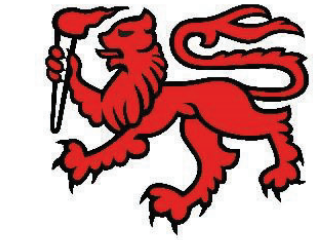

Clinical and imaging factors associated with chronic plantar heel pain

by

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Doctor of Philosophy (Medical Research)

May 2021

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Declaration of originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

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Statement of ethical conduct

The research associated with this thesis abides by the International and Australian codes on human experimentation, and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

Approval for the project was provided by the Human Research Ethics Committee (Tasmania) Network. Details as below:

Clinical factors and imaging abnormalities associated with chronic plantar heel pain.

H0013616 (20 March 2014)

Written informed consent was obtained from all participants.

Signed: ……

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Statement of co-authorship

This thesis includes papers for which Jason Rogers (JR) was not the sole author. JR was the first author in the research of each manuscript; however, he was assisted by the co-authors whose contributions are detailed below.

The paper reported in Chapter 4:

Rogers J, Jones G, Cook JL, Wills K, Lahham A, Winzenberg TM.

Chronic plantar heel pain is principally associated with waist girth (systemic) and pain (central) factors, not foot factors: A case-control study

J Orthop Sports Phys Ther. 2021 Sep;51(9):449-458.
doi:https://doi.org/0.2519/jospt.2021.10018 Epub 2021 May 7. PMID: 33962520.

The contribution of each author:

JR contributed to conception, design, acquisition, analysis, and interpretation, drafted and critically revised the manuscript and gave final approval.

GJ contributed to analysis, interpretation and critical review of the manuscript, and gave final approval.

JC contributed to analysis, interpretation and critical review of the manuscript, and gave final approval.

KW contributed to analysis, interpretation and critical review of the manuscript, and gave final approval.

AL contributed to acquisition, analysis, interpretation and critical review of the manuscript, and gave final approval.

TW contributed to conception, design, analysis, interpretation, and critically revised the manuscript and gave final approval.

All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

The paper reported in Chapter 5:

Rogers J, Jones G, Cook JL, Squibb K, Wills K, Lahham A, Winzenberg TM.

Chronic plantar heel pain modifies associations of ankle plantarflexor strength and body mass index with calcaneal bone density and microarchitecture.

Accepted *PLOS ONE*, November 25, 2021.

PLOS ONE 16(12): e0260925. https://doi.org/10.1371/journal.pone.0260925

The contribution of each author:

JR contributed to conception, design, acquisition, analysis, and interpretation, drafted and critically revised the manuscript and gave final approval.

GJ contributed to analysis, interpretation and critical review of the manuscript, and gave final approval.

JC contributed to analysis, interpretation and critical review of the manuscript, and gave final approval.

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KW contributed to analysis, interpretation and critical review of the manuscript, and gave final approval.

AL contributed to acquisition, analysis, interpretation and critical review of the manuscript, and gave final approval.

TW contributed to conception, design, analysis, interpretation, and critically revised the manuscript and gave final approval.

All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

The paper reported in Chapter 6:

Rogers J, Jones G, Cook JL, Squibb K, Halliday A, Wills K, Lahham A, Winzenberg TM.

Calcaneal bone marrow lesions and plantar fascia imaging biomarkers are associated with chronic plantar heel pain: a case-control study.

Accepted, *Arthritis Care & Research*, December 15, 2021.

The contribution of each author:

JR contributed to conception, design, acquisition, analysis, and interpretation, drafted and critically revised the manuscript and gave final approval.

GJ contributed to analysis, interpretation and critical review of the manuscript, and gave final approval.

JC contributed to analysis, interpretation and critical review of the manuscript, and gave final approval.

KS contributed to acquisition, analysis, interpretation and critical review of the manuscript, and gave final approval.

AH contributed to acquisition, interpretation and critical review of the manuscript, and gave final approval.

KW contributed to analysis, interpretation and critical review of the manuscript, and gave final approval.

AL contributed to acquisition, analysis, interpretation and critical review of the manuscript, and gave final approval.

TW contributed to conception, design, analysis, interpretation, and critically revised the manuscript and gave final approval.

All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

The paper reported in Chapter 7:

Rogers J, Jones G, Cook JL, Wills K, Lahham A, Winzenberg TM.

Clinical predictors of pain, function and quality of life in people with chronic plantar heel pain after 12-months: a prospective longitudinal study.

Manuscript being prepared for publication.

The contribution of each author:

JR contributed to conception, design, acquisition, analysis, and interpretation, drafted and critically revised the manuscript and gave final approval.

GJ contributed to analysis, interpretation and critical review of the manuscript, and gave final approval.

JC contributed to analysis, interpretation and critical review of the manuscript, and gave final approval.

KW contributed to analysis, interpretation and critical review of the manuscript, and gave final approval.

AL contributed to acquisition, analysis, interpretation and critical review of the manuscript, and gave final approval.

TW contributed to conception, design, analysis, interpretation, and critically revised the manuscript and gave final approval.

All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

The paper reported in the **Appendix 1**:

van Leeuwen KD, **Rogers J**, Winzenberg T, van Middelkoop M.

Higher body mass index is associated with plantar fasciopathy/'plantar fasciitis': systematic review and meta-analysis of various clinical and imaging risk factors.

Br J Sports Med. 2016 Aug;50(16):972-81. doi: https://doi.org/10.1136/bjsports-2015-094695 Epub 2015 Dec 7. PMID: 26644427.

The contribution of each author:

KVL contributed to conception, design, acquisition, analysis, and interpretation, drafted and critically revised the manuscript and gave final approval.

JR contributed to acquisition, analysis, interpretation, drafting and critical review of the manuscript, and gave final approval.

TW contributed to analysis, interpretation and critical review of the manuscript, and gave final approval.

MVM contributed to conception, design, analysis, interpretation, and critically revised the manuscript and gave final approval.

All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

We, the undersigned, endorse the above stated contribution of work undertaken for each of the above published (or submitted) peer-reviewed manuscripts contributing to this thesis:

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Abstract

Clinical & imaging factors associated with chronic plantar heel pain: The PHEEP Study

Background & Aims

Chronic plantar heel pain (CPHP) is a common clinical condition defined by pain and tenderness under the heel, aggravated by weightbearing. Despite treatment, many individuals with CPHP report persistent symptoms. This may be partly explained by the limited understanding of the factors that contribute to CPHP risk and prognosis.

The goal of this thesis was to better understand these factors with the specific aims of: (1) in a case-control design, to determine associations of clinical factors and imaging biomarkers with CPHP, and (2) in a longitudinal analysis, to determine which clinical factors predict outcomes of pain, foot-related physical function and quality of life in cases 12 months later.

Methods

We recruited 220 participants with a clinical diagnosis of CPHP of at least 3 months duration and compared them to 100 age- and sex-matched controls recruited randomly from the electoral roll. Cases and controls were assessed at baseline, and cases were also assessed after 1 year.

Clinical exposures measured in cases and controls were waist girth, body mass index, body composition by bio-impedance analysis, clinical measures of foot and leg function, physical activity via accelerometry, depression and pain catastrophising by validated questionnaire, and symptoms of morning stiffness, night pain and multisite pain. In cases only we also assessed neuropathic symptoms using the painDETECT questionnaire.

Imaging exposures measured in cases and controls were plantar fascia thickness, echogenicity and Doppler vascular signal by US, plantar fascia thickness and signal, plantar fat pad signal, plantar spurs and calcaneal bone marrow lesions (BML) by MRI, and calcaneal trabecular bone density, bone volume fraction (BV/TV), trabecular thickness, separation and number at a plantar and mid-calcaneal site by High-resolution peripheral Quantitative Computed Tomography (HR-pQCT).

These same exposures except for foot posture and QCT were re-assessed in cases a minimum of 12-months later.

Three analyses were performed:

Case-control analysis using conditional logistic regression to assess associations of clinical and US/ MRI exposures with CPHP status

Cross-sectional analysis using linear regression to assess associations of CPHP as an exposure with HR-pQCT bone outcomes, and

Mixed effects linear model analysis to assess longitudinal associations of clinical exposures with pain and foot-related physical function (by Foot Health Status Questionnaire) and quality of life outcomes (by Assessment of Quality of Life questionnaire).

Results

Clinical factors associated with the odds of having CPHP were waist girth (cm) (odds ratio [OR] 1.06 (95% CI: 1.03 to 1.09)), ankle plantar flexor strength (kg) (OR 0.98; 95% CI: 0.97 to 0.99), pain at multiple sites (pain at 4 or more other sites: OR 10.45 (95% CI 3.66 to 29.81)), and pain catastrophizing status (catastrophizer: OR 6.79 (95% CI 1.91 to 24.11)). Univariable associations with morning stiffness, BMI, first metatarsophalangeal joint extension mobility and depression did not persist after adjusting for potential confounders. There were no significant associations with physical activity.

Imaging biomarkers associated with the odds of having CPHP were plantar calcaneal BML size (mm^2, OR 1.03 (95% CI 1.02 to 1.05)), larger plantar spurs (>5mm, OR 2.15 (95% CI 1.13 to 4.10)), plantar fascia signal (penetrating > 50% of dorsoplantar width, OR 12.12 (95% CI 5.36 to 27.42)), plantar fascia thickness (mm, (MRI) OR 3.23 (95% CI 2.36 to 4.43), (US) OR 3.78 (95% CI 2.69 to 5.32)) and echogenicity (diffusely hypoechoic OR 7.89 (95% CI 4.02 to 15.48), focally hypoechoic OR 24.92 (95% CI 9.60 to 64.69)). Plantar fascia vascularity was uncommon, occurring exclusively in cases (cases with signal n=47(22%)).

At the plantar calcaneus only, in univariable models being a case was associated with higher trabecular density, BV/TV and trabecular thickness. In multivariable models, having CPHP was not independently associated with any HR-pQCT bone outcomes, but modified

associations of BMI and ankle plantarflexor strength with mid-calcaneal and plantar bone outcomes respectively. Beneficial associations of ankle plantarflexor strength with plantar trabecular density, thickness, separation and BV/TV were reduced in cases. In the mid-calcaneus, beneficial associations of BMI with trabecular density, thickness and BV/TV were also lower in cases.

At least 12 months later, 95% of participants returned surveys and 90% returned for clinical re-assessment. In longitudinal analyses, worse pain outcomes at 12 months were predicted by higher painDETECT (within-person (WP) β -1.34 (95% CI -1.86 to -0.82)), between-person (BP) β -1.28 (95% CI -2.02 to -0.54)) and pain catastrophising scores (WP β -0.91 (95% CI -1.57 to -0.26)), and for those who reported night pain at baseline (β -4.45 (95% CI -8.51 to -0.39)). Worse foot function was predicted by higher painDETECT scores (BP β -0.96 (95% CI -1.47 to -0.44)), pain catastrophising (BP β -0.937 (95% CI -1.34 to -0.53)), baseline depression (β -1.28 (95% CI -2.22 to -0.34)) and higher baseline BMI (β -0.60 (95% CI -1.09 to -0.12)). Greater baseline ankle plantarflexor strength was associated with better function at 12 months (β 0.14 (95% CI 0.02 to 0.25)). Worse quality of life was predicted by higher pain catastrophising (BP β -0.36 (95% CI -0.49 to -0.23)), and higher baseline scores for depression (β -1.21 (95% CI -1.54 to -0.89)), multisite pain (β -1.31 (95% CI -2.01 to -0.61)) and BMI (β -0.27 (95% CI -0.42 to -0.12)). Greater baseline ankle plantarflexor strength (β 0.08 (95% CI 0.04 to 0.11)) and lower baseline foot pain (β 0.04 (95% CI 0.01 to 0.07)) were associated with improved QOL.

Conclusion

Systemic, psychological and pain system processes play an important role in CPHP causation and prognosis. We have established that BMLs are a common finding, adding to our understanding of the role of bone in CPHP. Collectively, these results demonstrate the heterogeneity of CPHP, and suggest that different clinical phenotypes exist. These findings could allow clinicians to better target impairments associated with CPHP outcomes that to date have received little attention in CPHP management, such as bone-specific, psychological and pain science interventions.

Acknowledgements

I gratefully acknowledge the support, persistence, guidance and patience of my supervisory team, Tania, Graeme, Jill and Karen. I would like to thank Tania in particular, for placing her trust in a greenfield project, and a part-time one at that, and for helping to realise its potential. I was privileged to have the support of a world-class supervisory team with a flair for epidemiology, razor sharp research insight, an economy of words that I am still yet to master, and a connection to the 'so what' that as a clinician I always appreciated.

Thank-you must also go to the participants and supporters of this project through-out our community. Following an initial three-hour assessment process, that two hundred of you came back and volunteered your time again a year later, is wonderful testimony. In this same light, thank-you to the research support staff and amazing team of volunteers. I estimate the combined contribution of our selfless volunteers Jane, Robyn, Pam, Trish, Jane and Barbara saved me one year of FTE hours in leg work.

Thank-you also goes to my professional helpers in the trench in Dr Aroub Lahham and Dr Kate Squibb. Both provided technical support, many hours of back-room grunt and a cool head for sounding out the inevitable frustrations and uncertainties that arise in any project.

Behind the scenes, I thank Dr Ali Ghasem (HR-pQCT), Mr Tim Albion (database & teleforms) and Mr Brian Stokes (Data Linkage for controls) for their technical support.

Thank-you to my fellow students, in particular Ishanka, Anitra and William for their insights, short-cuts, survival tips, coding advice and political education.

Thank-you to my supporters and sponsor from my other life, at AllCare Physiotherapy. They provided financial surety for me through this period, an academic sounding board and positive moral support throughout the duration.

Although a small thank-you for all, this acknowledgment demonstrates the teamwork that underpins this journey, and the importance of collegiality.

Last but by no means least, thank-you to my beautiful family. Christy only ever had words of encouragement and was always available to offer a hand up, and occasionally two hands in the back when needed. My 3 kids transitioned whole school systems under my period of study. I hope they learned the power of application and persistence, and that learning is a life-long process. When my middle son wrote his grade 5 History Challenge paper on Sir Archibald Cochrane, espousing the power of the RCT in times when opinion rather than evidence ruled the day, I think something rubbed off. He didn't score a prize, but then in the field of grant writing and publishing, that's often how research goes.

Financial Assistance

This research was supported by an Australian Government Research Training Program (RTP) Offset Scholarship.

This project was made possible by the financial support of:

- Physiotherapy Research Foundation (Seeding grant S14-025)
- Rebecca L Cooper Medical Research Foundation (2015)
- Arthritis Australia Grant-in-aid (2015)
- Royal Hobart Hospital Research Foundation (17-203)
- AllCare Physiotherapy Tasmania
- Halifax Foundation

LIST OF TABLES

LIST OF FIGURES

Publications directly arising from the work described in this thesis

Manuscripts submitted to peer-reviewed journals

Chapter 4:

Rogers J, Jones G, Cook J, Lahham A, Wills K, Winzenberg T. **Chronic plantar heel pain is principally associated with waist girth (systemic) and pain (central) factors, not foot factors. A case-control study**. *J Orthop Sports Phys Ther*. 2021 Sep;51(9):449-458. doi: https://doi.org/10.2519/jospt.2021.10018 Epub 2021 May 7. PMID: 33962520.

Chapter 5:

Rogers J, Jones G, Cook J, Squibb K, Lahham A, Wills K, Winzenberg T. **Chronic plantar heel pain modifies associations of ankle plantarflexor strength and body mass index with calcaneal bone density and microarchitecture.** *PLOS ONE* 16(12): e0260925. https://doi.org/10.1371/journal.pone.0260925

Chapter 6:

Rogers J, Jones G, Cook JL, Squibb K, Halliday A, Wills K, Lahham A, Winzenberg TM. **Calcaneal bone marrow lesions and plantar fascia imaging biomarkers are associated with chronic plantar heel pain: a case-control study.**
Provisionally accepted, *Arthritis Care & Research*, 15 December 2021

Other publications during candidacy

van Leeuwen KDB, **Rogers J**, Winzenberg T, van Middelkoop M. **Higher body mass index is associated with plantar fasciopathy/'plantar fasciitis': systematic review and meta-analysis of various clinical and imaging risk factors** *Br J Sports Med* https://doi.org/10.1136/bjsports-2015-094695 Published Online First: 7 December 2015.

Rogers JA, Wilson A, Laslett LL, Winzenberg TM. **Physical interventions (orthoses, splints, exercise and manual therapy) for treating plantar heel pain**. *Cochrane Database of Systematic Reviews* 2016, Issue 8. Art. No.: CD012304. https://doi.org/10.1002/14651858.CD012304

Conference abstract: **Rogers J**, Jones G, Cook J, Lahham A, Wills K, Winzenberg T **'Central and systemic factors are more associated with chronic plantar heel pain than clinical foot factors: a matched case-control study'** *2020 Australian Rheumatology Association 60th Annual Scientific Meeting*, 16-19 May 2020*, Internal Medicine Journal/* volume 50/ supplement 2.

Conference abstract: **Rogers J**, Jones G, Cook J, Lahham A, Wills K, Winzenberg **'Calcaneal bone marrow lesions (BML's), plantar fascia signal, thickness, echogenicity and vascularity but not fat pad signal, are associated with chronic plantar heel pain (CPHP): a matched case-control study'** *2021 Australian Rheumatology Association 61st Annual Scientific Meeting*, 16-19 May 2021*, Internal Medicine Journal/* volume 51/ supplement 2. Doi:10.1111/imj.15302

Conference presentations using the work described in the thesis

Poster presentation: van Leeuwen K, **Rogers J**, Winzenberg T, Van Middelkoop M: *Clinical and Imaging Factors Associated with Plantar Heel Pain; a Systematic Review*. 55th ASM of Australian Rheumatology Association, Hobart, Tasmania, 17-20 May 2014

Oral Presentation: *'Clinical and imaging factors associated with plantar heel pain.'* Connect 2015 National Physiotherapy Conference, Gold Coast, Australia 3-6 October 2015.

Invited Speaker. *'Plantar heel pain; not just 'plantar fasciitis'*. Australian Physiotherapy Association Tasmanian State Conference, Launceston, Tasmania July 16, 2016.

Invited Speaker. '*Novel imaging in plantar heel pain'*. Australian Society of Medical Imaging and Radiation Therapy MedRad Conference, Hobart August 27, 2016.

Invited Speaker. *'Plantar heel pain: what works?'* & *Update on the PHEEP Study*". Tendon Injuries in Sport seminar, Sports Medicine Australia, Hobart, 12 July 2018

Invited speaker. Australian Podiatry Association Tasmanian Branch *'Physical interventions (orthoses, splints, exercise and manual therapy) for treating plantar heel pain'* Oct 2018 Hobart.

Oral presentation: Physiotherapy and Allied Health Research Network (PARTNER) *'Clinical factors associated with chronic plantar heel pain'* Sept 2019 Hobart.

Oral presentation: Australian Rheumatological Association Annual Scientific Meeting *'More central and systemic than foot factors are associated with chronic plantar heel pain: a case-control study'*. Sydney Oct 12, 2020 (virtual).

Oral presentation/ free paper Australian Rheumatological Association Annual Scientific Meeting *'Calcaneal bone marrow lesions and plantar fascia signal, thickness, echogenicity and vascularity are associated with chronic plantar heel pain.'* May 21-23, 2021 Sydney (virtual).

Invited speaker. APA Tasmanian State conference '*Calcaneal bone marrow lesions are associated with chronic plantar heel pain'* 5 June 2021, Launceston.

Frequently used abbreviations

ADL	activities of daily living
AQOL-6D	assessment of quality-of-life scale 6-dimension scale
BIA	bio-impedance analysis
BMI	body mass index
BML	bone marrow lesion
BV/TV	bone volume fraction
CI	confidence interval
CPHP	chronic plantar heel pain
CPM	counts per minute
CSI	corticosteroid injection
DF	dorsiflexion
DXA	dual energy X-ray absorptiometry
ESWT	extracorporeal shockwave therapy
FHSQ	Foot Health Status Questionnaire
FPI-6	Foot posture index 6-item scale
GP	general practice
HR-pQCT	high resolution peripheral quantitative computed tomography
IASP	International Association for the Study of Pain
ICC	intra-class correlation (co-efficient)
MD	mean difference

mg HA/cm^3	milligrams of hydroxyapatite per cubic centimetre
MRI	magnetic resonance imaging
MTP	metatarsophalangeal
MVPA	moderate to vigorous physical activity
OR	odds ratio
PA	physical activity
PCS	pain catastrophising scale
PF	plantar fascia
PHEEPS	plantar heel pain study
PHQ-9	patient health questionnaire 9-item
QOL	quality of life
RCT	randomised controlled trial
ROM	range of motion
SLR	straight leg raise
TNF-α	tumour necrosing factor alpha
US	ultrasound

CHAPTER 1

Introduction

1. Introduction

1.1 What is Chronic plantar heel pain (CPHP)?

Chronic plantar heel pain (CPHP) is a clinical condition defined by the presence of pain and or tenderness under the heel aggravated with heel loading, with characteristic ‘rest to rise’ or ‘first step’ discomfort. Symptoms may be further aggravated by prolonged weightbearing[1], and may also radiate into the medial arch[2], but by definition are restricted to the sole of the foot.

The use of the general term ‘plantar heel pain’ is not new[3], but has now mostly subsumed the use of synonymous terms in the research literature used to describe related heel pain states. These include: heel spur syndrome, painful heel syndrome, plantar fasciitis, plantar fasciopathy, plantar fasciosis, plantar talalgia, runners/ joggers heel, policeman’s heel, tennis heel, calcaneodynia and heel bruise syndrome[4, 5].

Use of the term plantar heel pain reflects a deliberate move away from pathoanatomical labels in acknowledgement of the potential of many tissues to contribute to pain[2]. It also seeks to distance itself from suffixes that imply a specific understanding of the pathophysiology of the disease such as ‘~itis’, that would imply an inflammatory process that is not supported by evidence[2, 5, 6].

For the purposes of this project, we treat the term ‘chronic’ to indicate a condition that has been present for at least 3 months. This is a common timepoint applied to musculoskeletal and pain research[7]. It is not meant to imply a specific pain mechanism or dominant pathology process but serves as a simple and clear definition for a persistent pain state.

1.2 Anatomy of the plantar heel and potential pain generators

Numerous structures about the heel receive sensory innervation from the tibial nerve and its medial calcaneal, and medial and lateral plantar nerve branches, offering the potential to generate nociceptive symptoms.

Whilst the plantar fascia is most commonly assumed to be a source of nociception, other structures including the plantar fat pad, intrinsic musculature, plantar

ligaments, flexor tendon and sheaths, calcaneal bone, the tibial nerve and its tributaries (medial and lateral plantar nerve, medial calcaneal nerve), vasculature, the subtalar joint and mid-tarsal joints, and variably, infracalcaneal bursal tissue, could also contribute. (**Figures 1-1 to 1-3**).

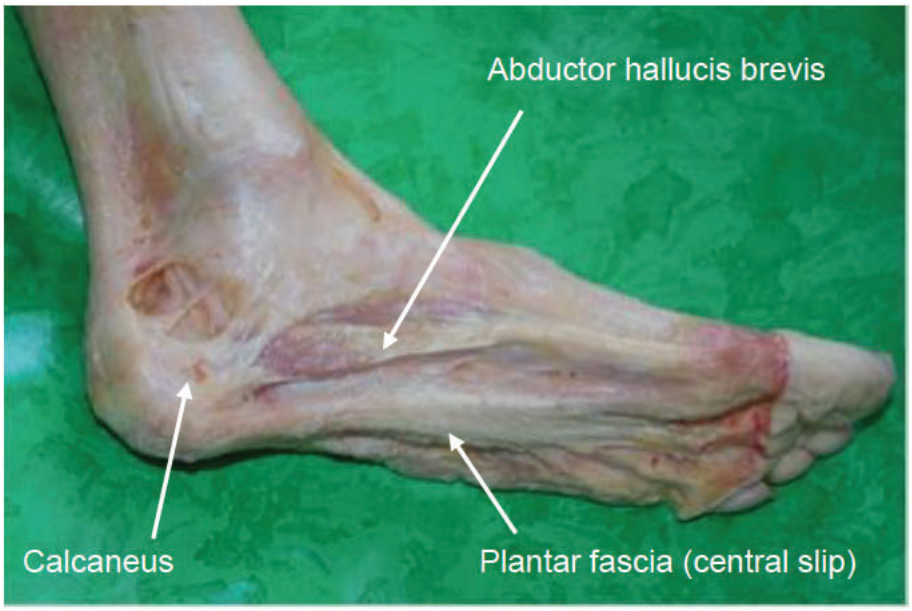

Figure 1-1: The plantar fascia
Anatomical dissection demonstrating central slip of plantar fascia, medial/plantar aspect. (Reprinted with permission from John Wiley and Sons.)[8]

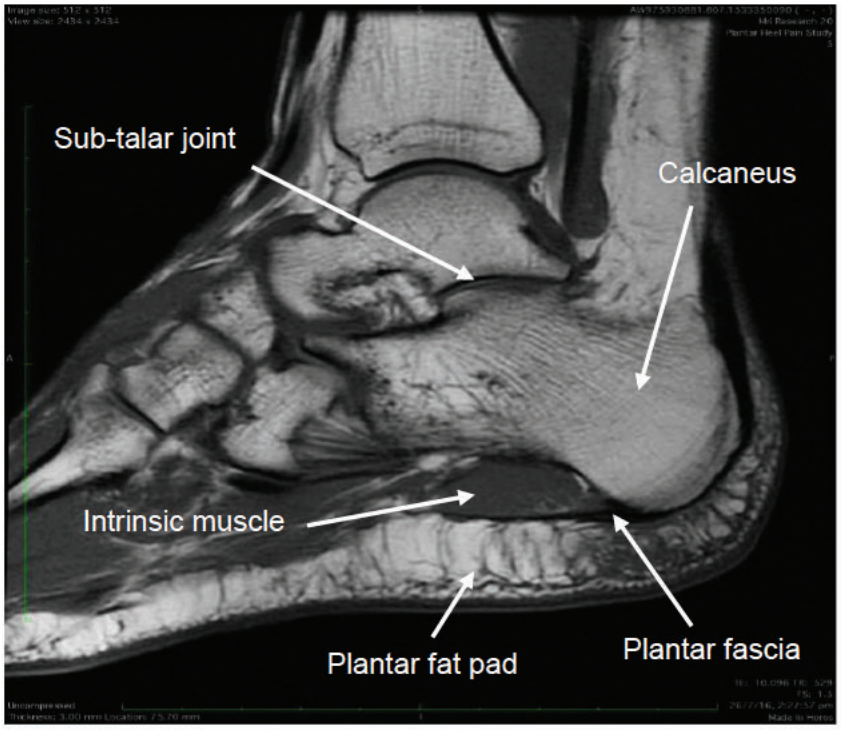

Figure 1-2: MRI anatomy of the heel and rear foot
(sagittal view magnetic resonance image (MRI), T1-weighted sequence)

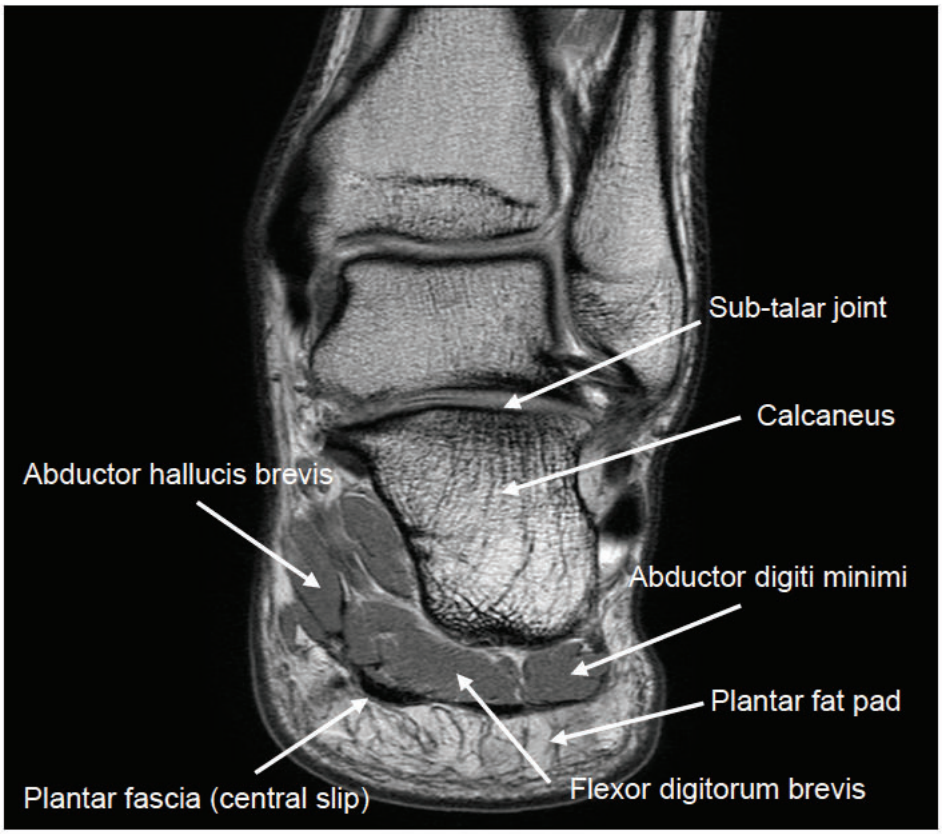

Figure 1-3: MRI anatomy of the heel and rear-foot
(coronal view MRI, Proton density sequence)

The anatomy of the plantar heel in histological section outlines the potential developmental sequence of enthesophyte (spur) formation (**Figure 1-4**)[9]. It also shows the largely trabecular nature of the plantar calcaneus and the attachment of the plantar fascia. As most cases of CPHP are thought to involve an entheseal/plantar fascia (PF) component, a brief review of the anatomy of the enthesis is warranted. The PF attaches to the calcaneus via a fibrocartilagenous enthesis, which involves a graduated transition from collagen to unmineralized fibrocartilage, crossing a tidemark into mineralised fibrocartilage and then trabecular rather than cortical bone[10, 11]. This mechanism provides for a graduated transition of stiffness from soft to hard tissue.

The enthesis is richly innervated[9, 12] and subject to degenerative change, which may serve as the genesis for spur development[9]. Plantar spurs are common, and typically develop on the deep side of the enthesis (and so not within the plantar fascia). They are composed predominantly of trabecular bone, in which trabecular alignment is variable but most commonly in a vertical plane that may be better suited to compressive loads[9, 12-14].

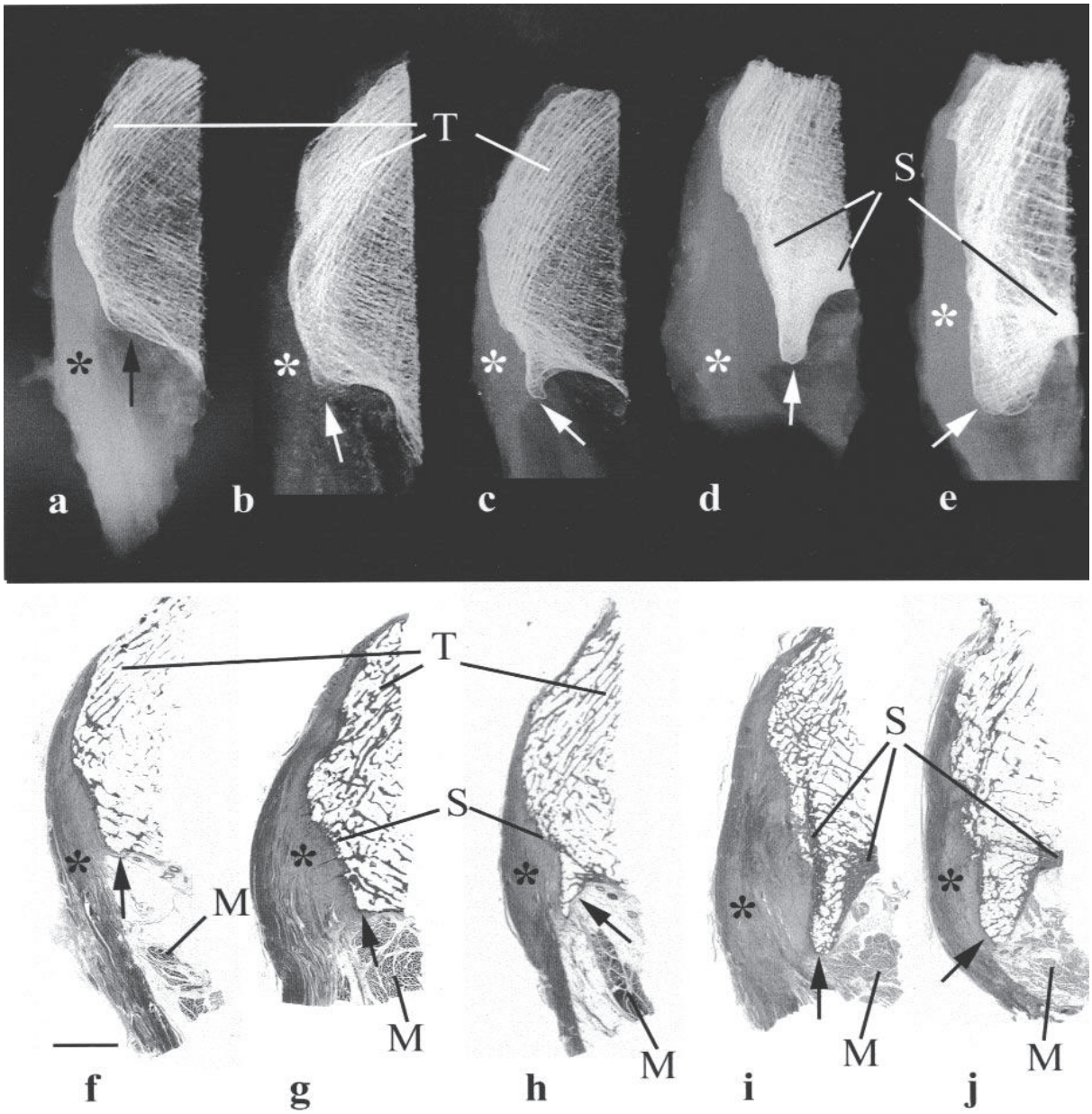

Figure 1-4: The plantar calcaneus, and plantar spur
(sagittal view, X-ray and histological section)

Sagittal view of the plantar calcaneus, radiographs (**a-e**) and accompanying histological section (**f-j**). This figure details the hypothesised progressive development of a plantar spur, in 'developmental sequence' from **a/f** to **e/j.** Note the largely trabecular make up of a plantar spur (**h, i, j**), and its deep relation to the plantar fascia.[9]

Abbreviations: * = plantar fascia, M = flexor digitorum brevis muscle, S = subchondral sclerosis in region of spur, T = parallel trabeculae linking the Achilles and plantar entheses, Scale bar = 5mm.

Reprinted by courtesy of Dr Kumai[9]

1.3 Scope of problem

CPHP is common and is considered the most frequent reason why individuals with musculoskeletal foot pain consult a health practitioner[1]. Despite a commonly held assumption of a benign self-limiting course, for a substantial number of individuals, symptoms do not resolve in a timely manner[15]. As the condition persists, people consult a wide range of practitioners[16], typically multiple times[17], and treatments are often ineffective[18]. The combination of being common and frequently recalcitrant make CPHP an important and often frustrating condition to encounter for patients and clinicians alike.

1.3.1 Incidence

Incidence is reported in a wide range of ways across different studies (**Table 1-1**). Nonetheless, onset of CPHP is common in active populations, specific occupational groups such as the military, in women particularly from non-athletic community groups, and in the middle aged to older population. For example, the incidence rate over 5-years in running athletes was as high as 31%[19], and ranged from 4.5 to 10% across different athletic populations in the systematic review by Lopes et al[20]. In a large military cohort new cases of PHP were more common in females 18/1000 rather than males (9.2/ 1000 person-years)[21], and rates across primary care ranged from 2.34[22] to 3.83 cases/ person-years[23], or 3.7/1000 registered patients[24].

Table 1-1: Incidence of CPHP

Author, year	Sample population	Sample number (N)	Incidence	Other
DiCaprio et al, 2010[19]	Italian running cohort, competitive & recreational	N=166	5-year new injury rate 31%	Males 37.2%, females 25% (not sig).
Lopes et al, 2012[20]	Systematic Review (8 papers, 2 reporting PHP prevalence)	N=98 (for 3 studies reporting PHP incidence)	4.5% to 10%	

Author, year	Sample population	Sample number (N)	Incidence	Other
Lievers et al, 2020[25]	USA College cohort (NCAA), 5-year injury surveillance across multiple sports	4.8M athlete-exposures	0.41/ 10,000 (95% CI* 0.35 to 0.47) athlete-exposures (196/ 1967 injuries)	PF most common in basketball, track and volleyball. Females more common (0.60 to 0.75/ 10,000 athlete-exposures)
Scher et al, 2009[21]	USA military Defense Medical Epidemiology Database	127,057/ 12,116,044 person-years	10.5/ 1000 person-years	Female 18/1000 person-years, male 9.2/1000 person-years ≥40 16.6/ 1000 person-years (20-24 y.o. referent group)
Owens et al, 2013[26]	USA military, Millenium Cohort Study	N=80,105, 1 year sample from baseline.	Adj OR# 1.27 (95% CI 1.04 to 1.56). 1228 PF cases/ 80,105=0.015	Females OR 1.85 (95% CI 1.62 to 2.12). Born ≥1980 OR 0.49 (95% CI 0.37 to 0.66)
Rasenberg et al, 2019[23]	Dutch primary care	N=1.9M (Dutch GP^ electronic medical records database)	3.83 (3.77 to 3.89) cases/ 1000 patient years (peak incidence 11.23 (10.16 to 12.31) cases/ 100 person-years at age 50 for females	Female 4.64 (95% CI 4.55 to 4.72) cases/ 1000 person-years Male 2.98 (95% CI 2.91 to 3.05). Mean age 50.25 yrs (sd 16.56)
Albers et al, 2016[22]	Single Dutch general practice (8 GPs)	10,651 person-years across 2012	2.34 cases/ 1000 person-years	2nd most frequent LL tendinopathy Mean age 46 yrs (43 to 49) for all tendinopathy
Riel et al, 2019[24]	Single Danish General Practice (3 GPs)	N=8836 New cases in one year (2016)	3.7/ 1000 registered patients (33 incident cases)	Mean age 45.1 years (sd 16.5) 61% female

*CI confidence interval, #OR odds ratio, ^GP general practice

1.3.2 Prevalence

CPHP is common across a range of active, community and elderly populations (**Table 1-2**). Sampling periods and prevalence metrics vary including reporting

sample percentages, person-years and encounters rather than person units, making numeric comparison difficult. Prevalence varies according to the age, activity level and source of the sample population, but generally CPHP is more common in active populations, in women, and those in middle age (~50yrs). These findings highlight that populations with CPHP are a heterogenous group, suggesting that risk factors may be different in each group, and that age and sex are potentially important confounders.

Table 1-2: Prevalence of CPHP

Author, year	Sample population	Sample number (N)	Prevalence	Other
Nahin et al, 2018[27]	Open-source internet survey, 2013 National Health & Wellness Survey	N=75,000	0.85% (95% CI 0.77 to 0.92) (prevalent if CPHP in last month)	Females 1.19% vs males 0.47% Aged 45-64 yrs 1.33% vs 0.53% aged 18-44 yrs
Hill et al, 2008[28]	N-W Adelaide general community (population based)	N=3206	17.4% (95% CI 16.2 to 20.9) for MSK foot pain generally, 20.9% (n=116) report heel as location of pain	Aches, pain or stiffness on most days
Whittaker et al, 2021[29]	GP/ primary care (BEACH dataset) (Apr 200 to Mar 2016)	N=1,568,100 GP encounters	19/10,000 GP encounters	Females 64.6% Patients aged 45-64 yrs largest group (50%)
Rasenberg et al, 2019[23]	Dutch primary care	N=1.9M (Dutch GP electronic medical records database)	0.4374% (95% CI 0.4639 to 0.4378%)	
Albers et al, 2016[22]	Single Dutch general practice (8 GPs)	10,651 person-years across 2012	2.44 cases/ 1000 person-years	2nd most frequent LL tendinopathy
Riel et al, 2019[24]	Single Danish General Practice (3 GPs)	N=8836 patients Consultations across 2015 & 2016	16.6/ 1000 registered patients (57 prevalent cases)	Mean age 45.1 years (sd 16.5) 61% female
Menz et al, 2010[30]	12 General practices in UK, using Consultations in Primary Care Archive (CiPCA) database	55, 033 musculoskeletal consultations in 2006 from 100,758 registered patients	'Plantar fasciitis' 7.5% of 3538 non-traumatic foot & ankle consultations (8% of all MSK consultations were foot & ankle based)	

Author, year	Sample population	Sample number (N)	Prevalence	Other
Dunn et al, 2004[31] (Feet First study)	Community based, multiethnic random sample USA, aged ≥65	N=784	6.9% (SE: 1.1)	Note plantar heel pad is listed separately; 4.2% (0.8). Men 6.4%, females 7.2%
Thomas et al, 2019[32]	4 UK General practices, aged ≥50	N=5109	9.6% (95% CI 8.8 to 10.5) 'Disabling' PHP 7.9% (95% CI 7.1 to 8.7)	PHP in last month
Taunton et al, 2002[33]	Sports Medicine setting, 2-year collection period	N=2002 with running related injuries	158/2002=7.9%	Mean age 48.1 years. 54% were male. Third most common injury.

1.3.3 Natural history

The natural or treated course of CPHP for many is slow and frustrating. Despite a commonly held assumption of an uncomplicated and timely resolution[16, 34, 35], an important sub-group of sufferers report persistent symptoms, often years later.

Resolution of symptoms has been reported in participants in the control arm of trials[36]. However most trials in CPHP report a short follow-up period (rarely more than 1 year), and these studies are designed to report on comparative rather than dedicated longitudinal outcomes. The results from a number of longer-term follow-up trials challenge this view. Controls in a shockwave trial with a 2-year follow-up demonstrated a mean improvement in VAS pain scores of only 37%, with high residual pain scores at 2 years[37]. Another shockwave trial with follow-up at 1-year reported a fair to poor outcome in 45% of controls[38], with recurrence rates as high as 55%, despite having received conservative treatment. The authors of an active 4-arm injection trial could not identify what features were associated with a good or poor outcome, and for 28% of participants the 'natural history of the condition was not one of improvement'[39]. Thus it appears that despite treatment not everyone gets better at the same rate or within the same time frame, and the natural course of CPHP may be extended.

