

## RESEARCH ARTICLE

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

Jason Andrew Rogers<sup>1</sup>, Graeme Jones<sup>1</sup>, Jill Cook<sup>2</sup>, Kathryn Squibb<sup>1,3</sup>, Karen Wills<sup>1</sup>, Aroub Lahham<sup>1,4</sup>, Tania Winzenberg<sup>1,5\*</sup>

**1** Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia, **2** La Trobe Sport and Exercise Medicine Centre, La Trobe University, Melbourne, Victoria, Australia, **3** Department of Health, Tasmanian Health Service, Scottsdale, Tasmania, Australia, **4** Department of Allergy, Clinical Immunology and Respiratory Medicine, Monash University, Melbourne, Victoria, Australia, **5** Faculty of Health, University of Tasmania, Hobart, Tasmania, Australia

\* [Tania.winzenberg@utas.edu.au](mailto:Tania.winzenberg@utas.edu.au)



## OPEN ACCESS

**Citation:** Rogers JA, Jones G, Cook J, Squibb K, Wills K, Lahham A, et al. (2021) 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>

**Editor:** Ewa Tomaszewska, University of Life Sciences in Lublin, POLAND

**Received:** July 3, 2021

**Accepted:** November 22, 2021

**Published:** December 9, 2021

**Copyright:** © 2021 Rogers et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** The dataset generated from this study will not be deposited in a public repository as the data contain sensitive participant information and the participant consent did not include data sharing permissions. A request for access to the data can be made to the corresponding author (Prof Tania Winzenberg, Menzies Institute for Medical Research, University of Tasmania [Tania.Winzenberg@utas.edu.au](mailto:Tania.Winzenberg@utas.edu.au)) or to a representative of our Institute (Mr Mark Bennett,

## Abstract

Chronic plantar heel pain (CPHP) is associated with calcaneal bone spurs, but its associations with other calcaneal bone features are unknown. This study therefore aimed to determine associations between having CPHP and bone density and microarchitecture of the calcaneus. We assessed 220 participants with CPHP and 100 age- and sex-matched population-based controls. Trabecular bone density, thickness, separation and number, BV/TV, and cortical density, thickness and area were measured using a Scanco Xtreme1 HR-pQCT scanner at a plantar and mid-calcaneal site. Clinical, physical activity and disease history data were also collected. Associations with bone outcomes were assessed using multivariable linear regression adjusting for age, sex, physical activity, BMI and ankle plantarflexor strength. We assessed for potential effect modification of CPHP on these covariates using interaction terms. There were univariable associations at the plantar calcaneus where higher trabecular bone density, BV/TV and thickness and lower trabecular separation were associated with CPHP. In multivariable models, having CPHP was not independently associated with any bone outcome, but modified associations of BMI and ankle plantarflexor strength with mid-calcaneal and plantar bone outcomes respectively. Beneficial associations of BMI with mid-calcaneal trabecular density (BMI-case interaction standardised X/unstandardised Y beta  $-10.8(\text{mgHA}/\text{cm}^3)$  (se 4.6), thickness  $-0.002(\text{mm})$  (se 0.001) and BV/TV  $-0.009(\%)$  (se 0.004) were reduced in people with CPHP. Beneficial associations of ankle plantarflexor strength with plantar trabecular density (ankle plantarflexor strength-case interaction  $-11.9(\text{mgHA}/\text{cm}^3)$  (se 4.4)), thickness  $-0.003(\text{mm})$  (se 0.001), separation  $-0.003(\text{mm})$  (se 0.001) and BV/TV  $-0.010(\%)$  (se 0.004) were also reduced. CPHP may have consequences for calcaneal bone density and microarchitecture by modifying associations of BMI and ankle plantarflexor strength with calcaneal bone outcomes. The reasons for these case-control differences are uncertain but could include a bone response to

Director- Research Development, [Mark.Bennett@utas.edu.au](mailto:Mark.Bennett@utas.edu.au)).

**Funding:** This research was funded by grants from the Physiotherapy Research Foundation (JR, seeding grant S14-025, <https://australian.physio/PRF>), grants from the Halifax Foundation (JR, philanthropic/ UTAS), grants-in aid from Arthritis Australia (JR, 2015, <https://arthritisaustralia.com.au/programs-research/national-research-program/our-grants/>), establishment grants from the Royal Hobart Hospital Research Foundation (GJ/ JR, 17-203, <https://www.rhhresearchfoundation.org/>), grants from the Rebecca L Cooper Medical Research Foundation (JR, 2015 <https://www.cooperfoundation.org.au/>), and a donation from Allcare Physiotherapy Tasmania (JR, 2015/ 2016, <https://allcarephysio.com.au/>). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** Competing interests: Jason Rogers is a Director and employee of Allcare Physiotherapy Tasmania, which provided funding support to conduct this study. No other author reports an affiliation or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the article. Funding bodies had no involvement in the design, implementation, analysis nor reporting of this study.

enthesal stress, altered loading habits and/or pain mechanisms. Confirmation with longitudinal study is required.

## 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 [1]. It is the most common reason why individuals with musculoskeletal foot pain consult a foot health practitioner [1], and is associated with significant foot-related disability and impaired quality of life (QOL) [2].

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 [3], plantar fascial thickening [4] and plantar enthesophytes [4] 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 enthesal 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.

## Participants and methods

### Study design

Cross-sectional analysis of a case-control study using case status (presence of CPHP) as the exposure of interest.

