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The Impact of varus and valgus alignment on knee cartilage quality assessed by magnetic resonance imaging: insights from the IMI-APPROACH cohort

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ABSTRACT

Background: Lower limb malalignment increases the risk of unicompartmental knee osteoarthritis (KOA). This study investigates the association between knee cartilage quality, assessed via MRI-based T2 mapping, and lower limb malalignment. It also examines whether cartilage quality is more influenced by bony or intra-articular malalignment.
Methods: In this cross-sectional analysis of 156 knees from the IMI-APPROACH cohort, tibiofemoral cartilage T2 values were measured using high-resolution MRI, distinguishing superficial and deep layers. Malalignment was categorized into entire leg, bony, and intra-articular malalignment (via the Joint Line Convergence Angle). Correlations between T2 values and alignment were assessed using Spearman's rho. A subgroup analysis evaluated cartilage quality in constitutional malalignment (malalignment without intra-articular deviation).
Results: Cartilage T2 values were significantly associated with alignment. Varus knees showed significantly longer T2 in the superficial medial cartilage ($\rho = -0.2$, $p = 0.04$), and valgus knees in the lateral compartment ($\rho = 0.1$, $p = 0.35$). Associations were strongest for intra-articular malalignment ($\rho = 0.3$, $p < 0.01$). In constitutional varus, a non-significant

Abbreviations: CT, Computed Tomography; FDR, False Discovery Rate; IMI-APPROACH, Applied Public-Private Research enabling OsteoArthritis Clinical Headway; JLCA, Joint Line Convergence Angle; K&L, Kellgren and Lawrence; KOA, Knee Osteoarthritis; mHKAA, Mechanical Hip Knee Ankle Angle; mLDFA, Mechanical Lateral Distal Femoral Angle; mMPTA, Mechanical Medial Proximal Tibial Angle; MRI, Magnetic Resonance Imaging; ODIA, Osteoarthritis Digital Image Analysis.

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medial T2 prolongation was observed (ρ = –0.2, p = 0.28); no changes were found in constitutional valgus.
Conclusion: Lower limb malalignment, particularly intra-articular malalignment, is associated with compartment-specific lower cartilage quality, as reflected by longer T2 values. Distinguishing between bony and intra-articular malalignment, rather than overall limb alignment, should be a focus of future studies on malalignment. Future research should explore whether constitutional malalignment and early cartilage alterations may trigger cartilage degeneration and KOA progression.

1. Introduction

Knee osteoarthritis (KOA) is the most common progressive joint disease worldwide [1]. The prevalence of KOA in individuals aged over 40 years is 22.9% worldwide, posing a significant health issue [1]. With aging and an increasingly obese population, it is becoming even more prevalent than in previous decades [1]. KOA is characterized by the gradual breakdown of the protective cartilage in the joint, accompanied by inflammation and changes in surrounding tissues, which contribute to pain, stiffness, and a diminished range of motion [2].

The radiological diagnosis of KOA is often made at a late stage, as radiographs reveal KOA changes at a relatively late stage [3]. T2 mapping using Magnetic Resonance Imaging (MRI) scans is a powerful tool for assessing cartilage composition, as it reveals water content and collagen fiber orientation [4,5], with prolonged T2 indicative of poorer cartilage quality [6,7]. T2 mapping, highly sensitive to changes in collagen concentration and fragmentation of the collagen matrix, has proven to be a valuable tool for assessing cartilage degeneration, with histological studies suggesting its reliability and providing critical insights into in vivo cartilage degeneration [8,9].

Individuals with lower limb joint malalignment are at increased risk of developing unicompartmental KOA [10,11], as the asymmetric loading of a single tibiofemoral compartment causes cartilage degeneration [12]. Lower limb malalignment encompasses both bony malalignment and intra-articular knee joint malalignment [13]. Bony alignment refers to the alignment of the tibial and/or femoral bones. Intra-articular malalignment, in contrast, refers to structural abnormalities within the knee joint itself, including cartilage degeneration, meniscal damage, and meniscal extrusion [14,15]. Some individuals exhibit constitutional varus, which means that only bony malalignment is present, without intra-articular knee joint malalignment [16]. As a result, these individuals do not show radiological evidence of KOA, but they do have lower limb malalignment. However, these individuals are at an increased risk of developing KOA over time [17]. MRI T2 mapping may offer a valuable tool for assessing cartilage quality in these individuals, potentially identifying those at elevated risk for developing unicompartmental KOA. By enabling timely interventions, this technique could play a critical role in mitigating disease progression and reducing long-term joint damage.