Studies designed to specifically report on CPHP longitudinal outcomes are limited. A recent longer-term longitudinal study of cases with mean follow-up from baseline of 8.9 years (mean 9.7 years post symptom onset, n=174)[15] showed the risk of having

plantar fasciitis at 1 year was 80.5%, 50% after 5-years, 45.6% after 10-years, and 44% after 15-years. The vast majority were not symptom free at 1 year, and for those who did not get better at an early stage, the trajectory of recovery was slow.

Other studies have reported follow-up outcomes from retrospective case reviews[33, 40, 41]. Eighteen percent of community-based participants reported a fair to poor outcome on telephone interview 12-months later[40]. In another community-based sample 15% of 157 respondents reported a poor outcome ('constant pain') following a standardised intervention plan, with 49% reporting some degree of ongoing symptoms in total (the timeframe for survey follow-up was unclear)[41]. In a sports medicine setting, 42% of CPHP patients assessed over a 2-year period reported incomplete resolution (follow-up period also not defined)[33]. These studies indicate that 20-40% of cases continue to report symptoms at least 1 year later.

Predictors of prognosis can offer insight into mechanisms that sustain disease and possibly inform treatment; however, we have little understanding of these factors in CPHP. Factors possibly associated with poorer outcomes include being female and having bilateral heel pain[15, 40], being overweight[40], and a longer duration of symptoms[40, 42]. These factors are unlikely to inform intervention as most are not modifiable, or difficult to modify. Another approach might be to examine the factors that differentiate acute from chronic cases with the view that differences in risk factors might explain chronicity. Two studies have investigated these differences[43, 44]. Age, gender, body mass index (BMI), physical function or symptom intensity did not differentiate cases with persistent pain (> 6 months) from those with symptoms of a lesser duration (< 6 months)[16]. Similarly, in a study comparing cases with chronic (>1 year) and acute (< 6 months) symptoms, some (ankle dorsiflexor and toe flexor) strength deficits were noted in chronic cases, but interestingly this group also self-reported better foot function[44]. There were no differences for BMI, ankle or big toe flexibility, hindfoot strength, and self-reported foot pain and physical activity as measured by the Foot Health Status Questionnaire (FHSQ)[44]. This may indicate that CPHP sufferers 'get on with things', but also that there is a disconnect between physical variables and functional outcomes in chronic disease. In neither of these approaches have psychosocial predictors such as pain catastrophising or depression been investigated.

In summary, a substantial percentage of CPHP cases report persistent symptoms and longitudinal predictors of CPHP outcomes are poorly understood. Physically assessed clinical variables do not appear to differentiate acute from chronic CPHP, however many potentially important psychosocial predictors have not been assessed. Most factors which have been identified are not modifiable (eg sex, symptom duration, bilateral symptoms), so there is a clinical imperative to improve our understanding of other predictors.

1.3.4 Healthcare cost/ Economic burden

CPHP is the most common musculoskeletal foot condition treated by healthcare professionals[45]. Because it is both common and persistent, it is likely to confer a significant personal and societal economic cost, however this is poorly studied. People with CPHP will access numerous providers across multiple occasions, and try many treatments, adding to the cost burden[16, 32]. In the USA from 1995-2000, a diagnosis of plantar fasciitis was attributed to approximately 1 million office-based and outpatient physician visits per year[17]. This number may underestimate healthcare utilisation as it does not include visits to other providers such as physiotherapists, tertiary centres or complementary health practitioners. Further, 65% of patients had visited their physician previously with a diagnosis of plantar fasciitis, indicating that for many it requires multiple visits. An economic evaluation of these data[46] determined that the cost of treatment for third party payers in the USA in 2007 ranged from $USD192 to 376 million. In a primary care setting in the United Kingdom (UK) foot and ankle presentations accounted for 8% of all musculoskeletal consultations surveyed across 12 General Practice (GP) clinics over the course of 1 year, with 7.5% of those specifically diagnosed as 'plantar fasciitis'[30]. Extrapolation from data obtained by survey of Australian GPs (cross sectional BEACH dataset, 2000-2016, 1000 GPs) found that PHP was responsible for 270,000 annual encounters as estimated for the year 2015-16 (19/10,000 encounters)[29]. Utilisation of healthcare resources in a UK setting over a 12-month period largely fell to GPs (43%) and podiatrists (32.8%), and then physiotherapists (15.1%)[32].

In summary, whilst a formal understanding of the costs and resource use associated with CPHP is limited, it is clearly a problem with a wide reach with most of the healthcare burden falling on the primary care sector.

1.3.5 Personal cost

The personal burden on social, work, home or self-care participation is sparsely acknowledged in the CPHP literature, though there is an understanding that CPHP has a negative impact on health-related quality of life. Compared to controls, cases report significantly poorer health-related quality of life, scoring lower on the FHSQ for foot pain, foot-related physical function, footwear choices and general foot health[47]. They self-report greater limitations in physical activity, are more socially isolated and lack the vigour or energy to participate in tasks compared to controls[47]. Based on disability index reporting, CPHP is frequently disabling, and associated with more physical and mental impairment, anxiety, stress and depression and lower levels of physical activity (PA) and participation, compared to controls[32, 48]. The personal lived experience for people with CPHP is often one of frustration, expressing doubt and uncertainty regarding their health journey, with needs often unmet[49].

If the aim of effective treatment is to meet these needs, then acknowledging the personal cost, and understanding the factors that are associated with function and quality of life (QOL) outcomes, must be important. It is also important to acknowledge that the factors that are associated with pain outcomes, are not necessarily the same as those affecting function and quality of life (vis-a-vis activity limitations and social participation)[48].

1.4 Aetiology and associations

1.4.1 Pathology

CPHP has traditionally been framed as a condition of mechanical overload with emphasis on the plantar fascia and its calcaneal enthesis[5]. Early beliefs were that cumulative trauma from tensile strain of the plantar fascia and mechanical compression and shear at the heel resulted in microtearing of the plantar fascia especially its calcaneal entheseal attachment. This could result in inflammation and given the exposure to repeated and persistent loading, a repetitive cycle of overload, failed healing and chronic inflammation.

This model has been challenged by histological data that indicates that cellular markers of classical inflammation are lacking[6]. Biopsy of the plantar fascia and enthesis in chronic cases of plantar fasciitis going to surgery demonstrate a

disorganised collagenous structure characterised by fragmentation, myxoid (mucoid) degeneration, and bone marrow vascular ectasia (proliferation) that has been collectively summarised as a degenerative process[6].

These findings build on previous often uncontrolled histologic studies that confirm an array of degenerative type lesions including angio- and fibroblastic hyperplasia, chondroid hyper- and metaplasia, mucoid and fibroid degeneration and matrix calcification[50-53]. These findings come from small case series studies in a heterogenous group of participants (athletes, non-athletes, varied ages, disease duration and BMI) who were at clinical end stage (thus requiring surgery), with limited documentation of past treatments such as injection therapies and comorbidities. It is therefore unclear to what extent these findings represent the typical pathophysiology of CPHP, even though it does clearly challenge the notion of an ‘ ’itis'**.**

1.4.2 Pain mechanisms; nociceptive, neuropathic and nociplastic

By definition, CPHP is a pain state. Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage,” with the recent addendum of the following six key notes:[54]

- Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.
- Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
- Through their life experiences, individuals learn the concept of pain.
- A person’s report of an experience as pain should be respected.
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
- Verbal description is only one of several behaviours to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain

The IASP defines many types of pain, and these definitions were revised recently for inclusion in the ICD11[55]. Mechanistic descriptors of chronic pain are summarised

as either nociceptive, neuropathic and/or nociplastic. The first two are familiar, but the latter is a newer label that brings together the concepts of a centrally generated, primary pain state in the absence of demonstrable neuropathic disease or damage, or other identifiable (secondary) nociceptive causes[55, 56]. These are not diagnostic terms, but describe the neurobiology of pain. CPHP may have contributions from nociceptive, neuropathic and nociplastic mechanisms. If treating pain is a goal in CPHP management, then understanding the mechanism behind it must be an important consideration.

The research describing pain mechanisms in CPHP is relatively recent. Lower limb tendinopathy (Achilles, patellar) is generally considered to display mostly nociceptive pain behaviours[57-59]. There is uniform agreement on the presence of mechanical allodynia and hyperalgesia on the plantar foot in cases, measured by lower pressure pain thresholds (PPTs) and considered to be representative of local nociceptive processes[59-63]. The presence of widespread pressure hypersensitivity at sites distant from the plantar foot implicates nociplastic changes, which was reported in two studies[60, 63], but not a third[59]. This latter study found no support for nociplastic mechanisms having examined other constructs of nociplasticity including conditioned pain modulation (an indirect measure of the efficacy of endogenous pain inhibition mechanisms), and cold and thermal pain thresholds. Other studies[60, 62] report a topographical spreading of symptoms beyond the plantar heel that may be discordant with the notion of primary hyperalgesia.

This is further supported by assessment with tools such as the Central Sensitisation Inventory[64]. A large cross-sectional assessment of lower limb ‘tendinopathy’ cases using the Central Sensitisation Inventory reported that 24% of CPHP cases scored above the traditional central sensitisation threshold score of 40%. Importantly, CPHP (‘plantar fasciitis’), like gluteal tendinopathy, behaved differently to other types of tendinopathy such as Achilles and patellar tendinopathy, presenting with considerably higher rates of sensitisation.

Reasons for these differences are uncertain, but may relate to the persistent nature of compressive load at these bone-tendon insertions (as opposed to the on-off nature of say mid-Achilles load)[57]. As pain mechanisms causing heel pain may be generated or maintained outside the foot, a broader consideration of risk factors

consistent with a biopsychosocial understanding of persistent pain is warranted.

CPHP as a peripherally generated neuropathic pain has been described for decades, including the original description by Baxter of compression of the first branch of the lateral plantar nerve[65]. Baxter's original reports estimated that up to 20% of heel pain cases could have a neuropathic component. Numerous other sites of compression or irritation are recognised such as the tarsal tunnel, or other sites involving compression of the medial calcaneal and medial plantar nerves directly[66]. Disease states targeting peripheral nerves such as diabetes would also fit the definition of peripheral neuropathic pain.

Despite the long history surrounding neuropathic heel pain, there are very few data to support these statements. A survey of attendees presenting with a variety of chronic lower limb tendinopathies using the *painDETECT* questionnaire, found that 29% of those with plantar fasciitis scored in the 'neuropathic pain likely' category (>=19)[67]. Case-control studies report an association between conduction changes in the lateral plantar nerve[68]. and imaging signal changes on MRI[69], indicating a physical correlate between heel pain and probable nerve entrapment. Assessment of neuropathic pain in the foot is notoriously difficult, as objective testing such as electrodiagnostic or quantitative sensory testing is difficult, often insensitive to early disease, or difficult to interpret with a lack of normative data[70]. Primary nerves of interest such as the first branch of the lateral plantar nerve innervate periosteum but do not have a testable cutaneous field, yielding sensory testing for this condition ineffective. With local nociceptive stressors such as oedema and space occupiers such as a thickened PF and a plantar spur, assessing the independent contribution of local nerve tissue is difficult.

Taken together, these findings indicate ongoing uncertainty about the predominant pain mechanisms in CPHP, and it is unclear if CPHP pain mechanisms share similarities with other lower limb tendon sites. Assessment for neuropathic pain by validated questionnaire with longitudinal follow up would be valuable in determining whether, if present, these pain measures predict future pain outcomes. Large differences in hamstring length between cases and controls have been reported but no attempt was made to determine if neural factors contributed to these deficits[71]. The addition of sensitising manoeuvres such as dorsiflexion and foot eversion can

add provocative load to medial ankle nerve structures[72, 73] and could be one simple way for the clinician to test for a potential neuropathic contributor. Lastly, changes such as oedema or fibrofatty atrophy of the abductor digiti minimi can be visualised on (PD) coronal MRI foot sequences and may serve as a marker for denervation indicative of a Baxters-type neuropathy.

This battery of tests incorporating patient reported outcomes (such as the *painDETECT*), physical clinical testing of neuromechanical sensitivity, and (MR) imaging may provide greater clinical insight into what is a difficult sub-group of CPHP to identify.

1.4.3 Associations of and risk factors for CPHP

We undertook a systematic review of the literature (published in 2016, **Appendix 1**) examining risk factors and associations with plantar fasciitis/ plantar heel pain in collaboration with researchers from Erasmus University[71].

Fifty-one studies were included for review and potential pooling, consisting of a single prospective cohort study, 46 case-control studies and 4 cross-sectional studies. The mean quality score (derived from a checklist from the Dutch Cochrane Centre) for all studies was low at 58% (range 11-100%). Only 15/51 studies assessed more than 50 participants and just 18/51 studies were considered to have adequately defined the study sample of interest. No study used controls that were randomly selected from the population. Heterogeneity scores (I^2) for those factors that could be pooled ranged from 0-97%, and was highest in those pooled analyses where most studies were included (eg BMI 83%, 19 studies, plantar fascia thickness (PFT) 97%, 20 studies). [See **Appendix 1**]

Exposures of interest in the review were broadly grouped as clinical factors and imaging associations. Other factors such as physical activity levels and footwear use wear also reviewed. Data could be pooled for meta-analysis for 12 variables. The following sections draw on the findings of this review as well as more recently published studies.

For the sake of the ensuing discussion, I refer to clinical factors and imaging factors. Clinical factors have been further subdivided (for convenience, and in reference to the biological and psychological elements of biopsychosocial factors) into physical

measures (including physical activity and footwear factors), and formal psychological measures.

1.4.3.1 Clinical factors - physical and other measures

The clinical factor most consistently associated with CPHP is BMI[71]. This is confirmed in a larger more recent Australian case-control study[74], and in a prospective study in a military cohort[26] that identified an association with both overweight and obesity, in a dose responsive manner. This association may not apply to athletic cases, with a 5-year prospective study of running athletes finding no association[19]. This may be because BMI in athletic cohorts, especially running athletes, is typically within normal range with narrow variance compared to general community-based cohorts[71]. No studies have investigated allied adiposity constructs such as waist girth or body composition, which could be useful in helping understand the potential metabolic versus mechanical contribution of excess weight. I discuss this in further detail section ***1.4.4.1*** under 'Other contributors; Obesity'.

Although physical assessment underpins current clinical practice, the association between clinical measures of the foot and leg for ankle and first metatarsophalangeal joint (MTP) mobility, ankle strength, foot posture, hamstring flexibility, and other measures of kinematic and kinetic function, is inconsistent or weak. Muscle strength deficits are reported in single studies in cases for the ankle plantarflexors (isokinetic dynamometry) and toe flexors[71], including more recent support for some attributes (ankle evertor and toe flexor strength)[74], but not others (calf endurance)[74, 75]. Interpretation of the cause-effect status of these findings is unclear due to the case-control nature of these studies.

Findings for flexibility and joint mobility provide limited support for decreased first MTP extension range of motion (ROM), and two of three studies reported large effect sizes for a reduction in hamstring flexibility[71]. Hamstring testing procedures did not differentiate the contribution of neural structures to straight leg raise hamstring flexibility test protocols, so the mechanism of this association is unclear. Ankle joint dorsiflexion (DF) mobility is critical for forward weight transfer in gait, important for shock attenuation in impact activity and loss of ROM increases arch bending (and plantar fascial) stresses, and so is considered an important clinical target. The results for the association of ankle DF joint ROM in our review were inconclusive, as

have been more recent case-control studies that have indicated an association[74], and no association[76].

There was some case-control support for an association with a pronated foot posture on the Foot Posture Index (FPI-6) in non-athletic participants[71], and prospective support for higher arched foot posture as a risk factor in track athletes[19]. Recent case-control studies however failed to find an association with foot posture[74, 76]. These results are almost certainly influenced by the study population, by the specific measure and by confounding, where those that adjust or match for potential confounders such as BMI, may be less likely to report a positive association[76].

Assessment of other kinetic and kinematic factors, including instrumented gait assessment, have yielded inconsistent results[71]. The case-control nature of these studies may capture the effect of pain, as evident in a more recent pressure-based gait analysis study that found cases demonstrate reduced heel loading by unweighting the heel in a protective manner[77]. Conversely, a prospective study in track and field running athletes over a 5-year period (n=166, incidence 31.3%) did find an association with varus knee alignment (OR 5.63 (95% CI 2.01 to 15.72)) and cavus arch posture (OR 5.52 (95% CI 2.12 to 14.33))[19], though these measures of alignment were subjectively rather than objectively quantified.

This same study also found associations with measures of activity and exercise load and CPHP: greater number of days of practice per week (OR 2.59 (95% CI 1.68 to 3.99)), greater number of years of activity (mean difference (MD) 3.30 (1.01 to 5.59)) and running more kilometres per week (MD 20.00 (12.12 to 27.88)). Recent deployment as a marker for increased physical activity was also prospectively associated with CPHP risk in a military cohort[26]. Other studies from our own review were inconsistent, and a more recent investigation of occupation standing time and self-reported physical activity[74], did not find an association. A key limitation in all of these studies was that physical activity was assessed by self-report rather than objectively measured.

Footwear has the potential to influence levels of support, cushioning and heel loads, but data in CPHP is lacking. Rotating footwear in an occupational setting was associated with decreased risk[78], use of spiked athletic shoes (OR 5.49 (95% CI

1.71 to 17.64)) in a running cohort[19] with increased risk, but wearing flat shoes not associated[79]. This is a difficult but important area of study that requires further consideration, as footwear advice in the management of CPHP lacks objective guidance but is an area that has the potential to deliver an immediate clinical return.

In summary, the evidence for associations of lower limb clinical physical findings with CPHP is limited or conflicting. BMI is consistently associated but other adiposity constructs have not been explored. Associations for commonly assessed clinical physical measures lack consistent support, especially in confounder-controlled or objectively measured prospective studies. There is insufficient information to assess the association of footwear factors and physical activity (including standing time), which to date have also not been measured objectively. All these are important evidence gaps.

1.4.3.2 Clinical factors - psychological measures

At the time our review was undertaken (search up to June 4, 2014), no studies had assessed the association between cognitive or affective dimensions of health and CPHP, despite the modern consideration of pain and disability as biopsychosocial.

Since then, there has been a more recent focus on psychological variables in CPHP[80]. Cross-sectional/case series[48, 81] and case-control[82] studies demonstrate associations between CPHP and depression, stress and anxiety[82], between foot function and depression, stress, anxiety, pain catastrophising and kinesiophobia, and between foot pain and pain catastrophising[48, 81] and in women, foot pain and stress and depression[48].

These studies add valuable insight towards potentially modifiable factors but are still limited as they are mostly derived from small studies (n=36 to 84) and largely from the work of a single group. Given the importance of biopsychosocial factors in chronic musculoskeletal pain, addressing our lack of understanding of these factors in CPHP, including for the first time in longitudinal study, appears warranted.

1.4.3.3 Imaging Factors

The assessment of imaging biomarkers in CPHP has traditionally focussed on ultrasound measures of plantar fascia thickness and echogenicity or plantar spurs using Xray[83]. There are surprisingly few larger series of controlled MRI, and little

objective consideration of associated structures such as the plantar fat pad, other bone factors such bone marrow oedema, and potentially more dynamic signal markers as opposed to structure (physiology versus morphology). Other biomarkers for consideration include evidence of nerve injury, such as muscle composition change or atrophy, and vascular signal within the plantar fascia. A newer bone assessment tool, high-resolution peripheral quantitative computed tomography (HR-PQCT, or 'QCT'), is also discussed.

I summarise the findings associating imaging biomarkers with CPHP below, considered in the sub-headings of soft tissue and bone factors.

1.4.3.3.1 Soft tissues

Imaging exposures associated with CPHP included a thickened, hypoechogenic and hyperaemic plantar fascia and perifascial fluid collection[71]. Based on simple linear measurements, participants with CPHP were more likely to have a thickened loaded and unloaded plantar fat pad[71]. No study quantified signal change in the fat pad although one small case-control study (n=8 cases, n=5 controls) failed to find an association with the presence of septal changes in the fat pad[84].

In contrast to plantar fat pad atrophy likely contributing to heel pain risk, a thickened plantar fat pad may be indicative of swelling. This is supported by the strong association of perifascial oedema with CPHP in imaging series[85]. The shock absorbing properties of the plantar fat pad are hypothesized to be important in protecting plantar heel structures. Whist this is thought to be largely dependent on the quantity (volume) of plantar fat tissue[86], the micro and macro fat chambers encased and supported by a specialised fibroelastic septal network[87], may also be important. Quantifying differences in the make-up of the plantar fat pad between cases and controls, as measured by signal change on T1 or T2-weighted sequences, has not been reported but may help clarify the association between the fat pad and CPHP.

Signal differences within the substance of the plantar fascia has received only slightly more attention, even though signal differences or change in allied structures such as tendon are well documented[88]. Berkowitz (1991)[84] identified increased intra-fascial signal in 9/10 feet, and (T1 weighted) signal changes have also been

reported by Grasel (1999)[89], and again more recently in a larger case series review[90]. The importance of intra-fascial signal remains uncertain in CPHP, as whilst it may serve as a potentially modifiable biomarker, these papers did not quantitatively measure exposures nor quantitatively analyse these signal outcomes. The results reflect findings from either small cross-sectional studies, or retrospective, uncontrolled case series.

The van Leeuwen review identified associations for novel imaging assessment tools[71]. Two studies, based on evidence for abductor digiti minimi signal change on MRI or electrodiagnostic testing, report an association with evidence of plantar nerve neuropathy. Sonoelastography identified a case-control association for a softer and less elastic plantar fascia (2 studies, n=230). In all however, there were surprisingly few controlled and quantitatively measured and analysed studies incorporating MRI. MRI is reasonably accessible in many health systems, offers improved sensitivity and specificity in CPHP above ultrasound[91], and presents a high-resolution, wide field of view sensitive to multiple tissues. Capturing markers of both structure and physiology (eg swelling/ signal events), it is considered the gold standard for imaging in research in CPHP.

1.4.3.3.2 Bone factors

Plantar calcaneal spurs have traditionally been considered the primary bony contribution to CPHP, and though associated with prevalent CPHP[71], their position in the causal pathway is unclear[12]. In cross-sectional studies, half of which matched for age and sex, cases are 8.21 the odds more likely to have a spur (95%CI 4.32 to 15.62, n=11 studies)[71]. This association may be stronger in cases with larger spurs[92]. Associations with function or quality of life outcomes are not clearly established. Mechanistically, spurs are thought to develop as a consequence of degenerative changes at the plantar enthesis[9]. They are more common in overweight, older persons and those with a history of osteoarthritis[9, 14]. The spur itself, often visualised in a sagittal view, is more like a horizontal shelf mostly sited on the deep aspect of the PF, and frequently found within the muscular attachments of flexor digitorum brevis (FDB), though this is variable[93]. Its trabecular bone structure is mostly oriented vertically, and may be better suited to ameliorating compressive forces[93] and could be considered an adaptive response to entheseal stress and

degenerative change. A causal role in generating pain is uncertain, though they can fracture, take up space in an area that traffics neurovascular structures, and it can exhibit signs of bone stress with oedema[13, 14].

An unexplored aspect of calcaneal bone health and performance in CPHP is its microstructural and density characteristics. This is important as the calcaneus is largely trabecular- 90% of the dry weight of the calcaneus is trabecular bone, encased in a thin cortical shell[94]. Bone mineral density is generally considered to explain most of the variation in bone strength, however the quality and organisation of bone microstructure is now also recognised as an important and necessary consideration in modelling bone performance[95]. The thickness, spacing (and therefore number per unit area and total bone volume per unit area) of trabeculae and their form (e.g. plate or rod-like), connectivity and directional arrangement (anisotropy) are some of the ultrastructural factors that explain the mechanical performance of bone. To date, we are not aware of any investigation of bone density or microstructural factors in CPHP. The recent extension into foot applications of high-resolution bone imaging tools such as peripheral quantitative computed tomography (HR-pQCT), have enabled the ability to examine these factors in the plantar calcaneus[96, 97]. If the dominant phenotype of CPHP is thought to be plantar fascia in origin and represents enthesopathic disease characterised by degenerative changes and bony remodelling (eg spurs), and given other potential changes to bone stimuli such as altered loading strategies[77], then alterations in bone structure and density might reasonably be expected.

Partitioning out the weightbearing portion of the plantar calcaneus and recording a further region of interest in the central calcaneus as a pure trabecular capture to act as a reference site, would provide a first insight into the nature, if any, of bone differences associated with CPHP. This is important as CPHP is largely viewed through a soft tissue lens. Acknowledging the entheseal nature of ‘plantar fasciitis’ logically brings into question - what happens on the bone side of the enthesis? Bone can be targeted by modalities (eg extracorporeal shockwave therapy (ESWT), low intensity pulsed ultrasound (LIPUS)), by exercise using bone stimulus parameters, by unloading including braces and boots, and by pharmacotherapy including medicines such as the bisphosphonates. Many of these are not routinely considered

in CPHP management, or specifically applied in recognition of addressing a bone phenotype of pain.

Bone marrow oedema, detected as signal change on MRI, represents another potential bone exposure that has not been extensively investigated in CPHP. Bone marrow lesions (BMLs) have been documented in CPHP cases[85, 90, 98]. These lesions are not simply oedematous change, but reflect a heterogenous group of pathologies involving trabecular degeneration, marrow necrosis, fibrosis and remodeling[99]. They are measured on T2-weighted MRI sequences as ill-defined signal hyperintensities. BMLs in osteoarthritis are associated with disease and pain outcomes in longitudinal studies and are a target for novel therapies[100, 101]. It is currently unclear whether the identification of BMLs in CPHP is of clinical or prognostic significance. In retrospective case series reports, BMLs have been associated with atypical presentations featuring greater night pain[98], but not necessarily worse pain outcomes[85]. However BMLs have neither been objectively quantified, nor analysed with adjustment for other potentially relevant covariates such as BMI or physical activity, nor assessed against validated outcomes in any of the pain, foot-related function or QOL domains. There are also no longitudinal data available that assesses how change in these lesions affects these outcomes. To summarise, bone factors in CPHP are poorly understood, but have the potential to define a specific phenotype of heel pain with specific assessment and treatment implications.

1.4.4 Other contributors: obesity, diabetes, inflammatory disease.

The aetiology of CPHP has been traditionally viewed through a mechanical lens. However, the lived experience of chronic musculoskeletal disease frequently includes comorbidities and other health issues that impact on its course. Chronic PHP is no different.

1.4.4.1 Obesity

Obesity is associated with incident and prevalent foot pain[102, 103]. Although prospective data for obesity in CPHP are lacking, there is strong support for a cross-sectional association[71]. Obesity and increased body mass may have direct consequences for increased foot and heel loads. Higher peak pressures in the heel were associated with increased foot pain at 2 years[104], and heel pressure changes

were also associated with changes in foot-related function. In the same study there was evidence that foot pain intensity and foot-related functional limitations are associated with changes in midfoot plantar pressures, which in turn were associated with changes in bodyweight. Midfoot pressure may mediate the link between *changes* in bodyweight and foot pain, and the effect of bodyweight is antecedent to foot pain. Given the PF is a key stabiliser connecting through the midfoot, (changing) body mass may be directly implicated in the mechanical aetiology of CPHP.

Alternatively, obesity can have effects through a systemic mechanism. Fat tissue, especially central abdominal or visceral fat, is endocrinologically active and produces a wide range of signalling molecules, especially from the cytokine class. Many of these molecules including species from the interleukins and tumour necrosing factor-alpha (TNF-α) are associated with chronic low grade systemic inflammation (meta-inflammation), known to target many organs including vasculature and collagen[105]. An association between upper limb tendinopathy and obesity, presumably with the mechanical effect of weightbearing removed, suggests a possible role for metabolic and meta-inflammatory processes[106]. Differences in risk are identified even in athletic cases where load related parameters might be assumed to be the dominant influence. Jumping male athletes with a larger waist girth are at higher risk of patellar tendinopathy, independent of body mass[107]. In the foot specifically, body fat (fat mass index- fat(kg)/height^2), but not bodyweight, was a key association for both prevalent and incident foot pain in a large community cohort[108]. These findings support that the composition and location of fat beyond its mechanical mass, matters. Whilst foot pain studies have investigated BMI or body composition (usually via dual energy X-ray absorptiometry (DXA)), we are unaware of any study examining waist girth or body composition in CPHP. Given BMI has the strongest clinical association with CPHP, this represents an important evidence gap.

Higher fat mass is also associated with multisite pain across the lower extremity and hands, independent of physical activity, psychological or sociodemographic factors[109]. Low grade systemic inflammation associated with obesity-related metabolic and meta-inflammatory dysregulation is hypothesised to contribute to widespread pain via the sensitisation of pain systems[109]. Multisite pain is more common than single site pain in chronic musculoskeletal disease[110]. It predicts

difficulties with physical and mental function[111], and greater multisite pain is associated with poorer psychosocial health, greater healthcare resource[112] and medication[113] use, and poorer work and activities of daily living (ADL) function[114]. Counting the number of pain sites beyond the heel is a simple way to take this association into account but has yet to be explored in CPHP research.

1.4.4.2 Diabetes

Collagen in the plantar fascia is frequently targeted by metabolic processes associated with diabetes. Indeed, plantar fascia thickness is considered an index for the accumulation of collagenous glycation end products associated with poor glucose regulation, and is a predictor of microvascular complications in diabetes[115]. Compared to non-diabetics, plantar fasciitis was 42% more common in individuals with diabetes, in particular with the far more common Type 2 variant (64%)[116] (5-year prevalence, n=535,000). Prevalence was greater in females and those with higher BMI, indicating a complex association with other factors. Given impaired glucose metabolism - either diabetes or 'pre-diabetes' - affects up to 25% of the Australian population[117], and for every diagnosed case of diabetes one case goes undiagnosed[117], and that changes to the PF happen early in the disease process before other microvascular markers are evident[118], a metabolic contribution towards CPHP should be considered. This is especially the case in the presence of overweight/obesity. Making an assumption that community-based samples are free of these comorbidities based on self-report is likely to misrepresent the true input of metabolics in CPHP.

1.4.4.3 Inflammatory disease

A painful heel can be a presentation of systemic disease of rheumatologic origin. Inflammatory disease such as rheumatoid arthritis, ankylosing spondylitis and Reiters disease result in enthesitis. In RA foot pain is the first symptom to present in 20 to 35%[119]. There may be clinical overlap between milder states of inflammatory disease and CPHP from other sources. For example rheumatoid arthritis and CPHP is more common in women with symptoms most commonly developing between the ages 40-60 years[43], with both reporting morning stiffness and weightbearing pain. In the absence of routine inflammatory marker blood screening, it is unclear to what extent inflammatory disease sub-groups present as community-based CPHP,

especially in younger age groups.

It is not the purpose of this thesis to explore a potential continuum of systemically supported CPHP, however systemic metabolic and meta-inflammatory factors are thought to play an increasingly important role in persistent musculoskeletal disease. Comparing the clinical features of sub-clinical or low-grade inflammatory presentations and non-inflammatory CPHP could help inform the evidence gap regarding the unknown overlap of these two heel pain mechanisms in a representative community sample.

1.5 Effectiveness of current treatments

There are a wide range of possible interventions for CPHP[2, 4]. Despite this, the optimal treatment is unclear[1, 2, 4]. The seminal Cochrane review by Crawford et al in 2003 (*Interventions for treating plantar heel pain*, since withdrawn in 2010) concluded that "at the moment there is limited evidence upon which to base clinical practice. Treatments that are used to reduce heel pain seem to bring only marginal gains over no treatment and control therapies such as stretching exercises"[120].

Despite 20 years of further research, it appears little has changed with a recent systematic review and network meta-analysis finding that the current evidence for the most effective management of PHP is equivocal (31 randomised controlled trials (RCTs), n=2450)[18]. In this network meta-analysis, ranking probability distributions for each treatment were generated from a simulation of 1000 replications, to create a comparative measure of treatment effect (lower mean ranks better). Of the modalities reviewed, best support was found for corticosteroid injection (CSI) alone (mean rank 2.4 short-term/ 3.9 medium-term/3.0 long-term) or with exercise (mean rank 2.8/4.6/3.6), and for ESWT (mean rank 3.8/3.6/4.2) for both pain and function outcomes, over all time periods. Exercise was not beneficial in the short and medium terms (mean rank 6.3/ 6.9) but provided longer-term benefit for pain (mean rank 3.7) and function (mean rank 1.7). On average however, commonly used treatments do not appear to be any more effective for pain and function outcomes than each other, especially in the medium to longer term[18].

When best practice guidelines incorporating lived patient experiences, expert clinical reasoning and systematic review are considered[121] a core group of interventions

(stretch, tape and advice) is recommended, followed by a stepped care approach. This stepped care next recommends the application of ESWT (focussed or radial), and failing that, customised orthoses. This provides general agreement with the findings of another recent review[2] and the American Physical Therapy Association guidelines,[1] but re-enforces the view that a linear stepped care approach based on trial and review rather than a specific diagnostic or impairment based assessment, still predominates.

The relative ineffectiveness of active treatments may highlight our limited understanding of pathophysiologic and causal mechanisms in CPHP, and/or the heterogeneity of the condition. Are treatment modalities ineffective, or just don't work for a particular aetiological subgroup? Are the impacts of effective treatments washed out against the backdrop of a heterogeneous patient group? The broad clinical definition of CPHP may contribute to this uncertainty. This emphasises the need to provide a wider understanding of the range of factors associated with CPHP. This may facilitate sub-grouping (and subsequent phenotyping) that allows for improved treatment targeting.

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Chapter 2

Aims of Study

2. Summary of study aims

Chapter 1 summarises our understanding of the literature for clinical and imaging factors associated with CPHP, and identifies evidence gaps in aetiology, risk factors and disease course. This chapter translates those evidence gaps into quantifiable aims.

Most studies have focussed on physical clinical ‘foot-level’ exposures such as foot posture, joint mobility and muscle strength. Body mass index (BMI) is widely supported as an association, but there has been no exploration of the obesity/ metabolic link by investigating other adiposity constructs such as waist girth or body composition. This may be important in helping to understand mechanical versus metabolic aetiological pathways.

The importance of physical activity in terms of overload (mechanical) and underload (sedentary/ metabolic considerations) is clinically assumed but has never been objectively measured in CPHP.

Psychological factors have only been examined recently, and include measures of depression, anxiety, kinesiophobia and pain catastrophising. These are consistent with a biopsychosocial framework for persistent musculoskeletal pain, but longitudinal data is lacking.

Pain quality, intensity, behaviour and distribution can provide insight into pain mechanisms. From chapter 1 we identify a range of mechanistic studies that have investigated, beyond nociceptive pain, nociplastic and neuropathic mechanisms in CPHP. Clarity is required on this issue as treatments should be aligned to pain mechanisms. Multisite pain, night pain and neuropathic symptoms measured by the painDETECT questionnaire, are promising options for further assessment.

An understanding of imaging biomarkers in CPHP is important as they may give insight into disease mechanisms, predict disease course, and define meaningful CPHP phenotypes. There has been widespread application of ultrasound imaging to investigate associations with the plantar fascia, for measures of PF thickness, echogenicity and to a lesser extent, vascular signal within the PF. There are comparatively few studies investigating MRI measures in CPHP. Bone marrow

lesions and intra-fascial signal have been identified, but a quantitative assessment of risk and prognosis has not been undertaken. These measures may reflect modifiable markers of physiology rather than structure, with potential treatment implications. The plantar fat pad is also recognised as a potential source of pain, and imaging studies have measured thickness and stiffness with ultrasound (US) and sonoelastography, but not fat pad structure by T1-weighted signal differences on MRI. Magnetic resonance imaging provides a high contrast multiplanar measure of fat pad structure[1], with signal change on T1w sequences an underexplored potential proxy for structural alteration.

Plantar bone spurs ('enthesophytes') have been widely studied but there are no data on bone density and microstructural changes that occur in the plantar calcaneus in CPHP. The advent of HR-pQCT and its recent application to the calcaneus allows for bone imaging at the micron level. Bone density and microstructure are important determinants of bone strength and health, and it is unknown whether cases and controls differ in these properties at the plantar enthesis.

For all of these measures- physical, physical activity, psychological and imaging, there is a paucity of information available on longitudinal outcomes for pain, foot-related function and quality of life. Most CPHP studies that report follow up are retrospective, case review based, lack confounder adjustment, or do not use validated outcome measures. Linear mixed model analyses that take into account time-varying exposures, and allow for random effects of individuals across time, are suitable for this type of study.

2.1 Primary aims

In light of the above, the primary aims of this project were therefore:

1. In a case-control comparison, to determine which clinical (symptom-based, physical, psychological, and physical activity) and demographic factors are associated with CPHP,

2. In a cross-sectional analysis of cases and controls, to determine if having CPHP (case status) is associated with calcaneal bone density and

microstructural factors as measured by High-Resolution peripheral Quantitative Computed Tomography (HR-pQCT or QCT),

3. In a case-control comparison, to determine which US (B-mode and power Doppler) and magnetic resonance imaging (MRI) factors are associated with CPHP, and

4. In cases, to determine which clinical factors predict change in foot pain, function and quality of life over 1 year.

A detailed explanation and measurement procedures for all exposures and outcomes are outlined in **Chapter 3 section 3.2.2. (**Methods).

2.2 Reference

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Chapter 3

Methods

3. Methods

3.1 Preface

The **P**lantar **HEE**l **P**ain **S**tudy (PHEEPS) was an age- and sex-matched case-control study of people with chronic plantar heel pain (cases) and population-based controls, with 12-month longitudinal follow-up of cases, undertaken in southern Tasmania.

This thesis contains four papers from PHEEPS as stand-alone chapters, listed in the order they were conducted. The format of each varies according to journal publication or submission requirements. The specific methods used in each paper are summarised in the relevant chapter. Chapter 3 provides a general overview of methods, with expanded explanation of some key parts of the methods which could not be accommodated within journal requirements for the papers.

3.2 The PHEEP Study

3.2.1 Study population

Participants in the PHEEP Study were recruited predominantly from Hobart and southern Tasmania.

Cases were recruited between November 2014 and May 2018 from a range of sources to maximise the representativeness of the sample. This included:

- General Practice, specialist and allied health practices
- Community sports and recreation clubs
- Large employers such as Tasmania Police, Department of Education, The University of Tasmania and the Royal Hobart Hospital
- Social media advertising, specifically Facebook
- Print media advertising, including The Mercury and the Kingborough Chronicle
- Word of mouth
- Cases who expressed interest and met the initial eligibility requirements were contacted by phone and formally screened.

Controls were recruited by a separate process between November 2016 and August 2018. To maximise representativeness and minimise selection bias, age- and sex-controls were recruited at random from the southern Tasmanian electoral roll (population 176,644). We engaged the support of the Tasmanian Data Linkage Unit (Mr Brian Stokes) to supply random lists of potential control participants.

Potential control participants were mailed a 'Letter of invitation' **(Appendix 3)** and 'Participant Information Sheet' **(Appendix 4)** with details of the study, time and follow-up commitments and a self-screening questionnaire. Participants could call or respond via reply-paid post to indicate their availability or otherwise. If a participant expressed interest and met the initial self-screening requirements, they were called and formally screened for suitability.

3.2.2 Inclusion & exclusion criteria

3.2.2.1 Cases

The diagnosis of CPHP is clinical. To be considered a case, participants must have pain under the inferior heel. Symptoms may radiate into the arch but must by definition be restricted to the plantar aspect of the foot[1, 2].

Symptoms may be intermittent or episodic, but the participant must have had symptoms in the week preceding assessment. To maximise representativeness of the sample, a minimum level of pain was not mandated. If symptoms were bilateral, the most painful heel was studied.

Detailed case inclusion and exclusion criteria are summarised in **Chapter 4, section 4.3.2**

3.2.2.2 Controls

Controls must not have currently or ever have had, CPHP, and be aged 18 years or over, but otherwise had the same inclusion and exclusion criteria as cases (see **Chapter 4, section 4.3.3**).

3.2.2.3 Matching

I matched controls to cases (1 control: 2 cases) on both age and sex (and foot side). This ratio was chosen for statistical efficiency, as the number of cases was first determined by the sample size needed for the longitudinal component of the study,

and the number of controls calculated taking this into consideration. Detail of sample size calculations is provided in our published paper, in Ch 4.3.3[3].

This required the full age and sex mix of cases be first known to populate the matched control strata.

Controls were matched to cases in 5-year age brackets starting from 25- 90 years. Proportionately equal numbers of males and females were recruited as controls for each 5-year tranche, starting from 25-29yrs, then 30-34 years, and so on **(Figure 3-1).** I matched in 5-year brackets to improve recruiting efficiency for controls (broader matching requirements facilitated recruitment), but also because we clinically expected a wide range of ages for potential participants (and therefore a lot of cells) and we wanted to preserve numbers in cell sizes across matching strata.

I also matched the testing foot side in controls against the symptomatic test foot side in cases. A proportionate number of controls left and right-sided feet were tested compared to cases, within each age strata.