### Setting & 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.

## Inclusion/Exclusion

Inclusion criteria for cases were: aged over 18 years, have CPHP defined as pain under the heel aggravated by '1<sup>st</sup> 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.

## Sample size calculations

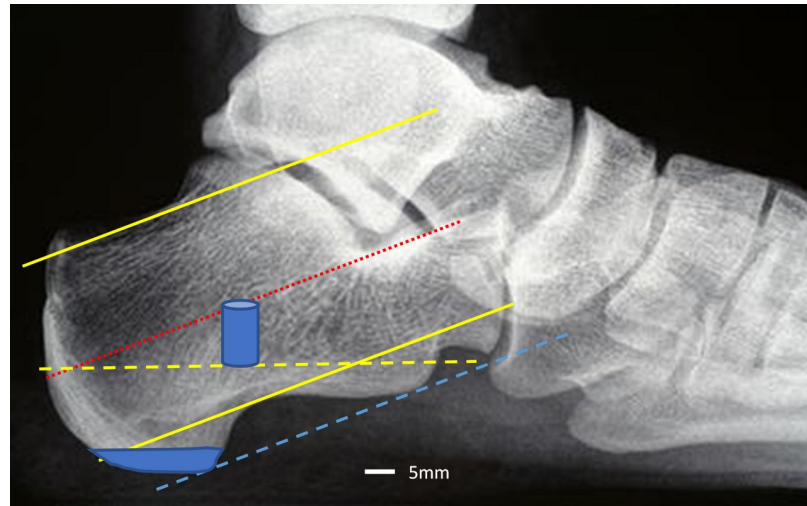
The case-control analysis is nested within a 12-month longitudinal study of cases. Sample size calculations for the longitudinal component of the study determined that 220 cases were required (assuming  $\alpha = 0.05$  (two-tailed) and 80% power for longitudinal hypotheses, with a loss to follow up 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  $\alpha$  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.

## Data collection

**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 82 $\mu$ m. 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.

**Region of interest (ROI) selection and analysis.** Plantar and mid-calcaneal regions were located on a scout image (Fig 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.



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

<https://doi.org/10.1371/journal.pone.0260925.g001>

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 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  $1\text{cm}^2$  by 1 stack high (110 slices/ $\sim 9\text{mm}$ ).

For each ROI, native Scanco analysis software (V6.5–3) was used to generate trabecular density (milligrams of hydroxyapatite/cubic centimetre ( $\text{mg HA}/\text{cm}^3$ )), separation (mm), thickness (mm) and number (1/mm) measures, bone volume fraction (BV/TV %), and cortical density ( $\text{mg HA}/\text{cm}^3$ ), mean thickness (mm) and area ( $\text{mm}^2$ ) 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  $1200\text{ mg HA}/\text{cm}^3$ .

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 ordinarily 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%,  $n = 50$ ).

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 ( $\text{weight(kg)/ht(m)}^2$ ). 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  $\text{ICC}_{3,1} = 0.96$ ,  $n = 18$ ) [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 ( $\geq 1,952$  CPM/ $\geq 1065$  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,  $\text{ICC} = 0.92$ ) [21]. Quality of life was measured with the Australian Quality of Life scale, AQoL-6D [22] (Cronbach's alpha 0.94,  $\text{ICC} = 0.85$  to 0.88), (<http://www.aqol.com.au/aqolquestionnaires/56.html>).

## 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).

**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.

## 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 2).

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 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%).

Bone density and microstructural parameters were similar in cases and controls at the mid-calcaneal site (Table 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.

