**Pain at sites outside the knee predicts knee cartilage volume loss in elderly people without knee osteoarthritis: a prospective study**

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**Funding sources:** National Health and Medical Research Council of Australia (302204), the Tasmanian Community Fund (D0015018), the Arthritis Foundation of Australia (MRI06161), and the University of Tasmania Grant-Institutional Research Scheme (D0015019).

**Conﬂict of interest:** None.

**Word count: 3,762**

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**Abstract**

**Objective:** Pain is common in the elderly. Knee pain may predict knee cartilage loss, but whether generalised pain is associated with knee cartilage loss is unclear. This study, therefore, aimed to determine whether pain at multiple sites predicts knee cartilage volume loss amongst community–dwelling older adults, and if so, to explore potential mechanisms.

**Methods:** Data from the prospective Tasmanian Older Adult Cohort study was utilised (n=394; mean age, 63 years; range 52 to 79). Pain experience at multiple sites was assessed using a questionnaire at baseline. T1–weighted fat saturated MRI of the right knee was performed to assess the cartilage volume at baseline and after 2.6 years. Linear regression modelling was used with adjustment for potential confounders.

**Results:** The median number of painful sites was 3 (range 0-7). There was a dose-response relationship between number of painful sites and knee cartilage volume loss at the lateral and total tibiofemoral compartments (Lateral: β=-0.28% per annum; Total: β=-0.25% per annum, both P for trend<0.05), but not the medial compartment. These associations were stronger in participants without radiographic knee osteoarthritis (P<0.05) and independent of age, sex, body mass index, physical activity, pain medication and knee structural abnormalities.

**Conclusion:** Number of painful sites independently predicts knee cartilage volume loss, especially in people without knee osteoarthritis, suggesting that widespread pain may be an early marker of more rapid knee cartilage loss in those without radiographic knee osteoarthritis. The underlying mechanism is unclear, but it is independent of anthropometrics, physical activity and knee structural abnormalities.

**Keywords:** Multiple-site pain, cartilage volume, osteoarthritis, mechanism

**Significance and Innovations**

* Number of painful sites independently predicts knee cartilage volume loss over 2.6 years, especially in people without knee osteoarthritis.
* This study adds to evidence of pain and systemic factors possibly being key factors in osteoarthritis progression, and highlights the importance of treating multiple-site pain to limit progression to end-stage osteoarthritis.

**Introduction**

Musculoskeletal pain commonly occurs in older people, with knees the most commonly reported painful site. Joint pain is associated with functional limitation and impaired quality of life ([1](#_ENREF_1)) and the primary reason why people seek help with knee osteoarthritis (OA) ([2](#_ENREF_2)). Isolated knee pain is uncommon in the elderly but rather knee pain is typically accompanied by pain at other sites ([3-5](#_ENREF_3)). Compared to single-site pain, multiple-site pain (MSP) is associated with poorer level of physical and psychological health, worse health-related quality of life, and more severe depressive symptoms in both cross-sectional and longitudinal studies ([4-6](#_ENREF_4)).

A number of studies have investigated associations between knee pain and development and progression of knee OA ([7-10](#_ENREF_7)). There is no evidence for an association between knee pain and progression of radiographic knee OA based on a previous meta-analysis ([11](#_ENREF_11)). Previous studies have demonstrated that loss of cartilage, a major hallmark of OA, is predictive of clinically relevant endpoint of knee replacement ([12-14](#_ENREF_12)); however, studies of the associations between knee pain and knee cartilage volume loss are inconsistent ([7-10](#_ENREF_7), [15](#_ENREF_15), [16](#_ENREF_16)). In a 2-year longitudinal study, Cicuttini *et al* ([7](#_ENREF_7)) reported that knee pain at baseline was associated with greater patella cartilage volume loss. A study with a 4.5-year follow-up reported that knee pain was associated with a higher rate of medial tibial cartilage volume loss ([8](#_ENREF_8)). Saunders *et al* ([9](#_ENREF_9)) found that knee pain independently predicted lateral but not medial tibial cartilage volume loss in a 2.9-year follow-up study. In addition, people with frequent knee pain had greater medial tibiofemoral cartilage volume loss than those without ([10](#_ENREF_10)), while [Raynauld](http://www.ncbi.nlm.nih.gov/pubmed/?term=Raynauld%20JP%5BAuthor%5D&cauthor=true&cauthor_uid=14872490) *et al* ([15](#_ENREF_15)) and Wluka *et al* ([16](#_ENREF_16)) did not find any associations between knee pain and change in cartilage volume.