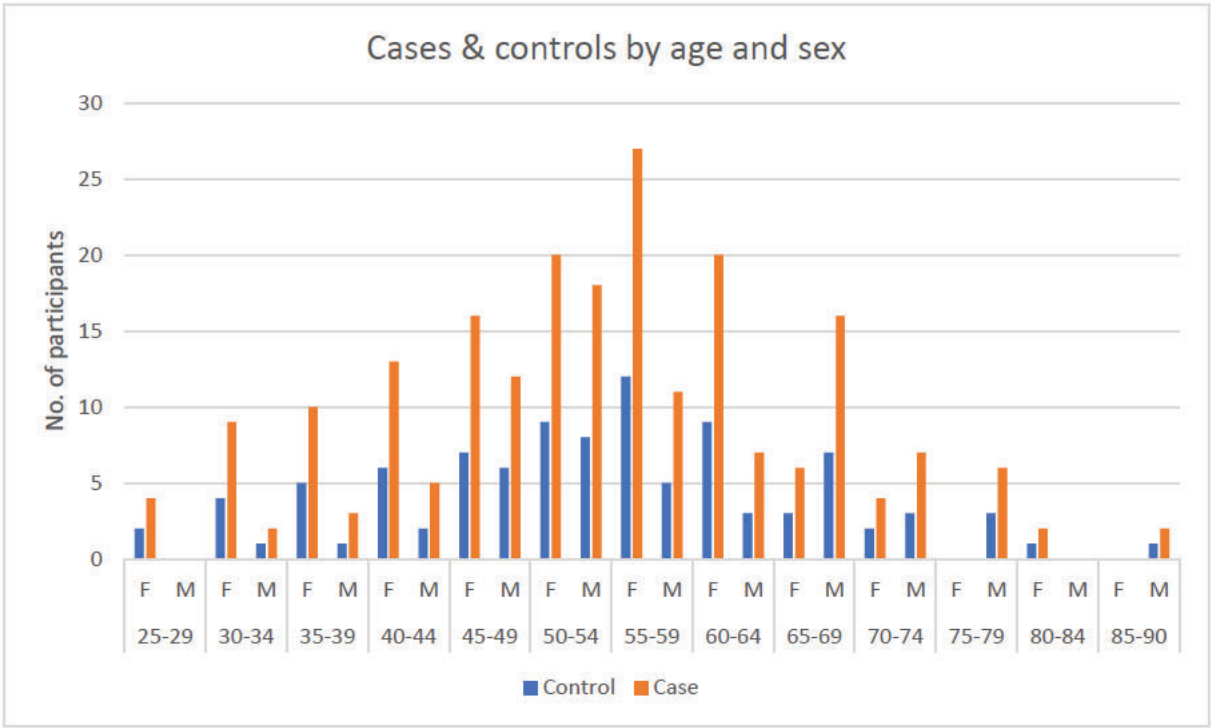

Figure 3-1 Case and control matching strata by sex and age distribution

3.3 Ethics

Ethics approval was obtained for the project entitled 'Clinical factors and imaging abnormalities associated with chronic plantar heel pain' from the Tasmania Health and Human Medical Research Ethics Committee (reference number H0013616) on 20 March, 2014. I applied for and received approval for a further nine amendments (**Appendix 8**). Informed written consent was obtained from all participants **(Appendix 5)**.

3.4 Clinical Assessment Process

The clinical assessment process is summarised below. An example of the intake questionnaire and clinical assessment forms for cases at baseline are provided in **Appendix 6 and 7.**

Table 3-1 Assessment schedule for cases and controls at baseline and follow-up

Task	Who	Location	Time	Baseline	12-month FU*
Intake mail-out	JAR/ Volunteer		5'	✓	✓
Greet & check paperwork	Volunteer	Clinic	15'	✓	✓
HR-pQCT	KSQ	Clinic	30'	✓	
Ultrasound	KSQ	Clinic	30'	✓	✓
Clinical exam:	JAR	Clinic	60'		
Height				✓	✓
Weight				✓	✓
Waist circumference				✓	✓
Bio-impedance analysis				✓	✓
Ankle DF ROM				✓	✓
Foot posture (FPI-6)^				✓	
1st MTP ROM				✓	✓
SLR ROM				✓	✓

Task	Who	Location	Time	Baseline	12-month FU*
Ankle plantarflexor strength				✓	✓
Accelerometer supply & instruction	Volunteer	Clinic	10’	✓	✓
Accelerometer return	JAR		2’	✓	✓
MRI screen	Volunteer	Clinic	2’	✓	✓
MRI	AH	RHH	20’	✓	✓

*Cases Only

JAR Jason Rogers, **KSQ** Dr Kathryn Squibb, **FU** follow-up, **AH** Dr Andrew Halliday, **RHH** Royal Hobart Hospital, **DF** dorsiflexion, **FPI-6** foot posture index-6, **MTP** metatarsophalangeal, **ROM** range of motion, **SLR** straight leg raise, **PF** plantarflexor, **MRI** magnetic resonance imaging

^ Foot posture was only measured at baseline, as factors which potentially govern foot posture change such as age-related changes, are considered to occur slowly over time.

3.4.1 Study measures

Clinical measures are reported in **Chapter 4 section 4.3.4**, high resolution peripheral quantitative computed tomography measures in **Chapter 5, section 5.3.5.1** and MRI and US measures in **Chapter 6, section 6.3.5.** I provide added detail below regarding specific questionnaires, bio-impedance body composition testing and accelerometry measurement procedures to supplement published material.

3.4.2 Questionnaire measures

Intake and follow-up surveys collected sociodemographic, footwear use, physical activity, general health and medical history data including medication use, symptom history and past and current treatments for heel pain. This data is described in **Chapter 4, section 4.3.4**, and a copy of the baseline intake questionnaire for cases is provided in the **Appendix 6.**

I provide additional information here on the exposure questionnaires for the Pain Catastrophising Scale, Patient Health Questionnaire-9 and painDETECT, and the longitudinal outcome questionnaires, the Foot Health Status Questionnaire and Assessment of Quality of Life (AQOL-6D).

3.4.3 Pain Catastrophising Scale

A 13-item questionnaire to assess for an exaggerated negative mental set associated with a painful experience[4]. It measures 3 dimensions related to catastrophisation; rumination, magnification and helplessness. Items are scored from 0-4 for a total score range from 0-52. There are no specific cut-off scores- rather it is a normally distributed continuous variable, however a threshold of >20 has been previously cited to define catastrophisation[5]. Reliability, internal consistency and concurrent and discriminant validity have been independently established[6].

3.4.4 Patient Health Questionnaire (9-item) (PHQ-9)

A validated 9-item instrument that measures symptoms of depression[7]. Item scores are graded from 0 to 3 and summed for a range of 0-27 with higher scores representing more severe depression. Scores of 5, 10, 15, and 20 represent cut-points for mild, moderate, moderately severe and severe depression, respectively.

3.4.5 painDETECT

A 7-item questionnaire to survey for symptoms of neuropathic pain[8]. Five questions ask about gradation of pain (scored 0-5), question 6 about the pain course pattern (-1 to 2) and question 7 about radiating pain symptoms (0 or 2), for a total score range from -1 to 38. A score of ≤ 12 indicates that pain is unlikely to be neuropathic and a score of ≥ 19 is likely to have a neuropathic component. Test-retest reliability is excellent (intraclass correlation coefficient (ICC)=0.93), with good internal consistency (Cronbachs alpha > 0.83).

3.4.6 Foot pain and foot function: The Foot Health Status Questionnaire (FHSQ)

The FHSQ is a 13-item questionnaire that covers four foot health domains: pain (4 questions), foot-related function (4 questions), footwear choices (3 questions) and general foot health (2 questions)[9]. We report on the results of the foot pain and foot-related function subscales, as outcomes in our study.

The FHSQ is one of the most widely used outcome measures in CPHP. It is a reliable tool with established content, criterion and construct validity in a musculoskeletal population[9]. Importantly, thresholds for determining clinically important change via the minimum important difference has been established for

both pain (14 points) and foot-related function (7 points), in a CPHP population[10].

Raw scores obtained by survey are transformed into a weighted score after entry into a purpose-built programme (The Foot Health Status Questionnaire v1.03, Care Quest Pty Ltd). This programme outputs data for each domain on a 0-100 scale with 100 representing the best outcome (i.e higher score is less pain and better function, for each respective domain).

3.4.7 Quality of life: The Assessment of Quality of Life Questionnaire (AQOL-6D)

The AQOL-6D is a validated 20-item health-related quality of life measure that assesses body related impairments and their social expressions (handicap) across 6 domains- independent living items, the senses, pain, coping, relationships and mental health[11, 12] (aqol.com.au). Although a multi-attribute utility-weighted score is possible, we use the unweighted (multi-attribute) psychometric instrument score. Scores are summed (range 20 -99) and then standardised on a 0-100 scale where higher scores represent better health-related quality of life. The 6D version of the AQoL was chosen as it was less burdensome than other AQoL scales (fewer questions), covered domains thought to be of particular interest in pain, coping and mental health, and personal communication with the Centre for Health Economics indicated that it would be more robust to use with a relatively healthier population.

3.4.8 Clinical Measures

Physical clinical measures taken in this study were:

- Dominant foot (as assessed by kicking leg dominance), test side and foot length (cm)
- Height (cm), weight (kg), waist circumference (cm)
- Body composition by Electrical bio-impedance (reactivity & reactance)
- Foot posture by the Foot Posture Index-6.[13] This is a 6-item (5 observational, 1 palpation) three-dimensional assessment of static weightbearing foot alignment. Each item is scored on a 5-point categorical scale (-2 to +2) for a raw summed score of -12 (highly supinated) to +12 (highly pronated). We summed FPI-6 scores as a continuous measure as applied in the clinical setting.[13] An alternative approach is to Rasch-transform this score which may

provide a better representation of the scales construct validity.[14] However, beyond the initial validation study, we are not aware of this approach being applied in clinical studies.

- Ankle dorsiflexion passive range of motion with knee flexed and extended (degrees)
- First metatarsophalangeal joint extension passive range of motion (degrees)
- Ankle plantarflexor force in sitting by dynamometry (kilograms)
- Straight leg raise passive range of motion with & without ankle dorsiflexion/ eversion (degrees)
- Physical activity by accelerometry

Methods for these measures are provided in **Chapter 4 section 4.3.4** with additional detail being provided here for body composition analysis and physical activity assessment by accelerometry.

3.4.9 Body composition by bio-impedance analysis

Resistance and reactance values were obtained from a Quantum II Bioelectrical Body Composition Analyzer (9-V battery, 50kHz current, RJL Systems, Clinton Twp., MI, USA). Electrodes were placed on the hand and foot of the right-hand side of the body, according to the manufacturers recommended protocol (**Figure 3-2**). When combined with anthropometric and self-reported physical activity data, these values may be used to calculate body composition masses and percentages with the application of an empirically determined algorithm.

3.4.10 Body composition calculation

We conducted an in-house study comparing the results of DXA obtained body fat measurements (from participants attending the Institute for another trial) and bio-impedance analysis (BIA) to determine the optimal study algorithm (n=11, mean BMI 26.7 kg/m^2, 7 F:4 M). The best fitting algorithm from a combination of previously reported[15] and RJL BIA supplied algorithms was the Analyzer supplied NHANES-III equation set[16, 17] (ICC (3,1)=0.9571).

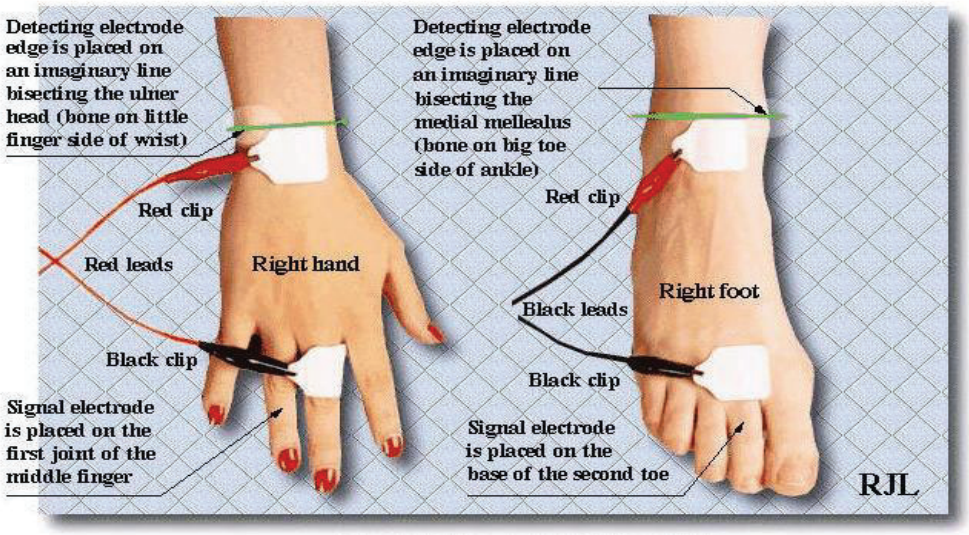

Figure 3-2 Bio-impedance Analyzer electrode placement

3.4.11 Physical Activity by Accelerometry

Participants were asked to wear a waist mounted accelerometer for 7 consecutive days[2], and to record adherence with a daily home diary (Actigraph Uniaxial GT1M accelerometers, Actigraph, Pensacola, FL, USA). After 7 days the participant returned the accelerometer in a supplied pre-paid envelope. Datasets were downloaded using Actilife version 6 (Actigraph, Pensacola, FL, USA).

To be included in analysis, datasets should contain a minimum of five valid days; a valid day contained at least 10 hours of monitored data. Wear time was determined by subtracting non-wear time from 24 hours. Non-wear was defined by an interval of 55-60 consecutive minutes of zero activity intensity counts, with allowance for 1–2 min of counts between 0 and 100.[18]

Daily physical activity variables of interest were 1) mean counts per minute (CPM), 2) number of minutes spent in intensity-specific categories, 3) number of steps registered per day. Cut-offs for intensity-specific categories were determined based on two main age groups of participants: adults 18–64 and older adults 65–85 years old.

For the adults age group, the threshold chosen for moderate to vigorous physical activity (MVPA) (⩾1,952 CPM) and sedentary time (<100 CPM) have been used extensively in calibration studies[19-21], large epidemiologic studies[18, 22-24] and

intervention trials[25-28]. Light intensity physical activity falls between (100–1,951 CPM).

For the older adult age group, the thresholds chosen for MVPA, light physical activity and sedentary time were ⩾1065 CPM, 50-1064 CPM and >50 CPM, respectively. This was previously established in laboratory-based calibration studies for older adults[29-32] and used widely through interventional[33] and observational cohort studies[34] according to a large systematic review.[35]

3.5 Imaging

3.5.1 Ultrasound

US was performed using a GE BT12 LOGIQ e (GE, China, Jiangsu) with a 10mHz linear transducer. Plantar fascia thickness and echogenicity was measured in B-mode and vascularity assessed using power Doppler imaging (PDI) with the participant prone and the foot suspended in 0 degrees dorsiflexion. All images were obtained on sagittal view. Key aspects of measurement and classification of US exposures are summarised in **Table 3-2.**

Table 3-2 Ultrasound measurement exposures

US Exposure	Method	Reliability
Plantar fascia thickness (mm)	Measure maximum vertical thickness of the PF at its deep, anterior calcaneal insertion[36]	ICC(3,1)=0.82, n=20 **Figure 3-3**
Echogenicity: Normal/ Isoechoic	In the region of the plantar enthesis the plantar fascia has slightly increased or similar levels of reflectivity relative to adjacent soft tissues. There is a homogenous fibrillar echotexture in the plantar fascia.	Weighted Kappa=0.84, n=20 **Figures 3-3, 3-4, 3-5**
Hypoechogenic-Diffuse	In the region of the enthesis, the plantar fascia has broadly decreased reflectivity relative to adjacent soft tissues.	
Hypoechogenic-Focal (or Anechoic):	In the region of the plantar fascia enthesis, there are distinct zone/s of absent reflectivity. There are focal defects in fibrillar echotexture. E.g. may reflect a defect such as a tear.	
Vascular signal within the plantar fascia	Count the number of vascular dots identified: mild increase (one red dot), moderate increase (2 dots) or a marked increase (3 or more dots)[37].	Weighted Kappa=0.91, n=20 **Figure 3-6**

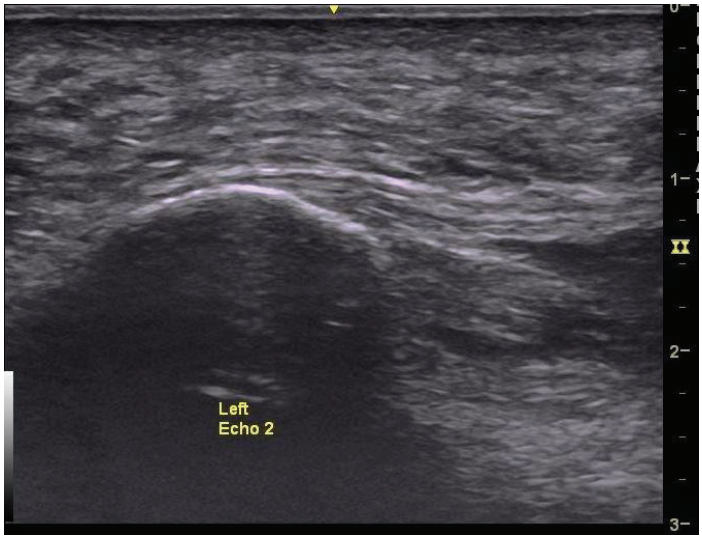

Figure 3-3 Normal plantar fascia on US imaging (sagittal view)

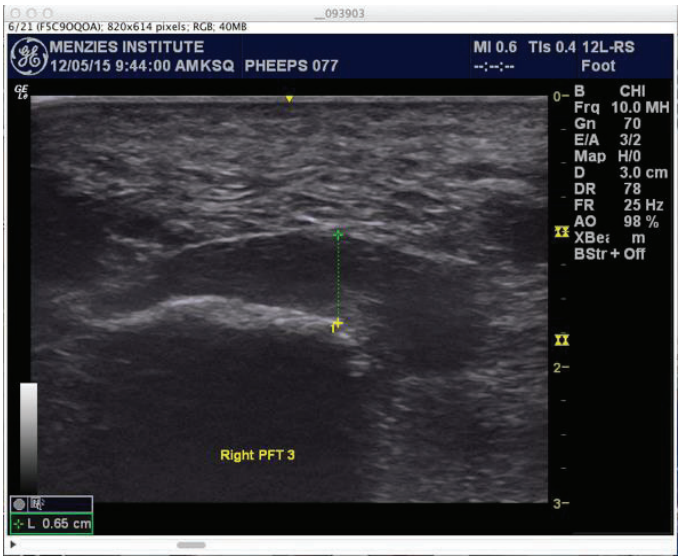

Figure 3-4 Diffusely hypoechoic and thickened plantar fascia on US imaging

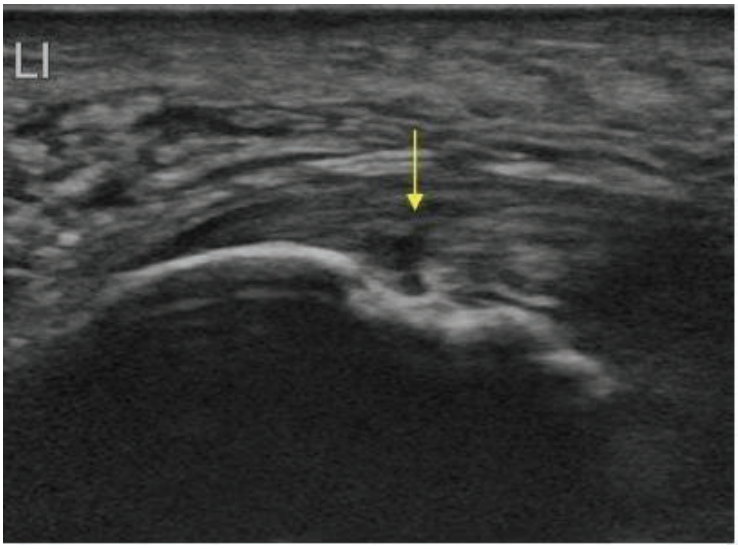

Figure 3-5 Focal hypoechoic lesion on plantar fascia on US imaging

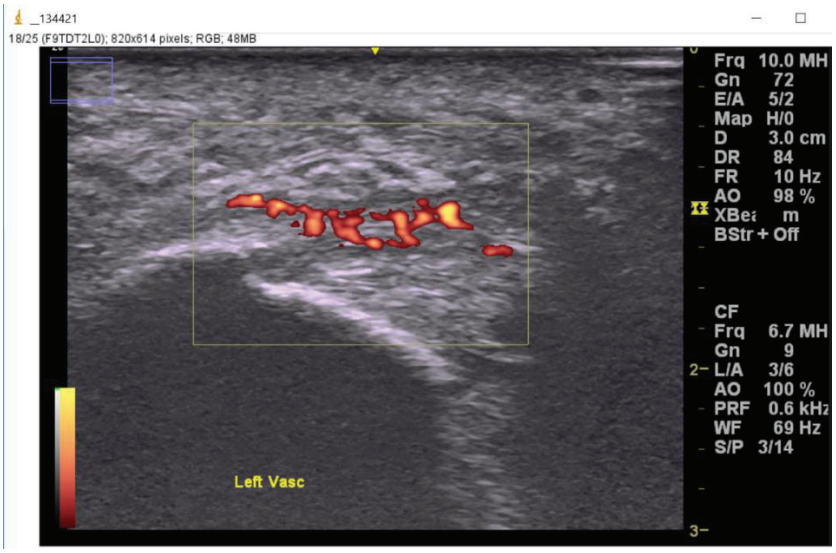

Figure 3-6 Vascular signal on power Doppler US imaging of the plantar fascia

3.5.2 Magnetic Resonance Imaging

MRI was performed on a 1.5T whole-body magnetic resonance unit (GE 1.5T OPTIMA MR450W) using an HD foot ankle array extremity coil (Invivo). The participant was positioned in supine with the foot scanned in a non-weightbearing plantigrade position. The three sequences obtained were:

- Sagittal T2 FS (TE 80ms, TR 3653ms, Flip angle 160, FOV14.0, 3.0mm slices)
- Sagittal T1 (TE Min Full, TR 578ms, Flip angle 160, FOV17.0, 3.0mm slices)
- Coronal PD FS (TE 34ms, TR 3840ms, Flip angle 160, FOV14.0, 3.5mm slices).

Details of MRI measures are provided in **Chapter 6, section 6.3.5**, and key aspects summarised below (**Table 3-3)**.

I conducted in-study blinded reliability measures for each exposure on 20 participants, conducted at least 1 week apart, also listed below.

Table 3-3 MRI measurement exposures

MRI Exposure	Method	Reliability
Calcaneal BMLs	Sagittal T2-w sequence Ill-defined signal hyperintensity, measured areally as largest lesion on a single slice (mm^2).	ICC (3,1)=0.99 **Figure 3-7 A, B**
Plantar Calcaneal spur	Sagittal T1-w sequence Graded ordinally as either 0 (absent), 1 (≤5mm in length), or 2 (>5mm in length) when measured along the anteroposterior long axis of the spur from tip to base.	weighted Kappa=1.0 **Figure 3-8 A, B**
Plantar fascia thickness	Coronal PD sequence Measured with digital calipers (mm) as the largest dorsoplantar thickness in a plane perpendicular to the calcaneus.	ICC (3,1)=0.86 **Figure 3-9**
Plantar fascia signal	Coronal PD sequence Measure extent of signal hyperintensity. Graded ordinally as 0 (absent), 1 (≤ 50% of dorsoplantar thickness) or 2 (>50%).	weighted Kappa=0.92 **Figure 3-10 A, B**
Plantar fat pad signal	Sagittal T1-w sequence Measure extent of signal hypointensity. Scored ordinally as 0 (no signal change), 1 (decrease in signal intensity ≤50% of fat pad dorsoplantar thickness), or 2 (signal intensity change >50% of fat pad thickness).	weighted Kappa=0.92 **Figure 3-11**

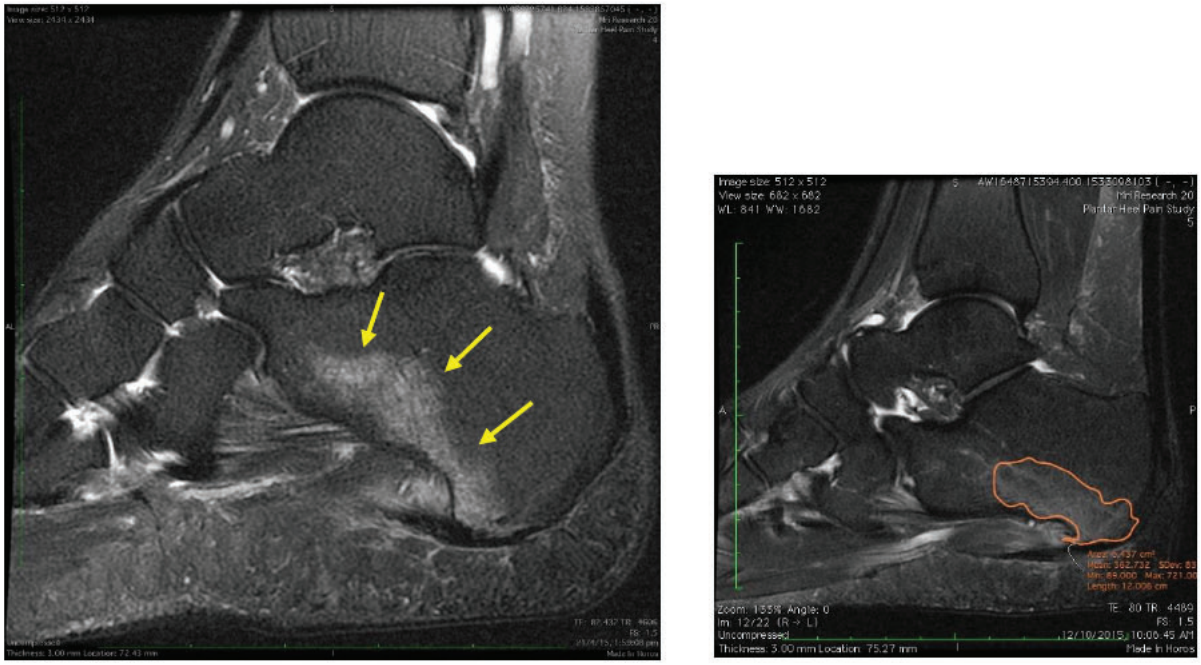

Figure 3-7 A Calcaneal bone marrow lesion (BML), sagittal T2-weighted sequence, **B** scored (different participant)

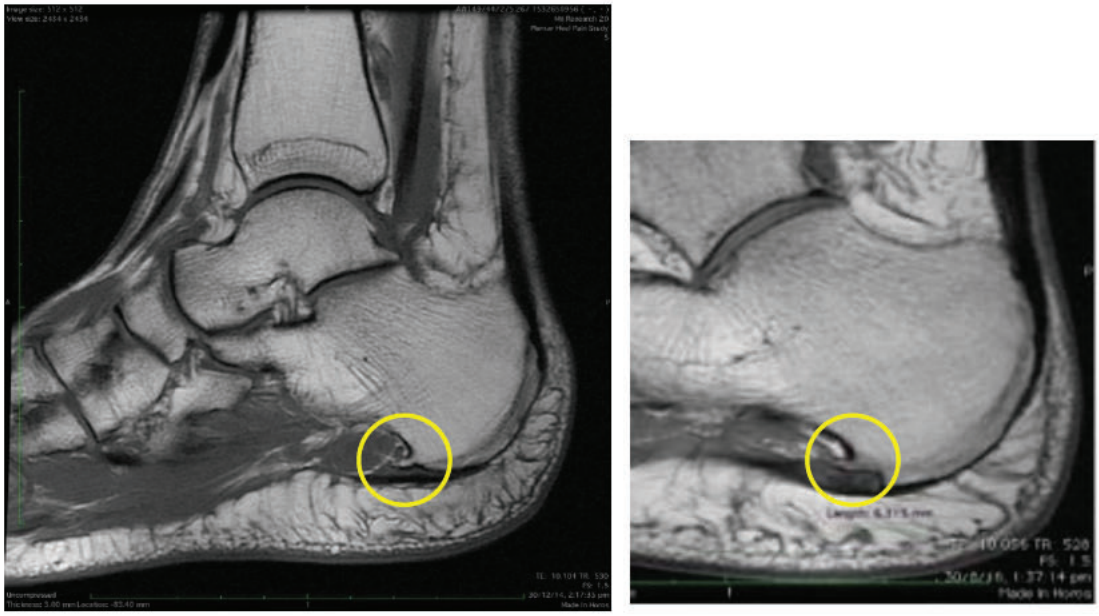

Figure 3-8 A Plantar calcaneal spur, sagittal T2-weighted sequence (Grade 2), **B** (Figure 3-9A up close). Horizontal length of spur measured with digital calipers from base to tip.

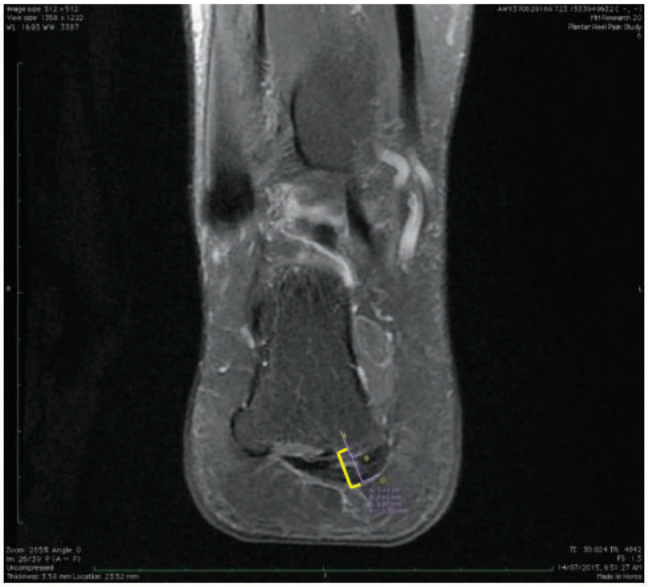

Figure 3-9 Plantar fascia thickness, coronal PD sequence. Thickness measured with digital calipers perpendicular to surface of calcaneum.

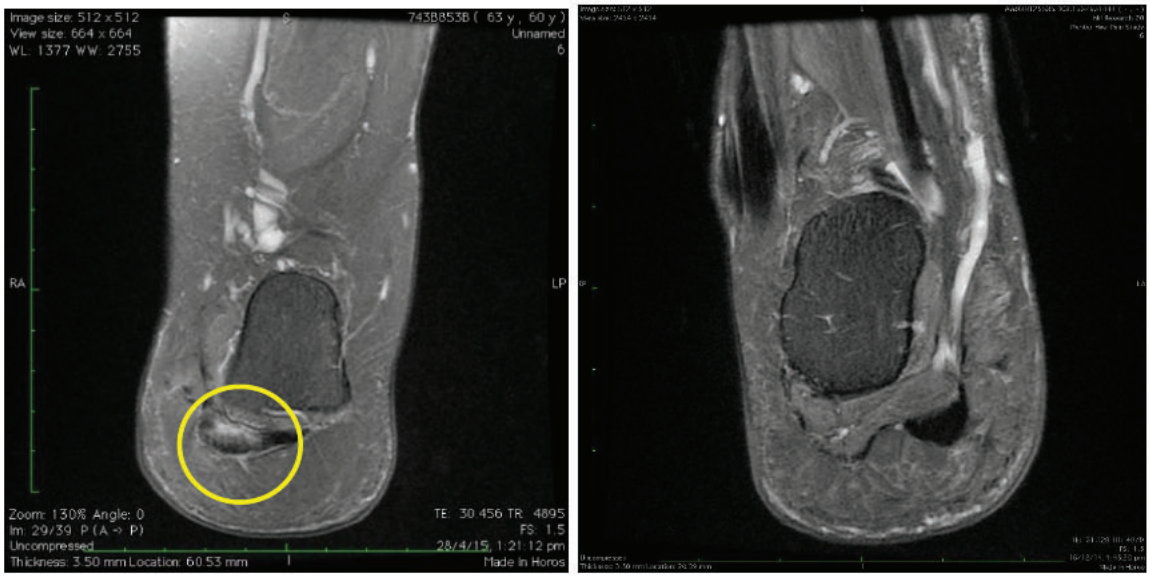

Figure 3-10 **A** Plantar fascia intra-substance signal, coronal PD sequence. Marked intra-fascial high signal (Grade 2). **B** has no intra-fascial signal but is thickened.

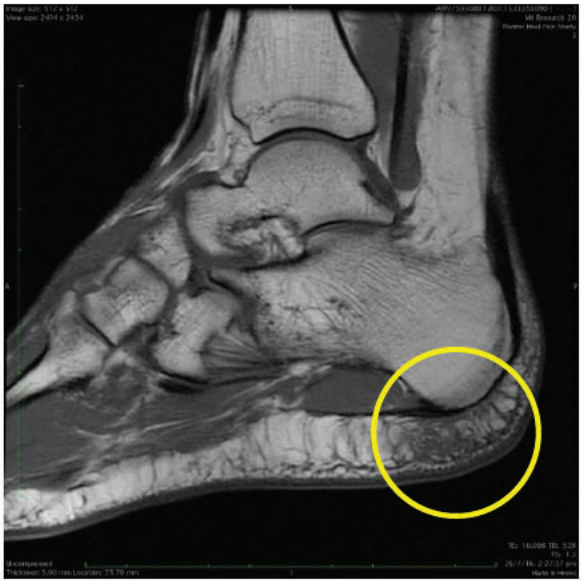

Figure 3-11 Plantar fat pad signal, sagittal T1-weighted sequence (Grade 2). Disorganised low signal intensity adjacent normal bright fat pad signal with intact vertically oriented septae.

3.5.3 High-resolution peripheral Quantitative Computed Tomography (HR-pQCT)

HR-pQCT scans were performed by the same experienced radiographer using a Scanco Xtreme CT I (Scanco Medical AG, Brüttisellen, Switzerland) (**Figure 3-12**).

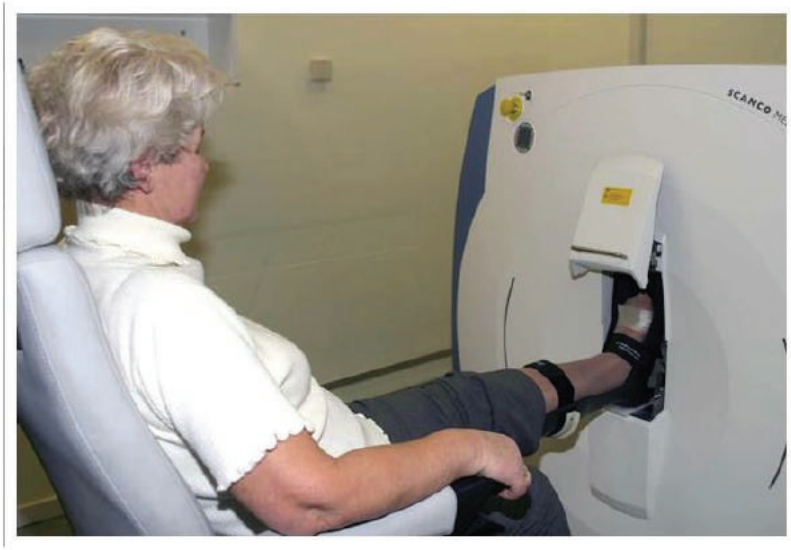

Figure 3-12 Participant set-up, Scanco Xtreme CT1

Two regions of interest were assessed for analysis: the weightbearing plantar calcaneus and a wholly trabecular mid-calcaneal reference site (**Figures 3-13, 3-14)**.

Calibration, quality control, and the scanning and measurement procedures are covered in detail in **Chapter 5, section 5.3.5**.

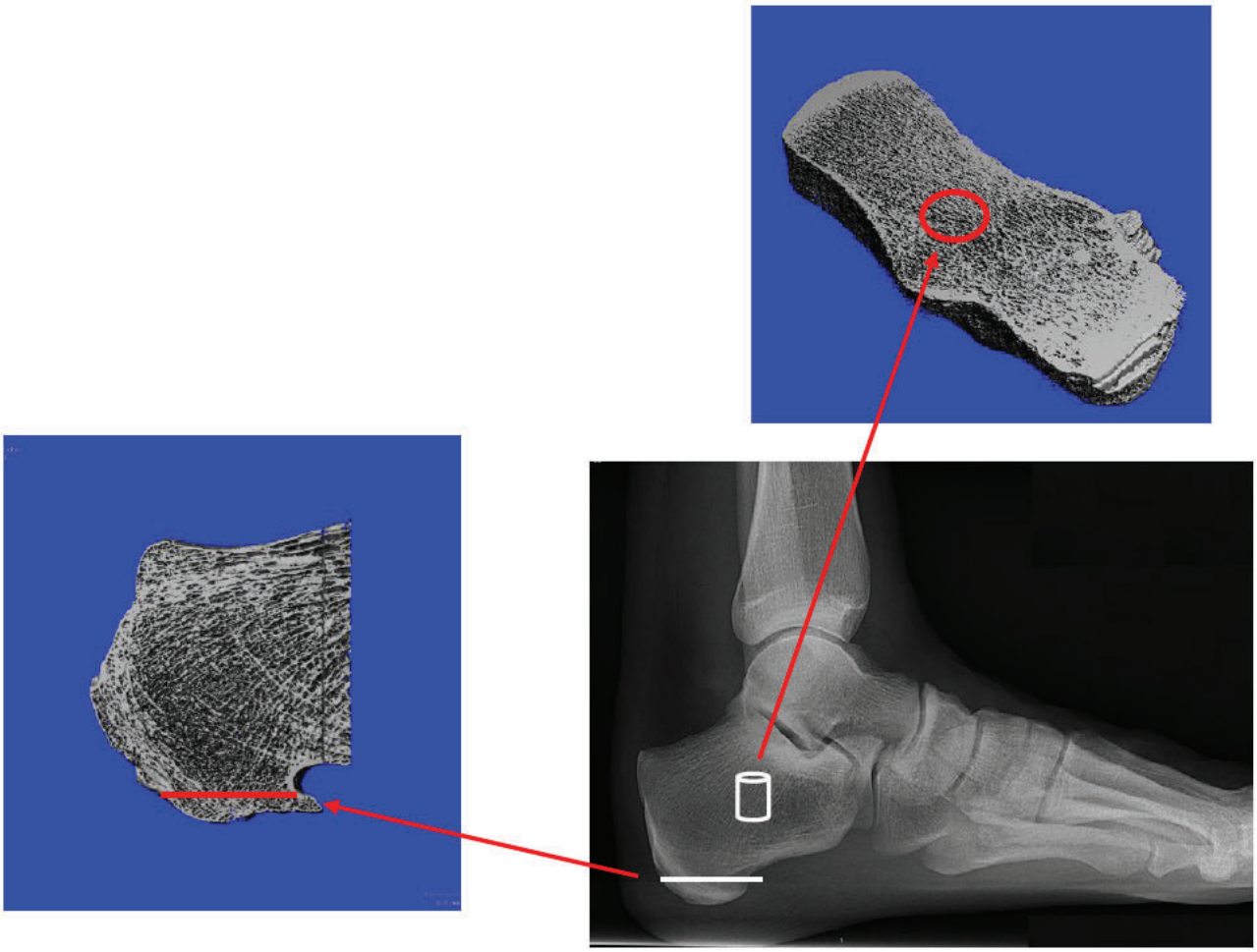

Figure 3-13 Calcaneal HR-pQCT regions of interest
X-ray demonstrating location of plantar (left) and mid-calcaneal (above) regions of interest.

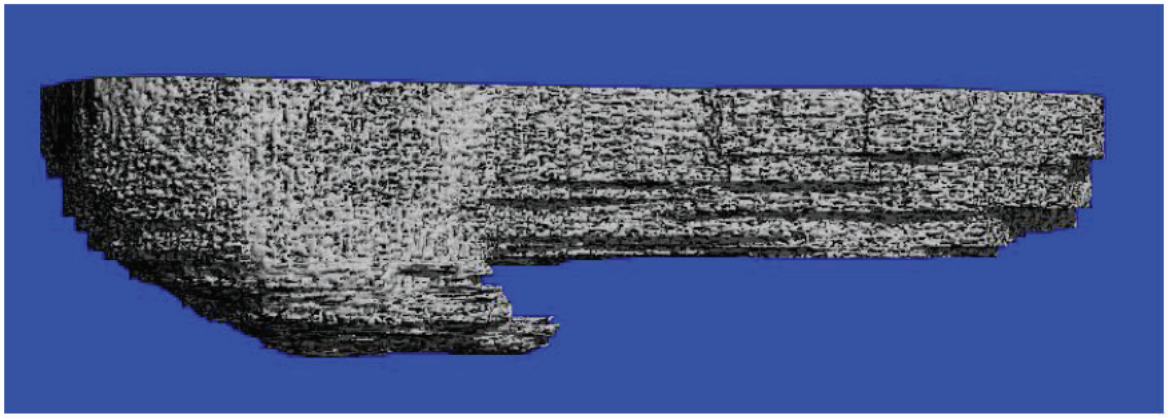

Figure 3-14 Sagittal view of plantar aspect of calcaneus, 3D HR-pQCT reconstruction

Density and microarchitecture outcomes are reported as recommended by the 'Guidelines for assessment of bone density and microarchitecture in vivo using high-resolution peripheral quantitative computed tomography'[38], as follows:

Table 3-4 HR-pQCT measurement exposures

Outcome	Details	Unit
Trabecular bone mineral density (Tb.BMD)	Average mineral density within the trabecular compartment Calculated directly.	mg HA/cm^3
Trabecular separation (Tb.Sp)	Average distance between trabeculae Derived: (1-BV/TV)/Tb.N	mm
Trabecular thickness (Tb.Th)	Average thickness of trabeculae Derived: ratio of BV/TV to Tb.N	mm
Trabecular number (Tb.N)	BV/TV/ Tb.Th Calculated directly.	1/mm (or mm^{-1})
Trabecular bone volume fraction (Tb.BV/TV)	Ratio of segmented bone volume to total volume of the trabecular compartment. Derived: (Tb.BMD/1200 mg HA/cm^3) x100	%

Intra-study ICCs assessing the repeatability of bone volume fraction (BV/TV) measures were excellent for both the plantar (ICC=0.99 (3,1), n=30) and mid-calcaneal regions of interest (ICC= 0.90 (3,1), n=30).

3.6 Statistical analyses

Key features of the statistical analysis approaches employed for each component of the PHEEP Study are listed in **Table 3-5.** The methods are described in detail in the statistics section of each paper in their respective chapter (Chapters 4,5,6 and 7).

Table 3-5 Statistical analyses

Study	Analysis	Outcome
Case-control clinical factors	Conditional logistic regression	Case status
Case-control* HR-pQCT	Linear regression	QCT bone measures
Case-control imaging factors	Conditional logistic regression	Case status
Longitudinal clinical factors	Mixed effects linear model (within- & between-person effects)	FHSQ pain FHSQ function Quality of life.

