Comparison of 1-year vs 2-year change in regional cartilage thickness in osteoarthritis results from 346 participants from the Osteoarthritis Initiative


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SUMMARY

Objective: To compare femorotibial cartilage thickness changes over a 2- vs a 1-year observation period in knees with radiographic knee osteoarthritis (OA).

Methods: One knee of 346 Osteoarthritis Initiative (OAI) participants was studied at three time points [baseline (BL), year-1 (Y1), year-2 (Y2) follow-up]: 239 using coronal fast low angle shot (FLASH) and 107 using sagittal double echo at steady state (DESS) MR imaging. Changes in cartilage thickness were assessed in femorotibial cartilage plates and subregions, after manual segmentation with blinding to time-point.

Results: The standardized response mean (SRM) of total joint cartilage thickness over 2 years was modestly higher than over 1 year (FLASH: 0.44 vs 0.32/0.28 [first/second year]; DESS: 0.42 vs 0.39/0.18). For the subregion showing the largest change per knee (OV1), the 2-year SRM was similar or lower (FLASH: 1.20 vs 1.22/1.61; DESS: 1.38 vs 1.64/1.51) than the 1-year SRM. The changes in total joint cartilage thickness were not significantly different in the first and second year (FLASH: −0.4% vs −0.3%/−0.18; DeSS: −0.42 vs −0.39/−0.18). For the subregion showing the largest change per knee (OV1), the 2-year SRM was similar or lower (FLASH: −1.20 vs −1.22/−1.61; DeSS: −1.38 vs −1.64/−1.51) than the 1-year SRM. The changes in total joint cartilage thickness were not significantly different in the first and second year (FLASH: −0.8% vs −0.7%; DeSS: −1.3% vs −0.8%) and were negatively correlated. Analysis of smallest detectable changes (SDCs) revealed that only few participants displayed significant progression in both consecutive periods. The location of the subregion contributing to OV1 in each knee was highly inconsistent between the first and second year observation period.

Conclusions: The SRM of region-based cartilage thickness change in OA is modestly larger following a 2-year vs a 1-year observation period, while it is relatively similar when an OV-approach is chosen. Structural progression displays strong temporal and spatial heterogeneity at an individual knee level that should be considered when planning clinical trials.

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Introduction

Magnetic resonance imaging (MRI)—based cartilage morphometry is increasingly used as a structural endpoint of osteoarthritis (OA) progression. This methodology is used in epidemiological studies and clinical trials, to explore the course of the disease (i.e., its natural history), risk factors involved in its onset and progression (i.e., its etiopathology), and to identify potential effects of disease modifying interventions. Although OA is a disease that affects all articular tissues, changes in cartilage thickness have been shown to be particularly sensitive to change. The Osteoarthritis Initiative (OAI, http://oai.ucsf.edu/) is an ongoing, publicly and privately sponsored multi-center study, targeted at identifying sensitive (imaging) biomarkers of symptomatic knee OA, that...
includes MRI suitable for cartilage morphometry. Recent technology has extended the analysis of cartilage morphology from total knee cartilage plates to femorotibial subregions\(^{10-11}\) and the latter has been proposed to be particularly useful when changes are ranked in each knee according to their magnitude [ordered value (OV) approach]\(^{14,15}\).

For clinical trials evaluating risk factors of OA progression or disease modifying interventions, the length of the observation period (and required sample size) is key in the study design, to be able to demonstrate the relevant risk factor relationship or treatment effect for a given sample size with statistical confidence. Whereas the ratio between the real changes occurring and factors affecting the variability of the measurement (i.e., inter-subject variability and precision errors) becomes more favorable with longer observation periods and thus the observed changes more reliable, longer study periods are associated with higher costs, higher participant drop-out, and less patient-life for a drug on the market. If rates of progression in individual knees vary over fairly short time intervals (e.g., from year-to-year), a longer follow-up may result in a more homogeneous outcome in terms of rate of loss. Further, epidemiological and interventional trials commonly rely on rates of change measured at several follow-up time points. Whether the observed rate of change in cartilage volume over two subsequent observation periods is constant or variable over time, both at a cohort and at an individual level, has additional implications for the trial design, for instance when statistical techniques are applied that include intra-patient variability in the analysis model (e.g., ANCOVA with repeated measurements). Also, from a perspective of studying risk factors of OA progression, it is important to explore whether knees in which high rates of progression are observed during an initial (longitudinal) observation period (e.g., year-1) are consistent with knees in which high rates of progression are also observed during a later follow-up period (e.g., year-2).