One possible explanation for these inconsistent results is that studies to date have not taken pain at other sites into account. This is important as MSP may be due to higher levels of disease activity, such as systemic factors, dysfunction in central pain processing, or genetic factors ([17-21](#_ENREF_17)), and thus may represent a different phenotype of pain from single-site pain. The prevalence of those with detectable levels of systemic inflammation was not low in the general population ([22](#_ENREF_22)). Furthermore, OA is the most common cause of pain in the elderly; therefore, people with MSP most likely represent the disease activity of OA in a general population. Potential risk factors for knee cartilage volume loss reported in previous studies include older age ([23](#_ENREF_23)), female sex ([23](#_ENREF_23)), body mass index (BMI) ([24](#_ENREF_24)), relevant knee structural abnormalities ([25](#_ENREF_25)) and genetic factors ([26](#_ENREF_26)). Studies that attempt to investigate the relationship between MSP and cartilage volume loss should assess the effect of these potential factors. Therefore, this study aimed to determine whether MSP is a predictor of knee cartilage volume loss, and if so, to explore potential mechanisms.

**Patients and Methods**

**Participants**

This study was conducted as part of the Tasmanian Older Adult Cohort Study (TASOAC)-a longitudinal, observational population-based study. The cohort consisted of both men and women and was selected from the electoral roll in Southern Tasmania generated by staff of the Tasmanian Electoral office on 31st January 2002 (total number of people on the roll n=229,593) using sex-stratified simple random sampling without replacement. See *Supplementary text 1* for more information on qualification and disqualification for electoral roll. The eligible cohort consisted of registered electors aged 50–80 years (n=61,715, men/women=29,484/32,231). Institutionalised older adults were excluded because TASOAC was designed to study community-dwelling older adults. Figure S1 shows an overview of subject recruitment and withdrawal during the study period. A total of 2,530 subjects were selected from the roll using 5-year age band information with equal number of men and women. Among them, 395 were deemed unable to participate due to illness or other reasons, and the remainder were contacted via mail by asking whether they would like to participate in the study. Of 2,135 subjects, 1,100 were enrolled in the study and 1,099 attended the first clinic between March 2002 and September 2004 (response rate 57%) at the Menzies Institute for Medical Research, Australia. The follow-up measures were taken approximately 2.6 years (range 1.4–4.8 years) later (n=875) (retention rate 80%). MRI scans were available for only approximately half of the follow-up participants (n=425 of 875). The current study consists of a sample of 394 TASOAC participants who had MRI measures at baseline and follow-up and data on pain at baseline. The study was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee (Ref. no: H0006488), and all participants provided informed written consent.

**Primary outcome measurement**

***Knee cartilage volume***

MRI scans of the right knee were performed at baseline and after 2.6 years. Knee cartilage volume was determined by means of image processing on an independent work station using Osiris (University of Geneva) and measured by two trained and blinded observers as previously described ([27](#_ENREF_27)). The volumes of individual cartilage plates (medial tibia and lateral tibia) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section by section basis. These data were then resampled by means of bilinear and cubic interpolation for the final three-dimensional rendering. The coefficient of variation (CV) for baseline and follow-up cartilage volume measures was 2.1% for medial tibial, and 2.2% for lateral tibial cartilage ([27](#_ENREF_27)). Knee femoral cartilage volume was determined by means of image processing on an independent workstation using Cartiscope ™ (ArthroVision Inc., Montreal) , as previously described ([15](#_ENREF_15)). The segmentation of the cartilage-synovial interfaces was carried out with the semi-automatic method under reader supervision and with corrections when needed. Cartilage volume was evaluated directly from a standardized view of three-dimensional cartilage geometry as the sum of elementary volumes. The CV was approximately 1.6% for medial femoral and 2.9% for lateral femoral cartilage at baseline and follow-up ([15](#_ENREF_15)). The cartilage volume assessment was done for the medial and lateral condyles delineated by the Blumensaat’s line. The medial, lateral and total tibiofemoral cartilage volume created for this study were the sum of cartilage volume of corresponding sites. Rates of change in cartilage volume were calculated as: percentage change per annum = [100 × ((follow-up cartilage volume - baseline cartilage volume)/baseline cartilage volume)/time between two scans in years].

