Exploring the differences between radiographic joint space width and MRI cartilage thickness changes using data from the IMI-APPROACH cohort

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Abstract

Objective. Longitudinal weight-bearing radiographic joint space width (JSW) and non-weight-bearing MRI-based cartilage thickness changes often show weak correlations. The current objective was to investigate these correlations, and to explore the influence of different factors that could contribute to longitudinal differences between the two methods.

Methods. The current study included 178 participants with medial osteoarthritis (OA) out of the 297 knee OA participants enrolled in the IMI-APPROACH cohort. Changes over 2 years in medial JSW (ΔJSWmed), minimum JSW (ΔJSWmin), and medial femorotibial cartilage thickness (ΔMFTC) were assessed using linear regression, using measurements from radiographs and MRI acquired at baseline, 6 months, and 1 and 2 years. Pearson R correlations were calculated. The influence of cartilage quality (T2 mapping), meniscal extrusion (MOAKS scoring), potential pain-induced unloading (difference in knee-specific pain scores), and increased loading (BMI) on the correlations was analyzed by dividing participants in groups based on each factor separately, and comparing correlations (slope and strength) between groups using linear regression models.

Result. Correlations between ΔMFTC and ΔJSWmed and ΔJSWmin were statistically significant ($p < 0.004$) but weak ($R < 0.35$). Correlations were significantly different between groups based on cartilage quality and on meniscal extrusion: only patients with the lowest T2 values and with meniscal extrusion showed significant moderate correlations. Pain-induced unloading or BMI-induced loading did not influence correlations.

Conclusions. While the amount of loading does not seem to make a difference, weight-bearing radiographic JSW changes are a better reflection of non-weight-bearing MRI cartilage thickness changes in knees with higher quality cartilage and with meniscal extrusion.

Keywords: MRI; JSW; Cartilage thickness; T2 mapping; Meniscus; Weight-bearing

Introduction

In knee osteoarthritis (OA) trials, tibiofemoral cartilage thickness is often monitored by measuring joint space width (JSW) from weight-bearing knee radiographs. Radiographic JSW is not only a measure of cartilage thickness, but is also influenced by other factors (e.g., meniscus and positioning errors) [1-3]. However, JSW is still often used as a surrogate measure for cartilage thickness, and is the only official endpoint for structural improvement [4].

Radiographic JSW has been compared with cartilage thickness measured on non-weight-bearing MRI. Cross-sectional correlations are generally strong [5,6,7]. However, longitudinally, JSW change shows non-significant or weak correlations with cartilage thickness changes [8-12]. A previous study suggested the poor longitudinal correlations are primarily the result of the difference in weight-bearing (radiographs) and non-weight bearing (MRI) [13]. The study speculated that cartilage quality (deformability) could play a role in weight-bearing-related differences, as could meniscal positioning, but this could not be investigated further in the small number of patients used. It could be expected that lower quality cartilage is compressed more during weight-bearing radiographic acquisition, affecting JSW but not cartilage thickness on non-weight-

bearing MRI, resulting in weaker correlations. Knees with meniscal extrusion could show better correlations between JSW changes and changes in MRI-defined cartilage thickness: if the meniscus is extruded, it would have less influence on JSW change, and JSW changes would more likely be due to cartilage changes than due to the meniscus. The amount of loading on the knee could also affect the longitudinal correlations, as more loading during weight-bearing radiographic acquisition could result in weaker correlations with non-weight-bearing MRI. Knowledge of structural parameters on joint level or other parameters outside the joint and their possible impact on longitudinal JSW changes is important particularly in a clinical trial setting given that assessment of potential structural benefits of disease-modifying OA drugs (DMOADs) is still primarily based on radiographic outcomes, while MRI will play a greater role in the future and has been used already in a phase II b context of DMOAD evaluation [14-15]. The APPROACH study was funded as part of the Innovative Medicine's Initiative (IMI). In this cohort, knee OA patients with an increased likelihood of two-year structural and/or pain progression were included. Many different types of data were collected, including radiographs and MRI scans, but also information on cartilage quality (T2 mapping), meniscal extrusion, and parameters that may cause increased loading (BMI) or unloading (as a result of knee pain).

The current objective was to investigate the correlation between changes in radiographic JSW and MRI cartilage thickness in the IMI-APPROACH cohort over 24 months, and to explore the influence of factors that could contribute to weight-bearing related differences between the two methods. It was hypothesized that correlations between JSW and cartilage thickness changes would be weak, and higher quality cartilage,

having meniscal extrusion, knee pain-induced unloading and a lower BMI would each result in stronger correlations.