Sharma et al.[12] investigated the relationship between KOA progression based on MRI and lower limb malalignment. Their study showed that varus knee malalignment was associated with the development of cartilage damage in the medial compartment and demonstrated reduced risk of cartilage damage in the less-loaded compartment in either varus or valgus knees. However, the study did not utilize T2 mapping and did not distinguish between malalignment attributable to bony and intra-articular knee joint malalignment. Identifying this difference is important, as intra-articular knee joint malalignment reflects unicompartimental cartilage and/or meniscal loss, which are part of the joint degeneration process [14].

Therefore, this cross-sectional study in participants with KOA examines the association between knee cartilage quality (T2) and lower limb malalignment, focusing on whether the association of the entire leg malalignment is primarily influenced by intra-articular or bony malalignment. We hypothesized that bony varus alignment is associated with lower cartilage quality reflected by longer T2 in the medial compartment. Conversely, bony valgus alignment was expected to be associated with lower cartilage quality (longer T2) in the lateral compartment, reflecting the isolated effects of lower limb malalignment on T2 related cartilage quality.

2. Methods

2.1. Participants

In the prospective Applied Public-Private Research enabling OsteoArthritis Clinical Headway (IMI-APPROACH) cohort, 297 KOA participants from five European centers were followed for 2 years [18]. Participants aged 18 years and older were selected based on the likelihood of experiencing structural and/or knee pain progression over a two-year period. The index knee was selected based on American College of Rheumatology (ACR) criteria. In case of equal symptoms in both knees, the right knee was chosen. The inclusion and exclusion criteria for the IMI-APPROACH cohort have been previously published [18]. Participants underwent low dose whole body computed tomography (CT) scan, weight-bearing posteroanterior radio-

graphs according to the Buckland-Wright protocol and 1.5 or 3.0T MRI scans of the index knee at baseline [18,19]. Participants with available baseline CT scans, radiographs, and 3T MRI scans, including T2-mapping, were included in this study.

The study was approved by the Institutional Review Boards, following protocols, Good Clinical Practice, the Declaration of Helsinki, and all ethical and legal regulations. The study was registered under clinicaltrials.gov nr: NCT03883568 and informed consent was obtained.

2.2. Imaging assessment

The Kellgren and Lawrence (K&L) score was determined by one experienced observer on knee radiographs with good reliability [20]. Based on these scores, participants were categorized into two groups: those with no or doubtful radiographic OA (K&L 0–1) and those with mild to severe radiographic OA (K&L 2–4). Furthermore, all weight-bearing knee radiographs were reproducibly and automatically analyzed using the Osteoarthritis Digital Image Analysis (ODIA) to determine the Joint Line Convergence Angle (JLCA) in weight-bearing position (Table 1) (Figure 1) [21]. The JLCA obtained from radiographs served as a measure of intra-articular alignment and can be considered a unicompartimental (non-symmetrical) loss of cartilage and/or meniscus of the knee, while JLCA alterations may also be influenced by soft tissue tension or laxity [14,15]. A JLCA between 0–2° is considered as healthy (Table 1), while a JLCA outside this normal range is considered pathological and a visible sign of KOA [22].