**Primary exposure measurement**

#### Multiple-site pain

The location of sites at which the participants experienced pain was measured by self-reported questionnaire at baseline. Participants were asked whether they had pain (yes/no) in the following sites at present: neck, back, hands, shoulders, hips, knees or feet. The number of painful sites was summed to create a total number of painful site with a range from 0 to 7, which was then categorised into four groups (non-painful site, 1-2, 3-4, 5-7 painful sites) according to the number of painful site groups with approximately equal numbers of participants reporting one or more painful sites ([28](#_ENREF_28)). Number of painful site types was also assessed on a regional basis, with total count of painful upper limb sites created by summing the number of painful upper limb sites (neck, hands and shoulders, range 0–3), and count of painful lower limb sites created by summing number of hip, knees and feet (range 0–3).

**Measurement of potential covariates**

#### Anthropometrics, physical activity and use of pain medication were measured. Detailed descriptions of these measurements are shown in Supplementary text 1.

***Radiographs***

A standing anteroposterior semiflexed view of the right knee was performed in all participants and scored individually using the Altman atlas for osteophytes and joint space narrowing (JSN) on a scale of 0-3 ([29](#_ENREF_29)). The presence of medial or lateral tibiofemoral JSN or osteophytes was defined as any score of 1 or greater in that site, and 1 or greater in either for whole tibiofemoral JSN or osteophytes. The presence of radiographic OA (ROA) was defined as any score ≥ 1 for JSN or osteophytes.

***Cartilage defects***

Cartilage defects were assessed at baseline on T1-weighted MR images at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites, as previously described ([30](#_ENREF_30)), as follows: grade 0 = normal cartilage; grade 1 = focal blistering and intracartilaginous low-signal intensity area with an intact surface and base; grade 2 = irregularities on the surface or base and loss of thickness < 50%; grade 3 = deep ulceration with loss of thickness > 50%; and grade 4 = full-thickness chondral wear with exposure of subchondral bone. The intraclass correlation coefficients (ICCs) ranged from 0.80–0.95 for intra-observer repeatability. The presence of any cartilage defect was defined as a score of ≥ 2 at any site.

***Bone marrow lesions***

Bone marrow lesions (BMLs) were assessed at baseline on T2–weighted MR images and defined as areas of increased signal adjacent to the subcortical bone at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites, as previously described ([31](#_ENREF_31)). The maximum area (mm2) of the lesion of different sites was measured, and the BML with the largest size was recorded if more than one lesion was present at the same site. The presence of any BML was defined as a score of greater than 0 at any site. The ICC was 0.97 for intra- observer repeat-ability.

**Statistical analysis**

T-tests and Chi-square were used to compare differences in means and percentages between the participants included and the rest of cohort where appropriate. ANOVA and ordinal χ2 test (Kruskal-Wallis test) were used to test if there was a trend of mean of each continuous and categorical variable across pain groups. Cartilage volume (either at baseline or % change) was normally distributed in this sample; therefore, linear regression was used to assess the potential associations between the number of painful sites and cartilage volume loss (% per annum), before and after adjustment for age, sex, BMI, physical activity, pain medication, baseline cartilage volume, cartilage defects, BMLs, JSN and osteophytes. Significant interactions between the number of painful sites and knee ROA were detected, suggesting that the effect of the number of painful site on cartilage volume loss was different in participants with and without ROA. Subgroup analyses according to ROA status were therefore performed. We also performed the analyses on the associations between pain at each specific site and cartilage volume loss using linear regression to explore the mechanisms underlying these associations. Sensitivity analyses were performed using inverse probability weighting to determine whether loss to follow-up biased our results. Multiple comparisons on the results of associations between site-specific pain and cartilage volume loss were controlled using the Hochberg method ([32](#_ENREF_32)). All statistical analyses were performed using Stata V.12.1 (StataCorp, USA).

**Results**

In the current study, 394 of 1,099 participants with MRI measures at baseline and follow-up and pain measures were included. The average follow-up time was 2.6 years (range 1.4–4.8). 705 participants were excluded from this study due to loss to follow-up or no data on the MRI and pain. There were no significant differences in age, sex, BMI, physical activity, pain medication, ROA, BMLs as well as the number of painful sites between the participants included (n=394) and the rest of cohort (n=705), except for a slightly higher prevalence of medial tibiofemoral cartilage defects in those who were not included in this study.