Materials and methods

Participants

In the IMI-APPROACH cohort, 297 participants with knee OA were included in five European centers and followed for 2 years. The cohort description, inclusion and exclusion criteria, and investigation schedule have been published previously [16]. For all participants, their index knee was selected based on American College of Rheumatism (ACR) criteria. If both knees met the ACR criteria, participants indicated their most affected knee to use as index knee; if participants indicated no difference, the right knee was chosen as index knee. Participants visited the hospital at baseline, 6 months, 1 year, and 2 years, where semi-flexed posteroanterior (PA) radiographs according to the Buckland-Wright protocol and 1.5 T or 3 T MRI scans of the index knee were performed [17]. Radiographic acquisition was standardized using a foot platform, which ensured the desired leg positioning and rotation with respect to the beam and detector. The most affected tibiofemoral compartment (medial or lateral) was determined for all knees by two readers in consensus by looking at the characteristics used in OA scoring systems (JSW, osteophytes, sclerosis), using radiographs at the latest follow-up moment (two years). In the current study, only participants with predominantly medial OA (medial most affected) were included.

The study was approved by the regional ethical committees and Institutional Review Boards (UMC Utrecht, Leiden University Medical Center, Complejo Hospitalario Universitario de A Coruña, AP-HP Saint-Antoine Hospital, and Diakonhjemmet

Hospital) and was conducted in compliance with the study protocol, Good Clinical Practice (GCP), the Declaration of Helsinki, and the applicable ethical and legal regulatory requirements. All participants have received oral and written information and provided written informed consent.

Longitudinal data acquisition

From all radiographs, the mean medial and minimum JSW were measured using Knee Images Digital Analysis (KIDA) software [18, 19]. The MRI protocol at all available time points included 3D SPGR scans (see Supplementary Table S1 for technical details), from which the quantitatively measured medial femorotibial cartilage thickness (MFTC) was obtained by manual, quality-controlled cartilage segmentation (Chondrometrics GmbH, Freilassing, Germany).

Influencing factors

Cartilage quality was assessed in all but one center using T2 mapping MRI taken at the 6-month visit. Similar to MFTC measurements, T2 values of the FT cartilage were obtained by manual, quality-controlled cartilage segmentation (Chondrometrics GmbH, Freilassing, Germany). The average medial FT cartilage T2 values were calculated for each participant, after which they were divided into three evenly sized groups (lowest, middle, and highest T2 values).

Meniscal extrusion was assessed using semi-quantitative MRI Osteoarthritis Knee Scores (MOAKS) on sagittal and coronal intermediate weighted fat suppressed sequences at baseline (Supplementary Table S1) by one experienced observer (FWR). In the medial compartment, anterior (on sagittal image) and medial (relative to medial

tibial margin on coronal image) meniscal extrusion were scored, with each score ranging 0–3: grade 0: < 2 mm; grade 1: 2 to 2.9 mm, grade 2: 3–4.9 mm; grade 3: > 5 mm [20]. Participants were divided into two groups: those without (MOAKS score 0 for both anterior and medial) or with (MOAKS score ≥ 1 for anterior and/or medial) any meniscal extrusion in the medial compartment.

Potential pain-induced unloading was assessed at baseline using the Numerical Rating Scale (NRS) of pain for the index knee and contralateral knee separately. It was speculated that participants might partially unload their index knee if it was significantly more painful than the contralateral knee. As this would influence the amount of loading during weight-bearing radiographic acquisition (but not during non-weight-bearing MRI acquisition), it could influence the correlations between ΔJSW and ΔMFTC as well. At least 3 points higher NRS in the index knee compared to the contralateral knee (at least two times the minimum clinically significant difference) was considered significantly more painful [21]. Participants were divided into two groups: those without (< 3 higher NRS pain in index knee) or with (≥ 3 higher NRS pain in index knee) potential pain-induced unloading.

Lastly, the amount of loading could be influenced by the participant's BMI as well, with higher BMI causing increased loading during weight-bearing radiographic acquisition. BMI was measured at baseline and participants were divided into three groups: healthy (BMI < 25), overweight (25 ≤ BMI < 30), and obese (BMI ≥ 30).

Statistical analysis

Medial and minimum JSW and MFTC were evaluated only descriptively at baseline and 2 years with mean and standard deviations (SD), as the 2-year changes in this cohort

have been reported more elaborately previously [22-24]. Influencing factors were evaluated descriptively for each group separately using mean and SD for continuous variables (T2 values and BMI) and number and percentage of participants for categorical variables (meniscal extrusion and NRS).

Changes in JSW (ΔJSWmed and ΔJSWmin) and MFTC (ΔMFTC) were calculated using linear regression, using the regression coefficients to express changes over the 2-year period. This way all available measurements (baseline, 6 months, 1 year, and 2 years) are taken into account, decreasing the influence of individual outliers or measurement errors. Only patients with JSW and MFTC measurements at baseline, 2 years, and at least one other time point were included in the current study.

