of studies investigating physical impairments in individuals with ankle OA. Meta-analyses indicated large impairments in ankle sagittal ROM and torque in ankle OA compared to controls. Single studies suggest that altered joint alignment, impaired standing balance and EMG activity, and limited arthrokinematic movements may be characteristic of ankle OA. Considerations of these impairments may lead to improved outcomes in the management of individuals with ankle OA. Further high-quality research is needed to better understand impairments in the different stages of ankle OA, particularly early OA which has received little attention in the literature, and the relation between specific impairments, function/disability and quality of life.

3.6 KEY POINTS

FINDINGS: Physical impairments are evident in the affected and unaffected sides in individuals with ankle OA compared to controls. In terms of mobility, ankle joints affected by OA are stiffer with less range of motion and translation. Leg muscle weakness and fatty

infiltrate along with altered neuromuscular function are characteristic of individuals with ankle OA. Balance deficits are also present in this population.

IMPLICATIONS: Identified physical impairments associated with ankle OA would likely compromise physical capacity. Targeted interventions to address those specific impairments in torque production, ROM, mechanical and sensorimotor outcomes may lead to improved outcomes.

CAUTION: Data pooling was not always possible due to single studies assessing the measure or different variables collected between studies. Thus, meta-analyses only included a small number of studies which had small sample sizes. This review has not identified different outcomes between stages of OA. Further research is required to assess the impact of ankle OA on individuals with the early-stage disease.

Chapter 4 Cross-sectional studies methodology

As reported in chapter 3, a systematic review of studies investigating physical impairments in ankle OA identified methodological limitations and limited generalisability of findings, which reinforces the need for further research into impairments characterising ankle OA, particularly in those not in end-stage of the condition. To address this gap in the literature, cross-sectional laboratory and survey studies were undertaken to improve our understanding of how ankle symptoms and OA affect physical measures and function, psychosocial health and QoL. This chapter describes the research methodology employed in the cross-sectional studies. Part 1 deals with physical laboratory examination and part 2 deals with self-reported outcomes collected via 2 independent online surveys.

4.1 Cross-sectional laboratory study

4.1.1 Study participants

4.1.1.1 Recruitment methods

Study participants were recruited via community advertising between February 2016 and November 2017. Advertisements targeting individuals aged between 18 and 75 years with and without ankle joint symptoms were placed in a university staff electronic newsletter, and on websites and communications from Arthritis Australia, Arthritis Queensland, Arthritis NSW, and The University of Queensland Ageing Mind Initiative 50+ Registry. Participants were also recruited through social media platforms such as Facebook, Twitter, Nabo, and WeekendNotes (targeting volunteers from different Australian states). The advertisements contained a link to an online screening survey which contained preliminary information about the study and questions to check eligibility. Responders to the online screening survey who met the study eligibility requirements were contacted by phone to confirm eligibility and were invited to participate. Ethical approval was gained from The University of Queensland's Medical Research Ethics Committee (Appendix 5), and all participants provided informed consent prior to participation (Appendix 6).

4.1.1.2 Eligibility criteria

To be eligible to participate in the laboratory study, participants were required to be between 18 and 75 years of age. Similar to criteria in other studies, eligibility for the ankle symptom group was based on an affirmative response to the following question: "Have you experienced any of the following ankle symptoms: 1) Pain or ache in/or around the ankle, 2) Ankle joint stiffness or reduced movement when you wake up in the morning for more than 3 months on most days over the past months?". Individuals in the asymptomatic group were required to have no injury or pain to either ankle or foot within last 12months and no previous ankle surgery. Exclusion criteria for both groups were: pain or injury to other areas of the lower limb or low back in the last 3 months that interfered with participation in daily activities, recreation or sport, or required consultation with a healthcare professional; previous surgery to the lower limb (aside from the ankle in the symptomatic OA group); ankle or foot joint fusion or replacement; any of the following conditions: neurological or vestibular disorders (i.e. stroke, epilepsy or Parkinson disease), peripheral vascular disease, diabetes, rheumatoid or inflammatory arthritis; and unable to be exposed to radiological investigations (e.g. pregnancy).

4.1.1.3 Matching of symptomatic and asymptomatic groups

Participants in the symptomatic and asymptomatic groups were required to be of similar sex and age (±10 years) and were matched for leg dominance (i.e. the leg tested in individuals in the asymptomatic group was matched for dominance to the symptomatic ankle of an individual of similar age and sex in the symptomatic group).The dominant foot was identified using the lateral preference inventory [276]. The inventory measures lateral preference on the four dimensions of handedness, footedness, eyedness, and earedness. Participants were asked four questions concerning foot preference: 1) 'Which foot would you use to kick a ball or hit a target?', 2) 'If you wanted to pick up a pebble stone with your toes, which foot would you use?', 3) 'Which foot would you use to step on a bug?', 4) 'When stepping up onto a chair, which foot would you use first?'. In participants with bilateral symptoms, the ankle with the greater pain or stiffness within the last 3 months was nominated as the symptomatic limb.

4.1.2 The definition of symptomatic ankle OA

Similar to definitions used in hip OA research [277], symptomatic ankle OA was defined as radiographic evidence of OA and symptoms of ankle pain and/or stiffness. Asymptomatic radiographic OA was defined as radiographic evidence of OA with no reported ankle symptoms (pain or stiffness). Evidence of radiographic OA was defined as KL grades of ≥ 2 [277,278,44,279,63] which is a minimum presentation of osteophytes with mild joint space narrowing [280]. Individuals with KL grades of 0–1 (no or doubtful OA) were categorized as no signs of radiographic OA.

4.1.3 Radiographic evidence of ankle OA

A mortise radiographic view of the ankle (an AP-view with the foot/ankle positioned in 10° internal rotation) with the beam centered on the ankle was taken for grading of OA features of the medial and lateral aspects of the tibiotalar and talofibular joints. A lateral ankle view (with the foot/ankle positioned in 15° external rotation) with the beam centered on the medial aspect of the ankle joint was taken for grading of OA features of the anterior and posterior aspects of the tibiotalar and subtalar joints) [280,281]. Assessment of radiographs to determine the presence and grade of OA in the tibiotalar, talofibular and subtalar joints was undertaken using the atlas of radiographic features of OA of the ankle and hindfoot and modified KL scale [280] (Table 4.1). The scale has been validated for defining ankle OA [60]. Radiographs were de-identified by a researcher uninvolved in the study or grading process. Grading of de-identified x-rays was undertaken by two independent assessors (MM and MS).

Table 4.1: Radiographic grades of severity of ankle OA

KL Grade	Description
0	No radiographic findings of OA
1	Minute osteophytes of doubtful clinical significance
2	Definite osteophytes with mild joint space narrowing
3	Definite osteophytes with moderate joint space narrowing
4	Definite osteophytes with severe joint space narrowing

4.1.4 Data collection sessions

4.1.4.1 Laboratory testing sessions

Participants attended a laboratory testing session for assessment of outcomes. Prior to testing, participants rated their current pain level on an 11-point numerical rating scale (NRS) from 0 to 10 (with 0 anchored with the words "no pain" and 10 anchored with "the worst pain imaginable"). The same scale was used to rate pain before and after each outcome tested (functional task, strength, ROM, ankle joint laxity, and plantarflexion endurance). Participants also rated their confidence in their ability to perform the task using an 11-point NRS (´0´ = Not at all confident and ´10´= Completely confident). If a participant reported severe pain or requested to discontinue, then the outcome measure was stopped. All measurements were taken by a single examiner. Participants either attended testing on one occasion (n=98) or on two different days (n=7) depending on participant preference and equipment availability. Participants also attended a local radiography clinic for ankle radiographs as described above.

4.1.4.2 Patient-reported outcomes data collection

Upon completion of the laboratory testing, participants with ankle symptoms, OA and asymptomatic controls were invited to complete an online survey to obtain information on the history of ankle injury, QoL, perceived function, pain, disability, kinesiophobia, ankle instability and physical activity. The survey took approximately 20-30 minutes to complete.

4.1.5 Outcome measures

4.1.5.1 Performance of functional tasks

Performance of tasks involved in daily function were measured using a timed 10-meter walk test and timed stair ascent and decent. The 10-meter walk test has excellent inter-rater reliability for use in healthy participants [282] and has been used with good reliability in adults with foot pain [283]. Participants walked along a 10-meter walkway as quickly as possible without running. Participants started 0.5 m behind a starting line in a stride stance with feet hip-width apart and even weight distribution. Participants were not allowed to transfer weight to their back leg to build momentum to start the test. The participant started walking when signalled by the investigator. The stopwatch was started when the participant

reached the starting line and stopped when the participant crossed the end line. For consistent encouragement of participants to maintain the effort to the end of the test, the phrase "Keep going" was repeated twice as they approach the finish line. The 10-m walk was repeated 3 times with no rest between trials. Time to complete each walking trail was recorded in seconds using a stopwatch, and the fastest of the 3 trials was used for analysis.

Stair ambulatory function was assessed using timed ascent and descent tests. This outcome measure has been used to assess function in other OA populations [284] and has been shown to have good inter-rater reliability in individuals with knee OA [285]. Study participants were instructed to descend a set of 20 stairs (17.5 cm high, 26 cm deep) as quickly as possible. Participants started at the top of the stairs in stride stance and with the feet hip-width apart. Time to complete the stair descent was recorded with a stopwatch which was started when the participant's first foot was lifted from the floor. The stopwatch was stopped when one of the participant's feet touched the floor below the bottom step. The same process was repeated to measure the time taken to ascend the set of stairs with the stopwatch stopped when the participant's foot reached the floor above the top step. Time to complete each test was recorded in seconds. Each test was repeated 3 times with a 1-minute rest between trials. The fastest of 3 trials was used for analysis.

4.1.5.2 Muscle strength and joint torque

Maximum isometric ankle dorsiflexor, plantar flexor, invertor, and evertor muscle strength was measured using a custom-build device and a portable hand-held dynamometer (HHD; 01165 manual muscle tester, Lafayette Instrument Company, USA). This HHD has been reported to be reliable and valid for measuring hip, knee [286] and ankle strength [287] in research and clinical practice [288]. The device consisted of a square wooden bench on which the participant's leg rested (secured to the bed with G clamps) and a vertical piece of wood at the distal end which was positioned against the plantar aspect of the participant's forefoot. A wooden wedge placed between the vertical piece of wood and the participant's heel to position the foot in slight plantarflexion. Two Velcro straps secured the lower leg to the testing device to minimize movement. Torque testing was undertaken in a set order. When testing symptomatic participants, the asymptomatic/less symptomatic side was assessed first.

For testing ankle dorsiflexion, plantarflexion, eversion and inversion participants were positioned supine with the knee and hip flexed to 90° (Figure 3-1.A). A rigid belt around the distal thigh (just above the knee) and vertical piece of wood were used to secure the thigh to the device and minimise the effect of knee movement on testing (Figure 3-1.B).

Ankle plantarflexion muscle strength testing was also performed with knee and hip extended (Figure 3-1.B). For this testing position, the wooden bench was removed and a rigid belt passed around the vertical piece of wood and over the shoulder to secure the participant to the device and minimize the effect of body movement on testing. The positioning of the HHD for each muscle group testing is shown in Figure 3-1 B-D. For dorsiflexion and plantarflexion strength, the HHD was placed against the metatarsal heads at the dorsum or plantar surface of the foot respectively (Figure 3-1.B and C). The HHD was placed against the first metatarsal head medially to test inversion strength, and against the head of the fifth metatarsal laterally to test eversion (Figure 3-1.D and E).

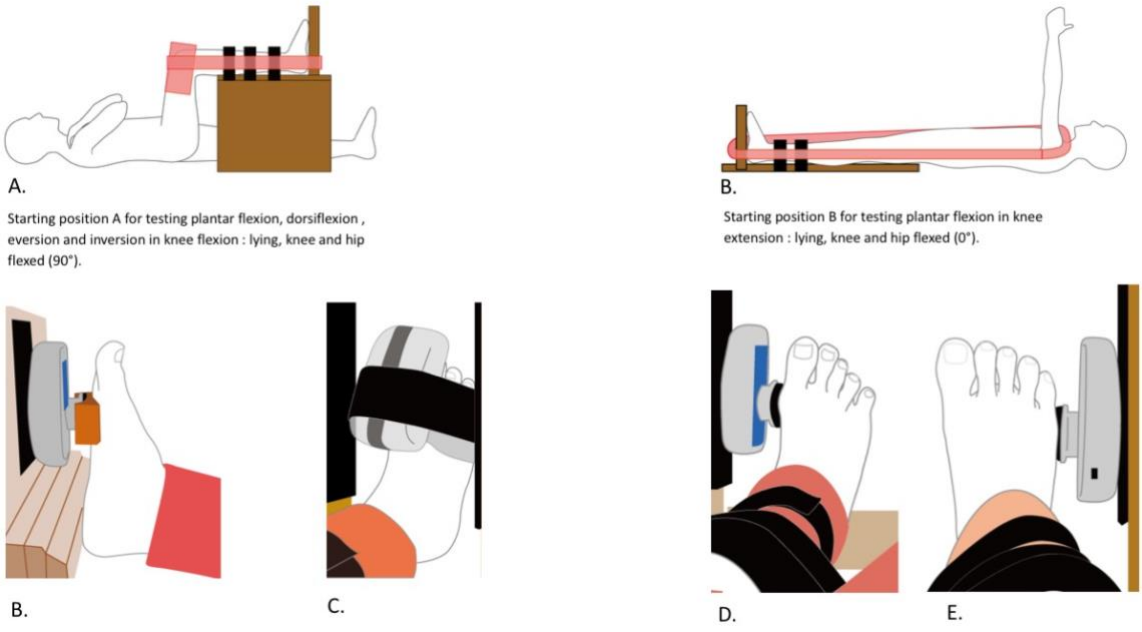

FIGURE 4. 1: Starting position and HHD placement for torque testing.

Participants were instructed to minimize hip and knee movement during testing and cross their arms over the chest. The movement to be performed was demonstrated, followed by a submaximal contraction (~50% of perceived maximal contraction) for familiarisation, and

then a practice contraction at 100% maximum voluntary contraction (MVC). Each participant was encouraged to perform MVC lasting for 5 seconds, with consistent verbal encouragement throughout testing. Each measurement was repeated 3 times with a 1-minute recovery time between measures. The mean force generated across trials was assessed. Torque was calculated by multiplying the force (measured in Newtons (N)) by the lever arm length (measured in meters (m). The lever arm was measured from the center of first metatarsal head medially to the center of the medial malleolus [289]. Torque data was normalized to body weight in kilograms (kg) and presented as Nm/kg.

4.1.5.3 Bent knee dorsiflexion range of motion (ROM)

Ankle dorsiflexion ROM was measured using a custom-built lunge ankle dorsiflexion measurement device (Figure 3- 2) and established testing procedures with excellent inter- and intra-rater reliability [290-292]. The participant stood on the measurement device with their longest toe just touching a front vertical upright. The mid-calcaneum of the test foot and web space between the second and third toe was placed on a line on the base of the device and the mid patella was placed on a line on the upright of the device. This foot and knee position was maintained throughout testing to avoid compensatory subtalar pronation [293]. The non-test leg was positioned with the heel in line with the longest toe of the test foot, and two fingers rested on a wall for balance.

The participant slowly lunged forward (the knee moving the vertical upright forward), with the heel maintaining contact with the floor, until they were unable to go any further. The assessor ensured maintenance of heel contact with the ground via verbal instructions, visual examination, and palpation. This was repeated five times per limb for familiarization, followed by four test trials per ankle. Participants were blinded to the outcome of previous trials to prevent motivational effects [294]. Maximal dorsiflexion ROM was defined as the maximum displacement of the anterior knee (resting on the device upright) measured in millimeters. The average of four DF measures was used for analysis

If a participant was unable to touch the upright with their knee when it was positioned at the end of the longest toe, the upright was moved to touch the knee (Figure 4. 4). The participant was then asked lunge forward as far as possible as described above. The measure

was recorded as the negative distance of the anterior knee/device upright and the longest toe (negative measure) [295].

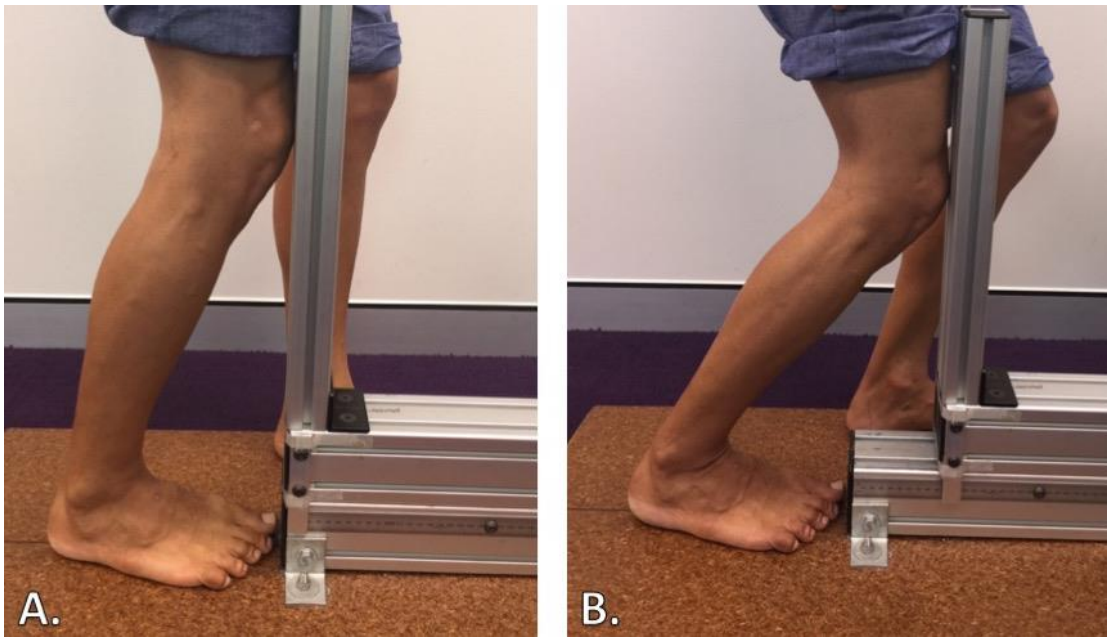

FIGURE 4. 2: Measure of ankle dorsiflexion ROM (A: starting position, B: end position)

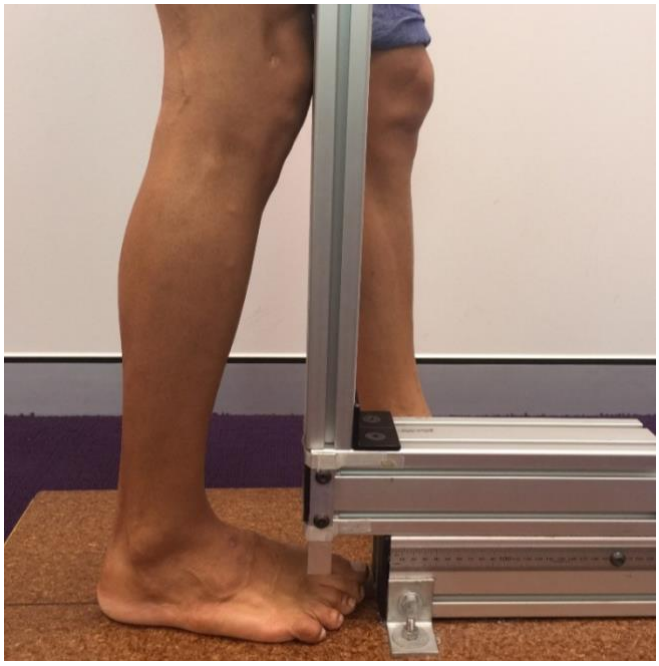

Figure 4. 3: Bent knee dorsiflexion ROM measurement for a severely compromised range

4.1.5.4 Ankle-subtalar joint laxity

A portable Hollis instrumented ankle arthrometer (Blue Bay Research Inc., Navarre, L) was used to quantify joint laxity at the ankle using a previously described procedure [296]. The reliability of ankle arthrometer has been established [296,297,298]. The participant was positioned in supine with the foot extended over the edge of the plinth. The lower leg was secured to the plinth with a strap placed above the malleoli. The foot was fixed to the arthrometer using clamps placed around the heel, at the dorsum of the foot and on the lower tibial. To begin all tests, the ankle was placed in a position of neutral dorsiflexion-plantarflexion and inversion-eversion [299]. An anterior load of 125 N was applied to the ankle joint to measure anterior displacement, with a similar posterior load applied to measure posterior displacement. For inversion-eversion rotation, a 4 Nm load was applied to the ankle, rotating it clockwise and then counter-clockwise. For all directions, the load was applied in a slow, controlled manner by the same examiner and stopped when the maximal load was reached (represented on a graphical interface as 125 N for anterior and posterior displacement and 4 Nm for inversion and eversion rotation). Each outcome was repeated 3 times and the mean value for each direction (Anterior and posterior displacements recorded in millimetres and inversion and eversion rotations in degrees) was calculated from exported raw files and was used for analysis.

4.1.5.5 Foot posture

The static foot posture was assessed using The Foot Posture Index (FPI). This is a valid and reliable [300] method of classifying foot postures as either pronated, supinated or normal, based on observations of six visual foot posture criteria. As per published protocol [301], participants were asked to march on the spot prior to settling into a relaxed double limb support stance, looking straight ahead with arms by the side. Observations of talar head palpation, curves above and below lateral malleolus, inversion /eversion of the calcaneus, talonavicular congruence, medial arch height and forefoot abduction /adduction were rated on a scale from -2 to +2. Total scores ranged from -12 to +12. Scores 0 to 5 denotes a normal foot posture, 6 to 9 a pronated posture, >10 a highly pronated posture, -1 to -4 a supinated posture, and -5 to -12 a highly supinated foot posture.

4.1.5.6 Foot mobility

Three different variables pertaining to foot mobility were assessed: difference in dorsal arch height (DAHDIFF), the difference in midfoot width (MFWDIFF) and the foot mobility magnitude (FMM) using the Foot Assessment Platform (Figure 4.4). Dorsal arch height (DAH) and midfoot width (MFW) was measured in both weight-bearing and non–weight-bearing, using a previously described protocol [302].

For weight-bearing measures, participants stood with equal weight on both feet on a foot measurement platform. Heels were positioned in heel cups 15.24 cm apart. To ensure consistent forefoot placement on the platform, a sliding first metatarsophalangeal joint indicator was positioned over the medial prominence of the first metatarsal head. Weight-bearing measurements included 1) foot length measured as the distance from the posterior tip of the heel to the tip of the longest toe; 2) 50% of the total foot length determined by dividing the measured total foot length in half; 3) dorsal arch height (DAH) measured as the vertical distance from the dorsal to plantar surface of the foot at 50% of total foot length and 4) midfoot width (MFW) measured as the distance from the medial to the lateral aspect of the foot at 50% of total foot length.

For the non-weight-bearing measurements, participants sat at the edge of a bed with thighs fully supported and knees in 90^{o} flexion. Measurements of DAH and MFW were taken using a portable platform lightly positioned under the plantar surface of the test foot. Foot mobility was calculated as the difference between weight-bearing and non-weight-bearing DAH and MFW. Foot mobility magnitude (FMM), a composite measure representing a change in both DAH and MFW, was determined using the following formula: FMM= square root of $(\text{Difference DAH})^2 + (\text{Difference MFW})^2$.

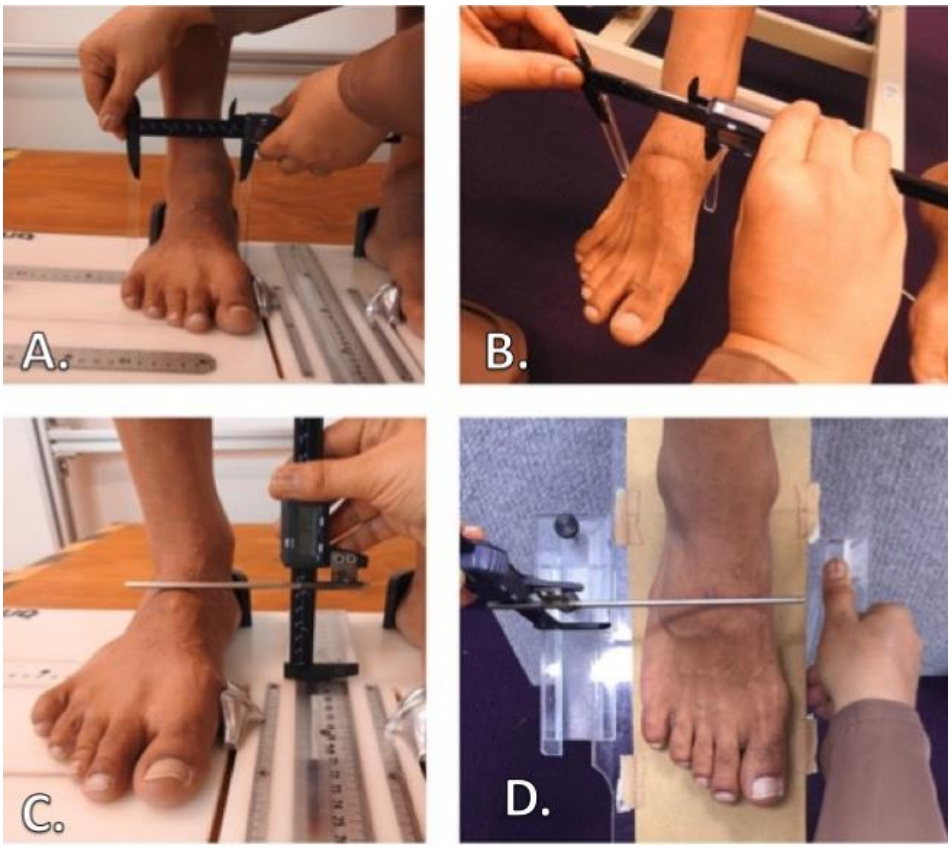

Figure 4. 4: Measure of mid-foot width (A: weight-bearing, B: non-weight-bearing) and dorsal arch height (C: weight-bearing, D: non-weight-bearing)

4.1.5.7 Plantarflexion endurance

Plantarflexion endurance was assessed using a custom built device based on that reported in previous research [303]. Participants stood on one leg facing a wall and placed fingertips against the wall for support. The knee of the non-test limb flexed to clear the foot from the floor. Heel raise height was standardized as 80% of the maximal height achieved when the participant lifted the heel as high as possible off the ground. A horizontal rod placed at the anterior ankle joint crease was used to measure maximal heel raise height, from which 80% height was calculated. The rod was then adjusted to 80% maximal height. The participant raised the heel up and down to the height of the horizontal rod at a pace cued with a metronome set at 46 beats/min (23 lifts/min) [304,305]. Participant continued to raise and lower the heel at the metronome pace until: vertical displacement fell below 80% of maximum for two consecutive repetitions, the participant leaned on the wall with more than fingertip

support or had decreased wall-to-body distance that was not corrected after one verbal warning, the non-tested leg touched the floor a second time after one verbal warning, the participant was unable to maintain pace with the metronome for two consecutive heel raises. This test was performed twice with a 1-minute rest between trails. The total time in seconds was recorded for each trial and the average time was used for analysis.

Figure 4. 5: Plantarflexion endurance testing (A: starting position, B: end position)

4.1.6 Assessment of measurement reliability

Inter-rater reliability of radiographic assessment completed by two independent assessors was performed using SPSS V.25 software (SPSS Inc, Chicago, Illinois, USA). Data from both left and right ankles in symptomatic individuals and the single matched ankle in asymptomatic individuals were used, with each ankle considered a separate unit in the analysis. This approach is considered appropriate to compare two sets of measurements and not to draw conclusions regarding individual subjects [306]. Kappa (κ) Statistics were used to

report the total inter-rater reliability which was interpreted as poor (<0.00), slight (0.00–0.2), fair (0.21–0.4), moderate (0.41–0.6), substantial (0.61–0.8) or almost perfect (0.81–1.0) [234].

The intra-rater reliability of physical measures was evaluated in a small sample of healthy adults, who were tested twice a minimum of seven days apart. Reliability was interpreted as: very good for intraclass correlation coefficients (ICCs) >0.9, good for ICCs 0.75-0.89, and moderate for ICCs 0.5 and 0.74 [307]. The reliability coefficients (one-way (ICCs)) were used to generate a measure of absolute reliability (standard error of measurement (SEM)), using the formula: (*SEM = SD X √(1 – ICC))* [308]. The following formula*(MDC = 1.96 X SEM X √2)* was used to calculate minimal detectable change (MDC) at the 95% confidence limit [309]. Results of reliability testing for the different outcomes are reported in Appendix 7.

4.2 Patient-reported outcomes

The cross-sectional surveys comprised of two independent online surveys designed to capture measures of pain, disability, function, QoL, falls related measures, work limitation, psychosocial variables as well as generic health data. These outcomes were measured to provide information on the body function and structure (pain, stiffness, instability), activities (ADL activities, balance confidence), participation (FAAM-Sport, physical activities, work) and contextual factors (comorbidities, multiple pain sites, pain self-efficacy,) domains of the ICF and QoL. An enhanced version of the online survey software (SurveyMonkey) was utilised to assemble and create the surveys and for data collection. This section provides detail information about the survey participants and a description of participant recruitment procedures employed in the cross-sectional surveys. Each survey took 20-30 minutes to complete.

4.2.1 Study participants

4.2.1.1 Recruitment method

The sample for each survey was recruited at a different time with independent community and social media advertisements via UQ Update, Twitter, Nabo, WeekendNotes and paid online advertising via Facebook. Advertisements were also placed on websites of Arthritis Australia, Arthritis Queensland, Arthritis NSW, and The University of Queensland Ageing Mind Initiative 50+ Registry. A variety of advertisement pictures were chosen to cater

to the target demographics. Pictures such as ankle joint, swollen ankles, sprain, and sports participation were used. Flyers were distributed to community sports-venues such as soccer, football and bowling clubs in Queensland and masters sporting groups e.g. Queensland Volleyball Association and Queensland Rugby League. All participants were asked to indicate the state they reside. At the completion of physical testing, participants were invited to complete an online survey.

4.2.1.2 Eligibility criteria

For the surveys, the participants were adult volunteer aged 18 to 82 years. To ensure that the survey retains an adequate sample size to offer valid results, the sample was drawn from Australian states and included symptomatic people who suffer ankle pain or stiffness lasting >3 months and asymptomatic controls.

4.2.2 Data and outcome measures

The severity of pain and stiffness was measured using separate 11-point NRS. The NRS has been reported as a valid and reliable measure of knee OA pain with an excellent test-retest reliability (ICC= 0.95) [310]. Participants rated their ankle pain at rest, average ankle pain over the past 24-hours, and worst pain over the past 7 days using NRS anchored at 0 with “no pain” and at 10 with “worst pain imaginable”. Similarly, participants rated their usual level of ankle stiffness felt over the past week on 11-point NRS anchored at 0 with “no stiffness” and at 10 with “worst stiffness imaginable”.

Number of musculoskeletal pain sites was assessed using a labeled body diagram as a reference. Participants rated the pain felt during the past 7 days in 13 musculoskeletal sites (including the ankle) using NRS where 0 is 'no pain' and 10 is 'the worst pain imaginable'. Participants were advised to select 0 if no pain was experienced in the body site. The number of bodily pain sites is the sum of the affirmed sites with a pain score of ≥2including the ankle.

A modified version of the 13 item-*Self-Administered Comorbidity Questionnaire (SCQ)* was used to collect data on comorbid health conditions [311]. The test-retest reliability for the original SCQ validated in patients with surgical and medical conditions was (ICC= 0.94) [311]. For the current study, the SCQ was adapted by adding auto-immune disease and gouty arthritis to the list of comorbid conditions and by rephrasing the question related to OA to specifically

indicate OA other than the ankle. Testing of psychometric properties of this modified SCQ was not undertaken. Participants indicated if they experienced any of the following 15 medical problems: heart disease, high blood pressure, lung disease, diabetes, ulcer or stomach disease, kidney disease, liver disease, anaemia or other blood disease, cancer, depression, auto-immune disease, back pain, rheumatoid arthritis, gouty arthritis and OA other than ankle). They were also asked if they received treatment for any of the defined health problem and whether it limited their activities. The number of comorbidities that participants reported they were receiving treatment for were summed (scores ranging from 0-15). This was calculated as an indication of multi-morbidity [312].

Quality of life was assessed using the *Assessment of Quality of Life questionnaire (AQoL-6D),* which is an Australian instrument with age- and gender-based population norms [313]. It comprises 20 questions in 6 dimensions (independent living, mental health, coping, relationships, pain, and senses). The unweighted responses of all questions were added to create an overall profile score (0-100) and individual scores for each of the six dimensions. Higher scores indicate better QoL. This instrument has been shown to have strong construct validity [314] and discriminative validity for use in OA populations [315]. Test-retest reliability (ICC=0.85-0.88) for this measure has been reported [316].

Function was measured using the *Foot and Ankle Ability Measure (FAAM)* [317]. This questionnaire consists of 21-item activities of daily living subscale (FAAM-ADL) and an 8-item sports subscale (FAAM-sport). Each item is scored on a 5-point Likert scale ranging from 'no difficulty' (4) to 'unable to do' (0). A "not applicable" option is available to indicate activities limited by factors other than foot or ankle problems, with these items removed from scoring. The total score (sum of responses) is converted to a percentage, with a higher percentage indicating a higher level of function. Test-retest reliability (ADL subscale; ICC= 0.87 and Sports subscale; ICC= 0.89) and internal consistency of the FAAM have been reported [317].

The Ankle Osteoarthritis Scale (AOS) is a disease-specific instrument used to assess pain and disability related to ankle OA. It contains pain and disability subscales, each of which has nine questions. Participants indicated how much pain and difficulty they experienced when performing certain activities over the past week, such as walking barefoot, standing barefoot or standing on tiptoes. The original scoring of the two subscales is measured along a

100-mm visual analogue scale (VAS) anchored with “No pain/difficulty” (0 mm) and “Worst pain imaginable/So difficult, unable” (100 mm). To enable this questionnaire to be used in an online format, an 11-point (0-10) NRS was used rather than a 100 mm VAS, with the same anchors as the original scale. The original AOS has been reported to be reliable (ICC= 0.94 to 0.97) and valid for individuals with ankle OA [318].

Perceived ankle instability was measured using *The Cumberland Ankle Instability Tool (CAIT)* [319]. This tool contains 9-items with scores assigned based on the rank of the chosen response [319]. Responses are summed separately for each limb. The maximum score is 30 with a higher score indicating less instability. The CAIT has been shown to be a reliable (ICC=0.96) and valid measure of instability in individuals with a history of recurrent ankle sprain [319].

Kinesiophobia was measured using The *Tampa Scale of Kinesiophobia (TSK-11)* [320]. It comprises 11 statements about the perception of movement that are scored on a 4-point Likert scale ranging from 1= strongly disagree to 4= strongly agree. Examples of statements include “My body is telling me I have something dangerously wrong’, and “I can't do all the things normal people do because it's too easy for me to get injured”. The answer to each question is summed to produce a total score from 0 to 44, with higher scores indicate a high degree of kinesiophobia. This scale has good internal consistency (Cronbach’s α=0.79) and test-retest reliability (ICC=0.81) [321].

The short form of the International Physical Activity Questionnaire (IPAQ-SF) was used to measure physical activity [322]. The total amount of time spent performing moderate, vigorous activities, walking or sitting in bouts of 10 minutes or greater over the last 7 days was recorded [322]. The IPAQ categorizes physical activity as “low”, “moderate” or “high". Published guidelines for data processing and analysis of IPAQ-SF were used (available from: http://www.ipaq.ki.se). Validity and test-retest reliability (ICC = 0.51) in hip and knee OA population has been reported [323].

Falls history in the last 12 months was determined by the question: “In the last 12 months, have you had any falls?”. A fall was defined as “an event which results in a person coming to rest inadvertently on the ground or floor or other lower level” [324]. Participants were categorised as fallers (an individual who fell at least once over the last 12 months [325]) or

non-fallers. Participants indicated the number of falls they experienced in the past 12 months, if they sustained an injury from falling, the type of injury experienced (i.e. bruises, cuts/grazes, sprain/strain, broken bones, dislocation), and if any fall resulted in hospitalization.