Table 1 presents the baseline characteristics of participants by category of number of painful sites. The median number of painful sites was 3 (range 0 to 7) and 87% of participants had pain at least one site. Among them, 115 (29%) reported having pain at one or two sites; 110 (28%) had three or four painful sites and 119 (30%) reported pain at five or more sites. Participants reporting a greater number of painful sites were more likely to be women, have higher BMI, higher reported use of pain medication, and a trend to less physical activity. There were no baseline differences in the proportion of participants with ROA, cartilage defects, BMLs and baseline cartilage volume. Increasing number of painful sites was associated with cartilage volume loss over 2.6 years in the lateral and total tibiofemoral compartments with higher rate of cartilage volume loss in participants reporting pain in greater numbers of painful sites. There was also a tendency towards increased medial tibiofemoral cartilage volume loss as number of painful sites increased (Table 1 and Figure 1).

Figure 1 describes the association between the number of painful sites and cartilage volume loss. In unadjusted analyses, cartilage volume loss increased with greater numbers of painful sites in a dose-response manner at all compartments (medial, lateral and total tibiofemoral compartments). After adjustment for age, sex, BMI, physical activity, osteophytes, JSN, cartilage defects and BMLs, these significant associations persisted at lateral (β=-0.28% per annum, 95% CI -0.52%, -0.03%, P=0.030) and total (β=-0.25% per annum, 95% CI -0.49%, -0.01%, P=0.046) tibiofemoral compartments. In the medial tibiofemoral compartment, the magnitude of the effect was only slightly less (β=-0.20% per annum) and did not reach statistical significance (P=0.191), but it showed a similar pattern with lateral and total tibiofemoral cartilage volume loss.

There was a significant interaction between number of painful sites and ROA status for lateral and total tibiofemoralcartilage volume loss, and thus subgroup analysis was conducted by the status of ROA. Table 2 and Table 3 show the results of association of number of painful sites and lateral and total tibiofemoralcartilage volume loss stratified by ROA status using “non-painful site” as a reference group. The significance of a linear trend was tested using Wald tests and there was a trend if P<0.05. For those without ROA, we found that having 1-2, 3-4 and 5-7 painful sites had greater cartilage volume loss in the fully adjusted model, and showed a dose-response relationship for lateral and total tibiofemoral cartilage volume loss (adjusted P for trend=0.002). However, we did not observe any significant associations or dose-response relationship in participants with ROA.

Further analyses using linear regression on the association between pain at each specific site and total tibiofemoral cartilage volume loss to explore whether weight bearing or systemic factors underlies the associations. As shown in Table S1, hand, shoulder and back pain showed statistically significant associations with cartilage volume loss in those without (but not with) ROA after adjustment for confounders, but pain at all lower limb sites was not associated with cartilage volume loss. The significant associations remained after adjusting for multiple testing (Table S1). Consistent results were found after further adjustment for knee injury and common comorbidities including diabetes, heart problems, hypertension, and rheumatoid arthritis, and even mutual adjustment for pain at other sites as well as after re-analyses of data using inverse probability weighting method (data not shown).

**Discussion**

This longitudinal study shows that greater number of painful sites is associated with knee cartilage volume loss, especially in those without ROA. These relationships persisted after adjustment for age, sex, BMI, physical activity, pain medication, and knee structural abnormalities at the lateral and total tibiofemoral compartments, suggesting that MSP may be an early marker of more rapid knee cartilage loss. The underlying mechanisms for this association are uncertain, but could include systemic, central or genetic factors. To our knowledge, this is the first to investigate the prospective relationship between MSP and cartilage volume loss.

The high prevalence of MSP (>2 sites) found in this study is similar to reported prevalence in previous studies ([4](#_ENREF_4), [33-35](#_ENREF_33)), despite differences in the methods of assessing pain and the number of pain sites. This finding corroborates the evidence that MSP is very common in the older general population. Consistent with some previous studies (but not all) ([15](#_ENREF_15), [16](#_ENREF_16)), knee pain was not found to be associated with high rates of cartilage volume loss in any compartments, whereas these findings differ from some of previous studies which identified the relationship between knee pain and cartilage volume loss ([7-10](#_ENREF_7)). These discordances could be attributed to the differences in characteristics of population included, follow-up time period, and measurement and/or definition of knee pain.