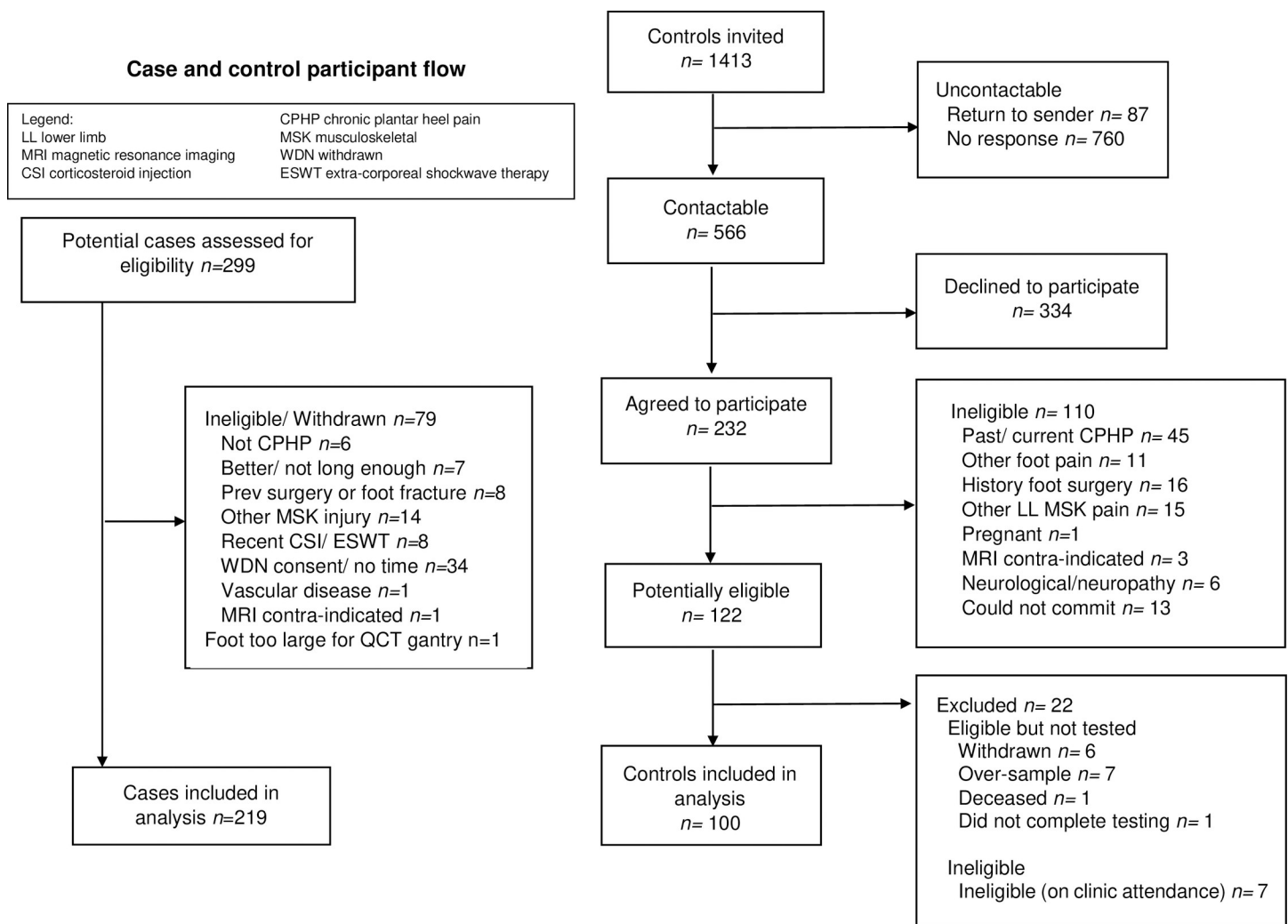


Fig 2. Case and control participant flow.

<https://doi.org/10.1371/journal.pone.0260925.g002>

**Table 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 <sup>a</sup> %(n)                         |        | 36.6 (48/131)     | 41.7 (25/60)       |
| On HRT <sup>a</sup> %(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)           |
| <b>Physical activity</b>                            |        |                   |                    |
| Accelerometry (median, IQR)                         |        |                   |                    |
| Average steps/day <sup>b</sup>                      |        | 7918 (6148, 9903) | 8373 (6080, 10205) |
| Moderate-to-vigorous (average min/day) <sup>c</sup> |        | 38 (18, 61)       | 42 (20, 58)        |
| Sedentary (average min/day) <sup>d</sup>            |        | 491 (437, 545)    | 502 (443, 561)     |
| <b>Quality of life &amp; function</b>               |        |                   |                    |
| AQOL-6D <sup>e</sup>                                |        | 76.4 (10.8)       | 86.38 (6.9)        |
| FHSQ function <sup>f</sup>                          |        | 65.74 (27.8)      | 99.13 (3.3)        |
| <b>Clinical measures</b>                            |        |                   |                    |
| BMI (kg/m <sup>2</sup> )                            |        | 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)                            |        | 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)       |
| 1 <sup>st</sup> MTP extension ROM (deg)             |        | 70.28 (15.1)      | 74.78 (14.4)       |

\* values are Mean (SD), unless specified otherwise.

<sup>a</sup> % of females only.

<sup>b</sup> case n = 207, control n = 96.

<sup>c</sup> case n = 211, control n = 96.

<sup>d</sup> case n = 211, control n = 96.

<sup>e</sup> Assessment of Quality of Life-6 Dimension scale, 0–100, higher is better.

<sup>f</sup> Foot Health Status Questionnaire (weighted), 0–100, higher = better function.

MTP metatarsophalangeal, ROM Range of motion.

<https://doi.org/10.1371/journal.pone.0260925.t001>

Univariable associations of CPHP and other factors with bone outcomes are given in [Table 3](#), with those associations having  $P < 0.05$  indicated in bold. Having CPHP was associated with higher trabecular density, BV/TV and trabecular thickness and lower trabecular separation in the plantar ROI but was not associated with any mid-calcaneal bone outcome ([Table 3](#), **all  $p < 0.05$ , ranging from 0.012 to 0.041**). 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

**Table 2. Bone indices.**

| Mid calcaneal ROI                           | Case (n = 219) |              | Control (n = 100) |              |
|---|----------------|--------------|-------------------|--------------|
|   | mean           | sd           | mean              | sd           |
| Trabecular density (mg HA/cm <sup>3</sup> ) | 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 <sup>3</sup> ) | <b>356</b>     | <b>37</b>    | <b>345</b>        | <b>47</b>    |
| Bone volume fraction (BV/TV)                | <b>0.30</b>    | <b>0.03</b>  | <b>0.29</b>       | <b>0.04</b>  |
| Trabecular number (/mm)                     | 3.95           | 0.15         | 3.92              | 0.16         |
| Trabecular separation (mm)                  | <b>0.178</b>   | <b>0.012</b> | <b>0.182</b>      | <b>0.015</b> |
| Trabecular thickness (mm)                   | <b>0.075</b>   | <b>0.008</b> | <b>0.073</b>      | <b>0.009</b> |
| Cortical density (mg HA/cm <sup>3</sup> )   | 641            | 69           | 647               | 79           |
| Mean cortical thickness (mm)                | 0.846          | 0.41         | 0.897             | 0.55         |
| Mean cortical area (mm <sup>2</sup> )       | 57.9           | 29.5         | 57.6              | 36.1         |

Bold denotes p for case-control comparison <0.05, t-test for continuous data.