Pearson correlations were calculated between ΔJSWmed and ΔMFTC and between ΔJSWmin and ΔMFTC. The possible influence of the four different factors mentioned above on these correlations was assessed using linear regression models, for each factor separately. Specifically, the correlation slope (B; i.e., unstandardized regression coefficient, indicating mm ΔJSWmed or ΔJSWmin in response to a mm ΔMFTC) and strength (Pearson R/standardized regression coefficient β) were compared between groups using univariate general linear models. For the slope, ΔJSWmed and ΔJSWmin were used as dependent variables (in separate models) and ΔMFTC, group, and interaction term as independent variables. For the strength, the same models were used, but with changes (ΔJSWmed, ΔJSWmin and ΔMFTC) standardized per group. If there was a statistically significant difference between groups in slope or strength (interaction term $p < 0.05$), correlations between ΔJSWmed and ΔMFTC and between ΔJSWmin and ΔMFTC were analyzed separately per group, and visualized in correlation graphs. Pearson R between 0.00 and 0.19 was considered very weak, 0.20–0.39 weak, 0.40–

0.59 moderate, 0.60–0.79 strong, 0.80–1.00 very strong; a *p*-value of < 0.05 was considered statistically significant [25].

Results

Participants

The required JSW and MFTC data was available for 178 participants with predominantly medial OA, with mean age 66.1 years (SD 7.1 years), BMI 27.6 (5.0) kg/m^2, and of which 47 (26.4%) were male.

T2 mapping data was available for 151 participants; group 1 (lowest values) and group 3 (highest values) both consisted of 50 patients and group 2 (middle values) of 51 patients. Data on MOAKS meniscal extrusion was available for 173 participants, of which 69 had no extrusion (group 1) and the other 104 did (group 2). Full MOAKS meniscal pathology is shown in Supplementary Table S2. NRS pain-induced unloading was available for 173 participants, of which 141 did not (group 1) and 32 did (group 2) show at least 3 points higher NRS pain in the index knee and thus possible pain-induced unloading. BMI was available for all 178 participants, of which 60 had a healthy BMI (group 1), 62 were overweight (group 2), and 56 were obese (group 3). Mean JSW and MFTC data at baseline and 2 years, as well as an overview of the influencing factors for each group, are shown in Table 1.

Correlations

For all participants together, correlations of ΔJSWmed ($B = 1.18$; $R = 0.34$; $p < 0.001$) and ΔJSWmin ($B = 0.88$; $R = 0.22$; $p = 0.003$) with ΔMFTC were statistically significant but weak.

Comparing the correlations between groups based on T2 values showed there was a statistically significant difference in strength for the correlation between ΔJSWmin and ΔMFTC ($p = 0.045$), while the slope did not differ significantly ($p = 0.058$) and the correlation between ΔJSWmed and ΔMFTC did not differ between groups for either slope ($p = 0.616$) or strength ($p = 0.200$). Further evaluation showed that those participants with the healthiest cartilage (lowest T2 values; group 1) showed statistically significant, moderate correlations, while the other two groups did not (Table 2). Comparing correlations between groups based on meniscal extrusion showed a statistically significant difference in slope ($p = 0.001$) and strength ($p = 0.001$) for the correlation between ΔJSWmed and ΔMFTC, while both slope ($p = 0.514$) and strength ($p = 0.258$) did not differ significantly for the correlation between ΔJSWmin and ΔMFTC. Further looking at the two groups showed that only those participants with meniscal extrusion (group 2) showed statistically significant and weak-moderate correlations, while participants without extrusion (group 1) did not (Table 3). Comparing groups based on potential pain-induced unloading showed there was no significant difference for correlations in either strength or slope (all $p > 0.65$; Supplementary Table S3). Similarly, comparing groups based on BMI-induced loading showed no difference in correlation strength or slope either (all $p > 0.21$; Supplementary Table S4).

Discussion

While statistically significant, longitudinal correlations between radiographic JSW and MRI cartilage thickness were weak in the IMI-APPROACH cohort. The amount of weight-bearing did not seem to influence these correlations, but cartilage quality and

meniscal extrusion did, as participants with the lowest T2 values and with meniscal extrusion showed the strongest correlations.

Values obtained by T2 mapping MRI reflect water content and cartilage collagen fiber content and orientation, and OA cartilage shows higher T2 values as a result of loss of collagen content and structure [26]. As hypothesized, participants with the lowest T2 values, indicating higher cartilage quality and collagen structure integrity, showed the best correlations between ΔJSW and ΔMFTC. Lower quality cartilage as a result of lower collagen structure integrity could be more influenced by compression during weight-bearing, amplifying weight-bearing related differences between radiographic JSW and MRI cartilage thickness and causing weaker correlations between the two. In other words, JSW changes would better reflect cartilage thickness changes for knees with higher quality cartilage than for knees with lower quality cartilage.

Similarly, knees in which meniscal extrusion was present showed the best correlations between ΔJSW and ΔMFTC. In knees without meniscal extrusion, correlations between ΔJSWmed and ΔMFTC even showed negative *B*- and *R*-values, indicating a decrease in MFTC would result in an increase in JSWmed and vice versa. It was already shown previously that JSW is influenced by the meniscus [2, 27-28]. An alternative interpretation could be that, when using JSW as a surrogate measure for cartilage thickness, the presence of the meniscus disturbs the relation they show. As such, JSW changes would better reflect cartilage thickness changes for knees with meniscal extrusion. In a future study, with a larger number of knees or more knees with severe meniscal extrusion, it could be worthwhile to evaluate whether the degree of extrusion matters as well.