The Falls Efficacy Scale-International (FES-I) is a short falls efficacy survey with an excellent internal and test-retest reliability (Cronbach's alpha=0.96, ICC=0.96) [326]. The FES-I was used to determine how concerned a person is about the possibility of falling when doing 16 different basic and more challenging physical (inside and outside the home) and social activities. The level of concern was rated using a four-point Likert scale (1=not at all concerned to 4=very concerned) [326]. The total score is a sum of scores that range from 16 to 64. A higher score indicates a greater fear of falling. Cut off –points are defined as to differentiate between low, moderate and high concern (16-item FES-I: 16–19, 20–27 and 28–64) [327].

To measure balance confidence when performing activities of daily living, *The Activities-Specific Balance Confidence Scale (ABC)* was used. It estimates the percent self-confidence that one would not lose balance during 16 separate theoretical activities; ranging from walking around the house to walking on icy sidewalks [328]. Participants rated confidence in performing each activity, with a score from (0%=not confident at all to 100%=completely confident) in increments of 10%. ABC score is the total ratings (possible range = 0 – 1600) divided by 16 which is an indication of balance confidence. Scores below 68 correlate with high fall risk [329]. Reliability of ABC in symptomatic knee OA was ICC= 0.95 [330].

The Hospital Anxiety and Depression Scale (HADS) [331] was used to rate anxiety and depression in the participants' sample. Participants were required to select the most appropriate response about how they have felt over the past 7 days to 14 statements where seven statements relate to anxiety and seven relate to depression. Each item is scored from 0-3, HADS responses are summed to obtain an anxiety score and a depression score. Scores range from 0 to 21 for either anxiety or depression. A score of 8/21 is identified as a cut-off point for anxiety or depression [332]. The total score can be used as a measure of global negative affect. Scores 8 to 10 indicate mild, 11 to 15 indicate moderate and scores ≥ 16 indicate severe anxiety or depression. The HADS is a valid scale for assessment of the

symptom severity, anxiety disorders and depression in different health conditions and in the general population [332]. The reliability for HADS (Cronbach's alpha 0.68 -0.93 for HADS-A) and (Cronbach's alpha 0.67 -0.90 for HADS-D) has been reported [332]. The HADs was reported as a good predictor of interview-diagnosed anxiety in a population with lower limb OA [211].

The Workplace Ability Limitation Scale (WALS) used to measure the extent to which health conditions interfere with the performance of workplace activities. It is comprised of 12 items, each item is rated on a four-point Likert scale (0=No difficulty to 3=not able to do). Not applicable to my job and difficulty unrelated to ankle response options are also available (both scored 0). Examples of statements are: "How much difficulty do you have getting to and from work (e.g., subway, bus, car, walking) and getting to and from work on time?", "How much difficulty do you have getting around the workplace (e.g., stairs, hallways, furniture)?" and "How much difficulty do you have standing for long periods of time at your job (e.g., more than 20 minutes)?". Higher scores indicate greater workplace activity limitations. WALS is identified as a preferred instrument for measuring productivity in workers with arthritis, it has high internal consistency and construct validity and was found to be the most responsive questionnaire to a perceived change in workplace ability in people with arthritis [333]. Reported reliability for WALS was Cronbach's alpha =0.87 in working populations with arthritis [333]. Scores of 0-4 indicate little work difficulty; scores of 5-8 reflect moderate disability related to workplace adaptations, and scores >9 indicate considerable workplace disability [334].

A 2-Item Short Pain Self-Efficacy Questionnaire(PSEQ-2) [335] which is an abbreviated 2 item pain self-efficacy tool was used to assess pain self-efficacy. The tool consists of two questions stating: "I can do some form of work, despite the pain (''work'' includes housework and paid and unpaid work)" and "I can live a normal lifestyle, despite the pain". The tool highly correlated with that of the original PSEQ. The test-retest reliability for PSEQ-2 was ICC=0.87, 95% CI =0.80- 0.91 in a heterogeneous population with chronic pain [335]. The total score is the sum of responses on the 2 items; range from 0 to 12 with a score of ≥8 indicating high self-efficacy and scores ≤ 5 indicating the need for assistance with confidence in functioning [335].

Pain Catastrophizing Scale (PCS), a 13-item reliable and valid self-report scale for catastrophizing [336]. The test-retest in a population with chronic pain is ICC= 0.67 [337]. The PCS

items are rated on a scale from 0= not at all and 4= all the time. A total score (range from 0-52) is a sum of all 13 item responses. Pain Catastrophizing Scale yields three different categories: Rumination (Sum of items 8, 9, 10, 11), Magnification (Sum of items 6, 7, 13) and Helplessness (Sum of items 1, 2, 3, 4, 5, 12). A total score of ≥30 is indicative of clinically relevant levels of catastrophizing [336].

4.7 Data management and statistical analyses

Detailed statistical procedures and analyses specific to each study within the thesis are outlined in the respective chapters. Extracted data variables were entered into Excel spreadsheets (Microsoft® Office Excel version16.13.1) for data management and analysis. All statistical analyses were completed using IBM®SPSS Statistics for Windows V.25.0 software (SPSS, Chicago, Illinois, USA).

4.8 Conclusion

This chapter has outlined the participant recruitment methods, measurement procedures and statistical methods underpinning the cross-sectional studies described in chapters (5- 9) of the thesis. The study findings, discussion, and conclusions from the cross-sectional studies are reported in respective chapters and in Chapter 10.

Chapter 5 Physical impairments and quality of life in individuals with ankle osteoarthritis: A cross-sectional laboratory study

5.1 Introduction

Ankle OA affects over 75 million adults worldwide [43,45]. Unlike hip and knee OA, ankle OA is typically post-traumatic in origin and occurs earlier in life [14,15,17,18,129] (possibly due to the majority of traumatic events occurring earlier in life and the reduced ankle OA onset latency following severe ankle sprains [13]). Although the investigation of the physical impairments associated with ankle OA is limited, evidence from a recent systematic review [338] reported that individuals with ankle OA have less ankle joint range of motion (ROM), strength, and altered ankle joint alignment compared to healthy controls. A single study has shown limited arthrokinematic joint mobility and poorer standing balance in this population [146]. Ankle OA is associated with poor QoL compared to the general population [173,214]. A limitation of previous research is that it focussed on individuals with end-stage ankle OA which limits the generalizability of those findings to the broader ankle OA population who are not candidates for ankle joint surgery. To optimise the management of ankle OA across the spectrum of disease severity, it is important to understand the physical impairments that characterise the condition and the relationship between impairments, function, and QoL. Such understanding could assist with the management of individuals with ankle OA and the selection of outcome measures used to determine treatment effectiveness in clinical and research settings.

It is becoming apparent that radiographic evidence of OA does not correlate well with symptoms in a range of musculoskeletal disorders [339,340]. For example, there is evidence that radiographic findings of knee OA may not closely relate to either symptoms or impairments [341,342]. However, the relation between radiographic evidence of ankle OA and ankle symptoms remains to be investigated. An improved understanding of that relationship could influence the assessment and management of individuals with ankle pain and disability.

The primary aim of this study was to compare physical measures (ambulatory function, ankle muscle strength, endurance, ROM, ankle -subtalar joint laxity, foot mobility and posture) and patient-reported outcomes (QoL, function, pain, disability, ankle instability,

kinesiophobia and physical activity) between the following groups: 1) symptomatic (pain or stiffness) individuals with radiographic evidence of ankle OA and individuals without any ankle symptoms (asymptomatic), and 2) asymptomatic individuals with radiographic evidence of ankle OA and asymptomatic individuals without radiographic evidence of ankle OA. A secondary aim was to explore the relationship between QoL, self-reported function and physical measures.

5.2 Methods

In order to identify the physical impairments that characterise individuals with ankle OA, this cross-sectional clinical laboratory study compared physical measures and patient-reported outcomes between individuals with and without ankle symptoms to ascertain the influence of ankle symptoms on the assessed outcomes, and between asymptomatic individuals with and without radiographic evidence of OA to ascertain the influence of radiographic OA on the assessed outcomes.

5.2.1 Participants

Symptomatic and asymptomatic individuals were recruited via community newsletters, social media and flyers between February 2016 and November 2017. Respondents were screened for eligibility using an online survey and via the telephone. Individuals were defined as symptomatic or asymptomatic based on the presence of ankle pain and stiffness. Individuals who reported pain or aching in or around the ankle and stiffness or reduced movement in the morning on most days for greater than 3 months and no lower limb injury within the last 12 months were defined as symptomatic. Individuals who reported no ankle pain/ache, stiffness or injury to the ankle or foot in the last 12 months and no previous ankle surgery were defined as asymptomatic. There was no specific definition of 'ankle' shared with participants. However, all participants underwent screening and physical exam prior to laboratory testing to discern the presence or absence of symptoms as well as locality of the symptoms. Asymptomatic participants were required to be of similar sex, and age (±10 years) to the symptomatic participants.

Individuals were excluded from participation in this study if they had pain or an injury in the lower limb (other than the ankle in the symptomatic group) or low back in the last 3

months that interfered with participation in daily activities, recreation or sport, or required consultation with a healthcare professional. Individuals were also excluded if they reported a history of previous lower limb surgery (other than surgery related to a previous ankle injury in symptomatic individuals), neurological or vestibular disorders, peripheral vascular disease, diabetes, rheumatoid or inflammatory arthritis, or if they were unable to undertake radiological investigations. Ethical approval was received from the institutional Human Research Ethics Committee and all participants provided informed written consent prior to participation.

5.2.2 Ankle OA definition

Mortise and lateral radiographic views of the ankle were captured and used to determine the presence and grade of ankle OA. Bilateral ankle x-ray images were captured for symptomatic individuals but due to the absence of clinical indication and associated radiation risks, only the matched ankle was imaged in the asymptomatic group. The test leg of asymptomatic participants was matched for dominance to that of the symptomatic participants prior to grouping based on radiographic findings. The dominant foot was determined according to the lateral preference inventory [276]. The modified Kellgren and Lawrence scale [280] was used to assess radiographs and identify radiographic features of OA at the talo-crural and subtalar joints. This scale has been validated for defining ankle OA [60]. Similar to definitions used in other studies [277,44,63,278,279], radiographic ankle OA was defined as a Kellgren and Lawrence (KL) grade of ≥ 2 (definite osteophytes with mild-severe joint space narrowing [280]). Participants with KL grades 0–1 (no radiographic findings of OA and minute osteophytes of doubtful clinical significance were categorized as non-OA. Radiographic assessment on de-identified x-rays was undertaken by two independent assessors (MM and MS).

5.2.3 Physical outcomes

For the assessment of unilateral physical outcomes (muscle strength, heel raise endurance, ROM, ankle-subtalar joint laxity, foot mobility, and posture), data from both sides in the symptomatic group and from the matched ankle in the asymptomatic group were analysed. Before and after each physical test, participants rated their current pain intensity on

an 11-point NRS anchored with “No pain” at 0 and “Worst pain imaginable” at 10. All physical outcomes were administered by a single examiner (MM) in a standardised order. When testing symptomatic participants, the asymptomatic/less symptomatic side was measured first. To determine intra-rater reliability, physical measures were evaluated in a small sample of healthy adults, with test-retest measures obtained a minimum of seven days apart.

5.2.3.1 Ambulatory function

Walking speed was assessed over a 10-meter distance. Participants started 0.5 m behind the “start line” and walked as quickly as possible for 10 metres across the ‘finish line’. Stair performance was assessed using timed ascent and descent tests. Participants were instructed to ascend/descend a set of 20 stairs (17.5 cm high, 26 cm deep) as quickly as possible. Time to complete each task was recorded in seconds using a stopwatch. Each test was repeated three times and the fastest time was used for analysis.

5.2.3.2 Ankle muscle torque

Maximum isometric ankle dorsiflexion, plantar flexion, inversion, and eversion muscle strength was measured with a handheld dynamometer (HHD) (01165 manual muscle tester, Lafayette Instrument Company, USA). Handheld dynamometry is a reliable and valid method for measuring muscle strength [287]. Torque measurement was undertaken in a set order. Participants were positioned in supine with the knee and hip flexed to 90° (Figure 5.1). Plantarflexion torque was also measured with the knee and hip extended (Figure 5.1). The HHD was secured to foot at the level of centre of the first metatarsal head using an external device (Figure 5.1). Participants were instructed to push as hard as they could into the device, building up to MVC over 5 seconds. For familiarization, two practice contraction were performed first: one at approximately 50% MVC, and a second at 100% MVC. Following this, three MVCs for each strength measure was performed with a 1-minute rest between repetitions. Consistent verbal encouragement was used throughout testing. Ankle joint torque was calculated by multiplying the muscle force (measured in Newton’s (N)) with the lever arm length (measured in meters (m)). The lever arm for all movement directions was the distance between the centre of the first metatarsal head (HHD position) and the centre of the medial malleolus (used to represent the axis of rotation of the ankle joint). Torque was

normalized to body weight (measured in kilograms (kg)) and presented as Nm/kg. The average of three torque measures was used for analysis.

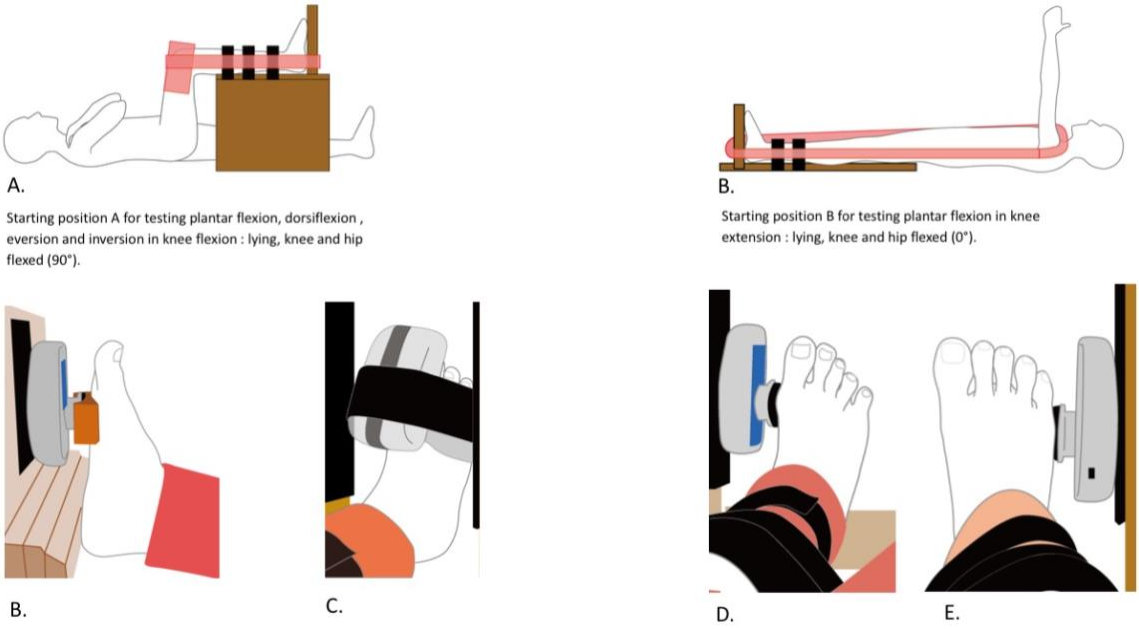

FIGURE 5. 1: Starting position and HHD placement for torque testing

5.2.3.3 Plantar flexion (Heel raise) endurance

Plantar flexion endurance was assessed by having participants perform single leg heel raises until fatigue. Participants stood on one leg (knee extended) on a custom-built device with the non-weight-bearing knee bent to 90° [303]. Heel raise height was standardised as 80% of the maximal height achieved when participants lifted their heel as high off the ground as possible. A horizontal rod at this height was set at the anterior ankle crease at this point. Participants performed heel raises to this pre-determined height at a pace of 23 lifts/minute controlled by a metronome [304,305] downloaded from App store. The test was stopped when the participant was unable to reach the rod or keep pace with the metronome for two consecutive heel raises, leaned on the wall or used the wall for assistance after one verbal warning, the non-weight-bearing leg touched the floor, or the participant was unable to continue due to pain or fatigue. This test was performed twice with a 1-minute rest between

trails. The total time in seconds was recorded for each trial and an average time was used for analysis.

5.2.3.4 Ankle dorsiflexion ROM

Dorsiflexion (DF) ROM was measured with a custom-built device during the weight-bearing lunge test using a previously described protocol [291]. This test has excellent inter- and intra-rater reliability [290,291]. Participants stood with their mid-calcaneum and web space between the second and third toe on a line on a platform and their longest toe just touching an upright [293]. With the knee resting on a vertical upright (and the patella aligned with the web space between the second and third toe), participants lunged their knee forward into DF ROM to move the vertical upright [292]. Participants were required to maintain heel contact with the floor at all times, and the knee remained aligned between the second and third toe. For familiarisation, five practice trials were completed before the test then the test was repeated four times on each side for data collection. Maximal DF ROM was defined as the distance between the end of the longest toe and the maximal horizontal projection of the knee measured in millimetres. Positive values indicate movement of the knee beyond the longest toe, and negative values indicate movement short of the longest toe [295]. The average of four measures was used for analysis.

5.2.3.5 Ankle -subtalar joint laxity

Anterior-posterior and inversion-eversion ankle joint arthrokinematics were assessed using a portable ankle arthrometer (Hollis instruments, Blue Bay Research Inc., Navarre, FL). Testing was based on a previously reported protocol with demonstrated reliability [296-298,343]. Participants were positioned supine with the foot extended over the edge of a plinth and the leg secured using a strap placed superior to the malleoli. The foot was fixed to the arthrometer using clamps around the heel and the dorsal side of the foot and tibia. To begin all tests, the ankle was placed in a neutral position (0° dorsiflexion/plantar flexion). To measure anterior displacement, an anterior load of 125 N was applied to the ankle joint. The same load was applied posteriorly to measure posterior displacement. For inversion-eversion rotation, a 4000N/mm load was applied to the ankle, rotating it into inversion and then eversion. For all directions the load was applied in a slow, controlled manner and was

stopped when the maximal load was reached (125 N for anterior and posterior displacement and 4000 N for inversion and eversion rotation). Joint laxity testing was stopped if the participant experienced pain during the assessment. Testing in each direction was repeated three times. The mean value for each direction was calculated from exported raw files and was used for analysis. Anterior and posterior displacements were recorded in millimetres and inversion and eversion rotations in degrees.

5.2.3.6 Dorsal arch height, mid-foot width and foot mobility

Dorsal arch height (DAH) and midfoot width (MFW) were assessed in weight-bearing and non-weight-bearing using the Foot Assessment Platform as previously described in the literature [302]. DAH was measured as the vertical distance from the dorsum of the foot at 50% of total foot length to the platform. MFW was measured from the medial to the lateral aspect of the foot at 50% of total foot length. Foot mobility was calculated as the difference between weight-bearing and non-weight-bearing DAH and MFW measures. Foot mobility magnitude (FMM), a composite measure representing a change in both DAH and MFW, was calculated using the following formula = $\sqrt{Difference\ DAH^2 + Difference\ MFW^2}$. DAH, MFW and FMM were recorded in millimetres [344, 345].

5.2.3.7 Static foot posture

The Foot Posture Index (FPI) was used to classify foot posture based upon the following six criteria: talar head palpation, curves above and below the lateral malleoli, inversion/eversion of the calcaneus, bulge in the region of the talonavicular joint, congruence of the medial longitudinal arch, and abduction/adduction of the forefoot on the rearfoot [346]. Each criterion was rated on a scale from -2 to +2, with total scores ranging from -12 to +12. Scores ranging from 0 to 5 denotes normal, 6 to 9 pronated, 10+ highly pronated, -1to -4 supinated and -5 to -12 highly supinated foot posture. High intra-rater reliability for the FPI has been reported [300].

5.2.4 Patient-reported outcomes

At the completion of physical testing, participants were invited to complete an online survey that provided information on QoL, perceived function, pain, disability, ankle instability, kinesiophobia and physical activity. The 20-questions Assessment of Quality of Life

questionnaire (AQoL-6D) [313] was used to assess QoL. It comprises 6 dimensions (independent living, mental health, coping, relationships, pain, and senses). The unweighted responses of all questions were added to create an overall profile score (0-100) and individual scores for each of the six dimensions. Higher scores indicate better QoL. Construct [314] and discriminative validity for use of AQoL-6D in OA populations [315] and test-retest reliability (ICC= 0.85- 0.88) have been reported [316].

The Foot and Ankle Ability Measure (FAAM) was used to assess perceived function [317]. It consists of a 21-item activities of daily living subscale (FAAM-ADL) and an 8-item sports subscale (FAAM-sport). Each item was scored on a 5-point Likert scale ranging from 'no difficulty' (4) to 'unable to do' (0). A "not applicable" option is available to indicate activities limited by factors other than foot or ankle problems, and those items were removed from scoring. The total sum of responses was converted to a percentage, with a higher percentage indicating a higher level of function. This questionnaire has excellent test-retest reliability (ADL subscale; ICC= 0.87 and Sports subscale; ICC= 0.89) and internal consistency [317].

The Ankle Osteoarthritis Scale (AOS) was used to measure ankle-related pain and disability when performing nine activities over the past week. Participants indicated how much difficulty or pain they experienced using an online version of the AOS with an 11-point NRS anchored with "No pain/difficulty" and "Worst pain imaginable/So difficult, unable". The original paper-based AOS has been shown to be reliable (ICC= 0.94 to 0.97) and valid patient-reported outcome for ankle arthritis [318]. The online version utilised in this study was only tested for intra-rater reliability, not for validity.

The Cumberland Ankle Instability Tool (CAIT) measured perceived ankle instability [319]. This valid and reliable tool (ICC=0.96) contains 9 items with scores assigned based on the rank of the chosen response [319]. Responses are summed separately for each limb. The maximum score is 30 with a higher score indicating less instability.

Kinesiophobia was measured using The Tampa Scale of Kinesiophobia (TSK-11) [320]. This scale has good internal consistency (Cronbach's α=0.79) and test-retest reliability (ICC=0.81) [321]. It comprises 11 statements about the perception of movement that are scored

on a 4-point Likert scale to produce a total score from 0 to 44. Higher scores indicate a high degree of kinesiophobia.

The short form of the International Physical Activity Questionnaire (IPAQ-SF) measured the total amount of time spent performing moderate, vigorous activities, walking or sitting in bouts of 10 minutes or greater over the last 7 days [322]. The IPAQ categorizes physical activity as “low”, “moderate” or “high". Published guidelines for data processing and analysis of IPAQ-SF were used (available from: http://www.ipaq.ki.se). The IPAQ-SF has been shown to have a moderate test retest reliability (ICC = 0.51) in hip and knee OA populations [323].

5.2.5 Statistical analysis

Inter-rater reliability of radiographic assessment was performed using data from both left and right ankles in symptomatic participants and the matched (for dominance) ankle in asymptomatic participants, with each ankle considered a separate unit in analysis [306] (n =134 ankles). The Kappa (κ) statistic was calculated and inter-rater reliability was interpreted as almost perfect (0.81–1.0), substantial (0.61–0.8), moderate (0.41–0.6), fair (0.21–0.4), slight (0.00–0.2) or poor (<0.00) [234]. Kappa statistic was also used to assess the reliability between the online and paper version of AOS. One-way model ICCs were calculated to determine the intra-rater reliability of physical outcomes taken one week apart. ICCs were interpreted as very good (ICC> 0.9), good (ICC 0.76-0.9) or moderate (ICC 0.5-0.75) [307].

Age and BMI were compared between groups using a one-way analysis of variance (ANOVA). Chi-square tests were conducted to compare categorical variables (sex, categories of physical activity, and KL grades of OA) between groups. Differences in physical measures and patient-reported outcomes between the symptomatic OA and the asymptomatic group (including both asymptomatic OA and asymptomatic non-OA), and between the asymptomatic OA and asymptomatic non-OA groups were examined using an analysis of covariance (ANCOVA) with age, sex and BMI entered as covariates. BMI was not entered as a covariate for torque measures as torque was normalized to body weight. To reduce chances of obtaining false-positive results (type I errors) with multiple comparisons, a Bonferroni adjustment method was used.

In participants with bilateral symptoms, the ankle with the greater pain or stiffness within the last 3 months was nominated as the symptomatic limb. For ankle strength, endurance, ROM, ankle joint laxity, foot mobility and foot posture, only data from the symptomatic limb were compared to the matched limb in asymptomatic participants. Cases with missing data were excluded on an analysis by analysis basis (pairwise deletion). Results are reported in the tables as mean values and their standard deviation (SD), mean differences (MD) between groups and their 95% confidence intervals [CI], and point estimate of effect expressed as SMDs and 95% CI for continuous variables. Frequencies and percentages with risk difference [95% CI] are reported for categorical and binary data. Effect sizes are reported in the results section and are interpreted as trivial: 0.0-0.2, small: 0.2-0.6, medium: 0.6-1.2, large: 1.2-2.0, very large: 2.0-4.0 and distinct:>4.0 [347].

Because not all variables were normally distributed, the bivariate relation between group, physical outcomes (10-m walk time, timed stair ascent, timed stair decent, plantar flexion, dorsiflexion, inversion, eversion muscle torque, heel raise endurance, DF ROM, total arthrokinematic displacement and rotation, FPI, differences in DAH and MFW, and FMM), QoL (AQoL-6D) and function (FAAM-ADL) was investigated using Spearman's Rank-Order Correlation. The correlation was interpreted as low (rho = 0.1-0.29), moderate (rho = 0.3-0.49), large (rho= 0.5-0.69) and very large (rho= 0.7-0.9) [347].

Separate univariate multiple regressions using backward elimination was conducted to investigate associations between physical outcomes (independent variables) with each of the dependent variables of QoL and FAAM-ADL. Independent variables were eligible for inclusion in the multiple regression model if they were significantly associated with QoL and FAAM ($p \leq 0.05$). Group was also entered into the model through a dummy coded variable (i.e., reference group = asymptomatic). The multiple regression model was tested for multicollinearity. Variables were systematically eliminated leaving only those with $p<0.1$. Statistical analysis was conducted using SPSS V.25 software (SPSS Inc., Chicago, Illinois, USA) and significance was set at $p \leq 0.05$.

5.3 Results

5.3.1 Participants

A total of 450 individuals (260 symptomatic and 190 asymptomatic) expressed interest in participating in this study, from which 105 individuals consented and attended the laboratory testing session (Figure 5.2). Of the 105 participants, four were excluded due to late disclosure of comorbidities (three knee OA and one hip OA) and three participants did not obtain ankle x-rays of their symptomatic ankles. Two symptomatic participants did not have evidence of ankle OA on imaging and were excluded as the group would be too small for meaningful comparison. Laboratory data for most outcomes were available from 96 participants (37 males and 59 females; mean age 52.4 years (SD=13.5, range=24 to 76 years) which formed the following study groups: 31 symptomatic OA and 65 asymptomatic (comprised of 41 asymptomatic OA and 24 asymptomatic non-OA) (Figure 5.2). Three symptomatic and one asymptomatic participants were unable to attend some sessions (ambulatory function, Plantar flexion endurance, foot mobility, and plantar flexion torque) of the full laboratory testing due to other personal commitments and time limitations. Seventeen participants (8 symptomatic and 9 asymptomatic) provided incomplete set of survey data. The sums of available data for each outcome are reflected in table 5.1.

Nineteen participants in the symptomatic group had bilateral x-rays while 12 did not obtain x-ray for the asymptomatic side. Of the 19 x-rays of the asymptomatic side in the symptomatic group, 13 asymptomatic ankles had radiographic evidence of joint degeneration defined as a KL grade of ≥ 2.The symptomatic group presented with bilateral ankle symptoms in 4 (12.9 %) cases. Six individuals in the symptomatic group had previous surgery to the ankle (2 reported arthroscopy, 1 talocalcaneal incision, 1 post fracture pins and screws and 2 provided no details of the type of surgery). Details of past fracture, ankle sprain history and Kellgren–Lawrence grades for the symptomatic OA, asymptomatic OA and asymptomatic non-OA are reported in Appendix 8. No participant had to discontinue physical testing due to ankle pain.

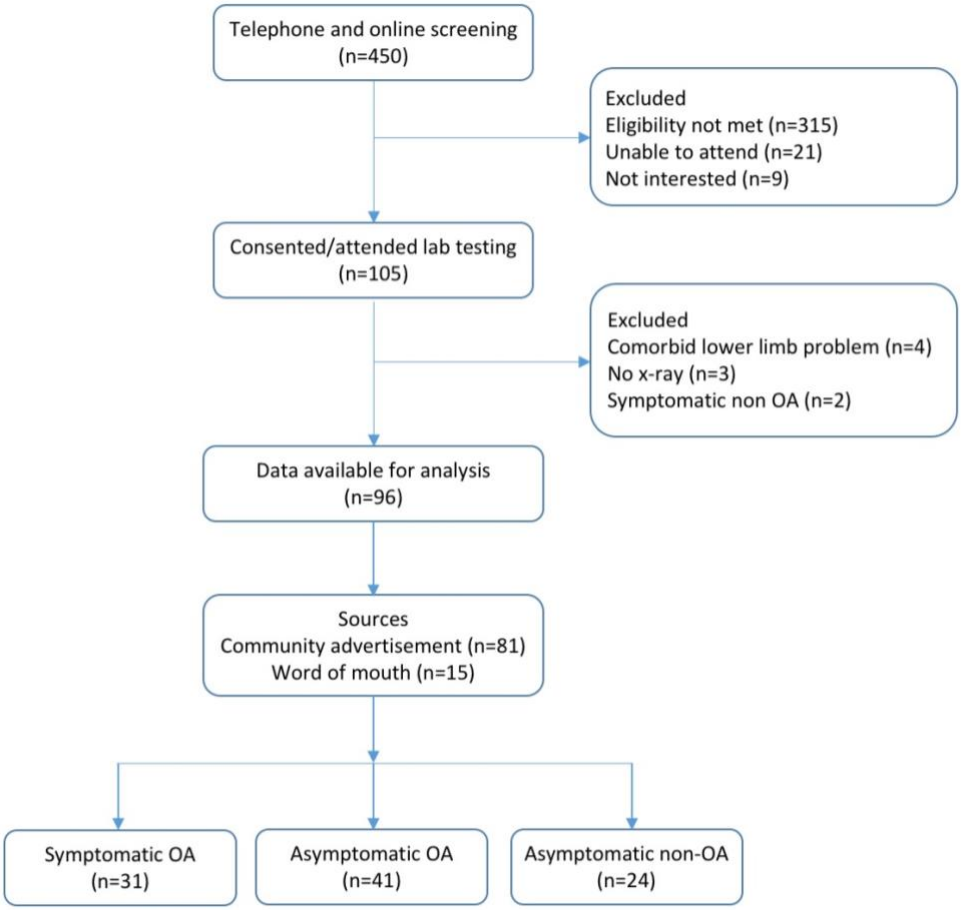

FIGURE 5. 2: Participant recruitment and grouping for cross-sectional laboratory study

5.3.2 Reliability of measures

Inter-rater reliability of radiographic assessment of 134 ankles (2 examiners) was substantial (Kappa = 0.69 (p <.0.001), 95% CI (0.59, 0.79)). Intra-rater reliability of physical measures taken on 10 subjects (one week apart) by a single examiner was good to very good (ICCs=0.84-1.00), see Appendix 7. Reliability between online NRS and paper VAS version of AOS was 0.898, with 95% CI (0.86, 0.92).

5.3.3 Comparison between symptomatic and asymptomatic groups

Participant characteristics and comparison of outcomes between symptomatic and asymptomatic participants are reported in Table 5.1. There were no differences in age or sex between the groups. BMI of the symptomatic group was significantly higher than that of the asymptomatic (SMD=0.93). There were significant large differences between groups in KL grades (SMD=1.07). Among the symptomatic group, 13 reported a history of 1 to 3 ankle

fractures and history of an ankle sprain on the symptomatic side while the asymptomatic groups reported no ankle fractures but 12 reported history of ankle sprain.

Symptomatic participants reported moderately lower scores for total AQol-6D (SMD=0.98), independent living (SMD=1.55) and higher pain (SMD=1.56) domains compared to asymptomatic participants. No differences were identified for coping, senses, relationships and mental health. Symptomatic participants had moderately higher levels of kinesiophobia (SMD=1.16), pain (SMD=1.70) and disability (SMD=1.44) on AOS and very large deficits in ADL (SMD=2.10) and Sports function (SMD=2.85) on FAAM. Greater perceived instability (SMD=3.92) was identified in symptomatic compared to asymptomatic participants. There were no differences in the self-report weekly total physical activity participation between groups.

Symptomatic participants were moderately slower in the 10-m walk (SMD=0.65), stair ascent (SMD=0.57) and descent (SMD=0.58) than asymptomatic participants. Symptomatic participants had moderate to very large deficits in muscle torque for all assessed muscle groups (SMDs from 0.73 to 1.71) in knee flexion. Plantar flexion in knee extension was markedly weaker (SMD= 8.9) in the symptomatic group. Moderate shorter time to fatigue during single leg heel raises (SMD=0.71) and large deficits in DF ROM (SMD=1.54) were also evident in symptomatic compared to asymptomatic participants. Results of the ankle arthrometer testing revealed small differences (SMDs from 0.48 to 0.56) where symptomatic participants had significantly less inversion, eversion, and total inversion-eversion rotation than asymptomatic participants. There were no differences in the other arthrometer measures, any of the foot mobility measures, or the total FPI score.

5.3.4 Comparison between asymptomatic OA and asymptomatic non-OA

There were no differences between asymptomatic participants with or without OA on imaging for most of the assessed measures (Table 5.2). There were medium effects for lower scores on the *Senses* domain of the AQoL-6D and for anterior displacement on the arthrometer.