HR-pQCT Quantitative computed tomography, **FHSQ** Foot health status questionnaire
*Study design was case-control but the analysis was cross-sectional; case status was key exposure of interest, with continuous bone measures as outcome.

3.6.1 Sample size calculations

Sample size calculations were undertaken in two steps. Firstly, I determined the number of cases required for the longitudinal component of the study. This case number then informed calculation of number of controls needed for the case-control comparison. While summarised in each of the following papers, the full detail of the determination of sample size calculations is provided here:

Sample size was calculated assuming α=0.05 (two-tailed) and 80% power for longitudinal hypotheses, with a loss to follow up of 10%. For these hypotheses, a sample size of 220 allows detection of small correlations (≥0.2) between outcomes and exposure (4% of variance).

For case-control comparisons, I calculated the number of controls required to detect sufficiently small differences with at least 80% power (and two-tailed α=0.05), given the number of cases is set at 220 for longitudinal analyses. The minimum detectable differences for the case-control hypotheses, given a sample size of 220 cases and 100 controls, are given in **Table 3.6**. Values for exposures in controls were taken from the published literature (included from our CPHP systematic review) and published and unpublished data from cohort studies within our institute such as the Tasmanian Older Adult Cohort (NHMRC 302204), the Childhood Determinants of Adult Health study (NHMRC 490006) and a cohort of pre- and peri-menopausal women (NHMRC APP1003437). These differences are comparable to or smaller than effect sizes reported in the CPHP, tendinopathy and OA literature discussed in the background relevant to these variables.

Table 3-6 Minimum detectable differences between cases and controls

Imaging	**Control**	**Detectable difference (% difference)**
PF vascularity (%)	1.6%	0.2% (12.5%)
PF hypoechogenicity (prevalence)	10%	24% prevalence in cases (difference 14%)
BML (prevalence)	2%	12% prevalence in cases (difference 10%)
Clinical Measures		
waist circumference (cm)	94.1	4.1 (4.3%)
% body fat	34	6.51 (19%)
ankle plantar flexor strength	132.1	8.6 (6.5%)
Ankle dorsiflexion ROM (degrees)	40.5	2.3 (5.7%)
1st MTP dorsiflexion ROM (degrees)	45	4.5 (10%)
Foot posture index-6	1.1	0.9 (82%)

PF plantar fascia; **BML** bone marrow lesions; **cm** centimetres; **%** percentage; **ROM** range of motion; **MTP** metatarsophalangeal joint

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Chapter 4

Chronic plantar heel pain is principally associated with waist girth (systemic) and pain (central) factors, not foot factors: A case-control study[123]

Published in 2021 in the:
Journal of Orthopaedic and Sports Physical Therapy
51(9), pp 449-458 (2021) https://doi.org/10.2519/jospt.2021.10018

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Chapter 5

Bone Factors

A cross-sectional study of CPHP cases and controls investigating bone density and microarchitecture outcomes in the calcaneus

Chronic plantar heel pain modifies associations of ankle plantarflexor strength and body mass index with calcaneal bone density and microarchitecture. (2022) *PLOS ONE* 16(12): e0260925. https://doi.org/10.1371/journal.pone.0260925

Rogers J, Jones G, Cook J, Squibb K, Lahham A, Wills K, Winzenberg T.

5. Chronic plantar heel pain modifies associations of ankle plantarflexor strength and body mass index with calcaneal bone density and microarchitecture.

5.1 Preface

As described in chapter 1 and my co-authored systematic review[1], our understanding of bone factors in chronic plantar heel pain (CPHP) is limited to having established the association with plantar 'spurs'. Calcaneal bone density and microarchitecture have not been investigated in CPHP, but this is now possible with the availability of high-resolution peripheral quantitative computed tomography (HR-pQCT).

This chapter explores for the first-time calcaneal bone density and microarchitecture outcomes using HR-pQCT, with CPHP case status as our key exposure of interest. It was accepted for publication in PLOS ONE on November 25, 2021 and is presented as formatted for that journal. PLOS ONE is an open access journal (Impact Factor 2021 3.240) with a wide audience across the 'multidisciplinary sciences'.

5.2 Introduction

Chronic plantar heel pain (CPHP) is a clinical condition that causes pain on the underside of the heel that is aggravated by weightbearing activity[2]. It is the most common reason why individuals with musculoskeletal foot pain consult a foot health practitioner[2], and is associated with significant foot-related disability and impaired quality of life (QOL)[3].

The plantar calcaneus is an important weightbearing bone that receives the proximal attachment of the plantar fascia. Degeneration of the plantar fascia at its enthesis[4], plantar fascial thickening[1] and plantar enthesophytes[1] are common findings in CPHP and are thought to be important in its aetiology. The consequences of these findings for calcaneal bone density and structure are currently unknown. As the plantar fascia transmits large forces through the plantar calcaneus[5], alteration in its structure or function in CPHP has the potential to influence calcaneal bone. There are also differences between cases and controls for potential bone modifying factors such as BMI[6] and ankle plantarflexor strength[6], yet nothing is known about how these factors influence calcaneal bone structure in CPHP.

The recent application of bone imaging tools such as high-resolution peripheral quantitative computed tomography (HR-pQCT) to the foot[7, 8] means it is now possible to provide a detailed, in-vivo examination of bone in CPHP. As a highly trabecular bone[9] subject to large active and weightbearing forces, the calcaneus is vulnerable to stress-related injury. Describing for the first time how trabecular density and microarchitecture differ between individuals with and without CPHP has the potential to fill an important evidence gap in our understanding of factors important to bone and entheseal health.

The aim of this study therefore, is to determine whether having CPHP is associated with calcaneal bone density and/or trabecular microarchitecture at the plantar calcaneus and at a mid-calcaneal reference site.

5.3 Participants and Methods

5.3.1 Study design

Case-control study with a cross-sectional analysis with case status (presence of CPHP) as the exposure of interest.

5.3.2 Setting and participants

Cases were recruited in southern Tasmania between November 2014 and May 2018 from general and specialist medical clinics, allied health practices, newspaper advertising, social media, sporting clubs and workplaces (hospitals and government departments). Sex- and age-matched control participants were recruited by random selection from the Tasmanian Electoral Roll (population 176,644, 2016) (one control:2 cases) from November 2016 to August 2018. This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Tasmanian Health & Medical Human Research Ethics Committee (H0013616, 20 March, 2014). All participants provided written informed consent.

5.3.3 Inclusion / exclusion

Inclusion criteria for cases were aged over 18 years, have CPHP defined as pain under the heel aggravated by '1st step' (pain under the heel on first step in the morning, or after a period of non-weightbearing rest) or pain aggravated by prolonged weightbearing, with symptoms present for at least 3 months. In the presence of bilateral heel pain, the most symptomatic heel was assessed. Control participants were matched for age (5-year brackets from 25-90 years) and sex and must never have had CPHP.

Both cases and controls were excluded if they had any contraindication to MRI, a history of previous foot fracture, ankle fracture (requiring cast or surgery) or orthopaedic foot surgery, current ankle pain, recent foot trauma or any other orthopaedic, congenital or painful lower limb condition that restricted mobility or activity in the preceding 3 months. Participants with peripheral vascular or central or peripheral neurological disease, including a current or recent history of lumbar radiculopathy, were also excluded. Cases who had a corticosteroid or any other injection, shockwave therapy or steroid iontophoresis within the previous 6 months were excluded.

5.3.4 Sample size calculations

The case-control analysis is nested within a 12-month longitudinal study of cases. Sample size calculations for the longitudinal component of the study determined that 220 cases were required (assuming α=0.05 (two-tailed) and 80% power for longitudinal hypotheses, with a loss to follow up of 10%). As previously published, we assumed controls would have values for key exposures seen in participants in community-based studies in our institution or from control participants in other CPHP studies[6]. Based on those values, and assuming power of 80%, and a two-tailed α of 0.05, we calculated that 100 controls were required to detect clinically important effect sizes that were comparable to or smaller than effect sizes reported in the CPHP, tendinopathy and osteoarthritis literature.

5.3.5 Data collection

5.3.5.1 HR-pQCT scanning procedure

HR-pQCT scans were performed by the same experienced radiographer (KS) using a Scanco Xtreme CT I (Scanco Medical AG, Brüttisellen, Switzerland). Prior to scanning, daily calibration using manufacturer supplied reference phantoms was undertaken, according to Scanco protocol. The test foot of the participant was immobilised in the manufacturer provided carbon fibre lower leg cast for insertion into the scanner gantry. A custom-made Perspex plantar foot cradle was fixed to the plantar aspect of the inside of the cast to move the plantar surface of the calcaneus proximally into the scan zone. Standard Scanco Xtreme scan parameters were used; 60 kVp effective energy and 95 mA (collecting tube current) collecting 750 projections over a 180° rotation of the X-ray source, integration time of 100ms, FOV 126mm and image matrix 1536 x 1536, yielding an isotropic voxel of 82μm. Scans were assessed at the time for movement artefacts including horizontal streaking, loss of cortical contiguity or significant trabecular smearing[10], and were repeated if there was clear evidence of artefact.

5.3.5.2 Region of interest (ROI) selection and analysis

Plantar and mid-calcaneal regions were located on a scout image (**Fig 5-1**).

The plantar ROI captured the site of attachment of the plantar fascia on the weightbearing plantar tuberosity of the calcaneus. The plantar stack was initiated at the plantar most aspect of calcaneal bone. Two stacks were captured (220 slices) and the first 60 slices (~5mm) of the calcaneal tuberosity were contoured and analysed.

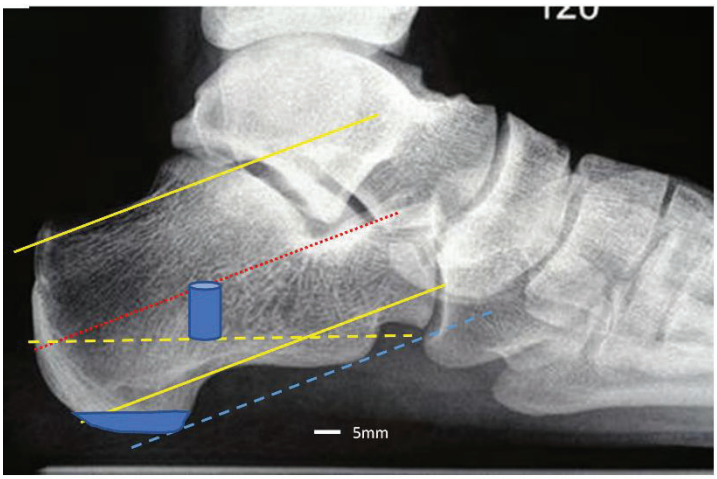

Figure 5-1 Location of mid-calcaneal and plantar ROI.
Mid-calcaneal (cylinder) and plantar ROIs are shaded

The mid-calcaneal ROI was positioned in a single mid-calcaneal stack half-way along the sagittal length of the calcaneus between its posterior and anterior-most margins (**Fig 5-1**). A plantar reference line, two parallel pitch lines hugging the superior and inferior waist of the calcaneus and a third parallel line bisecting these (representing the central pitch axis), were drawn. The posterior exit point of this last line located the inferior starting point of the mid-calcaneal stack. The mid-calcaneal ROI is cylindrical in shape measuring approximately 1cm^2 by 1 stack high (110 slices/ ~9mm).

For each ROI, native Scanco analysis software (V6.5-3) was used to generate trabecular density (milligrams of hydroxyapatite/ cubic centimetre (mg HA/cm^3)), separation (mm), thickness (mm) and number (1/mm) measures, bone volume fraction (BV/TV %), and cortical density (mg HA/cm^3), mean thickness (mm) and area (mm^2) measures, as described previously[11-13]. Trabecular bone mineral density and trabecular number are calculated directly whereas trabecular thickness, separation and BV/TV are derived from these measurements. Bone volume fraction was derived from trabecular density assuming fully mineralised bone of 1200 mg HA/cm^3.

Post scan processing was undertaken by a single blinded assessor for each region (plantar KS, mid-calcaneal AL) who placed and contoured all ROI's. This process has been described previously[13, 14] and includes semi-automatic edge contouring, visual checking for errors, and automatic bone compartment segmentation based on binarization with a fixed threshold.

Intra-study intra-class correlation co-efficients (ICCs) assessing the repeatability of BV/TV measures was excellent for both the plantar (ICC=0.99 (3,1), n=30) and mid-calcaneal ROIs (ICC= 0.90 (3,1), n=30).

Scan quality was assessed by visual assessment of the plantar stack image and consideration of the presence of ring artefacts and signal to noise ratio (graininess). Scans were graded ordinally as (3) poorer quality (ring artefacts approaching but outside of ROI and/or higher noise), (2) fair (minor ring artefacts and/ or moderate noise) and (1) good (no or minimal ring artefact, low noise). Repeatability for assessing scan quality was good (weighted kappa=0.82, percent agreement 94%, n=50).

5.3.5.3 Clinical measures

Clinical measures were taken in a single session, in the same order, by the same experienced physiotherapist. Shoes, socks and lower leg clothing were removed. Measurement and reliability of clinical measures for height, weight, BMI, ankle plantarflexor strength, and physical activity by accelerometry have been summarised previously[6].

In brief, height was measured to the nearest 0.1cm using a stadiometer. Weight was measured to the nearest 0.1kg by a single set of calibrated scales (A&D Medical UC321-PL, Adelaide, South Australia), and body mass index calculated (weight(kg)/ht(m)^2). Maximum isometric ankle plantarflexor strength was measured in sitting as the highest score from three attempts with the lower limb strapped by inelastic belt about the knee to a digital scale (Excell GW, Taiwan; sensitivity 0.05kg) (study $ICC_{3,1}$ =0.96, n=18)[15]. Physical activity was measured by uniaxial accelerometer worn at the waist (Actigraph GT1M, Fort Walton Beach, Florida) monitored over 7 consecutive days[16]. Participant's data were included if worn for a minimum of 5 days with at least 10 hours of monitored data. Wear-time was cross-checked with the use of a home diary. Non-wear time was defined by an interval of 55-60 consecutive minutes of zero activity intensity counts, with allowance for 1–2 min of counts between 0 and 100[17]. We measured steps

per day and mean counts per minute (CPM), classifying physical activity as minutes spent in moderate to vigorous (MVPA), light and sedentary activity. Separate thresholds were chosen for adults aged 18-64 years,[18] and older adults aged 65-85 years[19, 20], namely: MVPA (≥1,952 CPM/ ≥1065 CPM, respectively), light physical activity (100-1951 CPM/ 50-1064 CPM) and sedentary time (<100 CPM/ <50 CPM). Data were downloaded using Actilife version 6 (Actigraph, Pensacola, FL).

Questionnaires recorded footwear choices, time spent in standing, age, sex, menopausal status, level of education, employment, smoking history and co-morbidities (diabetes or rheumatological disease). Section two of the Foot Health Status Questionnaire (FHSQ) was used to assess foot function (Cronbach's alpha 0.86, ICC=0.92)[21]. Quality of life was measured with the Australian Quality of Life scale, AQoL-6D[22] (Cronbach's alpha 0.94, ICC=0.85 to 0.88), (http://www.aqol.com.au/aqolquestionnaires/56.html).

5.3.6 Statistical analysis

Characteristics of cases and controls were compared using descriptive statistics. Univariable and then multivariable linear regression models were used to estimate the association between CPHP status and QCT bone outcomes. We adjusted for age and sex, and then for other potential factors affecting bone including BMI, ankle plantarflexor strength and physical activity, based on biological plausibility. We assessed for effect modification by CPHP with these variables and retained interaction terms where significant ($p<0.05$). Coefficients are reported as standardized betas with the independent variables centred and standardized, giving a change in outcome per SD variation in exposure.

Sensitivity analyses were conducted to assess the effect of i) scan quality (by omitting lower quality (grade 3) scans), and ii) removal of outliers on parameter estimates and statistical inference. Standard model fit checks included lowess and design variable plots, and assessment of best power fit by fractional polynomials. Assessment of residuals, link and multi-collinearity checks were also undertaken. All analyses were performed using Stata 16 (Stata Corp., College Station 16, TX, USA).

5.3.7 Patient and public involvement

No patients or the public were involved in the planning, design or the implementation of this study. Patients were not invited to contribute to interpretation of the results, nor the writing or editing of this document.

5.4 Results

We tested 220 eligible cases from 299 potential cases screened, as previously described[6]. Of these, 219 who had HR-pQCT scans of their affected foot were included in this analysis. Of 566 contactable potential control participants, 232 agreed to participate. One-hundred and ten controls were excluded before consent, a further 22 withdrew or were excluded after consent but before testing was completed, leaving 100 control participants in the analysis (**Fig 5-2**).

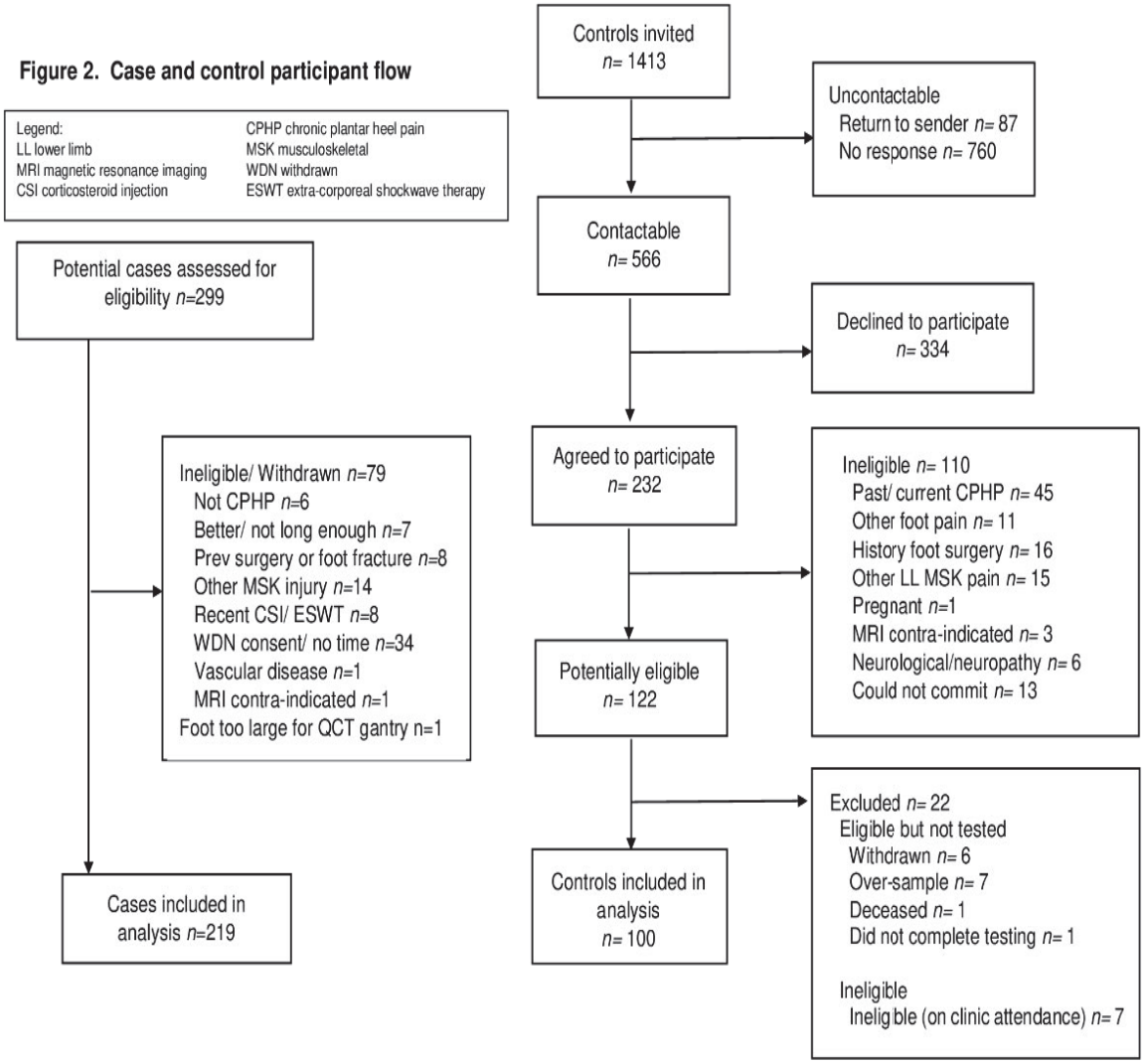

Figure 5-2 Case and Control participant flow

Data availability for exposures was similar for cases and controls, ranging between 95-100%. In-session quality checking resulted in repeating scans for 12 participants (3 cases/ 9 controls, 4 men/ 8 women, 8 plantar stack rescans/ 4 mid-calcaneal). As previously reported cases and controls reported similar levels of comorbidities such as inflammatory disease, diabetes and high cholesterol, similar levels of self-reported menopause and smoking rates and comparable levels of physical activity[6] (**Table 5-1**). Cases had higher BMI and waist girth, and lower ankle plantarflexor strength, QOL and foot-related function than controls. Use of prescribed bone density medication was low for both cases (1.7%) and controls (3%).

Table 5-1 Characteristics of case and controls.

		Case (n=219)*	Control (n=100)*
Age (years)	Male	58.5 (12.1)	59.2 (12.5)
	Female	52.2 (11.5)	52.0 (11.6)
Female %(n)		59.6 (131)	60 (60)
Menopause[a] %(n)		36.6 (48/131)	41.7 (25/60)
On HRT %(n)		6.9 (9/131)	8.3 (5/60)
Smoke- ever %(n)		33 (73)	28 (28)
Smoke- current %(n)		4.6 (10)	7 (7)
Diabetes %(n)		3.7 (8)	3 (3/99)
Inflammatory disease %(n)		8.2 (18)	6 (6)
High Cholesterol %(n)		25 (55)	30 (30)
Prescribed bone density medications %(n)		1.9 (4/214)	3 (3/99)
Physical activity			
Accelerometry (median, IQR)			
Average steps/day[b]		7918 (6148, 9903)	8373 (6080, 10205)
Moderate-to-vigorous (average min/day)[c]		38 (18, 61)	42 (20, 58)
Sedentary (average min/day)[d]		491 (437, 545)	502 (443, 561)
Quality of life & function			
AQOL-6D[e]		76.4 (10.8)	86.38 (6.9)
FHSQ function[f]		65.74 (27.8)	99.13 (3.3)
Clinical measures			
BMI (kg/m^2)		29.14 (5.4)	27.63 (5.6)
Waist girth (cm)		97.43 (13.9)	90.82 (15.1)
Fat mass (%)		34.24 (8.9)	33.86 (8.2)
Foot posture index (FPI)[g]		2.71 (3.9)	3.07 (3.7)
Ankle dorsiflexion ROM, knee flexed (deg)		43.26 (6.7)	44.15 (5.5)

Ankle plantarflexor strength (kg)	90.49 (23.8)	98.82 (26.4)
1st MTP extension ROM (deg)	70.28 (15.1)	74.78 (14.4)

* values are Mean (SD), unless specified otherwise.
[a] % of females only
[b] case n=207, control n=96
[c] case n=211, control n=96
[d] case n=211, control n=96
[e] Australian Quality of Life-6 scale, 0-100, higher is better
[f] Foot Health Status Questionnaire (weighted), 0-100, higher = better function
[g] Foot posture index-6, -12 (highly supinated) to +12 (highly pronated)
MTP metatarsophalangeal, **ROM** Range of motion

Bone density and microstructural parameters were similar in cases and controls at the mid-calcaneal site (**Table 5-2**). There were small differences at the plantar calcaneus with greater BV/TV and trabecular bone density, trabecular thickness and lower trabecular separation, in cases compared to controls.

Table 5-2 Bone indices

Mid calcaneal ROI	Case (n=219)		Control (n=100)	
	mean	sd	mean	sd
Trabecular density (mg HA/cm^3)	163	41	165	44
Bone volume fraction (BV/TV)	0.14	0.03	0.14	0.04
Trabecular number (/mm)	3.95	0.20	3.93	0.20
Trabecular separation (mm)	0.219	0.017	0.220	0.017
Trabecular thickness (mm)	0.034	0.008	0.035	0.009
Plantar ROI	Case (n=219)		Control (n=100)	
	mean	sd	mean	sd
Trabecular density (mg HA/cm^3)	**356**	**37**	**345**	**47**
Bone volume fraction (BV/TV)	**0.30**	**0.03**	**0.29**	**0.04**
Trabecular number (/mm)	3.95	0.15	3.92	0.16
Trabecular separation (mm)	**0.178**	**0.012**	**0.182**	**0.015**
Trabecular thickness (mm)	**0.075**	**0.008**	**0.073**	**0.009**
Cortical density (mg HA/cm^3)	641	69	647	79
Mean cortical thickness (mm)	0.846	0.41	0.897	0.55
Mean cortical area (mm^2)	57.9	29.5	57.6	36.1

Bold p<0.05, t-test for continuous data. **ROI** region of interest, **sd** standard deviation

Univariable associations of CPHP and other factors with bone outcomes are given in **Table 5-3.** Having CPHP was associated with higher trabecular density (p=0.017), BV/TV (p=0.016) and trabecular thickness (p=0.041) and lower trabecular separation (p=0.012) in the plantar ROI but was not associated with any mid-calcaneal bone outcome. At both ROIs, BMI and ankle plantarflexor strength were positively associated with trabecular bone density, BV/TV and thickness, negatively associated with trabecular separation, and positively associated with trabecular number except for ankle plantarflexor strength at the mid-calcaneal ROI. Female sex was negatively associated with all bone outcomes at both ROIs except for a positive association with trabecular separation, and no association with trabecular thickness. Age was negatively associated with trabecular density, BV/TV and thickness outcomes in the mid-calcaneum. In the plantar region age was not associated with trabecular density, but positively associated with trabecular number and negatively associated with trabecular thickness.

Table 5-3 Univariable results for mid-calcaneal and plantar ROI, standardized co-efficients(se)[a]

Mid-calcaneal ROI	**Trabecular density (mg HA/cm^3)**	**BV/TV (%)**	**Trabecular thickness (mm)**	**Trabecular number (/mm)**	**Trabecular separation (mm)**	
Case status[b]	-0.9 (2.4)	-0.001 (0.002)	-0.000 (0.001)	0.011 (0.011)	-0.000 (0.001)	
BMI	**11.6** (2.3)	**0.010** (0.002)	**0.002** (0.001)	0.021 (0.011)	-**0.004** (0.001)	
Age	-**10.3** (2.3)	-**0.009** (0.002)	-**0.002** (0.001)	0.008 (0.011)	0.002 (0.001)	
Female sex[c]	-**5.2** (2.3)	-**0.004** (0.002)	0.000 (0.001)	-**0.128** (0.009)	**0.008** (0.001)	
Ankle PF strength	**8.7** (2.3)	**0.007** (0.002)	**0.001** (0.001)	**0.088** (0.099)	-**0.007** (0.051)	
MVPA[d]	1.3 (2.4)	0.001 (0.002)	0.000 (0.001)	**0.035** (0.011)	-**0.002** (0.001)	
Plantar ROI	**Trabecular density**	**BV/TV**	**Trabecular thickness**	**Trabecular number**	**Trabecular separation**	**Cortical density (mg HA/cm^3)**
Case status[b]	**5.4** (2.3)	**0.005** (0.002)	**0.001** (0.001)	0.013 (0.009)	-**0.002** (0.001)	-2.7 (4.1)
BMI	**11.7** (2.1)	**0.010** (0.002)	**0.002** (0.001)	**0.046** (0.008)	-**0.005** (0.001)	1.1 (4.1)
Age	-3.4 (2.3)	-0.003 (0.002)	-**0.001** (0.001)	**0.025** (0.009)	-0.000 (0.001)	-**19.1** (3.9)
Female sex[c]	-7.7 (2.2)	-**0.006** (0.002)	0.000 (0.001)	-**0.093** (0.007)	**0.006** (0.001)	-**9.8** (4.0)
Ankle PF strength	**10.3** (2.2)	**0.009** (0.002)	**0.001** (0.001)	**0.059** (0.008)	-**0.005** (0.001)	**12.4** (4.0)
MVPA[d]	-1.1 (2.4)	-0.001 (0.002)	-0.001 (0.001)	**0.023** (0.009)	-0.001 (0.001)	2.0 (4.2)

ROI region of interest, **BV/TV** bone volume / total volume, **BMI** body mass index, **PF** plantarflexor
[a]Univariable linear regression model, standardized X co-efficient/ unstandardized Y (standard error). **Bold** p<0.05, all n=319 unless stated.
[b]case =1, control=0 [c]female=1, male=0
[d] **MVPA**, moderate to vigorous physical activity, average minutes per day, by accelerometry, n=306

Associations of CPHP status with bone outcomes were largely unchanged in an adjusted main effects model (**Supplementary Table 5-5**) but there were significant interaction terms in the final multivariable model (**Table 5-4**). The positive association of BMI with mid-calcaneal trabecular density (p=0.019 (interaction term)), BV/TV (p=0.018) and thickness (p=0.014) was less in cases compared to controls (**Fig 5-3 to 5-5**). In the plantar ROI, the positive association of ankle plantarflexor strength with plantar trabecular density (p=0.006), BV/TV (p=0.007) and thickness (p=0.007) (**Fig 5-6 to 5-8**), and the negative association with trabecular separation (p=0.019) **(Fig 5-9**), was less in cases compared to controls. Differences between cases and controls in these plantar bone indices are greater at lower levels of ankle plantarflexor strength. The associations of factors which did not show effect modification by CPHP status were similar to those in univariable models, except that ankle plantarflexor strength in the mid-calcaneal ROI and age in the plantar ROI had lower coefficients for most bone outcomes in the multivariable model.

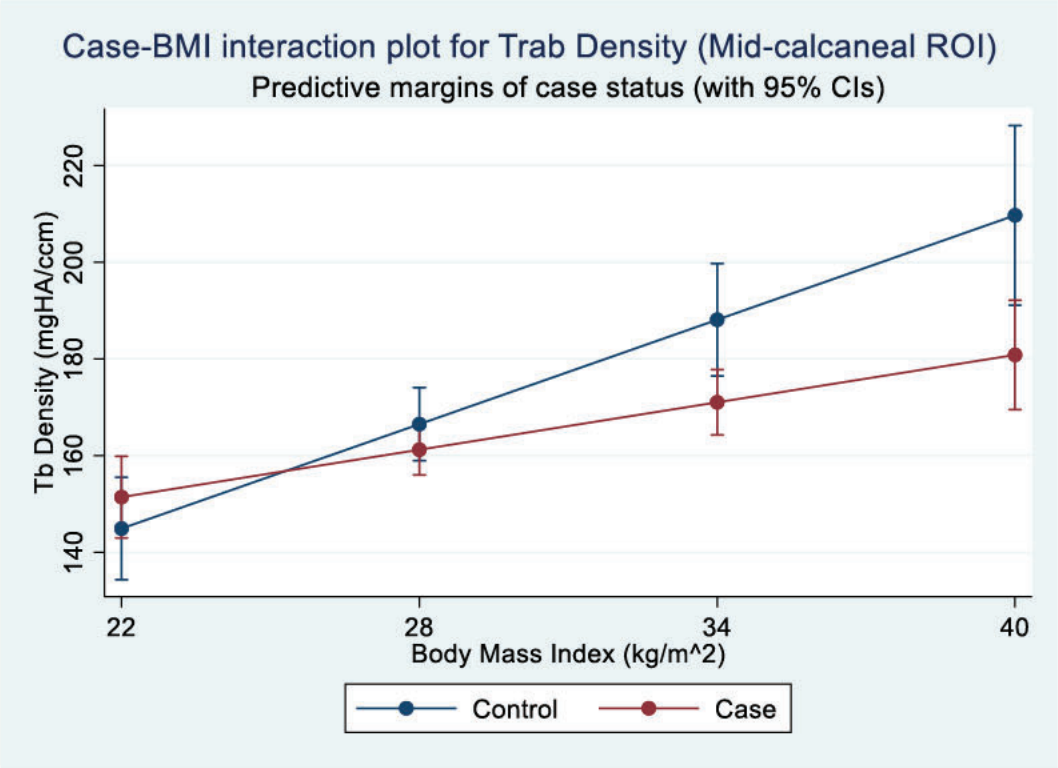

Figure 5-3 Case-BMI interaction plots for mid-calcaneal ROI trabecular density. Bone outcomes plotted from the 10th to 90th percentile of BMI.

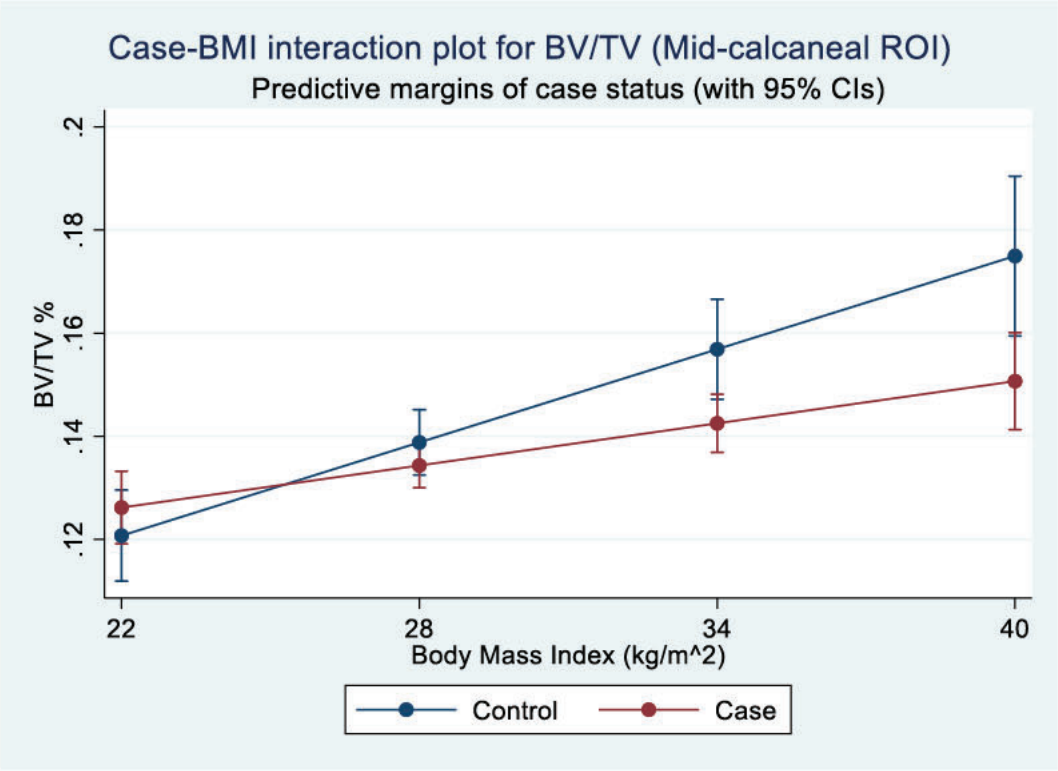

Figure 5-4 Case-BMI interaction plots for mid-calcaneal ROI BV/TV. Bone outcomes plotted from the 10th to 90th percentile of BMI.

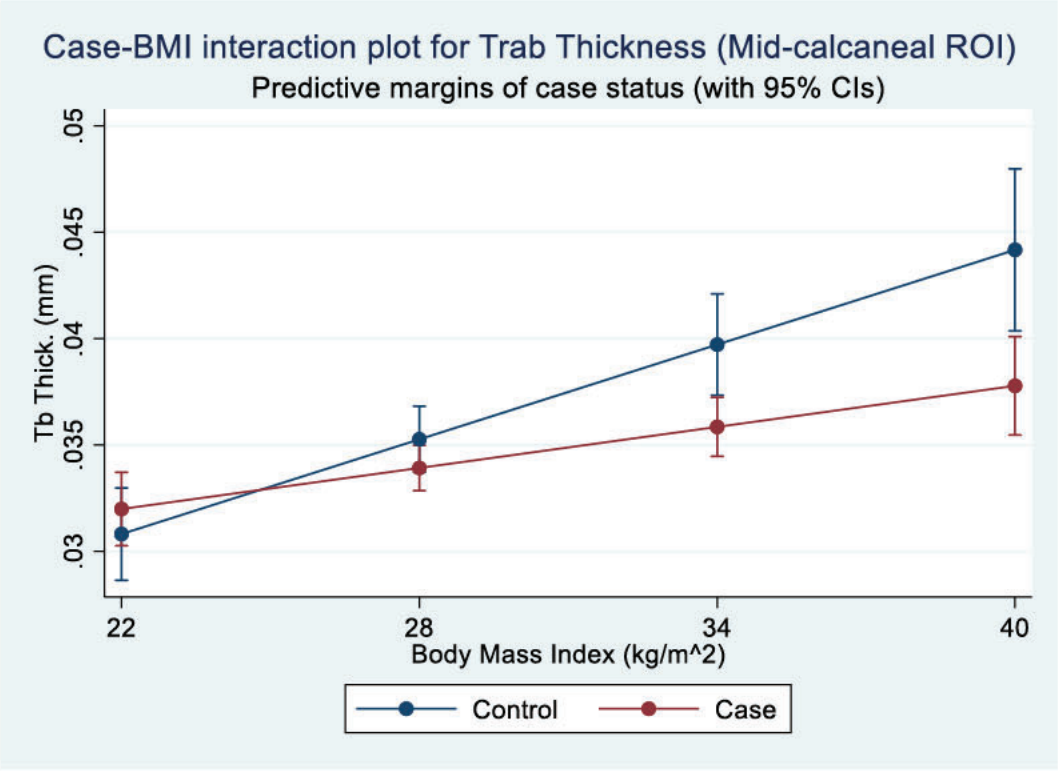

Figure 5-5 Case-BMI interaction plots for mid-calcaneal ROI trabecular thickness. Bone outcomes plotted from the 10th to 90th percentile of BMI.

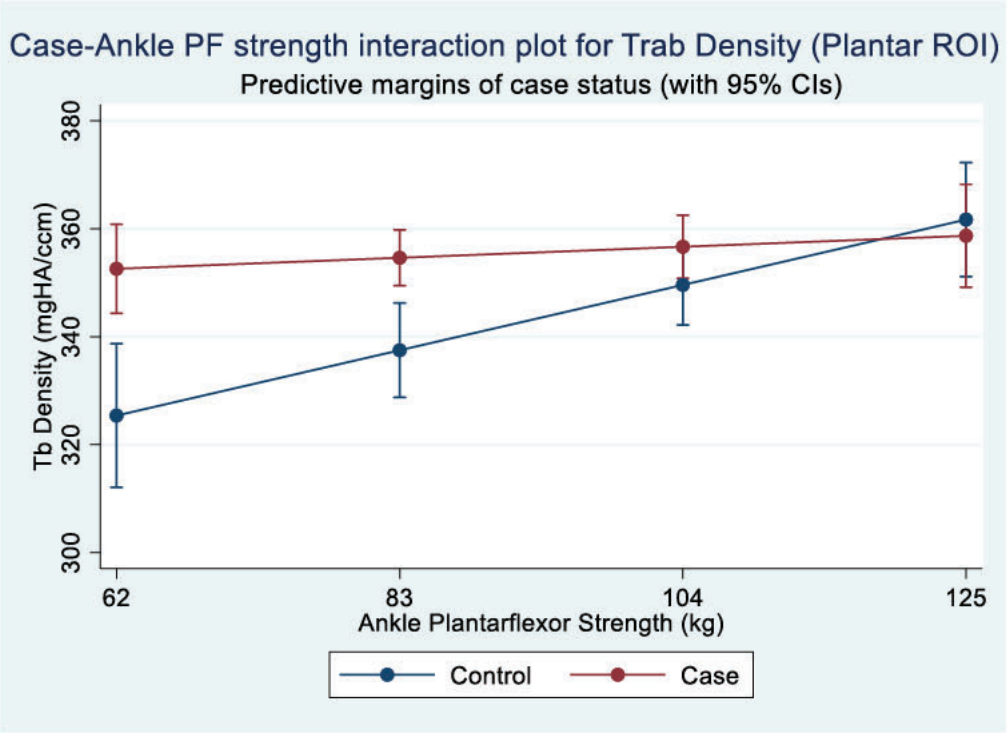

Figure 5-6 Case-ankle plantarflexor strength interaction plot for plantar ROI trabecular density. Bone outcomes plotted from the 10th to 90th percentile of ankle plantarflexor strength

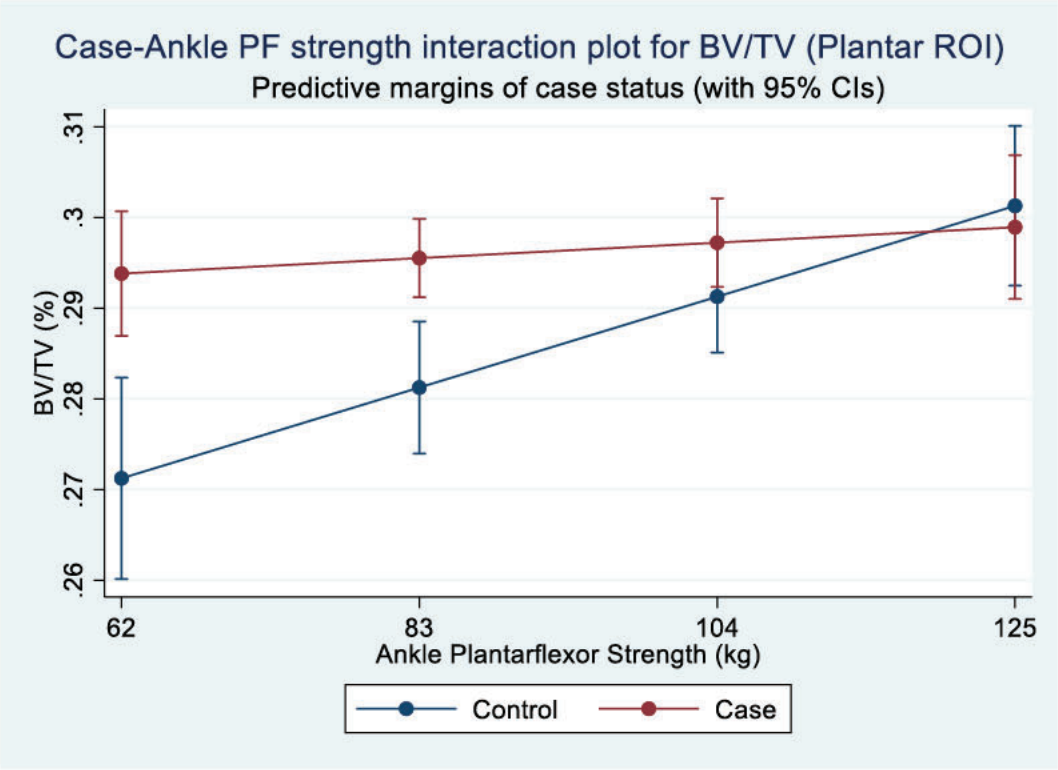

Figure 5-7 Case-ankle plantarflexor strength interaction plot for plantar ROI trabecular BV/TV. Bone outcomes plotted from the 10th to 90th percentile of ankle plantarflexor strength

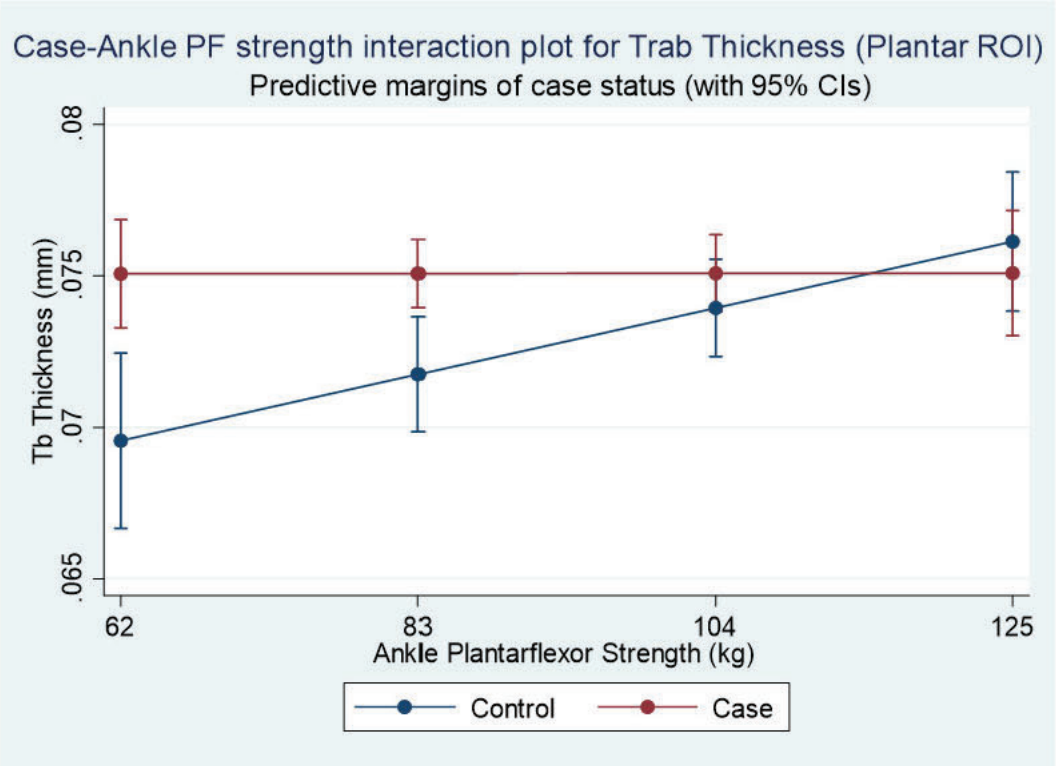

Figure 5-8 Case-ankle plantarflexor strength interaction plot for plantar ROI trabecular thickness. Bone outcomes plotted from the 10th to 90th percentile of ankle plantarflexor strength.