The present study found that increasing number of painful sites is associated with greater cartilage volume loss. One possible explanation for this link is the involvement of systemic inflammation which have been shown to be a critical contribution to both pain ([19](#_ENREF_19)) and OA pathogenesis ([36](#_ENREF_36)). In the process of inflammation, inflammatory factors are released, such as cytokines, chemokines, prostanoids, proteolytic enzymes and nerve and vascular growth factors, which can activate peripheral nociceptors, thereby leading to peripheral sensitisation and hyperexcitability of dorsal horn transmission neurons in the central nervous system (central sensitisation) ([2](#_ENREF_2), [37](#_ENREF_37)). These inflammatory factors are also associated with increased cartilage turnover and matrix degradation ([38](#_ENREF_38)). Furthermore, heightened pain sensitivity can contribute to increased level of inflammatory factors releases, thus creating a cycle of inflammation, high pain sensitivity and pain severity ([17](#_ENREF_17)). Based upon this evidence, it is plausible that people reporting pain at greater numbers of painful sites are more likely to have a higher level of systemic inflammation, leading to more loss of cartilage volume. Serum levels of inflammatory markers were only measured a subsample of this population (n=182). We observed a higher level of interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α) in those reporting 3-4 and 5-7 painful sites as compared to those having non-painful site and 1-2 painful sites, although they did not approach statistical significance. This may be due to small sample size to detect the significance.

Overweight or obesity is widely considered as an important risk factor for developing pain ([2](#_ENREF_2), [39](#_ENREF_39)). Potential mechanisms include increased physical loading as well as systemic inflammation. Increasingly, evidence supports a more important role for systemic inflammation rather than physical loading, as the mechanical effect of overloading is insufficient to explaining pain at non-weight bearing joint, such as hand pain ([40](#_ENREF_40)). Those with greater numbers of painful sites were heavier in this study, supporting this hypothesis. However, the relationship between number of painful sites and knee cartilage volume loss did not change after adjustment for BMI, suggesting that this relationship is independent of BMI. Moreover, we found that cartilage volume loss is associated with upper limb pain rather than lower limb pain. This further supports that it is not simply due to loading.

Previous studies demonstrate a considerable genetic influence on pain. Genetic components can account for approximately 50% heritability estimates for different pain traits in twin studies ([41](#_ENREF_41)). Candidate gene studies have identified multiple genes associated with pain sensitivity ([42-44](#_ENREF_42)). Furthermore, evidence suggests that peripheral/central nervous system sensitisation and multiple biologic/psychological processes are shared pain mechanisms in multiple conditions including back pain, neck pain, shoulder pain, OA and chronic widespread pain (CWP), etc ([45](#_ENREF_45), [46](#_ENREF_46)) and are strongly affected by underlying genetic factors ([40](#_ENREF_40)). A recent twin study also demonstrates a single underlying genetic factor which can explain pain reporting at different sites ([47](#_ENREF_47)), and Malkin et al reports that back pain and CWP are linked by shared genetic factors ([48](#_ENREF_48)). This indicates that back pain/upper limb pain may be a group with CWP, and could explain why back pain/upper limb pain are more predictive of cartilage volume loss. In the current study, we found that cartilage volume loss is greater in those with pain at multiple sites. It is likely that MSP in older people represents generalised OA which has a strong genetic component implicated in its’ pathogenesis ([49](#_ENREF_49)). Therefore, combined with the finding that cartilage volume loss is greater in those with MSP, these studies imply that genetic factors may have a crucial role in determining the additive effects of MSP. Nonetheless, it is currently unknown which genes explain a larger proportion of the susceptibility to pain or cartilage loss, and whether genes linked to cartilage loss have any role in the regulation of pain, although several articular cartilage related genes were found to be associated with characterised pain phenotypes ([50](#_ENREF_50)).

The present study failed to detect any significant association between cartilage volume loss and MSP in people with ROA, which could be explained by the stage of disease. Radiographically evident changes represent later stage OA, and therefore individuals with ROA would lose cartilage volume faster than those without ROA ([51](#_ENREF_51)). This is supported by our finding that people without ROA have more cartilage volume at baseline (data not shown). Conceivably, this finding may not only have great practical implications for early diagnosis, but also highlights the importance of treatment targeted at MSP as it might have beneficial effects to limit progression to end-stage disease. Also, our results showed a tendency towards increased cartilage volume loss at the medial tibiofemoral compartment, although it did not show a statistically significant association. The reason for this is unclear. This could be attributable to more mechanical effects on medial compartment, subsequently, contributing to less medial tibiofemoral cartilage volume at baseline compared with lateral compartment, so there were not too much room to move on the scale theoretically.