One study reported relatively consistent cartilage volume changes for 2-year and 4.5-year observation periods\(^{2}\). In contrast, other studies either found the annualized rate of cartilage volume loss over 24 months to be higher than that over 6 and 12 months, respectively\(^9\), or the annualized cartilage thickness loss over 24 months to be higher than that over 6 and 12 months, respectively\(^8\). The findings of these studies were thus inconsistent, as to whether annualized rates of change for longer study periods are generally equal, smaller, or larger than those from shorter periods, but all reported a greater standardized response mean (SRM) for longer study periods, the SRM being a measure of the sensitivity to change. Whereas the above studies compared several follow-up time points with baseline (BL), they did not examine the consistency of the observed rates of change over two subsequent observation periods, either at a cohort or an individual knee level. Also, no prior study has investigated the behaviour of OVs\(^{14,15}\) over 1-year and 2-year observation periods, respectively.

Therefore, the primary objective of this study was to compare the SRM for changes in cartilage plates, subregions and OVs in a given cohort for a 2-year vs a 1-year study period. Secondary objectives were to explore (1) how observed annualized rates of change (in femorotibial cartilage plates, subregions, and OVs) in the first year relate to those in the second year and to those over 2 years, and (2) how consistent the individual changes are over the two 1-year periods, i.e., are first year progressors corresponding with second year progressors, and are the subregions with the greatest observed rate of change (OV 1) during the first year consistent with those during the second year? Please note that the “first” and “second” year observation periods were defined by the study and not by individual disease state, since the beginning of disease is challenging to define in OA, and since this reflects the way in which participants are recruited in clinical trials.

### Methods

**MRI sequences and participants**

In the OAI, 4796 participants are studied at annual time intervals over a period of 4 years\(^{16}\) using fixed flexion radiographs\(^{17,18}\) and MRI\(^{19}\). The OAI involves MRI acquisitions of a coronal fast low angle shot (FLASH) sequence in the right knee\(^{13,19-22}\) and sagittal double echo at steady state (DESS) images in both knees\(^{23,24}\). A recent study reported similar rates of change between FLASH and DESS in the same knees\(^{25}\). The current study was funded by a consortium of the OAI Coordinating Center and several companies (see acknowledgements) and relied on two samples, one based on coronal FLASH and one on sagittal DESS. The OAI inclusion and exclusion criteria and imaging protocol have been described previously\(^{3,20,22,26}\).

The FLASH sample consisted of 239 knees from 239 participants of the progression subcohort (see Table I), who were selected for comparing the rate of change between DESS and FLASH in a cohort with unilateral medial JSN\(^{19,25}\), or were chosen by ascending OAI ID from the first half of the OAI cohort (public-use data sets O.C1 and I.C1), based on calculated Kellgren–Lawrence (cKLG) grades from the clinical site screening readings. The ascending order of OAI IDs was chosen to comprise a “random” sample; only the first half of the total cohort was used, because the 2-year imaging data of the second half of the cohort were not yet public when the participants were selected for segmentation. The inclusion criterion for the knees selected from the first half of the OAI cohort was presence of cKLG 2 or 3 in the study knee (Table I), independent of symptom status or other factors.

The DESS sample has been previously released for public-use (http://www.oai.ucsf.edu/dataload/SASDocs/kMRI_QCart_Eckstein_descrip.pdf) and consisted of 107 knees with frequent pain (defined as: pain on most days of a month in past 12 months); it was selected by the OAI coordinating center as part of a “core image assessment sample” of the progression subcohort (Table I). Central KLG readings were available.

### Table I

BL demographics and acquisition intervals for the coronal FLASH (n = 239 knees) and the sagittal DESS sample (n = 107 knees)

<table>
<thead>
<tr>
<th>Demographics at BL</th>
<th>FLASH</th>
<th>DESS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(Mean)</strong></td>
<td><strong>(SD)</strong></td>
<td><strong>(Mean)</strong></td>
</tr>
<tr>
<td>#Knees</td>
<td>239 (238 right, 1 left)</td>
<td>107 (58 right, 49 left)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.6</td>
<td>9.4</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>29.3</td>
<td>4.6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.6</td>
<td>9.9</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>28.9</td>
<td>4</td>
</tr>
</tbody>
</table>

**Radiographic readings**

<table>
<thead>
<tr>
<th>(cKLG)</th>
<th>(cKLG)</th>
<th>(cKLG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>96</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>2</td>
</tr>
</tbody>
</table>