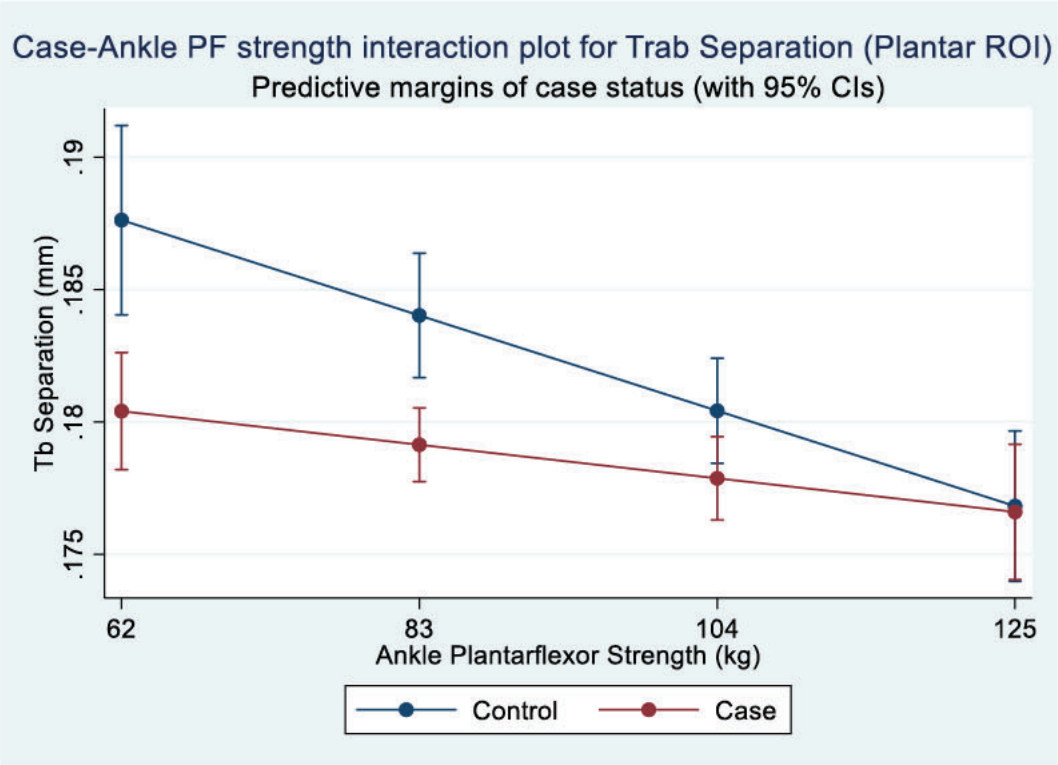

Figure 5-9 Case-ankle plantarflexor strength interaction plot for plantar ROI trabecular separation. Bone outcomes plotted from the 10th to 90th percentile of ankle plantarflexor strength

Table 5-4 Multivariable results for mid-calcaneal and plantar ROI, standardized co-efficients(se)[a]

Mid-calcaneal ROI	Trabecular density[c] (mg HA/cm^3)	BV/TV (%)[c]	Trabecular thickness (mm)[c]	Trabecular number (/mm)[c]	Trabecular separation (mm)[d]	
Case status[b]	-**6.617** (4.747)	-**0.006** (0.004)	-**0.0016** (0.001)	0.0290 (0.018)	-0.0007 (0.0017)	
BMI	**19.856** (3.802)	**0.017** (0.003)	**0.0041** (0.001)	**0.0214** (0.008)	-**0.0045** (0.0008)	
BMI*Case interaction	-**10.842** (4.588)	-**0.009** (0.004)	-**0.0023** (0.001)	-	-	
APFS	-0.046 (2.634)	0.000 (0.002)	-0.0003 (0.001)	**0.0363** (0.010)	-**0.0027** (0.0009)	
Age	-**13.083** (2.423)	-**0.011 (0.002)**	-**0.0026 (0.000)**	-0.0150 (0.009)	**0.0036** (0.0009)	
Female sex	-**8.995** (2.591)	-**0.008 (0.002)**	-0.0018 (0.001)	-**0.1180** (0.010)	**0.0081** (0.0009)	
MVPA	-	-	-	-	-**0.0018** (0.0008)	
Plantar ROI	**Trabecular density (mg HA/cm^3)[e]**	**BV/TV (%)[e]**	**Trabecular thickness (mm)[e]**	**Trabecular number (/mm)[f]**	**Trabecular separation (mm)[e]**	**Cortical density (mg HA/cm^3)[e]**
Case status[b]	**12.307** (4.596)	**0.0103** (0.0038)	**0.0023** (0.0010)	0.0271 (0.0144)	-**0.0038** (0.0012)	-7.316 (8.545)
APFS	**14.357** (3.790)	**0.0119** (0.0032)	**0.0026** (0.0008)	**0.0259** (0.0080)	-**0.0043** (0.0010)	-0.931 (4.755)
APFS*Case interaction	-**11.940** (4.357)	-**0.0099** (0.0036)	-**0.0026** (0.0009)	-	**0.0028** (0.0012)	-
BMI	**10.349** (2.111)	**0.0086** (0.0018)	**0.0013** (0.0005)	**0.0472** (0.0070)	-**0.0043** (0.0006)	2.827 (3.939)
Age	-3.657 (2.345)	-0.0031 (0.0020)	-0.0009 (0.0005)	0.0072 (0.0075)	0.0005 (0.0006)	-**23.816** (4.389)
Female sex	-**6.355** (2.509)	-**0.0053** (0.0021)	0.0002 (0.0005)	-**0.0840** (0.0081)	**0.0051**(0.0007)	-**16.614** (4.695)
MVPA	-	-	-	0.0085 (0.0072)	-	-

ROI region of interest, **BV/TV** bone volume / total volume, **BMI** body mass index, **APFS** ankle plantarflexor strength, **MVPA** moderate to vigorous physical activity

[a]Multivariable linear regression model, standardized X co-efficients, unstandardized Y (standard error). Bold p<0.05

[b]case =1, control=0

[c]Adjusted for age, sex & ankle plantarflexor strength, n=319

[d]Adjusted for age, sex, ankle plantarflexor strength and physical activity (MVPA), n=306

[e]Adjusted for age, sex, & BMI, n=319

[f]Adjusted for age, sex, BMI & physical activity (MVPA), n=306

5.4.1 Sensitivity analyses

Scan quality was lower in 83 participants (16 controls and 67 cases) who were mostly men (76/83). A longer foot was associated with scan quality classification (foot length: good (1) 11.2 (0.7) cm, fair (2) 11.7 (0.8) cm, poor (3)12.3 (0.7) cm). Sensitivity analysis omitting lower quality (grade 3) resulted in only small changes (~6%) in mid-calcaneal BV/TV and trabecular density interaction term co-efficients (**Supplementary Table 5-6**) (p-values =0.050 and 0.051 respectively). Other interactions were similar. The only substantial

changes in coefficients for other factors were a decrease in effect size for sex for trabecular density and BV/TV and an increase for MVPA with plantar trabecular number. Sensitivity analyses omitting influential observations did not otherwise result in significant changes in parameter estimates for bone outcomes in either ROI (**Supplementary Table 5-7**).

5.5 Discussion

Having CPHP modified the effect of BMI and ankle plantarflexor strength on trabecular bone outcomes in the mid- and plantar calcaneus, respectively. Higher BMI had beneficial associations with bone outcomes (higher trabecular density, thickness and BV/TV) in the mid-calcaneal region in controls but not in cases. Higher ankle plantarflexor strength had beneficial associations with bone outcomes (higher trabecular density, thickness and BV/TV and lower trabecular separation) in the plantar region in controls but not in cases. The reasons for differences in associations between cases and controls are not clear but could include being due to a stress-related entheseal reaction in cases, altered physical loading strategies due to pain, or other mechanisms associated with pain, systemic inflammation or neurogenic factors. Confirmation of effects of CPHP on bone health in longitudinal studies is needed.

The finding that having CPHP modifies the association between ankle plantarflexor strength and plantar trabecular bone is new. The ankle plantarflexors transmit large forces through the posterior and plantar calcaneus to the plantar fascia[5], creating a plausible mechanism for local bone stimulation as seen in controls. As seen in **Fig 5-6 to 5-9**, trabecular density, BV/TV and thickness are higher and trabecular separation is lower in cases than controls at low levels of ankle plantar flexor strength but similar at higher levels. Cases appear to respond differently to locally applied active loads. Cases may have a stimulatory bone response to entheseal stress that over-rides or precedes the normal stimulatory effect of locally applied forces by the Achilles/ plantar fascia complex seen in controls. Increased bone turnover is a common feature of bone under stress, and parallels can be drawn to similar reactions observed in subchondral bone in OA[23]. The higher prevalence of plantar enthesophytes in CPHP[1] supports this. These are thought to develop in response to entheseal degenerative change[4] and hypothesized to serve a load sharing, adaptive function in response to such stress[4, 24]. Another feature of this degenerative process which might add bone mineral to the plantar heel is calcification of the large fibrocartilaginous enthesis attachment of the plantar fascia[4]. The interaction

plots (**Figure 5-6 to 5-9**) suggest that there could be a ceiling beyond which the capacity for further bone adaptation, despite increased local loads, is exhausted. Overall, these findings may indicate disturbed coupling of the effects of actively applied local loads to the plantar calcaneus. Conversely, ankle plantarflexor strength was not consistently associated with mid-calcaneal bone outcomes, which is perhaps expected as this ROI is situated well away from the trabecular pathways associated with Achilles-plantar fascia force transmission.

The finding that CPHP modifies the effect of BMI on mid-calcaneal bone outcomes is also novel. This may be explained by differences in calcaneal loading. BMI has a stimulatory effect on bone likely via mechanical loading pathways[25]. Gait studies indicate that cases load the heel differently[26], which may reduce the weightbearing stimulus in the mid-calcaneum. A second possibility for the differences in bone outcomes could include metabolic and /or meta-inflammatory mechanisms. BMI is correlated with waist girth, which is itself strongly associated with CPHP[6]. Waist girth is an important proxy for cardiometabolically active central adiposity, which is known for its cytokine-producing systemic meta-inflammatory effects[27]. Osteoclast function in trabecular bone is sensitive to cytokine activity[28] associated with systemic inflammation. The positive effect of body mass on bone may be countered in cases by the negative effect of central adiposity, especially in older people[29]. A final consideration is the action of local peripheral nerve tissue which is important in bone homeostasis[30]. As a pain condition, sensory afferents associated with nociception release osteotrophic neurotransmitters such as CGRP, substance p and glutamate[31], which may have a direct effect on bone metabolism. Regardless, these findings underscore that there are consequences for bone distant to the enthesis in CPHP.

The effects of age and sex were generally consistent with their known effect on trabecular bone with both female gender and increasing age associated with a decrease in bone structure. An exception to this was that greater age was consistently not associated with bone outcomes in the plantar ROI. Ageing is associated with increased mineralization of the fibrocartilage transitional zone and subchondral plate thickening at the enthesis (in the presence of cortical thinning) potentially countering age-related trabecular bone loss in this region[32]. It may also be that at this site, the usual negative influence of age may be countered by the stimulatory effect of locally applied plantar fascia-ankle plantarflexor forces.

Previous HR-pQCT data for the calcaneus are very sparse, with two studies of 18 and 5 people respectively[7, 8]. Comparisons with our study is difficult as the study samples are different, being young athletic males[7] and aged cadaveric/ ex vivo women[8]. They analysed different regions within the calcaneus[7] or summed wider regions of interest[8]. These differences make it difficult to generalize results and technical parameters across studies and indicate that more in vivo work across a greater range of age, sex and calcaneal sites is required. We are re-assured however by the consistency of our results across bone outcomes and between ROIs. Furthermore, in unadjusted analyses age, sex and BMI follow known biologic patterns for their effect on bone and provides further evidence of the validity of our measures.

5.5.1 Limitations

This is the first study to compare bone microstructure and density outcomes in participants with CPHP. Its strengths include its large sample size, extensive covariate set, and the comparison with population-derived controls, however there are limitations. Our results describe cross-sectional differences in bone outcomes between cases and controls and cannot assign causation. Longitudinal studies of these bone outcomes would provide further insight on the relationship between these findings and CPHP. Selection bias is possible. This was minimized in controls by recruiting randomly from the electoral role and we maximised the representativeness of cases by recruiting from a range of sources, print and social media, community clubs and organisations, healthcare practices and from word of mouth. Cases and controls were recruited from the same local catchment area and were matched for the key demographics of age and sex. Scan quality may impact findings. However, a sensitivity analysis removing poorer quality scans had little effect on the magnitude of associations at both ROIs for our primary exposure of interest (case status) and its interaction effects, and our overall conclusions remain unchanged. The analysis did alter the coefficient for sex in both ROIs, probably because poorer quality scans were mostly in males.

5.6 Conclusion

Having chronic plantar heel pain may have consequences for calcaneal bone structure by modifying associations of BMI and ankle plantarflexor strength with bone outcomes at the mid- and plantar calcaneus respectively. The beneficial associations of BMI with bone outcomes seen in controls in the mid-calcaneal region and with greater ankle plantarflexor strength in the plantar calcaneal region is either reduced or absent in cases. The reasons

for differences in associations between cases and controls are not clear but could include a bone response to entheseal stress in cases, altered physical loading strategies in response to pain or other mechanisms associated with pain, systemic inflammation and neurogenic factors. These findings require further validation and ideally confirmation with longitudinal data.

5.7 Supporting information

Table 5-5 Main effects model, standardized co-efficients (se)[a]

Mid-calcaneal ROI	Trabecular density (mg HA/cm^3)[c]	BV/TV (%)[c]	Trabecular thickness (mm)[c]	Trabecular number (/mm)[c]	Trabecular separation (mm)[d]	
Case status[b]	-2.5 (2.2)	-0.002 (0.002)	-0.001 (0.001)	0.014 (0.008)	-0.000 (0.001)	
BMI	**12.5** (2.2)	**0.010** (0.002)	**0.003** (0.000)	**0.021** (0.008)	**-0.005** (0.001)	
Ankle PF strength	0.5 (2.6)	0.000 (0.002)	-0.000 (0.001)	**0.036** (0.010)	**-0.003** (0.001)	
Age	**-12.9** (2.4)	**-0.011** (0.001)	**-0.003** (0.001)	-0.015 (0.009)	**0.004** (0.001)	
Female sex	**-8.9** (2.6)	**-0.007** (0.002)	-0.001 (0.001)	**-0.118** (0.010)	**0.008** (0.001)	
MVPA	-	-	-	-	**-0.002** (0.001)	
Plantar ROI	**Trabecular density (mg HA/cm^3)[c]**	**BV/TV (%)[c]**	**Trabecular thickness (mm)[c]**	**Trabecular number (/mm)[d]**	**Trabecular separation (mm)[c]**	**Cortical density (mg HA/cm^3)[c]**
Case status[b]	**5.0** (2.1)	**0.004** (0.002)	0.001 (0.001)	0.013 (0.007)	**-0.002** (0.001)	-3.4 (4.0)
BMI	**10.8** (2.1)	**0.009** (0.002)	**0.001** (0.001)	**0.047** (0.007)	**-0.004** (0.001)	2.8 (3.9)
Ankle PF strength	**6.7** (2.6)	**0.006** (0.002)	0.001 (0.001)	**0.026** (0.008)	**-0.003** (0.001)	-0.9 (4.8)
Age	-3.7 (2.4)	-0.003 (0.002)	-0.001 (0.001)	0.007 (0.008)	0.001 (0.001)	**-23.8** (4.4)
Female sex	**-6.3** (2.5)	**-0.005** (0.002)	0.000 (0.001)	**-0.084** (0.008)	**0.005** (0.001)	**-16.6** (4.7)
MVPA	-	-	-	0.009 (0.007)	-	-

ROI region of interest, **BMI** body mass index, **PF** plantarflexor, **BV/TV** bone volume fraction, **MVPA** moderate to vigorous physical activity

[a]Multivariable linear regression model, standardized X co-efficients/ unstandardized Y (standard error). **Bold** $p<0.05$

[b]case =1, control=0

[c]Adjusted for age & sex, n=319

[d]Adjusted for age, sex and physical activity (MVPA), n=306

Table 5-6 Sensitivity analysis for scan quality; omitting poorer quality (grade 3) scans, standardised co-efficients (se)[a]

Mid-calcaneal ROI	Trabecular density (mg HA/cm^3)[d]	BV/TV (%)[d]	Trabecular thickness (mm)[d]	Trabecular number (/mm)[d]	Trabecular separation (mm)[e]
Case status[b]	-7.1 (5.5)	-0.006 (0.005)	-0.002 (0.001)	0.016 (0.022)	0.001 (0.002)
BMI	**21.8** (4.4)	**0.018** (0.004)	**0.005** (0.001)	0.020 (0.010)	**-0.005** (0.001)
BMI*Case interaction	-10.5 (5.3)	-0.009 (0.004)	**-0.002** (0.001)	-	-
APFS	1.0 (3.0)	0.001 (0.003)	-0.000 (0.001)	**0.042** (0.012)	**-0.003** (0.001)
Age	**-12.3** (2.9)	**-0.010** (0.002)	**-0.003** (0.001)	-0.019 (0.012)	**0.004** (0.001)
Female sex	-5.7 (3.0)	-0.005 (0.003)	-0.002 (0.002)	**-0.078** (0.012)	**0.005** (0.001)
MVPA[c]	-	-	-	-	**-0.003** (0.001)

Plantar ROI	Trabecular density (mg HA/cm^3)[f]	BV/TV (%)[f]	Trabecular thickness (mm)[f]	Trabecular number (/mm)[g]	Trabecular separation (mm)[f]	Cortical density (mg HA/cm^3)[f]
Case status[b]	**9.8** (5.6)	**0.008** (0.005)	**0.002** (0.001)	0.020 (0.016)	**-0.003** (0.002)	-9.7 (10.4)
APFS	**13.2** (4.4)	**0.011** (0.004)	**0.002** (0.001)	**0.032** (0.009)	**-0.004** (0.001)	-2.1 (5.7)
APFS*Case interaction	**-13.4** (5.3)	**-0.011** (0.004)	**-0.003** (0.001)	-	**0.003** (0.001)	-
BMI	**10.8** (2.6)	**0.009** (0.002)	**0.001** (0.001)	**0.052** (0.008)	**-0.005** (0.001)	1.9 (4.9)
Age	-3.9 (2.9)	-0.003 (0.002)	-0.001 (0.001)	0.003 (0.009)	0.001 (0.001)	**-27.3** (5.5)
Female sex	-2.7 (3.0)	-0.002 (0.003)	0.001 (0.001)	**-0.054** (0.009)	**0.003** (0.001)	**-14.0** (5.7)
MVPA[c]	-	-	-	**0.021** (0.008)	-	-

ROI region of interest, **BV/TV** bone volume / total volume, **BMI** body mass index, **APFS** ankle plantarflexor strength, **MVPA** moderate to vigorous physical activity

[a]Multivariable linear regression, standardized X/ unstandardized Y co-efficients (standard error). Bold $p<0.05$, Underline = changed significance, [b]case =1, control=0, [c]Moderate to vigorous physical activity, average minutes per day, by accelerometry

[d]Adjusted for age, sex & ankle plantarflexor strength, n=236

[e]Adjusted for age, sex, ankle plantarflexor strength and physical activity (MVPA), n=227

[f]Adjusted for age, sex, & BMI, n=236

[g]Adjusted for age, sex, BMI & physical activity (MVPA), n=227

Table 5-7 Sensitivity analysis; omitting influential observations, standardised co-efficients (se)[a]

Mid-calcaneal ROI	Trabecular density (mg HA/cm^3)[d]	BV/TV (%)[d]	Trabecular thickness (mm)[d]	Trabecular number (/mm)[d]	Trabecular separation (mm)[e]
Case status[b]	**-6.6** (4.8)	**-0.007** (0.004)	**-0.002** (0.001)	0.030 (0.018)	-0.001 (0.002)
BMI	**19.8** (3.9)	**0.018** (0.003)	**0.005** (0.001)	**0.022** (0.008)	**-0.005** (0.001)
BMI*Case interaction	**-10.7** (4.7)	**-0.011** (0.004)	**-0.003** (0.001)	-	-
APFS	-0.1 (2.7)	0.001 (0.002)	-0.000 (0.001)	**0.036** (0.010)	**-0.003** (0.001)
Age	**-13.0** (2.5)	**-0.011 (0.002)**	**-0.003** (0.001)	-0.016 (0.009)	**0.003** (0.001)
Female sex	**-9.0** (2.6)	**-0.007 (0.002)**	-0.001 (0.001)	**-0.240** (0.020)	**0.008** (0.001)
MVPA[c]	-	-	-	-	**-0.002** (0.001)
N	313	316	315	313	295

Plantar ROI	Trabecular density (mg HA/cm^3)[f]	BV/TV (%)[f]	Trabecular thickness (mm)[f]	Trabecular number (/mm)[g]	Trabecular separation (mm)[f]	Cortical density (mg HA/cm^3)[f]
Case status[b]	**12.6** (4.7)	**0.009** (0.004)	**0.002** (0.001)	0.026 (0.014)	**-0.004** (0.001)	-8.0 (8.6)
APFS	**13.7** (3.9)	**0.012** (0.003)	**0.003** (0.001)	**0.030** (0.008)	**-0.004** (0.001)	-1.1 (4.8)
APFS*Case interaction	**-11.5** (4.5)	**-0.010** (0.004)	**-0.002** (0.001)	-	**0.003** (0.001)	-
BMI	**10.3** (2.1)	**0.009** (0.002)	**0.001** (0.001)	**0.048** (0.007)	**-0.004** (0.001)	2.8 (4.0)
Age	-3.4 (2.4)	-0.002 (0.002)	-0.001 (0.001)	0.006 (0.007)	0.001 (0.001)	**-24.1 (4.4)**
Female sex	**-6.5** (2.6)	**-0.005** (0.002)	0.000 (0.001)	**-0.082** (0.008)	**0.010** (0.001)	**-16.2 (4.7)**
MVPA[c]	-	-	-	0.009 (0.007)	-	-
N	305	308	314	302	314	315

ROI region of interest, **BV/TV** bone volume / total volume, **BMI** body mass index, **APFS** ankle plantarflexor strength, **MVPA** moderate to vigorous physical activity

[a]Multivariable linear regression, standardized X/ unstandardized Y co-efficients (standard error). Bold p<0.05

[b]case =1, control=0

[c]Moderate to vigorous physical activity, average minutes per day, by accelerometry

[d]Adjusted for age, sex & ankle plantarflexor strength

[e]Adjusted for age, sex, ankle plantarflexor strength and physical activity (MVPA)

[f]Adjusted for age, sex, & BMI

[g]Adjusted for age, sex, BMI & physical activity (MVPA)

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Chapter 6

Imaging Abnormalities

Calcaneal bone marrow lesions and plantar fascia imaging biomarkers are associated with chronic plantar heel pain: A case-control study.

Provisionally accepted *Arthritis Care & Research* (15 Dec 2021)

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Note: In the published paper we were unable to include the table showing results of one sensitivity analysis (the effect of removing participants with diabetes or inflammatory disease), instead stating (data not shown) in section 6.4, page 129. This table is provided in the thesis as a postscript to the chapter.

6. Calcaneal bone marrow lesions and plantar fascia imaging biomarkers are associated with chronic plantar heel pain: A case-control study.

6.1 Preface

Chapter 4 described the associations of a wide range of clinical factors with CPHP status, but in chapter 1 major evidence gaps in our understanding of imaging biomarkers in chronic plantar heel pain (CPHP) (section 1.4.3.3) are also identified. There is a lack of large-scale MRI studies to investigate imaging biomarkers in the calcaneum such as bone marrow lesions and signal differences in other structures such as the plantar fascia and plantar fat pad.

The identification of abnormal imaging biomarkers associated with CPHP could improve our understanding of disease mechanisms. These biomarkers could in turn assist with diagnostic sub-grouping, with treatment targeting implications.

Chapter 6 reports on the results of our investigation into imaging biomarkers in chronic plantar heel pain (CPHP). It is presented as submitted to *Arthritis Care & Research* (Journal Impact factor 4.797, ranked 13/34 in rheumatology journals by JIF), where it is currently undergoing peer review.

6.2 Introduction

Chronic plantar heel pain (CPHP) is a clinical diagnosis characterised by pain and tenderness at the inferior heel [(1)], that affects up to 10% of adults in their lifetime [(2)]. In a seminal Cochrane review on interventions for treating plantar heel pain, the effectiveness of then current interventions was questioned citing that “there was limited evidence upon which to base clinical practice”[(3)]. Despite almost 20 years of further research, the effectiveness of today’s interventions, above and beyond each other, remains unclear [(4)]. The effectiveness of interventions may be hampered by our inability to direct specific treatment to the individuals who need them. An improved understanding of the pathological markers that differentiate individuals with and without CPHP, may help inform this clinical decision- making process.

The study of pathoanatomical contributors to CPHP has to-date been focussed on structural changes to the plantar fascia and its enthesis, including plantar spurs. However,

there are a range of tissues at the heel that are a potential source of nociception such as muscle, ligament, fat, bursa, bone, joint and nerve tissue. The contribution of these other structures to CPHP is poorly understood. Determining what imaging biomarkers contribute to prevalent CPHP is important as it may inform our future understanding of CPHP phenotypes.

In particular there has been very limited quantitative assessment of MRI-based measures such as signal within the plantar fascia, plantar fat pad or calcaneus. The significance of some of these measures has been established in musculoskeletal conditions such as knee osteoarthritis, where MRI has uncovered the potential role of bone marrow lesions (BMLs) in the pathogenesis of pain [5]. Bone marrow lesions are ill-defined signal hyperintensities on T2-weighted MRI sequences that reflect a range of histopathologies beyond oedema that include marrow necrosis, fibrosis, trabecular degeneration and remodelling [6]. BML-type lesions occur in people with CPHP, but it is not clear if they are associated with pain, function or disease status [7, 8]. Knowledge of biomarkers associated with prevalent CPHP can help inform tissue-specific interventions, such as seen in plantar fascia targeted high-load exercise [9]. However a stepped care approach that trials one modality after the other that is poorly aligned to pathoanatomy or clinical phenotypes, still predominates in CPHP management [10].

Therefore, the aim of this study is to improve our understanding of pathoanatomical markers in CPHP by determining the associations between CPHP and the presence and severity of MRI- and US-derived imaging biomarkers.

6.3 Materials and methods

6.3.1 Study design

Age- and sex-matched case-control comparison of participants in the Plantar Heel Pain Study (PHEEPS). We first recruited cases with a clinical diagnosis of CPHP, and then selected population-based controls on the basis of not having CPHP. Exposures were then measured once, only after case-control ascertainment.

6.3.2 Setting & participants

As summarised previously, cases with CPHP were recruited in southern Tasmania between November 2014 and July 2016, from medical and allied health practices, local community and sporting clubs and events, and from newspaper and social media

advertising [11]. CPHP was clinically defined as the presence of pain and tenderness at the inferior heel, that may spread to the arch but by definition was restricted to the sole of the foot [1, 12]. Symptoms are typically aggravated by weightbearing, which is frequently characterized as 'first-step' pain. Sex- and age-matched control participants were recruited via random selection from the southern Tasmanian electoral roll between November 2016 and August 2018 (population 176,644, 2016) (one control: two cases). The study was approved by the Tasmanian Health & Medical Human Research Ethics Committee (H0013616). All participants provided written informed consent.

6.3.3 Inclusion / exclusion

Cases were aged 18 and over with a clinical diagnosis of CPHP [1, 11], of at least 3 months duration. If heel pain was bilateral, the most symptomatic heel was assessed. Control participants were matched for age (5-year brackets from 25-90 years) and sex and had never had CPHP.

Both cases and controls were excluded if they had any contraindication to MRI, a history of previous foot/ ankle fracture or orthopaedic foot surgery, current ankle pain, recent foot trauma or other orthopaedic, congenital, vascular, neurological, or painful lower limb condition that restricted mobility or activity in the preceding 3 months. Cases who had a corticosteroid or any other injection, shockwave therapy or steroid iontophoresis within the previous 6 months were excluded.

6.3.4 Sample size calculations

The case-control analysis is nested within a 12-month longitudinal study of cases. We used sample size calculations for the longitudinal component of the study (n=220, α=0.05 (two-tailed) and 80% power for longitudinal hypotheses, with a loss to follow up of 10%) to inform case numbers for the case-control component of the study. Based on these numbers, and previously published values for key exposures [11], and assuming power of 80% and a two-tailed α of 0.05, we calculated that 100 controls were required to detect clinically important effect sizes that were comparable to or smaller than effect sizes reported in the CPHP, tendinopathy and osteoarthritis literature [13].

6.3.5 Data collection

The choice of imaging measures is informed by evidence gaps identified in a recent review [13] and by research that identifies the potential role of BMLs in the pathogenesis of pain in musculoskeletal disease such as osteoarthritis [5].

These markers of interest include the plantar fascia, trabecular bone, vascular tissue and the plantar fat pad, measured by US and MRI.

6.3.5.1 MRI

MRI was performed in the medical imaging department of the Royal Hobart Hospital by staff unaware of the clinical status of participants on a 1.5T whole-body magnetic resonance unit (GE 1.5T OPTIMA 450W) using an HD foot ankle array extremity coil (Invivo). Only a single foot was scanned: the most painful foot in cases, and in controls, a single foot matched to the test-foot side in cases across age- and sex-strata.

The following three sequences were obtained:

- Sagittal T2 FS (TE 80ms, TR 3653ms, Flip angle 160, FOV14.0, 3.0mm slices)
- Sagittal T1 (TE Min Full, TR 578ms, Flip angle 160, FOV17.0, 3.0mm slices)
- Coronal PD FS (TE 34ms, TR 3840ms, Flip angle 160, FOV14.0, 3.5mm slices).

6.3.5.2 MRI scoring

A single assessor (AL) blinded to participant status performed all MRI measurements in imaging software (Horosproject.org). Plantar fascia thickness (PFT) was measured with digital calipers (mm) in the coronal PD sequence as the largest dorsoplantar thickness in a plane perpendicular to the calcaneus (**Figure 6-1A**). The mean of three measures was taken as the final score. Repeatability for MRI measures was assessed across two time points by re-scoring 20 participants by the same blinded assessor (AL) (PFT ICC(3,1)=0.86). Signal within the plantar fascia was assessed using the coronal PD sequence in the slice demonstrating the largest intra-substance signal (**Figure 6-1B**). Signal score was graded ordinally as 0 (absent), 1 (≤ 50% of dorsoplantar thickness) or 2 (>50%) (weighted Kappa=0.92, n=20). Calcaneal bone signal was assessed and BMLs identified as an area of ill-defined hyperintensity on sagittal T2w FS sequences. If present, BML size was assessed as the areal measurement (mm^2) of the largest lesion identified on a single slice (**Figure 6-1C**) [(5)]. We recorded the number of contiguous slices in which the BML was identifiable, as well as the relative location of the lesion (plantar, posterior, central/ mid or anterior calcaneus). We measured all lesions if more than one was present but used the largest lesion for analysis. The final score was the mean of 3 measures (ICC(3,1)=0.99, n=20). Signal margins were delineated with the assistance of image processing tools including contrast settings, black body and picture inversion. Plantar enthesophytes detected on T1w sagittal sequences were graded ordinally as either 0 (absent), 1 (≤5mm in length), or 2 (>5mm in length) when measured along the

anteroposterior long axis of the spur from tip to base (weighted Kappa=1.0, n=20). The fat pad plantar to the calcaneus was assessed for signal change on T1 sequence and scored ordinally as 0 (no signal change), 1 (decrease in signal ≤50% of fat pad dorsoplantar thickness), or 2 (signal change >50%) (**Figure 6-1D**) (weighted Kappa=0.92, n=20).

6.3.5.3 Ultrasound

Ultrasound measures were undertaken by the same experienced sonographer (KS) with participants positioned prone with feet suspended off the bed end. We measured both feet but only used the most painful foot for analysis. Measurements were taken using a clinical ultrasound device (GE LOGIQe, General Electric Healthcare, Milwaukee, WI) with 10mHz linear array, using standardised musculoskeletal and foot settings. Plantar fascia thickness (mm) was assessed as the mean of 3 measures taken in a longitudinal plane at the plantar calcaneal drop off as reported previously[14-16] (study reliability (ICC(3,1)=0.82, n=20).

Echogenicity was recorded ordinally as either normal/ isoechoic (intact iso or hyperechoic fibrillar echotexture), diffusely hypoechoic (fibrillar echotexture intact but reduced signal intensity) or as a focal anechoic lesion (fibrillar echotexture defect/ anechoic zone) at a region of interest at the proximal calcaneal attachment of the plantar fascia (weighted Kappa=0.84, n=20) [17, 18].

Power Doppler results were scored ordinally as 0, 1, 2 or 3 (or more) according to the number of vascular dots identified within a 1x1.5cm window in the proximal plantar fascia at its calcaneal attachment (weighted Kappa=0.91, n=20) [19, 20]. The US was placed in power Doppler mode with a low wall filter and PRF set at 0.7kHz [21, 22]. The participant was stationary for 30 minutes prior to scanning and room temperature standardised to 21-22°C [23]. The sonographer scored all images at the time of assessment.

6.3.5.4 Clinical Measures

Clinical measures were taken in a single session, in the same order, by the same experienced physiotherapist (JR). Shoes, socks and lower leg clothing were removed.

Methods for clinical measures assessing height, weight, BMI, body composition by bioelectrical impedance analysis, waist girth, foot posture, ankle dorsiflexion and 1st metatarsophalangeal joint range of motion and ankle plantarflexor strength have been published previously [11]. Briefly, in further detail, maximum isometric ankle plantarflexor strength was measured in sitting as the highest score from three attempts with the lower limb strapped by inelastic belt about the knee to a digital scale (Excell GW, Taiwan;

sensitivity 0.05kg). Ankle dorsiflexion (°) was measured by a gravity inclinometer (Plurimeter, Switzerland) placed on the mid anterior shin in a weightbearing lunge position with the knee both extended [24] and flexed (ICC ⩾0.88) [25]. Passive first metatarsophalangeal joint extension (°) was measured with the foot plantigrade in supine, as the mean of three goniometric measurements (ICC=0.95) [26]. Static foot alignment was measured with the Foot Posture Index-6 [27]. Reliability was good to excellent for these measures [11].

Physical activity was measured by uniaxial accelerometer worn at the waist (Actigraph GT1M, Fort Walton Beach, Florida) monitored over 7 consecutive days [28]. Steps per day and mean counts per minute were measured, and physical activity classified as minutes spent in moderate to vigorous (MVPA), light and sedentary activity. Criteria for acceptable wear time, activity thresholds and data processing have been published previously [11].

Questionnaires recorded footwear choices, age, sex, menopausal status, smoking history, presence of morning stiffness symptoms (at any joint) and co-morbidities (diabetes or rheumatological disease). Foot pain and function was assessed by the Foot Health Status Questionnaire (FHSQ) (Cronbach's alpha 0.86, ICC=0.92) [29]. Quality of life was measured with the Assessment of Quality of Life scale, AQoL-6D [30] (Cronbach's alpha 0.94, ICC=0.85 to 0.88), (http://www.aqol.com.au/aqolquestionnaires/56.html). Pain laterality, duration of symptoms, number of previous episodes, treatment history and pain intensity via 100mm VAS were recorded by questionnaire in cases only.

6.3.6 Statistical Analysis

Characteristics of cases and controls are given using descriptive statistics. Conditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals for the association between each imaging exposure and CPHP status. All models were adjusted for BMI. Any model with an imaging exposure involving the plantar fascia was adjusted for ankle plantarflexor strength as they are mechanically coupled [31] and ankle plantarflexor strength is associated with CPHP [11]. Bone marrow lesion size was analysed in continuous form and categorized as none (0 mm^2), 'some' (> 0mm^2 but ≤100mm^2), and 'large' (> 100mm^2) based on descriptive convenience. We also checked for potential confounding by self-reported diabetes or inflammatory disease.

The independent association of imaging biomarkers with case status were assessed by modelling biomarkers in a common model. Four models were assessed to separate

potentially correlated plantar fascia measures (thickness on US & MRI, echogenicity and intrinsic signal).

Lastly, imaging biomarkers were classified as either present or absent, the number present counted, and the total number modelled as an additional assessment of their combined effect. Plantar fascia thickening was considered present if thickness was greater than 4mm [14]. For this additive modelling approach only, we chose to include the MRI but not US measure of plantar fascia thickness to avoid duplication. We also excluded the vascularity measure given there were no control events, resulting in a range of 0-6 biomarkers for analysis.

Assumptions of linearity in the logit were checked and optimal power fit for continuous exposures further evaluated with fractional polynomials. We tested for plausible interactions between imaging biomarkers and BMI and/or ankle plantarflexor strength. Standard model fit, link and multicollinearity checks were undertaken. Sensitivity analyses were conducted to assess the effect of removing influential observations on parameter estimates and statistical inference. All analyses were performed using Stata 16 (Stata Corp., College Station 16, TX, USA).

6.4 Results

We recruited 220 cases from 299 potentially eligible cases screened (**Figure 6-2**). Two cases were unable to complete an MRI so were excluded, yielding a case sample of 218. Of 566 contactable potential control participants, 232 agreed to participate. One-hundred and ten controls were excluded before consent, a further 22 withdrew or were excluded after consent but before testing was completed, leaving 100 control participants in the analysis.

Cases had higher BMI and waist girth and weaker ankle plantarflexors, lower quality of life and foot function and more often reported morning stiffness (**Table 6-1**). The median duration of symptoms in cases was 10 months (range 3 to 636 months).

Plantar calcaneal BMLs, plantar fascia thickness greater than 4mm (on US or MRI; US data not shown), plantar fascia hypoechogenicity and greater plantar fascia signal were common in CPHP cases but not controls (**Table 6-2**). Plantar heel spurs and T1-weighted fat pad signal differences were equally common in cases and controls. Plantar fascia vascularity was not common and occurred exclusively in cases.

BML size, plantar fascia thickness (measured by US or MRI), plantar fascia signal, echogenicity and plantar spur size increased the odds of being a case in univariable and multivariable models (**Table 6-3**). There was no association with T1-weighted plantar fat pad signal. There was no evidence of effect modification.

In models including multiple imaging biomarkers a measure of plantar fascia morphology, (thickness, signal or echogenicity), and plantar BML's were always independently associated with the odds of being a case (**Table 6-4**). Fat pad signal or plantar spur grade were not independently associated with having CPHP in any model.