Table 5.1: Characteristics of the symptomatic and asymptomatic groups

Mean (Standard deviation, n) of between-group mean differences and point estimate of effect expressed as standardised mean difference and its 95% confidence interval (95% CI)

Characteristic	Symptomatic	Asymptomatic	MD (95%CI)	Point estimate of effect (95%CI)	p value
Age years	51.19 (14.24,31)	53.00 (13.26, 65)	1.81[-4.08,7.69]	-0.13 [-0.56, 0.30]	0.544
Sex, Female n (%)	16 (51.6%)	43 (66.2%)		0.55 [0.23, 1.31]~	0.17
BMI kg/m^2	28.45 (5.37,31)	24.37 (3.8, 65)	-4.08[-5.70,-2.20]	0.93 [0.48, 1.38]	**<0.001**
Kellgren–Lawrence grade	2.72 (0.89, 31)	1.78 (0.86, 65)	0.94 [0.56, 1.32]	1.07 [0.62, 1.53]	**<0.001**
Patient-reported outcomes					
AQoL-6D Total range 0-100	77.48 (9.93, 26)	87.02 (9.47, 60)	-9.54 [-14.33, -4.75]	-0.98 [-1.47, -0.50]	**<0.001**
Independent Living range 0-100	80.24 (11.06, 26)	96.99 (10.55, 60)	-16.75 [-22.09, -11.41]	-1.55 [-2.07, -1.03]	**<0.001**
Relationships range 0-100	88.47 (12.39, 26)	94.0 (11.82, 60)	-5.53 [-11.51, 0.46]	-0.46 [-0.92, 0.01]	0.070
Mental Health range 0-100	76.05 (15.95, 26)	79.75 (15.23, 60)	-3.70 [-11.41, 4.00]	-0.21 [-0.67, 0.25]	0.342
Coping s range 0-100	74.96 (16.18, 26)	79.04 (15.45, 60)	-4.08 [-11.90, 3.74]	-0.26 [-0.72, 0.20]	0.302
Pain range 0-100	63.22 (17.03, 26)	89.11 (16.25, 60)	-25.89 [-34.11, -17.66]	-1.56 [-2.07, -1.04]	**<0.001**
Senses range 0-100	80.25 (11.01, 26)	82.53 (10.50, 60)	-2.29 [-7.60, 3.03]	-0.21 [-0.67, 0.25]	0.395
FAAM- ADL%	77.04 (10.48, 26)	98.98 (10.28, 60)	-21.94 [-27.011, -16.86]	-2.10 [-2.66, -1.54]	**<0.001**
FAAM- Sport %	55.27 (15.13, 26)	97.46 (14.44, 60)	-42.19 [-49.50, -34.88]	-2.85 [-3.49, -2.22]	**<0.001**
AOS- Overall %	27.86 (15.83, 26)	2.68 (15.10, 60)	25.18 [17.53, 32.82]	1.63 [1.11, 2.15]	**<0.001**
AOS- Pain %	28.50 (15.44, 26)	2.80 (14.73, 60)	25.69 [18.24, 33.15]	1.70 [1.18, 2.23]	**<0.001**
AOS- Disability %	27.34 (17.55, 26)	2.66 (16.75, 60)	24.69 [16.21, 33.16]	1.44 [0.93, 1.95]	**<0.001**

CAIT score range 0-30	10.57 (4.67, 26)	28.45 (4.45, 61)	-17.88 [-20.13, -15.63]	-3.92 [-4.68, -3.17]	**<0.001**
Tampa scale score range 0-44	23.965 (5.79, 23)	17.336 (5.63, 56)	6.63 [3.71, 9.54]	1.16 [0.64, 1.68]	**<0.001**
IPAQ-Total activity MET-min/week	3220.85 (3504.69, 26)	3982.63 (3344.14, 60)	-761.78 [-2454.17, 930.60]	-0.22 [-0.68, 0.24]	0.373
High physical activity n (%)	11 (35.5%)	33 (50.8%)		-13% [-35, 10]^	
Moderate physical activity n (%)	8 (25.8%)	10 (15.4%)		14% [-6, 34]^	
Low physical activity n (%)	7 (22.6%)	17 (26.2%)		-1% [-22, 19]^	
Ambulatory function					
10-m walk sec.	5.08 (0.72, 30)	4.62 (0.70, 65)	0.46 [0.14, 0.79]	0.65 [0.20, 1.09]	**0.006**
Stair ascent sec.	7.46 (1.49, 29)	6.62 (1.44, 64)	0.85 [0.16, 1.53]	0.57 [0.13, 1.02]	**0.016**
Stair descent sec.	7.94 (1.99, 29)	6.81 (1.91, 64)	1.13 [0.22, 2.040]	0.58 [0.13, 1.03]	**0.016**
Mobility and joint range					
WB lunge test mm	60.08 (42.33, 31)	124.4 (40.93, 65)	-64.36 [-83.25, -45.47]	-1.54 [-2.02, -1.06]	**<0.001**
DAHDIFF mm	12.88 (5.25, 30)	14.24 (5.09, 65)	-1.36 [-3.72, 1.01]	-0.26 [-0.70, 0.17]	0.26
MFWDIFF mm	9.40 (3.71, 30)	10.13 (3.59, 65)	-0.73 [-2.40, 0.94]	-0.20 [-0.63, 0.23]	0.39
FMM mm	16.38 (5.37, 30)	17.78 (5.18, 65)	-1.40 [-3.81, 1.00]	-0.27 [-0.70, 0.17]	0.25
FPI score range -12 to 12	0.86 (2.43, 31)	1.14 (2.36, 65)	-0.28[-1.37, 0.81]	-0.12 [-0.54, 0.31]	0.609
Normal FPI n (%)	21 (67.7%)	57 (87.7%)		-20% [-38, -2]^	**0.019**
Pronated FPI n (%)	2 (6.5%)	0 (0%)		6% [-3, 16]^	
Supinated FPI n (%)	8 (25.8%)	7 (10.8%)		15% [-2, 32]^	
Arthrometer measurements					
Anterior displacement mm	10.15 (3.57, 31)	10.86 (3.46, 65)	-0.71 [-2.31, 0.88]	-0.20 [-0.63, 0.23]	0.376

Posterior displacement mm	9.83 (3.17, 31)	9.63 (3.07, 65)	0.20 [-1.21, 1.62]	0.06 [-0.36, 0.49]	0.777
Total displacement mm	19.961 (6.17, 31)	20.70 (5.97, 65)	-0.74 [-3.49, 2.01]	-0.12 [-0.55, 0.31]	0.60
Inversion Rotation °	23.49 (9.28, 31)	28.55 (8.97, 65)	-5.06 [-9.19, -0.92]	-0.55 [-0.99, -0.12]	**0.02**
Eversion Rotation °	22.83 (7.78, 31)	26.55 (7.53, 65)	-3.72 [-7.20, -0.25]	-0.48 [-0.92, -0.05]	**0.04**
Total Rotation °	46.31 (15.72, 31)	55.05 (15.20, 65)	-8.74 [-15.75, -1.72]	-0.56 [-1.00, -0.13]	**0.015**
Torque and endurance					
PF in knee Flex. N.m/kg	0.30 (0.17, 31)	0.42 (0.16, 65)	-0.13 [-0.20, -0.05]	-0.73 [-1.17, -0.29]	**0.001**
DF in knee Flex. N.m/kg	0.24 (0.08, 31)	0.32 (0.07, 65)	-0.08 [-0.12, -0.05]	-1.08 [-1.54, -0.63]	**<0.001**
Inversion in knee Flex. N.m/kg	0.15 (0.06, 31)	0.21 (0.01, 65)	-0.06 [-0.09, -0.03]	-1.71 [-2.20, -1.21]	**<0.001**
Eversion in knee Flex. N.m/kg	0.18 (0.08, 31)	0.25 (0.07, 65)	-0.08 [-0.11, -0.04]	-0.95 [-1.40, -0.50]	**<0.001**
PF in knee Ext. N.m/kg	0.61 (0.04, 30)	0.91 (0.03, 65)	-0.30 [-0.43, -0.18]	-8.90 [-10.26, -7.54]	**<0.001**
Endurance heel raises sec.	63.15 (43.55, 28)	93.48 (41.92, 65)	-30.33 [-50.44, -10.23]	-0.71 [-1.16, -0.25]	**0.004**

*~ Odds Ratio; ^ Risk Difference; *based on data from 61 asymptomatic and 26 symptomatic*
Continuous data are reported as mean (SD), and dichotomised/binary data presented as frequency (%), point estimates of effect are reported as SMD for interval data, OR odds ratio or RD risk difference for binary data
Abbreviations and definitions: n=number; BMI= body mass index; SD=standard deviation; SMD= standardised mean difference; CI=confidence interval; P=P value/significance level; AOS=ankle osteoarthritis scale; FAAM=Foot and Ankle Ability Measure; AQoL-6D= The Assessment of Quality of Life questionnaire-6D; CAIT= The Cumberland Ankle Instability Tool; IPAQ=The International Physical Activity Questionnaire; sec.=seconds; FMM=Foot mobility magnitude; DAHDIFF=dorsal arch height difference; MFWDIFF= mid-foot width difference; FPI= foot posture index ;PF=Plantarflexion; DF=dorsiflexion; ROM=range of movement; Ext=extension; Flex=flexion
All outcomes adjusted for age, sex and body mass index except for torque measures,
Significance level based on ANCOVA post-hoc comparisons with Bonferroni correction or Pearson's Chi-squared
Higher scores in AQoL, FAAM, CAIT, IPAQ, Lunge test, muscle torque, ROM and endurance heel raises are better than lower scores. Higher AOS and timed ambulatory scores are worse than lower scores.

Table 5.2: Characteristics of asymptomatic OA and asymptomatic non-OA

Mean (Standard deviation, n) of between-group mean differences and point estimate of effect expressed as standardised mean difference and its 95% confidence interval (95% CI)

Characteristics	Asymptomatic OA	Asymptomatic non-OA	MD (95%CI)	Point estimate of effect (95%CI)	p-value
Age years	55.6 (12.75, 41)	48.6 (13.2, 24)	7.002 [-1.37, 15.37]	0.54 [0.02, 1.05]	0.133
Sex, Female n (%)	29 (70.7%)	14 (58.3%)		0.58 [0.20, 1.66] ~	0.308
BMI kg/m^2	24.27(3.82, 41)	24.53 (3.76, 24)	-0.26 [-3.00, 2.47]	-0.07 [-0.57, 0.44]	1.00
Kellgren–Lawrence grade	2.36 (0.49)	0.89(0.49)	1.47 [1.22, 1.73]	2.96 [2.24, 3.69]	**<0.001**
Patient-reported outcomes					
AQoL-6D Total score range 0-100	85.55 (9.33, 38)	89.54 (9.24, 22)	-3.99 [-10.01, 2.03]	-0.42 [-0.95, 0.11]	0.33
Independent Living score range 0-100	96.43 (10.53, 38)	97.95 (10.45, 22)	-1.53 [-8.33, 5.28]	-0.15 [-0.67, 0.38]	1.00
Relationships score range 0-100	93.07 (11.78, 38)	95.59 (11.67,22)	-2.52 [-10.12, 5.09]	-0.22 [-0.75, 0.31]	1.00
Mental Health score range 0-100	77.82 (15.07, 38)	83.08 (14.93, 22)	-5.26 [-14.99, 4.47]	-0.35 [-0.87, 0.18]	0.57
Coping score range 0-100	77.96 (15.40, 38)	80.90 (15.26, 22)	- 2.94 [-12.88, 7.00]	-0.19 [-0.72, 0.34]	1.00
Pain score range 0-100	87.25 (16.12, 38)	92.28 (15.98, 22)	- 5.03 [-15.43, 5.38]	-0.31 [-0.84, 0.22]	0.72
Senses score range 0-100	79.90 (10.07, 38)	87.04 (9.98, 22)	-7.14 [-13.64, -0.64]	-0.70 [-1.24, -0.16]	**0.026**
FAAM- ADL%	98.94 (10.49, 40)	99.04 (10.35, 22)	-0.10 [-6.80, 6.60]	-0.01 [-0.53, 0.51]	1.00
FAAM- Sport %	97.72 (14.44, 40)	97.01 (14.32, 22)	0.71 [-8.61, 10.03]	0.05 [-0.47, 0.57]	1.00
AOS- Overall %	3.62 (15.07, 38)	1.07 (14.94, 22)	2.55 [-7.18, 12.28]	0.17 [-0.36, 0.69]	1.00

AOS- Pain %	3.59 (14.71, 38)	1.46 (14.58, 22)	2.13 [-7.36, 11.63]	0.14 [-0.38, 0.67]	1.00
AOS- Disability %	3.71 (16.71, 38)	0.85 (16.56, 22)	2.86 [-7.93, 13.64]	0.17 [-0.36, 0.70]	1.00
CAIT score range 0-30	28.23 (4.45)	28.84 (4.39)	-0.62 [-3.46, 2.23]	-0.62 [-3.46, 2.23]	1.00
Tampa scale score range 0-44	17.43 (5.72, 36)	17.17 (5.66, 20)	0.26 [-3.65, 4.17]	0.04 [-0.50, 0.59]	1.00
IPAQ-Total activity MET-min/week	4021.77 (3345.37, 38)	3915.54 (3315.74, 22)	106.22 [-2053.11, 2265.55]	0.03 [-0.49, 0.56]	1.00
High physical activity n (%)	23 (60.5.1%)	10 (45.5.7%)		15% [-11, 41]^	
Moderate physical activity n (%)	6 (15.8%)	4 (18.2%)		-2% [-22, 17]^	
Low physical activity n (%)	9 (23.7%)	8 (36.4%)		-13% [-37, 12]^	
Ambulatory function					
10-m walk sec.	4.68 (0.70, 41)	4.51 (0.69, 24)	0.18[-0.26,0.62]	0.24 [-0.26, 0.75]	0.98
Stair ascent sec.	6.73 (1.46, 40)	6.43 (1.42, 24)	0.30[-0.60,1.21]	0.21 [-0.30, 0.71]	1.000
Stair descent sec.	7.01 (1.94, 40)	6.49 (1.88, 24)	0.52[-0.69,1.72]	0.27 [-0.24, 0.78]	0.892
Mobility and joint range					
WB lunge test mm	123.57 (41.44, 41)	125.86 (40.57, 24)	- 2.29[-27.91,23.33]	-0.06 [-0.56, 0.45]	1.00
DAHDIFF mm	14.40 (5.15, 41)	13.97 (5.06, 24)	0.43 [-2.77, 3.62]	0.08 [-0.42, 0.59]	1.00
MFWDIFF mm	10.43 (3.63, 41)	9.65 (3.56, 24)	0.78 [-1.47, 3.03]	0.21 [-0.29, 0.72]	1.00
FMM mm	18.07 (5.24, 41)	17.30 (5.14, 24)	0.77 [-2.48, 4.02]	0.15 [-0.36, 0.65]	1.00
FPI score range -12 to 12	1.31 (2.41, 41)	0.87 (2.33, 24)	0.44 [-1.04, 1.92]	0.18 [-0.32, 0.69]	1.00
Normal FPI n (%)	36 (87.8%)	21 (87.5%)		0% [-16, 17]^	0.971
Pronated FPI n (%)	0 (0%)	0 (0%)		0% [-6, 6]^	
Supinated FPI n (%)	4 (9.8%)	3 (12.5%)		-3% [-19, 13]^	

Arthrometer measurements					
Anterior displacement mm	9.99 (3.28, 41)	12.24 (3.26, 24)	-2.25 [-4.33, -0.18]	-0.68 [-1.20, -0.16]	0.03
Posterior displacement mm	9.19 (3.00, 41)	10.21 (2.98, 24)	-1.02 [-2.92, 0.87]	-0.34 [-0.84, 0.17]	0.575
Total displacement mm	19.48 (5.76, 41)	22.53 (5.71, 24)	-3.05 [-6.68, 0.59]	-0.52 [-1.04, -0.01]	0.132
Inversion Rotation °	27.65 (8.79, 41)	29.97 (8.73, 24)	-2.32 [-7.87, 3.23]	-0.26 [-0.77, 0.24]	0.931
Eversion Rotation °	26.20 (7.45, 41)	27.91 (7.40, 24)	-1.71 [-6.42, 3.00]	-0.23 [-0.73, 0.28]	1.00
Total Rotation °	53.77 (14.92, 41)	57.88 (14.80, 24)	-4.11 [-13.52, 5.31]	-0.27 [-0.78, 0.23]	0.872
Torque and endurance					
PF in knee Flex. N.m/kg	0.44 (0.17, 41)	0.44 (0.16, 24)	-0.01[-0.11,0.10]	0.00 [-0.50, 0.50]	1.00
DF in knee Flex. N.m/kg	0.30 (0.07, 41)	0.34 (0.07, 24)	-0.03[-0.08,0.02]	-0.56 [-1.08, -0.05]	0.56
Inversion in knee Flex. N.m/kg	0.22 (0.05, 41)	0.21 (0.06, 24)	0.01[-0.03,0.05]	0.18 [-0.32, 0.69]	1.00
Eversion in knee Flex. N.m/kg	0.24 (0.07, 41)	0.26 (0.07, 24)	-0.02[-0.07,0.03]	-0.28 [-0.79, 0.22]	1.00
PF in knee Ext. N.m/kg	0.91 (0.27, 41)	0.90 (0.26, 24)	0.01[-0.18,0.20]	0.04 [-0.47, 0.54]	1.00
Endurance heel raises sec.	97.06 (42.49, 41)	87.71 (41.33, 24)	9.35 [-16.90, 35.60]	0.22 [-0.29, 0.72]	1.00

*~ Odds Ratio; ^ Risk Difference; *Based on data from 22 asymptomatic non-OA and 39 asymptomatic OA*
Continuous data reported as mean (SD), and dichotomised/binary data presented as frequency (%), point estimates of effect are reported as SMD for interval data, OR odds ratio or RD risk difference for binary data
Abbreviations and definitions: ROA =radiographic osteoarthritis; n=number; BMI= body mass index; SD=standard deviation; SMD= standardised mean difference; MD=mean difference; CI=confidence interval; P=P value/significance level; AOS=ankle osteoarthritis scale; FAAM=Foot and Ankle Ability Measure; AQoL-6D= The Assessment of Quality of Life questionnaire-6D; CAIT= The Cumberland Ankle Instability Tool; IPAQ=The International Physical Activity Questionnaire; sec.=seconds; FMM=Foot mobility magnitude; DAHDIFF=dorsal arch height difference; MFWDIFF= mid-foot width difference; PF=Plantarflexion; DF=dorsiflexion; ROM=range of movement; Ext=extension; Flex=flexion= foot posture index.
All outcomes adjusted for age, sex and body mass index except for torque measures.
Significant difference at ($p < 0.05$) based on ANCOVA post-hoc comparisons with Bonferroni correction or Pearson's Chi-squared

5.3.5 The association between physical outcomes, QoL and function

Spearman's Correlations between physical outcomes, QoL (total AQoL-6D), function (FAAM-ADL), and between independent variables are presented in Appendix 9. Spearman's correlation revealed no significant association between total displacement, total rotation, FPI, difference in DAH, difference in MFW, and FMM and QoL or FAAM. These variables were therefore not included in the multiple regression model. Tests for multicollinearity revealed a variance inflation factor of less than 10 for all included variables in the models. The initial full model including group (Ref. – asymptomatic), 10-m walk time, timed stair ascent and descent, muscle torque (plantar flexion, dorsiflexion, inversion, and eversion), heel raise endurance, and DF ROM explained 66% of the variance in FAAM-ADL and 51% of the variance in QoL. Independent variables with p>0.1 were systematically excluded. In the final regression model (Table 5.3), stair descent (β=-0.82, p<.001), stair ascent (β=-0.44, p=0.047) and group (Ref. – asymptomatic) (β=-0.26, p=0.008) explained 48% of the total variance in AQoL-6D. For self-reported function, group (Ref. – asymptomatic) (β=-0.64, p<.001) and stair descent (β=-0.59, p=0.001) explained 64% of the total variance in FAAM-ADL (Table 5.4).

Table 5.3: Multiple linear regression model total AQoL-6D as the dependent variable

Significant predictor variables	Standardized β weight	p-value	R^2
Stair descent time	-0.818	0.000	0.48
Group (Ref. – asymptomatic)	-0.260	0.008	
Stair ascent time	0.443	0.047	
Eversion strength in knee 90◦ Flexi.	0.184	0.077	
Variables not retained in the model			**Change in R^2**
Inversion strength in knee 90◦ Flex.	0.024	0.870	0.000
Heel raises total time	-0.027	0.785	-0.001
WB lunge test -DF ROM	0.060	0.617	-0.002
Plantar flexion strength in knee 90◦ Flex.	0.057	0.605	-0.002
10-m. walk time	0.134	0.281	-0.008
Dorsi flexion strength in knee 90◦ Flex.	0.130	0.294	-0.007
Plantar flexion strength in knee Ext.	-0.138	0.301	-0.007

Analysis based on sample of 86 participants, DF=dorsiflexion, ROM=range of movement, Ext=extension; Flex=flexion
Independent variables with p>0.1 were systematically excluded.

Table 5.4: Multiple linear regression model with self-reported function (FAAM-ADL) as the dependent variable

Significant predictor variables	Standardized β weight	p-value	R^2
Group (Ref. – asymptomatic)	-0.642	0.000	0.64
Stair descent time	-0.593	0.001	
Stair ascent time	0.308	0.085	
Variables not retained in the model			**Change in R^2**
Heel raises total time	-0.005	0.955	0.000
10-m. walk time	0.018	0.866	0.000
Plantar flexion strength in knee Ext.	0.023	0.842	0.000
WB lunge test -DF ROM	0.047	0.604	-0.001
Plantar flexion strength in knee 90◦ Flex.	-0.047	0.599	-0.001
Eversion strength in knee 90◦ Flex.	0.115	0.279	-0.005
Inversion strength in knee 90◦ Flex.	-0.078	0.402	-0.003
Dorsi flexion strength in knee 90◦ Flex.	0.122	0.160	-0.008

Analysis based on sample of 90 participants, DF=dorsiflexion, ROM=range of movement, Ext=extension; Flex=flexion
Independent variables with p>0.1 were systematically excluded.

5.4 Discussion

This study aimed to identify impairments that characterize individuals with ankle OA by comparing physical measures and patient-reported outcomes between the symptomatic OA group and the pooled asymptomatic group (asymptomatic OA + asymptomatic non-OA) and between the asymptomatic OA group and asymptomatic non-OA group. Analysis of physical outcome measures revealed significant deficits in ambulatory function, muscle strength, and DF ROM in individuals with symptomatic OA compared to individuals without ankle symptoms. Symptomatic ankle OA was associated with greater pain, patient-reported disability, instability and kinesiophobia, and lower self-reported function and QoL. These findings highlight the impairments characterising individuals with symptomatic ankle OA.

Interestingly, 41 of the 65 individuals with no clinical signs of ankle OA (i.e. no pain or stiffness) and 13 asymptomatic ankles in the symptomatic group had radiographic evidence of joint degeneration based on evaluation using the KL scale. This is consistent with evidence from a systematic review reporting that radiographic OA of the knee is an imprecise guide to the likelihood that knee pain will be present [340]. Further, most physical and patient-reported

outcomes were similar between individuals with asymptomatic OA and asymptomatic non-OA. It is unlikely that degenerative joint changes are the only cause of limited ROM and strength deficits. It seems likely that pain is a contributing factor because 41 asymptomatic individuals with evidence of ankle OA presented with comparable ROM to that of asymptomatic non-OA. In the knee, the inhibitory effect of joint pain on range of motion has been established [348]. This also applies to the ankle strength deficits identified in the symptomatic but not the asymptomatic OA group which is consistent with findings of deficits in isometric knee extensor and flexor strength related to knee pain and not to the structural status of the knee on radiographs [67]. Our findings suggest that the presence of ankle symptoms may present a greater impact on an individual's overall function and QoL than the presence of radiographic evidence of joint degeneration. Further, our findings highlight the need to assess symptoms when interpreting the impact of radiographic joint degeneration and raise questions regarding the relevance of radiographs alone when determining the management of individuals with ankle OA.

Clinical tests of physical function such as timed level walking and stairs ascent/descent have not previously been investigated in individuals with ankle OA. Stair ascent/descent has been related to independence and community participation [349,350,351] and stair descent time is a significant marker of functional decline among older adults [350]. Our results reveal slower timed walking and stair ascent/descent in symptomatic individuals with ankle OA than individuals without ankle symptoms. Additionally, these physical measures associated with QoL and function indicate that addressing deficits in the ability to ascend and descend stairs may be important in the management of individuals with ankle OA. While the correlation was large for function (r 0.64), it is clear that the strength of that correlation is moderate for QoL (r 0.48) and much of the variance in the total AQoL-6D remain unexplained or unaccounted for. Stair descent is a complex functional task that relies on strength but also on visual processing, motor planning and coordination. Association of stair descent time with pain, strength of knee extensors and flexors, proprioception, balance and fear of falling has been reported [352] and it is possible that these factors may also influence QoL and function.

There is evidence to indicate that ankle strength may influence the performance of functional tests. Ankle dorsiflexor and plantar flexor muscles strength have been shown to be

correlated with walking speed [353] stair tests [354] and stair ascent [355]. Taking into account that muscle strength improvements have shown to improve function [356], there may be a role for strengthening exercises to increase strength in individuals with ankle symptoms and thereby improve function and QoL.

Limited ROM is a common impairment in OA. It has been suggested that osteophytes in OA create bone blocks that can contribute to capsular contracture and subsequently limit physiological ROM [146,357]. Previous research identified less total sagittal plane (dorsiflexion and plantar flexion) ROM on the affected ankle compared to the unaffected ankle in individuals with ankle OA and to healthy controls [338]. Our data indicate that decreased DF ROM contributes to the loss of sagittal plane ankle ROM. This is important because reduced ankle DF has been associated with impaired gait, compromised balance and function [168,169,165,166,167], greater perceived ankle instability [358,359], falls [360] and to the development of lower limb musculoskeletal pain and injuries (such as patellar tendon injury [361]). Addressing deficits in ankle DF ROM should be included in the management of individuals with symptomatic ankle OA.

Even though ankle ligament sprains are thought to contribute to ankle OA development [13,14,15] and are associated with increased joint displacement [362,363], the one study [146] that investigated arthrokinematics in ankle OA reported less anterior displacement and inversion-eversion rotation in the osteoarthritic ankle compared to the unaffected ankle and healthy controls. Although the anterior displacement, inversion and eversion rotation observed in asymptomatic individuals who participated in our study were not different from the healthy controls in that single study. Our investigation revealed deficits in rotational arthrokinematics in the symptomatic compared to the asymptomatic group, but no differences in displacement were identified between groups. It is possible that differences in arthrokinematics findings between this study and that reported by Hubbard [146] are due to heterogeneity in the ankle OA population or may be due to small sample size in Hubbard's study (8 ankle OA and 8 controls). However, the control group variability in that single study was extremely small. It is likely more complex than just sample size.

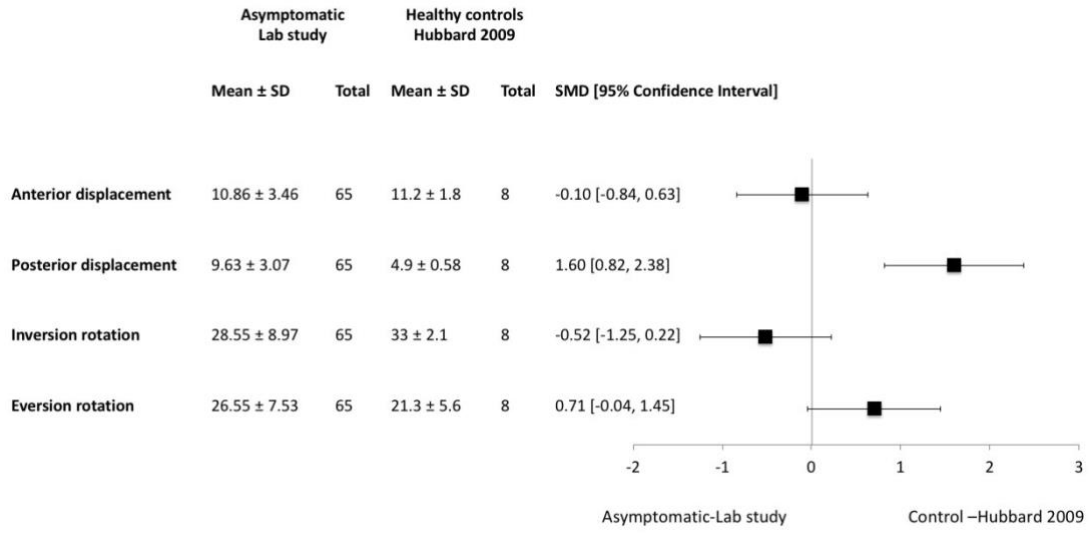

FIGURE 5. 3: Comparison between laboratory study asymptomatic group and data for healthy control from Hubbard 2009 study

Despite physical and patient-reported impairments identified in symptomatic individuals with OA, and while expected that these impairments may affect the ability to exercise, self-reported physical activity did not differ between groups in our study. It is possible that individuals with symptomatic OA adapt activity choices in line with their pain and physical capabilities as previous research reported [364]. Evidence suggests that pain relief can make it tolerable for people with OA to maintain a certain level of physical activity [365,366]. Alternatively, the absence of significant differences in physical activity may be due to the limitations of using the IPAQ-SF to determine self-reported physical activity. IPAQ responses depend on the perception of the different levels of activity (what activities fit in the vigorous or moderate categories [367]) and recall of activity pattern over the last 7 days. It is also likely that individuals will report the highest or desired physical activity participation rather than the actual activity performed [368]. Further, evidence of weak specificity of IPAQ-SF to accurately estimate physical activity compared with objective measures of activity and fitness has been reported [369].

Findings from this study should be considered in light of the following limitations. This study provided information on the association of physical outcomes, QoL and self-reported function but no causal relationship between any of the assessed variables can be derived due

to the cross-sectional design of this study. Data related to the history of injury including the number of ankle sprains and fractures were collected retrospectively. This method can be a potential source of error as the ability to reliably and accurately recall this information vary among individuals of different age. Conclusions reached in this study were limited by the small number of individuals who presented with symptoms but no radiographic evidence of ankle OA. This small sample limited our ability to report findings related to the presence of symptoms without OA and whether the combination of symptoms and radiographic OA or symptoms alone contributed to ankle joint impairments. We were also unable to determine the relationship between radiographic evidence of ankle OA and physical asymmetry in symptomatic individuals with evidence of unilateral ankle OA due to the number of missing images of the asymptomatic ankles. Further, it is known that OA coincides with other comorbid disease [214,370-372]. Since individuals with comorbid conditions were excluded from the laboratory examination in this study, this limits the ability to generalise these findings to the wider ankle OA population who typically present with other comorbidities. Volunteers with a wide age range and high physical activity levels participated in this study with all participants able to complete the functional tasks. Our findings may not be generalizable to populations with higher levels of physical disability. Due to a lower representation of severe OA (grade 4 KL), findings from this study may not be reflective of end-stage ankle OA. Asymptomatic participants may have had degenerative joint changes on the opposing unexrayed ankle. However, based on the results of comparison between asymptomatic with and without OA, we, therefore, assume that the presence of OA on the opposing unexrayed ankle may not change the results of comparison between symptomatic and asymptomatic groups. Finally, while muscle torque was lower in the symptomatic group than the asymptomatic, our data is not able to ascertain whether this is related to atrophy, weakness, or inhibition.

This study was not designed to determine the association between grades of OA and function/symptoms. Further research to determine if higher grades of OA have greater deficits (and whether this is related to pain and stiffness symptoms) is warranted. We have only assessed association of physical measures with QoL and perceived function, however, QoL and function can be influenced by non-physical factors which were not within the scope

of this study. Hence the inclusion of other physiological and psychological factors will likely yield different findings. Self-reported physical activity using IPAQ-SF may have yielded an overestimation. Hence future studies may utilise objective measures such as activity monitors to substantiate the level of physical activity in populations with ankle OA. Since presence of chronic joint pain, limited ankle DF and muscles weakness have been associated with risk of fall [373,168,198, 360], coexistence of these impairments may suggest an increased risk of falls in individuals with symptomatic ankle OA. Future research assessing the incidence of falls and the contribution of the identified impairments to the occurrence of falls in individuals with ankle OA seem warranted.

In summary, individuals with symptomatic (but not asymptomatic) ankle OA present with higher pain, patient-reported disability, instability, kinesiophobia, lower self-reported function and QoL, impaired calf muscle strength, lower calf muscle endurance, less ankle ROM and slower ambulatory function compared to asymptomatic individuals without ankle OA. The asymptomatic individuals with radiographic OA did not have physical deficits or impairments in patient-reported outcomes compared to the control group. Our findings suggest that stair function is related to impaired QoL and self-reported function. Until further research provides a better understanding of the mediators of the observed physical impairments and self-reported outcomes in a symptomatic ankle OA population, management should be guided by the clinical presentation and functional status of those individuals rather than radiological findings.

Chapter 6 Health-related quality of life, pain, function, and disability in individuals with symptomatic ankle problems: a cross-sectional online survey

In the previous chapter, evidence from the cross-sectional laboratory study revealed that the presence of radiographic OA with no ankle symptoms was not associated with impairments in physical and patient-reported outcomes. In this chapter, we opted to focus on the presence of ankle symptoms rather than radiographic evidence of ankle OA. The sample was drawn from Australia wide to retain adequate sample size and access to individuals in distant locations. This study aimed to compare self-reported ankle symptoms (pain, stiffness and instability), function, disability, physical activity and QoL between individuals with ankle symptoms and asymptomatic controls. A secondary aim was to explore factors associated with QoL.

6.1 Introduction

Musculoskeletal conditions represent the second leading cause of disability affecting 20-33% of individuals world-wide [1]. Pain associated with musculoskeletal conditions is reported as the main reason for seeking medical care [5,374]. Chronic musculoskeletal ankle conditions (mostly due to an ankle injury) affect nearly 20% of Australian adults [2]. Other population estimates for ankle pain range from 9-15% of adults from different studies [3-5].

Pain and physical impairments related to musculoskeletal conditions negatively impact function, mental health and QoL [7,375]. However, the relation between ankle pain and physical function, social interaction, and QoL remains unclear. After the 3rd decade of life, ankle pain and stiffness may be related to OA, particularly in individuals who have had previous ankle injuries [128]. There is some evidence to suggest poor QoL in late-stage ankle OA [173,214] but this only represents a small proportion of the ankle pain population.

Symptoms from lower limb joints (other than the ankle) were significantly associated with lower physical QoL but not asymptomatic radiographic evidence of OA [376]. Several studies [64,377,378,379] reported that the severity of lower limb joint pain had a greater impact on disability than the structural changes observed on radiographs. Hence, it seems reasonable to

focus on symptoms rather than radiographic evidence of joint changes when studying populations with joint symptoms in relation to QoL and disability.

In accordance with the biopsychosocial approach for chronic pain management [380], addressing all aspects of chronic pain presentations (physical, psychological, and social components) seems warranted in the management of individuals with chronic ankle conditions. As a first step, the relation between the clinical presentation and self-reported pain, disability, function, and QoL in individuals with chronic ankle symptoms requires investigation. The aim of this study was to compare self-reported pain, function, ankle instability, physical activity, and QoL outcome measures between individuals with ankle symptoms and asymptomatic controls. A secondary aim was to identify which of those outcome measures are most associated with QoL.

6.2 Methods

An online survey of individuals with and without ankle pain and/or stiffness was implemented to address the following questions: (i) what are the differences in function, ankle instability, physical activity and QoL between those who report ankle symptoms and asymptomatic controls and (ii) what outcome measures are associated with QoL.

6.2.1 Recruitment

Between July 2015 and February 2017, 1948 volunteers aged 30 to 75 years with and without a history of ankle pain and/or stiffness present on most days for >3 months duration sought to participate in this cross-sectional survey. Of those 270 symptomatic, and 124 asymptomatic controls participated in the study. Participants were recruited via community advertisements placed in a local university staff and community newsletters, communications from National and State arthritis organisations, and social media. Participants were asked to indicate if they "experienced any of the following ankle symptoms for more than 3 months on most days": 1) Pain or ache in/or around the ankle, 2) Ankle joint stiffness or reduced movement in the morning. Participants who indicated they did not experience any ankle pain or stiffness in the last 3 months were included in the asymptomatic control group. The study was approved by the institutional human research ethics committee and all participants provided informed consent.

6.2.2 Outcome measures

Participants provided information about their age, sex, body weight, height and history of ankle injuries and health-care consultations. They also completed the following questionnaires and scales.

6.2.2.1 Severity of Pain and Stiffness

Participants rated their ankle pain at rest, average ankle pain over the past 24-hours, and worst pain over the past 7 days using an 11-point NRS anchored at 0 with “no pain” and at 10 with “worst pain imaginable”.

Similarly, participants rated their usual level of ankle stiffness over the past week on 11-point NRS anchored at 0 with “no stiffness” and at 10 with “worst stiffness imaginable”. Validity and reliability of The NRS (ICC= 0.95) as a measure of knee OA pain has been reported [310].

6.2.2.2 Quality of Life

The Assessment of Quality of Life questionnaire (AQoL-6D) was used to evaluate QoL. The AQoL-6D is an Australian multi-attribute utility instrument [313]. It comprises 20 questions in 6 separate dimensions (independent living, mental health, coping, relationships, pain, and senses). The unweighted responses of all questions were added to create an overall profile score (0-100) and individual scores for each of the six dimensions. Higher scores indicate better QoL. Strong construct [314] and discriminative validity for use in OA population have been reported [315]. Test-retest reliability (ICC=0.85-0.88) for this measure has been reported [316].

6.2.2.3 Function

Foot and Ankle Ability Measure (FAAM) was used to assess function [317]. It consists of a 21-item Activities of Daily Living subscale (FAAM-ADL) and an 8-item sports subscale (FAAM-sport). Each item is scored on a 5-point Likert scale (0-4) ranging from no difficulty (4) to unable to do (0). A “NA” option is available to indicate activities limited by factors other than foot or ankle problems. The total score is a sum of responses that range from 0 to 84 for the FAAM-ADL and from 0 to 32 for the FAAM-Sport. Items selected as “NA” are excluded from

scoring, resulting in a lower total number of possible points (denominator). The total score is divided by the denominator and multiplied by 100 to create a percentage, with a higher percentage indicating a higher level of function. In a separate question, participants also rated their current level of function as “normal”, “nearly normal”, “abnormal”, or “severely abnormal”. Test-retest reliability (ADL subscale; ICC= 0.87 and Sports subscale; ICC= 0.89) and internal consistency of the FAAM have been reported [317].

6.2.2.4 Pain and Disability

Ankle Osteoarthritis Scale (AOS) was used to evaluate disability and pain. The AOS is a disease-specific instrument used to measure pain and disability related to ankle OA. The AOS has been reported to be a reliable and valid self-reported outcome for ankle arthritis [318]. It consists of two subscales: pain and disability, with nine questions each. Participants indicate how much pain and difficulty they experience when performing certain activities over the past week. The original scoring of the two subscales was measured along a 100-mm visual analogue scale (VAS) anchored with “No pain” (0mm) and “Worst pain imaginable” (100mm), and “No difficulty” (0mm) and “So difficult, unable” (100mm), respectively. The original AOS was modified to an online format with an 11-point (0-10) NRS and same anchors as the original scale (paper version).