BMI = Body Mass Index; KLG = Kellgren and Lawrence grade obtained from central readings. cKLG = Kellgren and Lawrence grades calculated from osteophyte and joint space narrowing readings at the clinical sites of the OAI (cKLG: no radiographic signs of OA, cKLG1: doubtful or minute osteophytes if doubtful significance, or isolated mild to moderate joint space narrowing; cKLG2: definite osteophytes and unimpaired joint space or isolated severe JSN in combination with no or questionable osteophytes; cKLG3: Definite osteophytes and OARSI grade 1 to 2 joint space narrowing; cKLG4: definite osteophytes and OARSI grade 3 joint space narrowing).
for the DESS but not for the FLASH sample and differed from the clinical site cKLG readings (Table I).

Image analysis

After initial quality control (MH), segmentation of the weight-bearing femorotibial cartilage plates was performed in the FLASH and DESS images by seven experienced operators, with blinding to the time-point of acquisition and to the BL radiographic readings. One randomly selected time-point was used as the “reference” data set and was displayed for comparison during the segmentation of the other time points. Segmentation of the subchondral bone area (tAB) and the area of the cartilage surface (AC) were completed in the medial (MT) and lateral tibia (LT), and in the weight-bearing part of the medial (cMF) and the lateral (cLF) femoral condyle. A 60% distance criterion between the trochlear notch and the posterior ends of the femoral condyles was applied to define the weight-bearing portion of the condyles in both the coronal and sagittal MR images. Segmentation underwent quality control by an expert (S.M.) and was corrected by the operators, if necessary. The mean cartilage thickness over the tAB (ThCTaB) was computed in femorotibial cartilage plates (MT, LT, cMF, and cLF), the medial and lateral femorotibial compartment (MFTC = MT + cMF; LFTC = LT + cLF), the total femorotibial joint (FTJ = MFTC + LFTC), and in 16 femorotibial subregions [five in MT and LT, three in cMF and cLF, respectively; Fig. 1 (c, d)]

Statistical analysis

The mean change (MC), the 95% confidence interval of the change (CI: lower/upper limit), and the standard deviation of the observed change (SD) in ThCTaB (µm) were determined between BL and year-1 follow-up (Y1), between Y1 and year-2 follow-up (Y2), and between BL and Y2. Percent changes were obtained by relating the MC to the mean ThCTaB of the reference time-point and the SRM was computed by relating the MC to the SD. All observed changes were normalized to a 365-day-period: The average ± SD BL to Y1 period was 389 ± 38 days, and the Y1 to Y2 period was 353 ± 46 days.

Statistical significance of the differences between the changes observed in year-1 vs year-2 was tested using the Wilcoxon signed rank test. To facilitate the comparison between the three intervals, we calculated the relationship (factor) between the observed averaged second and first-year changes [(Y2–Y1)/(Y1–BL)] and between the observed averaged 2-year and first year changes [(Y2–BL)/(Y1–BL)]. The correlation of the observed changes (first year vs second year, and first year vs 2-year) was determined using both parametric (Pearson r) and non-parametric (Spearman rho) coefficients.

The recently proposed OVs approach was applied to observed longitudinal changes in ThCTaB in all 16 (medial and lateral)
femorotibial subregions.\textsuperscript{12} The rates of subregional change between BL and follow-up were sorted in each knee in ascending order, i.e., the subregional value with the largest observed thickness decrease being assigned to OV1, the value with the second-largest observed decrease to OV2, and so forth.\textsuperscript{12} The value of the subregion with the smallest observed thickness decrease (or largest increase) was assigned to OV16. Separate sets of OV variables were computed for the first and second year, and for the 2-year-period.

The smallest detectable change (SDC) method\textsuperscript{29} was used to identify knees with significant loss of ThCtAb (progression). Test-retest precision errors for repeated measurements were used for this purpose, as derived from paired analysis of FLASH and DESS images in the OAI pilot study.\textsuperscript{10}

Results

The SRM for the FTJ in the FLASH/DESS sample was 0.44/−0.42 over the 2-year observation period and was higher than that in the first year (−0.32/−0.39) and second year (−0.28/−0.18) (Tables II & III). In the FLASH cohort, the 2-year SRM of MT was twice that over the first year, but in cLF it was only 1.1 times that of the first year. In the DESS sample, the medial cartilage plates (MT, cMF) displayed an approximately 25% greater SRM over 2 years than in the first year, but the SRM was similar between the 2-year-period and the first year for the lateral plates (LT, cL). For OV1, the 2-year SRM (−1.20) was similar to the first-year SRM (−1.22) for FLASH (Table II) and was lower over 2 years (−1.38) than in the first year (−1.64) with the DESS (Table III).