It was also hypothesized the amount of weight-bearing would influence the relation between ΔJSW and ΔMFTC, as it was expected less loading would result in stronger correlations, but that was not the case. Both pain-induced potential unloading and BMI-induced increased loading did not influence the correlations. In the case of pain-induced potential unloading, the amount of loading was not measured directly. Instead, it was assumed that participants with significantly more pain in their index knee would slightly unload this knee and put more weight on the contralateral knee. It might be that, despite significantly higher pain, participants did not actually put more weight on their contralateral knee during the acquisition of weight-bearing radiographs, possibly due to the use of a positioning frame during acquisition. However, the fact that increased loading in case of higher BMI did not significantly influence the relations between ΔJSW and ΔMFTC either suggests the amount of loading by itself does not matter. A previous study showed that for cross-sectional correlations between radiographic JSW and MRI cartilage thickness, loading may play a more important role in OA knees than healthy knees [29]. In the IMI-APPROACH cohort, around half of participants did not have radiographic OA, which might have influenced results in the current study, at least with respect to loading [23].

Unlike the other factors, T2 value cutoffs to determine the different groups were not based on a specific clinically relevant value. It would have been more ideal to, for example, separate healthy and OA cartilage or represent different stages of cartilage degradation. It is unfortunately difficult to determine appropriate cutoffs for this, as T2 values are highly dependent on the local MRI setup and hardware (e.g., field strength) [30], which is why three evenly sized groups were created instead. In the current study, three centers acquired T2 mapping MRI using a 3.0 T scanner, but one center used 1.5

T. Excluding this center as a sensitivity analysis did not greatly changes the results: the groups with lowest and middle T2 values both showed significant relations between ΔJSWmed and ΔMFTC and between ΔJSWmin and ΔMFTC (all $p < 0.04$ and $R > 0.33$), while the participants with the highest T2 values did not (both $p > 0.29$ and $R < 0.18$). Also, to ensure the T2 mapping results are not just a bystander effect of OA severity influencing correlations, another sensitivity analysis was done by performing the T2 value analyses for participants with and without radiographic OA separately. Both for knees without (Kellgren-Lawrence grade ≤ 1; 57% of knees) and with (grade ≥ 2; 43% of knees) radiographic OA, correlations differed significantly between the three groups based on T2 values, and in both cases only those with the lowest T2 values showed statistically significant correlations (data not shown). Also, there were no statistically significant differences in ΔJSWmed, ΔJSWmin or ΔMFTC between the three T2 groups (all $p > 0.05$), so the amount of change likely did not influence the conclusions for T2 values either. Of note, knees with meniscal extrusion did show a significantly higher decrease in ΔJSWmed, ΔJSWmin and ΔMFTC than those without meniscal extrusion (all $p < 0.02$). This might have influenced the difference between groups based on meniscal extrusion, as smaller changes might be mainly the result of precision errors instead of actual change.

An important limitation of the current study is that possible variations in knee positioning during acquisition, which is known to influence JSW measurements, was not taken into account. While radiographic positioning was standardized as much as possible, using one specific acquisition protocol in all centers and including a foot plate with triangular wedge to fixate rotation and positioning of the foot, small variations might still have occurred and could have influenced JSW measurements [3]. JSW

progression over time was checked for each knee individually by two readers to see whether there were deviating values, and if this was the case, all index knee radiographs of that knee were compared. If images showed incorrect positioning, JSW (and other radiographic measurement) values were removed. Also, regression coefficients were used for changes over time in the current study specifically to decrease the influence of outliers at one time point, which could be caused by positioning or measurement errors. Still, despite these measures, radiographic positioning might have had some influence on JSW changes.

While the current study provides some indications which factors are important when comparing changes in radiographic JSW and MRI cartilage thickness and which are not, future studies should investigate a combination of factors, for example with stepwise regression analyses. It could be possible that the amount of loading, for example, is not an important factor by itself, but could result in a stronger effect of other factors. For instance, a higher BMI might result in a more pronounced effect of cartilage quality or meniscal extrusion when comparing ΔJSW and ΔMFTC. Furthermore, other potentially important factors could be included that were not taken into account in the current study, such as radiographic positioning or force plate measurements during radiographic acquisition to accurately measure the amount of loading. This way, it could be possible to detect how exactly weight-bearing JSW is made up of cartilage thickness, cartilage quality, meniscal extrusion, and other factors. As it is likely that radiographic JSW will keep being used in regular care and in clinical trials with little funding, it would be valuable to better understand what a change in JSW means and how it relates to a change in MRI cartilage thickness. Well-designed loaded and unloaded MRI studies would be of value in answering this question as well. Also, other measures of cartilage

change over time could be included, such as worsening of semi-quantitative scores in the relevant central subregions.