For significant associations, higher grades representing increased biomarker severity or intensity were always associated with an increased effect size. As the number of biomarkers increased, so too did the odds for case association (**Supplementary Table 6-5**), with significant associations identified once four or more biomarkers were present (four biomarkers present: OR 6.97, 95% CI 2.17 to 22.36).

Results were similar following model checks assessing the effect of removing influential observations (**Supplementary Table 6-6**), and after adjusting for self-reported diabetes or inflammatory disease (Postscript **Supplementary Table 6-7,** 'data not shown' in published paper).

6.5 Discussion

In addition to measures of the plantar fascia, plantar BMLs are prevalent and associated with having CPHP. Risk for having CPHP increases with the size of the bone lesion and this risk persists independent of the presence of other imaging biomarkers. In contrast, differences in plantar fat pad signal and having a plantar spur did not differentiate cases from controls, independent of other imaging biomarkers. These findings demonstrate that there may be important and under-recognised bone and soft tissue differences between CPHP cases and controls. Further research is required to determine if these biomarker differences can inform our understanding of CPHP phenotypes. If the case, particularly for BMLs, this may offer a novel treatment target for bone specific approaches in heel pain. It would also be valuable to know whether these biomarkers have longitudinal associations with the course of disease and clinical outcomes.

Our finding of an association between BMLs and CPHP that is sensitive to the size of the lesion is consistent with associations between BMLs and pain at other bone sites such as

the vertebral body (Modic lesions) [32, 33] and knee [5, 34]. Our understanding of bone in CPHP has been limited to plantar spurs and in the case of BML-type lesions, descriptive, retrospective case series [7, 8] or small non-quantitative case-control investigations [35]. While our results support a potential role for BMLs in CPHP, longitudinal data are needed to determine whether BMLs predict symptomatic and functional outcomes. If this is the case, BMLs could be a novel treatment target for CPHP using bone active agents such as bisphosphonates as is being investigated in knee OA [36]. New or existing treatments with a potential bone supporting effect could be specifically evaluated in CPHP against a bone-specific phenotype, such as shockwave [37, 38], low intensity pulsed ultrasound (LIPUS), and exercise therapies.

The fact that most BMLs were in the plantar calcaneus could be due to a mechanical relationship with the plantar fascia and its enthesis, or the direct consequence of weightbearing. Load transferred through the enthesis (compressive/ tensile) and trauma may be factors in CPHP BML development [39]. Given the highly trabecular, thinly corticated nature of the calcaneus, stress injury can occur in active populations (e.g. military) [40]. BMLs could be a manifestation of a bone response along this stress pathway. The presence of spurs, although not an independent association, indicate that the calcaneus is a dynamic bone, sensitive to remodelling demands at the enthesis [41]. The observation of a self-limiting natural history for many people with CPHP may reflect time frames consistent with bony healing [42].

Measures of plantar fascia morphology; thickness (by US or MRI), echogenicity, and intrinsic signal were all strongly associated with CPHP. A thicker plantar fascia in cases than controls (mean difference 1.52mm) is consistent with existing literature [13]. Signal within the plantar fascia of CPHP cases has been described but not previously documented in a quantitative manner [35]. Increased intra-tendinous signal is seen in connective tissue pathology including the Achilles tendon but it is unclear whether in non-inflammatory conditions this is associated with pain and functional impairment [43]. The basis for signal increase is uncertain but may reflect changes to the extra-cellular matrix and the water holding capacity of tendon [43, 44] and/or changes in perivascular flow or perivascular leakage [44]. Identifying fluid sensitive signal change is important as it can be an early sign of tendon abnormality [45] and offers a functional alternative to structural markers such as thickness. If similarly applicable to the plantar fascia, understanding its longitudinal associations with symptoms and its modifiability, should be a goal of future

CPHP research.

Consistent with other studies, plantar fascia vascularity was also associated with CPHP [17, 21, 23]. Twenty-one percent of cases had some signal but no controls, so we could not calculate an OR from our data. It has been postulated that angiogenic signalling in response to (oxidative) stress may drive neovascularisation [46], or that these vessels opportunistically occupy voids within a failing collagenous matrix [47], and so act as a marker for an advanced degenerative state. Whether these processes operate on a continuum from adaptation to failed healing is unclear, however our findings are consistent with the view that detectable vascular flow on PDUS within resting tendon-like structures is abnormal [20].

Fat pad (T1-weighted) signal and plantar spurs were not associated with CPHP independent of other imaging biomarkers. The fat pad measure was intended to capture structural degradation, including a thicker, degenerate septal connective tissue network in the plantar heel pad ('fibrosis') [48, 49]. Our results do not support the clinical assumption that disordered connective tissue structure, with subsequent hypothesised changes to the mechanical properties of the plantar fat pad [50, 51], are associated with pain. This is based however on measuring the distribution of signal change and not the thickness or volume of heel tissue itself, which may be more important in determining heel pad mechanical function [49, 52, 53].

6.5.1 Limitations

Strengths of this study are its large case sample, use of novel BML biomarkers, extensive covariate set, blinded MRI assessment and the use of population-based controls. However, the case-control design restricts our interpretation of results to association rather than causation. Ultrasound assessment was potentially unblinded due to sequencing effects - controls were recruited (and then tested) on a matched basis once the age and sex mix of case participants were known. Efforts were made to preserve blinding by de-identifying controls with a participant ID and isolating survey/ history data from the imaging session.

6.6 Conclusion

Plantar calcaneal BMLs as well as measures of plantar fascia morphology, but not plantar fad pad signal or spurs, were associated with CPHP independent of other imaging biomarkers.

The identification of novel, specific bone and soft tissue-based differences between cases and controls may help to inform clinical phenotyping. The significance of these findings requires longitudinal validation but have the potential to inform how treatment choices are targeted.

Table 6-1 Characteristics of cases and controls

		Case (n=218)*	Control (n=100)*
Age (years)	Male	58.5 (12.1)	59.2 (12.5)
	Female	52.2 (11.5)	52.0 (11.6)
Female n(%)		131 (59.6)	60 (60)
Menopause n(%)		48/131 (37)	25/60 (42)
Smoke- ever n(%)		73 (33)	28 (28)
Smoke- current n(%)		10 (4.6)	7 (7)
Diabetes n(%)		8 (3.7)	3/99 (3)
Inflammatory disease n(%)		18 (8.2)	6 (6)
Night pain n(%)		138 (65)	0
Morning stiffness >30min n(%)		48 (22)	6 (6)
High Cholesterol n(%)		55 (25)	30 (30)
Physical activity			
Accelerometry (median, IQR)			
Average steps/day[a]		7918 (6148, 9903)	8373 (6080, 10205)
Moderate-to-vigorous (average min/day)[b]		37.7 (18.3, 61.1)	42.4 (20.0, 57.5)
Sedentary (average min/day)[b]		491 (437, 545)	502 (443, 561)
Quality of life & function			
AQOL-6D[c]		76.4 (10.8)	86.4 (6.9)
FHSQ function[d]		65.7 (27.8)	99.1 (3.3)
Clinical measures			
BMI (kg/m^2)		29.14 (5.4)	27.63 (5.6)
Waist girth (cm)		97.4 (13.9)	90.8 (15.1)
Foot posture index (FPI)[e]		2.71 (3.9)	3.07 (3.7)
Ankle DF ROM, knee flexed (deg)		43.3 (6.7)	44.1 (5.5)
Ankle PF strength (kg)		90.5 (23.8)	98.8 (26.4)
1st MTPJ Ext ROM (deg)		70.3 (15.1)	74.8 (14.4)

*Values are mean (SD), unless specified.

[a]n=207/96, [b]n=211/96

[c]Assessment of Quality of Life-6 scale, 0-100, higher better

[d]Foot Health Status Questionnaire (weighted), 0-100, higher = better function

[e]Foot Posture Index, -12 highly supinated to +12 highly pronated

Table 6-2 Size and prevalence of imaging biomarkers in cases and controls

		Case (218)	Control (100)
MRI		**n (%)***	**n (%)***
BML (mm^2), median (IQR)		25.7 (77.4)	0 (0)
BML (plantar)⁺	none	106 (49)	89 (89)
	>0-100mm^2	73 (33)	9 (9)
	>100 mm^2	39 (18)	2 (2)
PF thickness (mm), mean (SD)		5.0 (1.5)	3.5 (1.0)
PF thickness	≤4mm	57 (26)	76 (76)
	>4mm	161 (74)	24 (24)
PF T2-w signal^	none	68 (31)	67 (67)
	≤50%	50 (23)	24 (24)
	>50%	100 (46)	9 (9)
Plantar spur#	none	79 (36)	55 (55)
	≤5mm	57 (26)	22 (22)
	>5mm	82 (38)	23 (23)
Plantar fat pad T1-w signal^	none	97 (45)	44 (44)
	≤50%	35 (16)	11 (11)
	>50%	86 (39)	45 (45)
Ultrasound		**n (%)**	**n (%)**
PF thickness (mm), mean (SD)		5.3 (1.5)	3.6 (0.9)
PF echogenicity	normal	35 (16)	62 (62)
	diffusely hypoechoic	110 (50)	31 (31)
	focally hypoechoic	73 (34)	7 (7)
PF vascular signal	none	171 (79)	100 (100)
	1 dot	16 (7)	
	2 dots	13 (6)	
	3 or more dots	18 (8)	

*values are n (%) unless specified otherwise.
⁺**BML** size categorised as none (absent/ 0mm^2), some (>0 to ≤100mm^2) or large (>100mm^2)
^dorsoplantar width, #axial length, base to tip, **BML** bone marrow lesion, **PF** plantar fascia, **SD** standard deviation, **IQR** interquartile range

Table 6-3 Univariable and multivariable associations of individual imaging biomarkers with chronic plantar heel pain

MRI measures		**Univariable OR (95% CI)**	**Multivariable OR (95% CI)**
BML (any calcaneal site)(mm^2)[1]		**1.02** (1.01, 1.03)	**1.02** (1.01, 1.03)
BML (plantar) (mm^2)[1]		**1.03** (1.02, 1.05)	**1.03** (1.02, 1.05)
BML (plantar)[1]	none	ref	ref
	up to 100mm^2	**7.24** (3.40, 15.45)	**7.06** (3.30, 15.11)
	>100mm^2	**17.98** (4.17, 77.64)	**17.14** (3.96, 74.32)
PF thickness (mm)[2]		**3.07** (2.29, 4.13)	**3.23** (2.36, 4.43)
PF signal[2]	none	ref	ref
(dorsoplantar	≤50%	**2.13** (1.15, 3.94)	1.85 (0.98, 3.51)
width)	>50%	**12.47** (5.59, 27.80)	**12.12** (5.36, 27.42)
Plantar spur[2]	none	ref	ref
(tip to base	≤5mm	**1.89** (1.03, 3.47)	1.74 (0.94, 3.22)
length)	>5mm	**2.75** (1.50, 5.03)	**2.15** (1.13, 4.10)
Fat pad signal[1]	no signal change	ref	ref
(dorsoplantar	≤50%	1.44 (0.67, 3.11)	1.50 (0.69, 3.26)
width)	>50%	0.87 (0.52, 1.44)	0.95 (0.57, 1.60)
Ultrasound measures[3]		**OR (95% CI)**	**OR (95%CI)**
PF thickness (mm)[2]		**3.44** (2.53, 4.68)	**3.78** (2.69, 5.32)
PF echogenicity[2]	Normal/ isoechoic	ref	ref
	Hypoechoic- diffuse	**7.69** (4.09, 14.45)	**7.89** (4.02, 15.48)
	Hypoechoic- focal	**22.04** (8.81, 55.11)	**24.92** (9.60, 64.69)

Conditional logistic regression model, bold = sig P<0.05.
BML bone marrow lesion, **PF** plantar fascia, **OR** odds ratio, **CI** confidence interval, **MRI** magnetic resonance imaging
[1] Age- & sex-matched, adjusted for BMI, [2] Age- & sex-matched, adjusted for BMI and ankle plantarflexor strength
[3] ORs for PF vascularity not calculable as no control events

Table 6-4 Independent associations of imaging biomarkers with CPHP status

Multivariable^		M1a* OR (95% CI)	M1b OR (95% CI)	M2 OR (95% CI)	M3 OR (95% CI)
PF thickness MRI >4mm		**7.96** (3.99, 15.90)			
PF thickness US >4mm			**8.30** (4.06, 16.96)		
PF signal	none			ref	
	≤50%#			1.46 (0.73, 2.94)	
	>50%			**7.53** (3.15, 18.03)	
PF hypoechogenicity	normal				ref
	diffuse				**5.60** (2.71, 11.60)
	focal				**13.81** (4.98, 38.31)
Spur length	none	ref	ref	ref	ref
	≤5mm	1.15 (0.54, 2.44)	1.20 (0.55, 2.60)	1.01 (0.49, 2.09)	1.06 (0.50, 2.26)
	>5mm	0.76 (0.33, 1.77)	0.81 (0.35, 1.85)	1.39 (0.64, 3.02)	0.87 (0.38, 1.98)
Plantar BML	none	ref	ref	ref	ref
	>0-100mm^2	**3.86** (1.61, 9.23	**2.49** (1.05, 5.92)	**4.38** (1.95, 9.88)	**3.33** (1.42, 7.79)
	>100mm^2	**8.66** (1.89, 39.71)	**7.25** (1.54, 34.14)	**7.92** (1.70, 36.97)	**7.48** (1.59, 35.23)
Fat pad	none	ref	ref	ref	ref
	≤50%#	0.76 (0.28, 2.09)	1.18 (0.44, 3.22)	0.85 (0.32, 2.23)	1.02 (0.38, 2.71)
	>50%	0.76 (0.41,1.42)	0.76 (0.40, 1.42)	0.75 (0.41, 1.36)	0.82(0.43, 1.50)

Multivariable model; conditional logistic regression (age- & sex-matched). Bold = sig p<0.05.
^Adjusted for BMI, ankle strength, spur, plantar BML, fat pad & [PF thickness MRI (Model 1a) *or* US (Model 1b) *or* signal (Model 2) *or* echogenicity (Model 3)]
* Four models required to separate correlated plantar fascia measures.
# Percentage of dorsoplantar width signal penetration
PF plantar fascia, **OR** odds ratio, **CI** confidence interval, **BML** bone marrow lesion

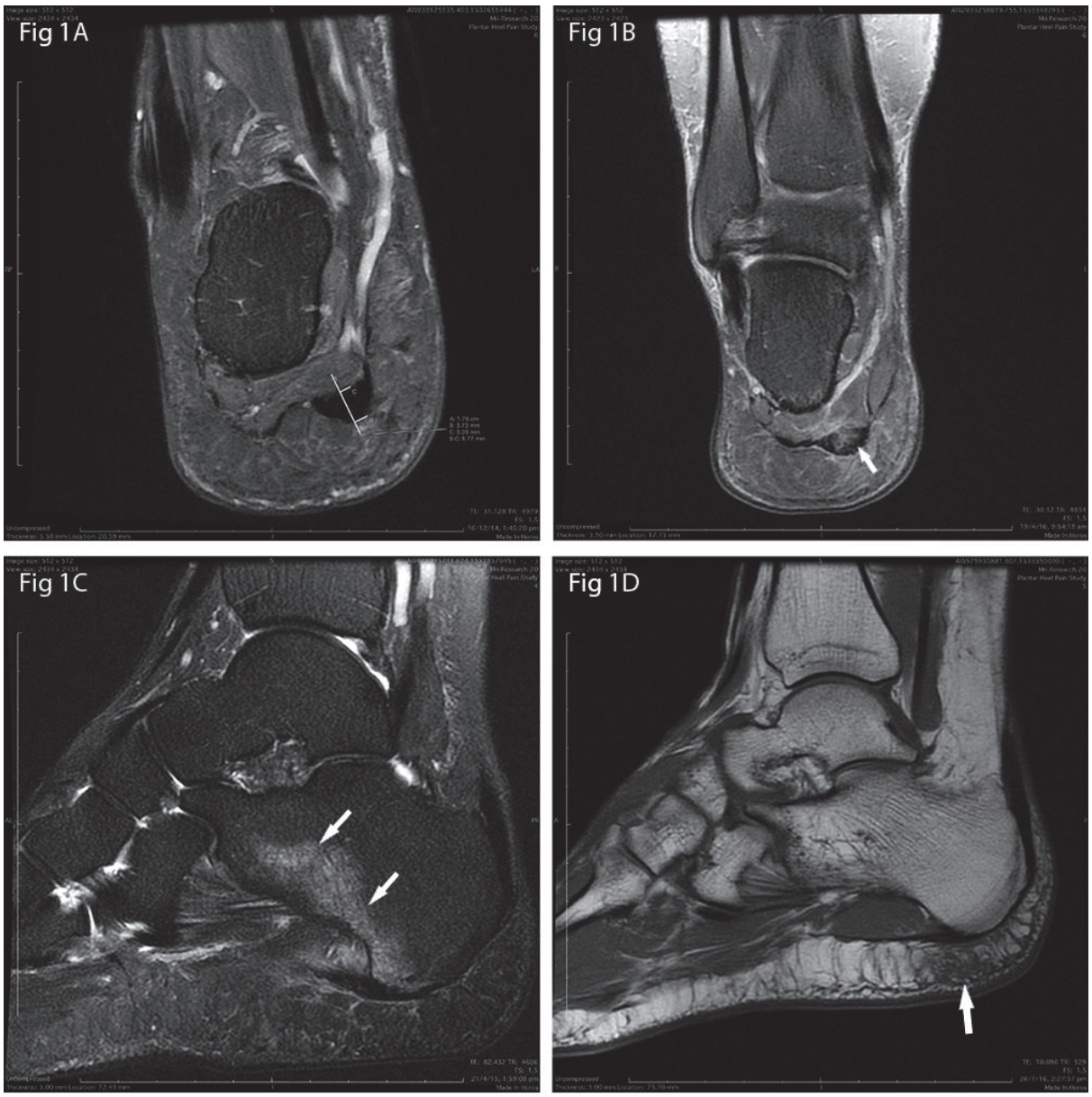

Figure 6-1 **A** Plantar fascia thickness, coronal PD sequence, **B** Intra-substance plantar fascia signal (Grade 2), coronal PD sequence, **C** Calcaneal BML signal, sagittal T2-weighted sequence, **D** Plantar fat pad signal, sagittal T1-weighted sequence (Grade 2)

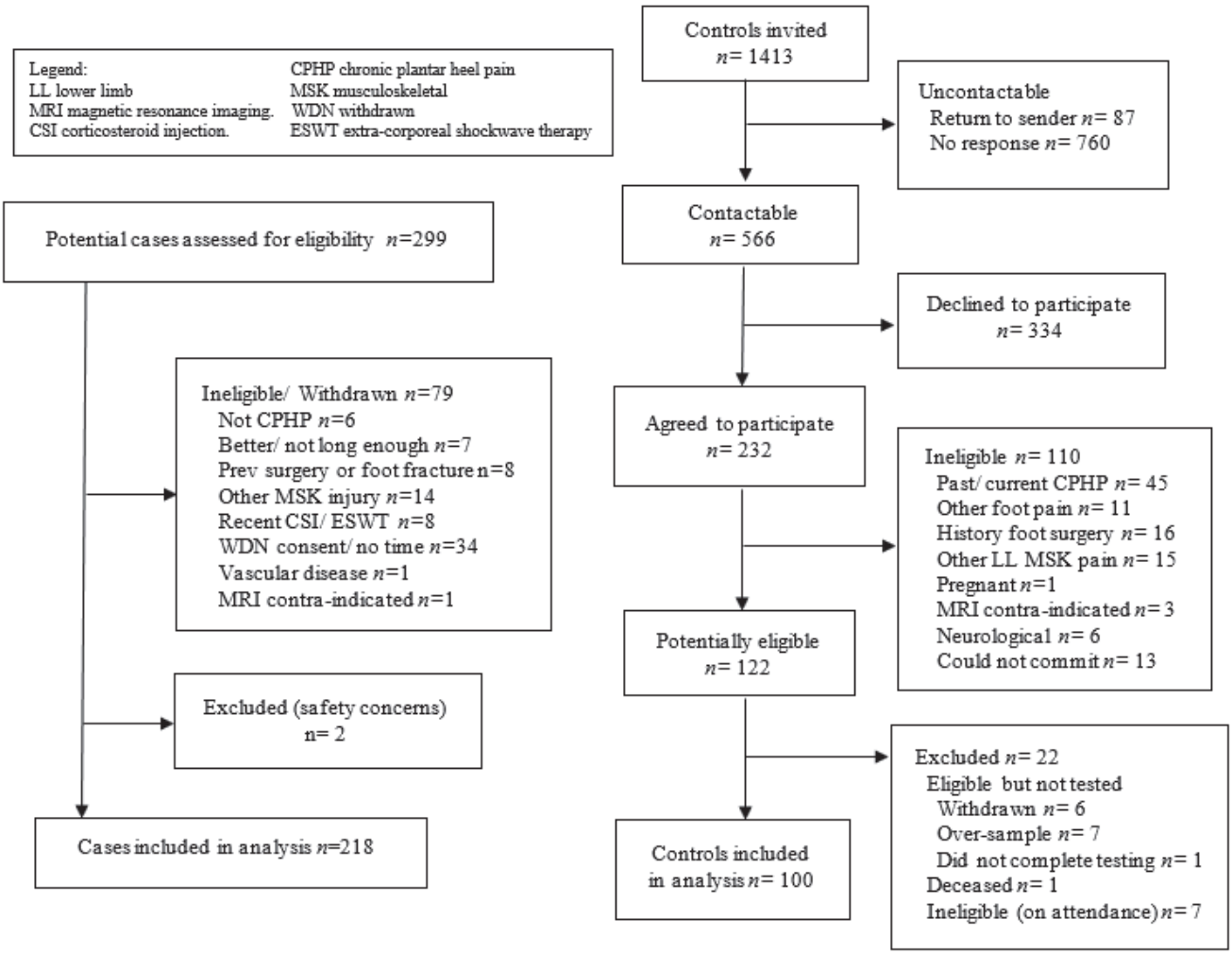

Figure 6-2 Case and control participant flow

Table 6-5 Supplementary Table: Additive effect of number of imaging biomarkers^

Number of biomarkers	Odds Ratio	95% CI	
1	0.77	0.25	2.37
2	1.06	0.35	3.36
3	2.70	0.86	8.51
4	**6.97**	2.17	22.36
5	**17.47**	4.56	66.96
6	**58.67**	6.52	528

Multivariable conditional logistic regression model, age and sex-matched adjusted for BMI and ankle plantarflexor strength. Bold = sig $p<0.05$. Reference is zero biomarkers.
^ Biomarkers include: (MRI) PF thickness, BMLs, spur, fat pad, PF signal, & (US) echogenicity; excludes PF thickness (US) and PF vascular signal.

Table 6-6 Supplementary Table: Sensitivity analysis omitting influential observations; full multivariable model (clear table) vs sensitivity model (shaded)

		OR[3]	95% CI		OR	95% CI		n
BML(plantar)(mm²)[1]		**1.03**	1.02	1.05	**1.04**	1.02	1.05	314
PF thickness MRI (mm)[2]		**3.23**	2.36	4.33	**4.25**	2.89	6.26	305
PF signal[2]	≤50%	1.85	0.98	3.51	**2.04**	1.05	3.98	310
	>50%	**12.12**	5.36	27.42	**21.58**	7.89	59.04	
Spur[2]	≤5mm	1.74	0.94	3.22	**1.91**	1.01	3.61	307
	>5mm	**2.15**	1.13	4.10	**2.78**	1.40	5.49	
Fat pad[1]	≤50%	1.50	0.69	3.26	1.37	0.61	3.09	312
	>50%	0.95	0.57	1.60	0.84	0.49	1.45	
PF thickness US (mm)[2]		**3.78**	2.69	5.32	**4.59**	3.09	6.83	312
PF echogenicity[2]	diffuse	**7.89**	4.02	15.48	**8.44**	4.21	16.92	312
	focal	**24.92**	9.60	64.69	**45.08**	13.86	146.60	

[1]full multivariable model, age- & sex-matched, adjusted for BMI
[2]full multivariable model, age- & sex-matched, adjusted for BMI & ankle plantarflexor strength
[3] full model: n=318
OR odds ratio, CI confidence interval, PF plantar fascia, BML bone marrow lesion, US ultrasound, MRI magnetic resonance imaging

Table 6-7 Supplementary Table: Sensitivity analysis omitting diabetic and inflammatory conditions

		Multivariable model			**Remove inflamm.**			**Remove diabetes**		
		n=318			n= 294			n=307		
		OR	95%CI		OR	95%CI		OR	95%CI	
BML[1] (plantar) (mm^2)		**1.03**	1.02	1.05	**1.05**	1.03	1.07	**1.03**	1.02	1.05
PF thickness[2] mri (mm)		**3.23**	2.36	4.43	**3.54**	2.51	5.00	**3.28**	2.39	4.52
PF signal[2]	≤50%^	1.85	0.98	3.51	**2.26**	1.15	4.45	1.83	0.95	3.52
	>50%	**12.12**	5.36	27.42	**15.86**	6.35	39.62	**11.49**	5.05	26.15
Plantar spur[1]	≤5mm	1.74	0.94	3.22	1.76	0.92	3.34	1.74	0.94	3.24
	>5mm	**2.15**	1.13	4.10	**2.17**	1.12	4.19	**2.39**	1.23	4.65
Fat pad signal[1]	≤50%^	1.50	0.69	3.26	1.81	0.78	4.18	1.59	0.71	3.56
	>50%	0.95	0.57	1.60	0.93	0.54	1.58	0.94	0.56	1.58
PF thickness[2] us (mm)		**3.78**	2.69	5.32	**4.28**	2.92	6.27	**4.12**	2.85	5.96
PF hypoecho[2] us	diffuse	**7.89**	4.02	15.48	**11.63**	5.57	24.28	**8.65**	4.29	17.46
	focal	**24.92**	9.60	64.69	**37.01**	12.90	106.20	**29.17**	10.65	79.85

Conditional logistic regression model, bold = sig P<0.05.

BML bone marrow lesion, **PF** plantar fascia, **OR** odds ratio, **CI** confidence interval, **mri** magnetic resonance imaging, **us** ultrasound

[1] Age- & sex-matched, adjusted for BMI, [2] Age- & sex-matched, adjusted for BMI and ankle plantarflexor strength

^dorsoplantar width of structure

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Chapter 7

Clinical predictors of pain, function and quality of life in people with chronic plantar heel pain after 12-months: A prospective longitudinal study

7. Clinical predictors of pain, function and quality of life in people with chronic plantar heel pain after 12-months: A prospective longitudinal study

7.1 Preface

In chapter 4, associations of a wide-range of clinical factors with chronic plantar heel pain (CPHP) as determined by a case-control comparison are presented. However, our understanding of prognosis in CPHP is limited by a lack of longitudinal studies. We discuss these evidence gaps in chapter 1 (section 1.3.3). Prospective longitudinal study provides a stronger level of evidence than case-control investigation for our understanding of causation and mechanisms in heel pain. We address this limitation in this chapter by presenting the results of our 12-month follow-up study in cases examining longitudinal associations of clinical factors with key patient outcomes.

7.2 Introduction

Chronic plantar heel pain (CPHP) is commonly assumed to follow a favourable, self-limiting natural course[1] but this position is not clearly informed by longitudinal research. To date most longitudinal research in CPHP is based on retrospective case series analyses, with a narrow assessment of exposures, short follow-up period and limited application of validated outcome measures[2-4]. A recent prospective study indicated that the long-term course of CPHP may be more recalcitrant, with as many as 46% of cases reporting persistent symptoms an average of 10-years after onset[5].

Our understanding of the factors that affect CPHP outcomes is limited and improving this understanding could help to identify potential causal mechanisms and direct treatments against factors likely to matter. Our current understanding of prognostic factors for CPHP is restricted to a few clinical, demographic or disease factors such as bilateral symptoms[3, 5], female sex[5], overweight[3] and longer duration of symptoms[3] [6]. Most of these are not modifiable and are therefore of limited clinical value. Other clinical factors with an established cross-sectional association[7], such as pain catastrophising, depression, calf strength or multisite pain, have not been evaluated for longitudinal associations. We know even less about the role of

neuropathic symptoms in CPHP even though some authors indicate that nerve injury may affect up to one in five cases[8, 9] and neuropathic symptoms are associated with poorer clinical outcomes in a range of other musculoskeletal pain states such as LBP and osteoarthritic knee pain[10] [11]. Many of these factors have a time-varying course, are potentially modifiable and an improved understanding could help guide clinical decision making.

The primary aim of this prospective longitudinal study therefore was to determine which clinical factors including psychological (pain catastrophising, depression), physical factors (calf strength, BMI) and symptom-related factors (neuropathic, night and multisite pain) predict CPHP pain, function and quality of life outcomes at 12 months.

7.3 Methods

7.3.1 Study design

Prospective longitudinal study of people with chronic plantar heel pain.

7.3.2 Setting & participants

Cases with CPHP were recruited in southern Tasmania between November 2014 and May 2018 from general and specialist medical clinics, allied health practices, newspaper advertising, social media, sporting clubs and workplaces (hospitals and government departments), as summarised previously[7]. Participants were invited back for a follow up visit one-year later, with re-assessments taking place between December 2015 and August 2017.

The study was approved by the Tasmania Health & Medical Human Research Ethics Committee (H0013616). All participants provided written informed consent.

7.3.3 Inclusion / exclusion

Cases were aged 18 and over with a clinical diagnosis of CPHP (described previously[7]), of at least 3 months duration. If heel pain was bilateral, the most symptomatic heel was assessed.

Potential cases at baseline were excluded if they had any contraindication to MRI, a history of previous foot/ ankle fracture or orthopaedic foot surgery, current ankle

pain, recent foot trauma or other orthopaedic, congenital, vascular, neurological, or painful lower limb condition that restricted mobility or activity in the preceding 3 months. Cases who had a corticosteroid or any other injection, shockwave therapy or steroid iontophoresis within the previous 6 months were excluded.

7.3.4 Sample size calculations

Based on previously published values for key exposures[7, 12], and assuming power of 80% and a two-tailed α of 0.05 with 10% loss to follow-up, we calculated that 220 cases were required at baseline to detect clinically important effects sizes longitudinally that were comparable to or smaller than effect sizes reported in the CPHP, tendinopathy and osteoarthritis literature.

7.3.5 Data collection

7.3.5.1 Outcomes

Foot pain and foot function were assessed by the Foot Health Status Questionnaire (FHSQ) (Cronbach's alpha 0.86, ICC=0.92)[12]. Quality of life was measured with the Assessment of Quality of Life scale, AQoL-6D[13] (Cronbach's alpha 0.94, ICC=0.85 to 0.88), (http://www.aqol.com.au/aqolquestionnaires/56.html).

7.3.5.2 Exposures

Except for foot posture which was not expected to change over the course of one year, all exposures were measured at baseline and 12 months as previously published[7]. Clinical measures were taken in a single session at both timepoints, in the same order, by the same experienced physiotherapist.

In brief, height was measured to the nearest 0.1cm using a stadiometer. Weight was measured to the nearest 0.1kg by a single set of calibrated scales (A&D Medical UC321-PL, Adelaide, South Australia), and body mass index calculated (weight(kg)/ht(m)^2). Ankle dorsiflexion (°) was measured by a gravity inclinometer (Plurimeter, Switzerland) placed on the mid anterior shin in a weightbearing lunge position with the knee flexed (ICC ≥0.88)[14]. Passive first metatarsophalangeal joint extension (°) was measured with the foot plantigrade in supine, as the mean of three goniometric measurements [15]. Maximum isometric ankle plantarflexor strength was measured in sitting as the highest score from three attempts with the lower limb strapped by inelastic belt about the knee to a digital scale (Excell GW, Taiwan;

sensitivity 0.05kg). Reliability was good to excellent for these measures [7]

Physical activity (PA) was measured by uniaxial accelerometer worn at the waist (Actigraph GT1M, Fort Walton Beach, Florida) monitored over 7 consecutive days[16]. Steps per day and mean counts per minute were measured, and physical activity classified as minutes spent in moderate to vigorous (MVPA), light and sedentary activity. Criteria for acceptable wear time, activity thresholds and data processing have been published previously[7].

Questionnaires recorded age, sex, menopausal status, smoking history, presence of morning stiffness symptoms (at any joint) and co-morbidities (diabetes or rheumatological disease). Symptoms of depression were measured by the Patient Health Questionnaire-9[17, 18] and pain-related catastrophising by the Pain Catastrophizing Scale[18]. Pain laterality, duration of symptoms, number of previous episodes and treatment history were also recorded. Presence of night pain was assessed at baseline only. The presence of neuropathic-like symptoms was assessed using the painDETECT questionnaire. Possible scores range from -1 to 38 with a score of 19 or greater considered likely to have a neuropathic component[10].

7.3.6 Statistical Analysis

Characteristics of cases at baseline and follow-up are described using mean (standard deviation) or median (interquartile range) for continuous variables and percentage (frequency) for categorical variables.

Mixed effects linear models were used to estimate the association of pain, function and quality of life outcomes with clinical and demographic exposures. We expect to observe fluctuation in these outcomes over time for individuals, rather than systematic increase or decrease, so we estimated separate within-person and between-person effects for time-varying predictors. If an exposure varied across time (based on mean change and examination of individual trajectory plots), it was modelled as a time-varying predictor[19] and decomposed into ‘between-person’ and ‘within-person’ effects. The between-person component is an individual’s average score for the exposure across occasions, whilst the within-person component is the deviation of an individual’s score at each occasion from their average score. Potentially important non time-varying exposures were also included using their

baseline values. All models were adjusted for baseline age, sex and BMI. All models included a random intercept for individuals, and we tested the contribution of a random coefficient for time to allow for differences in individual trajectories over time. We specified an independent covariance matrix for the random effects, and repeated observations for individuals were modeled using an independent residual structure.

Model building proceeded by combining predictors established as potentially important from prior research[7] into a common model. For the pain outcome model, we purposefully chose to include other pain descriptors as predictor variables to capture clinically important pain constructs that reflect different aspects of the multidimensional nature of pain[20]. For example, the painDETECT measures aspects of neuropathic pain quality rather than intensity or frequency as measured by the FHSQ. Night pain (as a baseline binary predictor only) has no reference to intensity, quality or frequency, but may capture pain information relating to other tissue or pain-based mechanisms. Inclusion of these variables satisfied model building assumption checks such as testing for the presence of multicollinearity. Model parsimony was assessed with likelihood ratio testing for nested models including whether model fit improved with the addition of random effects for time. Information criteria were used to assess model fit.

To handle missing data, we used inverse probability weighting, assuming data were missing at random[21, 22]. We estimated the probability of an outcome being observed by fitting a logistic regression model using the background characteristics age, sex, BMI, employment and marriage status, depression, and FHSQ pain score, for which complete data were available. All models were weighted by the inverse of their estimated probabilities of being observed.

Model assumptions were checked by examining level 1 time-specific and level 2 person-specific residuals for normality and constant variance. All analyses were performed using Stata 16 (Stata Corp., College Station 16, TX, USA).

7.3.7 Patient and public involvement

No patients or the public were involved in the planning, design, implementation or interpretation of this study, nor the writing or editing of this document.

7.4 Results

Of 220 cases assessed at baseline, 210 returned surveys and 202 attended clinical re-assessment one year later (**Figure 7-1**).

Participants lost to follow up had similar baseline characteristics to those retained in the study except for having worse pain catastrophising, depression and painDETECT scores (**Supplementary Table 7-5**).

From baseline to follow up, mean pain scores decreased by 56% (from 48.8 to 75.9), foot-related function improved by 31% (from 65.7 to 86.1), and AQOL scores improved 7% (from 76.4 to 81.6) (**Table 7-1**). Twenty-one percent of participants reported no symptoms at follow-up (FHSQ =100/100), and 67% improved by at least the minimally important difference detectable by this scale (13 points)[23].

From baseline to follow-up, the number of cases reporting morning stiffness decreased, and both the median score and number reaching clinically important cut-points for painDETECT and pain catastrophising also decreased. These factors were subsequently modelled as time-varying predictors. Depression (PHQ-9), BMI, PA, multisite pain and clinical measures of the foot and ankle were similar at baseline and follow up and so modelled using baseline values as was night pain which was common at baseline (65%).

In the model adjusted for age and sex, higher average painDETECT scores were associated with greater pain (lower average FHSQ scores) over the 12-month study period (beta= -1.89, 95% CI -2.30 to -1.48) (BP, between-person effect) **(Table 7-2**). In addition, at times when an individual had a higher painDETECT score than their personal average, their pain at that time was also higher (beta= -1.21, 95% CI -1.82 to -0.60) (WP, within-person effect). When adjusted for age and sex, higher average PCS scores and PCS scores which fluctuated higher than the personal average were associated with worse pain outcomes at 12 months (BP beta= -0.96, 95% CI -1.37 to -0.55, WP beta= -1.05, 95% CI -1.61 to -0.48). In the model adjusted for age and sex, baseline night pain and baseline BMI were associated with greater pain as indicated by lower average FHSQ pain scores (night pain -9.67, 95% CI -14.35 to -4.99, BMI -0.76, 95% CI -1.24 to -0.28). In the fully adjusted model, the associations with pain persisted for the within and between person effects of painDETECT and

pain catastrophising and baseline night pain.

In models adjusted for age and sex, worse average function outcomes at 12-months were associated with higher average painDETECT (BP beta= -2.24, 95% CI -2.77 to -1.70), and higher average PCS scores (BP beta= -1.56, 95% CI -1.90 to -1.20). Similarly, baseline depression (beta= -2.84, 95% CI -3.52 to -2.17) and BMI (beta= -1.16, 95% CI -1.72 to -0.59) were associated with worse, and ankle plantarflexor strength (beta= 0.19, 95% CI 0.05 to 0.33) better, average foot-related physical function scores. These associations persisted in the fully adjusted model, and in addition, when an individual had a higher painDETECT score than their personal average, their function at that time was worse (WP beta= -0.75, 95% CI -1.40 to -0.11).

When adjusted for age and sex, higher average PCS scores (BP beta= -0.66, 95% CI -0.79 to -0.53) were associated with worse average QOL outcomes at 12-months. At times when an individual's PCS score fluctuated higher than their personal average, their QOL score at that time improved (WP beta = 0.17, 95% CI 0.03 to 0.32). In the age and sex adjusted model baseline depression (beta = -1.61, 95% CI -1.89 to -1.33), multisite pain (beta= -3.06, 95% CI -4.04 to -2.07) and BMI (beta= -0.54, 95% CI -0.80 to -0.29) were associated with worse average QOL scores, and baseline ankle plantarflexor strength, better average QOL scores at 12-months (beta= 0.09, 95% CI 0.03 to 0.15). The association with these factors persisted in the fully adjusted model except for the WP effect for PCS.

Models not weighted for missing values are provided in the Supplementary tables for comparison (**Supplementary Tables 7-6**, **7-7**, **7-8**). Model fit was not improved by adding time as a random effect.

7.5 Discussion

Most clinical predictors of pain, function and quality of life at 12 months are psychological and symptom-based rather than foot-specific physical measures. This indicates that pain mechanisms and pain beliefs may be more important for CPHP prognosis and causation than physical factors. These findings could be used to predict individuals at risk of poorer prognosis and assist with how we sub-group and subsequently treat CPHP. Future research should determine if targeting treatments

according to the CPHP phenotypes apparent in these findings can result in more effective management of this condition. Testing the application of pain science principles, weight loss and ankle plantarflexor strengthening to sub-groups of CPHP where these impairments are identified, are potential avenues for future research.

The novel finding that neuropathic symptoms predict worse pain and foot-related function 12-months later indicates that non-nociceptive pain mechanisms are important in CPHP. This has implications for treatment, as effective treatment should target the specific mechanism of pain. Having access to a simple tool such as the painDETECT that is sensitive to neuropathic pain is important as the clinical assessment of nerve-injury in CPHP is notoriously difficult[8], yet original case reports based on electrodiagnostic testing identify nerve injury in up to 15-20% of CPHP cases[9, 24]. Using the traditional painDETECT cut-point of ≥19 as 'probably neuropathic' we found that 7.7% of cases met this criteria at baseline. It is unclear if this cut-point is optimal for CPHP. Further, the painDETECT was originally developed in a cohort of LBP patients to differentiate neuropathic from nociceptive pain[10], and did not directly consider nociplastic mechanisms. As both of these non-nociceptive mechanisms have been identified in CPHP[25, 26], the potential benefits of augmenting use of the painDETECT with tools sensitive to nociplastic pain such as the Central Sensitisation Index[27], may be an area of future research. The identification of neuropathic pain opens up care to approaches not routinely practiced in CPHP. Particularly in the presence of neuropathic 'gain', this includes medication classes targeting neuropathic (or nociplastic) pain processes including topicals such as capsaicin, desensitisation techniques, graded motor imagery, exercise and neural mobilisation techniques, and pain science education to minimise an over-protective pain system response[28].

Pain catastrophising beliefs are independently associated with a worse prognosis for all three outcomes, reinforcing the importance of psychological factors in CPHP. When an individual experiences pain, they make an individual and highly contextual 'threat' appraisal of that pain. According to the Fear-Avoidance Belief model[29], one possible outcome is that the pain *is* considered threatening and warrants a protective response. This leads to a cascade of events including catastrophising thoughts, fear, hypervigilance, avoidance, disuse and disability[29]. A fear-dominant response leads

to movement consequences that may explain poorer foot-related physical function. Whilst pain intensity and pain catastrophising (PC) are associated[30], the two should not be conflated as the association between persistent musculoskeletal pain states such as LBP and PC persist after adjusting for pain severity[31]. This indicates the cognitive mechanism underlying PC is independent of pain intensity and targeting pain alone may therefore be insufficient. Treatments for CPHP should address psychological impairments where identified and could include cognitive strategies to reconceptualise pain by 'explaining pain', which has been shown to be effective at reducing pain catastrophising[32].

Worse foot-related physical function and quality of life, but not pain, was predicted by higher baseline scores on the PHQ-9 depression scale. The effect of depression on QOL is well established, especially through role limitations associated with poorer physical functioning, emotional and mental health, vitality and social functioning[33]. The effects of depression on physical function likely reflects a bidirectional relationship[34]; symptoms of depression such as low energy levels, low mood, poor sleep, and decreased physical activity are negatively associated with physical function, but reduced physical engagement and social roles will in turn support a depressive affect[35]. Overall, these findings reinforce the complex, biopsychosocial nature of persistent heel pain and the need to consider person-level factors beyond the foot.