The strengths of the current study are the longitudinal study design, the relatively large sample size and the objectively measured outcome (cartilage volume loss, as measured by MRI). Some potential limitations in this study have to be considered when interpreting these results. These include the self-reported binary nature of the assessments of pain ([2](#_ENREF_2)), which did not allow investigation of any effect of pain intensity on cartilage volume loss; therefore, to what extent more severe pain is associated with cartilage volume loss is still unclear. Furthermore, pain may result from other musculoskeletal diseases; however, we have not screened for these conditions. Second, we do not have images of other sites to know whether they have any site pathology, which might explain localized pain. Lastly, a possible problem with this study was loss to follow-up which may bias our results as people with more painful sites were more likely to have lower physical function which may underestimate the association. Also, for the current study, repeat MRI scans at 2.6 years were only available in a subset of the TASOAC study; however, there were no significant differences between the participants included in this study and the rest of the cohort in terms of in demographics, physical activity, ROA and the number of painful sites, apart from a higher prevalence of medial tibiofemoral cartilage defects in those not included, and the results did not alter after using inverse probability weighting, indicating that our results are robust.

**Conclusion**

The presence of MSP independently predicts knee cartilage volume loss, especially in people without knee OA, suggesting that widespread pain may be an early marker of more rapid knee cartilage loss in those without ROA. The underlying mechanism is unclear, but it is independent of anthropometrics, physical activity and knee structural abnormalities, possibly mediated by systemic, central or genetic factors.

**Author contributions**

FP participated in the design of the study, analysis and interpretation of the data and manuscript preparation. LL participated in the analysis, interpretation of the data and revising manuscript. JT participated in the analysis, interpretation of the data and revising manuscript. FC participated in the design of the study and revising manuscript. TW participated in interpretation of the data and revising manuscript. CHD participated in interpretation of the data and revising manuscript. GJ participated in the design of the study, interpretation of the data and manuscript preparation. All authors read and approved the final manuscript.

**Acknowledgements**

We thank the study participants, who made this study possible, and Catrina Boon and Pip Boon for their role in collecting the data. The authors also thank Rob Warren, André Pelletier and Josée Thériault for the MRI reading and Drs. Marie-Josée Berthiaume and Thomas Moser, specialists in musculoskeletal radiology, for their expert advice on the reading of MR images.

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**C:\Feng\OA\Papers\Submitted\4_pain&volume\Submission\ACR\revision\final\final_submit\Figure 1.tifFigure 1** The association between number of painful sites and cartilage volume loss in the total sample. With increasing number of painful sites, there is greater annual cartilage volume loss at lateral and total, but not at medial tibiofemoral compartment. The β coefficients and P values are from tests of trend of cartilage volume loss on number of painful sites determined by linear regression. **\***represents the univariable analysis; #represents multivariable analysis with adjustment for age, sex, body mass index, physical activity, pain medication, baseline cartilage volume, cartilage defects, bone marrow lesions, joint space narrowing and osteophytes for corresponding compartment. MTF medial tibiofemoral compartment; LTF lateral tibiofemoral compartment; TF tibiofemoral compartment.

**Table 1 Descriptive characteristics of participants at baseline, by number of painful sites**\*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Number of painful sites | | | | P value |
|  | 0  (N=50) | 1-2  (N=115) | 3-4  (N=110) | 5-7  (N=119) |
| Age, years | 62.2±7.6 | 64.6±8.0 | 62.3±6.3 | 62.6±7.0 | 0.676 |
| Female (%) | **44** | **40** | **57** | **72** | **0.005** |
| Body mass index (kg/m2) | **26.5±4.4** | **27.1±4.1** | **27.9±4.4** | **28.4±4.8** | **<0.001** |
| Physical activity (steps per day) | **9849.4±4090.6** | **8677.3±2940.5** | **8588.3±2933.8** | **8486.2±3407.4** | **<0.001** |
| Any pain medication (%) | **43** | **47** | **56** | **74** | **<0.001** |
| Radiographic knee OA (%) | 61 | 52 | 61 | 61 | 0.151 |
| Any knee cartilage defects (%) | 24 | 32 | 31 | 33 | 0.176 |
| Any knee BMLs (%) | 42 | 42 | 45 | 45 | 0.583 |
| **Cartilage volume at baseline (ml)** |  |  |  |  |  |
| MTF | 6.3±1.5 | 6.4±1.7 | 6.4±1.5 | 6.1±1.6 | 0.324 |
| LTF | 7.1±1.7 | 7.3±1.9 | 7.3±1.6 | 6.8±1.7 | 0.190 |
| TF | 13.4±3.1 | 13.8±3.5 | 13.7±3.1 | 13.0±3.3 | 0.235 |
| **Percentage change in cartilage volume (per annum)** |  |  |  |  |  |
| MTF | **-1.3±2.8** | **-1.3±2.3** | **-1.8±2.5** | **-2.0±2.7** | **0.040** |
| LTF | **-0.9±2.2** | **-1.1±1.7** | **-1.5±2.1** | **-1.8±2.2** | **0.003** |
| TF | **-1.1±2.3** | **-1.2±1.7** | **-1.7±2.1** | **-2.0±2.0** | **0.004** |