ROI region of interest, sd standard deviation.

<https://doi.org/10.1371/journal.pone.0260925.t002>

was not associated with trabecular density, but positively associated with trabecular number and negatively associated with trabecular thickness.

**Table 3. Univariable results for mid-calcaneal and plantar ROI, standardized co-efficients(se)<sup>a,b</sup>.**

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

<sup>a</sup>Univariable linear regression model, standardized X co-efficient/unstandardized Y (standard error). All n = 319 unless stated.

<sup>b</sup>Bold denotes statistically significant with p<0.05.

<sup>c</sup>case = 1, control = 0.

<sup>d</sup>female = 1, male = 0.

<sup>e</sup> MVPA, moderate to vigorous physical activity, average minutes per day, by accelerometry, n = 306.

<https://doi.org/10.1371/journal.pone.0260925.t003>



Associations of CPHP status with bone outcomes were largely unchanged in an adjusted main effects model (S1 Table) but there were significant interaction terms in the final multivariable model, with those associations having  $p < 0.05$  highlighted in bold (Table 4, all interaction terms  $p < 0.05$ , ranging from 0.006 to 0.019). The positive association of BMI with mid-calcaneal trabecular density, BV/TV and thickness was less in cases compared to controls (Fig 3A–3C). In the plantar ROI, the positive association of ankle plantarflexor strength with plantar trabecular density, BV/TV and thickness (Fig 4A–4C), and the negative association with trabecular separation (Fig 4D), 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.

### 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 (S2 Table) ( $p$ -values = 0.050 and 0.051 respectively). Other interactions

**Table 4. Multivariable results for mid-calcaneal and plantar ROI, standardized co-efficients(se)<sup>a,b</sup>.**

| Mid-calcaneal ROI        | Trabecular density <sup>d</sup><br>(mg HA/cm <sup>3</sup> ) | BV/TV (%) <sup>d</sup>         | Trabecular thickness<br>(mm) <sup>d</sup> | Trabecular number<br>(/mm) <sup>d</sup> | Trabecular separation<br>(mm) <sup>e</sup> |   |
|--------------------------|---|--------------------------------|---|---|--|---|
| Case status <sup>c</sup> | -6.6 (4.8)  | <b>-0.006</b> (0.004)          | <b>-0.002</b> (0.001)                     | 0.029 (0.018)                           | -0.001 (0.002)                             |   |
| BMI                      | <b>19.9</b> (3.8)   | <b>0.017</b> (0.003)           | <b>0.004</b> (0.001)                      | <b>0.021</b> (0.008)                    | <b>-0.005</b> (0.001)                      |   |
| BMI*Case interaction     | <b>-10.8</b> (4.6)  | <b>-0.009</b> (0.004)          | <b>-0.002</b> (0.001)                     | -                                       | -  |   |
| APFS                     | -0.05 (2.7)   | 0.000 (0.002)                  | -0.000 (0.001)                            | <b>0.036</b> (0.010)                    | <b>-0.003</b> (0.001)                      |   |
| Age                      | <b>-13.1</b> (2.4)  | <b>-0.011</b> ( <b>0.002</b> ) | <b>-0.003</b> ( <b>0.000</b> )            | -0.015 (0.009)                          | <b>0.004</b> (0.001)                       |   |
| Female sex               | <b>-9.0</b> (2.6)   | <b>-0.008</b> ( <b>0.002</b> ) | -0.002 (0.001)                            | <b>-0.118</b> (0.010)                   | <b>0.008</b> (0.001)                       |   |
| MVPA                     | -   | -                              | -   | -                                       | <b>-0.002</b> (0.001)                      |   |
| Plantar ROI              | Trabecular density<br>(mg HA/cm <sup>3</sup> ) <sup>f</sup> | BV/TV (%) <sup>f</sup>         | Trabecular thickness<br>(mm) <sup>f</sup> | Trabecular number<br>(/mm) <sup>g</sup> | Trabecular separation<br>(mm) <sup>f</sup> | Cortical density<br>(mg HA/cm <sup>3</sup> ) <sup>f</sup> |
| Case status <sup>c</sup> | <b>12.3</b> (4.6)   | <b>0.010</b> (0.004)           | <b>0.002</b> (0.001)                      | 0.027 (0.014)                           | <b>-0.004</b> (0.001)                      | -7.3 (8.6)  |
| APFS                     | <b>14.4</b> (3.8)   | <b>0.012</b> (0.003)           | <b>0.003</b> (0.001)                      | <b>0.026</b> (0.008)                    | <b>-0.004</b> (0.001)                      | -0.9 (4.8)  |
| APFS*Case interaction    | <b>-11.9</b> (4.4)  | <b>-0.010</b> (0.004)          | <b>-0.003</b> (0.001)                     | -                                       | <b>0.003</b> (0.001)                       | -   |
| BMI                      | <b>10.4</b> (2.1)   | <b>0.009</b> (0.002)           | <b>0.001</b> (0.001)                      | <b>0.047</b> (0.007)                    | <b>-0.004</b> (0.001)                      | 2.8 (3.9)   |
| Age                      | -3.7 (2.4)  | -0.003 (0.002)                 | -0.001 (0.001)                            | 0.007 (0.008)                           | 0.001 (0.001)                              | <b>-23.8</b> (4.4)  |
| Female sex               | <b>-6.4</b> (2.5)   | <b>-0.005</b> (0.002)          | 0.000 (0.001)                             | <b>-0.084</b> (0.008)                   | <b>0.005</b> (0.001)                       | <b>-16.6</b> (4.7)  |
| MVPA                     | -   | -                              | -   | 0.009 (0.007)                           | -  | -   |

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

<sup>a</sup>Multivariable linear regression model, standardized X co-efficients, unstandardized Y (standard error).