In conclusion, weight-bearing radiographic JSW changes are reflecting non-weight-bearing MRI cartilage thickness changes particularly in knees with higher quality cartilage compositional parameters and with meniscal extrusion. The amount of loading on the knee does not influence the relation between these changes by itself, but combining multiple important factors in the future could provide a model that reflects how exactly changes in JSW represent relevant structural parameters, including cartilage thickness. This will be primarily of high relevance in the context of clinical trials given that structural success of DMOADs is still commonly based on radiographic outcomes.

Funding

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under Grant Agreement no 115770, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and EFPIA companies' in kind contribution. See www.imi.europa.eu and http://www.approachproject.eu

Ethics declarations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical

standards. Informed consent was obtained from all individual participants included in the study.

FWR: shareholder of Boston Imaging Core Lab (BICL), LLC and consultant to Calibr and Grünenthal.

MK: consulting fees from Abbvie, Pfizer, Kiniksa, Flexion, Galapagos, Jansen, CHDR, Novartis, UCB, all paid to institution.

FJB: funding from Gedeon Richter Plc., Bristol-Myers Squibb International Corporation (BMSIC), Sun Pharma Global FZE, Celgene Corporation, Janssen Cilag International N.V, Janssen Research & Development, Viela Bio, Inc., Astrazeneca AB, UCB BIOSCIENCES GMBH, UCB BIOPHARMA SPRL, AbbVie Deutschland GmbH & Co.KG, Merck KGaA, Amgen, Inc., Novartis Farmacéutica, S.A., Boehringer Ingelheim España, S.A, CSL Behring, LLC, Glaxosmithkline Research & Development Limited, Pfizer Inc, Lilly S.A., Corbus Pharmaceuticals Inc., Biohope Scientific Solutions for Human Health S.L., Centrexion Therapeutics Corp., Sanofi, MEIJI FARMA S.A., Kiniksa Pharmaceuticals, Ltd. Grunenthal, Asofarma Mexico, Gebro Pharma, Roche, Galapagos, Regeneron.

IKH: research grant (ADVANCE) from Pfizer (payment to institution) and consulting fees from Novartis and GSK, outside of the submitted work.

FB: Institutional grants from TRB Chemedica and Pfizer. Consulting fees from AstraZeneca, Boehringer Ingelheim, Bone Therapeutics, Cellprothera, Galapagos, Gilead, Grunenthal, GSK, Eli Lilly, MerckSerono, Nordic Bioscience, Novartis, Pfizer, Sanofi, Servier, Peptinov, 4P Pharma. Honoraria for lectures from Pfizer, Eli Lilly, Viatris, Aché Laboratories. SShareholder of 4Moving Biotech, 4P Pharma and Peptinov.

WW: Employee and shareholder of Chondrometrics GmbH and consulting fees from Galapagos NV.

The other authors have nothing to disclose.

References

1. Guermazi A, Roemer FW, Burstein D, Hayashi D. Why radiography should no longer be considered a surrogate outcome measure for longitudinal assessment of cartilage in knee osteoarthritis. Arthritis Res Ther. 2011;13:1–11.
2. Hunter DJ, Zhang YQ, Tu X, LaValley M, Niu JB, Amin S, et al. Change in joint space width: hyaline articular cartilage loss or alteration in meniscus? Arthritis Rheum. 2006;54:2488–95.
3. Kinds MB, Vincken KL, Hoppinga TN, Bleys RLAW, Viergever MA, Marijnissen ACA, et al. Influence of variation in semiflexed knee positioning during image acquisition on separate quantitative radiographic parameters of osteoarthritis, measured by Knee Images Digital Analysis. Osteoarthr Cartil. 2012;20:997–1003.
4. Oo WM, Little C, Duong V, Hunter DJ. The Development of disease-modifying therapies for osteoarthritis (DMOADs): the evidence to date. Drug Des Devel Ther. 2021;15:2921.
5. Gudbergsen H, Lohmander LS, Jones G, Christensen R, Bartels EM, Danneskiold-Samsøe B, et al. Correlations between radiographic assessments and MRI features of knee osteoarthritis - a cross-sectional study. Osteoarthr Cartil. 2013;21:535–43.
6. Lonza GC, Gardner-Morse MG, Vacek PM, Beynnon BD. Radiographic-based measurement of tibiofemoral joint space width and magnetic resonance imaging derived articular cartilage thickness are not related in subjects at risk for post traumatic arthritis of the knee. J Orthop Res. 2019;37:1052–8.