6.2.2.5 Ankle Instability

The Cumberland Ankle Instability Tool (CAIT) was used to evaluate ankle instability. The CAIT is a valid, and reliable (ICC=0.96) tool used to measure perceived ankle instability [319]. The tool contains 9-items with scores assigned based on the rank of the chosen response. Responses were summed separately for each limb. The maximum score is 30 with a higher score indicating less instability.

6.2.2.6 Physical Activity

The International Physical Activity Questionnaire- short form (IPAQ-SF) was used to capture data on self-reported physical activity. The IPAQ (short-form) measures the total amount of time spent performing a moderate activity, vigorous activity, walking or sitting in bouts of 10 minutes or greater over the last 7 days [322]. The time (in minutes) spent on each activity is multiplied by the defined metabolic equivalent of each task category and scores are

presented as MET-minutes per week. The IPAQ categorises physical activity into “low”, “moderate” or “high". Data processing, scoring and analysis were done according to the published guidelines for IPAQ-SF (available from: http://www.ipaq.ki.se). Validity and test-retest reliability (ICC = 0.51) in hip and knee OA population have been reported [323].

6.2.3 Statistical analysis

Body mass index (BMI) was calculated from self-reported height and body weight. Statistical analysis was performed using IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp). To assess the reliability of the online version of AOS, both versions were administered to 10 volunteers with ankle pain with an average time of 3 days between administrations. After completing one randomly selected version, individuals were sent the other version to complete. Kappa statistics were used to assess the reliability between the online and paper version of AOS. Reliability was categorized as poor (<0.00), slight (0.00–0.2), fair (0.21–0.4), moderate (0.41–0.6), substantial (0.61–0.8) or almost perfect (0.81– 1.0) [234]. Reliability between online NRS and paper VAS version of AOS was 0.898, with 95% CI (0.86, 0.92).

A univariate analysis of covariance (ANCOVA) with age, sex and BMI entered as covariates and group as a fixed factor was used to compare differences between groups for all outcomes. AQoL-6D data was compared between controls and published norms for AQoL-6D. Data representing point estimates of effect are presented as mean differences (MDs) and their confidence intervals (CI) in tabular format and as standardized mean differences (SMDs) and (CI) in forest plots. The SMD was calculated as the difference between the two groups means divided by the pooled SDs. Differences in outcomes were calculated such that negative differences indicated a deficit in the measure for the symptomatic group compared to that for the asymptomatic controls, and positive differences indicated the opposite. Effect sizes were interpreted as trivial: 0.0-0.2, small: 0.2-0.6, medium: 0.6-1.2, large: 1.2-2.0, very large: 2.0-4.0 and distinct:>4.0 [347.]

Chi-square test was conducted to compare categorical variables (sex and categories of physical activity) between groups. Odds ratio (OR) and risk difference (RD) were reported for categorical and binary data.

As bivariate normality was not assumed, the relationship between variables (AQoL-6D, group, sex, BMI, Age, ankle stiffness, CAIT, AOS-Pain, FAAM-Sport, FAAM-ADL and AOS-Disability) was investigated using nonparametric Spearman's Rank-Order Correlation. The correlation was interpreted as low (0.1 to 0.3), moderate (0.3 to 0.5), high (0.5-0.7) and very high(0.7-0.9) [347]. A stepwise backward elimination regression was conducted to establish the most influential independent variables associated with the dependent variable of AQoL-6D. The independent variables were group, sex, BMI, age, ankle stiffness, CAIT, AOS (pain and disability), and FAAM (ADL and sport). Those with a higher correlation to AQoL-6D were entered first. The multiple regression model was tested for multicollinearity. Statistical significance was set at $p<0.05$.

6.3 Results

There were 1948 volunteers who responded to advertisements seeking to participate for the study, of which 1388 were excluded, largely due to not providing any data for the AOS, FAAM, AQoL-6D, IPAQ and CAIT questionnaires (1055), not meeting selection criteria (298) and not providing consent (20). Fifteen records were removed as they were duplicates (Figure 6.1). Participants with missing item responses in questionnaires were followed up by email and invited to complete the missing data. Survey data were available for analysis from 394 participants (263 female) with a mean age 48.83 years (SD=12.05, range=30 to 75 years) and mean BMI 28.7(7.68), range=17.4 to 74.3). The cohort consisted of 270 symptomatic, and 124 asymptomatic controls reporting no ankle symptoms or history of ankle injury (Figure 6.1).

The majority of the symptomatic group reported both ankle pain and stiffness (93%), while a few reported either ankle pain/ache (5.9 %) or stiffness (1.1%) in the previous 3 months. The majority of symptomatic individuals 92.6 % had sought help from a health care practitioner for their symptoms (Table 6.1).

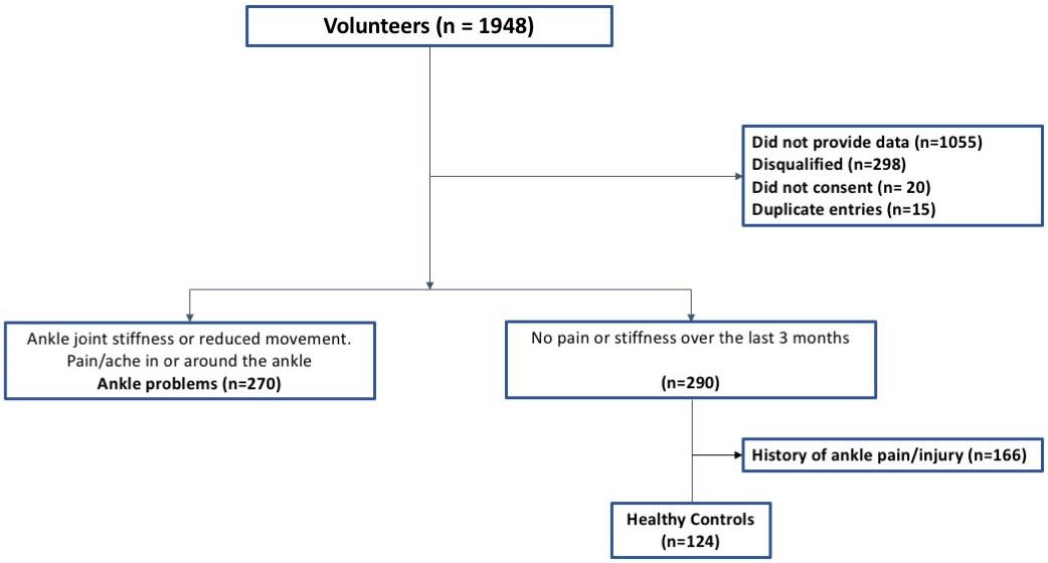

FIGURE 6. 1: Flow chart of recruitment and group allocation

Table 6.1: Characteristics (symptoms, injury history and health care consultation) of the symptomatic group.

Characteristic	Symptomatic
Pain intensity at rest, mean (SD)	2.91 (2.27)
Pain intensity at worst, mean (SD)	6.52 (2.42)
Average pain intensity mean (SD)	4.62 (2.36)
Usual level of stiffness mean (SD)	4.41 (2.68)
Unilateral ankle pain n (%)	167 (61.9%)
Bilateral ankle pain n (%)	100 (37%)
Unilateral ankle stiffness n (%)	164 (60.7%)
Bilateral ankle stiffness n (%)	90 (33.3%)
Previous injury n (%)	
No ankle sprain	73 (27%)
Single ankle sprain	35 (13%)
Multiple ankle sprains	162 (60%)
No fracture	186 (68.9%)
Single fracture	53 (19.6%)
Multiple fractures	31 (11.5%)
Healthcare practitioner consultation for ankle n (%)	
General practitioner GP	182(33.2%)
Orthopaedic surgeon	114 (20.8%)
Rheumatologist	26 (4.7%)
Sports physician	35 (6.4%)
Physiotherapist	136 (24.8%)
Osteopath	15 (2.7%)
Not visited a healthcare practitioner	40 (7.3 %)

6.3.1 Individuals with symptomatic ankle problems compared to asymptomatic controls

The symptomatic ankle group had a higher BMI (SMD = 1) and had 22% fewer females than the control group but were similar in age (Table 6.2 and Figure 6.2). There were significant differences between symptomatic ankle and control groups for all measures (AQoL-6D, AOS, FAAM, CAIT; SMD ranging from 1.1 to 3.2), with the exception of self-report physical activity (IPAQ short) ($p<0.001$).

In the separate FAAM question, where responders rate the level of functional normality, control participants were more likely to rate their function as "normal" RD 90% [85, 95]. More than half of symptomatic individuals rated their level of function as abnormal (47%), or severely abnormal(10.7%) while no controls rated their function as abnormal or severely abnormal.

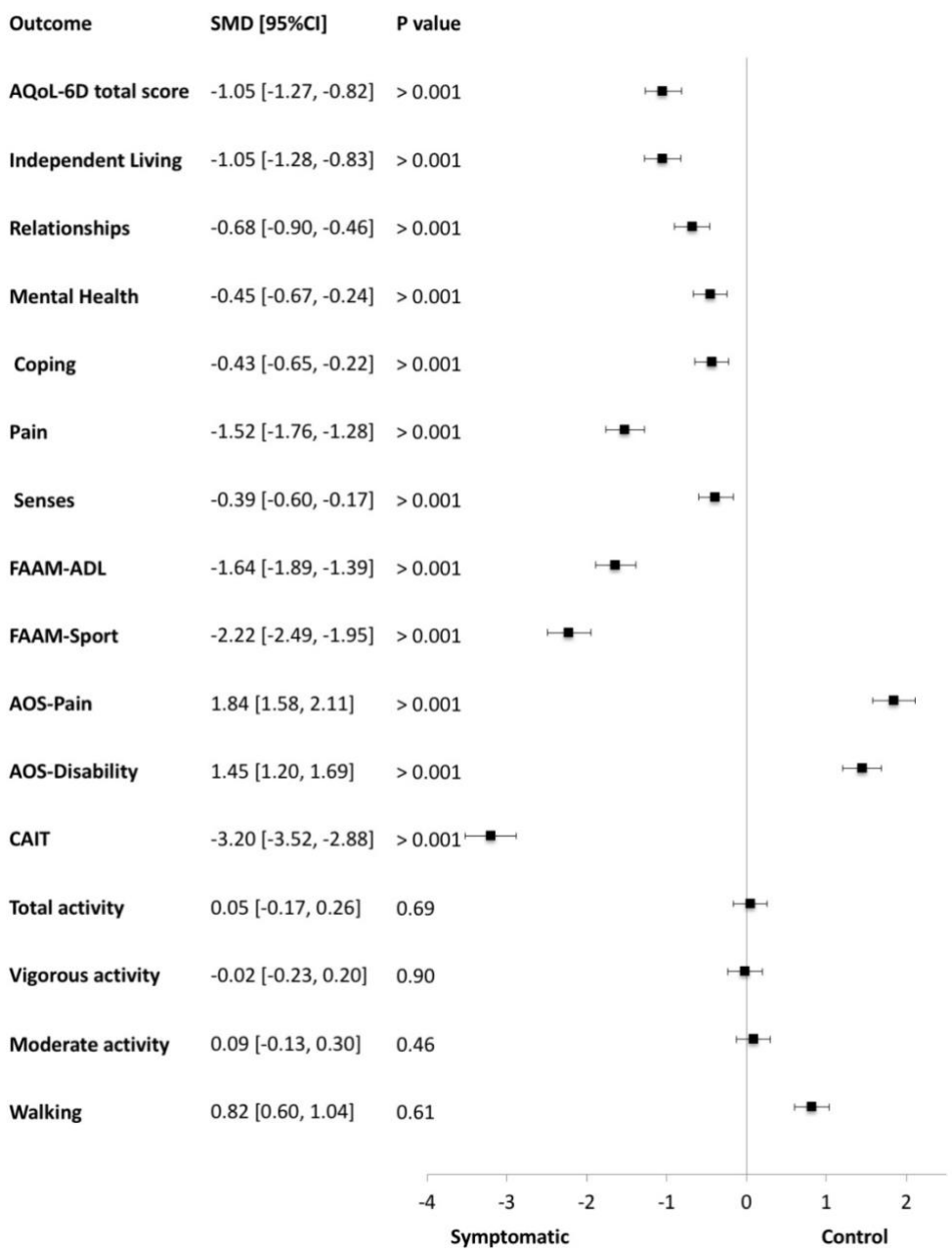

Figure 6. 2: Forest plot representing the differences between symptomatic and control

Table 6.2: Comparison of participant characteristics and outcomes between symptomatic (n=270) and asymptomatic control (n=124) groups.

Characteristic	Symptomatic	Asymptomatic controls	Point estimate of effect* (95%CI)	p value
Age years	48.4 (11.9, 270)	49.9 (12.3, 124)	1.5 [-1.1, 4.1]	0.249
Sex, Female n (%)	162 (60%)	101 (81.5%)	0.34 [020, 0.57] #	**< 0.001**
BMI kg/m^2	30.9 (8.1, 266)	24.1 (3.9, 124)	-6.8 [-8.0, -5.6]	**< 0.001**
AQoL-6D /100				
Total	72.3 (11.8, 263)	84.9 (12.4, 124)	-12.6 [-15.4, -9.9]	**< 0.001**
Independent Living	76.9 (15.8, 263)	93.8 (16.5, 124)	-16.9 [-20.6, -13.3]	**< 0.001**
Relationships	81.3 (16.1, 263)	92.4 (16.8, 124)	-11.1 [-14.8, -7.3]	**< 0.001**
Mental Health	69.5 (17.0, 263)	77.3 (17.8, 124)	-7.7 [-11.7, -3.8]	**< 0.001**
Coping	67.1 (16.4, 263)	74.3 (17.1, 124)	-7.2 [-11.0, -3.4]	**< 0.001**
Pain	54.1 (20.5, 263)	85.8 (21.4, 124)	-31.8 [-36.5, -27.0]	**< 0.001**
Senses	81.0 (10.9, 263)	85.3 (11.4, 124)	-4.3 [-6.8, -1.8]	**0.001**
FAAM- ADL %	67.7 (16.9, 266)	95.9 (17.7, 113)	-28.2 [-32.2, -24.1]	**< 0.001**
FAAM- Sport %	48.5 (21.0, 266)	95.9 (22.0, 111)	-47.4 [-52.4, -42.3]	**< 0.001**
FAAM-level of function n (%)				
Severely abnormal	29 (10.7%)	0 (0%)	11% [7, 15] ^	
Abnormal	127 (47.0%)	0 (0%)	47% [41, 53] ^	
Nearly normal	106 (39.3%)	9 (7.3%)	32% [25, 39] ^	
Normal	8 (3.0%)	115 (92.7%)	-90% [-95, -85] ^	
AOS- Overall %	37.4 (19.4, 266)	3.9 (20.4, 108)	33.5 [28.8, 38.2]	**< 0.001**
AOS- Pain %	38.0 (18.7, 266)	3.0 (19.6, 99)	35.0 [30.3, 39.6]	**< 0.001**
AOS- Disability %	37.1 (22.1, 266)	4.6 (23.2, 108)	32.5 [27.2, 37.9]	**< 0.001**
CAIT /30	10.4 (5.7, 229)	28.9 (5.9, 124)	-18.5 [-19.8, -17.1]	**< 0.001**
IPAQ (MET-min/week)				
Total activity	3417.4 (3339.5, 265)	3259.3 (3492.7, 124)	158.0 [-616.8, 932.9]	0.689
Vigorous activity	1251.1 (1843.7, 265)	1279.4 (1928.3, 124)	-28.3 [-456.1, 399.5]	0.897
Moderate activity	822.8 (1179.9, 265)	719.2 (1234.0, 124)	103.7 [-170.1, 377.4]	0.457
Walk	1343.4 (83.9, 265)	1260.8 (128.4, 124)	82.7 [-234.4, 399.7]	0.609
IPAQ, level of activity %(n)				
High	131 (48.5%)	61 (49.2%)	0 % [-10, 11] ^	
Moderate	79 (29.3%)	48 (38.7%)	-9 % [-19, 1] ^	

Low	59 (21.9%)	15 (12.1%)	10 % [3, 18] ^

 # Odds ratio, ^ risk difference

Abbreviations: n=number; BMI= body mass index; SD=standard deviation; MD= mean difference; CI=confidence interval; p=p value/significance level; AOS=ankle osteoarthritis scale; FAAM=Foot and Ankle Ability Measure; AQoL-6D= The Assessment of Quality of Life questionnaire-6D; CAIT= The Cumberland Ankle Instability Tool; IPAQ=The International Physical Activity Questionnaire;

All outcomes adjusted for age, sex and BMI

Significant difference at ($p < 0.05$) based on ANCOVA post-hoc comparisons with Bonferroni correction or Pearson's Chi-squared

Data presented as group mean (SD, n) and MD (CI), unless otherwise stated

Comparison between AQoL-6D results of controls with published age and sex-matched population norms [313] revealed that they were similar to published norms except for female controls between 55-64 years old who had higher AQoL-6D than published norms (Figure 6.3).

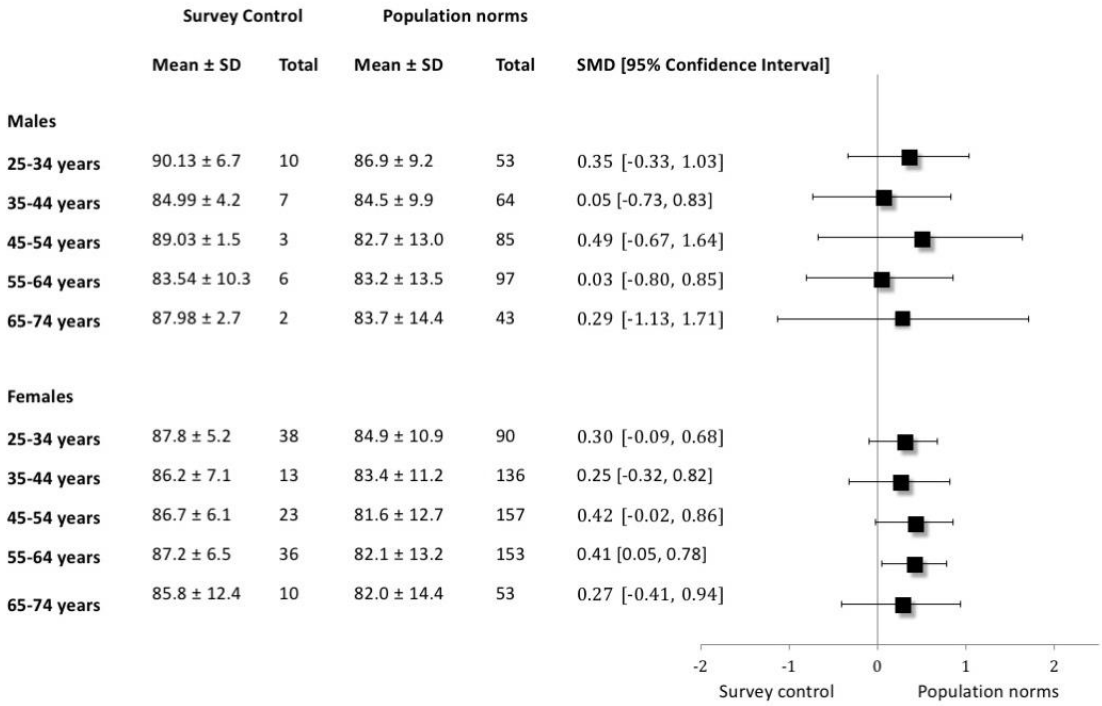

FIGURE 6. 3: Comparing AQoL results between survey asymptomatic respondents and published norms

6.3.2 Outcomes associated with QoL

The bivariate correlations between the different survey variables are presented in appendix 9. Higher BMI was associated with poorer patient-reported outcomes. The most important single factor independently associated with QoL was the FAAM-ADL as it accounted for the largest amount of variance in the regression model, which explained 65.7% of the total variance (Table 6.3).

Table 6.3: Multiple linear regression model with the quality of life (AQoL-6D) as the dependent variable

*Significant predictor variables	Standardized β weight	P value	R^2
FAAM-ADL	0.819	0.000	0.657
Age	0.067	0.087	
Variables not retained in the model			**Change in R^2**
Ankle stiffness	0.021	0.732	0.00
FAAM Sport	-0.055	0.583	0.00
AOS-Pain	-0.085	0.301	-0.002
Sex	-0.044	0.265	-0.002
BMI	-0.062	0.159	-0.003
Group	0.089	0.138	-0.003
CAIT	0.060	0.372	-0.001

Abbreviations: p-value/significance level; AOS=ankle osteoarthritis scale; FAAM=Foot and Ankle Ability Measure; ADL=Actvitiesof daily living; AQoL-6D= The Assessment of Quality of Life; BMI= body mass index; CAIT= The Cumberland Ankle Instability Tool.
**Initial multiple regression revealed that FAAM-ADL had the greatest contribution to AQoL-6D (β=-0.520, p<0.001) then the AOS-Disability (β=-0.314, p=0.001) both explaining 66.9% of the total variance. Multicollinearity test revealed a 10.35 variance inflation factor for FAAM and 9.36 for AOS-Disability. A Hierarchical multiple Linear regression was re-run after removing AOS-Disability based on β and p values.*

6.4 Discussion

This survey compared ankle symptoms (pain, stiffness, and instability), self-reported function, disability, physical activity and QoL between individuals with and without ankle symptoms and investigated the factors associated with QoL. The relation between the three ankle specific measures (CAIT, FAAM and AOS) and QoL in a large population of individuals with and without ankle symptoms was also evaluated. Our data indicate that individuals with ankle symptoms reported higher BMI, ankle related pain and disability, and lower ankle stability, function and QoL than asymptomatic controls. FAAM-ADL scores were shown to be a good representation of QoL in this population. This suggests that FAAM-ADL scores could be used as an outcome measure to determine the effectiveness of ankle management on ADL ability and QoL in both clinic and research.

Although the symptomatic sample in this study does not have confirmed ankle OA, we propose that the prevalence of ankle OA in this sample is likely to be high. This proposition is based on the presence of classical OA symptoms for more than 3 months on most days [52].

There is evidence from a cross-sectional laboratory study [381], which revealed that 94% (n=31) of participants who presented with ankle symptoms also had evidence of radiographic ankle OA defined as a Kellgren and Lawrence grade of ≥ 2 (definite osteophytes with mild-severe joint space narrowing [280]). This is also consistent with findings in knee OA where radiographic changes on imaging is common in those who have had >3 months of knee pain in the past 12 months and >90 days of pain in the past 6 months [52].

Understanding the association between the different variables and QoL has important implications. Our data indicate that functional disability at the ankle contributes to a lower QoL. In people with knee difficulties 5 to 20 years post anterior cruciate ligament reconstruction, improved function (in the form of return to sport at the same or higher level) was related to better QoL as measured by AQoL-8D [382]. This highlights the interplay between function and QoL and the importance of using function as an outcome measure in the management of individuals with ankle symptoms. The outcomes of this study may guide the selection of patient-reported outcome measures for clinicians managing patients with ankle symptoms and researchers investigating the effectiveness of interventions.

High BMI in our study population was associated with higher pain and disability, lower functional capacity and lower QoL. These findings are comparable to a large body of evidence reporting negative consequences for QoL in individuals with higher BMI [383,384,385-387]. The BMI of more than 65% of participants in the symptomatic group exceeded values for normal weight (>24.99 kg/m^2) [388]. There are possible mechanical and inflammatory mechanisms by which increased BMI is associated with OA. Obesity is characterized by excessive adipokine expression on the surface of chondrocytes [389,390], synoviocytes and subchondral osteoblasts [391] which increases degradative enzymes and pro-inflammatory cytokines production [392-394]. Obesity also modifies the joint mechanical environment due to increased joint load, inducing cartilage damage through activation of the mechanoreceptors (the stretch-activated channels, the a-5b1 integrin, and CD44) on chondrocytes [389,390]. Following mechanoreceptor activation, proinflammatory mediators such as prostaglandins and nitric oxide may be generated which fuel cartilage degradation [395,396]. Research has shown that weight management through exercise [397] and diet [398] improves self-reported function [397,399,400], pain[397,400] and QoL[397,398] in over-weight individuals with knee OA. In light of the relation

between obesity and pain, disability and QoL and the effect of weight loss intervention on these outcomes, providing weight loss interventions may be important in the management of this population.

Individuals reporting ankle symptoms demonstrated significantly poorer FAAM- ADL and AOS-Disability outcomes than asymptomatic controls. This is consistent with findings that 65% of people with musculoskeletal ankle conditions limit or modify their physical activity (predominantly sports) because of the ankle problem, with more significant limitation in individuals with OA (80%) than those with ankle sprains (55%) [2].

Individuals in the symptomatic group reported severe ankle instability defined as a CAIT score less than or equal to 23 [401] that is similar to the instability experienced by individuals with chronic ankle instability [100]. Further research is needed to understand the implications of instability in individuals with ankle pain and stiffness, and to determine if other symptoms common in a chronic ankle instability population, such as giving way, are also a problem in this population. It is important to ascertain the extent to which differences in outcomes between groups are clinically relevant. For most of these measures, information related to the minimal clinically important difference (MCID) or minimal detectable change (MDC) have not been specifically explored in a population with ankle symptoms. To supply clinical context, effect sizes can be used to measure the magnitude of difference between groups in the absence of MCID or MDC. In terms of effect size, group comparisons for ankle specific outcomes (AOS, FAAM, and CAIT) was large to very large and medium for total QoL, with most QoL related subscales indicating that individuals in the symptomatic group experienced significantly compromised QoL compared to asymptomatic controls.

Despite reports of lower ADL function and higher disability in the symptomatic group, the level of self-reported physical activity did not differ between groups in our study. Although unexpected, a limitation of self-reported outcomes compared to objective measures is the reduced sensitivity to low or moderate activity [368,402]. Nonetheless, the physical activity findings from the symptomatic group is similar to that reported for other joint pain populations. Previous studies have not identified any difference in self-reported physical activity between individuals with rheumatoid arthritis and controls [403], or in physical activity assessed using an activity monitor in individuals with knee and hip OA compared with

controls, despite lower scores on a physical function questionnaire [365]. There are possible reasons why activity may not be limited in the symptomatic group despite the reported increased disability and impaired function. It is possible that symptomatic individuals may alter the type of physical activity performed, such as participating in non-weight-bearing activities, to enable pain-free or low pain physical activity participation. Alternatively, as suggested by previous authors, use of analgesics may enable symptomatic individuals to maintain a certain level of physical activity [365].

Although this study provides important information on the relationship between ankle symptoms, function and QoL and the factors that influence QoL in this population, there are limitations that must be considered. First, data for this survey was collected using an online survey, which limited participation to internet users. Second, all data collected was self-reported and required long-term recall which may affect the ability to reliably self-report and may contribute to reporting bias. Third, responses related to the assessment of physical activity using the IPAQ depend on the perception of the different levels of activity (what activities fit in the vigorous or moderate categories [367]), and increase the likelihood of reporting the highest or desired level of physical activity participation rather than the actual activity performed [368]. These factors can lead to inaccuracies and over-reporting [404,405]. Future studies may verify levels of physical activity in individuals with ankle symptoms using objective measures. Although participants were specifically asked to indicate their level of function, ability and pain based on ankle symptoms, other comorbid factors may have also influenced our findings. Therefore, studies to identify the presence of comorbid conditions, psychologic status and balance confidence in individuals with ankle symptoms, and to explore the influence of those factors on pain and function, are warranted.

In summary, this study highlighted the significant burden of ankle symptoms. Individuals with ankle symptoms are characterized by lower QoL, lower function and high disability. Quality of life in symptomatic ankle population was positively associated with FAAM-ADL. Based on these findings, the management of ankle symptoms should target improvements in function and the FAAM-ADL is an appropriate tool to evaluate the change in function associated with management.

Chapter 7 The psychological features of symptomatic ankle problems: a cross-sectional survey

7.1 Introduction

Musculoskeletal conditions are a major cause of chronic pain and disability [7]. The World Health Organisation estimates that approximately 20-33% of people live with a painful musculoskeletal condition [1]. Chronic ankle conditions affect up to 20% of the Australian adult population [2], with ankle pain being the most common symptom affecting 73.5% of this population. Psychological morbidities such as pain-related fear of movement, anxiety, depression, catastrophizing and poor self-efficacy have been associated with pain [201]. Further, psychological morbidities can have a stronger influence on function than pain itself. For example, research on individuals with chronic low back pain identified kinesiophobia as a more disabling factor than the presence of back pain [202]. In another study involving individuals with chronic pain conditions, pain self-efficacy explained 30% of the variance of patient-reported disability, while pain intensity only explained 9% of the variance [406]. This highlights the interplay between psychological factors and disability, and the importance of addressing these factors when assessing and managing individuals with chronic pain.

While there is evidence to suggest that individuals with ankle pain present with higher levels of disability and lower levels of function than the asymptomatic population [407], the contribution of possible psychological factors has not been assessed. There is recent evidence that 29% and 33% of individuals with symptomatic ankle OA experience anxiety and depression respectively; however, this incidence was not compared to a control group [408]. Thus, it remains unclear whether individuals with ankle symptoms present with psychological features that are different than the asymptomatic population. In light of the relationship between depression, anxiety and pain-related fear of movement and higher levels of pain severity, greater disability, poorer health-related QoL and poorer treatment outcomes in individuals with chronic pain,[409,410-412,213], it is important to understand possible associations between these variables in individuals with ankle symptoms.

This cross-sectional survey aimed to (1) identify whether the psychological characteristics of individuals with symptomatic ankle problems differ from that of controls

and (2) investigate whether an association is present between psychological characteristics, ankle pain and self-reported function in this population.

7.2 Methods

A cross-sectional online survey of individuals with and without ankle symptoms was implemented to address the study aims.

7.2.1 Recruitment

Volunteers aged 18 to 82 years participated in this cross-sectional online survey between March 2017 and February 2018. Participants were recruited via community advertisements placed in university and community newsletters, communications from national and state arthritis organizations, and social media. Participants were asked if they experienced pain/aching in or around the ankle and/or stiffness or reduced movement of the ankle in the morning on most days for more than three months. Presence of pain was defined as pain ≥2 out of 10 on an 11-point NRS anchored with 'no pain' at 0 and 'worst pain imaginable' at 10. Symptomatic individuals were those with stiffness and/or pain. Participants were excluded from the symptomatic group if they reported pain in other body sites which is more or equal to that reported at the ankle. Participants who indicated not having ankle pain and/or stiffness on most days for more than three months or ankle pain less than 2 out of 10 on the NRS was were included in the control group. The institutional human research ethics committee approved this study. All participants provided informed consent.

7.2.2 Outcome measures

Participants completed an online survey to obtain information on general demographics (age, and sex), pain severity, pain self-efficacy, pain catastrophizing, kinesiophobia, anxiety, depression, and daily activities function.

Pain severity was rated on an 11-point NRS anchored with 'no pain' at 0 and 'worst pain imaginable' at 10. The NRS has been reported as a valid and reliable measure of knee OA pain with an excellent test-retest reliability (ICC= 0.95) [310]. Participants rated the worst pain they experienced at the ankle/s and 12 other musculoskeletal body sites during the past 7 days.

A 2-Item Abbreviated Pain Self-Efficacy Questionnaire (PSEQ-2) [335] was used to assess pain self-efficacy. Participants indicated their level of confidence to perform 'some type of work' and' live a normal life style', despite experiencing pain. The tool is highly correlated with the original PSEQ [335]. The test-retest reliability for PSEQ-2 was ICC=0.87, 95% CI =0.80-0.91 in a heterogeneous population with chronic pain [335]. Each item was scored on a 7-point scale with 0=not at all confident and 6=completely confident. Responses for the 2 items were summed to form a total score (0-12) with scores of ≥8 indicating high pain self-efficacy.

The Pain Catastrophizing Scale (PCS), a 13-item reliable and valid self-report scale, was used to assess pain catastrophizing [336]. The test-retest reliability in a population with chronic pain is ICC= 0.67 [337]. PCS items are rated on a scale from 0 (not at all) to 4 (all the time). PCS yields three different categories: Rumination (Sum of items 8, 9, 10, 11), Magnification (Sum of items 6, 7, 13) and Helplessness (Sum of items 1, 2, 3, 4, 5, 12). A total score (sum of all 13 item responses) was used as the outcome measure. Total scores range from 0 – 52, with a score of ≥30 indicative of clinically relevant levels of catastrophizing [336].

The Tampa Scale of Kinesiophobia -11 (TSK-11) [320] is a scale that consists of 11 statements about the perception of movement. It has good internal consistency (Cronbach's α=0.79) and test-retest reliability (ICC=0.81) [320]. Participants selected the most appropriate response on a 4-point Likert scale (1=strongly disagree to 4=strongly agree) to each statement. The total score was the sum of responses to the 11 items. Scores ranged from 0 to 44, with higher scores indicative of a greater degree of kinesiophobia. The specific cut-off score for high or low kinesiophobia for TSK-11 has not been established.

The Hospital Anxiety and Depression Scale (HADS) ***[331]*** was used to assess psychological distress (HADS total), anxiety and depression. The HADS is a valid scale to assess the severity of anxiety and depression symptoms in the general population and in somatic, psychiatric and primary care patients [332]. The reliability for HADS (Cronbach's alpha 0.68 -0.93 for HADS-A) and (Cronbach's alpha 0.67 -0.90 for HADS-D) has been reported [332]. Participants selected the most appropriate response to seven statements related to feelings of anxiety and seven statements related to the feeling of depression over the past 7 to 14 days. Each item was scored from 0-3. Responses were summed to obtain separate anxiety and depression scores. Scores ranged from 0 to 21 for both anxiety and depression. The HADS subscale scores were

classified as mild=8 to 10, moderate=11-15 and severe=≥16. A score of 8/21 was used as the cut-off point to indicate the presence of anxiety or depression [332].

Foot and Ankle Ability Measure Activities of Daily Living subscale (*FAAM-ADL)* is a 21-item scale that is used to assess ADL function [317]. Each item is scored on a 5-point Likert scale ranging from no difficulty (4) to unable to do (0). An ”NA” option is available to indicate activities limited by factors other than foot or ankle problems. The total score is the sum of responses (range from 0 to 84) divided by the denominator (number of possible points based on questions answered) and multiplied by 100 to create a percentage. A higher percentage indicates a higher level of function. Items selected as “NA” are excluded from scoring, resulting a lower total number of possible points (denominator). Test-retest reliability (ADL subscale; ICC= 0.87 and Sports subscale; ICC= 0.89) and internal consistency of the FAAM have been reported [317].

7.2.3 Statistical analysis

Chi-squared tests were conducted to compare the binary variable (sex) and dichotomised scores for the anxiety, depression, pain catastrophising and pain self-efficacy between groups. Depression and anxiety scores were dichotomised using 8 as a cut-off (>8=presence of anxiety/depression or ≤8=absence of anxiety/depression) [332]. For the PSEQ, scores of ≥8/12 indicated high pain self-efficacy [335]. Pain catastrophising scores were dichotomised to ≥30 (clinically relevant levels of catastrophizing) or <30 (no clinically relevant levels of catastrophizing) [336].

A univariate analysis of covariance (ANCOVA) was used to compare differences in continuous variables (anxiety, depression, pain catastrophizing, and function) between individuals with ankle symptoms and controls, with age, sex and pain severity in areas other than the ankle included as covariates. Wilcoxon rank-sum (Mann-Whitney) tests were used for skewed continuous variables and effect size (*r)* was calculated by dividing the Z statistic by the square root of sample size [413]. Missing data were excluded pairwise on analysis. Results for continuous variables are reported in the table as means and standard deviation (SD), as well as the between-group mean differences (MD), standardized mean differences (SMDs) and 95% confidence intervals (CI). Frequencies and percentages with risk differences (95% CI)

are reported for categorical and binary data. Effect sizes were interpreted as trivial: 0.0-0.2, small: 0.2-0.6, medium: 0.6-1.2, large: 1.2-2.0, very large: 2.0-4.0 and distinct: > 4.0 [347].

Using data from the symptomatic group only, the bivariate (nonlinear) relationship between age, sex, FAAM-ADL, PCS, HADS-A, TSK, HADS-D, and worst ankle pain was investigated using Spearman's correlation coefficient. Correlations were interpreted as per Hopkins recommendations as trivial (0.0-0.1), minor (0.1 to 0.3), moderate (0.3 to 0.5), major (0.5-0.7), huge (0.7-0.9) and distinct (0.9-1.0) [347]. For all analyses, the alpha level was set at $p \leq 0.05$.