<sup>b</sup>Bold denotes statistically significant with  $p < 0.05$ .

<sup>c</sup>case = 1, control = 0.

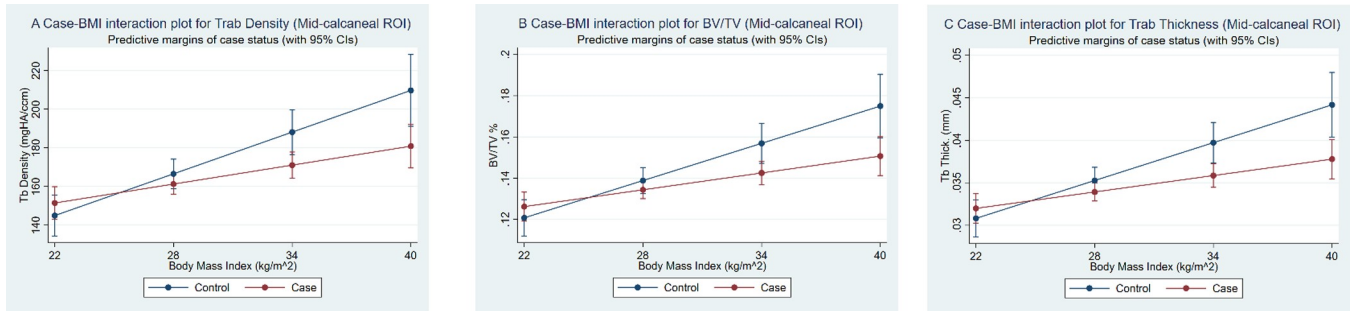
<sup>d</sup>Adjusted for age, sex & ankle plantarflexor strength,  $n = 319$ .

<sup>e</sup>Adjusted for age, sex, ankle plantarflexor strength and physical activity (MVPA),  $n = 306$ .

<sup>f</sup>Adjusted for age, sex, & BMI,  $n = 319$ .

<sup>g</sup>Adjusted for age, sex, BMI & physical activity (MVPA),  $n = 306$ .

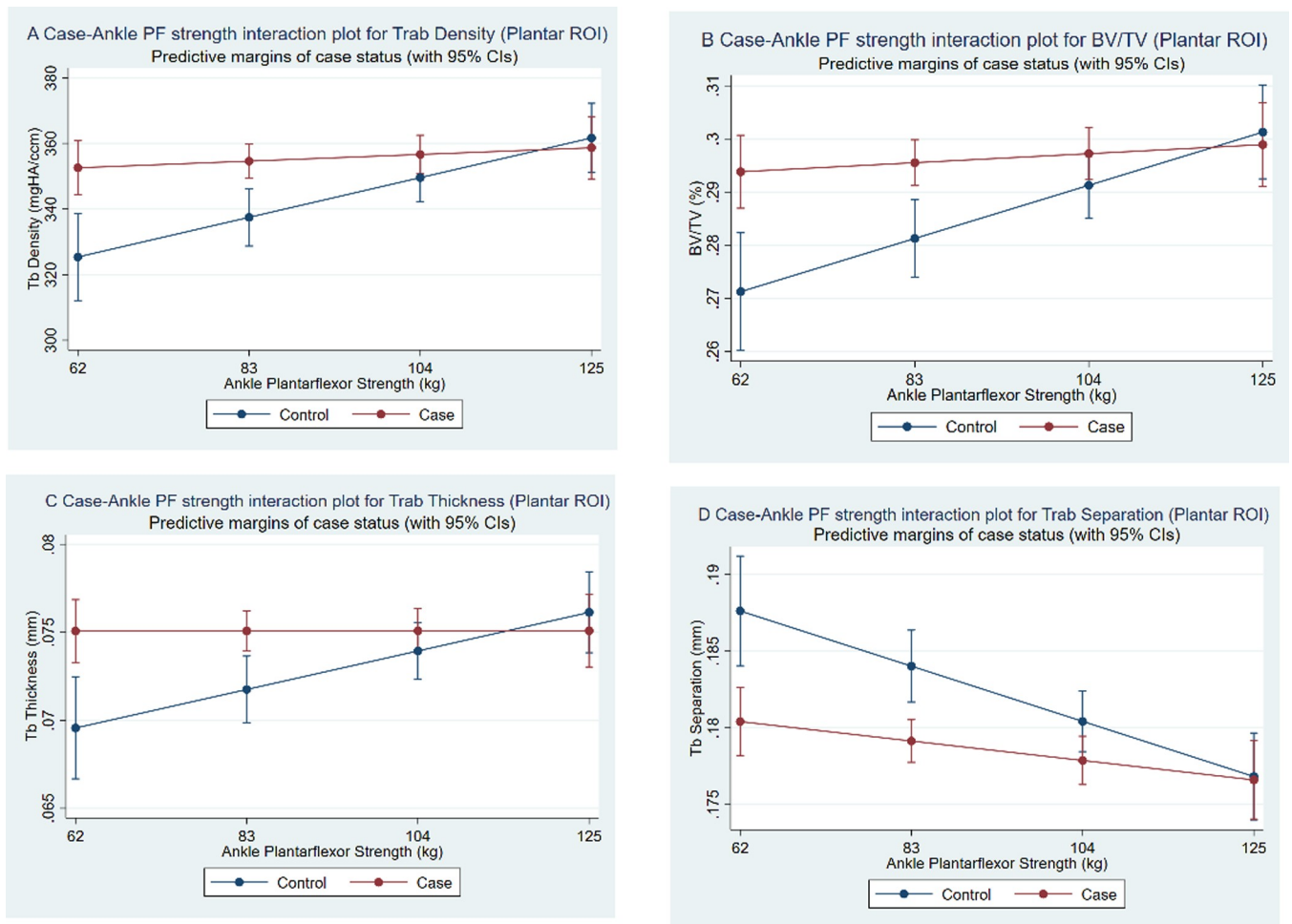
<https://doi.org/10.1371/journal.pone.0260925.t004>