7. Segal NA, Frick E, Duryea J, Roemer F, Guermazi A, Nevitt MC, et al. Correlations of medial joint space width on fixed-flexed standing computed tomography and radiographs with cartilage and meniscal morphology on magnetic resonance imaging. Arthritis Care Res. 2016;68:1410–6.
8. Cicuttini F, Hankin J, Jones G, Wluka A. Comparison of conventional standing knee radiographs and magnetic resonance imaging in assessing progression of tibiofemoral joint osteoarthritis. Osteoarthr Cartil. 2005;13:722–7.
9. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Beaudoin G, Choquette D, Haraoui B, et al. Long term evaluation of disease progression through the quantitative magnetic resonance imaging of symptomatic knee osteoarthritis patients: Correlation with clinical symptoms and radiographic changes. Arthritis Res Ther. 2005;8:R21.
10. Duryea J, Neumann G, Niu J, Totterman S, Tamez J, Dabrowski C, et al. Comparison of radiographic joint space width with magnetic resonance imaging cartilage morphometry: Analysis of longitudinal data from the osteoarthritis initiative. Arthritis Care Res (Hoboken). 2010;62:932–7.
11. Bruyere O, Genant H, Kothari M, Zaim S, White D, Peterfy C, et al. Longitudinal study of magnetic resonance imaging and standard X-rays to assess disease progression in osteoarthritis. Osteoarthr Cartil. 2007;15:98–103.
12. Wirth W, Duryea J, Hellio Le Graverand MP, John MR, Nevitt M, Buck RJ, et al. Direct comparison of fixed flexion, radiography and MRI in knee osteoarthritis: responsiveness data from the Osteoarthritis Initiative. Osteoarthr Cartil. 2013;21:117–25.
13. Jansen MP, Mastbergen SC, Eckstein F, van Heerwaarden RJ, Spruijt S, Lafeber FPJG. Comparison between 2D radiographic weight-bearing joint space width and 3D MRI non-weight-bearing cartilage thickness measures in the knee using non-weight-bearing 2D and 3D CT as an intermediary. Ther Adv Chronic Dis. 2021;12.

14. Hunter DJ, Altman RD, Cicuttini F, Crema MD, Duryea J, Eckstein F, et al. OARSI Clinical Trials Recommendations: knee imaging in clinical trials inosteoarthritis. Osteoarthr Cartil. 2015;23:698–715.
15. Hochberg MC, Guermazi A, Guehring H, Aydemir A, Wax S, Fleuranceau-Morel P, et al. Effect of intra-articular sprifermin vs placebo on femorotibial joint cartilage thickness in patients with osteoarthritis: The FORWARD Randomized Clinical Trial. JAMA - J Am Med Assoc. 2019;322:1360–70.
16. van Helvoort EM, van Spil WE, Jansen MP, Welsing PMJ, Kloppenburg M, Loef M, et al. Cohort profile: the applied public-private research enabling osteoarthritis clinical headway (IMI-APPROACH) study: a 2-year, European, cohort study to describe, validate and predict phenotypes of osteoarthritis using clinical, imaging and biochemical mark. BMJ Open. 2020;10:e035101.
17. Buckland-Wright JC, Ward RJ, Peterfy C, Mojcik CF, Leff RL. Reproducibility of the semiflexed (metatarsophalangeal) radiographic knee position and automated measurements of medial tibiofemoral joint space width in a multicenter clinical trial of knee osteoarthritis. J Rheumatol. 2004;31:1588–97.
18. Marijnissen ACA, Vincken KL, Vos PAJM, Saris DBF, Viergever MA, Bijlsma JWJ, et al. Knee Images Digital Analysis (KIDA): a novel method to quantify individual radiographic features of knee osteoarthritis in detail. Osteoarthr Cartil. 2008;16:234–43.
19. Jansen MP, Welsing PMJ, Vincken KL, Mastbergen SC. Performance of knee image digital analysis of radiographs of patients with end-stage knee osteoarthritis. Osteoarthr Cartil. 2021;29:1530–9.
20. Hunter DJ, Guermazi A, Lo GH, Grainger AJ, Conaghan PG, Boudreau RM, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthr Cartil. 2011;19:990–1002.
21. Kendrick DB, Strout TD. The minimum clinically significant difference in patient-assigned 11-point numeric pain scale scores for pain. Ann Emerg Med. 2004;44:S86–7.