Associations between ankle pain and psychological factors were determined using a multiple regression (backward elimination) model with PCS, HADS-A, TSK, HADS-D, included as independent variables (entered concurrently). A second multiple regression was run to investigate factors associated with a self-reported function (FAAM-ADL). The independent variables included were PCS, HADS-A, TSK, HADS-D, and worst ankle pain. Independent variables were eligible for inclusion in the multiple regression (backward elimination) model if results of Spearman's correlation coefficient showed they were associated significantly with FAAM and ankle pain ($p \leq 0.05$). The regression models were tested for multicollinearity. Variables were sequentially eliminated leaving only those with $p < 0.1$. Statistical analysis was performed using IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp).

7.3 Results

Two hundred seventy-four volunteers responded to study advertisements seeking participants with ankle symptoms and controls. After removing entries with incomplete data for HADS, PCS, TSK and PSEQ (n=20), data from symptomatic participants with pain from other body sites that was more or equal to that at the ankle pain (n=17), duplicate entries (n=5), and age ineligibility (n=1), survey data was available for analyses from 231 individuals (Figure 7- 1). Survey participants were 67% female (154 Females) with an overall mean (SD, range) age of 54.24 (12.96, 18 to 82) years. The cohort was comprised of 137 symptomatic participants (reporting ankle pain or/and stiffness on most days for more than three months), and 94 control participants (reporting no ankle stiffness or pain ≥2 out of 10). Two participants in the control group reported ankle pain of 1 out of 10 during the past week.

Data were available for analysis from all participants except for FAAM-ADL which was only completed by the final 121 participants.

7.3.1 Comparison between individuals with symptomatic ankle problems and controls

Participant characteristics and comparison of outcomes between symptomatic and controls are reported in Table 7.1. There were no age (p=0.97) or sex (p=0.85) differences between symptomatic and control groups. The symptomatic group reported worse pain at the ankle (medium effect; p <0.001, *r* =0.85) and worse pain at sites excluding the ankle (small effect; p<0.001, *r* =0.54) during the past week compared to the controls. There was a large difference between groups in function, with symptomatic participants reporting lower ADL function than controls (SMD=1.67). The symptomatic group reported moderately higher depression compared to controls (SMD=0.60).

Small but significant differences were identified for higher total psychological distress (HADS-Total; SMD=0.38), and greater risk of depression (28% higher risk) and anxiety (21% higher risk) in the symptomatic group compared to the asymptomatic control group. While the groups were comparable in pain catastrophizing, total and sub-scores (p>0.05), the symptomatic group presented with 12% higher risk of clinically relevant levels of catastrophizing than controls.

Table 7.1: Function and psychological characteristics of the symptomatic and control participants

Mean (standard deviation (SD)), mean difference (MD; 95% confidence intervals (CI)) and effect size **#**, unless otherwise indicated^

Outcome	Symptomatic (n=137)	Control (n=94)	Mean Difference (95%CI)	Effect size #	p-value
Age years [#]	54.2 (12.5)	54.3 (13.7)	0.06 [-3.4, 3.5]	-0.01 [-0.27, 0.25]	0.97
Sex, Female n (%) ^	92 (67.2%)	62 (66%)		1% [-11, 14] ^	0.85
Worst ankle pain /10 [†]	7 (5-8.5)	0 (0- 0)		0.85[†]	**<0.001**
Worst pain excluding ankle /10 [†]	6 (3- 8)	2 (0- 3.3)		0.54[†]	**<0.001**
PCS /52[#&]	12.5 (10.4)	11.1 (10.7)	1.5 [-1.5, 4.5]	0.13 [-0.13, 0.40]	0.337
PCS Magnification[#&]	2.7 (2.5)	2.2 (2.5)	0.5 [-0.2, 1.2]	0.20 [-0.06, 0.46]	0.180
PCS Rumination[#&]	3.9 (3.9)	4.0 (4.1)	-0.1 [-1.2, 1.0]	-0.03 [-0.29, 0.24]	0.867
PCS Helplessness[#&]	6.0 (4.9)	4.9 (5.1)	1.1 [-0.3, 2.5]	0.22 [-0.04, 0.48]	0.137
Clinical PCS n (%)^	21 (15.3%)	3 (3.2%)		12% [0.05, 0.19] ^	**0.003**
HADS-Total /42[#&]	10.04 (6.7)	7.45 (6.9)	2.60 [0.65, 4.55]	0.38 [0.12, 0.65]	**0.009**
HADS-A /21[#&]	5.3 (3.9)	4.8 (4.0)	0.5 [-0.6, 1.6]	0.13 [-0.14, 0.39]	0.392
Anxious n (%)^	41 (29.9%)	8 (8.5%)		21% [0.12, 0.31]^	**<0.001**
HADS-D /21[#&]	4.8 (3.6)	2.6 (3.7)	2.1 [1.1, 3.2]	0.60 [0.33, 0.87]	**<0.001**
Depressed n (%)^	41 (29.9%)	2 (2.1%)		28% [0.20, 0.36] ^	**<0.001**
FAAM-ADL % [#&]	66.3 (15.2)	92.2 (15.6)	-25.90 [-32.0, -19.77]	-1.67 [-2.09, -1.25]	**<0.001**

PSEQ-2 /12 #	8.7 (3.1)	NA	NA	NA	NA
High PSEQ n (%)^	98 (71.5%)	NA	NA	NA	NA
TSK-11 /44 #	27.7 (7)	NA	NA	NA	NA

 # Interval data reported as mean (SD) and point estimates of effect reported as standardised mean difference (SMD;95% CI).
^ Dichotomised/binary data presented as frequency (%) and RD (risk difference).
† Skewed continuous variables presented as median (interquartile range) and effect scores reported as the Mann-Whitney U test r.
& Analysis adjusted for age, sex and pain excluding ankle
Abbreviations: n=number; HADS= The Hospital Anxiety and Depression Scale; FAAM-ADL= The Foot and Ankle Ability Measure Activities of Daily Living subscale, PSEQ-2= 2-Item Short Pain Self-Efficacy Questionnaire; PCS=pain Catastrophizing Scale; TSK-11=Tampa Scale of Kinesiophobia, NA=not applicable.
Analysis for FAAM based on 70 symptomatic and 51 controls due to missing data.
PSEQ and TSK-11 were only assessed in symptomatic participants.

7.3.2 Factors associated with pain and function

Correlation levels among different variables are reported in Table 7.2. Spearman's correlation indicated that sex and age were not associated with pain or function (p>0.5) and therefore were not included in the regression analyses.

Table 7.2: Spearman's correlation product among different variables.

Spearman's rho	Ankle pain	FAAM ADL	PCS	PSEQ-2	HADS-D	TSK-11	HADS-A	Sex
FAAM ADL	-0.596** (0.00)							
PCS	0.579** (0.00)	-0.607** (0.00)						
PSEQ-2	-0.505** (0.00)	0.827** (0.00)	-0.645** (0.00)					
HADS-D	0.431** (0.00)	-0.599** (0.00)	0.674** (0.00)	-0.630** (0.00)				
TSK-11	0.410** (0.00)	-0.574** (0.00)	0.608** (0.00)	-0.551** (0.00)	0.525** (0.00)			
HADS-A	0.402** (0.00)	-0.415** (0.00)	0.630** (0.00)	-0.463** (0.00)	0.615** (0.00)	0.411** (0.00)		
Sex	0.13 (0.12)	-0.22 (0.07)	0.06 (0.48)	-0.05 (0.58)	-0.03 (0.73)	-0.06 (0.50)	0.16 (0.06)	
Age	0.02 (0.78)	-0.06 (0.65)	-0.03 (0.72)	-0.173* (0.04)	-0.03 (0.73)	-0.06 (0.51)	-0.197* (0.02)	-0.08 (0.37)

*** Correlation is significant at the 0.01 level (2-tailed).*
** Correlation is significant at the 0.05 level (2-tailed).*
P=Sig. (2-tailed)
All variables n=137 except for FAAM ADL based on n=70 due to missing data.

Multiple regression indicated that depression (p=1.0), anxiety (p=0.622), pain self-efficacy (p=0.532) and kinesiophobia (p=0. 230) did not significantly affect ankle pain scores. Pain catastrophizing as a whole (β=-0.511, p<0.001) was the independent variable associated with ankle pain, where an increase in catastrophizing was a predictor of increased ankle pain. The final model explained 26% of the total variance in ankle pain (Table 7.3).

Regression analysis with self-reported function (FAAM-ADL) as the dependent variable revealed that pain self-efficacy (β=-0.554, p<0.001) was positively associated with function, while ankle pain (β=-0.274, p<0.001), and kinesiophobia (β=-0.229, p=0.005) were negatively associated with function. Pain catastrophizing (p=0.98), anxiety (p=0.53) and depression (p=0.213) were not associated with function. The final model explained 74% of the total variance in reported function (Table 7.4).

Table 7.3: Multiple linear regression model with ankle pain as the dependent variable

Significant predictor variables	Standardized β weight	P value	R^2
PCS	0.511	0.000	0.261
Variables not retained in the model			**Changes in R^2**
HADS-D	0.000	1.0	0.000
HADS-A	0.049	0.622	-0.001
PSEQ-2	-0.061	0.532	-0.002
TSK-11	0.116	0.230	-0.008

Analysis based on a sample of 137 participants due to missing FAAM-ADL data.
PSEQ-2= 2-Item Short Pain Self-Efficacy Questionnaire; HADS= The Hospital Anxiety and Depression Scale; TSK-11=Tampa Scale of Kinesiophobia; PCS=pain Catastrophizing Scale.

Table 7.4: Multiple linear regression model with self-reported function (FAAM-ADL) as the dependent variable

Significant predictor variables	Standardized β weight	P value	R^2
PSEQ-2	0.28	0.00	0.738
TSK-11	-0.26	0.00	
Worst ankle pain	-0.38	0.00	
Variables not retained in the model			**Change in R^2**
PCS	-0.003	0.977	0.000
HADS-A	0.055	0.526	-0.002
HADS-D	-0.106	0.213	-0.006

Analysis based on a sample of 70participants due to missing FAAM-ADL data.
PSEQ-2= 2-Item Short Pain Self-Efficacy Questionnaire; FAAM-ADL= The Foot and Ankle Ability Measure-activities of daily living subscale; HADS= The Hospital Anxiety and Depression Scale; TSK-11=Tampa Scale of Kinesiophobia; PCS=pain Catastrophizing Scale.

7.4 Discussion

The present study aimed to identify whether psychological characteristics of individuals with symptomatic ankle problems differed from that of controls and to determine associations between psychological features, function and ankle pain. Results indicate that individuals with ankle symptoms report higher levels of depressive symptoms than individuals without such symptoms, and they are more likely to have clinical levels of pain catastrophizing, anxiety and depression than controls. Regression analysis showed that ankle pain severity and kinesiophobia were negatively associated with self-reported ADL function, and that pain self-efficacy was positively associated with self-reported ADL function. Further, pain catastrophizing was positively associated with ankle pain severity.

There is limited data from previous studies to compare the psychological characteristics of individuals with symptomatic ankle problems with the present study. Although HADS scores for depression in our study participants with ankle symptoms were within normal values, the symptomatic group presented with higher scores and a higher risk of reporting anxiety and depression than controls. The mean HADS depression and anxiety scores in individuals with ankle symptoms in our study were similar to previously reported values for hip and knee OA [414] and chronic knee pain [257,415]. This is important as anxiety and depression are reported to adversely affect QoL in individuals with chronic foot and ankle diseases, including ankle OA [408].

While clinical pain catastrophizing was more common in symptomatic than control participants, only a small percentage of symptomatic individuals in our study (15.3%) presented with clinical pain catastrophizing. There was no difference in pain catastrophizing scores between symptomatic and controls, and the mean pain catastrophizing score for participants with chronic ankle symptoms was lower than that reported for other chronic pain populations [415,416]. It is possible that high pain self-efficacy in participants with chronic ankle problems may have contributed to the lower levels of pain catastrophizing in our study population.

As pain self-efficacy and kinesiophobia are only appropriate to assess in symptomatic individuals, these data were not compared between the symptomatic and control groups in this study and thus data can only be discussed in relation to previous literature. Self-efficacy is a positive emotion defined as an individual's confidence in his/her ability to attain a specific goal or outcome [417]. Pain self-efficacy is therefore the confidence to attain the goals despite the presence of pain [418]. High mean pain self-efficacy scores and the majority of symptomatic individuals (71.5%) presenting with high pain self-efficacy suggest a desirable level of confidence in functioning, despite the presence of pain. This may represent an accommodation to ankle impairments overtime, an adaptation or a shifting focus away from pain and impairments. Evidence from a systematic review has concluded that higher self-efficacy in individuals with chronic pain conditions is associated with better function and activity participation, and less disability and depressive symptoms [419]. Thus, high pain self-efficacy may be an important coping mechanism in individuals with chronic ankle problems. It

is also possible that individuals with higher pain self-efficacy may push themselves harder, which may lead to provocation of symptoms. While the cross-sectional design limits conclusions of causal relationships, further research into pain self-efficacy in individuals with chronic ankle symptoms is warranted.

While no cut off scores for identifying high kinesiophobia has been established for the TSK-11, authors of a recent study suggested that a score of greater than or equal to 35 indicates high kinesiophobia [420]. Based on this cut-off value, 16.8% of the symptomatic participants in this current study presented with high kinesiophobia. One previous study looked at kinesiophobia in a cohort study of 85 individuals with mixed foot and ankle pathologies (such as lateral and syndesmotic ankle sprains, fractures, tendonitis, strains, heel pain, instability, general ankle pain and OA) attending a physiotherapy clinic. Individuals with ankle symptoms from our study had higher kinesiophobia and higher pain severity than this previous work [421]. The higher pain in our sample may explain the higher kinesiophobia reported. It is also possible that ankle symptoms may be associated with more kinesiophobia than foot problems as only 2% (n=2) of the heterogenous sample had ankle pain.

Self-reported ADL function was significantly lower in individuals with ankle symptoms than controls, and severity of ankle pain, kinesiophobia and pain self-efficacy were related to function, explaining 74% of the variance in function in this population. These findings are consistent with research reporting a relationship between kinesiophobia, pain intensity and self-reported function in individuals with symptomatic hip and knee OA [422], and studies that identified an inverse correlation between kinesiophobia and ADL activities and disability in individuals with an anterior cruciate ligament rupture [423] and low back pain [202], respectively. Findings from a cross-sectional survey revealed a strong association between self-reported function and health-related QoL in individuals with chronic ankle symptoms, with those with lower ADL function (measured with the FAAM-ADL) reporting lower QoL [424]. This suggests that there may also be a relationship between ankle pain severity, kinesiophobia, pain self-efficacy and QoL in individuals with ankle symptoms and that the symptomatic cohort in our study may have had lower QoL compared to the controls. This reinforces the importance of assessing these characteristics when managing individuals with chronic ankle pain and stiffness.

Perhaps unsurprisingly, our study data identified a relationship between greater pain catastrophizing and higher severity of ankle pain. This is consistent with previous research that reported a relationship between pain catastrophizing and pain intensity [415,425,426,427], but not self-reported function [428]. Thus, pain catastrophizing should be assessed in individuals with chronic ankle symptoms, particularly those with high pain severity.

This study has some limitations that must be acknowledged. First, online methods were used for participant recruitment and data acquisition. This may have introduced a selection bias by limiting participation to internet users. Second, the cross-sectional design prevents inferences regarding causality or changes of psychological features with changes in symptoms. Further longitudinal evaluation of psychological impairments is needed in order to understand the prospective and longitudinal effect of depression, kinesiophobia, pain self-efficacy on QoL and objective functional outcomes in this population. Third, the use of self-report methods may be associated with response bias and potential error in the participant's interpretation of the questions. Fourth, participants in this study presented with ankle pain and/or stiffness but were not diagnosed with a specific pathology. Based on previous research and our data from a laboratory study, these symptoms are thought to represent ankle OA. We have shown that 93.9% of participants (n=33) with ankle pain and/or stiffness lasting for at least three months have radiographic OA of a grade of 2 or greater on the Kellgren and Lawrence scale. The association between symptom and radiographic degeneration has also been identified at the knee [52]. X-rays to confirm the presence of ankle OA were not possible for this study due to the large sample size and diverse geographical locations of participants.

Findings from this study indicate that individuals with symptomatic ankle conditions present with higher depression scores and greater risk of depression, anxiety and clinical catastrophizing than controls, and that pain severity, pain self-efficacy and kinesiophobia are associated with the self-reported function. These data suggest that clinicians should assess for psychological impairments in individuals with chronic ankle problems and consider the need for an interdisciplinary approach to management. There is evidence from a randomised controlled trial that recognition and treatment of comorbid depression have the potential to improve pain, function and QoL outcomes in individuals with chronic painful arthritis [429].

Research to determine the effect of detection and management of psychological impairments on physical and functional outcomes in individuals with chronic ankle problems is warranted.

Chapter 8 Work limitation and function among working individuals with symptomatic ankle problems compared to controls: Cross-sectional survey

8.1 Introduction

Chronic musculoskeletal pain is a prevalent problem affecting 11-24% of European populations [430,431]. The negative impact of chronic pain on QoL is well documented [407,152,208]. Chronic pain has also been reported to negatively impact on work performance [432] and attendance [433]. A Finnish study of 1.2 million employees identified that musculoskeletal conditions (OA, disc disorders and rheumatoid arthritis) were associated with long episodes of sick leave [433]. A myriad of factors can influence employment and work participation, such as depressive symptoms [434], lower self-efficacy [435], physical work conditions and work stress [436], work ergonomics [437] feeling of control at work [438], and multiple pain sites [439].

In the young, active population, employment is a vital dimension in overall QoL [440,441]. Work is a mean for individuals to shape their personal identity and social status [442], and be financially independent. Musculoskeletal conditions are the principal causes of disability in people in their working years [443]. Research indicates that individuals with chronic musculoskeletal conditions want to remain involved in productive work [444]. Working individuals with chronic health conditions value work, as it provides them with financial independence, social contact and opportunities to contribute to society [445]

Chronic ankle pain is a prevalent musculoskeletal concern among adults aged 50–64 years [3] and may have significant implications for people who are working and caring for families, particularly as the population is living [446], and possibly remaining in the workforce, longer. Ankle symptoms are associated with a range of physical and QoL impairments [381] which could negatively impact work capacity. Thus, it is critical to understand the work limitations experienced by individuals with chronic ankle symptoms and factors that may influence work capacity in this population.

This study aimed to assess work limitations experienced by individuals with ankle symptoms and compare function, psychological stress, pain self-efficacy and kinesiophobia

between individuals with ankle symptoms and controls who are involved in paid or unpaid work. In addition, this study aimed to investigate potential differences in these outcomes between working and non-working individuals with ankle symptoms and identify factors associated with work limitation.

8.2 Methods

A cross-sectional online survey of individuals with and without ankle pain and/or stiffness was implemented to identify differences in work limitation, self-reported function and psychological features between individuals with ankle symptoms and controls and between working and non-working individuals with ankle symptoms. The survey also aimed to identify factors associated with work limitation among working individuals with ankle symptoms.

8.2.1 Participants

Volunteers aged 18 to 82 years with and without persistent ankle pain and/or stiffness participated in this cross-sectional survey between March 2017 and February 2018. Participants were recruited via community advertisements placed in a local university staff and community newsletters, communications from National and State arthritis organisations, and on social media. Persistent ankle pain or stiffness was defined as pain or stiffness on most days for >3 months, and the presence of pain was defined as pain ≥2 out of 10 on an 11-point NRS with 0='no pain" and 10='worst pain imaginable'. Participants were defined as *symptomatic* if they experienced pain/aching in or around the ankle and/or stiffness or reduced movement of the ankle in the morning on most days for more than three months and did not report pain in any other body sites that was equal to or greater than that reported at the ankle. Participants were defined as *controls* if they did not experience any ankle pain or stiffness on most days for more than three months, and any reported ankle pain was <2 out of 10 in the last week. The study was approved by the institutional human research ethics committee and all participants provided informed consent.

8.2.2 Data and measures

General demographic (age and sex) and health information were assessed. Based on The Self-Administered Comorbidity Questionnaire [311], participants were asked if they

experienced any of 15 defined medical problems. The participant indicated if they receive treatment for the health problem and whether it limited their activities.

The 12 item *Workplace Ability Limitation Scale (WALS)* was used to measure the extent to which the presence of ankle symptoms interfere with the performance of workplace activities. The WALS has high internal consistency and construct validity in people with arthritis [333]. A four-point Likert scale (0=No difficulty to 3=Not able to do) is used to rate each item. There are also options to indicate that the item is "not applicable to my job" or "difficulty unrelated to ankle", both of which result in a score of 0 for that item. Responses for all answers are summed for a total score ranging from (0–36). Higher scores indicate greater workplace activity limitations. Scores of 0-4 indicate little work difficulty, scores of 5-8 reflect moderate disability related to workplace adaptations, and scores >9 indicate considerable workplace disability [334].

The daily Living function was assessed using the 21-item *Activities of Daily Living* sub-scale of the *Foot and Ankle Ability Measure* (*FAAM-ADL)* [317]. Excellent test-retest reliability and internal consistency for the FAAM-ADL have been reported [317]. A 5-point Likert scale (0-4) ranging from 4=No difficulty to 0=Unable to do is used to rate each item. A "NA" (not applicable) option was available to indicate activities limited by factors other than foot or ankle problems. Items rated as "NA" are excluded from scoring, resulting in a lower total number of possible points. The total score (sum of responses) is converted to a percentage. Higher scores indicate a better level of function.

Psychological distress was assessed using *The Hospital Anxiety and Depression Scale (HADS)* [331] which has seven anxiety (HADS-A) and seven depression (HADS-D) related items. Participants select the most appropriate response about how they felt over the past 7 days. Each item is scored from 0-3. Scores are summed for the anxiety and depression subscales to obtain total subscale score ranging from 0 to 21. A score of 8/21 is identified as a cut-off point for the presence of anxiety or depression [332], with higher scores indicated greater anxiety or depression. The subscales are further classified as mild=8 to 10, moderate=11-15 and severe=≥16. This scale has been reported to be a good predictor of interview-diagnosed anxiety in a population with lower limb OA [211]. The validity of the HADs in assessing the

symptom severity, anxiety disorders and depression in somatic, psychiatric and primary care patients and in the general population has also been reported [332].

Pain-related fear of movement was assessed using the 11-item *Tampa Scale of Kinesiophobia (TSK-11)* [320]. The TSK-11 has good internal consistency (Cronbach's α=0.79) and test-retest reliability (ICC=0.81). Participants select the most appropriate response on a 4-point Likert scale (ranging from 1= Strongly disagree to 4= Strongly agree) to each statement. Responses to all items are summed to create a total score ranging from 0 to 44. Higher scores indicate a high degree of kinesiophobia.

Pain self-efficacy was assessed using the *2-Item Short Pain Self-Efficacy Questionnaire (PSEQ-2)* [335]. The PSEQ-2 is highly correlated with that of the original PSEQ [335]. Responses range from 0 (Not at all confident) to 6 (Completely confident) for each of the two items. The total score is the sum of responses from the two items. Scores range from 0 to 12, with scores of ≥8 indicating high self-efficacy.

The *Pain Catastrophizing Scale (PCS)* was used to assess catastrophizing. The reliability and validity of the PCS have been established [336]. The 13 items are rated on a scale from 0 (Not at all) and 4 (All the time). A total score (range from 0–52) is a sum of all individual item responses. A total score of ≥30 is indicative of clinically relevant levels of catastrophizing [336].

Number of musculoskeletal pain sites was assessed using a labeled body diagram. Participants rated the pain experienced during the past 7 days in 13 musculoskeletal sites including the ankle. The pain was rated using the 11-point NRS described previously, with participants advised to select 0 if no pain was experienced in the body site. The number of bodily pain sites is the sum of sites with a pain score of ≥2 out of 10 including the ankle.

8.2.3 Statistical analysis

A univariate analysis of covariance (ANCOVA) was used to compare differences in pain, work limitation, function, anxiety, depression and catastrophising between working individuals with ankle symptoms and controls. Pain self-efficacy and kinesiophobia where only assessed in symptomatic participants and were therefore only included in comparisons between working and non-working individual with ankle symptoms.

A second comparison (ANCOVA) for pain, number of pain sites, number of comorbid conditions, function, pain self-efficacy, kinesiophobia, anxiety, depression and pain catastrophising was undertaken between working and non-working individuals of the symptomatic ankle group. Age, sex and severity of pain in sites other than the ankle were controlled as covariates. Wilcoxon rank-sum (Mann-Whitney) tests were used to compare skewed continuous variables (pain scores, number of pain sites and number of comorbid conditions) between working individuals with ankle symptoms and controls and between working and non-working individuals of the symptomatic ankle group. From Mann-Whitney test output, a measure of effect size (*r*) was calculated by dividing the absolute standardized test statistic (Z) by the square root of the sample size (N) ($r = Z / \sqrt{N}$). Depression, anxiety [332], pain self-efficacy [335] and clinical catastrophizing [336] scores were dichotomized using cut-off scores as defined above. Chi-square tests were conducted to compare sex proportions, clinical catastrophizing and high PSEQ between groups.

Results for continuous variables are reported in the table as mean and standard deviation (SD), as well as the between-group mean difference (MD) and standardized mean differences (SMD) with 95% confidence intervals (CI). Frequencies and percentages with risk differences (95% CI) are reported for categorical and binary data. Measures of effect sizes (SMD and r) are reported in the results section and are interpreted as trivial: 0.0-0.2, small: 0.2-0.6, medium: 0.6-1.2, large: 1.2-2.0, very large: 2.0-4.0 and distinct:>4.0 [347].

Using data only from individuals with ankle symptoms, bivariate (nonlinear) relationships between (age, sex, HADS-A, TSK, HADS-D, PCS, ankle pain and WALS) was investigated using Spearman's correlation coefficient (normal distribution not assumed). Hopkins recommendations were used to interpret correlation as very small (0.0-0.1), small (0.1 to 0.3), medium (0.3 to 0.5), large (0.5-0.7), very large (0.7-0.9) and nearly perfect (0.9-1.0) [347]. For all analyses, the alpha level was set at $p \leq 0.05$.

Associations between work limitation and other survey factors were assessed using a multiple regression (backward elimination) model with ankle pain, TSK-11, HADS-D, HADS-A, PSEQ-2, PCS, number of pain sites and comorbid conditions included as independent variables in the models. Independent variables were eligible for inclusion in the multiple regression model if they were significantly associated with work limitation at $p \leq 0.05$. The regression

models were tested for multicollinearity. Variables were sequentially eliminated leaving only those with p<0.1. Statistical analysis was performed using IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp).

8.3 Results

Two hundred thirty-one individuals (154 females and 77 males) with a mean (SD, range) age of 54.2 (13.0, 18 to 82) years participated in this survey. A flow chart of recruitment and group allocation has been reported in chapter 7. Data were available from all participants except for the FAAM-ADL which was completed by 121 participants due to a late addition to the survey. Missing data were excluded pairwise on analysis. Only 65.5 % (n=90) of symptomatic participants and 55.3 % (n=52) of controls were involved in paid or unpaid employment. There were no differences in the type of occupations between groups (Table 8.1). Among the employed respondents, 67.6 % (n=96) were females and mean age was 50.3 (SD: 12.1, range: 18 to 77) years.

Table 8.1: Characteristics of the working symptomatic and control participants

Mean (Standard deviation) with between-group mean difference (MD) and point estimate of effect expressed as standardised mean difference (SMD) and its 95% confidence interval (CI) unless otherwise specified

Outcome	Symptomatic (n=90)	Control (n=52)	MD (95%CI)	SMD (95%CI)	p value
WALS # &	7.2 (4.5)	2.1 (4.7)	5.1 [3.4,6.8]	1.11 [0.74, 1.47]	**<0.001**
WALS score levels, n (%) ^					
Little work disability	29 (32.2%)	51 (98.1%)	-66% [-76, -56] ^		
Moderate work disability	25 (27.8%)	1 (1.9%)	26% [16, 36] ^		
Considerable work disability	36 (40%)	0 (0%)	40% [30, 50] ^		
Occupational grouping n (%) ^					
Technical	21 (23.3%)	11 (21.2%)	2% [-12, 16] ^		
Clerical/Administration	19 (21.1%)	15 (28.8%)	-8% [-23, 7] ^		
Training -related &	19 (21.1%)	9 (17.3%)	4% [-9, 17] ^		
Manual labour	9 (10%)	6 (11.5%)	4% [-5, 13] ^		
Allied health	9 (10%)	3 (5.8%)	4% [-5, 13] ^		
Academic	5 (5.6%)	4 (7.7%)	-2% [-11, 7] ^		

Catering & Services	5 (5.6%)	3 (5.8%)	-0% [-8, 8] ^		
Research	3 (3.3%)	1 (1.9%)	1% [-4, 7] ^		
FAAM-ADL% # &	69.3 (13.6)	95.2 (14.1)	-25.9 [-33.0,-	-1.86 [-2.43, -	**<0.001**
Number of pain sites †	7 (3- 10)	1 (0- 3)		0.594†	**<0.001**
Ankle pain †	7 (5- 8)	0 (0- 0)		0.813†	**<0.001**
Pain excluding ankle †	5.5 (3- 7)	2 (0.3- 4)		0.486†	**<0.001**
comorbidity †	1.0 (0- 1)	0 (0- 0)		0.354†	**<0.001**
HADs total # &	9.3 (6.0)	7.1 (6.2)	2.3 [0.0,4.5]	0.36 [0.02, 0.70]	**0.049**
HADS-A # &	5.2 (3.5)	4.8 (3.7)	0.4 [-0.9,1.7]	0.11 [-0.23, 0.45]	0.525
Anxiety levels n (%)					
No anxiety	65 (72.2%)	48 (92.3%)	-20% [-32, -8] ^		
Mild anxiety	12 (13.3%)	3 (5.8%)	8% [-2, 17] ^		
Moderate anxiety	10 (11.1%)	1 (1.9%)	9% [2, 17] ^		
Severe anxiety	3 (3.3%)	0 (0%)	3% [-1, 8] ^		
HADS-D # &	4.1 (3.3)	2.3 (3.5)	1.8 [0.6,3.1]	0.53 [0.18, 0.88]	**0.004**
Depression levels n (%) ^					
No depression	73 (81.1%)	51 (98.1%)	-17% [-26, -8] ^		
Mild depression	7 (7.8%)	1 (1.9%)	6% [-1, 13] ^		
Moderate depression	9 (10%)	0 (0%)	10% [3, 17] ^		
Severe depression	1 (1.1%)	0 (0%)	1% [-3, 5] ^		
PCS # &	11.5 (9.2)	9.7 (9.5)	1.8 [-1.6,5.3]	0.19 [-0.15, 0.53]	0.290
Clinical catastrophising n (%) **^**	10 (11.1%)	1 (1.9%)	9% [2, 17] ^		**0.048**

 # Interval data reported as mean (SD) and point estimates of effect reported as standardised mean difference (SMD;95% CI).
^ Dichotomised/binary data presented as frequency (%) and RD (risk difference).
† Skewed continuous variables presented as median (interquartile range) and effect scores reported as the Mann-Whitney U test r.
& Analysis adjusted for age, sex and pain excluding ankle
WALS= workplace ability limitation scale; FAAM-ADL= The Foot and Ankle Ability Measure-activities of daily living subscale; HADS= The Hospital Anxiety and Depression Scale; PCS=pain Catastrophizing Scale. Analysis of FAAM based on 46 symptomatic and 26 control participants.

8.3.1 Comparison between working individuals with and without symptomatic ankle problems

Working individuals with ankle symptoms were 68.9% (n=62) females with a mean (SD) age of 50.5 (11.6) years. Control participants who were working were 65.4% (n=34) female with a mean (SD) age of 50.0 (13.0) years. There were no differences in age (p=0.83)

or sex (p=0.67) between groups. Types of employment and study outcomes for symptomatic and control participants who reported being involved in paid or unpaid work are reported in Table 8-1. There was a large effect for lower ADL function in symptomatic participants than controls (SMD=1.9), and a moderate effect for higher work limitations in symptomatic individuals than controls (SMD=1.1). Two-thirds of the symptomatic group reported moderate to considerable work limitation. Individuals with ankle symptoms were 26% more likely to report moderate work limitation and 40% more likely report considerable work limitation than controls.

A Mann-Whitney U test revealed medium effects for greater ankle pain (p <0.001, *r*=0.813), and number of pain sites (p <0.001, *r*=0.594), and small effects for greater pain in sites other than ankle (p<0.001, *r*=0.486) and number of comorbidities (U =3236, p<0.001, *r*=0.354) in symptomatic participants compared to controls. There were small effect for higher levels of psychological distress (HADS total score: SMD=0.36) and depression (HADS-D score; SMD=0.53) in individuals in the symptomatic group compared to controls, but no significant differences for anxiety (p=0.53). While no significant differences were identified between symptomatic and controls in total pain catastrophizing score (p=0.290), the symptomatic group were 9% more likely to present with clinical catastrophizing.

8.3.2 Comparison between working and non-working individuals with ankle symptoms

In the symptomatic group, 65.7% (n=90) of individuals participated in paid or unpaid work. No sex differences were identified between working (68.9% (n=62) female) and non-working (63.8% (n=30) female) groups (p=0.55). Working individuals were moderately younger than those who were not working (mean (SD) 50.5 (11.6) vs 61.4 (11.1) years; SMD=0.95). Comparisons of outcomes between working and non-working individuals with ankle symptoms are reported in Table 8.2.

There were moderate effects for higher function and pain self-efficacy, and lower depression scores in working individuals with ankle symptoms compared to those who were not working (all SMD>0.6). The non-working symptomatic group was 20% more likely to present with mild depression than the working group. There were small effects for greater pain both at the ankle (p =0.025, *r* = 0.191) and at other body sites (p = 0.019, *r* = 0.200), and

a greater number of comorbidities (p =0.005, *r* = 0.239) in non-working compared to working individuals with ankle symptoms. A small difference in pain catastrophysing (SMD=0.4) was identified with better outcomes reported by working than non-working symptomatic participants. A trivial, but significant difference for a greater number of pain site in non-working compared to working individuals in the symptomatic groups (p =0.502, *r* = 0.057). No between-group differences were identified for anxiety (p=0.16) or kinesiophobia (p=0.66).

Table 8.2: Characteristics of working and not working individuals in the symptomatic ankle group

Mean (standard deviation) with between-group mean differences (MD) and point estimate of effect expressed as standardised mean difference (SMD) and 95% confidence interval (CI) unless otherwise indicated

Outcome	Symptomatic Working (n=90)	Symptomatic Not working (n=47)	Mean Difference (95%CI)	SMD (95%CI)	P value
FAAM-ADL # &	64.3 (16.4)	54.5(16.7)	9.8 [1.1, 18.4]	0.59 [0.08, 1.09]	**0.028**
Number of pain sites †	7 (3- 10)	6 (4- 11)	-1.5 [-3.0, 0.1]	0.0573†	0.502
Worst ankle pain †	7 (5- 8)	8 (6- 9)	-1.1 [-2.2, -0.1]	0.191†	**0.025**
Pain excluding ankle †	5.5 (3- 7)	7 (4- 8)	-1.4 [-2.5, -0.3]	0.200†	**0.019**
Multimorbidity †	1 (0- 1)	1 (0- 3)	-0.8 [-1.4, -0.3]	0.239†	**0.005**
PSEQ-2 # &	9.3 (2.8)	7.6 (2.9)	1.6 [0.6, 2.7]	0.60 [0.24, 0.96]	**0.003**
High pain efficacy ^	76 (84.4%)	22 (46.8%)	38% [22, 54]^		**<0.001**
TSK-11 # &	27.5 (6.8)	28.1 (7.0)	-0.6 [-3.2, 2.0]	-0.09 [-0.44, 0.27]	0.663
HADs total # &	10.6 (7.3)	14.2 (7.6)	-3.7 [-6.5, -0.9]	-0.48 [-0.84, -0.13]	**0.011**
HADS-A # &	5.9 (4.2)	7.0 (4.3)	-1.1 [-2.7, 0.5]	-0.26 [-0.61, 0.10]	0.162
Anxiety levels n (%) ^					
No anxiety	65 (72.2%)	31 (66%)	6% [-10, 23]^		
Mild anxiety	12 (13.3%)	4 (8.5%)	5% [-6, 15]^		
Moderate anxiety	10 (11.1%)	9 (19.1%)	-8% [-21, 5]^		
Severe anxiety	3 (3.3%)	3 (6.4%)	-3% [-11, 5]^		
HADS-D # &	4.7 (4.0)	7.2 (4.2)	-2.5 [-4.1, -1.0]	-0.61 [-0.97, -0.25]	**0.001**
Depression levels n (%) ^					
No depression	73 (81.1%)	23 (48.9%)	32% [16, 49]^		

Mild depression	7 (7.8%)	13 (27.7%)	-20% [-34, -6]^		
Moderate depression	9 (10%)	9 (19.1%)	-9% [-22, 4]^		
Severe depression	1 (1.1%)	2 (4.3%)	-3% [-9, 3]^		
PCS[# &]	13.9 (10.6)	18.2 (11.0)	-4.4 [-8.4, -0.3]	-0.40 [-0.75, -0.04]	**0.036**
Clinical catastrophising ^	10 (11.1%)	11 (23.4%)	-12% [-26, 1]^		0.058

[#] Interval data reported as mean (SD) and point estimates of effect reported as standardised mean difference (SMD;95% CI).