Bold denotes statistically significant result; OA osteoarthritis; BMLs bone marrow lesions; MTF medial tibiofemoral compartment; LTF lateral tibiofemoral compartment; TF tibiofemoral compartment;

\*Values are the Mean±SD except for percentages; ANOVA and ordinal χ2 test (Kruskal-Wallis test) were used to test if there was a trend of mean of each continuous and categorical variable (increase or decrease) across pain groups.

**Table 2 Association between the number of painful sites and lateral tibiofemoral cartilage volume loss, by ROA status**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | No. of pain  sites | Annual percentage | Univariable | |  | Multivariable† | |
|  | cartilage volume loss (mean, %) | β | 95% CI |  | β | 95% CI |
| Without ROA |  |  |  |  |  |  |  |
|  | 0 | -0.41 | Ref. |  |  | Ref. |  |
|  | 1-2 | -1.00 | -0.59 | -1.67, 0.50 |  | -0.73 | -1.84, 0.39 |
|  | 3-4 | -1.69 | **-1.28** | **-2.43, -0.14** |  | **-1.37** | **-2.52, -0.22** |
|  | 5-7 | -1.96 | **-1.55** | **-2.67, -0.44** |  | **-1.71** | **-2.92, -0.49** |
|  | **P for trend** |  |  | **0.001** |  |  | **0.002** |
| With ROA | 0 | -1.10 | Ref. |  |  | Ref. |  |
|  | 1-2 | -1.19 | -0.09 | -1.29, 1.11 |  | 0.18 | -0.99, 1.36 |
|  | 3-4 | -1.38 | -0.28 | -1.45, 0.89 |  | -0.02 | -1.19, 1.15 |
|  | 5-7 | -1.73 | -0.63 | -1.79, 0.53 |  | -0.16 | -1.39, 1.06 |
|  | **P for trend** |  |  | 0.201 |  |  | 0.635 |

Bold denotes statistically significant result. β regression coefficient; CI confidence interval; ROA radiographic osteoarthritis; Ref reference group;

†Adjusted for age, sex, body mass index, physical activity, any pain medication, baseline lateral cartilage volume, cartilage defects and bone marrow lesions.

**Table 3 Association between the number of painful sites and total tibiofemoral cartilage volume loss, by ROA status**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | No. of pain  sites | Annual percentage | Univariable | |  | Multivariable† | |
|  | cartilage volume loss (mean, %) | β | 95% CI |  | β | 95% CI |
| Without ROA |  |  |  |  |  |  |  |
|  | 0 | -0.34 | Ref. |  |  | Ref. |  |
|  | 1-2 | -0.97 | -0.63 | -1.70, 0.43 |  | -0.82 | -1.94, 0.30 |
|  | 3-4 | -1.97 | **-1.63** | **-2.76, -0.51** |  | **-1.66** | **-2.83, -0.50** |
|  | 5-7 | -1.76 | **-1.42** | **-2.52, -0.32** |  | **-1.69** | **-2.90, -0.48** |
|  | **P for trend** |  |  | **0.003** |  |  | **0.002** |
| With ROA |  |  |  |  |  |  |  |
|  | 0 | -1.48 | Ref. |  |  | Ref. |  |
|  | 1-2 | -1.45 | 0.04 | -1.13, 1.20 |  | 0.27 | -0.87, 1.41 |
|  | 3-4 | -1.52 | -0.03 | -1.16, 1.11 |  | 0.33 | -0.80, 1.47 |
|  | 5-7 | -2.08 | -0.60 | -1.73, 0.53 |  | 0.02 | -1.16, 1.20 |
|  | **P for trend** |  |  | 0.204 |  |  | 0.930 |

Bold denotes statistically significant result. β regression coefficient; CI confidence interval; ROA radiographic osteoarthritis; Ref reference group;

†Adjusted for age, sex, body mass index, physical activity, any pain medication, baseline cartilage volume, cartilage defects and bone marrow lesions.