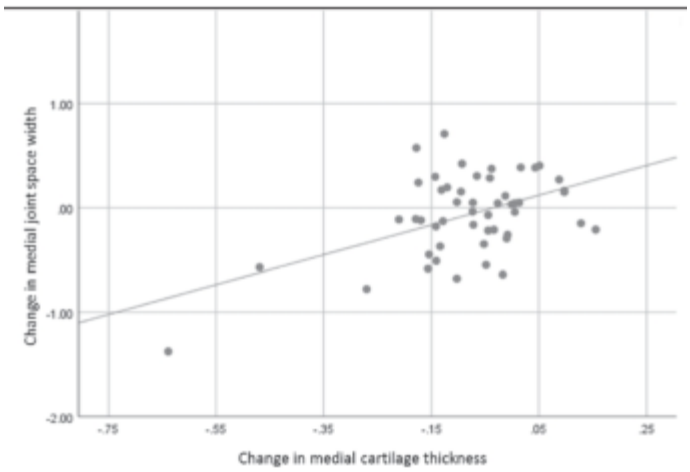
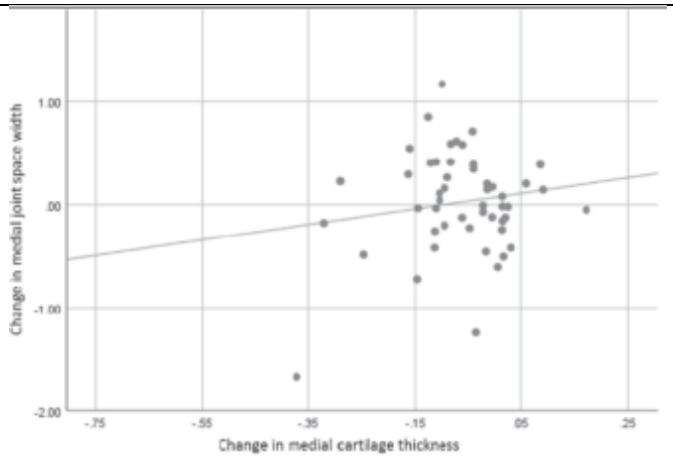
22. Wirth W, Maschek S, Lalande A, Blanco FJ, Berenbaum F, Van de Stadt LA, et al. Test-retest precision and longitudinal cartilage thickness loss in the IMI-APPROACH cohort. Osteoarthr Cartil. 2022;
23. Roemer FW, Jansen M, Marijnissen ACA, Guermazi A, Heiss R, Maschek S, et al. Structural tissue damage and 24-month progression of semi-quantitative MRI biomarkers of knee osteoarthritis in the IMI-APPROACH cohort. BMC Musculoskelet Disord. 2022;23:1–20.
24. Jansen MP, Wirth W, Bacardit J, Van Helvoort EM, Marijnissen ACA, Kloppenburg M, et al. Machine-learning predicted and actual two-year structural progression in the IMI-APPROACH cohort. Quant Imaging Med Surg. 2022.
25. Evans JD. Straightforward statistics for the behavioral sciences. 1st ed. Pacific Grove: Pacific Grove: Brooks/Cole Pub. Co.; 1996. 146
26. Choi JA, Gold GE. MR imaging of articular cartilage physiology. Magn Reson Imaging Clin N Am. 2011;19:249–82.
27. Roth M, Emmanuel K, Wirth W, Kwoh CK, Hunter DJ, Eckstein F. Sensitivity to change and association of three-dimensional meniscal measures with radiographic joint space width loss in rapid clinical progression of knee osteoarthritis. Eur Radiol. 2018;28:1844–53.
28. Roth M, Wirth W, Emmanuel K, Culvenor AG, Eckstein F. The contribution of 3D quantitative meniscal and cartilage measures to variation in normal radiographic joint space width—Data from the Osteoarthritis Initiative healthy reference cohort. Eur J Radiol. 2017;87:90–8.
29. Marsh M, Souza RB, Wyman BT, Hellio Le Graverand MP, Subburaj K, Link TM, et al. Differences between X-ray and MRI-determined knee cartilage thickness in weight-bearing and non-weight-bearing conditions. Osteoarthr Cartil. 2013;21:1876–85.
30. Gold GE, Han E, Stainsby J, Wright G, Brittain J, Beaulieu C. Musculoskeletal MRI at 3.0 T: relaxation times and image contrast. Am J Roentgenol. 2004;183:343–51.

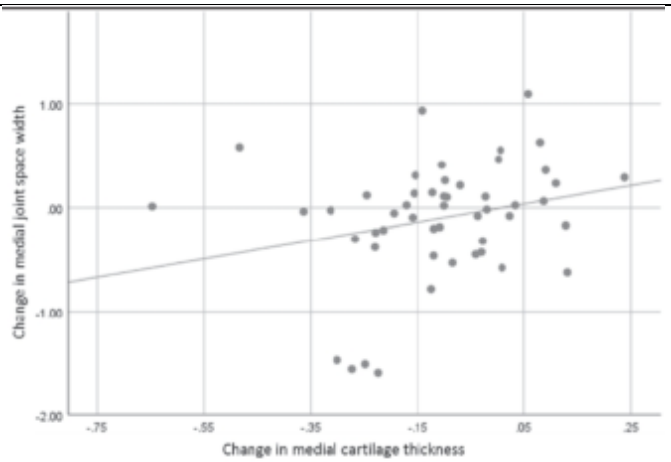
Table 1 Overview of data and groups used in this study