^ Dichotomised/binary data presented as frequency (%) and RD (risk difference).

† Skewed continuous variables presented as median (interquartile range) and effect scores reported as the Mann-Whitney U test r.

[&] Analysis adjusted for age, sex and pain excluding ankle

PSEQ-2= 2-Item Short Pain Self-Efficacy Questionnaire; FAAM-ADL= The Foot and Ankle Ability Measure-activities of daily living subscale; HADS= The Hospital Anxiety and Depression Scale; TSK-11=Tampa Scale of Kinesiophobia; PCS=pain Catastrophizing Scale.Analysis of FAAM based on 46 working and 24 not working participants.

Table 8.3: Correlation levels of each independent variable with WALS and other variables.

Spearman's rho (*p*-value)	WALS	PSEQ-2	PCS	HADS-D	TSK-11	Ankle pain	HADS-A	Number of comorbidities	Number of pain sites	Sex
PSEQ-2	-0.708** (0.00)									
PCS	0.602** (0.00)	-0.640** (0.00)								
HADS-D	0.559** (0.00)	-0.512** (0.00)	0.614** (0.00)							
TSK-11	0.545** (0.00)	-0.484** (0.00)	0.573** (0.00)	0.452** (0.00)						
Ankle pain-	0.444** (0.00)	-0.455** (0.00)	0.568** (0.00)	0.421** (0.00)	0.338** (0.00)					
HADS-A	0.412** (0.00)	-0.410** (0.00)	0.618** (0.00)	0.565** (0.00)	0.308** (0.00)	0.366** (0.00)				
Number of comorbidities	0.412** (0.00)	-0.230* (0.03)	0.330** (0.00)	0.17 (0.11)	0.16 (0.12)	0.362** (0.00)	0.283** (0.01)			
Number of pain sites	0.410** (0.00)	-0.304** (0.00)	0.384** (0.00)	0.301** (0.00)	0.14 (0.18)	0.479** (0.00)	0.408** (0.00)	0.443** (0.00)		
Sex	0.12 (0.25)	-0.07 (0.49)	0.10 (0.34)	-0.03 (0.81)	-0.11 (0.32)	0.07 (0.51)	0.17 (0.10)	0.260* (0.01)	-0.02 (0.87)	
Age	0.02 (0.84)	-0.19 (0.07)	-0.03 (0.75)	-0.05 (0.66)	0.02 (0.83)	0.08 (0.46)	-0.08 (0.44)	0.09 (0.42)	-0.05 (0.64)	0.03 (0.78)

*** Correlation is significant at the 0.01 level (2-tailed).*

** Correlation is significant at the 0.05 level (2-tailed).*

*N= 90, **p**= Sig. (2-tailed)*

WALS= workplace ability limitation scale; PSEQ-2= 2-Item Short Pain Self-Efficacy Questionnaire; HADS-D= Depression; HADS-A= Anxiety; TSK-11=Tampa Scale of Kinesiophobia; PCS=pain Catastrophizing Scale.

8.3.3 Factors associated with work limitations

The correlations between different variables are presented in Table 8.3. Spearman's correlation indicated that age (p=0.84) and sex (p=0.25) were not associated with work limitations (WALS scores). Regression revealed that pain self-efficacy (PSEQ) was negatively associated with work limitation, while depression (HADS-D), and kinesiophobia (TSK-11) were positively associated with work limitations in the backward regression model. Pain self-efficacy recorded the highest beta value (β=0.2382, p<0.001) followed by TSK-11 (β=-0.196, p=0.036) and then HADS-D (β=0.192, p=0.041). Lower pain self-efficacy and higher depression and kinesiophobia were associated with greater work limitations. This model explained 55% of the total variance in work limitation (Table 8.4).

Table 8.4: Multiple linear regression model with WALS as the dependent variable

Significant predictor variables	Standardized β weight	*p*-value	R^2
PSEQ	-0.382	0.000	0.55
TSK	0.196	0.036	
HADS-D	0.192	0.041	
Number of pain areas	0.150	0.082	
Number of comorbidities	0.140	0.097	
Variables not retained in the model			**Change in R^2**
PCS	0.031	0.813	0.000
Ankle pain	0.029	0.761	-0.001
HADS-A	-0.055	0.579	-0.002

Analysis based on a sample of 90 participants
PSEQ-2= 2-Item Short Pain Self-Efficacy Questionnaire; HADS= The Hospital Anxiety and Depression Scale; TSK-11=Tampa Scale of Kinesiophobia; PCS=pain Catastrophizing Scale.

8.4 Discussion

This study aimed to compare work limitation, psychological stress and self-reported function between individuals with persistent ankle pain and or stiffness and controls involved in paid or unpaid work. Our data indicate that individuals with ankle pain and stiffness reported higher work limitation, higher levels of depression and lower function than controls. Total WALS scores in individuals with ankle symptoms suggest moderate work disability. These scores are similar to WALS scores (mean (SD) 6.4 (4.4)) reported for individuals with OA and inflammatory arthritis, which were associated with workplace modification [334]. It is alarming that most of the symptomatic respondents in our study were not in manual labour.

Besides, 67.8% of them reported moderate to considerable work limitations, compared to only 1.9% of controls reporting moderate work limitations.

Three factors were significantly associated with work limitations: pain self-efficacy, depression, and kinesiophobia. These findings are supported by previous research in other populations. Previous research found that decreased kinesiophobia was associated with increased work ability among participants with persistent pain who were involved in a cognitive behavioral rehabilitation programme [447].

Associations between lower self-efficacy, the presence of depressive symptoms and unemployment have been reported in individuals with chronic persistent musculoskeletal pain presenting to rheumatology clinic [435,200]. Research has suggested two types of coping responses in individuals with pain: confrontation, which is an adaptive response linked to self-efficacy, and avoidance, which is a non-adaptive response [174]. Research on chronic back pain [448] reported that self-efficacy, which is an example of an adaptive response, mediates the relationship between pain-related fear and disability and was a stronger predictor of disability than fear. This is important because self-efficacy is a central factor that drives how individuals decide their actions and determine how to deal with challenges and impediments based on their perception of their potential capabilities [449]. Conceptually, individuals with adaptive responses exhibit resilience and attempt to deal with pain, rather than avoiding pain. This makes them less susceptible to functional decline. For example, higher pain self-efficacy was related to lower disability and depression in retired adults with persistent pain [450]. In contrast to this, avoidance responses are associated with avoiding painful experiences and activities, which lead to a range of physical and psychological consequences [174]. In chronic pain, avoidance stems from a belief that exposure to certain activity is a threat that will increase suffering from pain [176]. With this in mind, individuals who are fearful enter into a loop of avoidance, inactivity, pain, limited participation and disability [175,176]

Research has shown individuals (n=290) with depression and depressive symptoms present with work limitations, and significant missed days [451]. Enrolment to rehabilitation directed to improve depression yielded positive outcomes in form of less missed days and work disability [451]. Interestingly, while the severity of ankle pain was associated with work limitations in univariate analysis, it was not retained in the linear regression model. One

possible explanation for this could be that the majority of our sample (60%) presented with an ankle pain intensity of ≥7 out of 10. Thus, there may not have been sufficient variability in pain intensity in our sample. Further, as ankle pain is strongly associated with other psychological factors, such as pain self-efficacy and catastrophizing, it may mediate relationships between work limitations and these other variables.

There is growing evidence of the beneficial effects of work and employment on wellbeing [442]. Employment can be viewed as an indicator of the wellbeing and functional ability. Comparisons between working and non-working participants with symptomatic ankle problems identified that working individuals in the symptomatic group were older and reported higher pain self-efficacy, lower depression, and less comorbid conditions and catastrophizing than non-working symptomatic participants. This is in line with research showing individuals who were off work as a result of hip OA were older and had poorer physical function and more functional limitations from comorbidities compared to individuals with hip OA who were still working [452]. Similar findings were reported in research including working and non-working individuals with rheumatoid arthritis, the study reported that the non-working individuals reported worse pain scores than the working participants [453]. Findings from our study and previous work reinforce the importance of working on psychological wellbeing and self-efficacy in individuals with chronic health conditions. We, however, should not overlook that the non-working group was older and their unemployment may be related to age rather than symptoms [454]. However, we did not find a relationship between age and work limitations among working individuals.

The FAAM- ADL scores suggest a reduced function in individuals with ankle symptoms compared to controls and among non-working symptomatic participants compared to working symptomatic participants. Findings from an earlier cross-sectional survey revealed a strong association between lower self-reported function (using the FAAM-ADL) and poorer QoL in individuals with chronic ankle symptoms [424]. Although QoL was not assessed in the present study, previous data suggest that non-working individuals with ankle symptoms may have poorer QoL than individuals with ankle symptoms who are working.

A previous study that investigated how individuals with chronic musculoskeletal pain remained working showed that those who were still working scored higher on self-efficacy

and utilised self-management approaches [455]. In light of the finding of decreased pain self-efficacy in non-working individuals with symptomatic ankle problem and the relationship between pain self-efficacy and work limitations in our study, teaching self-management approaches and educating these individuals about their pain may be important to help them remain at work. As evidence suggests that individuals with chronic health conditions want to remain involved in productive work [444] and that work is important for psychological health [440,441], further research is needed to investigate strategies to assist with this. There is evidence that exercising in the workplace improves work ability, pain, physical function and depressive symptoms in workers with knee or hip OA [456]. There may be a role for workplace exercise in addressing work limitations and psychological health in individuals with ankle symptoms. Other examples of strategies that could improve the ability of these individuals to remain at work involve cognitive behavioral therapy to empower individuals and teaching self-management, or a workplace assessment to inform environmental or process modifications. Workplace modifications could include changes to physical set-up or job responsibilities, implementation of assistive devices or technology, or reorganization of work and rest time, structuring of job processes, and the use of assistive devices and equipment. Most of these suggestions would likely require expenses from the employer. Thus, cost-benefit analysis is warranted to show employers suggestions that may help those with chronic joint pain (who often have higher work limitations [457]) to remain at work.

The application of our findings is limited by the reliance on self-report which may have resulted in inaccurate reporting. Further, the cross-sectional study design limits conclusions of causal relationships between different variables and reduced work ability. While we have accounted for age, sex, pain in areas other than the ankle and multi-morbidity, the reasons for not working among the non-working participants were not investigated. Thus, we are unable to comment if not working is related to ankle pain or other factors. Individuals with ankle symptoms reported having a greater number of comorbidities and body pain sites. These characteristics may have contributed to the work and functional limitations experienced by this group. Previous research has shown that individuals with multiple pain areas present with impaired ADL [435,458] and lower work capacity [439]. Further, individuals with multiple areas of pain have more frequent health consultation and use of anti-inflammatory

and analgesic medication than individuals with no pain [459,460]. These features may be associated with impaired work ability and/or interrupted work time, which may have led to greater work limitations.

It is important to note that, in order to obtain a full picture of the work disability among individuals with ankle symptoms, personal and environmental factors must also be considered. For example, a number of work-related factors, such as work stress [436], work ergonomics [437], work control [438] have been shown to explain a substantial part of occupational differences in sickness absence due to musculoskeletal diseases. Some of these factors may be important predictors that were not measured in our model. Our study has not investigated the house hold income, the need to work for financial motives, family stressors, type of work involvement (full or part-time), the number of hours, or productivity. A lucid understanding of the various factors specific to this population that influence work disability is vital and may help explain some of the variances. Future research should aim to include a balanced cohort of working individuals across the different types of work. Further research is needed to examine the impact of family, societal and financial stressors, working hours and job control on reported work limitation.

In conclusion, this study highlights the presence of workplace activity limitations in individuals with ankle symptoms, and the relationship between depression, kinesiophobia, pain self-efficacy and work limitations in these individuals. Individuals with ankle problems who remained in the workplace were significantly younger with less pain in the ankle and in other body sites and higher function and pain self-efficacy compared to non-working symptomatic individuals. Total psychological stress, depression and catastrophizing were significantly lower among the working than non-working symptomatic individuals. The relationship between these factors and the decision to stop working has not been investigated. Future research could examine former work limitations and related factors in those who are no longer working to promote understanding of the reason for ceasing work in this population.

Chapter 9 Falls, falls self-efficacy and balance confidence in adults with ankle symptoms compared to controls: A cross-sectional survey study

9.1 Introduction

Falls are a major public health concern around the world [324]. Falls can result in serious injuries, loss of independence, functional decline, restricted activity, increased health care utilization, hospitalization, admission to a nursing facility, and death [461-466]. Although falls occur across the lifespan [467], they are more common among older adults with one in three adults 65 years of age and older falling annually [468]. Chronic joint pain is associated with an increased risk of falls [373], greater fear of falling [469], and greater pain severity is linked to lower balance confidence in older adults [470]. Persistent knee [471] and hip [472] pain have specifically been identified as falls risk factors. Although high levels of chronic ankle pain are prevalent [3 153,173], the incidence of falls and fear of falling has not been investigated in individuals with chronic ankle pain. It remains unclear whether persistent ankle pain is also a risk factor for falling.

Many factors (balance and gait impairments, limited mobility, fear of falling, muscle weakness and use of multiple medications [473]) have been suggested to increase falls risk in adults [474]. A systematic review [338] has identified a number of physical impairments in individuals with ankle OA (impaired balance, decreased muscle strength and reduced joint motion) that are commonly associated with falls [188,189,270,475;168,191]. Further, individuals with ankle joint symptoms walked with a slower speed [476-479] and a shorter stride length [149,476,477] compared to controls. In light of these impairments and the evidence of a relation between persistent joint pain and the risk of falling [182-184], individuals with ankle joint pain may be at an increased risk of falling.

A recent cross-sectional laboratory study demonstrated that ankle pain and stiffness had a greater impact on physical impairments and function [381] than radiographic evidence of ankle joint degeneration. It was identified that individuals with ankle symptoms present with lower QoL, self-reported function, muscle strength and ankle range of motion and slower ambulatory function compared to asymptomatic individuals. The presence of radiographic OA without symptoms was not associated with any physical impairments or deficits in function or

QoL [381]. As this data suggests that impairments associated with falls are present in individuals with ankle pain and stiffness, rather than those with radiographic signs of joint pathology, it may be important to investigate falls specifically in those with symptoms.

Thus the primary aim of this study was to compare the self-reported history of falls (including frequency of falls, associated injuries, and hospitalization), falls self-efficacy and balance confidence in adults with and without persistent ankle symptoms. A secondary aim of this study was to identify factors associated with the frequency of falling in adults with and without persistent ankle symptoms.

9.2 Methods

9.2.1 Participants

Adult volunteers (18 to 82 years of age) participated in this online cross-sectional survey between March 2017 and February 2018. Participants were recruited via community advertisements placed in university and community newsletters, communications from National and State arthritis organizations, and social media (targeting volunteers from different Australian states). Participants were eligible for inclusion in the *symptomatic group* if they experienced pain/aching in or around the ankle and/or stiffness or reduced movement of ankle in the morning on most days for more than three months and did not report pain equal to or greater than that reported at the ankle in any other body site. Inclusion criteria for the *control group* were no ankle pain and/or stiffness on most days for more than three months, and ankle pain less than two out of ten in the last week (reported on an 11-point NRS anchored with the 'No pain' at 0 and 'Worst pain imaginable' at 10). The study was approved by the institutional human research ethics committee and all participants provided informed consent.

9.2.2 Outcome measures

Participants completed an online survey to obtain information on general demographics (age, and sex), falls history, falls efficacy, balance confidence, function, and health status (comorbid conditions and pain).

Falls history in the last 12 months was determined by the question: "In the last 12 months, have you had any falls?" A fall was defined as "an event which results in a person coming to rest inadvertently on the ground or floor or other lower level" [324]. Participants were categorised as fallers (an individual who fell at least once over the last 12 months [325]) or non-fallers. Participants indicated the number of falls they experienced in the past 12 months by selecting on of the options including 0, 1, 2, 3, 4, 5 or more. Fallers indicated if they sustained an injury from falling, the type of injury experienced (i.e. bruises, cuts/grazes, sprain/strain, broken bones, dislocation), and if any fall resulted in hospitalization.

The Falls Efficacy Scale-International (FES-I) was used to determine how concerned a participant was about the possibility of falling during the performance of 16 different physical and social activities inside and outside the home [326]. The level of concern was measured on a four-point Likert scale ranging from 1 (not at all concerned) to 4 (very concerned) [326]. The total (summed) score ranged from 16 to 64, with a higher score indicating a greater level of concern about falling (i.e. lower falls self-efficacy). Previous publications have categorised the level of concern about falling as: low (scores of 16-19), moderate (scores of 20-27) and high (scores of 28–64) [327]. This instrument has excellent internal and test-retest reliability (Cronbach's alpha=0.96, ICC=0.96) [326].

The Activities-Specific Balance Confidence (ABC) Scale was used to measure balance confidence during activities of daily living. Participants were asked to indicate their level of self-confidence when performing a range of 16 activities without losing balance or becoming unsteady. Activities ranged from walking around the house to walking on icy sidewalks. Confidence was rated on a scale ranging from 0% (not confident at all) to 100% (completely confident) with answers provided in 10% increments [328]. A total score for the scale was obtained by calculating the average score/percentage per question (the sum of individual question scores divided by 16). Scores ranged from 0 to 100%, with higher scores indicating better balance confidence. The ABC has been shown to have good test-retest reliability (ICC=0.88) and strong internal consistency (Cronbach's alpha=0.9) [480].

The 21-item activities of the daily living subscale of the Foot and Ankle Ability Measure (FAAM-ADL) were used to assess function [317]. Each item was scored on a 5-point Likert scale ranging from 'no difficulty' (4) to 'unable to do' (0). A "not applicable" option was available to

indicate activities limited by factors other than foot or ankle problems, with those items removed from scoring. The total score (sum of responses) was converted to a percentage (0-100%), with a higher percentage indicating a higher level of function. This questionnaire has excellent test-retest reliability and internal consistency [317].

The severity of ankle pain was measured using an 11-point NRS as described above. Participants were asked to indicate the worst pain experienced during the past 7 days. Pain in 12 other bodily regions (identified on a body chart) was also recorded using a NRS. The number of bodily regions (including the ankle) with pain ≥2 out of 10 were summed as a measure of the number of pain sites (score ranging from 0 to 13).

A modified version of the Self-Administered Comorbidity Questionnaire (SCQ) was used to collect data on comorbid health conditions [311]. Participants indicated if they experienced any of the following 15 medical problems: heart disease, high blood pressure, lung disease, diabetes, ulcer or stomach disease, kidney disease, liver disease, anaemia or other blood disease, cancer, depression, auto-immune disease, back pain, rheumatoid arthritis, gouty arthritis, and OA other than ankle. Participants were also asked if they received treatment for any of those defined health problems and whether those health problems limited their activities. The number of comorbidities that participants reported receiving treatment for were summed (scores ranging from 0-15). This was calculated as an indication of multi-morbidity [312].

9.2.3 Data and statistical analysis

Survey data was reviewed for completion and participants who did not complete the questions on falls history, falls self-efficacy (FES-I) and balance confidence (ABC scale) were followed up by email and invited to provide the missing data. Participants who did not subsequently complete these questions were excluded from the study.

Statistical analysis was performed using IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp). Age was compared between groups using an independent t-test. A univariate analysis of covariance (ANCOVA) was used to compare differences in falls self-efficacy, balance confidence, and ADL function between symptomatic individuals and asymptomatic controls. Age, sex and severity of pain in body areas other than the ankle were

included as covariates to control for their confounding influence on the dependant variables. Wilcoxon rank-sum (Mann-Whitney) test was used to compare the number of bodily pain sites, the severity of pain, and number of comorbid conditions (multi-morbidity) between symptomatic individuals and asymptomatic controls. The effect size (*r)* from Wilcoxon rank-sum (Mann-Whitney) tests were calculated by dividing the Z statistic by the square root of sample size [413]. Chi-square tests were conducted to compare categorical and binary variables (sex, falls status, number of falls, falls-related injuries, hospitalization, categories of concern about falling and balance confidence) between groups. Data are presented in Table 9-1 as mean, standard deviation (SD), mean difference (MD) and point estimate of effect expressed as SMDs and their 95% confidence intervals (CI) for continuous variables. For categorical and binary variables, frequency (percentages) with risk differences (CI) are presented (Table 9-1). Effect sizes were interpreted as trivial: 0.0-0.2, small: 0.2-0.6, medium: 0.6-1.2, large: 1.2-2.0, very large: 2.0-4.0 and distinct: > 4.0 [347].

The bivariate nonlinear relationship between dependent and independent variables was investigated using Spearman's correlation coefficient (normal distribution not assumed). Correlation was interpreted as low (0.1 to 0.3), moderate (0.3 to 0.5), high (0.5-0.7) and very high (0.7-0.9) [347]. For all analyses, the alpha level was set at $p \leq 0.05$. Backward elimination regression models were conducted to investigate factors associated with falls status (i.e. being a faller compared to non-faller coded as faller=1, non-faller=0) and number of falls. The independent variables included in the bivariate correlations were age, sex, falls self-efficacy, balance confidence, ADL function, worst ankle pain, worst pain excluding the ankle, number of morbidities, and depression. Depression data was obtained as a binary outcome from the Self-Administered Comorbidity Questionnaire and was entered into the model coded as 1=Yes and 0=No. Group was also entered into the model through a dummy coded variable (i.e., symptomatic=1 and control=0). The multiple regression model was tested for multicollinearity. Variables were sequentially eliminated leaving only those with $p<0.1$.

9.3 Results

9.3.1 Participant demographics

A total of 282 surveys were received with 56 surveys excluded due to incomplete survey data (n=31), ankle pain was not the most severe area of pain (n=17), duplicate entries (n=5), individuals in the control group with ankle pain>1/10 (n=2) and age (n=1). The survey was completed by 226 participants (134 symptomatic participants and 92 controls).

Characteristics of symptomatic and control participants are reported in Table 9.1. Mean (SD) age of study participants was 54.28 (12.86) with 152 females and 74 males. There were significant moderate differences in ankle pain ($p < 0.001$, $r = 0.86$) and pain excluding ankle ($p < 0.001$, $r = 0.57$) between groups. The median (interquartile range, IQR) severity of ankle pain in symptomatic participants was 7 (5- 9) vs 0 (0- 0). The symptomatic group reported greater pain intensity in body sites other than the ankle (6 (3- 8) vs 2 (0- 3)). The symptomatic group reported moderately higher number of musculoskeletal pain sites (7 (4-10) vs 1 (0- 3) ($p < 0.001$, $r = 0.69$)), higher number of comorbidities (1 (0- 2) vs 0 (0- 1) ($p < 0.001$, $r = 0.37$)) and lower ADL function (SMD= 1.6) compared to controls. Reported morbidities are listed in Table 9.2.

9.3.2 Falls related outcomes

More than 220 falls were reported by survey participants. Nearly half (48.7%; n=110) of all participants reported one or more falls in the last 12 months. Among fallers, 40.5% sustained a fall-related injury. The most commonly reported injuries associated with falling were bruises and cuts and grazes (45.5%)

There were significantly more fallers (individuals with one or more fall; $p<0.001$) with a greater number of falls in the symptomatic group than the control group. One-third (34%) of symptomatic individuals reported more than two falls in the previous 12 months compared to 4.2% in the control group. In the symptomatic group, 47.7 % of fallers sustained a falls-related injury compared to 12.5 % of controls (p=0.002). Most injury categories and hospitalisation due to a fall were more common in symptomatic than control participants.

Table 9.1: Fall and fall-related outcomes compared between symptomatic and Control groups

Mean (Standard deviation, n) of characteristics of the symptomatic and Control groups, between-group mean differences and point estimate of effect expressed as standardized mean difference and its 95% confidence interval (95% CI) unless otherwise stated

Group characteristic	Symptomatic	Control	MD (95%CI)	SMD (95%CI)	p value
Age years	54.2 (12.3, 134)	54.5 (13.7, 92)	0.3 [-3.2, 3.7]	-0.02 [-0.29, 0.24]	0.87
Female (%)	91 (67.9%)	61 (66%)	2% [-11, 14]^		0.80
Number of bodily pain sites /13	6.9 (3.2,134)	1.4 (3.2,92)	0.69†		**<0.001**
Worst ankle pain /10	6.7 (1.9, 134)	0.02 (1.9,92)	0.86†		**<0.001**
Worst pain excluding ankle /10	5.5 (2.4, 134)	2.0 (2.4, 92)	0.57†		**<0.001**
Multimorbidity/15	1.3(1.2,134)	0.4 (1.2,92)	0.37†		**<0.001**
FAAM-ADL % *	67.1 (14.9, 69)	91.5 (15.4, 51)	-24.4 [-30.5, -18.3]	-1.60 [-2.02, -1.19]	**<0.001**
Falls related outcomes					
Number of fallers	86 (64.2%)	24 (26.1%)	38% [26, 50] ^		**<0.001**
Number of falls (%)					
One fall	33(38.4%)	17 (70.8%)	-32% [-53, -12]^		
Two falls	24 (27.9%)	6 (25%)	3% [-17, 23]^		
Three falls	16 (18.6%)	0 (0%)	19% [9, 29]^		
Four falls	8 (9.3%)	0 (0%)	9% [1, 18]^		
Five or more falls	5 (5.8%)	1 (4.2%)	2% [-8, 11]^		
Number of injured fallers	41 (47.7%)	3 (12.5%)	35% [18, 52] ^		**0.002**
ABC % *	78.4 (19.9,134)	88.4 (20.7,92)	-10.0 [-15.9, -4.1]	-0.49 [-0.76, -0.22]	**0.001**
FES-I 16-64 *	24.3 (7.9, 134)	21.4 (8.2, 92)	2.9 [0.5, 5.2]	0.36 [0.09, 0.63]	**0.017**
Concern about falling					
High concern	44 (32.8%)	1 (1.1%)	32% [24, 40] ^		
Moderate concern	52 (38.8%)	12 (13%)	26% [15, 37] ^		
Low concern	38 (28.4%)	79 (85.9%)	-58% [-68, -47] ^		
Number of fallers with fall-related injuries (%)					
Bruises, Cuts/grazes	47 (54.7%)	3 (12.5%)	42% [25, 59] ^		
Sprain/strain	16 (18.6%)	1 (4.2%)	14% [3, 26] ^		

Fractures/dislocation	14 (16.3%)	0 (0%)	16% [7, 26]^
Hospitalisation	13 (31.7%)	0 (0%)	32% [-4, 67] ^

Dichotomised/binary data presented as frequency (%) and RD^ (95% confidence interval)

**Adjusted for age, sex and severity of pain excluding ankle.*

† Effect sizes based on Wilcoxon rank-sum (Mann-Whitney) tests, calculated by dividing the absolute Standardised test statistic z by the square root of the number.

Abbreviations: ABC=The Activities-Specific Balance Confidence Scale, FES-I=The Falls Efficacy Scale-International, FAAM-ADL= The Foot and Ankle Ability Measure-activities of daily living subscale.

FAAM data based on 51 control and 69 symptomatic due to a late addition to the survey

Table 9.2: Number (%) of each comorbid condition reported by symptomatic and asymptomatic participants

Conditions	Symptomatic group	Control group
High blood pressure	30 (22.4%)	14 (15.2%)
Osteoarthritis other than ankle	30 (22.4%)	1 (1.1%)
Back pain	30 (22.4%)	3 (3.3%)
Depression	22 (16.4%)	9 (9.8%)
Rheumatoid arthritis	15 (11.2%)	
Auto-immune disease	14 (10.4%)	3 (3.3%)
Ulcer or stomach disease	9 (6.7%)	
Diabetes	5 (3.7%)	
Cancer	5 (3.7%)	
Lung disease	5 (3.7%)	
Gouty arthritis	4 (3%)	
Anaemia or other blood disease	3 (2.2%)	1 (1.1)
Heart disease	3 (2.2%)	5 (5.4%)
kidney disease	2 (1.5%)	
Liver disease	1 (0.7%)	

Fear of falling (FES-I) was higher with small effect in the symptomatic group compared to the control group (SMD=0.36). Individuals in the symptomatic group were 32% more likely to report a high concern about falling and 26% more likely to report moderate concern than the control group (Table 9-1). Symptomatic participants reported lower balance confidence (ABC scale) with a small effect compared to controls (SMD=0.49).

9.3.3 Outcomes associated with falls status

Bivariate correlation between falls status (being a faller or non-faller), FAAM-ADL, ankle pain, pain sites excluding the ankle, number of pain sites, number of morbidities, depression, group, ABC, FES-I, age and sex are reported in Appendix 11. Spearman's rho correlation showed that sex and age were not significantly associated with falls status and were therefore not included in the regression model. To avoid multicollinearity, the number of pain sites was excluded from the model due to high correlation with ankle pain and pain in sites excluding the ankle. All other variables were included in the regression model with each variable removed sequentially leaving only FES-I (β=0.313, p=0.001) and group (β=0.233, p=0.012) (Table 9.3).

Table 9.3: Multiple linear regression model with fall status (coded as faller=1, non-faller=0) as the dependent variable

Significant predictor variables	Standardized β weight	p-value	R^2
FES-I	0.313	0.001	0.218
Group (Ref. – control)	0.233	0.012	
Variables not retained in the model			**Change in R2**
Worst ankle pain	-0.88	0.73	-0.001
ABC	-0.072	0.61	-0.002
Pain excluding ankle	0.076	0.56	-0.002
Comorbidities	0.076	0.49	-0.003
Depression	0.045	0.60	-0.002
FAAM-ADL	-0.184	0.29	-0.008

ABC=The Activities-Specific Balance Confidence Scale, FES-I=The Falls Efficacy Scale-International, FAAM-ADL= The Foot and Ankle Ability Measure-activities of daily living subscale

9.3.4 Outcomes associated with the number of falls

Correlation levels between the number of falls, FAAM-ADL, ankle pain, pain excluding ankle, number of pain sites, number of morbidities depression, group, ABC, FES-I, age, and sex are reported in Appendix 12. Spearman's correlation indicated that sex (p=0.6) and age (p=0.7) were not associated with the number of falls. Because a high correlation was identified between the number of pain sites and ankle pain and pain excluding ankle, the number of pain sites was excluded from the regression model.

All other variables were included in the initial regression model. Depression, group, comorbidities, pain excluding the ankle, ABC and FAAM-ADL were all removed from the model because p-values were >0.1. The FES-I had the greatest contribution to the number of falls (β=0.3, p=0.001) followed by worst ankle pain in the last week (β=0.3, p=0.006). This model explained 30% of the total variance in the number of falls (Table 9.4).

Table 9.4: Multiple linear regression model with the number of falls as the dependent variable

Significant predictor variables	Standardized β weight	p-value	R^2
FES-I	0.331	0.001	0.295
Worst ankle pain	0.275	0.006	
Variables not retained in the model			**Change in R2**
Depression	0.051	0.59	-0.002
Group (Ref. – control)	0.089	0.60	-0.002
Comorbidities	-0.067	0.47	-0.003
Pain excluding ankle	0.096	0.47	-0.003
ABC	-0.112	0.40	-0.004
FAAM-ADL	0.174	0.35	-0.005

ABC=The Activities-Specific Balance Confidence Scale, FES-I=The Falls Efficacy Scale-International, FAAM-ADL= The Foot and Ankle Ability Measure-activities of daily living subscale

9.4 Discussion

Falls is a major problem that has not been investigated in individuals with ankle symptoms. This study aimed to compare the self-reported history of falls, fear of falling and balance confidence between adults with and without ankle symptoms. Our data indicate that individuals with persistent ankle symptoms are more likely to experience a fall than individuals without ankle symptoms. Our study also identified that independent of age, individuals with symptomatic ankle problems experience a greater number of falls and a greater number of injurious falls compared to asymptomatic controls. Symptomatic participants reported being hospitalised related to a fall with greater frequency than controls. The finding that nearly half of the fallers suffered an injury and nearly one third required hospitalisation as a result of falling suggests that falls may be a serious issue among individuals with ankle pain and stiffness.

As most research on falls has focused on older adults it is difficult to compare our falls data (from individuals with a mean age of 54 years) to that from other studies. Although almost half of our study participants were fallers, only 26% of individuals in our control group fell in the last 12 months. Our control data is similar to that of a previous study which reported a 12-month falls rate of 20% in individuals aged 20–87 years [481]. Other studies have reported that 55% of older adults with chronic pain experienced a fall in the previous 18 month period [373] and 59 % of individuals with rheumatoid arthritis experiences a fall in the

previous 12 month period [482]. This is similar to our finding that 64% of individual with ankle symptoms experienced a fall in the previous year.

This study assessed fear of fall and balance confidence which stand for two different fall-related psychological constructs [483].The FES-I measures concern about falling- fear of falling- which illustrate anxiety and depression characteristics [484,485]. On the other hand, the ABC assesses balance confidence which is related to self-efficacy [486] and does not directly address fear. Further, the ABC includes a broader range of functional activities than the FES-I. Individuals with chronic ankle problems had a greater fear of falling and lower balance confidence compared to controls. Those characteristics have been linked to an increased risk of falls in other populations [487,488]. Among our participants, falls status (being a faller or non-faller) and the number of falls was related to fear of falling. Fear of falling may be associated with altered movement strategies, such as muscular coactivation [489] and altered gait [490,491], which may increase the risk of falling [492]. Falls status was also associated with whether individuals had ankle pain and stiffness (compared to no ankle symptoms) and the number of falls was associated with higher intensity of ankle pain. The presence of pain [373] and more severe pain has been associated with an increased risk of falls in older adults [373]. Because age was not retained in our regression analyses, our data suggest that individuals with ankle symptoms and higher severity of ankle pain are at increased risk of falls regardless of age.

There are a number of possible reasons why individuals with ankle pain and stiffness may experience a high prevalence and number of falls. Ankle symptoms are associated with impairments in muscle strength, ankle range of motion and ambulatory function [381]. There is evidence of balance deficits in individuals with ankle OA [338]. Muscle weakness and decreased balance have been linked to falls in previous studies [187,493; 494,495]. Because the risk of falling increases with an increasing number of falls risk factors [463], together these factors may lead to a significant increase in falls risk in individuals with chronic ankle problems. A slower ambulatory function has been identified as an important predisposing factor for falling [463] and has been observed in individuals with chronic ankle symptoms [381]. Further research should investigate the relation between the level of physical ambulatory deficits and the risk of falls in this population. Our data suggest that individuals with ankle pain and stiffness are also more likely to experience multi-morbidity compared to controls. Many of the health

conditions reported by the symptomatic group, such as OA [496], back pain [497], depression [498,499], rheumatoid arthritis [500], and anaemia [501] in this study are associated with an increased risk of falls [497-502]. These comorbid conditions may also contribute to lower physical function and decreased QoL in this population [503,504].

Data from this study suggest the need to incorporate falls risk assessment into clinical assessment of individuals with chronic ankle symptoms to allow timely identification of modifiable risk of falls and implementation of falls prevention interventions. Although multi-morbidities was not associated with falls in regression modeling, due to the high number of comorbidities reported by individuals with chronic ankle problems, a multi-disciplinary management approach may be important. Implementation of cognitive-behavioral therapies to reduce the fear of falling and improve self-efficacy has been shown to be effective in reducing falls in previous research [505-507]. In light of the association between fear of falling and falls risk in individuals with ankle symptoms, a cognitive-behavioral therapy may be a beneficial intervention to moderate the fear of falling and enhance self-efficacy for this population and should be investigated in future studies.

Although impairments linked to increased falls risk have been identified in individuals with chronic ankle symptoms, studies have not investigated the association between specific impairments and falls in this population. This warrants further investigation to attempt to determine key falls-related impairments that can be targeted in the management of ankle problems. Furthermore, research on the effects of falls prevention programs on ambulatory and ADL function, fear of falling, related impairments, and falls in this population is warranted.