Ankle plantarflexor strength is a potentially modifiable physical factor with the most consistent positive effect on foot outcomes (function and QOL). There is a logical connection between increased ankle plantarflexor strength and improved function and QOL given these muscles are critical to mobility and gait (function), and potentially therefore social engagement (QOL). However, baseline ankle plantarflexor strength did not predict improvements in pain- mean strength scores changed little over 12 months but 2/3 of cases reached the minimum important difference for improvement in FHSQ pain. These results challenge the value of calf strengthening as an intervention for pain. This is consistent with findings for calf-based exercise loading programmes that include dosed/ self-dosed protocols[36] and isometric and isotonic[37] exercise regimens that did not find comparably better short-term effects for pain. Another high-load calf strengthening programme did find a

medium-term benefit (at 3 months) for pain compared to a stretching regimen[38]. These papers specifically studied a plantar fasciopathy sub-group of CPHP (defined by US-confirmed plantar fascia thickening exceeding 4mm) and it is unclear if these conclusions extend to other phenotypes of CPHP. Importantly, they did not document the presence of strength impairments upon entry into the study, nor whether or to what degree the intervention improved strength. The small sample sizes employed in these studies (n=20-70) are a further limitation. Calf loading programmes may be valuable to address symptoms related to function and quality of life, but further research is required to understand the role of strengthening for pain outcomes in the presence of strength impairments.

Higher body mass index is consistently associated with CPHP[7, 39] and our findings confirm a longitudinal association between baseline BMI and poorer function and QOL outcomes, but not pain. Weight loss is frequently recommended in CPHP management guidelines[40], however there is very little guidance on how changing BMI affects prognosis and little real-world data to support its implementation or efficacy in CPHP[41]. As BMI remained relatively stable across the 12 months it was not evaluated as a time-varying term, and thus we cannot comment on how *change* in BMI affects prognosis. Limited information supporting weight loss for CPHP comes from a single observational study of a sub-group of bariatric individuals with CPHP (n=163) assessed pre and post bariatric surgery[42]. Ninety percent of cases reported symptom resolution a mean of 35 months after bariatric surgery. This study was uncontrolled and so it is unclear whether improvement can be attributed to weight loss alone. Another study compared people reporting general foot pain who received bariatric surgery (n=29) with wait list controls (n=18). No between group comparison was performed but foot pain improved at 6 months in those receiving surgery, but not in controls[43], suggesting the potential for an effect of weight loss. Overweight/ obesity is a major health burden in its own right, and more work including RCTs are required to understand whether weight change is meaningful and feasible in the clinical context of CPHP. If so, do important (mass) thresholds exist, and are they driven by mechanical, metabolic or psychologic factors?

Multisite pain predicts poorer QOL, adding to the list of symptom-based factors that indicate that pain processes are important in CPHP mechanisms. The longitudinal

findings for multisite pain confirm a previous cross-sectional association with having CPHP[7], and with research that demonstrates that number of pain sites is linearly related with poorer HR QOL[44]. As multisite pain is associated with higher risk for future pain and greater healthcare resource access and costs[45, 46) (47], investigating ways to target multisite pain itself may have merit. Further, multisite pain was relatively stable across the year indicating that time alone is unlikely to address this potential risk factor.

Night pain was common at baseline and associated with worse pain outcomes. We have previously demonstrated that BMLs are prevalent in CPHP (50%)[48], and past research has demonstrated a relationship between night pain and this form of bone lesion[49]. Further exploration of this relationship may be useful to determine if night pain may act as a clinical marker for a bone pain phenotype, especially as there is preliminary evidence that specific modalities (such as shockwave) may preferentially target this condition[50) (51].

The strengths of this study are the large case sample, high follow-up rate, detailed longitudinal exposure set including for the first-time neuropathic and psychological factors, and an analysis approach that catered for the time-varying nature of key exposures and the random effect of individuals across time (by allowing for within-person effects). Comparison of weighted and unweighted models confirms that missing values did not affect outcomes. Results are strengthened for findings that demonstrate a significant WP association, as WP analyses reduce confounding by controlling for individual variability across time. We did not adjust for treatments being received at baseline as these were very diverse and we lacked sufficient data (dose, adherence, medical record confirmation) for meaningful analysis. We also considered treatment may be a mediator rather than a potential confounder for pain outcomes.

7.6 Conclusion

Worse pain, foot-related function and quality of life at 12 months was mostly predicted by a combination of psychological and symptom-based factors rather than foot-specific physical measures. These factors that could be used to predict individuals at risk of poorer prognosis and assist with tailoring and targeting CPHP

treatments. Future research should determine if targeting treatments according to the CPHP phenotypes apparent in these findings can result in more effective management of this condition. Testing the application of pain science principles, weight loss and ankle plantarflexor strengthening to CPHP sub-groups where these impairments are identified, are potential such avenues for future research.

Figure 7-1 Participant Flow

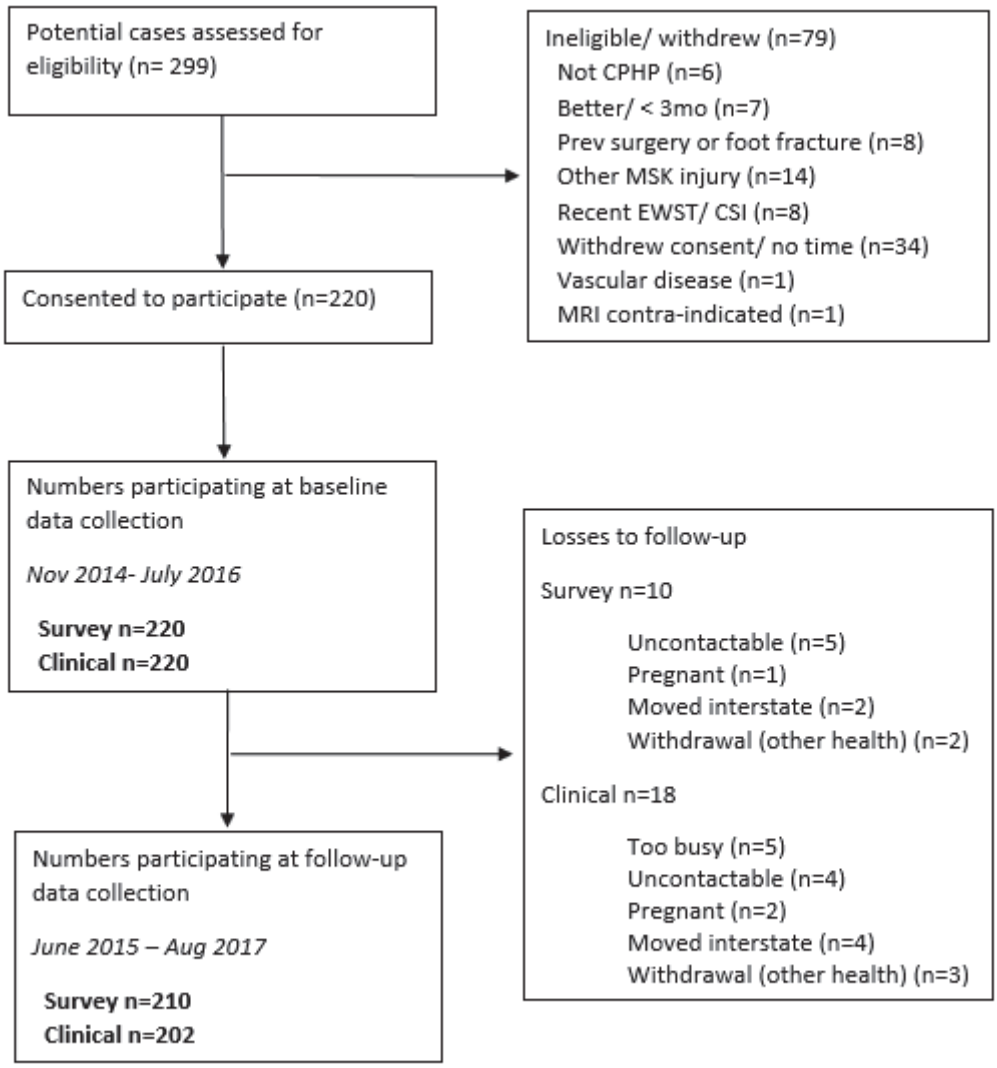

Table 7-1 Characteristics of cases at baseline and follow-up.

		Baseline			Follow up		
		Mean	**SD**	**n**	**Mean**	**SD**	**n**
female %(n)		60 (131)		220	60 (126)		210
age (yrs)		54.78	12.13	220	55.98	12.04	211
smoke ever %(n)		33.2 (73)		220	31.4 (66)		210
diabetes %(n)		3.7 (8)		218	3.8 (8)		202
inflammatory %(n)		8.7 (18)		207	10.0 (20)		201
high cholesterol %(n)		25 (55)		220	23.4 (49)		209
osteoporosis/paenia %(n)		12.1 (7)		58	12.7 (8)		63
morning stiffness %(n)		22.2 (48)			13.9 (29)		
multisite pain %(n)	0	18.6 (41)			19.1 (40)		
	1	21.8 (48)			19.5 (41)		
	2	17.3 (38)			15.7 (33)		
	≥3	42.3 (93)			45.7 (96)		
BMI (kg/m^2)		29.1	5.4	220	29.5	5.5	202
ankle DF, knee flexed (deg)		43.3	6.7	220	43.3	7.0	202
ankle PF strength (kg)		90.5	23.8	220	91.2	24.6	201
1st MTP ext ROM (deg)		70.3	15.1	220	71.7	16.4	202
		med	**iqr**		**med**	**iqr**	
PHQ-9 (depression) (/27)		2	(1,5)	220	2	(0,5)	209
mod depression (≥10)[b] %(n)		15.5 (34)		220	10.5 (22)		209
painDETECT (/38)		9	(5,13)	220	3	(0,8)	209
'probably neuropathic' (≥19)[c] %(n)		7.7 (17)		220	5 (10)		210
PCS (catastrophising) (/52)		8	(4,16)	220	3	(0,9)	209
catastrophiser (>20)[d] %(n)		17.3 (38)		220	7.2 (15)		209
Physical activity		**med**	**iqr**		**med**	**iqr**	
average steps/day		7760	(6046, 9871)	211	7702	(5837, 9839)	182
MVPA (mins/day)		37.7	(16.9, 55.4)	211	32.0	(18.3, 61.1)	198
sedentary (mins/day)		491	(437, 545)	211	507	(442, 551)	183
Outcomes							
FHSQ pain (/100)		48.8	21.6	220	75.9	23.3	210
'improved'[a] (≥13) %(n)					67 (140)		210
FHSQ function (/100)		65.7	27.8	220	86.1	22.3	210
AQOL (/100)		76.4	10.8	220	81.6	9.7	209

Mean (SD) unless specified otherwise.

SD standard deviation, **FHSQ** Functional health status questionnaire (higher better), **AQOL** Assessment of quality of life- 6D (higher better), **BMI** body mass index, **DF** dorsiflexion, **PF** plantarflexor, **MTP** metatarsophalangeal, med median, **iqr** interquartile range, **PHQ-9** Patient health questionnaire-9 (higher worse), **PCS** Pain catastrophising scale (higher worse), **MVPA** moderate to vigorous physical activity

[a] FHSQ pain minimal important difference ≥13 points, Landorf 2010[23]

[b] Kroenke et al, 2001[52]

[c] Freynhagen et al, 2006[10]

[d] Slepian et al, 2014[53]

Table 7-2 FHSQ Pain: simple (age- & sex-adjusted) and full multivariable models

FHSQ pain[b]	**Simple MV (age- & sex-adj)**[a]			**Full MV**[a]		
	Coeff	95% CI		Coeff	95% CI	
painDETECT[c] BP	**-1.89**	-2.30	-1.48	**-1.28**	-1.77	-0.79
painDETECT WP	**-1.21**	-1.82	-0.60	**-1.26**	-1.92	-0.60
pain catastrophising[d] BP	**-0.96**	-1.37	-0.55	**-0.57**	-0.98	-0.16
pain catastrophising WP	**-1.05**	-1.61	-0.48	**-0.73**	-1.26	-0.19
BMI[e] (kg/m^2)	**-0.76**	-1.24	-0.28	-0.26	-0.64	0.12
night pain[e f]	**-9.67**	-14.35	-4.99	**-4.56**	-8.26	-0.85

[a] inverse probability weighted for missing data, Bold significant $p<0.05$

[b] Foot health status questionnaire pain, 0-100, higher is better (less pain)

MV multivariable, **BP** between-person effect, **WP** within-person effect, **BMI** body mass index, **CI** confidence interval

[c] painDETECT neuropathic symptoms questionnaire, -1 to 38, higher worse

[d] Pain catastrophising scale 0-52, higher worse

[e] baseline factors

[f] present/ absent

Table 7-3 FHSQ Function: simple (age- & sex-adjusted) and full multivariable models

FHSQ function[b]	Simple MV (age- & sex-adj)			Full MV[a]		
	Coeff	95% CI		Coeff	95% CI	
painDETECT[c] BP	**-2.24**	-2.77	-1.70	**-0.99**	-1.51	-0.48
painDETECT WP	0.03	-0.70	0.75	**-0.75**	-1.40	-0.11
pain catastrophising[d] BP	**-1.56**	-1.9	-1.20	**-1.00**	-1.40	-0.59
pain catastrophising WP	-0.02	-0.57	0.53	-0.10	-0.63	0.44
depression[e f]	**-2.84**	-3.52	-2.17	**-0.93**	-1.69	-0.17
ankle plantarflexor strength[f] (kg)	**0.19**	0.05	0.33	**0.13**	0.03	0.23
BMI[f] (kg/m^2)	**-1.16**	-1.72	-0.59	**-0.48**	-0.96	0.00

[a] inverse probability weighted for missing data, Bold significant $p<0.05$
[b] Foot health status questionnaire function, 0-100, higher is better function
MV multivariable, **BP** between-person effect, **WP** within-person effect, **BMI** body mass index, **CI** confidence interval
[c] painDETECT neuropathic symptoms questionnaire, -1 to 38, higher worse
[d] Pain catastrophising scale 0-52, higher worse
[e] Patient Health Questionnaire-9 survey, 0-27, higher worse
[f] baseline factors

Table 7-4 Quality of Life: simple (age- & sex-adjusted) and full multivariable models

Quality of Life[b]	**Simple MV (age- & sex-adj)**[a]			**Full MV**[a]		
	Coeff	95% CI		Coeff	95% CI	
pain catastrophising[c] BP	**-0.66**	-0.79	-0.53	**-0.37**	-0.51	-0.22
pain catastrophising WP	**0.17**	0.03	0.32	-0.12	-0.28	0.04
depression[d,f]	**-1.61**	-1.89	-1.33	**-0.93**	-1.27	-0.59
ankle plantarflexor strength[f] (kg)	**0.09**	0.03	0.15	**0.08**	0.03	0.12
multisite pain[e,f]	**-3.06**	-4.04	-2.07	**-1.30**	-1.96	-0.63
BMI[f] (kg/m^2)	**-0.54**	-0.80	-0.29	**-0.22**	-0.37	-0.06

[a] inverse probability weighted for missing data, Bold significant $p<0.05$

[b] Assessment of quality of life scale-6D, 0-100, higher is better

MV multivariable, **Between**: between-person effect, **Within**; within-person effect, **BMI** body mass index, **CI** confidence interval

[c] Pain catastrophising scale 0-52, higher worse

[d] Patient Health Questionnaire-9 survey, 0-27, higher worse

[e] number of pain sites by region, beyond heel, continuous measure (0,1,2,3 or more)

[f] baseline factors

[g] Foot heath status questionnaire 0-100, higher better (less pain)

7.7 Supplementary tables

Table 7-5 Characteristics of missing data.

	Baseline Mean (SD) (n=220)	Follow-up Mean (SD)	Baseline values for those lost to follow-up Mean (SD)	N missing
Female sex % (n)	60 (131)	60 (126)	50 (5)	10
Age (years)	54.78 (12.13)	55.98 (12.04)	52.71 (13.33)	10
BMI (kg/ m^2)	29.1 (5.4)	29.5 (5.5)	29.48 (5.97)	18
FHSQ pain (/100)	48.8 (21.6)	75.9 (23.3)	51.81 (23.18)	10
FHSQ function (/100)	65.7 (27.8)	86.13 (22.3)	55.63 (34.54)	10
AQOL (/100)	76.4 (10.8)	81.6 (9.7)	68 (11.98)	11
Pain catastrophising scale (/52)	11.6 (10.9)	6.4 (8.8)	22 (10.54)	11
painDETECT (/38)	9.64 (5.93)	5.04 (6.17)	13.8 (7.76)	10
PHQ-9 (/27)	3.67 (4.01)	2.97 (3.29)	4.40 (2.32)	11

SD standard deviation, **BMI** body mass index, **FHSQ** Foot health status questionnaire, **AQOL** Assessment of quality of life-6D, **PHQ-9** Patient health questionnaire

Table 7-6 FHSQ Pain; multivariable model (Not weighted for missing values)

FHSQ pain[b]	**Full MV- unweighted**[a] Coeff	95% CI	
painDETECT[c] BP	**-1.26**	-1.70	-0.83
painDETECT WP	**-1.27**	-1.91	-0.64
pain catastrophising[d] BP	**-0.58**	-0.82	-0.34
pain catastrophising WP	**-0.74**	-1.17	-0.30
BMI[e] (kg/m^2)	-0.27	-0.64	0.10
night pain[e]	**-4.75**	-8.88	-0.61

MV multivariable, **BP** between-person effect, **WP** within-person effect, **BMI** body mass index, **CI** confidence interval

[a] Bold significant $p<0.05$
[b] Foot health status questionnaire pain, 0-100, higher is better (less pain)
[c] painDETECT neuropathic symptoms questionnaire, -1 to 38, higher worse
[d] Pain catastrophising scale 0-52, higher worse
[e] baseline factors

Table 7-7 FHSQ Function; multivariable model (Not weighted for missing values)

FHSQ function[b]	**Full MV- unweighted**[a]		
	Coeff	95% CI	
painDETECT[c] BP	**-0.98**	-1.45	-0.51
painDETECT WP	**-0.75**	-1.39	-0.12
pain catastrophising[d] BP	**-0.10**	-1.30	-0.70
pain catastrophising WP	-0.12	-0.57	0.33
depression[e,f]	**-0.97**	-1.63	-0.31
ankle PF strength[f] (kg)	**0.13**	0.02	0.23
BMI[f] (kg/m^2)	**-0.49**	-0.90	-0.08

MV multivariable, **BP** between-person effect, **WP** within-person effect, **BMI** body mass index, **CI** confidence interval, **PF** plantarflexor

[a] Bold significant $p<0.05$
[b] Foot health status questionnaire pain, 0-100, higher is better (less pain)
[c] painDETECT neuropathic symptoms questionnaire, -1 to 38, higher worse
[d] Pain catastrophising scale 0-52, higher worse
[e] Patient health questionnaire- 9, 0-27, higher worse
[f] baseline factors

Table 7-8 Quality of life; multivariable model (Not weighted for missing values)

Quality of Life[b]	**Full MV- unweighted**[a]		
	Coeff	95% CI	
pain catastrophising[c] BP	**-0.36**	-0.48	-0.25
pain catastrophising WP	-0.13	-0.28	0.02
depression[d]	**-0.94**	-1.22	-0.66
ankle plantarflexor strength[e] (kg)	**0.08**	0.03	0.12
multisite pain[e,f]	**-1.31**	-2.10	-0.53
BMI[e] (kg/m^2)	**-0.22**	-0.39	-0.05

MV multivariable, **Between**: between-person effect, **Within**; within-person effect, **BMI** body mass index, **CI** confidence interval

[a] Bold significant p<0.05
[b]Assessment of quality of life scale-6D, 0-100, higher is better
[c] Pain catastrophising scale 0-52, higher worse
[d] Patient Health Questionnaire-9 survey, 0-27, higher worse
[e] baseline factors
[f] number of pain sites by region, beyond heel, continuous measure (0,1,2,3 or more)
[g]Foot health status questionnaire, 0-100, higher is better (less pain)

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Chapter 8

Summary, implications and future directions

8. Future Directions

8.1 Overview

Chronic plantar heel pain is a heterogeneous condition that has resisted a clear description of risk and prognostic factors. The assumption that it runs an uncomplicated and short course is incorrect for many and underestimates the high personal burden. Our poor understanding of risk factors hampers our ability to recognise important sub-groups, and therefore to provide effective, targeted intervention.

Much of our understanding of aetiology and subsequent management strategies for CPHP are linked to legacy views of a mechanical condition that requires mechanical intervention. This is inconsistent with the growing body of knowledge for musculoskeletal pain states such as osteoarthritis (OA), back pain and tendinopathy that emphasise the multidimensional nature of persistent pain. A modern view of chronic pain encompasses biological, cognitive, affective and social dimensions, yet there has been very little recognition of most of these aspects in CPHP research. This is not to say that recognising local drivers of pain is not important. Clinically measured factors, or imaging-based biomarker assessment can provide insight into the biological aspects of disease.

The aims of this thesis were to better understand the range of clinical and imaging factors associated with the risk of having CPHP, and to determine what clinical factors are associated with chronicity.

The **key findings are:**

1. Clinical risk factors for CPHP largely originate outside of the foot, including psychological and symptom-based factors and anthropometric measures of BMI and waist girth. This conclusion is supported by data from both case-control and longitudinal analyses. Multisite pain (OR 2.76; 95% CI 1.29 to 5.91 (pain at 1 other site), to OR 10.45; 95% CI 3.66 to 29.81 (pain at 4 or more other sites)) and pain catastrophising beliefs (none, some or catastrophiser) (OR 2.91; 95% CI 1.33 to 6.37 (some), OR 6.79; 95% CI 1.91 to 24.11 (catastrophising)) have case-control associations with having CPHP.

Neuropathic symptoms, pain catastrophising beliefs and baseline night pain symptoms, depression and multisite pain are longitudinally associated with CPHP outcomes (within-person effect range β= -0.73 to -1.26, between-person effect size β= -0.37 to -1.28, baseline factor effect size β= -0.93 to -4.56).

2. Waist girth (cm) (OR 1.06; 95% CI 1.03 to 1.09) has a case-control association with CPHP and baseline BMI is longitudinally associated with worse function (β= -0.48, 95%CI -0.96 to 0.00) and QOL (β= -0.22, 95%CI -0.37 to 0.06) outcomes.

3. Ankle plantarflexor strength (kg) was the only clinical foot-related variable consistently associated with having CPHP (case-control OR 0.98; 95% CI 0.97 to 0.99) and with foot function and QOL longitudinally (kg) (function β= 0.13, 95%CI 0.03 to 0.23; QOL β= 0.08, 95%CI 0.03 to 0.12).

4. All measures of the plantar fascia (thickness, echogenicity, T2-weighted and vascular signal) and plantar calcaneal bone marrow lesions are independently associated with having CPHP in case-control analyses. There was no association with other imaging biomarkers such as plantar fat pad signal, and the multivariable association with larger plantar spurs disappears when adjusted for the presence of other imaging biomarkers.

5. Bone marrow lesions are common (51%) but have not been previously quantified in CPHP. Their presence and size are associated with CPHP risk (mm^2, OR 1.03 (95% CI 1.02 to 1.05)). Our findings confirmed previous associations of CPHP with PF thickness and hypoechogenicity and demonstrated associations with additional PF characteristics including for the first-time quantification of intra-fascial signal (penetrating > 50% of dorsoplantar width, OR 12.12 (95% CI 5.36 to 27.42)) and a perfect association with vascular signal.

6. The presence of CPHP modifies the effect of ankle plantarflexor strength on bone density and microarchitecture outcomes in the plantar calcaneus, and

the effect of BMI on bone density and microarchitecture outcomes in the mid-calcaneum. Beneficial associations of ankle plantarflexor strength with plantar trabecular bone density, trabecular thickness and separation and trabecular bone volume fraction were reduced in people with CPHP (ankle plantarflexor strength -case interactions all $p< 0.02$). Beneficial associations of BMI with mid-calcaneal trabecular density, thickness and trabecular bone volume fraction were also reduced in cases (BMI-case interactions all $p< 0.02$).

8.2 Implications of study

8.2.1 Implications for understanding mechanisms and causation in CPHP.

This thesis provides evidence to challenge the view of clinical foot factors in isolation, and to a lesser extent mechanical drivers of foot pain having major roles in CPHP. Instead, potential roles of pain system processes, psychological and metabolic factors in CPHP are highlighted.

The predominance of associations of markers of pain system processes and psychological factors with CPHP in both case-control and longitudinal analyses is consistent with a biopsychosocial view of persistent musculoskeletal pain. The findings strengthen the argument that nociplastic and neuropathic pain mechanisms, and cognitive mechanisms underlying pain beliefs, are important in CPHP. This understanding is not new for well-studied areas such as persistent LBP, but these principles have yet to be properly considered in CPHP where understanding is informed by a legacy view of foot-specific and mechanical aetiologies. The longitudinal findings supporting either or within- and between-person effects for pain catastrophising beliefs and neuropathic symptoms across all three outcomes, provides particularly strong evidence for this. A range of other baseline factors including multisite pain, night pain and depression further speaks of mechanisms attuned to sensitisation, nerve processes and potentially systemic mechanisms, as opposed to mechanical aetiologies.

Associations with body mass index have been widely reported and this is the most consistent (case-control) association with CPHP[1]. We add to this the important finding of a case-control association with waist girth and confirm a longitudinal association for baseline BMI with foot-related physical function and QOL outcomes.

The association with waist girth strengthens the argument for metabolic rather than mechanical or load-based mechanisms. The metabolic and meta-inflammatory effects of central adiposity are well recognised. The negative consequences of metabolic risk factors for musculoskeletal disease are only recently recognised however[2, 3], and these systemic mechanisms may also be implicated in CPHP.

My case-control and cross-sectional data for imaging biomarkers and bone density and microarchitecture provide insight into local patho-anatomical contributors to CPHP. Associations with measures of the plantar fascia and plantar BMLs highlight the contribution of tissues on both sides of the plantar enthesis. This is confirmed by HR-pQCT findings demonstrating sclerotic type changes at the enthesis in univariable analyses and a modified bone- load coupling response in the presence of CPHP in multivariable models. This thesis provides strong evidence for potential roles of other previously under-recognised bone abnormalities (but not necessarily spurs) in heel pain. As well as morphology (plantar fascia thickness), these abnormalities include measures of signal variation ((BML, intra-fascial, vascular and potentially hypoechogenicity). These markers are seen on fluid sensitive T2-weighted sequences and reflect differences in the fluid state/ haemodynamics of tissue, potentially signalling sites of local tissue stress. As opposed to structural measures signal is changeable over time and therefore potentially modifiable[4].

The associations of imaging biomarkers come only from case-control analyses, so I cannot attribute causation, nor determine whether they are markers of other disease processes or predict change in heel pain. Nonetheless, case-control analyses do seek to look back in time from disease to exposure to estimate relative risk with causal intent. Measures of association form one part of the evidence chain for causation, and I believe these findings reflect biologic plausibility. It is therefore possible that these markers could be potential causal contributors to plantar heel pain. This may seem to sit in juxtaposition to the strong central and systemic arguments made for heel pain mechanisms, but it is possible that one or more of these abnormalities could be a pain source that triggers sensitisation processes or fear beliefs.

Physical activity (PA) measured objectively, regardless of intensity, was not associated with having CPHP. I could find no case-control evidence to support the

notion that too little or too much activity increases the risk for having CPHP. I acknowledge the difficulty in representing the relationship between physical activity and heel loading by these categories, where for example sedentary time might involve prolonged standing (low PA, high heel loads), and conversely high MVPA efforts could involve low heel loads (eg cycling). Further, this case-control analysis did not capture historical levels of PA and cannot clarify whether activity levels in cases changed as a result of pain, although longitudinal data suggests that PA was relatively stable across time. The role of PA in CPHP therefore, in terms of potential mechanical overload or metabolic underload, remains unclear.

8.2.2 Implications for clinical practice

The assessment of CPHP needs to take into account a wide range of tissues and mechanisms. Beyond the plantar fascia, this includes bone, nerve tissue, fat (adiposity) and the brain. Understanding these different domains could clinically define CPHP phenotypes and be used in a more precision or personalised medicine approach to this condition[5]. There may be mechanical, metabolic, bone, plantar fascial, psychosocial, neuropathic and nociplastic contributors to CPHP. The individual mix of these factors requires clinicians to provide an individualised and person-centred assessment of CPHP.

Managing persistent musculoskeletal pain requires a biopsychosocial framework[6], and these results confirm that CPHP is no different. This may start with clincians having a greater awareness of the potential role of non-foot factors and considering assessing these in people with CPHP. Measuring neuropathic symptoms with scales such as the painDETECT, pain catastrophising beliefs with the PCS, depression with the PHQ-9 and waist girth with a tape measure is required. Symptom based factors that have predictive capacity such as multisite and night pain are also easy to measure but have not been reported as assessment targets in the CPHP literature.

Treating negative pain beliefs and symptom-based measures of nociplastic change and sensitivity is not often considered in CPHP. Current guidelines or reviews are largely silent on this component of intervention[7-10], although a recent review of expert clinical opinion recommended patient education incorporating pain science[11]. This included a component of pain science, although the authors acknowledged the efficacy of this inclusion had not been tested in isolation. Pain science principles

including ‘explain(ing) pain’, graded motor imagery, graded exercise exposure, desensitisation, and potentially specific neuropathic or centrally acting medications, are less accessed (and unstudied) forms of intervention for CPHP, that warrant consideration.

Depression and obesity are potential risk factors for chronic plantar heel pain but whether addressing these issues would improve CPHP outcomes is unknown. Both these factors are modifiable, but require complex, sustained and interdisciplinary care that highlights the need for a wider view of CPHP, beyond clinical foot factors. There is limited support for weight loss coming from a cohort of individuals (n=163) who had CPHP prior to undergoing bariatric surgery[12]. Ninety percent achieved symptom resolution a mean of 35 months later, although the lack of control group means it is difficult to ascribe this improvement to weight loss alone. In another post bariatric surgery group with wait-list controls, at 6-months foot pain (not CPHP specific) only improved in the surgical group[13]. In this study depressive symptoms, but not BMI was associated with pain outcomes, indicating a complex and potential mediating role for non-mechanical factors beyond the foot. From a holistic perspective, addressing obesity and depression are important for a patient’s well-being and contribute to a wide range of health issues beyond the foot. Clinicians should be aware these conditions can be present in CPHP and take steps to address these, including onward referral.

My results challenge the value of calf strengthening as an intervention for pain. These findings are consistent with a recent best practice guide that failed to find consistent support for resistance exercises, nor a clear set of recommendations based on expert consensus[11]. A recent study comparing isometric and isotonic[14] calf loading exercise with walking controls did not find comparably better short-term effects for pain [14], and dosed versus self-dosed calf loading protocols[15] yielded similar results with clinically questionable gains in patient accepted symptom state. One high-load calf strengthening programme did find a medium-term benefit (at 3 months) compared to a stretching for pain [16]. These studies were of a plantar fasciopathy sub-group of CPHP (defined by US-confirmed plantar fascia thickening exceeding 4mm) and it is unclear if these conclusions extend to other phenotypes of CPHP. Importantly, they did not document the presence of strength impairments

upon entry into the study, nor if strength changed as a result of intervention. Calf loading programmes may be valuable to address symptoms related to function and quality of life, but further research is required to understand the role of strengthening for pain outcomes, specifically in the presence of strength impairments.

The clinical implications of the possible roles of imaging biomarkers are less certain as this requires longitudinal information to determine if changes in these factors is associated with changes pain, foot function or quality of life. I discuss the implications for research of this in the next section.

8.3 Future directions

Clinical phenotyping is only useful if it informs clinical practice and improves treatment outcomes. Systematic reviews of interventions for treating CPHP[10, 17] identify an array of treatments applied almost exclusively at the foot. Treatments have not historically been aligned to the bone (BML), psychological, pain mechanisms or metabolic phenotypes that we have identified. Few if any address CPHP within a biopsychosocial framework. There is a pressing need to strengthen evidence with clinical trials that test the value of phenotyping heel pain to tailor treatments. Further research qualifying these phenotype sub-groups is also required.

Addressing catastrophising pain beliefs with cognitive and pain-science education with treatments such as cognitive-behavioural therapy, active physical approaches such as exercise and combinations of these reduces catastrophising in chronic LBP[18]. Treatments that de-threaten movement, address unhelpful beliefs, reduce hypervigilance and improve coping skills can help address the fear-avoidance cycle that overprotects[19, 20]. These interventions could be tested in CPHP, in people with high PCS scores. Pain beliefs are modifiable, but as pain beliefs persist independent of pain intensity[21], addressing pain catastrophising entails a specific intervention that does more than just treat pain.

The painDETECT assesses neuropathic symptoms. A treatment trial that targets neuropathic symptoms with nerve specific interventions in people with CPHP identified by high painDETECT scores, could determine the utility of this phenotype. The original painDETECT questionnaire was developed in a large cohort of LBP patients[22]. It sought to differentiate nociceptive from neuropathic pain mechanisms

but did not consider nociplastic mechanisms. There would be value in defining the relative input of nociplastic mechanisms in CPHP as different pain mechanisms warrant different treatment approaches. Augmenting painDETECT assessment with use of the Central Sensitisation Inventory[23], a questionnaire designed to assess nociplastic mechanisms may achieve this.

The International Association for the Study of Pain added to the definition of nociplastic pain a requirement for some measure of objectively testable hypersensitivity[24, 25]. These relate to central nervous system mechanisms of 'gain' that include allodynia, hyperalgesia, temporal and spatial summation, and painful after-sensations. The collective approach for physically assessing this is called Quantitative Sensory Testing, and this may help differentiate neuropathic from nociplastic pain mechanisms.

Clinical trials could test bone-specific treatments for CPHP cases identified as having a BML. Fifty percent of cases had a BML, and BML size was independently associated with having CPHP, but we don't know how BMLs change over time and whether those changes are associated with CPHP outcomes. We plan to analyse longitudinal data on imaging exposures to better understand if BMLs are a meaningful and modifiable treatment target. BMLs themselves are not homogenous and come in at least 3 sub-types at other bone regions such as the spine[26]. The association with pain outcomes may be different for different BML sub-types. Evaluating BMLs with different MRI sequences or co-locating existing HR-pQCT data with BML lesions in the calcaneus, may give further insight as to the 'phenotype' of BML. Analysing the clinical and pain data could determine if there are specific features that identify a BML without the requirement to image, or target people at high risk of having a BML to proceed to having MRI performed. Preliminary evidence indicates that individuals with night pain are more likely to have a BML[27]. BMLs can be specifically targeted in treatment with bone supporting medications[28] and physical modalities such as extra-corporeal shockwave[29, 30] as successfully applied in the treatment of BMLs in knee osteoarthritis. Future clinical trials could explore these modalities in CPHP participants identified as having a BML pain phenotype.

Measures of adiposity may reflect a metabolic phenotype. We have collected bloods from cases and controls at baseline for metabolic and meta-inflammatory marker

analysis. This will provide a more sensitive estimate of the metabolic profile of participants, with an initial plan to measure lipids (cholesterol, HDL, LDL, triglycerides), plasma glucose, HbA1c (%), high sensitivity C-reactive protein, IL-6, TNFα and leptin. These measures could help inform the mechanism of adiposity association, including whether specific metabolic or meta-inflammatory profiles are important.

Calf strengthening exercise is a commonly applied intervention in CPHP (typically for a plantar fascia phenotype of heel pain)[16], yet there is a disconnect from pain outcomes. Further research to understand the mechanism of effect of calf strengthening could help define cases with impairments likely to respond and improve exercise prescription parameters. This may involve examining different attributes of ankle plantarflexor performance such as power output, cortical inhibition studies, beliefs around movement and strengthening, and functional attributes such as jump or hop for which calf output may be a proxy.

Prognostic factors could be clarified by assembling an inception cohort of people with plantar heel pain immediately after symptom development. Tracking important clinical and imaging factors from symptom onset would provide clarity about the timeline of events and changes associated with CPHP progression, in particular progression to chronic, recalcitrant disease. For this thesis, recruiting cases was not difficult, but with a disease onset range from 3 to 636 months (median 10 months), it is likely that there is some imprecision in prognostic indicators as participants present at different ‘life stages’ of the condition. An inception cohort would avoid the bias associated with case-control study such as case selection and control representativeness and help inform our understanding of risk for new versus persistent disease. Given the incidence of CPHP, this type of study would require larger resources, but the potential to start by following up our existing controls is a possibility.

My blood samples could be accessed to evaluate genetic associations with CPHP. The role of genetics in CPHP has not been evaluated but associations have been established for other musculoskeletal conditions such as tendinopathy[31] and OA[32]. Genetic studies may help sub-group CPHP for a personalised medicine approach.

In summary, this thesis identified potential avenues for improving the assessment of CPHP. CPHP can be viewed as a heterogeneous condition presenting from a range of tissue, pain mechanism, metabolic, mechanical and psychosocial factors. Clinical decision making may be improved by identifying the personal mix or predominant CPHP phenotype based on presenting impairments. Future research should further define these CPHP phenotypes, and then investigate the merit of targeting treatment along these lines. Many of these approaches are not foot-specific, are commonly applied in the management of chronic musculoskeletal pain elsewhere but are yet to be fully considered in CPHP.

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Appendices

9. Appendices

9.1 Appendix 1: Paper by van Leeuwen, Rogers et al., (2016)

BJSM

Higher body mass index is associated with plantar fasciopathy/'plantar fasciitis': systematic review and meta-analysis of various clinical and imaging risk factors

K D B van Leeuwen, J Rogers, T Winzenberg and M van Middelkoop

Br J Sports Med published online December 7, 2015

Appendix 1 has been removed for copyright or proprietary reasons.

Appendix 2 has been removed for copyright or proprietary reasons.

It is the following published article: Rogers, J., Jones, G., Cook, J. L., Wills, K., Lahham, A., Winzenberg, T. M. 2021. Chronic plantar heel pain is principally associated with waist girth (systemic) and pain (central) factors, not foot factors: A case-control study, Journal of orthopaedic & sports physical therapy, 51(9), 449-458.
It is the published version of chapter 4.

9.3 Appendix 3: Letter of Invitation

UNIVERSITY of TASMANIA | MENZIES Institute for Medical Research

Letter of Invitation

The Menzies Research Institute Tasmania is conducting research into Plantar Fasciitis (chronic plantar heel pain-CPHP). If you have had pain under the heel for longer than 3 months, which is worse on standing in the morning, then you may be eligible to enter the study.

Why are we investigating it?
CPHP can be painful, stubborn and impact on your lifestyle.
We believe that not all CPHP is the same, and this study will help to describe sub-groups within this condition. We plan to use this information to help develop new ways to treat this condition.

What is involved?
1. An assessment that takes about 2 hours. The assessment will include:
   - Questionnaires asking you about your symptoms, medical history and activity levels, including consent to view your medical records specifically regarding any treatments received for your heel pain.
   - A foot and leg assessment: measures of ankle and leg flexibility, ankle strength and foot alignment.
   - Measures of height, weight, waist and fat levels.
   - Ultrasound: to image your plantar fascia (the main ligament which attaches to the underside of your heel).
   - Blood work: a small amount of blood will be taken to look for inflammation.
   - MRI: we will take an MRI (magnetic resonance image) of your heel bone.
   - High Resolution peripheral Quantitative CT: a special type of X-ray that provides a very detailed picture of the structure and density of your heel bone.

2. Wearing an accelerometer for seven days. This is a small pedometer like unit that records your daily activity.

Who cannot join the study?
There are a few reasons why you might not be able to enter the study.
These include if you have:
- had an injection into the heel in the last 6 months (e.g. with steroid)
- had heel surgery
- recent foot trauma
- if you are pregnant or have a pacemaker

There are a few other reasons, but these are the main ones.

How do I register my interest or get more information?
1. With your permission your treating health care worker can pass your contact details on to the research team.
2. Or if you prefer you can contact us directly by either calling one of the team members listed below, or using the stamped addressed envelope provided to send us your contact details. Your health care worker has these envelopes.

The research team will send you out an information package and call you to organize a time. If you need more information you can call members of the research team directly (Jason **04** or Tania **6226 7770**) or e-mail **Jason.rogers@utas.edu.au** .

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9.4 Appendix 4: Participant information sheet

PARTICIPANT INFORMATION SHEET

Clinical factors and Imaging Abnormalities Associated with Chronic Plantar Heel Pain

Invitation
You are invited to participate in a research study into chronic heel pain.
The study is being conducted by

- Professor Tania Winzenberg, Principal Research Fellow- Primary Health Care, Menzies Research Institute Tasmania (MRIT), University of Tasmania
- Mr Jason Rogers, Physiotherapist, Research Higher Degree candidate, MRIT
- Professor Graeme Jones, Head of Musculoskeletal Unit, MRIT
- Professor Jill Cook, Physiotherapist, Monash University, Victoria
- Doctor Karen Wills, Statistician, MRIT

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. 'What is the purpose of this study?'
The purpose is to investigate how findings on imaging (Ultrasound, Magnetic Resonance Imaging, High Resolution peripheral Quantitative Computed Tomography), common clinical physical tests and blood based markers of inflammation affect pain and function in people who have long standing heel pain.

2. 'Why have I been invited to participate in this study?'
You have been invited to participate in this study because you have symptoms consistent with chronic (> 3 months) plantar fasciitis or plantar heel pain (i.e. pain under the heel of your foot).

3. 'What if I don't want to take part in this study, or if I want to withdraw later?'
Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.

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9.5 Appendix 5: Participant consent form

UNIVERSITY of TASMANIA | MENZIES Institute for Medical Research

CONSENT FORM

Title of Project: Clinical factors and imaging abnormalities associated with chronic plantar heel pain.

1. I acknowledge that the nature, purpose and contemplated effects of the project so far as it affects me, have been fully explained to my satisfaction by the research worker and my consent is given voluntarily.