Parameter	Mean ± SD or n (%)
JSWmed, mm	
- Baseline	- 3.96 ± 1.18
- Two years	- 3.92 ± 1.34
JSWmin, mm	
- Baseline	- 2.52 ± 1.23
- Two years	- 1.44 ± 1.23
MFTC, mm	
- Baseline	- 2.93 ± 0.66
- Two years	- 2.83 ± 0.71
Cartilage quality, T2 mapping values in ms	
- Group 1 (lowest; n = 50)	- 35.1 ± 1.9
- Group 2 (middle; n = 51)	- 40.1 ± 1.7
- Group 3 (highest; n = 50)	- 48.4 ± 9.7
Meniscal extrusion, score	
- Group 1 (no; n = 69)	
• Anterior 0	• 69 (100)
• Medial 0	• 69 (100)
- Group 2 (yes; n = 104)	
• Anterior 0/1/2/3	• 55 (53)/31 (30)/17 (16)/1 (1)
• Medial 0/1/2/3	• 7 (7)/46 (44)/33 (32)/16 (15)
Pain-induced unloading, NRS difference index knee—contralateral knee	
- Group 1 (no; n = 141)	
• -2/-1/0/1/2	• 4 (3)/3 (2)/62 (44)/37 (26)/35 (25)
- Group 2 (yes; n = 32)	
• 3/4/5/6/7	• 17 (53)/7 (22)/4 (13)/1 (3)/3 (9)
BMI-induced loading, BMI in kg/m^2	
- Group 1 (healthy; n = 60)	- 22.5 ± 1.7
- Group 2 (overweight; n = 62)	- 27.1 ± 1.4
- Group 3 (obese; n = 56)	- 33.6 ± 3.3

SD standard deviation, JSWmed medial joint space width, JSWmin minimum joint space width, MFTC medial femorotibial cartilage, NRS numeric rating scale, BMI body mass index

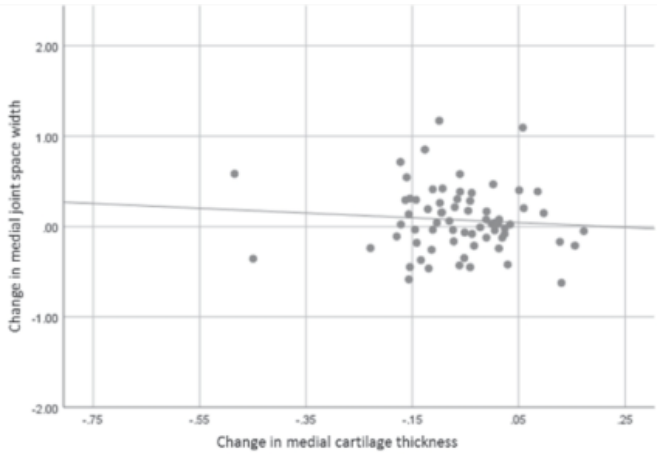
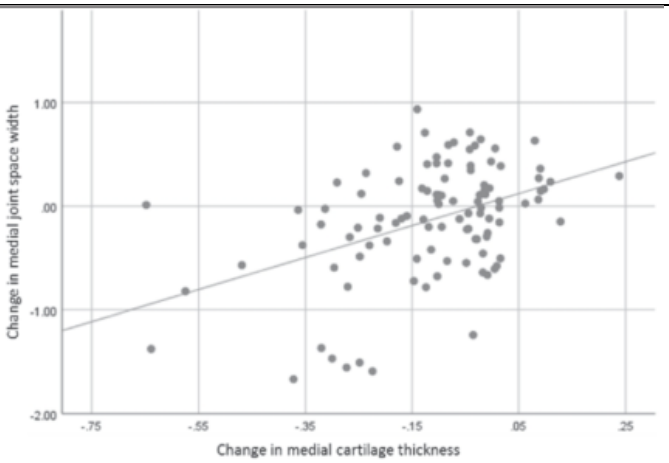
Table 2 Correlations between ΔJSW and ΔMFTC for each group based on cartilage quality

Cartilage quality group	Correlation ΔJSW and ΔMFTC
Lowest T2 values; n=50	 ΔJSWmed: B=1.426; R=0.491; **p<0.001** ΔJSWmin: B=2.012; R=0.526; **p<0.001**
Medium T2 values; n=51	 ΔJSWmed: B=0.753; R=0.155; p=0.278 ΔJSWmin: B=0.556; R=0.107; p=0.454

Highest T2 values; n=50	 ΔJSWmed: B=0.880; R=0.251; p=0.079 ΔJSWmin: B=0.369; R=0.100; p=0.489

Figures show correlations between ΔJSWmed and ΔMFTC. *JSWmed* medial joint space width, *JSWmin* minimum JSW, *MFTC* medial femorotibial cartilage

Table 3 Correlations between ΔJSW and ΔMFTC for each group based on meniscal extrusión

Meniscal extrusión group	Correlation ΔJSW and ΔMFTC
Without extrusion; n=69	 ΔJSWmed: B=-0.264; R=-0.082; p=0.505 ΔJSWmin: B=0.532; R=0.109; p=0.374
With extrusion; n=104	 ΔJSWmed: B=1.514; R=0.432; **p<0.001** ΔJSWmin: B=0.955; R=0.282; **p=0.004**

Figures show correlations between ΔJSWmed and ΔMFTC. *JSWmed* medial joint space width; *JSWmin* minimum JSW, *MFTC* medial femorotibial cartilage