**Fig 3.** (A) Case-BMI interaction plots for mid-calcaneal ROI trabecular density, (B) BV/TV and (C) trabecular thickness. Bone outcomes plotted from the 10th to 90th percentile of BMI.

<https://doi.org/10.1371/journal.pone.0260925.g003>

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 (S3 Table).



**Fig 4.** (A) Case-ankle plantarflexor strength interaction plot for plantar ROI trabecular density, (B) BV/TV, (C) thickness and (D) separation. Bone outcomes plotted from the 10th to 90th percentile of ankle plantarflexor strength.

<https://doi.org/10.1371/journal.pone.0260925.g004>

## 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 enthesal 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 4A–4D, 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 enthesal 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 [4] supports this. These are thought to develop in response to enthesal degenerative change [3] and hypothesized to serve a load sharing, adaptive function in response to such stress [3,24]. 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 [3]. The interaction plots (Fig 4A–4D) 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.

## 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.

## 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 enthesal 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.

## Supporting information

**S1 Table. Main effects model, standardized co-efficients (se)<sup>a</sup>.** ROI region of interest, BMI body mass index, PF plantarflexor, BV/TV bone volume fraction, MVPA moderate to vigorous physical activity. <sup>a</sup>Multivariable linear regression model, standardized X co-efficients/unstandardized Y (standard error). Bold denotes statistically significant with  $p < 0.05$ . <sup>b</sup>case = 1, control = 0. <sup>c</sup>Adjusted for age & sex, n = 319. <sup>d</sup>Adjusted for age, sex and physical activity (MVPA), n = 306. (DOCX)

**S2 Table. Sensitivity analysis for scan quality; omitting poorer quality (grade 3) scans, standardised co-efficients (se)<sup>a</sup>.** ROI region of interest, BV/TV bone volume/total volume, BMI body mass index, APFS ankle plantarflexor strength, MVPA moderate to vigorous physical activity. <sup>a</sup>Multivariable linear regression, standardized X/unstandardized Y co-efficients (standard error). Bold denotes statistically significant with  $p < 0.05$ , Underline = changed significance, <sup>b</sup>case = 1, control = 0, <sup>c</sup>Moderate to vigorous physical activity, average minutes per day, by accelerometry. <sup>d</sup>Adjusted for age, sex & ankle plantarflexor strength, n = 236 <sup>e</sup>Adjusted for age, sex, ankle plantarflexor strength and physical activity (MVPA), n = 227. <sup>f</sup>Adjusted for age, sex, & BMI, n = 236. <sup>g</sup>Adjusted for age, sex, BMI & physical activity (MVPA), n = 227. (DOCX)

**S3 Table. Sensitivity analysis; omitting influential observations, standardised co-efficients (se)<sup>a</sup>.** ROI region of interest, BV/TV bone volume/total volume, BMI body mass index, APFS ankle plantarflexor strength, MVPA moderate to vigorous physical activity. <sup>a</sup>Multivariable linear regression, standardized X/unstandardized Y co-efficients (standard error). Bold denotes statistically significant with  $p < 0.05$ . <sup>b</sup>case = 1, control = 0. <sup>c</sup>Moderate to vigorous physical activity, average minutes per day, by accelerometry. <sup>d</sup>Adjusted for age, sex & ankle plantarflexor strength. <sup>e</sup>Adjusted for age, sex, ankle plantarflexor strength and physical activity (MVPA). <sup>f</sup>Adjusted for age, sex, & BMI. <sup>g</sup>Adjusted for age, sex, BMI & physical activity (MVPA). (DOCX)

## Acknowledgments

Menzies volunteers for assistance with scheduling, co-ordination and study administration. Dr Kate Squibb for assistance in the clinic, Mr Tim Albion for assistance with configuring the database, Mr Brian Stokes for supplying access to study controls and Dr Ali Ghasem-Zadeh for HR-pQCT technical advice and scanner support.