2. The details of the procedure proposed have also been explained to me, including the anticipated length of time it will take, the frequency with which the procedure will be performed, and an indication of any discomfort, which may be expected. I understand that my involvement means:

    - I will be required to fill out questionnaires detailing my medical history, current level of pain, function and activity levels
    - I understand that the study team will need to access my medical records specifically to see what treatments I have received for my heel pain.
    - Wear an accelerometer for a period of 7 consecutive days
    - Have my foot alignment, ankle strength and mobility, and leg flexibility assessed
    - Have my height, weight, body fat levels and waist girth measured
    - Have tissues in my heel measured by Ultrasound
    - Have my heel bone imaged in a High Resolution peripheral Quantitative Computed Tomography scanner (HRp-QCT).
    - Have my heel assessed by Magnetic Resonance Imaging (MRI)
    - Have some blood taken (approximately 10mls)

    The clinical assessment process will be undertaken at the Menzies Research Institute and is anticipated to take 2 hours. The MRI will be conducted at the Royal Hobart Hospital, and is expected to take 30 minutes.

    I understand that I will be asked to return for repeat measures of the Ultrasound, questionnaires, accelerometry and some of the clinical tests (ankle strength and flexibility, leg flexibility, body composition) at 12 months.

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3. I understand that there are the following risks or possible discomfort:
    - Some minor discomfort or bruising from taking a blood sample from your arm
    - Possibly a short-term increase in heel pain following the physical testing procedures
    - The amount of radiation involved in the HRp-QCT scan is small and is well below the National Health and Medical Research Council guidelines for volunteers in research studies. This is unlikely to be associated with an increased risk of disease based on current evidence.

4. I understand that any excess blood sample provided will be kept for 15 years in case any future follow up studies should require different tests to those performed in this study.

5. Although I understand that the purpose of this research project is to improve the quality of medical care, it has also been explained that my involvement may not be of any benefit to me.

6. I have been given the opportunity to have a member of my family or friend present while the project was explained to me.

7. I am informed that no information regarding any medical history will be divulged and the results of any tests involving me will not be published so as to reveal my identity.

8. I understand that my involvement in the project will not affect my relationship with my medical advisers in their management of my health. I also understand that I am free to withdraw from the project at any stage and any of my data/specimens that have been collected. My withdrawal will not affect my legal rights, my medical care or my relationship with the hospital or my doctors.

9. I understand that I will be given a signed copy of this patient information sheet and consent form. I am not giving up my legal rights by signing this consent form.

10. I understand that the study will be conducted in accordance with the latest versions of the *National Statement on Ethical Conduct in Human Research 2007* and applicable privacy laws.

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11. I would like my GP to be informed about my participation in this study:

YES / NO (please circle)

Name of GP:

Name of participant _____

Signature of participant _____ Date _____

The following section regarding the witness is not essential but may be appropriate for patients where the research teams feel that the participant should have a witness to the consent procedure or where the protocol insists upon witnesses.

Name of witness (if appropriate) _____

Signature of witness _____ Date _____

_____

10. I have explained this project and the implications of participation in it to this volunteer and I believe that the consent is informed and that he/she understands the implications of participation.

Name of investigator _____

Signature of investigator _____ Date _____

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9.6 Appendix 6: Intake questionnaires (baseline)

Menzies Research Institute Tasmania

Subject ID: ☐☐☐

Date: ☐☐ / ☐☐ / ☐☐☐☐

Plantar Heel Pain Study (PHEEPS) Phase 1

Study team: Mr Jason Rogers (Co-ordinator)
Prof. Tania Winzenberg
Prof. Graeme Jones
Prof. Jill Cook
Dr Karen Wills
Dr Kathryn Squibb

Instructions for completing the questionnaire:

All questionnaires will be submitted electronically. By following these instructions you will be assisting with this process.

Please answer all questions to the best of your ability (leave blank if unknown).
Do not put lines through irrelevant questions as it upsets the scanning machine.

Write in **BLOCK LETTERS** using the boxes where provided

Use a blue pen

Cross out any mistake & write correct answer just below the relevant box

Indicate your response by filling in the circle next to the most appropriate answer or by writing clearly in the box or space provided.

Your answers will be completely confidential.

Please notate any queries and they will be reviewed at your appointment.

Example:

Shade Circles Like This--> ●

Not Like This--> ⊗ ⊘

Demographics

Title

Given Name(s)

Surname

Preferred Name

Maiden Name

Home Address

Address

Suburb

State Postal Code

Postal Address Same as above ○

Address

Suburb

State Postal Code

Contact details

Home Phone ( )

Work Phone ( )

Mobile Phone

Email Address

Date of birth / /

Sex Male ○ Female ○

Please provide details of a contact person (family or friend) NOT living at the same address as you, who we could contact should we need to trace you.

Title

Given Name(s)

Surname

What relationship is this person to you?

Postal Address

Address

Suburb

State

Postal Code

Contact details

Home Phone ( )

Work Phone ( )

Mobile Phone

Email Address

General Practitioner Details

Given Names:

Surname:

Practice name:

Address:

City/Suburb:

State:

Postal Code:

Phone: -

email:

Which of the following best describes your present relationship status?

Single ○
Married, living together ○
Married, separated ○
Unmarried, living together (defacto) ○
Unmarried, not living together ○
Divorced ○

Which of the following describes your current employment status? (select the option that accounts for *most* of your time).

Employed full-time (employed, self-employed or volunteering) ○
Employed part-time ○
Home duties ○
Student ○
Sole parent pension ○
Disability pension ○
Retired ○
Unemployed ○

What is the highest level of education you have completed?

Primary School ○
High school grade 7 - 10 ○
High school grade 11 - 12 ○
Certificate/diploma (Trade/vocational) ○
University degree ○
Post-graduate degree ○

Heel Pain Details

Details of your heel pain (for the most painful foot)

1. Which heel do you have pain in? Left ○ Right ○ Both ○

   If 'Both', which foot is currently most severe? Left ○ Right ○

For the most painful foot

2. How long have you had your current heel pain? ☐☐ months ☐☐ years

3. For the most painful foot, is this your first episode of heel pain? Yes ○ No ○

4. If 'No', how many prior episodes have you had?
   (An episode refers to a period of distinct pain separated by at least 1 month of no pain)
   1 ○
   2 ○
   3 ○
   4 or more ○

5. How old were you when you had your first episode of heel pain? ☐☐ years

6. Are you **currently** receiving treatment for your heel pain? Yes ○ No ○

7. If 'Yes', for how long? ☐☐ months ☐☐ weeks

8. Have you had treatment for your heel pain in the past - either for a prior episode or for this episode which you have since stopped? Yes ○ No ○

9. When did treatment first start? ☐☐ months ago ☐☐ years ago

10. Have you had any heel pain in your other foot in the past? Yes ○ No ○

10a. Do you have pain in your heel at night? Yes ○ No ○

11. Do you also have pain at any of these sites? (Please answer Yes or No)

Neck	Yes ○ No ○
Back	Yes ○ No ○
Hands	Yes ○ No ○
Shoulders	Yes ○ No ○
Hips	Yes ○ No ○
Knees	Yes ○ No ○
Toes	Yes ○ No ○

About your heel symptoms
Please mark your answers by putting an 'X' through the horizontal line.

An 'X' at the left-hand end of the line indicates that you **feel no pain**.
An 'X' at the right-hand end of the line indicates that you **feel extreme pain**.

EXAMPLES:

1. If you put your "x" at the left-hand end of the line as shown below, then you are indicating that you feel no pain.

2. If you put your "x" at the right-hand end of the line as shown below, then you are indicating that you feel extreme pain.

3. Please note:
   a) that the further to the right you place your "x", the more pain you feel.
   b) that the further to the left you place your "x", the less pain you feel.
   c) please do not place your "x" past either end of the line.

Please answer the following questions with respect to your current heel pain (specifically your MOST PAINFUL heel if both heels hurt).

Study Coordinator use only

12. How much heel pain do you have at the moment?

13. On average, how much pain did you have in your heel over the last week?

First-step pain
The next two questions ask you about any heel pain you experience when you first step out of bed in the morning.

14. How much pain did you have with your first step upon arising THIS morning?

15. On average, how much pain did you have in your heel with your first step over the last week?

Medical History

Smoking history

1. Have you ever been a "regular smoker"? Yes ○ No ○
(A regular smoker is someone who has smoked at least 7 cigarettes, cigars or pipes every week for at least 3 months)

If 'Yes':

2. If 'Yes', are you currently a regular smoker? Yes ○ No ○

3. How many years in TOTAL have you been a regular smoker? ☐☐ Years

Medical history

4. Has a doctor ever diagnosed you with Familial Hypercholesteraemia?
(Familial hypercholesteraemia is a genetic disorder (runs in families) that leads to high levels of cholesterol from a young age).
Yes ○
No ○
Don't know ○

5. Has a doctor ever diagnosed you with high cholesterol, blood lipids or triglycerides (High 'fats' in your blood)?
Yes ○
No ○
Don't know ○

If 'Yes':

6. How many years in TOTAL have you been diagnosed with high cholesterol, blood lipids or triglycerides? ☐☐ Years

7. Are you taking medications for this?
Yes ○
No ○
Don't know ○

8. If 'Yes', for how long?
<1 year ○
1 - 4 years ○
5 - 10 years ○
>10 years ○

9. Has a doctor ever diagnosed you with diabetes?

Yes O
No O
Don't know O

If 'Yes':

10. What type of diabetes?

Type 1 O
Type 2 O
Don't know O

11. How many years in TOTAL have you been diagnosed with diabetes?

[ ][ ] Years

12. Are you currently taking medications for your diabetes to help regulate your blood sugar?

Yes O
No O
Don't know O

13. Are you currently injecting insulin or insulin substitutes?

Yes O
No O
Don't know O

14. If you are currently injecting or taking medications for your diabetes, how long have you been doing so (the longest period for either)?

<1 year O
1 - 4 years O
5 - 10 years O
>10 years O

15. Has a doctor ever diagnosed you with an inflammatory bone, joint or muscle disease? (excluding 'osteoarthritis')

Yes O
No O
Don't know O

If 'Yes':

16. What was your diagnosis?

Rheumatoid Arthritis O
Ankylosing spondylitis O
Reiters Syndrome (reactive arthritis) O
Psoriatic arthritis O
Don't know O
Other O [ ]

17. Was this confirmed by a specialist (such as a Rheumatologist)?

Yes O
No O
Don't know O

18. In the last week have you experienced morning stiffness lasting longer than 30 minutes?

Yes O
No O

19. Have you ever had a bone density test?

Yes O
No O

20. If 'Yes', what was the result?

Osteoporosis O
Osteopaenia O
Low bone density O
Normal O
Don't know O

21. Are you currently taking medications for prescribed by your doctor (either tablets or by injection) for Osteoporosis?

Yes O
No O
Don't know O

22. If 'Yes', for how long?

<1 year O
1 - 4 years O
5 - 10 years O
>10 years O

23. Have you ever taken antibiotics from the fluoroquinolones class?
eg Ciproflaxin (eg C-flox, Ciprol), norfloxacin (eg Roxin, Noroxin), gatifloxacin (Tequin), enoxacin (Enoxin), moxifloxacin (Avelox)

Yes O
No O
Don't know O

24. If 'Yes', how long ago did you take them?

☐☐ Years

Females only

25. Have you ever used the oral contraceptive pill? Yes ○ No ○

If 'Yes':

26. Are you currently taking the oral contraceptive pill? Yes ○ No ○

27 How many years in TOTAL have you ever taken the oral contraceptive pill?

Less than one year ○
1 - 4 years ○
5 - 10 years ○
11 - 20 years ○
More than 20 years ○

28. Have you gone through menopause ("Change of Life")

Yes ○
No ○
Don't know ○
Currently going through menopause ○

29. Have your periods NOW stopped for more than 12 months?

Yes ○
No ○
Never had a period ○

30. Have you had a hysterectomy (uterus removed)? Yes ○ No ○

31. If "Yes" age when had hysterectomy? ☐☐ Years

32. Have you had an operation to remove both ovaries?

Yes ○
No ○
Don't know ○

33 If 'Yes', Age when ovary/ovaries removed? ☐☐ Years

34 Are you currently on hormone replacement therapy (HRT)? Yes ○ No ○

35 If 'Yes', for how many years in TOTAL have you ever used hormone replacement therapy?

Less than one year ○
1 - 4 years ○
5 - 10 years ○
11 - 20 years ○
More than 20 years ○

36. Treatments for your heel pain

This section is about treatments you have received for your heel pain. Select as many options as appropriate to reflect any and all treatment choices you have tried in the past month, or have tried but since stopped (either for this episode or a past episode).

	In PAST MONTH	That you have since STOPPED (either for this or a past episode)
Rest or stop activity	Yes O	Yes O
Stretching lower leg/calf	Yes O	Yes O
Stretching the plantar fascia or arch	Yes O	Yes O
Massage the lower leg/calf (self or health worker)	Yes O	Yes O
Massage the arch/plantar fascia (self or health worker)	Yes O	Yes O
Strengthening exercises for the leg (excluding foot)	Yes O	Yes O
Strengthening exercises for the foot (toes and arch)	Yes O	Yes O
Manual therapy (hands on mobilisation/manipulation) of the foot or ankle joints by a health worker	Yes O	Yes O
Orthotics (arch supports/shoe inserts) *custom made* (by a health professional based on a cast, scan or imprint of your foot)	Yes O	Yes O
Orthotics (arch supports/shoe inserts) *over the counter* (an insert that comes ready made to use, though it may have been adjusted by heat, grinding or gluing)	Yes O	Yes O
Heel cups or pads	Yes O	Yes O
Footwear - specific running or walking shoes or sandals	Yes O	Yes O
Taping/strapping of your foot	Yes O	Yes O
Night splints or (foot stretching) socks worn at night	Yes O	Yes O
Other exercise eg pilates, pool	Yes O	Yes O
Ultrasound	Yes O	Yes O
Heating or icing eg hot packs, infra red lamps, ice packs or baths	Yes O	Yes O
Electric stimulation eg TENS	Yes O	Yes O
Magnetic therapy	Yes O	Yes O
Acupuncture or dry needling	Yes O	Yes O
Prescription medications from your doctor	Yes O	Yes O
Over the counter medications, supplements or topical applications	Yes O	Yes O
Any other treatments, please list		
	Yes O	Yes O
	Yes O	Yes O
	Yes O	Yes O

More than 6 months ago

37. Have you had any of the following?

Steroid injection into the heel — Yes ○ / No ○ / Don't know ○ — If 'Yes', how many ☐☐

Blood or other injection into the heel (other than steroid) — Yes ○ / No ○ / Don't know ○ — If 'Yes', how many ☐☐

Iontophoresis (using electrical patches to deliver steroid into your heel) — Yes ○ / No ○ / Don't know ○ — If 'Yes', how many ☐☐

Shockwave therapy ('ESWT', high energy sound pulses delivered by a machine into your heel) — Yes ○ / No ○ / Don't know ○ — If 'Yes', how many ☐☐

List all medication, prescribed by a doctor that you have taken in the last 2 weeks, include dosage and frequency.

Please bring all current prescription medication with you to your interview.

	Medication	Dosage	Frequency
a			
b			
c			
d			
e			
f			
g			
h			
i			

List any other over the counter medication you have taken in the last 2 weeks, include dosage and frequency. eg Panadol, Aspirin, Vitamin or mineral supplements, natural or herbal medications and antihistamines.

	Medication	Dosage	Frequency
a			
b			
c			
d			
e			
f			
g			
h			
i			

Physical Activity

For purposes of this questionnaire consider your physical activity over the past 12 months.

1. On how many days during the last 14 days did you spent at least 20 minutes doing strenuous exercise? E.g. bicycling, brisk walking, jogging, aerobics, etc. Exercise that was severe enough to raise your pulse rate and/or cause you to breathe faster.

No days ○
1 to 2 days ○
3 to 5 days ○
6 to 8 days ○
9 or more days ○

2. On how many days during the last 14 days have you spent at least 20 minutes doing light exercise? E.g. walking, light housework, slow bicycling, etc. Exercise which was not severe enough to cause a pulse rate rising and/or breathing to increase.

No days ○
1 to 2 days ○
3 to 5 days ○
6 to 8 days ○
9 or more days ○

3. During a normal week, how many hours a day do you spend watching T.V. or videos?

No hours a day ○
1 hour or less a day ○
between 1 and 3 hours ○
more than 3 but less than 6 hours ○
6 or more hours a day ○

4. During a normal week, how many hours a day do you spend on your feet e.g. standing or walking?

No hours a day ○
1 hour or less a day ○
between 1 and 3 hours ○
more than 3 but less than 6 hours ○
6 or more hours a day ○

5. Since the onset of your current episode of heel pain, how have the above activity levels changed?

	Decreased a lot	Decreased a little	Same	Increased a little	Increased a lot	If changed, is this because of your heel pain?
Strenuous activity	○	○	○	○	○	Yes ○ No ○
Light activity	○	○	○	○	○	Yes ○ No ○
Sitting time	○	○	○	○	○	Yes ○ No ○
Time on your feet	○	○	○	○	○	Yes ○ No ○

6. During the last 12 months, how many team or individual sports activities did you participate in either on a competitive or professional level? E.g. tennis, netball or golf.

No sports or activities O
1 sport or activity O
2 sports or activities O
3 sports or activities O
4 or more sports or activities O

What sports or activities did you participate in?

1. [ ]
2. [ ]
3. [ ]
4. [ ]
5. [ ]
6. [ ]
7. [ ]

7. Please select all the sports or activities which you participated in more than 10 times during the last 12 months. Please include team sports.

Aerobics O
Basketball O
Netball O
Volleyball O
Bicycling O
Bowling O
Dancing O
Gardening O
Bushwalking O
Rollerblading O
Swimming O
(Laps or water sports like water polo or underwater hockey)
Power walking O
Jogging O
Soccer O
Softball O
Hockey O
Tennis O
Squash O
Badminton O
Gym-work weight training O
Golf O

Any other activities or sports which are not mentioned here [ ]

Footwear

This section is about your current footwear choices.
Use the chart below to answer the questions on the following page.

A. Walking shoe

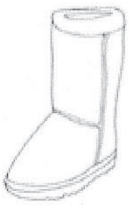
B. Athletic shoe / Runner

C. Oxford shoe

D. Moccassin

E. Boot

F. Ugg boot



G. High heel / Stiletto

H. Thong / Flip flop

I. Slipper

J. Backless slipper

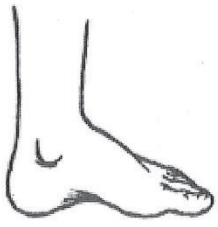
K. Court shoe

L. Mule

M. Sandal

N. Surgical / Bespoke footwear

O. Barefoot



P. Other

1. From the chart on the previous page, for an average *week day*, list the two footwear types that you would most commonly wear.

Footwear 1: ☐ If 'P. Other', please specify footwear style: ☐

Footwear 2: ☐

2. From the chart on the previous page, for an average *weekend day*, list the two footwear types that you would most commonly wear.

Footwear 1: ☐ If 'P. Other', please specify footwear style: ☐

Footwear 2: ☐

3. For the most common footwear choice on an average week day, estimate its heel height:

0 cm ○
Between 0 and 2.5 cm ○
Between 2.5 and 5 cm ○
More than 5 cm ○
Unsure ○

4. For the most common footwear choice on an average weekend day, estimate its heel height:

0 cm ○
Between 0 and 2.5 cm ○
Between 2.5 and 5 cm ○
More than 5 cm ○
Unsure ○

Thoughts and Feelings About Your Pain (PCS)

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

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

Rating	0	1	2	3	4
Meaning	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

When I'm in pain ...

Number	Statement	Rating
1	I worry all the time about whether the pain will end.	☐
2	I feel I can't go on	☐
3	It's terrible and I think it's never going to get any better.	☐
4	It's awful and I feel that it overwhelms me.	☐
5	I feel I can't stand it anymore.	☐
6	I become afraid that the pain will get worse.	☐
7	I keep thinking of other painful events.	☐
8	I anxiously want the pain to go away.	☐
9	I can't seem to keep it out of my mind.	☐
10	I keep thinking about how much it hurts.	☐
11	I keep thinking about how badly I want the pain to stop.	☐
12	There's nothing I can do to reduce the intensity of the pain.	☐
13	I wonder whether something serious may happen.	☐

Personal Health Questionnaire

Over the **last 2 weeks**, how often have you been bothered by any of the following problems (Fill in **one** circle on each line)

How often during the past 2 weeks were you bothered by ...

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things.	○	○	○	○
2. Feeling down, depressed or hopeless.	○	○	○	○
3. Trouble falling or staying asleep, or sleeping.	○	○	○	○
4. Feeling tired or having little energy.	○	○	○	○
5. Poor appetite or overeating.	○	○	○	○
6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down.	○	○	○	○
7. Trouble concentrating on things, such as reading the newspaper or watching television.	○	○	○	○
8. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.	○	○	○	○
9. Thoughts that you would be better off dead, or of hurting yourself in some way.	○	○	○	○

General Comments

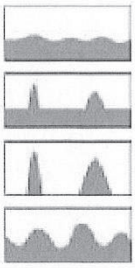
Pain Detect Questionnaire

Please answer these questions with respect to your foot pain.

Development/Reference: R. Freynhagen, R. Baron, U. Gockel, T.R. Tölle / Curr Med Res Opin, Vol.22, No. 10 (2006)

Staff Initials: ☐☐☐

Mark the picture that best describes the course of your pain



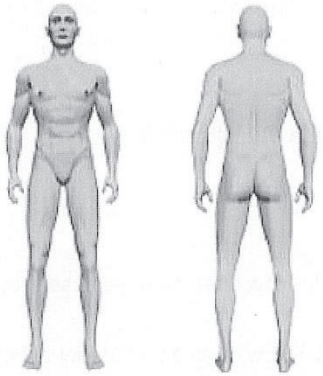
Persistent pain with slight fluctuations ○

Persistent pain with pain attacks ○

Pain attacks without pain between them ○

Pain attacks with pain between them ○

Please mark your **pain in or around your heel.**



Does your pain spread up the leg or into the toes from your heel? ○ No ○ Yes

If yes, please draw the direction in which the pain radiates.

Do you suffer from a burning sensation (e.g. stinging nettles) in the marked areas?

Never ○ Hardly noticed ○ Slightly ○ Moderately ○ Strongly ○ Very Strongly ○

Do you have tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?

Never ○ Hardly noticed ○ Slightly ○ Moderately ○ Strongly ○ Very Strongly ○

Is light touching (clothing, a blanket) in this area painful?

Never ○ Hardly noticed ○ Slightly ○ Moderately ○ Strongly ○ Very Strongly ○

Do you have sudden pain attacks in the area of your pain, like electric shocks?

Never ○ Hardly noticed ○ Slightly ○ Moderately ○ Strongly ○ Very Strongly ○

Is cold or heat (bath water) in this area occasionally painful?

Never ○ Hardly noticed ○ Slightly ○ Moderately ○ Strongly ○ Very Strongly ○

Do you suffer from a sensation of numbness in the areas that you marked?

Never ○ Hardly noticed ○ Slightly ○ Moderately ○ Strongly ○ Very Strongly ○

Does slight pressure in this area, e.g. with a finger, trigger pain?

Never ○ Hardly noticed ○ Slightly ○ Moderately ○ Strongly ○ Very Strongly ○

To be filled out by the physician

___ x 0 = 0 ___ x 1 = ☐ ___ x 2 = ☐☐ ___ x 3 = ☐☐ ___ x 4 = ☐☐ ___ x 5 = ☐☐

Total score ☐☐ out of 35

Pattern score ☐☐ Picture score ☐☐ Final score ☐☐

The Foot Health Status Questionnaire

The following questions are about the foot pain you have had during the past week.

1. What level of foot pain have you had **during the last week**?

None ○
Very mild ○
Mild ○
Moderate ○
Severe ○

During the last week ...

	Never	Occasionally	Fairly Many Times	Very often	Always
2. How often have you had foot pain?	○	○	○	○	○
3. How often did your feet ache?	○	○	○	○	○
4. How often did you get sharp pains in your feet?	○	○	○	○	○

These questions are about how much your feet interfere with activities you might do during a typical day.

During the last week ...

	Not at all	Slightly	Moderately	Quite a bit	Extremely
5. Have your feet caused you to have difficulties in your work or activities?	○	○	○	○	○
6. Were you limited in the kind of work you could do because of your feet?	○	○	○	○	○

During the last week ...

	Not at all	Slightly	Moderately	Quite a bit	Extremely
7. How much does your foot health limit you walking?	○	○	○	○	○
8. How much does your foot health limit you climbing stairs?	○	○	○	○	○

9. How would you rate your overall foot health?

Excellent ○
Very good ○
Good ○
Fair ○
Poor ○

The following questions are about the shoes that you wear. Please select the response which best describes your situation.

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly Disagree
10. It is hard to find shoes that do not hurt my feet	○	○	○	○	○
11. I have difficulty in finding shoes that fit my feet.	○	○	○	○	○
12. I am limited in the number of shoes I can wear.	○	○	○	○	○

13. In general, what condition would you say your feet are in?

Excellent ○
Very good ○
Good ○
Fair ○
Poor ○

Foot and Ankle Ability Measure (FAAM)

Activities of Daily Living Subscale

These questions are about how your heel pain condition affects your ability to do everyday activities.

Please select one option in each row that matches your current ability to perform each of the listed tasks. If the activity in question is limited by something other than your foot or ankle select "Not Applicable".

	No difficulty	Slight difficulty	Moderate difficulty	Extreme difficulty	Unable to do	Not applicable
Standing	○	○	○	○	○	○
Walking on even ground	○	○	○	○	○	○
Walking on even ground without shoes	○	○	○	○	○	○
Walking up hills	○	○	○	○	○	○
Walking down hills	○	○	○	○	○	○
Going up stairs	○	○	○	○	○	○
Going down stairs	○	○	○	○	○	○
Walking on uneven ground	○	○	○	○	○	○
Stepping up and down curbs	○	○	○	○	○	○
Squatting	○	○	○	○	○	○
Coming up on your toes	○	○	○	○	○	○
Walking initially	○	○	○	○	○	○
Walking 5 minutes or less	○	○	○	○	○	○
Walking approximately 10 minutes	○	○	○	○	○	○
Walking 15 minutes or greater	○	○	○	○	○	○

Because of your foot and ankle how much difficulty do you have with:

	No difficulty at all	Slight difficulty	Moderate difficulty	Extreme difficulty	Unable to do	Not applicable
Home responsibilities	○	○	○	○	○	○
Activities of daily living	○	○	○	○	○	○
Personal care	○	○	○	○	○	○
Light to moderate work (standing, walking)	○	○	○	○	○	○
Heavy work (push/pulling, climbing, carrying)	○	○	○	○	○	○
Recreational activities	○	○	○	○	○	○

How would you rate your current level of function during your usual activities of daily living from 0 to 100 with 100 being your level of function prior to your foot or ankle problem and with 0 being the inability to perform any of your usual daily activities?

☐☐☐.0%

Foot and Ankle Ability Measure (FAAM)

Sports Subscale

These questions are about how your heel pain condition affects your ability to do sports activities.

Because of your foot and ankle how much difficulty do you have with:

	No difficulty at all	Slight difficulty	Moderate difficulty	Extreme difficulty	Unable to do	Not applicable
Running	○	○	○	○	○	○
Jumping	○	○	○	○	○	○
Landing	○	○	○	○	○	○
Starting and stopping quickly	○	○	○	○	○	○
Cutting/lateral movements	○	○	○	○	○	○
Low impact activities	○	○	○	○	○	○
Ability to perform activity with your normal technique	○	○	○	○	○	○
Ability to participate in your desired sport as long as you like	○	○	○	○	○	○

How would you rate your current level of function during your sports related activities from 0 to 100 with 100 being your level of function prior to your foot or ankle problem and with 0 being the inability to perform any of your usual daily activities?

☐☐☐.0%

Overall, how would you rate your current level of function?

Normal ○
Nearly normal ○
Abnormal ○
Severely abnormal ○

Assessment of Quality of Life (AQoL-6D)

INSTRUCTIONS:
This form asks questions about your 'quality of life'.
Please fill *one circle only* for the answer that best describes your current situation.

1. How much help do you need with jobs around the house (e.g. cooking, cleaning the house or washing clothes):

I can do all these tasks very quickly and efficiently without any help ○
I can do these tasks relatively easily without help ○
I can do these tasks only very slowly without help ○
I cannot do most of these tasks unless I have help ○
I can do none of these tasks by myself ○

2. Thinking about how easy or difficult it is for you to get around by yourself outside your house (e.g., shopping, visiting):

Getting around is enjoyable and easy ○
I have no difficulty getting around outside my house ○
A little difficulty ○
Moderate difficulty ○
A lot of difficulty ○
I cannot get around unless somebody is there to help me ○

3. Thinking about your mobility, including using any aids or equipment such as wheelchairs, frames, sticks:

I am very mobile ○
I have no difficulty with mobility ○
I have some difficulty with mobility (for example, going uphill) ○
I have difficulty with mobility. I can go short distances only. ○
I have a lot of difficulty with mobility. I need someone to help me. ○
I am bedridden ○

4. Thinking about dressing, washing yourself, eating or looking after your appearance:

These tasks are very easy for me ○
I have no real difficulty in carrying out these tasks ○
I find some of these tasks difficult, but I manage to do them on my own ○
Many of these tasks are difficult, and I need help to do them ○
I cannot do these tasks by myself at all ○

5. Your close and intimate relationships (including any sexual relationships) make you:

Very happy ○
Generally happy ○
Neither happy or unhappy ○
Generally unhappy ○
Very unhappy ○

6. Thinking about your health and your relationship with your family:

My role in the family is unaffected by my health ○
There are some parts of my family role I cannot carry out ○
There are many parts of my family role I cannot carry out ○
I cannot carry out any part of my family role ○

7. Thinking about your health and your role in your community (that is to say neighbourhood, sporting, work, church or cultural groups):

My role in the community is unaffected by my health ○
There are some parts of my community role I cannot carry out ○
There are many parts of my community role I cannot carry out ○
I cannot carry out any part of my community role ○

8. How often did you feel in despair over the last seven days?

Never ○
Occasionally ○
Sometimes ○
Often ○
All the time ○

9. And still thinking about the last seven days, how often did you feel worried?

Never ○
Occasionally ○
Sometimes ○
Often ○
All the time ○

10. How often do you feel sad?

Never ○
Rarely ○
Some of the time ○
Usually ○
Nearly all the time ○

11. When you think about whether you are calm and tranquil or agitated: I am

Always calm and tranquil ○
Usually calm and tranquil ○
Sometimes calm and tranquil, sometimes agitated ○
Usually agitated ○
Always agitated ○

12. Thinking about how much energy you have to do the things you want to do: I am

Always full of energy ○
Usually full of energy ○
Occasionally energetic ○
Usually tired and lacking energy ○
Always tired and lacking energy ○

13. How often do you feel in control of your life?

Always ○
Mostly ○
Sometimes ○
Only occasionally ○
Never ○

14. How much do you feel you can cope with life's problems?

Completely ○
Mostly ○
Partly ○
Very little ○
Not at all ○

15. Thinking about how often you experience serious pain: I experience it

Very rarely ○
Less than once a week ○
Three to four times a week ○
Most of the time ○

16. How much pain or discomfort do you experience?

None at all ○
I have moderate pain ○
I suffer from severe pain ○
I suffer unbearable pain ○

17. How often does pain interfere with your usual activities?

Never O
Rarely O
Sometimes O
Often O
Always O

18. Thinking about your vision (using your glasses or contact lenses if needed)?

I have excellent sight O
I see normally O
I have some difficulty focusing on things, or I do not see them sharply. O
e.g. small print, a newspaper or seeing objects in the distance.
I have a lot of difficulty seeing things. My vision is blurred. I can see just enough to get by with. O
I only see general shapes. I need a guide to move around. O
I am completely blind O

19. Thinking about your hearing (using your hearing aid if needed)?

I have excellent hearing O
I hear normally O
I have some difficulty hearing or I do not hear clearly. O
I have trouble hearing softly-spoken people or when there is background noise.
I have difficulty hearing things clearly. Often I do not understand what is said. O
I usually do not take part in conversations because I cannot hear what is said.
I hear very little indeed. I cannot fully understand loud voices speaking directly to me. O
I am completely deaf O

20. When you communicate with others, e.g. by talking, listening, writing or signing:

I have no trouble speaking to them or understanding what they are saying O
I have some difficulty being understood by people who do not know me. O
I have not trouble in understanding what others are saying to me.
I am understood only by people who know me well. O
I have great trouble understanding what others are saying to me.
I cannot adequately communicate with others O

9.7 Appendix 7: Clinical assessment form

Menzies Research Institute Tasmania

Subject ID: ☐☐☐

Assessor: ☐☐☐

Date: ☐☐ / ☐☐ / ☐☐☐☐

AM ○ PM ○

Initial ○ 12 Month followup ○

Plantar Heel Pain Study (PHEEPS)

Clinical Assessment Sheet

Dominant foot: Left ○ Right ○ Test side: Left ○ Right ○

1. Height ☐☐☐.☐ cm

Stadiometer Type Leicester ○
Other ○ ☐☐☐☐☐☐☐☐☐☐☐☐

Stadiometer Number ☐☐

2. Weight ☐☐☐.☐ kg

Scales Type Heine ○
Other ○ ☐☐☐☐☐☐☐☐☐☐☐☐

Scales Number ☐☐

3. Waist circumference

Reading 1 ☐☐☐.☐ cm Reading 2 ☐☐☐.☐ cm

If there is a difference of 1cm or more between readings 1 and 2 then a third reading should be taken.

Reading 3 ☐☐☐.☐ cm

5310471865 Page 1 of 8

4. Bioimpedance

Side tested: Left ○ Right ○

Body frame size:

Wrist circumference ☐☐.☐ cm

Height / Wrist circumference ☐☐.☐

Small frame (more than 10.4) ○

Medium frame (between 9.6 and 10.4) ○

Large frame (Less than 9.6) ○

	Measurement 1	Measurement 2	Measurement 3	Measurement 4
Resistance (R)	☐☐☐	☐☐☐	☐☐☐	☐☐☐
Reactance (Xc)	☐☐☐	☐☐☐	☐☐☐	☐☐☐

* Resistance values must be within 1% of each other, otherwise repeat

Daily activity level

The "Daily Activity Level" describes the amount of physical work associated with the individual's typical daily routine. It is important to select an activity level that is appropriate to the amount of activity that the person sees on an average daily basis.

Very light (no exercise) ○

Seated and standing activities, painting, driving, laboratory work, typing, sewing, ironing, cooking, paying cards, playing a musical instrument

Light (Some exercise) ○

Walking on a level surface at 4 - 4.8 kph, garage work, carpentry, restaurant trades, house-cleaning, child care, golf, sailing, table tennis

Moderate (Moderate exercise) ○

Walking at 5.6 - 6.5 kph, weeding and hoeing, carrying a load, cycling, tennis, dancing

Heavy (athletic) ○

Walking with a load uphill, tree felling, heavy manual digging, basketball, climbing, football, soccer

Exceptional (Elite Athlete) ○

Extremely strenuous physical activity

5. Ankle Dorsiflexion ROM (degrees)

Mark midpoint on shin between tibial tuberosity and ankle joint line.
Flip coin for testing order. Pre condition into ankle DF x5.

	Left			Right		
	Order	Measure 1	Measure 2	Order	Measure 1	Measure 2
Knee FLEX						
Knee EXT						

6. 1st Metatarsophalangeal Extension ROM (degrees)

Pre condition x6

Left			Right		
Measure 1	Measure 2	Measure 3	Measure 1	Measure 2	Measure 3

7. Calf Torque (kg)

Measure distance from lateral malleolus to 5th MTP jt axis.
Shin is inclined 20 degrees from vertical. Practice x2.

Left: . cm Right: . cm

	Measure 1	Measure 2	Measure 3	Pain / 10
Left	.	.	.	
Right	.	.	.	

8. Straight Leg Raise (degrees)

In supine insert roll in lordosis, apex at L4.
Flip coin for order of SLR or SLR/DF/Ever testing.
Pre-condition x5.

Zones:
1: foot, below malleolar axis
2: calf
3: popliteal
4: hamstrings
5: gluteals (gluteal fold to iliac crest)
6: back (above iliac crest)

	Left					Right				
	Order		Degrees	Pain / 10	Zone	Order		Degrees	Pain / 10	Zone
SLR ROM	☐	Measure 1	☐☐	☐☐	☐	☐	Measure 1	☐☐	☐☐	☐
		Measure 2	☐☐	☐☐	☐		Measure 2	☐☐	☐☐	☐
SLR/DF/ Ever	☐	Measure 1	☐☐	☐☐	☐	☐	Measure 1	☐☐	☐☐	☐
		Measure 2	☐☐	☐☐	☐		Measure 2	☐☐	☐☐	☐

9. Foot Posture Index-6

	Left	Right
Rearfoot		
Talar head palpation	☐	☐
Curves above / below lateral malleolus	☐	☐
Inversion / eversion of calcaneus	☐	☐
Forefoot		
Prominence in region of TNJ	☐	☐
Congruence of MLA	☐	☐
Abd / adduction FF on RF	☐	☐

Score: -2 -1 0 1 2
Max supination Max pronation

Heel Ultrasound

Sonographer: ☐☐☐

Date: ☐☐ / ☐☐ / ☐☐☐☐

Same as clinical exam date (leave above date field unfilled) ○

Room Temperature ☐☐.☐ °C

Test foot: Left ○ Right ○

If ultrasound not taken but eligible, why?

Refusal ○

Physical restrictions ○

Other (please specify) ○ ☐

Participant sitting quietly for 30 minutes before ultrasound? Yes ○ No ○

Plantar Fascia thickness

	PFT 1	PFT 2	PFT 3
Left	☐☐.☐☐ mm	☐☐.☐☐ mm	☐☐.☐☐ mm
Right	☐☐.☐☐ mm	☐☐.☐☐ mm	☐☐.☐☐ mm

Save 3 images for each side.

Comments: ☐

Plantar Fascia echogenicity

Left	**Right**
Isoechoic ○	Isoechoic ○
Hypoechoic - diffuse ○	Hypoechoic - diffuse ○
Hypoechoic - focal ○	Hypoechoic - focal ○
Heterogeneous ○	Heterogeneous ○

Gain: ☐☐ db

Save 1 image for each side.

Comments: ☐

Plantar Fascia vascularity

	Left	Right
Grade	☐	☐

Gain: ☐☐ db

Grade: 0: No signal
1: mild increase in vascular flow: 1 red dot
2: moderate: 2 red dots
3: marked: 3 or more red dots

PRF = 0.6 kHz. Save 1 image for each

Comments: ☐

Blood taken

Date: ☐☐ / ☐☐ / ☐☐☐☐

Time Taken ☐☐ : ☐☐ AM ○ PM ○

Location

Gregory Street ○

Kirksway house ○

Other - name ○ ☐

Total cholesterol	Yes ○	No ○
Total triglycerides	Yes ○	No ○
TC:HDL-C ratio	Yes ○	No ○
HbA1C (%)	Yes ○	No ○
Fasting glucose	Yes ○	No ○
hs-CRP	Yes ○	No ○
TNF-α	Yes ○	No ○
IL-6	Yes ○	No ○
Leptin	Yes ○	No ○

If 'No', reason for Incomplete blood Sample

Refusal ○

Patient felt faint ○

Difficulty finding vein ○

Vein Collapsed ○

Has the blood been transferred to MRIT for storage? Yes ○ No ○

If 'No', reason for why not ☐

If 'Yes',
date transferred ☐☐ / ☐☐ / ☐☐☐☐

transferred by ☐☐☐

Accelerometer

Accelerometer Issued? Yes ○ No ○

If Yes...

Date given ☐☐ / ☐☐ / ☐☐☐☐

Same as Interview date (no requirement to fill this date field) ○

Accelerometer number: ☐☐☐

Issued by: ☐☐☐

If No, specify reason...

Refused ○

Other (Please Specify) ○ ☐

Accelerometer returned:

Date returned ☐☐ / ☐☐ / ☐☐☐☐

Received by: ☐☐☐

Data downloaded successfully? Yes ○ No ○

If Yes...

Downloaded by: ☐☐☐

If No, why?

Data insufficient/incomplete (invalid for entry) ○

Data corrupt/fail (software) ○

Unit lost, broken or not returned (hardware) ○

Other, please specify ○ ☐

QCT of heel

Date completed ☐☐ / ☐☐ / ☐☐☐☐

Same as Interview date (no requirement to fill this date field) ○

Radiographer: ☐☐☐

Foot scanned: Left ○ Right ○

3 stacks? Yes ○ No ○

If No, why not? ☐

If QCT not taken but eligible, reason why

Refusal ○

Physical restrictions ○

Other (please specify) ○ ☐

Comments: ☐

MRI

MRI completed? Yes ○ No ○

If Yes,

Date completed ☐☐ / ☐☐ / ☐☐☐☐

Technician: ☐☐☐

Foot scanned: Left ○ Right ○

If No, state reason

Refusal ○

Physical restrictions ○

Claustrophobic ○

Other (please specify) ○ ☐

Comments: ☐

9.8 Appendix 8: Ethics amendments

1	Add HR-pQCT, change outcome measure from Foot function index to FHSQ, expand pain VAS assessment tools to current, past 24hrs & first-step pain, discontinue 6-month follow up, remove adiponectin from blood test regime (bloods not part of this thesis), changes to US scoring, include controls.	03/06/2014
2	Add PHQ-9, Pain Catstrophising Scale and pain DETECT questionnaires to assessment. Request consent to examine treatment records.	11/09/2014
3	Change QOL outcome measure from SF-36 to AQOL-6D	16/09/2014
4	Request to advertise project by social media, flyers and internet/ email	31/10/2014
5	Increase recruitment of cases from 50 to 220	16/02/2015
6	Approval to mail out recruitment material to sporting clubs and workplaces	20/10/2015
7	MRI case participants at follow up time point	24/11/2015
8	Update paperwork for controls (letter of invitation, follow-up letter of invitation, and consent).	04/09/2016
9	Add transverse US scan data collection for control participants	08/11/2016

9.9 Appendix 9: Licence approval to reproduce images

9.9.1 Figure 1-1 printed on page 3:

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