The observed rate of change across the entire (FTJ) joint was −1.5%−2.0% for FLASH/DESS over the 2-year-period, −0.8%−1.3% in the first year, and −0.7%−0.8% in the second year (Tables II & III). For the entire FTJ, the changes observed over 2-year were 83% higher than the first year changes in the FLASH sample, and they were 60% higher than the first year changes in the DESS sample; The rates of change in cartilage plates and subregions were not significantly different between the first and the second year (Table II & III).

The rates of change measured for OVs were also similar in the first and second year, except for some of the extreme OVs, specifically OV1 (P = 0.004), OV14 (P = 0.013), OV15 (P = 0.002) and OV16 (P < 0.001) with the FLASH, and OV16 (P = 0.015) with the DESS. OV1 decreased by −150 μm (95% CI: −166 μm to −135 μm) in the first year.
and by −169 μm (95% CI: −182 μm/−156 μm) in the second year with the FLASH, while a loss of −221 μm (95% CI: −247 μm/−196 μm) was noted in the first and a loss of −228 μm (95% CI: −257 μm/−199 μm) in the second year with the DESS [Tables II & III, Fig. 2(c)]. The observed 2-year change in OV1 was higher than that over 1-year, the factor being 1.3 for FLASH and 1.2 for DESS (Tables II & III). Although the changes observed during the first year were moderately strongly positively correlated with the changes during the full 2-year-period. (Table IV), the changes observed during the second year were negatively correlated with those in the first year, except for the first OVs (Table IV). This finding was consistent between the FLASH and the DESS cohort [Fig. 3 (a, b)].

In the FLASH cohort, 19% FTJ progressors were observed (SD analysis) in the first and 24% in the second year (Table V), and with the DESS there were 31% (first year) vs only 18% progressors (second year), respectively. Only 5% of the FLASH and 7% of the DESS cases, however, showed progression above the respective threshold during both periods (Table V).

OV1 rarely originated from the same subregion in the first and second year (FLASH: 3.3%; DESS: 2.8%). OV1 came from a different subregion but from the same cartilage plate in about 20% of the cases (both FLASH and DESS), it came from a different subregion of the same compartment but not the same plate in 27% (FLASH) to 31% (DESS) of the cases, and it even came from a subregion of the opposite femoral condyle: femorotibial subregions: (c = central, e = external, i = internal, a = anterior, and p = posterior); OV = ordered values of change in cartilage thickness. JSW = joint space width.