## Author Contributions

**Conceptualization:** Jason Andrew Rogers, Tania Winzenberg.

**Data curation:** Jason Andrew Rogers, Kathryn Squibb, Aroub Lahham.

**Formal analysis:** Jason Andrew Rogers, Karen Wills.

**Funding acquisition:** Jason Andrew Rogers, Tania Winzenberg.

**Investigation:** Jason Andrew Rogers, Kathryn Squibb, Aroub Lahham.

**Methodology:** Jason Andrew Rogers, Graeme Jones, Jill Cook, Karen Wills, Tania Winzenberg.

**Project administration:** Jason Andrew Rogers, Kathryn Squibb, Tania Winzenberg.

**Resources:** Graeme Jones, Tania Winzenberg.

**Supervision:** Graeme Jones, Jill Cook, Tania Winzenberg.

**Validation:** Jason Andrew Rogers, Karen Wills.

**Visualization:** Jason Andrew Rogers.

**Writing – original draft:** Jason Andrew Rogers, Tania Winzenberg.

**Writing – review & editing:** Jason Andrew Rogers, Graeme Jones, Jill Cook, Kathryn Squibb, Karen Wills, Aroub Lahham, Tania Winzenberg.

## References

1. McPoil TG, Martin RL, Cornwall MW, Wukich DK, Irrgang JJ, Godges JJ, et al. Heel pain-plantar Fasciitis—Clinical practice guidelines linked to the international classification of function disability, and health from the orthopaedic section of the American Physical Therapy Association. *Journal of Orthopaedic & Sports Physical Therapy*. 2008; 38(4):A1–A18. PubMed PMID: WOS:000254759700009.
2. Irving DB, Cook JL, Young MA, Menz HB. Impact of chronic plantar heel pain on health-related quality of life. *J Am Podiatr Med Assoc*. 2008; 98(4):283–9. Epub 2008/08/08. <https://doi.org/10.7547/0980283> PMID: 18685048.
3. Kumai T, M B. Heel spur formation and the subcalcaneal entheses of the plantar fascia. *Journal of Rheumatology*. 2002; 29(9):1957–64. PubMed PMID: 34988707 Embase Accession Number 2002321162 PMID PMID: 12233893 [<http://www.ncbi.nlm.nih.gov/pubmed/?term=12233893>] Status Embase.
4. 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; 50(16):972–81. Epub 2015/12/09. <https://doi.org/10.1136/bjsports-2015-094695> PMID: 26644427.
5. Erdemir A, Hamel AJ, Fauth AR, Piazza SJ, Sharkey NA. Dynamic loading of the plantar aponeurosis in walking. *J Bone Joint Surg Am*. 2004; 86(3):546–52. Epub 2004/03/05. <https://doi.org/10.2106/0004623-200403000-00013> PMID: 14996881.
6. 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; 51(9):449–58. Epub 2021/05/09. <https://doi.org/10.2519/jospt.2021.10018> PMID: 33962520; PubMed Central PMCID: PMC33962520.
7. Best A, Holt B, Troy L, Hamill J. Trabecular bone in the calcaneus of runners. *PLoS One*. 2017; 12(11): e0188200. Epub 2017/11/16. <https://doi.org/10.1371/journal.pone.0188200> PMID: 29141022; PubMed Central PMCID: PMC5687755.
8. Metcalf LM, Dall'Ara E, Paggiosi MA, Rochester JR, Vilayphiou N, Kemp GJ, et al. Validation of calcaneus trabecular microstructure measurements by HR-pQCT. *Bone*. 2018; 106:69–77. Epub 2017/10/08. <https://doi.org/10.1016/j.bone.2017.09.013> PMID: 28986143.
9. Vogel JM, Wasnich RD, Ross PD. The clinical relevance of calcaneus bone mineral measurements: a review. *Bone Miner*. 1988; 5(1):35–58. Epub 1988/10/01. [https://doi.org/10.1016/0169-6009\(88\)90005-0](https://doi.org/10.1016/0169-6009(88)90005-0) PMID: 3063317.
10. Pialat JB, Burghardt AJ, Sode M, Link TM, Majumdar S. Visual grading of motion induced image degradation in high resolution peripheral computed tomography: impact of image quality on measures of bone density and micro-architecture. *Bone*. 2012; 50(1):111–8. Epub 2011/10/25. <https://doi.org/10.1016/j.bone.2011.10.003> PMID: 22019605.
11. Boutroy S, Bouxsein ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab*. 2005; 90(12):6508–15. Epub 2005/09/29. <https://doi.org/10.1210/jc.2005-1258> PMID: 16189253.
12. Laib A, Hauselmann HJ, Rueggsegger P. In vivo high resolution 3D-QCT of the human forearm. *Technol Health Care*. 1998; 6(5–6):329–37. Epub 1999/04/01. PMID: 10100936.
13. Whittier DE, Boyd SK, Burghardt AJ, Paccou J, Ghasem-Zadeh A, Chapurlat R, et al. Guidelines for the assessment of bone density and microarchitecture in vivo using high-resolution peripheral quantitative computed tomography. *Osteoporos Int*. 2020; 31(9):1607–27. Epub 2020/05/28. <https://doi.org/10.1007/s00198-020-05438-5> PMID: 32458029; PubMed Central PMCID: PMC7429313.