**Table S1 Association between** **pain at each site and total tibiofemoral cartilage volume loss, by ROA status**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Pain  site | Univariable | |  | Multivariable† | |
|  | β | 95% CI |  | β | 95% CI |
| Without ROA |  |  |  |  |  |  |
|  | Neck | -0.57 | -1.22, 0.07 |  | -0.67 | -1.37, 0.03 |
|  | Hand | **-0.83** | **-1.47, -0.19**‡ |  | **-0.83** | **-1.52, -0.13**‡ |
|  | Shoulder | **-0.78** | **-1.42, -0.14**‡ |  | **-0.81** | **-1.50, -0.13**‡ |
|  | Back | -0.52 | -1.17, 0.13 |  | **-0.83** | **-1.50, -0.17**‡ |
|  | Knee | -0.54 | -1.20, 0.13 |  | -0.55 | -1.22, 0.12 |
|  | Hip | -0.30 | -0.95, 0.34 |  | -0.47 | -1.14, 0.20 |
|  | Foot | -0.50 | -1.16, 0.16 |  | -0.22 | -0.92, 0.47 |
|  | Upper limb | **-0.38** | **-0.62, -0.14**‡ |  | **-0.47** | **-0.72, -0.21**‡ |
|  | Lower limb | -0.28 | -0.58, 0.02 |  | -0.27 | -0.58, 0.04 |
| With ROA |  |  |  |  |  |  |
|  | Neck | -0.37 | -1.08, 0.33 |  | -0.09 | -0.78, 0.60 |
|  | Hand | 0.00 | -0.71, 0.71 |  | 0.17 | -0.53, 0.87 |
|  | Shoulder | -0.59 | -1.33, 0.14 |  | -0.43 | -1.15, 0.29 |
|  | Back | -0.52 | -1.24, 0.21 |  | -0.22 | -0.96, 0.52 |
|  | Hip | 0.10 | -0.61, 0.82 |  | 0.28 | -0.46, 1.02 |
|  | Knee | -0.37 | -1.07, 0.33 |  | -0.02 | -0.74, 0.71 |
|  | Foot | -0.05 | -0.76, 0.67 |  | 0.23 | -0.50, 0.95 |
|  | Upper limb | -0.18 | -0.43, 0.07 |  | -0.07 | -0.33, 0.19 |
|  | Lower limb | -0.09 | -0.43, 0.25 |  | 0.10 | -0.27, 0.48 |

Bold denotes statistically significant result. β regression coefficient; CI confidence interval; ROA radiographic osteoarthritis; Ref reference group;

†Adjusted for age, sex, body mass index, physical activity, any pain medication, baseline cartilage volume, cartilage defects and bone marrow lesions.

‡Denotes significant association that passes Hochberg adjustment for multiple testing.

**ONLINE SUPPLEMENTARY TEXT – 1**

***Qualification and disqualification for electoral roll:***

People were qualified to be included on the roll if they were: (1) 18 years of age or older, (2) an Australian citizen, (3) an elector entitled to vote at a house of representatives election or qualified to become such an elector. Disqualified from the roll were those who were (1) a member of a state or territory parliament, (2) a citizen or subject of a foreign power, (3) serving a prison sentence of 12 months or more, (4) an undischarged bankrupt or insolvent, (5) holding an office of profit under the Crown (e.g. Public Servant), or (6) a permanent member of the Australian Defence Force. They amounted to about 15% of residents.

***Anthropometrics***

Weight was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707) calibrated using a known weight at the beginning of each clinic. Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. BMI (kg/m2) was calculated.

***Physical activity***

Physical activity was assessed at baseline as steps/day determined by pedometer. Each participant was instructed to wear a pedometer for seven consecutive days and to record the number of steps each day and the duration and type of physical activity for any activities in which the pedometer could not be worn (for example, swimming). This was repeated six months later to account for seasonal variation. Mean steps/day was calculated as the average of the days worn at both time points.

#### Use of pain medication

Participants were asked to list all medication prescribed by a doctor, and any other over-the-counter medications they had taken in the last two weeks, including dosage and frequency. Medications used for pain relief were extracted from this list, and dichotomised into whether they were used or not (yes/no).