The femur and tibia were automatically segmented from the low dose whole body Computed Tomography (CT) using a deep learning approach [23]. Bony deformities in the individual bones of the tibia (mechanical medial proximal tibial angle (mMPTA)) and femur (mechanical lateral distal femoral angle (mLDFA)) were automatically determined from CT-scan as proposed by Paley [22,24] (See Figure 1). The bony alignment was determined by mMPTA – mLDFA + 180°, as proposed by MacDessi et al.[13] and represents the alignment of the tibial and femoral bones. A bony varus alignment was defined as 178° or less, and a bony valgus alignment as 182° or more [25] (Table 1). The deformity of the entire leg (mechanical hip-knee-ankle angle (mHKAA)) reflects both bony deformity and intra-articular knee joint deformity (JLCA) and can be calculated using the formula mMPTA – mLDFA – JLCA + 180°. The mMPTA and mLDFA were obtained from CT imaging, which is independent of patient positioning, whereas the weight-bearing JLCA was assessed using weight-bearing radiographs. A neutral mHKAA ranges from 178° to 182°, with varus alignment defined as 177° or less, and valgus alignment as 183° or more [22]. Coronal lower limb malalignment was classified into three categories: entire leg alignment (1), bony alignment in femur and/or tibia (2), and intra-articular alignment (3) (Figure 1).

Cartilage T2 times, reflecting cartilage matrix quality, were determined using high-resolution MRI for both tibial and femoral cartilage. T2 times were obtained by manual, quality-controlled cartilage segmentation (Chondrometrics GmbH, Freilassing, Germany) [26,27]. Due to the recognized spatial variation of cartilage T2 with tissue depth [28], the cartilage was divided into the top 50% (superficial) and bottom 50% (deep) [28], based on the local distance between the segmented cartilage surface and bone interface [26] and the superficial and deep layer T2 times were calculated for both the medial and lateral compartment [29] (Figure 2).

2.3. Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 29.0 software. Descriptive statistics, including means and standard deviations (SD) were computed. The Shapiro-Wilk test was used to assess the normality of the data. Spearman's rho (ρ) was used to assess correlations between cartilage T2 in medial and lateral knee compartments and the three alignment parameters: entire leg alignment (1), bony alignment (2), and intra-articular alignment knee joint alignment (3) (Figure 1). Spearman's rho 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 [30]. Furthermore, Spearman's rho (ρ) were conducted for the subset of participants with constitutional joint malalignment without any intra-articular knee joint deformity (non-pathological JLCA of 0-2°). The latter subset may strengthen the pure effects of valgus or varus on T2 related car-

Table 1
The alignment classification for normal, varus and valgus alignment. The alignment was determined for JLCA on standing knee radiographs, and bone morphology on rendered 3D models of the CT-scans.

		JLCA	Bony alignment
Normal		|0° – 2°|	|178° – 182°|
Varus	Intra-articular	> 2°	|178° – 182°|
	Bones	|0° – 2°|	< 178°
Valgus	Intra-articular	< 0°	|178° – 182°|
	Bones	|0° – 2°|	> 182°

JLCA, joint line convergence angle;

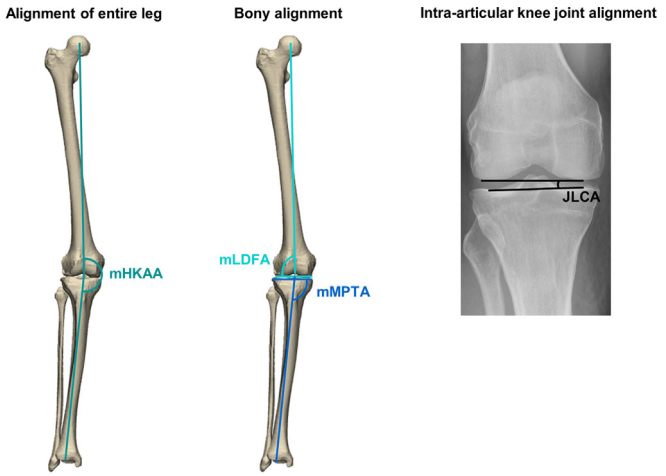

Figure 1. Illustration of coronal lower limb malalignment: Entire leg alignment (mechanical hip-knee-ankle angle (mHKAA)), bony alignment (mechanical medial proximal tibial angle (mMPTA)), mechanical lateral distal femoral angle (mLDFA)), and intra-articular knee joint alignment (joint line convergence angle (JLCA)).