Although this study provides important information related to falls in individuals with ankle symptoms, there are limitations that need to be taken into consideration. First, the study was retrospective and relied on recall to report falls, the number of falls and fall-related injuries experienced in the past 12 months. Prospective studies could be designed to confirm these findings. Second, the online method of the survey may have limited participation to internet users. Third, the presence of other sites of bodily pain is a potential confounder in this study, even though analyses were adjusted accordingly. Fourth, the survey did not enquire about medication use. There is evidence to suggest an association between some

medications and risk for falls [508]. Data was also not collected on previous falls (i.e. prior to the 12-month window), the location of falls and circumstances surrounding a fall, which may be helpful to identify behaviors and circumstances associated with falling. Finally, as the risk of fall increases with age, it is possible that this study would yield different results if only those 50-82 years old were examined. However, this study aimed to examine falls and falls related variables in individuals with ankle symptoms. Since ankle symptoms/ problems are prevalent in a wider age group, analyses were undertaken while controlling for the effect of age.

The population investigated in this study were individuals with and without chronic ankle symptoms. This group was chosen because our previous research has identified that physical impairments and functional deficits were related to symptoms of pain and stiffness rather than radiographic joint pathology at the ankle [381]. We have shown that 93.9% of the participants with ankle pain and stiffness lasting for at least three months have radiographic OA of ≥ a grade of 2 on the Kellgren and Lawrence scale (definite osteophytes with mild-severe joint space narrowing [280]). This is not that dissimilar to findings at the knee [52]. This suggests that the symptomatic group in this study is likely to have symptomatic radiographic ankle OA, and our findings can likely be extrapolated to that population. Further research could examine the links between pain, symptoms and radiographic findings in the ankle and falls.

9.5 Conclusion

Individuals with chronic ankle symptoms have an increased risk of falling and sustaining an injury from a fall compared to asymptomatic controls. Fear of falling and the presence and severity of ankle pain are also important to consider due to their relationship with the number of falls experienced.

Chapter 10 General Discussion

The overall objective of this thesis was to promote a better understanding of the impairments characterizing individuals with ankle symptoms and OA. In order to capture a broad range of information on the impact of ankle pain and OA, laboratory studies and surveys were used. These complementary methods facilitated the collection of data on objective measures and data from the participant perspective. The series of studies included in this thesis explored the impact of ankle symptoms and OA in relation to elements of the ICF. Interpretation of the results and the specific discussion of each study is presented within the respective chapters. This chapter summarises the thesis in relation to its objectives, clinical and research implications, as well as outlining methodological considerations.

10.1 Summary of thesis findings in relation to the objectives

The first objective of this thesis was to systematically review available evidence of physical impairments in individuals with ankle OA. Study 1 (see Chapter 3) systematically reviewed the literature to identify studies of physical impairments in individuals with ankle OA. The review identified eight studies, three of which were included in meta-analyses. The review provided a synthesis and quality appraisal of the included studies. Meta-analyses revealed large impairments of ankle sagittal plane range of motion (ROM) on the affected compared to the unaffected side in ankle OA and less sagittal plane torque in ankle OA compared to controls. Evidence from single studies identified deficits in frontal plane ROM and strength, talar translation and rotation on arthrometry, balance and electromyography of ankle joint muscles, abnormal bony alignments and greater fatty infiltrate in all calf muscle compartments in individuals with ankle OA. The review highlighted the scarcity of research in relation to impairments characterising individuals with ankle OA. One of the key limitations was lack of generalization of findings as most studies used convenience samples of participants with end stage ankle OA who may not be representative of the broader ankle OA population. The findings from the systematic review informed the development of the laboratory study (Study 2).

A cross-sectional laboratory study was conducted to build on findings from the systematic review. Study 2 aimed to further understand physical impairments in individuals

with ankle OA, and the relationships between physical measures and patient-reported outcomes (Chapter 5). This study addressed the second thesis objective. Participants underwent a clinical and radiographic assessment of the ankle which facilitated comparisons of the following three groups: 1) symptomatic individuals with radiographic evidence of OA, 2) asymptomatic individuals with radiographic evidence of ankle OA and 3) asymptomatic controls with no evidence of radiographic OA. This study examined well-characterised groups and utilised three ankle specific measures (CAIT, FAAM and AOS) when comparing patient-reported outcomes between groups. As self-report measures reflect an individual's perceived ability which may differ from their actual functional ability [509,510], this study collected data on physical function by means of self-report and functional performance tests to account for the limitation of using only self-reported measures of function. This study also explored the relationships between QoL, self-reported function and physical measures (thesis objective 2).

Symptomatic individuals with ankle OA reported greater pain, instability, and disability as well as lower self-reported function compared to asymptomatic individuals. Significant deficits in muscle strength, DF ROM, and ambulatory function were identified in the symptomatic individuals with ankle OA compared to the asymptomatic individuals with and without ankle OA. This data builds on evidence from the systematic review (Chapter 3), confirming multi-directional strength deficits and identifying that deficits in DF ROM contribute to the total deficit in sagittal plane ankle ROM. While the identification of these impairments is important, the understanding of what mechanisms underlie these deficits is also important. Further research is needed to determine what factors contributed to the deficit in DF ROM and the lower torque production identified in this population.

The ability to ambulate independently can have a number of health benefits and consequences [511]. Together, lower torque production and limited ROM identified in the symptomatic group can impair the normal function of which ambulation is a central component. There is evidence to indicate that ankle strength may influence performance in functional tests including walking speed [353] and stair tests [354,355]. Likewise, reduced ankle DF has been associated with impaired gait, compromised balance and function [165-169].

Despite the availability of clinically applicable functional tests, previous research had not examined timed level walking and stair negotiation specifically in a population with ankle

OA. One previous study [512] measured the functional level of individuals with ankle OA scheduled for ankle surgery using an activity monitor for two weeks. The study results showed individuals with ankle OA walked a smaller number of steps per day compared with population norms. Not only did the assessed population in that study represent the severe end stage of ankle OA, but also the population norms were extracted from previous research on the knee and hip OA [513] that did not specify the size or characteristics of the comparator group. We, therefore, do not know whether age or sex are comparable between the assessed groups. From the laboratory study in this thesis, slower walking speed and stair ascent/descent identified in the symptomatic OA group and the association between these tests and function and QoL suggest the importance of including these outcomes when assessing individuals with ankle symptoms, and when addressing deficits in the management of symptomatic ankle OA.

Radiographic joint degeneration was identified in 41 asymptomatic individuals (i.e. no ankle pain or stiffness) and in 13 asymptomatic ankles (i.e. the unaffected side in the symptomatic group). This suggests as previously shown at the knee [340], that radiographic joint degeneration does not necessarily equate to symptoms. A comparison of physical and patient-reported outcome measures between the two asymptomatic groups (i.e. asymptomatic OA and asymptomatic non-OA) revealed no significant differences. This absence of differences between the two asymptomatic groups adds to the existing body of evidence that the presence of symptoms but not joint degeneration is the relevant determinant of impairments [64-66]. These findings also highlight the need to assess and treat based on symptoms and queries the relevance of radiographs in isolation when managing ankle OA.

Chronic ankle symptoms are a common musculoskeletal concern with an estimated prevalence of 9%-20% of adults cited in the literature [2-5]. It can be caused by different aetiologies including sprains, strains, fractures, dislocations, rheumatoid arthritis and OA [514]. A substantial body of literature has established that persistent pain is associated with a number of outcomes investigated in this thesis including fear of falling [469], lower balance confidence [470] fear avoidance [515], depressive and anxiety symptoms [516], and impaired QoL [152]. However, to our knowledge, psychological stress, falls and falls related outcomes and work limitation

has not been analysed among a population with persistent ankle pain in comparison with control group.

Questionnaires and surveys are common methods of collecting information about a population of interest [517,518]. An online survey method was used (see chapters 6-9) to address thesis objectives (3-6) relating to identifying differences in self-reported outcomes. This method has been shown to have comparable validity and reliability to a classical paper-based survey [519,520] and also it provides access to individuals in distant locations. The cross-sectional survey studies also explored factors associated with QoL, number of falls, the severity of ankle pain, self-reported function and work limitation. Since persistent pain is the main reason for seeking medical care [149], the survey studies focussed on the presence of ankle symptoms rather than radiographic evidence of ankle OA. Survey participants included individuals with chronic ankle symptoms (pain and/or stiffness lasting >3 months) [2] and asymptomatic individuals with no persistent ankle symptoms.

General findings from the survey studies 4-6 (chapters 6-9) reinforce the impact that ankle symptoms have on an individual, it revealed that aside from ankle pain, the symptomatic individuals reported worse pain elsewhere and presented with more pain sites and comorbidities when compared to the controls. It is also evident from the survey studies that the symptoms brought about by ankle problems impinge functioning, mental health, and work ability further diminishing the QoL.

Similar to findings from the cross-sectional laboratory study, survey participants with persistent ankle symptoms reported worse scores for self-reported function, pain and disability, ankle instability, and QoL but not physical activity when compared to controls (see chapter 6). Individuals with ankle symptoms also reported higher depressive symptoms in comparison to the control (see chapter 7). The majority of symptomatic individuals (71.5%) presented with high pain self-efficacy and only a small proportion (16.8%) of the symptomatic participants presented with high kinesiophobia. Previous research reported that Kinesiophobia and self-efficacy were significantly correlated with function in individuals with knee OA [521]. A similar correlation between kinesiophobia and function has been reported in research involving individuals with ruptured anterior cruciate ligament [423] and back pain [202]. In

the same way, regression analysis of our survey data showed that ankle pain, pain self-efficacy and kinesiophobia were associated with self-reported ADL function.

It is not surprising that individuals with ankle symptoms reported higher work limitations than the controls; as 67% of the symptomatic reported moderate to considerable work limitations compared to 1.9% of the control (see chapter 8). The negative impact of chronic pain on work participation has been reported in the literature [432,433]. The symptomatic group also reported higher levels of depression, lower function and were 9% more likely to present with clinical catastrophizing than controls. Symptomatic individuals with ankle pain who remained in the workforce were significantly younger with less pain in the ankle and elsewhere, had fewer comorbid conditions and higher function and pain self-efficacy than those with ankle symptoms who were not working. These findings are consistent with findings identified in a hip OA population [452]. Further, the total psychological stress, depression and catastrophizing were significantly lower among the working than non-working symptomatic individuals. While these findings highlight the beneficial effects of work and employment reported in research on wellbeing [442]. It is not clear if unemployment is owing to age, ankle symptoms and related impairments, or that the nonworking group may have experienced more pain from the ankle or from comorbidities than the working population and depicted worse outcomes.

Comparison between symptomatic individuals with ankle pain and/or stiffness and asymptomatic controls revealed more falls, greater fear of falling, lower balance confidence and function in the symptomatic group when compared to controls (see chapter 9). This study also identified that nearly half of the symptomatic fallers suffered a fall-related injury and nearly one third required hospitalisation as a result of a fall. Previous research indicated that a history of fall is among the most predictive risk factors for future falls [487]. Further, the presence of depressive symptoms was associated with a marked increase in the risk of falls in older adults [522]. This same sample in study 4 (see chapter 7) has been found to present with higher depression scores and a higher risk of reporting anxiety and depression than controls. This places individuals with ankle symptoms at high risk of fall and if we use the fall history to denote high-risk individuals, our data suggest that 64% of the symptomatic individuals can be considered at high risk of falls as they reported at least one fall in the last 12 months.

These findings underscore that falls may be a serious issue among individuals with ankle symptoms and underline the importance of preventing falls and its negative consequences in this population.

10.2 Methodological consideration and limitation

This thesis used a number of methods (systematic review and cross-sectional studies) to address the aims, as well as an assortment of designs (including meta-analysis, exploratory laboratory and survey, and correlation). This section provides an overview of some methodological considerations and limitations pertaining to the different studies of this thesis

10.2.1 Systematic review

The search strategy used for the systematic reviews included within this thesis (Chapter 3), was completed by a single investigator (MM), which may have introduced a risk of selection bias or missing potential studies. However, this potential bias was minimized by systematically searching for publications using pre-established search terms, and inclusion/exclusion criteria. The included studies were limited in their methodological quality which might impact on the robustness of the conclusions drawn from the systematic review. Granting all this, the review highlighted the gaps in the literature pertaining to ankle OA research and provided a summarised appraisal of current knowledge.

10.2.2 Cross-sectional laboratory study

All clinical examinations and data collection was completed by a single investigator. This approach can introduce the possibility for bias, as the investigator could not be blinded to the group allocation (Symptomatic OA vs. asymptomatic OA or asymptomatic controls) during data collection. De-identified x-rays were assessed for presence and grade of OA by two independent assessors whom inter-rater agreement was substantial. A standard eligibility criterion was employed in the recruitment to eliminate the inclusion of individuals with diseases or medical conditions that are known to limit the ability to participate in daily activity or exercise, this led to a more homogenous group. While this is a strength of the study design, it is established that that OA coincides with other comorbid diseases. Since individuals with comorbid conditions were excluded from the laboratory study this limits the ability to generalize these findings to the wider ankle OA population. This research was strengthened

by the inclusion of controls of the same age, and sex, and with no history of back or lower limb injuries (Chapter 4) which limit potential confounders when analyzing the data and strengthens the validity of the research findings. The laboratory study was also limited by the number of missing imaging of the asymptomatic ankle. This factor limited our ability to draw any conclusions on physical asymmetry due to radiographic OA in those symptomatic individuals with evidence of OA on one side.

External validity may have been affected by the participant's awareness of their participation in these exploratory research studies and motivation to participate. Participants may have been eager to stress their pain experience and show it as a burden or reluctant to report how their symptoms affect the different investigated variables [523,524]. This may have influenced their answers on surveys or affected the extent of effort shown on functional performance test in laboratory studies. Further, OA is characterized by remission and fluctuation of symptoms and performance-based measures are limited in that they reflect a single point of time [525].

10.2.3 Cross-sectional survey studies

Data for this survey was collected using an online survey platform, this may have caused a selection bias as internet using population may represent only a percentage of the target population. The application of our findings is limited by the cross-sectional design of these studies. Although self-reported OA is frequently used in arthritis research (i.e. other studies have ascertained the presence of OA by self-report [184,526-529]), self-report relies upon an individual's recall regarding x-ray findings which may introduce a potential error based on their understanding of their diagnosis. Hence, the focus of comparison in the survey studies was based on the presence of symptoms rather than radiographic OA.

While the symptomatic sample in these studies is not a confirmed ankle OA population, the sample presents with classical OA symptoms for more than 3 months on most days. There is evidence from research on symptomatic knee pain that radiographic knee OA was common in those who had >3 months [52,530] of knee pain in the past year (12 months) and >90 days of pain in the past 6 months [52]. Further, data from our cross-sectional laboratory study revealed that most participants who presented with ankle symptoms had also evidence

of radiographic ankle OA, also results of patient-reported outcomes from the laboratory study (chapter 4) are no different than that of survey 1 (chapter 5). Based on that and after analysing the rest of survey data (chapters 6, 7 and 8) we have some confidence that the surveyed population is likely represents symptomatic ankle OA at least clinically if not radiographically because results were in line and consistent with research finding from other weight-bearing OA. Nevertheless, these studies are exploratory, and its results should be regarded as preliminary until a replicate study is conducted in a population with a confirmed diagnosis of ankle OA.

Data related to falls frequency and falls related injury were collected retrospectively requiring the participant to indicate a number of falls over the last 12 months. This method will likely under-report falls [531]. Evidence shows a decline in the ability to reliably and accurately self-report a fall event with age [532] and revealed that long-term tracking methods > 3 months result in inaccurate fall reports [532,533]. The same concern applies when assessing injury history including a number of ankle sprains and fractures as the ability to accurately recall this information vary among participants and potentially be a source of error.

When assessing work limitation, we have accounted for age, sex, and pain other than the ankle, but the reasons for unemployment among the non-working participants were not investigated. Given that, we are unable to comment if unemployment is related to ankle pain and related impairments, unemployment negative effects or that individuals who are non-working may have been sicker than the working population and depicted worse outcomes.

10.3 Clinical implications from this thesis

As ankle injury/trauma is the major risk factor for the development of OA, programmes to prevent the onset or delay the progression to OA are warranted. This may be achieved by preventing ankle sprains through prophylactic measures (activity appropriate footwear, optimisation of ankle passive restraints, external restraints and bracing as well as postural stability enhancement) [169,534-536]. Likewise, early recognition of ankle injuries by identifying individuals at risk for OA following ankle injury/trauma, avoiding re-injury [537] and targeting potentially modifiable factors such as post-injury treatment approach, joint

mechanics, fitness and strength, BMI and behavioral characteristics (i.e. physical activity and return to sport) [538] can assist in limiting the progression to OA.

A key finding from this thesis is confirming the influence of symptoms reported from research on pain and musculoskeletal conditions, this thesis highlights that ankle symptoms impact on physical and psychological wellbeing and place individuals with ankle symptoms at high risk of falling. An important implication therefore, is to develop management (educational, psychological, behavioural, and physical) strategies that help in modifying the pain which is the hallmark of musculoskeletal conditions. It is also vital for health care providers to specifically target the limitations identified from this thesis and other scientific evidence when managing individuals with ankle symptoms and OA.

Individuals with ankle OA may benefit from the implementation of the international recommendations for management of knee and hip OA [539]. For example, education about the condition, management objectives and options is a key recommendation that can be used with ankle OA population to improve pain [540], disability [540], QoL [541], coping and self-efficacy [540]. Exercise of different forms makes a corner stone of the clinical practice guidelines for hip and knee OA and can also be utilised for managing ankle symptoms and OA. Given that ankle dorsiflexor and plantar flexor strength is correlated with walking speed [353], stair tests [354] and stair ascent [355] and that increased muscle strength can improve function [356], there may be a role for strengthening exercises in the management of individuals with ankle symptoms to prevent declines in function and QoL.

Since individuals with chronic ankle symptoms are more likely to fall and become injured as a result of fall than those without chronic ankle symptoms, there is unquestionable benefit to incorporate fall risk assessments in the assessment of individuals with ankle symptoms to allow timely identification of risk of falls especially the modifiable factors (such as fear of falling, strength, balance, and range of movement) that can be used in the fall prevention interventions. Besides, well-tailored exercises (such as balance, functional, strength/resistance, three-dimensional, flexibility, and aerobic endurance) [542] according to the level of fall risk play an important role in the prevention of falls and its consequences.

Our data showed that individuals with persistent ankle symptoms reported higher depression than the control group and depression is associated with heightened pain, increased functional disability [211] and reduced QoL [215,543]. The number of falls in the symptomatic population was also related to fear of fall. These findings imply that screening for psychological distress might be useful to identify those cases who require psychological support and assistance in adapting to ankle symptoms. A multidisciplinary approach integrating the medical and psychological management to prepare the chronic pain patients to better deal with the burdens of symptoms/OA are warranted. Therapies that utilize support groups and integrate cognitive-behavioral approaches and gradual exposure to feared activities may play role in preventing consequences of pain-related fear, fear of falling and psychological impairments. The effectiveness of these approaches in improving activity levels and preventing falls has been reported [506].

Disability and QoL are intertwined and can be influenced by a number of factors (see chapter 2). Previous research has shown that comorbidities are associated with lower QoL [503,544] and physical function [215,504], and account for the higher risk of falling [545]. Since the symptomatic group presented with significant multimorbidity compared to controls, this further underscores the importance of a multidisciplinary approach to care for all relevant morbidities. Further, in light of the relationship between obesity and pain, disability and QoL and the effect of weight loss intervention on these outcomes [398,400], providing weight loss interventions which are among the key recommendations for managing hip and knee OA may be important in the management of this population. Since FAAM-ADL scores were shown to be a good representation of QoL; FAAM-ADL could be used as an outcome measure to determine ADL function and QoL.

10.4 Implications for future research

The findings presented in this thesis could be developed in future research for example, the laboratory study cohort was a highly selected group of participants with no comorbid pain and conditions. This had the advantage of ensuring that findings could not be due to other than ankle OA. However, further research is a requisite to determine whether these findings can be generalised to the broader ankle OA population who often have some degree of pain elsewhere and other comorbid conditions. There is a body of evidence already

available on the risk of falls, but more research is needed to identify these in populations with ankle symptoms and OA. For example, previous research identified physical impairments (including balance, muscle strength and joint motion) as risk factors for falls [188,495]. Research focusing on how these physical impairments contribute to occurrence and frequency of fall in a population with ankle symptoms and confirmed ankle OA is needed.

This thesis also identified self-efficacy, pain intensity and pain-related fear as determinants of self-reported function, there is no information available as to the contribution of self-efficacy and fear of movement to objectively measured physical function in a population with ankle pain or OA. Since self-reported function showed best association with QoL, future research may examine the contribution of self-efficacy to objectively measured physical performance and determine the relationship between self-efficacy and QoL in a population with ankle symptoms.

Although ankle joint is a common English term that refers to the joint between foot and leg and broadly to the ankle region, a limitation that must be acknowledged was the absence of a shared definition of ankle joint with survey participants. This may have caused an ambiguity and possible confusion and may have resulted in the inclusion of cases with pain in neighbouring body areas such as midfoot. For more clarity, using a highlighted or labeled body diagram to define the intended anatomical body site when recruiting future survey participants is warranted.

The study on work limitation has not investigated the type of work involvement (full or part-time), the number of hours, and the productivity loss. Some important personal and environmental factors in relation to work such as postural constraints, and occupational hazards were beyond the scope of this study and were not measured in our model. Research is needed to understand the various factors specific to the population with persistent ankle pain that influence work disability and the effect of modifying these factors on the reported work disability.

This thesis did not collect data on the falls prior to the 12-month, venues of falls and circumstances preceding a fall, such knowledge is warranted to identify high-risk situations and behaviours, and to develop targeted fall prevention strategies. Prospective research of

individuals with clinical OA symptoms (pain and stiffness) with and without radiographic evidence of OA, may help identify whether radiographic evidence of OA, as opposed to clinical symptoms is valuable tool to explain falls in this population. Research suggests that retrospective recall can yield inaccurate reports of fall [532,533]. To precisely estimate the frequency of falls, prospective fall ascertainment methods such as post cards [546] calendars [547] or diaries [548,549] on weekly or monthly intervals [532,550] should be utilised in future research. In the same way, self-reported measurement of physical activity used in this thesis may have yielded overestimation due to its limited sensitivity to low or moderate activity and weak specificity to accurately estimate physical activity compared with objective measures of activity. Hence, future studies may validate and assess physical activity in a population with ankle symptoms with objective measures such as activity monitors and differentiate between the types of activities performed.

The multitude of deficits identified in individuals with ankle symptoms and OA reinforces the impact this condition has on an individual. There are few studies and no clinical recommendations to guide management of ankle symptoms and OA. A 2015 systematic review of conservative management of ankle OA determined that the quality of evidence is poor and there are insufficient data to inform ankle OA management [551]. Well-designed research into the management of ankle OA with consideration of the impairments and key outcomes identified in this thesis is needed. Furthermore, research on the effects of therapeutic programs targeting the modifiable physical risk factors such as muscle strength, dorsiflexion ROM and gait outcomes on falls and fall efficacy in a population with symptomatic ankle problems and OA is warranted. Longitudinal studies to determine if targeting early radiographic ankle OA can slow or prevent OA progression are also needed.

10.5 Conclusion

This PhD thesis determined the function, disability, and health profile of individuals with ankle pain and /or stiffness and confirmed ankle OA through a systematic review of previous research, cross-sectional laboratory and survey studies. This thesis has demonstrated that individuals with symptomatic ankle OA present with impairments in ambulatory function, ROM, muscle strength and endurance compared to asymptomatic individuals. No differences in these outcomes between individuals with and without

radiographic OA who did not have ankle symptoms were identified. This suggests that the presence of symptoms of pain and stiffness have a greater influence on function and impairments than signs of radiographic joint disease at the ankle. Further, survey results indicate that persistent ankle pain and stiffness negatively impact on disability, QoL and function and is associated with limitations at work, increased falls and psychological impairments. For more directed investigations of the effect of interventions for this population, further research is needed to better understand the mediators of the impairments, psychological distress and QoL identified in populations with ankle pain and OA.

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Appendices

Appendix 1

Search terms

tibiotalar OR talofibular OR talotibial OR talocrural OR talocalcaneal OR ankle

AND

osteoarthritis OR osteoarthrosis OR -arthritis OR osteo-arthrosis OR arthrosis

AND

"force plate" OR muscle OR kinematic OR kinematics OR kinetics OR kinetic OR kinesthe* OR valgus OR varus

OR atrophy OR isometric OR isotonic OR isokinetic OR strength OR weakness OR dynamometer OR power OR force OR endurance OR speed OR fatigue OR contraction OR EMG OR latency OR electromyograph* OR activation OR laxity OR stiffness OR displacement OR "anterior drawer" OR motion OR "range of movement"

OR dorsiflex* OR plantarflex* OR inver* OR ever* OR supinat* OR pronat* OR flex OR flexor* OR flexion OR extens* OR adduct* OR abduct* OR "reaction time" OR "joint position" OR sensorimotor OR "movement detection" OR accelerometer OR "stride length" OR cadence OR stability OR control OR arthrometer OR balance OR proprioception OR postur* OR coordinate* OR "center of mass" OR "centre of mass" OR "center of pressure" OR "centre of pressure" OR gait OR walk* OR locomot* OR step OR steps OR stepping OR hop

OR hops or hopping OR jump* OR run OR instability

Not terms

Cadaver OR cadaveric OR rabbit OR rat OR rats OR mouse OR mice OR Paediatric OR pediatric OR juvenile OR child OR children OR "Cruciate ligament" OR Cruciate OR "Collateral ligament" OR meniscus OR menisci OR hip OR patellofemoral OR Diabetic OR diabetes OR Rheumatic OR "rheumatoid arthritis" OR Rheumatologic

OR rheumatism OR Hallux OR "hallux rigidus" OR "hallux valgus" OR "hallux limitus" OR "hallux varus" OR Cancer or tumor

Databases search algorithm

Search in PubMed

1. Main search terms linked with "AND"
2. "NOT" review in "publication type" search field
3. Combining the NOT term sets resulted in higher numbers hence the option to search each set of

terms independently.

4. “NOT” term sets searched independently in “title/abstract” search field:

Cadaver OR cadaveric OR rabbit OR rat OR rats OR mouse OR mice Paediatric OR pediatric OR juvenile OR child OR children

“Cruciate ligament” OR Cruciate OR “Collateral ligament” OR meniscus OR menisci OR hip OR patellofemoral

Diabetic OR diabetes

Rheumatic OR “rheumatoid arthritis” OR Rheumatologic OR rheumatism

Hallux OR "hallux rigidus" OR "hallux valgus" OR "hallux limitus" OR "hallux varus" Cancer or tumor

---

Search in SPORDiscus

Notes:

1. Relevant search fields for our set of NOT terms were either in title, subjects (descriptor) or abstract.
2. I removed the term review from “title” (subject field).
3. Experimented removing the terms from titles and again from abstracts and identified the difference.
4. Removing the terms from abstracts included all terms that were removed from titles. Hence NOT terms were removed from abstracts (subject field)

Search in CINAHL

Notes:

1. Search fields are different in CINAHL with an option to select human in the “search option” table as well as the option to search “publication type” in the search field.
2. I removed the term review from “publication type” (search field).
3. Experimented removing the terms from titles and again from abstracts and identified the difference.
4. Removing the terms from abstracts included all terms that were removed from titles. Hence NOT terms were removed from abstracts (subject field)

Search in EMBACE

Notes:

1. There are no specific search fields to select from.
2. The main Boolean operators listed are AND and OR.
3. I searched for the different sets of main terms independently then I combined them with AND.
4. When I typed the# presenting the combined main searches followed by NOT terms e.g. #4 NOT Cadaver OR cadaveric OR rabbit OR rat OR rats OR mouse OR mice, the numbers were

higher instead of being lower.

5. I then searched for the different sets of NOT terms separately.
6. Within the entry box I typed the # presenting the combined main searches followed it with NOT and the # representing search results for each set of NOT terms.
7. Same results was achieved by typing # presenting the combined main searches followed by NOT and all NOT terms in brackets.
8. NOT and the # representing search results for each set of NOT terms.

Search in Web of Science

Notes:

1. Relevant search fields for our set of NOT terms were either in title or topic.

a. Search main terms linked with “AND”

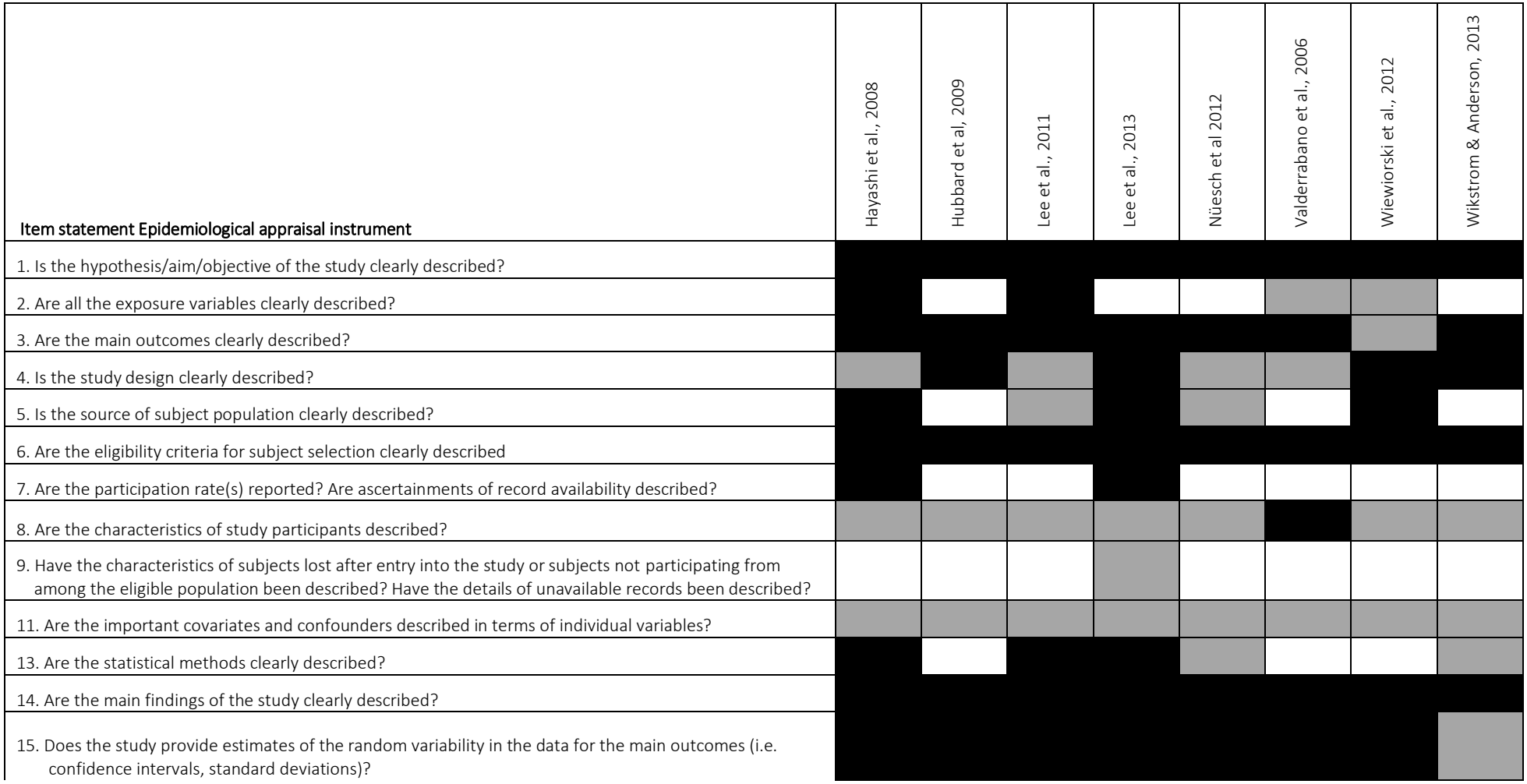
b. “NOT” in title:

- Cadaver OR cadaveric OR rabbit OR rat OR rats OR mouse OR mice
- Paediatric OR pediatric OR juvenile OR child OR children
- “Cruciate ligament” OR Cruciate OR “Collateral ligament” OR meniscus OR menisci OR hip OR patellofemoral
- Diabetic OR diabetes
- Rheumatic OR “rheumatoid arthritis” OR Rheumatologic OR rheumatism
- Hallux OR "hallux rigidus" OR "hallux valgus" OR "hallux limitus" OR "hallux varus"

2. Refining to web of science subject category and document type is possible only after the search is done.

Review, letter, meeting abstracts, book chapters, editorial material, reprints and proceedings paper (document types) were excluded from the results.

Appendix 2


Item statement Epidemiological appraisal instrument
Hayashi et al., 2008
Hubbard et al, 2009
Lee et al., 2011
Lee et al., 2013
Nüesch et al 2012
Valderrabano et al., 2006
Wiewiorski et al., 2012
Wikstrom & Anderson, 2013
1. Is the hypothesis/aim/objective of the study clearly described?
2. Are all the exposure variables clearly described?
3. Are the main outcomes clearly described?
4. Is the study design clearly described?
5. Is the source of subject population clearly described?
6. Are the eligibility criteria for subject selection clearly described
7. Are the participation rate(s) reported? Are ascertainments of record availability described?
8. Are the characteristics of study participants described?
9. Have the characteristics of subjects lost after entry into the study or subjects not participating from among the eligible population been described? Have the details of unavailable records been described?
11. Are the important covariates and confounders described in terms of individual variables?
13. Are the statistical methods clearly described?
14. Are the main findings of the study clearly described?
15. Does the study provide estimates of the random variability in the data for the main outcomes (i.e. confidence intervals, standard deviations)?

16. Does the study provide estimates of the statistical parameters (e.g. regression coefficients or parameter estimates such as odds ratio or mean differences)?								
17. Are sample size calculations performed and reported?								
18. Is the comparison/reference group comparable to the exposed group?								
19. Is the participation rate adequate? Is the ascertainment of record availability adequate?								
20. Are the study subjects from different groups recruited over the same period of time?								
21. Are subject losses or unavailable records after entry into the study taken into account?								
25. Are the exposure variables reliable?								
26. Are the exposure variables valid?								
27. Are the methods of assessing the exposure variables similar for each group?								
29. Are the observers blinded to subject groupings when the exposure assessment was made or the disease status of subjects when conducting exposure assessment?								
31. Are the main outcome measures reliable?								
32. Are the main outcome measures valid?								
33. Are the methods of assessing the outcome variables standard across all groups?								
34. Are the observations taken over the same time for all groups?								
35. Is prior history of disease and/or injury collected and included in the analysis?								
36. Is there adequate adjustment for covariates and confounders in terms of individual variables in the analyses?								
40. Are outcome data reported by levels of exposure?								
41. Are the outcome/exposure data reported by subgroups of subjects?								
42. Can the study results be applied to the eligible population?								
43. Can the study results be applied to other relevant populations?								
Quality score (0-1)	0.56	0.33	0.39	0.36	0.35	0.36	0.41	0.30

Appendix 3

Table A3.1: stages of ankle OA in two classification systems and the adopted stages for the current systematic review

Stages	Morrey and Wiedeman classification [54]	Modified Takakura classification [116](from Lee et al 2011[241])	Adopted grouping
0	Normal	-	
1	Minimum narrowing and osteophyte formation	Early sclerosis and formation of osteophytes, No joint space narrowing	Mild OA
2	Moderate narrowing and osteophyte formation	Narrowing of the medial joint space	Moderate OA
3	Gross deformity and ankylosis	a. Obliteration of the medial joint space with subchondral bone contact limited to the medial malleolus	Advanced OA
	-	b. b. Subchondral bone contact extending to the roof of the dome of the talus	
4	-	Obliteration of the entire joint space, resulting in bone contact throughout the ankle	

Table A 3.2: Adopted stages for the current systematic review

Stage	Description
Mild	Early sclerosis, minimum joint space narrowing and osteophyte formation
Moderate	Moderate narrowing and osteophyte formation
Advanced	Obliteration of the entire joint space, subchondral bone contact /ankylosis

Appendix 4

Physical outcomes compared between the affected side in people with ankle OA versus the unaffected side or healthy control.