14. Laib A, Ruegsegger P. Comparison of structure extraction methods for in vivo trabecular bone measurements. *Comput Med Imaging Graph.* 1999; 23(2):69–74. Epub 1999/05/05. [https://doi.org/10.1016/S0895-6111\(98\)00071-8](https://doi.org/10.1016/S0895-6111(98)00071-8) PMID: 10227372.
15. Moraux A, Canal A, Ollivier G, Ledoux I, Doppler V, Payan C, et al. Ankle dorsiflexion and plantar-flexion torques measured by dynamometry in healthy subjects from 5 to 80 years. *BMC Musculoskelet Disord.* 2013; 14:104. Epub 2013/03/26. <https://doi.org/10.1186/1471-2474-14-104> PMID: 23522186; PubMed Central PMCID: PMC3617997.
16. Trost SG, McIver KL, Pate RR. Conducting accelerometer-based activity assessments in field-based research. *Med Sci Sports Exerc.* 2005; 37(11 Suppl):S531–43. Epub 2005/11/19. <https://doi.org/10.1249/01.mss.0000185657.86065.98> PMID: 16294116.
17. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc.* 2008; 40(1):181–8. Epub 2007/12/20. <https://doi.org/10.1249/mss.0b013e31815a51b3> PMID: 18091006.
18. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. *Med Sci Sports Exerc.* 1998; 30(5):777–81. Epub 1998/05/20. <https://doi.org/10.1097/00005768-199805000-00021> PMID: 9588623.
19. Gorman E, Hanson HM, Yang PH, Khan KM, Liu-Ambrose T, Ashe MC. Accelerometry analysis of physical activity and sedentary behavior in older adults: a systematic review and data analysis. *Eur Rev Aging Phys Act.* 2014; 11:35–49. Epub 2014/04/26. <https://doi.org/10.1007/s11556-013-0132-x> PMID: 24765212; PubMed Central PMCID: PMC3990855.
20. Copeland JL, Eslinger DW. Accelerometer assessment of physical activity in active, healthy older adults. *J Aging Phys Act.* 2009; 17(1):17–30. Epub 2009/03/21. <https://doi.org/10.1123/japa.17.1.17> PMID: 19299836.
21. Bennett PJ, Patterson C, Wearing S, Baglioni T. Development and validation of a questionnaire designed to measure foot-health status. *J Am Podiatr Med Assoc.* 1998; 88(9):419–28. Epub 1998/10/15. <https://doi.org/10.7547/87507315-88-9-419> PMID: 9770933.
22. Richardson J DN, Peacock S and Iezzi A. Measurement of the Quality of Life for Economic Evaluation and the Assessment of Quality of Life (AQoL) Mark 2 Instrument. *The Australian Economic Review.* 2004; 37(1): 62–88.
23. Burr DB, Gallant MA. Bone remodelling in osteoarthritis. *Nat Rev Rheumatol.* 2012; 8(11):665–73. Epub 2012/08/08. <https://doi.org/10.1038/nrrheum.2012.130> PMID: 22868925.
24. Smith S TP, Gilheany M, Grills B, Kingsford A. The inferior calcaneal spur- Anatomical and histological considerations. *The Foot.* 2007; 17:25–31. <https://doi.org/10.1016/j.foot.2006.10.002>
25. Cao JJ. Effects of obesity on bone metabolism. *J Orthop Surg Res.* 2011; 6:30. Epub 2011/06/17. <https://doi.org/10.1186/1749-799X-6-30> PMID: 21676245; PubMed Central PMCID: PMC3141563.
26. Sullivan J, Burns J, Adams R, Pappas E, Crosbie J. Plantar heel pain and foot loading during normal walking. *Gait & posture.* 2015; 41(2):688–93. <https://doi.org/10.1016/j.gaitpost.2015.01.025> PMID: 25724260
27. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes.* 2007; 56(4):1010–3. Epub 2007/02/09. <https://doi.org/10.2337/db06-1656> PMID: 17287468.
28. Redlich K, Smolen JS. Inflammatory bone loss: pathogenesis and therapeutic intervention. *Nat Rev Drug Discov.* 2012; 11(3):234–50. Epub 2012/03/02. <https://doi.org/10.1038/nrd3669> PMID: 22378270.
29. Shapses SA, Pop LC, Wang Y. Obesity is a concern for bone health with aging. *Nutr Res.* 2017; 39:1–13. Epub 2017/04/08. <https://doi.org/10.1016/j.nutres.2016.12.010> PMID: 28385284; PubMed Central PMCID: PMC5385856.
30. Grassel SG. The role of peripheral nerve fibers and their neurotransmitters in cartilage and bone physiology and pathophysiology. *Arthritis Res Ther.* 2014; 16(6):485. Epub 2014/01/01. <https://doi.org/10.1186/s13075-014-0485-1> PMID: 25789373; PubMed Central PMCID: PMC4395972.
31. Jones KB, Mollano AV, Morcuende JA, Cooper RR, Saltzman CL. Bone and brain: a review of neural, hormonal, and musculoskeletal connections. *Iowa Orthop J.* 2004; 24:123–32. Epub 2004/08/07. PMID: 15296219; PubMed Central PMCID: PMC1888423.
32. Shea JE, Vajda EG, Bloebaum RD. Evidence of a hypermineralised calcified fibrocartilage on the human femoral neck and lesser trochanter. *J Anat.* 2001; 198(Pt 2):153–62. Epub 2001/03/29. <https://doi.org/10.1046/j.1469-7580.2001.19820153.x> PMID: 11273040; PubMed Central PMCID: PMC1468213.