<table>
<thead>
<tr>
<th>Subregion</th>
<th>BL → Y1</th>
<th>Y1 → Y2</th>
<th>BL → Y2</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTJ</td>
<td>IC: 130/−44</td>
<td>−1.3−0.39</td>
<td>−51 (−105/2)</td>
</tr>
<tr>
<td>MTFIC</td>
<td>IC: 80/−20</td>
<td>−0.5−0.32</td>
<td>−36 (−71/2−1)</td>
</tr>
<tr>
<td>LFTC</td>
<td>IC: 59/−15</td>
<td>−1.1−0.32</td>
<td>−15 (−44/14−4)</td>
</tr>
<tr>
<td>MT</td>
<td>IC: 35/−4</td>
<td>−1.2−0.24</td>
<td>−12 (−29/5)</td>
</tr>
<tr>
<td>cMF</td>
<td>IC: 40/−11</td>
<td>−1.8−0.30</td>
<td>−24 (−47/−1)</td>
</tr>
<tr>
<td>LT</td>
<td>IC: 38/−12</td>
<td>−1.4−0.36</td>
<td>−11 (−26/5)</td>
</tr>
<tr>
<td>cLF</td>
<td>IC: 26/3</td>
<td>−0.7−0.16</td>
<td>−4 (−24/6)</td>
</tr>
<tr>
<td>cMT</td>
<td>IC: 94/−34</td>
<td>−2.9−0.41</td>
<td>−41 (−70/−12)</td>
</tr>
<tr>
<td>eMT</td>
<td>IC: 87/−15</td>
<td>−3.7−0.31</td>
<td>−38 (−58/−6)</td>
</tr>
<tr>
<td>iMT</td>
<td>IC: 96/0.3</td>
<td>−0.19−0.19</td>
<td>−8 (−21/4)</td>
</tr>
<tr>
<td>aMT</td>
<td>IC: 20/12</td>
<td>−0.3−0.05</td>
<td>−10 (−32/12)</td>
</tr>
<tr>
<td>pMT</td>
<td>IC: 15/11</td>
<td>−0.2−0.03</td>
<td>−10 (−7/27)</td>
</tr>
<tr>
<td>ccMF</td>
<td>IC: 75/−18</td>
<td>−2.5−0.31</td>
<td>−34 (−66/−3)</td>
</tr>
<tr>
<td>ecMF</td>
<td>IC: 56/−10</td>
<td>−2.5−0.28</td>
<td>−26 (−52/1)</td>
</tr>
<tr>
<td>icMF</td>
<td>IC: 33/8</td>
<td>−0.7−0.12</td>
<td>−12 (−36/12)</td>
</tr>
<tr>
<td>cLT</td>
<td>IC: 74/−6</td>
<td>−2.0−0.40</td>
<td>−25 (−55/6)</td>
</tr>
<tr>
<td>eLT</td>
<td>IC: 34/3</td>
<td>−1.0−0.16</td>
<td>−15 (−34/4)</td>
</tr>
<tr>
<td>ILT</td>
<td>IC: 50/−9</td>
<td>−1.7−0.28</td>
<td>−30 (−59/0)</td>
</tr>
<tr>
<td>cLT</td>
<td>IC: 24/7</td>
<td>−0.6−0.11</td>
<td>−8 (−11/27)</td>
</tr>
<tr>
<td>pLT</td>
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<td>−13 (−17/14)</td>
</tr>
<tr>
<td>eLF</td>
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<td>−14 (−41/12)</td>
</tr>
<tr>
<td>eLF</td>
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<td>−0.1−0.02</td>
<td>−13 (−29/23)</td>
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<tr>
<td>iLCF</td>
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<td>−13 (−29/23)</td>
</tr>
<tr>
<td>OV1</td>
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<td>−9.2−1.48</td>
<td>−157 (−179/−135)</td>
</tr>
<tr>
<td>OV1</td>
<td>IC: 131/*102</td>
<td>−6.9−1.54</td>
<td>−119 (−138/−100)</td>
</tr>
<tr>
<td>OV1</td>
<td>IC: 101/*106</td>
<td>−5.2−1.36</td>
<td>−90 (−106/−73)</td>
</tr>
<tr>
<td>OV1</td>
<td>IC: 82/*59</td>
<td>−4.1−1.14</td>
<td>−68 (−83/−53)</td>
</tr>
<tr>
<td>OV1</td>
<td>IC: 67/*44</td>
<td>−3.3−0.93</td>
<td>−48 (−61/−34)</td>
</tr>
<tr>
<td>OV1</td>
<td>IC: 50/*22</td>
<td>−2.5−0.71</td>
<td>−33 (−45/−20)</td>
</tr>
<tr>
<td>OV1</td>
<td>IC: 27/*16</td>
<td>−1.6−0.49</td>
<td>−17 (−29/4)</td>
</tr>
<tr>
<td>OV1</td>
<td>IC: 12/*21</td>
<td>−0.7−0.22</td>
<td>−0 (−13/3)</td>
</tr>
<tr>
<td>OV1</td>
<td>IC: 8/*12</td>
<td>0.2−0.04</td>
<td>17 (4/29)</td>
</tr>
<tr>
<td>OV1</td>
<td>IC: 8/*29</td>
<td>1.1−0.35</td>
<td>29 (17/42)</td>
</tr>
<tr>
<td>OV1</td>
<td>IC: 26/*46</td>
<td>2.1−0.08</td>
<td>49 (36/61)</td>
</tr>
<tr>
<td>OV1</td>
<td>IC: 40/*61</td>
<td>3.0−0.93</td>
<td>68 (55/80)</td>
</tr>
<tr>
<td>OV1</td>
<td>IC: 59/101</td>
<td>4.3−1.24</td>
<td>88 (75/101)</td>
</tr>
<tr>
<td>OV1</td>
<td>IC: 105/*135</td>
<td>5.7−1.61</td>
<td>120 (105/135)</td>
</tr>
<tr>
<td>OV1</td>
<td>IC: 151/*190</td>
<td>8.6−1.66</td>
<td>186 (164/207)</td>
</tr>
</tbody>
</table>

**Discussion**

The primary objective of this study was to compare the SRM for changes in cartilage plates, subregions and OVs in a given cohort following a 2-year vs a 1-year study period; secondary objectives were to explore how the observed annualized rate of change in the first year relates to that in the second year (across that over 2 years), and how consistent the observed individual changes are over the two 1-year periods. Key results were that the SRM for region-based parameters over 2 years was modestly larger than that obtained during the first year, while the 2-year SRMs for OVs were similar or
In addition, the observed rates of change in region-based parameters were negatively correlated and did not differ statistically significantly between the first and the second year. The location of the subregion with the greatest observed rate of change (OV1) was found to be highly inconsistent between the first and the second year.