Outcome	Stage of OA	Affected side in ankle OA Mean (SD, n)	Unaffected side in ankle OA Mean (SD, n)	Between sides SMD [CI]	Healthy control Mean (SD, n)	Affected side v control SMD [CI]	Unaffected side vs control SMD [CI]
TMM (∘) [241]	Moderate	24.9 (2.8, 68)			22.6 (6.1, 80)	0.47 [0.14, 0.80]	
	Advanced	28.78 (8.58, 87)			22.6 (6.1, 80)	0.82 [0.50, 1.14]	
TTS (∘) [238]	Mild	85.3 (2.6, 26)			87.2 (2.8, 62)	-0.69 [-1.16, -0.22]	
	Moderate	82.7 (3.5, 39)			87.2 (2.8, 62)	-1.45 [-1.90, -1.00]	
	Advanced	77.44 (7.6, 68)			87.2 (2.8, 62)	-1.66 [-2.07, -1.26]	
Talar tilt (∘) [241]	Moderate	2.5 (2.8, 68)			0 (0, 80)		
	Advanced	5.4 (5.3, 87)			0 (0, 80)		
TPC (∘) [238]	Mild	88.2 (6.1, 26)			88.3 (5.8, 62)	-0.02 [-0.47, 0.44]	
	Moderate	91.0 (8.7, 39)			88.3 (5.8, 62)	0.38 [-0.02, 0.78]	
	Advanced	84.1 (10.9, 68)			88.3 (5.8, 62)	-0.47 [-0.82, -0.12]	
SIA (∘) [238]	Mild	2.9 (7.0, 26)			1.5 (5.9, 62)	0.22 [-0.24, 0.68]	
	Moderate	8.0 (8.6, 39)			1.5 (5.9, 62)	0.91 [0.49, 1.33]	
	Advanced	6.6 (9.0, 68)			1.5 (5.9, 62)	-10.93 [-12.33, -9.54]	
TAS (∘) [238]	Moderate	84.5 (3.1,39)			87.4 (2.7,62)	-1.01 [-1.43, -0.58]	
	Advanced	82.7 (3.7,68)			87.4 (2.7,62)	-1.43 [-1.82, -1.05]	
TAS (∘) [241]	Moderate	86.9 (2.4,68)			88.9 (2.4,80)	-0.83 [-1.17, -0.49]	
	Advanced	84.9 (4.4,87)			88.9 (2.4,80)	-1.09 [-1.41, -0.76]	

TLS (◦) [238]	Moderate	80.4 (3.2,39)			81.13 (2.8,62)	-0.24 [-0.65, 0.16]	
	Advanced	78.4 (5.2,68)			81.13 (2.8,62)	-0.64 [-0.99, -0.29]	
TLS (◦) [241]	Moderate	76.8 (3.5,68)			79.8 (3.8,80)	-0.81 [-1.15, -0.48]	
	Advanced	72.4 (4.8,87)			79.8 (3.8,80)	-1.69 [-2.05, -1.34]	
Hind foot alignment (◦) [241]	Moderate	0.5 (8.1, 68)			-0.5 (5.4, 80)	0.15 [-0.18, 0.47]	
	Advanced	5.3 (8.63, 87)			-0.5 (5.4, 80)	0.79 [0.48, 1.11]	
Calcaneal alignment (°) † [145]	Moderate+ Advanced	3.0 (8.9, 15)	7.0 (3.55, 15)	-0.57 [-1.31, 0.16]	4.6 (1.24, 15)	-0.25 [-0.96, 0.47]	
Tibiotalar ratio [240]	Advanced	28.3 (2.47, 104)			35.0 (3.0, 50)	-2.51 [-2.95, -2.07]	
Total range of movement (◦)							
Inversion /Eversion [145]	Moderate+ Advanced	19.7 (11.1, 15)	43.3 (10.97, 15)	-2.08 [-2.99, -1.17]	50.7 (8.4, 15)	-3.07 [-4.16, -1.97]	-0.74 [-1.48, 0.01]
Dorsiflexion/plantar flexion [145]	Moderate+ Advanced	16.0 (7.6, 15)	56.7 (5.23, 15)	-6.07 [-7.87, -4.27]	58.7 (5.2, 15)	-6.39 [-8.27, -4.52]	-0.37 [-1.10, 0.35]
Dorsiflexion/plantar flexion [239]		18.1 (9.15, 21)	56.0 (6.25, 21)	-4.75 [-5.97, -3.52]			
Mechanical stability							
Anterior displacement (mm) [146]		7.1 (1.9, 8)	10.6 (1.5, 8)	-1.93 [-3.18, -0.69]	11.2 (1.8, 8)	-2.09 [-3.38, -0.81]	-0.34 [-1.33, 0.65]
Posterior displacement (mm) [146]		4.6 (1.3, 8)	5.0 (1.3, 8)	-0.29 [-1.28, 0.70]	4.9 (0.58, 8)	-0.28 [-1.27, 0.70]	0.09 [-0.89, 1.07]
Inversion rotation (°) [146]		21.6 (6.4, 8)	31.1 (4.5, 8)	-1.62 [-2.80, -0.45]	33.0 (2.1, 8)	-2.26 [-3.60, -0.93]	-0.51 [-1.51, 0.49]
Eversion rotation (°) [146]		9.4 (2.8, 8)	15.2 (5.1, 8)	-1.33 [-2.45, -0.22]	21.3 (5.6, 8)	-2.54 [-3.95, -1.13]	-1.08 [-2.15, -0.01]
Calf circumference (cm)							
Calf circumference (cm) [155]		38.19 (2.36,12)	39.42 (2.74,12)	-0.46 [-1.28, 0.35]	38.29 (2.67, 12)	-0.04 [-0.84, 0.76]	0.41 [-0.40, 1.22]

Calf circumference (cm) [145]	Moderate+ Advanced	32.7 (3.45, 15)	34.8 (3.44, 15)	-0.59 [-1.33, 0.14]	33.6 (2.8, 15)	-0.28 [-1.00, 0.44]	0.37 [-0.35, 1.10]
Calf circumference (cm) [239]	Moderate+ Advanced	33.2 (2.65, 21)	35.3 (2.76, 21)	-0.76 [-1.39, -0.13]			
CSA (cm^2)							
Anterior tibial group [239]	Moderate+ Advanced	10.3 (2.6, 21)	11.0 (2.9, 21)	-0.25 [-0.86, 0.36]			
Peroneal muscle group [239]	Moderate+ advanced	5.8 (1.7, 21)	6.5 (1.5, 21)	-0.43 [-1.04, 0.18]			
Deep posterior muscles [239]	Moderate+ Advanced	4.5 (1.3, 21)	5.4 (1.5, 21)	-0.63 [-1.25, -0.01]			
Gastroc. med. muscle [239]	Moderate+ Advanced	12.0 (3.3, 21)	13.3 (3.5, 21)	-0.37 [-0.99, 0.24]			
Gastroc. Lat. muscle [239]	Moderate+ Advanced	5.7 (2.0, 21)	6.7 (2.0, 21)	-0.49 [-1.11, 0.12]			
Soleus muscle [239]	Moderate+ Advanced	18.6 (5.4, 21)	24.7 (6.0, 21)	-1.05 [-1.70, -0.40]			
Anatomical calf CSA [239]	Moderate+ Advanced	57 (13.4, 21)	67.5 (11.9, 21)	-0.81 [-1.44, -0.18]			
Fatty infiltration							
Anterior tibial group [239]	Moderate+ Advanced	1.3 (0.8, 21)	0.4 (0.5, 21)	1.25 [0.58, 1.92]			
Peroneal muscle group [239]	Moderate+ Advanced	1.4 (0.6, 21)	0.5 (0.5, 21)	1.60 [0.90, 2.30]			
Deep posterior muscles [239]	Moderate+ Advanced	1.4 (0.8, 21)	0.2 (0.4, 21)	1.86 [1.13, 2.60]			

Gastroc. med. muscle [239]	Moderate+ Advanced	1.3 (0.5, 21)	0.6 (0.6, 21)	1.24 [0.58, 1.91]			
Gastroc. Lat. muscle [239]	Moderate+ Advanced	1.1 (0.7, 21)	0.4 (0.5, 21)	1.13 [0.47, 1.78]			
Soleus muscle [239]	Moderate+ Advanced	2.5 (0.5, 21)	0.8 (0.6, 21)	3.02 [2.11, 3.93]			
Maximal isometric torque							
Dorsiflexion [145]	Moderate+ Advanced	16.4 (4.9, 15)	25.9 (8.2, 15)	-1.37 [-2.17, -0.56]	27.1 (9.4, 15	-1.39 [-2.20, -0.58]	-0.13 [-0.85, 0.58]
Dorsiflexion [155]		11.1 (7.96,12)			26.3 (13.86,12)	-1.30 [-2.19, -0.40]	
Plantarflexion [145]	Moderate+ Advanced	15.8 (7.6, 15)	25.6 (7.4, 15)	-1.27 [-2.07, -0.48]	30.7 (15.5, 15)	-1.19 [-1.97, -0.40]	-0.41 [-1.13, 0.32]
Plantarflexion [155]		20.9 (7.62, 12)			36.9 (13.51, 12)	-1.41 [-2.32, -0.50]	
Isometric strength (N.m/kg)							
Plantar flexion [146]		0.18 (0.09, 8)	0.22 (0.07, 8)	-0.47 [-1.47, 0.53]	0.39 (0.1, 8)	-2.09 [-3.37, -0.80]	-1.86 [-3.09, -0.63]
Dorsiflexion [146]		0.16 (0.05, 8)	0.2 (0.06, 8)	-0.68 [-1.70, 0.33]	0.36 (0.1, 8)	-2.39 [-3.76, -1.02]	-1.83 [-3.06, -0.61]
Inversion [146]		0.09 (0.03, 8)	0.14 (0.04, 8)	-1.34 [-2.45, -0.22]	0.22 (0.04, 8)	-3.48 [-5.17, -1.78]	-1.89 [-3.13, -0.65]
Eversion [146]		0.1 (0.03, 8)	0.14 (0.03, 8)	-1.26 [-2.36, -0.16]	0.22 (0.04, 8)	-3.21 [-4.82, -1.60]	-2.14 [-3.44, -0.84]
Muscle EMG Amplitude (μV)							
Anterior tibial muscle [145]	Moderate+ Advanced	39.8 (21.9, 15)	67.8 (53.4, 15)	-0.67 [-1.41, 0.07]	62.6 (43.4, 15)	-0.65 [-1.38, 0.09]	0.10 [-0.61, 0.82]
Medial gastrocnemius [145]	Moderate+ Advanced	6.9 (10.9, 15)	20.2 (23.0, 15)	-0.72 [-1.46, 0.02]	24.7 (19.0, 15)	-1.12 [-1.90, -0.34]	-0.21 [-0.93, 0.51]

Peroneus longus [145]	Moderate+ Advanced	14.1 (19.4, 15)	26.9 (25.3, 15)	-0.55 [-1.28, 0.18]	33.0 (43.3, 15)	-0.55 [-1.28, 0.18]	-0.17 [-0.88, 0.55]
Soleus [145]	Moderate+ Advanced	19.9 (55.6, 15)	17.9 (25.1, 15)	0.05 [-0.67, 0.76]	25.7 (29.4, 15)	-0.13 [-0.84, 0.59]	-0.28 [-1.00, 0.44]
Muscle EMG Frequency (Hz)							
Anterior tibial muscle [145]	Moderate+ Advanced	119.4 (31.8, 15)	142 (29.1, 15)	-0.72 [-1.46, 0.02]	144.9 (26.1, 15)	-0.85 [-1.61, -0.10]	-0.10 [-0.82, 0.61]
Medial gastrocnemius [145]	Moderate+ Advanced	159.2 (19.9, 15)	186.5 (26.7, 15)	-1.13 [-1.91, -0.35]	184.8 (23.8, 15)	-1.14 [-1.91, -0.36]	0.07 [-0.65, 0.78]
Peroneus longus [145]	Moderate+ Advanced	147.5 (35.4, 15)	176.1 (31.7, 15)	-0.83 [-1.58, -0.08]	159.8 (28.6, 15)	-0.37 [-1.09, 0.35]	0.53 [-0.20, 1.26]
Soleus [145]	Moderate+ Advanced	124.2 (33.1, 15)	150.1 (21.0, 15)	-0.91 [-1.67, -0.15]	146.8 (32.6, 15)	-0.67 [-1.41, 0.07]	0.12 [-0.60, 0.83]
Static balance variables.							
COP total displacement (mm) [146]		219.5 (193.6, 8)			27.0 (6.6, 8)	1.33 [0.21, 2.44]	
COP total velocity (mm/s) [146]		36.8 (16.4, 8)			11.4 (2.1, 8)	2.05 [0.78, 3.33]	
COP ML displacement (mm) [146]		2.8 (4.5, 8)			0.88 (0.55, 8)	0.57 [-0.44, 1.57]	
COP AP displacement (mm) [146]		1.9 (2.2, 8)			0.35 (0.4, 8)	0.93 [-0.12, 1.97]	
COP ML velocity (mm/s) [146]		0.53 (0.61, 8)			0.01 (0.09, 8)	1.13 [0.05, 2.21]	
COP AP velocity (mm/s) [146]		0.68 (0.83, 8)			0.15 (0.13, 8)	0.84 [-0.19, 1.88]	
AP sway (cm) [147]		3.94 (1.36, 5)			2.31 (0.25, 5)	1.51 [0.01, 3.01]	
ML Sway (cm) [147]		2.14 (1.03, 5)			1.02 (0.21,5)	1.36 [-0.10, 2.82]	
†Alignment was measured with goniometer in standing.							

Abbreviations and definitions: *SD=standard deviation; SMD=standardized mean difference; CI=confidence interval ;TMM (◦)=The angle between the distal third of the tibial shaft and the medial malleolar joint surface ; Hind foot alignment (◦)=the angle between tibial and calcaneal axes; TTS (◦)=The angles between the tibial shaft the articular surface of the talar dome ; TPC (◦)=The angle between the tibial shaft axis and the articular surface of the posterior facet of the calcaneus; TAS (◦)=The angle between the tibial shaft and tibial articular surface in the frontal plane on weight-bearing x-ray ; TLS (◦)=The angle between the tibial shaft axis and the articular surface of the tibial shaft in the sagittal plane on weight-bearing x-ray; SIA= angle between the articular surface of the talar dome and the posterior facet of the calcaneus; Tibiotalar ratio= ratio into which the mid-longitudinal axis of the tibial shaft divides the longitudinal talar length; CSA=cross sectional area; EMG=electromyography; Anterior tibial muscle group= (tibialis anterior, extensor digitorum and hallucis longus); Gastroc.med.muscle= Gastrocnemius medialis muscle; Gastroc Lat.muscle= Gastrocnemius lateralis muscle; Deep dorsal muscle group = (tibialis posterior, flexor digitorum longus, and flexor hallucis longus); Peroneal muscle group= (peroneus longus and brevis); AP= Anterior-posterior; ML= Medial-lateral.*

Appendix 5

THE UNIVERSITY OF QUEENSLAND

Institutional Human Research Ethics Approval

Project Title:	Impairments and Consequences of Lateral Ankle Sprains and Their Sequellae - 03/01/2017 - AMENDMENT
Chief Investigator:	Dr Michelle Smith
Supervisor:	None
Co-Investigator(s):	Prof Bill Vicenzino, Dr David MacDonald, Ms Munira Al Mahrouqi, Mr Mark Matthews, Dr Kylie Tucker, Ms Nafiseh Khalaj
School(s):	SHRS
Approval Number:	2014001194
Granting Agency/Degree:	UQ HABS & MABS Collaborative Research Seeding Grant
Duration:	30th September 2019

Comments/Conditions:

Amendment:

Addition of tasks for participants to perform including walking, stepping up or down, raising onto toes, lunging, squatting, twisting, hopping, jumping on and off a box, and reaching limbs in different directions while standing on one leg.

Updated participant information sheet & consent form

Note: If this approval is for amendments to an already approved protocol for which a UQ Clinical Trials Protection/Insurance Form was originally submitted, then the researchers must directly notify the UQ Insurance Office of any changes to that Form and Participant Information Sheets & Consent Forms as a result of the amendments, before action.

Name of responsible Committee:
University of Queensland Human Research Ethics Committee A
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:
Professor Emerita Gina Geffen
Chairperson
University of Queensland Human Research Ethics Committee A
Registration: EC00456

G. Geffen

08/02/2017

Signature _____ Date _____

Appendix 6

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

School of Health and Rehabilitation Sciences

CONSENT FORM

TITLE: **Impairments and consequences of ankle injuries and osteoarthritis**

INVESTIGATORS: Dr Michelle Smith, Professor Bill Vicenzino, Dr David MacDonald, Dr Kylie Tucker, Ms Munira Al Mahrouqi, Ms Nafiseh Khalah, Mr Mark Matthews
The University of Queensland, Brisbane, Australia

1. I, _____ (PLEASE PRINT) hereby consent to take part in the research project titled: *"Impairments and consequences of ankle injuries and osteoarthritis"*.
2. I acknowledge that I have read the information sheet provided, and that I have had the project, so far as it affects me, fully explained to my satisfaction by the investigators. I freely consent to my participation in the project.
3. The details of my specific involvement have been explained to me, including what is involved in participation, anticipated length of time it will take, and an indication of any discomfort or possible risks.
4. I understand that the purpose of this research is to improve the quality of medical care, and it has been explained that this is a research project may not be of any direct benefit to me.
5. I am informed that the results of any tests involving me will not be published so as to reveal my identity and that my privacy will be maintained at all times.
6. I understand that I am free to withdraw from the project at any stage without penalty and that this will not affect in any way the ongoing management of my condition.
7. In giving my consent, I acknowledge that the researchers directly involved in the study may examine my medical imaging records of my ankle. This will be done to determine the need for ankle x-rays to be taken as part of this research project.
8. I consent for my x-rays to be used without identifying information in medical publication, including medical journals, textbooks, and electronic publications. I understand that the x-ray images may be seen by members of the general public, in addition to scientists and medical researchers that regularly use these publications in their professional education.
9. I am happy to be contacted by researchers at a later date in regards to follow-up for this study and future research opportunities.

   ☐ Yes Contact details: _____

Your name: .....

Today's date (DD/MM/YYYY): .....

Your signature: .....

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Appendix 7

Test-retest reliability for physical measures					
	Sample (n ankles)	ICC	95% CI	SEM	MDC
Maximum isometric dorsiflexion strength-Knee flexion (N)	10 (10 ankles)	0.93	0.759 to 0.982	8.50	23.56
Maximum isometric inversion strength-Knee flexion (N)	10 (10 ankles)	0.96	0.861 to 0.990	8.38	23.23
Maximum isometric eversion strength-Knee flexion (N)	10 (10 ankles)	0.96	0.868 to 0.991	7.76	21.51
Maximum isometric plantarflexion-Knee flexion (N)	10 (10 ankles)	0.97	0.895 to 0.993	22.30	61.81
Maximum isometric plantarflexion-Knee Extension (N)	10 (10 ankles)	0.98	0.923 to 0.995	20.40	56.54
Stair ascent and descent (sec)	10	0.93	0.764 to 0.982	0.39	1.09
Timed 10-m walk (sec)	10	0.60	0.034 to 0.883	0.29	0.81
DF ROM (mm)	10 (10 ankles)	1.00	0.987 to 0.999	1.08	2.98
Foot posture index (score -12 to +12)	10 (20 ankles)	0.84	0.620 to 0.935	0.72	2.00
AP-PA displacement (mm)	10 (10 ankles)	0.91	0.703 to 0.977	1.24	3.43
Inversion-Eversion rotation (◦)	10 (10 ankles)	0.99	0.98 to 1.00	2.12	5.87
Dorsal arch height-weight-bearing (mm)	5 (10 ankles)	0.89	0.78 to 0.96	0.7	1.9
Dorsal arch height -non weight-bearing (mm)	5 (10 ankles)	0.98	0.95 to 0.99	0.81	1.9
Midfoot width- weight-bearing (mm)	5 (10 ankles)	0.99	0.98 to 1.00	0.5	1.4
Midfoot width-non-weight-bearing (mm)	5 (10 ankles)	0.97	0.95 to 0.98	1.1	3.1
ICC = intraclass correlation coefficient; CI = confidence interval; SEM = standard error of measurement; MDC=minimal detectable change (at 95% confidence limit) *All measures were taken seven days apart by a single examiner*					

Appendix 8

Past fracture, ankle sprain history and Kellgren–Lawrence grades n(%) of the study groups and risk difference between groups

	Frequency and percentage for each group			Risk difference (95% confidence interval)		
Characteristic	Symptomatic OA n=31	Asymptomatic OA n=41	Asymptomatic non-OA n=24	Symptomatic vs Asymptomatic	Symptomatic OA vs Asymptomatic OA	Asymptomatic OA vs Asymptomatic non-OA
Past fracture	13(50.0%)*	0 (0%)	0 (0%)	50% [31, 69]	50% [31, 69]	0% [-6, 6]
Ankle sprains						
No sprain	13 (50.0%)*	30 (75%)	19 (79.2%)	30% [-52, -9]	23% [-47, 0]	18% [0, 35]
One sprain	2 (7.6%)*	6 (14.6%)	2 (8.3%)	5% [-18, 8]	7% [-22, 8]	6% [-9, 22]
Two sprains	1 (3.8%)*	0 (0%)	0 (0%)	4% [-5, 13]	4% [-5, 13]	0% [-6, 6]
Three sprains	1 (3.8%)*	3 (7.3%)	0 (0%)	1% [-10, 8]	3% [-14, 7]	7% [-3, 17]
> 3 sprains	9 (34.6%)*	0 (0%)	1 (4.2%)	33% [15, 52]	35% [16, 53]	4% [-14, 6]
Kellgren–Lawrence						
Grade 0	0 (0%)	0 (0%)	3 (12.5%)	5% [-12, 2]	0% [-5, 5]	13% [-26, 1]
Grade 1	0 (0%)	0 (0%)	21 (87.5%)	32% [-44, -20]	0% [-5, 5]	88% [-100, -74]
Grade 2	17 (54.8%)	27 (65.9%)	0 (0%)	9% [-30, 11]	11% [-34, 12]	66% [50, 81]
Grade 3	8 (25.8%)	13 (31.7%)	0 (0%)	6% [-12, 24]	6% [-27, 15]	32% [17, 47]
Grade 4	6 (19.4%)	1 (2.4%)	0 (0%)	18% [4, 32]	17% [2, 32]	2% [-5, 10]
**Data on fracture and sprains based on 26 responses from the symptomatic OA, 31 asymptomatic OA and 41 asymptomatic non-OA.*						

Appendix 9

Correlation levels between the different physical outcomes, quality of life and function

Spearman's rho	Group	10-m. walk	Stair descent	Stair ascent	DF ROM	PF-knee Flex	Inv-knee Flex	Ever-knee Flex	DF-knee Flex	PF-knee Ext	Heel raises	FPI	DAHDIFF	MFWDIFF	FMM	Total AP displacement	Total rotation	FAAM ADL
10-m. walk	0.32**																	
Sig. (2-tailed)	0.00																	
N	95																	
Stair descent	0.21*	0.61**																
Sig. (2-tailed)	0.05	0.00																
N	93	93																
Stair ascent	0.17	0.65**	0.91**															
Sig. (2-tailed)	0.11	0.00	0.00															
N	93	93	93															
DF ROM	-0.56**	-0.13	-0.14	-0.13														
Sig. (2-tailed)	0.00	0.20	0.18	0.22														
N	96	95	93	93														
PF-knee Flex	-0.48**	-0.30**	-0.35**	-0.31**	0.40**													
Sig. (2-tailed)	0.00	0.00	0.00	0.00	0.00													
N	96	95	93	93	96													
Inv- knee Flex	-0.57**	-0.39**	-0.42**	-0.37**	0.49**	0.71**												
Sig. (2-tailed)	0.00	0.00	0.00	0.00	0.00	0.00												
N	96	95	93	93	96	96												
Ever- knee Flex	-0.56**	-0.29**	-0.37**	-0.32**	0.43**	0.73**	0.76**											
Sig. (2-tailed)	0.00	0.00	0.00	0.00	0.00	0.00	0.00											
N	96	95	93	93	96	96	96											
DF in knee Flex	-0.56**	-0.38**	-0.37**	-0.33**	0.57**	0.66**	0.69**	0.71**										
Sig. (2-tailed)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00										
N	96	95	93	93	96	96	96	96										
PF in knee Ext	-0.55**	-0.35**	-0.48**	-0.42**	0.39**	0.71**	0.74**	0.76**	0.66**									
Sig. (2-tailed)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00									
N	95	95	93	93	95	95	95	95	95									
Heel raises	-0.44**	-0.37**	-0.26*	-0.25*	0.22*	0.44**	0.43**	0.49**	0.48**	0.50**								
Sig. (2-tailed)	0.00	0.00	0.01	0.01	0.04	0.00	0.00	0.00	0.00	0.00								
N	93	93	92	92	93	93	93	93	93	93								

FPI	-0.11	0.11	-0.10	-0.11	.23*	0.12	0.14	0.15	0.10	0.09	0.01							
Sig. (2-tailed)	0.31	0.31	0.36	0.28	0.02	0.25	0.18	0.15	0.36	0.39	0.95							
N	95	94	92	92	95	95	95	95	95	94	92							
DAHDIFF	-0.03	0.23*	0.21*	0.19	.23*	-0.12	-0.16	-0.06	-0.09	-.20*	-0.24*	0.31**						
Sig. (2-tailed)	0.75	0.03	0.05	0.07	0.02	0.25	0.13	0.56	0.40	0.05	0.02	0.00						
N	95	94	92	92	95	95	95	95	95	94	92	94						
MFWDIFF	-0.09	0.08	0.04	0.04	0.18	0.11	0.13	0.29**	0.17	0.13	-0.03	0.31**	0.22*					
Sig. (2-tailed)	0.36	0.44	0.68	0.72	0.09	0.28	0.21	0.01	0.09	0.20	0.78	0.00	0.03					
N	95	94	92	92	95	95	95	95	95	94	92	94	95					
FMM	-0.09	.212*	0.16	0.15	.27**	0.00	-0.03	0.11	0.05	-0.07	-0.18	0.39**	0.86**	0.64**				
Sig. (2-tailed)	0.39	0.04	0.13	0.14	0.01	0.98	0.77	0.29	0.64	0.49	0.08	0.00	0.00	0.00				
N	95	94	92	92	95	95	95	95	95	94	92	94	95	95				
Total AP displacement	-0.07	0.02	-0.02	0.04	0.34**	-0.11	-0.07	-0.10	0.06	-0.09	0.04	0.04	0.01	-0.10	0.00			
Sig. (2-tailed)	0.53	0.86	0.89	0.67	0.00	0.30	0.52	0.32	0.56	0.39	0.72	0.68	0.92	0.32	0.99			
N	96	95	93	93	96	96	96	96	96	95	93	95	95	95	95			
Total rotation	-0.30**	-0.01	0.13	0.14	0.51**	0.02	0.14	0.17	0.27**	0.09	0.00	0.26*	0.31**	0.31**	0.35**	0.43**		
Sig. (2-tailed)	0.00	0.93	0.22	0.18	0.00	0.82	0.16	0.09	0.01	0.40	0.99	0.01	0.00	0.00	0.00	0.00		
N	96	95	93	93	96	96	96	96	96	95	93	95	95	95	95	96		
FAAM ADL	-0.85**	-0.34**	-0.31**	-0.26*	0.47**	0.47**	0.54**	0.61**	0.56**	0.60**	0.50**	0.16	-0.02	0.18	0.10	0.07	0.220*	
Sig. (2-tailed)	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.14	0.88	0.10	0.36	0.50	0.04	
N	90	89	88	88	90	90	90	90	90	89	88	89	89	89	89	90	90	
AQoL-6D	-0.47**	-0.26*	-0.34**	-0.28*	0.42**	0.47**	0.49**	0.51**	0.52**	0.42**	0.26*	0.13	0.01	0.10	0.06	0.07	0.08	0.54**
Sig. (2-tailed)	0.00	0.02	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.24	0.95	0.38	0.57	0.54	0.47	0.00
N	86	85	84	84	86	86	86	86	86	85	84	85	85	85	85	86	86	86

Abbreviations: *N=number; FAAM=Foot and Ankle Ability Measure; AQoL-6D= The Assessment of Quality of Life questionnaire-6D; FMM=Foot mobility magnitude; DAHDIFF=dorsal arch height difference; MFWDIFF= mid-foot width difference; FPI= foot posture index ;AP=Anteroposterior; PF=Plantarflexion; DF=dorsiflexion; Inv=inversion; Ever=eversion; ROM=range of movement; Ext=extension; Flex=flexion*

*** Correlation is significant at the 0.01 level (2-tailed).*

** Correlation is significant at the 0.05 level (2-tailed).*

Appendix 10

Nonparametric (Spearman's rho) Correlations between variables

Correlation Coefficient	AQoL-Total score	FAAM- ADL	AOS-Disability	AOS-Pain	FAAM-Sport	CAIT	Group	BMI	Ankle stiffness	Age
FAAM- ADL	0.795 (p<0.001,n = 380)									
AOS-Disability	-0.793** (p<0.001,n=375)	-0.942** (p<0.001,n=371								
AOS-Pain	-0.756** (p<0.001,n=366)	-0.899** (p<0.001,n=364)	0.923** (p<0.001,n=369)							
FAAM-Sport	0.738** (p<0.001,n=378)	0.926** (p<0.001,n=378)	-0.905** (p<0.001,n=372)	-0.828** (p<0.001,n=365)						
CAIT	0.714** (p<0.001,n=356)	0.865** (p<0.001,n= 346)	-0.842** (p<0.001,n=341)	-0.810** (p<0.001,n=332)	0.855** (p<0.001,n=344)					
Group	-0.409** (p<0.001,n=391)	-0.551** (p<0.001,n=383)	0.539** (p<0.001,n=378)	0.552** (p<0.001,n=369	-0.548** (p<0.001,n=381)	-0.689** (p<0.001,n= 357)				
BMI	-0.464** (p<0.001,n=387)	-0.507** (p<0.001,n=379)	0.514** (p<0.001,n=374)	0.459** (p<0.001,n=365)	-0.476** (p<0.001,n=377)	-0.506** (p<0.001,n=353)	0.368** (p<0.001,n=390)			
Ankle stiffness	-0.404** (p<0.001,n=266)	-0.489** (p<0.001,n=269)	0.497** (p<0.001,n=269)	0.498** (p<0.001,n=269)	-0.405** (p<0.001,n=269)	-0.267** (p<0.001,n=232)	-0.233** (p<0.001,n=269)	0.136* (p=0.03,n=265)		
Age	-0.10 (p=0.05,n=391)	-0.144** (p=0.01,n=383)	0.108* (p=0.04,n=378)	0.10 (p=0.07,n=369)	-0.09 (p=0.07,n=381)	-0.03 (p=0.63,n=357)	-0.145** (p<0.001,n=394)	0.06 (p=0.22,n=390)	0.123* (p=0.04,n=269)	
Sex	0.06 (p=0.26,n=391)	0.137** (p=0.01,n=383)	-0.09 (p=0.07,n=378)	0.133* (p=0.01,n=369)	0.129* (p=0.01,n=381)	0.114* (p=0.03,n=357)	-0.197** (p<0.001,n=394)	-0.10 (p=0.06,n=390	-0.04 (p=0.57,n=269)	0.125* (p=0.01,n=394)

*** Correlation is significant at the 0.01 level (2-tailed).*

** Correlation is significant at the 0.05 level (2-tailed).*

Abbreviations: p value/significance level; AOS=ankle osteoarthritis scale; FAAM=Foot and Ankle Ability Measure; AQoL-6D= The Assessment of Quality of Life; BMI= body mass index; CAIT= The CumberlandAnkle Instability Tool.

Appendix 11

Correlation levels of each independent variable with fall status (coded as faller=1, non-faller=0) and other variables.

Spearman's rho (p-value)	Fallers	FAAM ADL	FESI	ABC	Ankle pain	Number of pain sites	Pain excluding ankle	Group	Comorbidities	Depression	Age
FAAM ADL	-0.472** (0.00)										
FESI	0.443** (0.00)	-0.697** (0.00)									
ABC	-0.440** (0.00)	0.747** (0.00)	-0.842** (0.00)								
Ankle pain	0.407** (0.00)	-0.913** (0.00)	0.683** (0.00)	-0.701** (0.00)							
Number of pain sites	0.385** (0.00)	-0.748** (0.00)	0.636** (0.00)	-0.645** (0.00)	0.750** (0.00)						
Pain excluding ankle	0.382** (0.00)	-0.716** (0.00)	0.640** (0.00)	-0.651** (0.00)	0.771** (0.00)	0.822** (0.00)					
Group	0.374** (0.00)	-0.875** (0.00)	0.574** (0.00)	-0.572** (0.00)	0.864** (0.00)	0.687** (0.00)	0.575** (0.00)				
Comorbidities	0.252** (0.00)	-0.450** (0.00)	0.509** (0.00)	-0.483** (0.00)	0.440** (0.00)	0.471** (0.00)	0.463** (0.00)	0.369** (0.00)			
Depression	0.152* (0.02)	-0.202* (0.03)	0.254** (0.00)	-0.257** (0.00)	0.187** (0.01)	0.209** (0.00)	0.261** (0.00)	0.10 (0.16)	0.477** (0.00)		
Age	0.05 (0.50)	0.01 (0.88)	0.02 (0.81)	-0.07 (0.29)	-0.04 (0.58)	-0.13 (0.05)	-0.03 (0.64)	-0.05 (0.45)	0.13 (0.06)	0.04 (0.57)	
Sex	-0.04 (0.58)	-0.07 (0.46)	0.147* (0.03)	-0.189** (0.00)	0.05 (0.43)	0.13 (0.06)	0.134* (0.04)	0.02 (0.80)	0.11 (0.09)	0.06 (0.38)	-0.04 (0.54)

*** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).*
Group (Ref. – asymptomatic).
FES-I=The Falls Efficacy Scale-International, ABC=The Activities-Specific Balance Confidence Scale, FAAM-ADL= The Foot and Ankle Ability Measure-activities of daily living subscale
All data based on full sample n=226 except FAAM ADL n=120

Appendix 12

Correlation levels of each independent variable with number of falls and other variables.

Spearman's rho (p-value)	Number of falls	FESI	FAAM ADL	ABC	Ankle pain	Pain excluding ankle	Number of pain sites	Group	Comorbidities	Depression	Age
FESI	0.510** (0.00)										
FAAM ADL	-0.509** (0.00)	-0.697** (0.00)									
ABC	-0.502** (0.00)	-0.842** (0.00)	0.747** (0.00)								
Ankle pain	0.475** (0.00)	0.683** (0.00)	-0.913** (0.00)	-0.701** (0.00)							
Pain excluding ankle	0.449** (0.00)	0.640** (0.00)	-0.716** (0.00)	-0.651** (0.00)	0.771** (0.00)						
Number of pain sites	0.448** (0.00)	0.636** (0.00)	-0.748** (0.00)	-0.645** (0.00)	0.750** (0.00)	0.822** (0.00)					
Group	0.411** (0.00)	0.574** (0.00)	-0.875** (0.00)	-0.572** (0.00)	0.864** (0.00)	0.575** (0.00)	0.687** (0.00)				
Comorbidities	0.260** (0.00)	0.509** (0.00)	-0.450** (0.00)	-0.483** (0.00)	0.440** (0.00)	0.463** (0.00)	0.471** (0.00)	0.369* (0.00)*			
Depression	0.167* (0.01)	0.254** (0.00)	-0.202* (0.03)	-0.257** (0.00)	0.187** (0.01)	0.261** (0.00)	0.209** (0.00)	0.10 (0.16)	0.477** (0.00)		
Age	0.02 (0.74)	0.02 (0.81)	0.01 (0.88)	-0.07 (0.29)	-0.04 (0.58)	-0.03 (0.64)	-0.13 (0.05)	-0.05 (0.45)	0.13 (0.06)	0.04 (0.57)	
Sex	-0.03 (0.63)	0.147* (0.03)	-0.07 (0.46)	-0.189** (0.00)	0.05 (0.43)	0.134* (0.04)	0.13 (0.06)	0.02 (0.80)	0.11 (0.09)	0.06 (0.38)	-0.04 (0.54)

p Sig. (2-tailed)
** Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed). Group (Ref. – asymptomatic)*
FES-I=The Falls Efficacy Scale-International, FAAM-ADL= The Foot and Ankle Ability Measure-activities of daily living subscale ABC=The Activities-Specific Balance Confidence Scale. All data based on full sample n=226 except FAAM ADL n=120