A limitation of the study is that cartilage segmentation of the intermediate (1-year) time-point was used in the calculation of the rate of change in both 1-year observation periods. The reported negative correlation between the first and second year changes may thus partly originate from the precision errors occurring when measuring this time-point, e.g., overestimating the cartilage thickness at 1 year follow-up causes too small changes during the first and too large changes during the second year in knees showing loss of cartilage thickness, whereas underestimating the cartilage thickness at 1 year follow-up causes too large changes during the first and too small changes during the second year in knees showing negative changes. The non-linearity of the rate of change, however, was also confirmed by the results from the SDC analysis, which accounts for the precision errors of the measurement methodology. Another limitation of the study is the difference in the length of the first and the second year of the observation period, as well as the variability of the observation periods between participants. To allow for a quantitative comparison of both time intervals, all changes were normalized to the respective length of the observation periods in each of the participants. A strength of the study is the inclusion of two separate cohorts that were imaged with different MR sequences, involving both different image orientations and contrasts. The inclusion of different image orientations was particularly relevant in context of the subregional and OV analysis, because the largest partial volume effects for the coronal (FLASH) images occur at different locations than for the sagittal (DESS) images.

As reported in previous studies, the SRM was higher over a 2 year than over 1 year observation period for region-based changes.
the FLASH sample, however, the SRM was less than twice (and often
cartilage loss over longer follow-up intervals. Except for the MT of
measurement error becomes more favorable with longer observa-
tion periods and may result in a greater homogeneity in rates of
changes.

Correlation of observed longitudinal changes in cartilage thickness (ThCtAB)
Bold correlation coefficients were significant at \( P < 0.001 \), CM/xF = weight-bearing (central) part of the medial/lateral femoral condyle; Femoral subre-
gions: (c = central, e = external, i = internal, a = anterior, and p = posterior); 
OV = ordered values of change in cartilage thickness.

parameters. This is because the ratio of the real change to the
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consecutive observation periods was observed only in a minority of
the knees. These results indicate that the observed rate of
progression over two consecutive 1-year period may not be highly
stable at an individual level. Further, apparently consistent rates of
change of OV1 in two consecutive years in a cohort were not driven
by identical subregions. Instead, the observed structural progres-
sion of cartilage loss in OA was found to display a strong temporal
and spatial heterogeneity that needs to be taken in account when
investigating the potential impact of disease- or structure modi-
fying drugs or when studying risk factors of OA progression.

Authors’ contributions

All authors have made substantial contributions to: (1) the
conception and design of the study, or acquisition of data, or
analysis and interpretation of data, (2) drafting the article or
revising it critically for important intellectual content, (3) final
approval of the version to be submitted. WW and FE felix.
eckstein@pmu.ac.at) take responsibility for the integrity of the work as a whole, from inception to finished article.

WW was involved in the conception and design of the study, the analysis (computation of quantitative cartilage morphometry outcomes and statistics) and interpretation of the data, assembly of the data, drafting and critical revision of the article for important intellectual content, and final approval of the article.

SL was involved in statistical analysis, analysis and interpretation of the data, critical revision of the article for important intellectual content, and final approval of the article.

RD was involved in statistical analysis, analysis and interpretation of the data, obtaining funding, critical revision of the article for important intellectual content, and final approval of the article.

MN was involved in the acquisition, statistical analysis, analysis and interpretation of the data, collection and assembly of data, logistic support, critical revision of the article for important intellectual content, and final approval of the article.

AG was involved in conception and design of the study, obtaining of funding, critical revision of the article for important intellectual content, and final approval of the article.

FB was involved in conception and design of the study, obtaining of funding, critical revision of the article for important intellectual content, and final approval of the article.

JL was involved in conception and design of the study, obtaining of funding, critical revision of the article for important intellectual content, and final approval of the article.

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