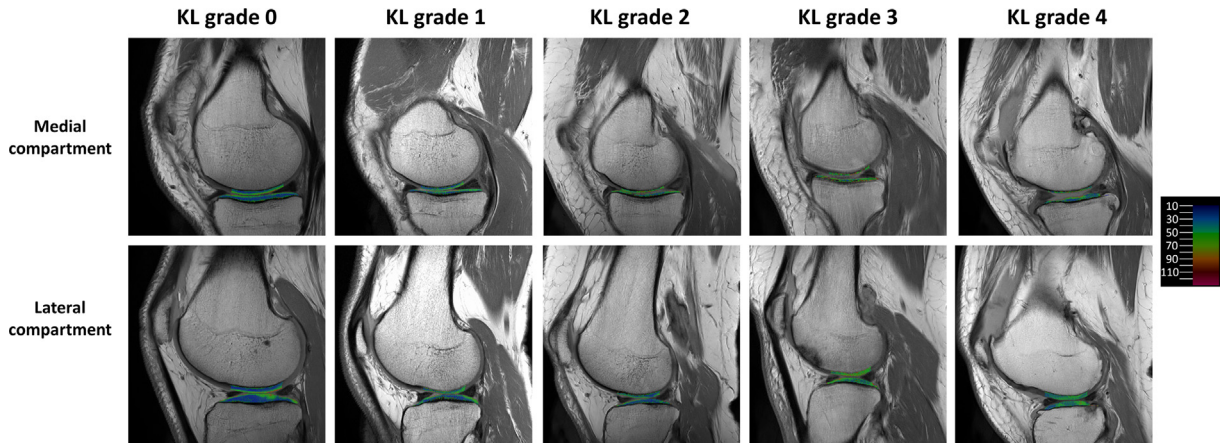

Figure 2. Representative T2 mapping images of the medial (top row) and lateral (bottom row) compartments across Kellgren-Lawrence (KL) grades 0–4. Color-coded overlays indicate T2 relaxation times, with higher values (warmer colors) reflecting lower cartilage quality.

tilage quality. Finally, a Mann-Whitney *U* test was performed to determine whether T2 times differed significantly between K&L scores.

The False Discovery Rate (FDR) (the rate of Type I errors due to multiple testing) was controlled at 5% through the Benjamini-Hochberg method [31]. The obtained p-values were sorted in ascending order and corrected using the Benjamini-Hochberg method. With m tests and $p(n)$ as the smallest obtained p-value, the corrected p-value was determined as $p(n) \cdot \frac{m}{n}$.

A priori power analysis was conducted using G*Power version 3.1 to determine the required sample size for detecting a statistically significant correlation [32]. Assuming a significance level (α) of 0.05 and a desired power ($1 - \beta$) of 0.80, with a medium effect size ($r = 0.30$) based on Cohen's conventions, the analysis indicated that a minimum of 84 participants would be needed. With this sample size, the actual statistical power to detect the specified correlation was 80%.

3. Results

3.1. Participants

Of the 297 participants of the IMI-APPROACH cohort, 152 participants had the required baseline data (knee radiographs, T2-mapping on 3T MRI, and CT scans) and were included. Average age was 66.7 ± 7.0 years and the participants were pre-

dominantly female (81.4%). 79 participants (50.6%) had a K&L score of 0 or 1, while 70 participants (49.4%) had a K&L score between 2 and 4. See Table 2.

The mean mHKAA (providing the total alignment of the entire leg including the intra-articular portion) was 179.8 ± 3.0°, with 29.5% exhibiting varus and 18.6% exhibiting valgus alignment. The mean bony alignment was 180.0 ± 2.7°. A total of 71 participants (45.5%) exhibited a bony malalignment without any intra-articular knee joint deformity. Of these participants, 26.8% exhibiting a varus bony alignment and 73.2% a valgus bony alignment. Finally, the mean JLCA was 1.5 ± 2.1°. A total of 71 participants (45.5%) had a JLCA within the normal range, 57 (36.5%) demonstrated a varus JLCA, and 28 (17.9%) exhibited a valgus JLCA.

3.2. Kellgren and Lawrence and T2 times

The deep layer of the medial compartment demonstrated a significantly shorter T2 time (better cartilage quality) in the K&L 0–1 group in comparison to K&L 2–4 (median 30.9 ms vs 35.8 ms) ($P < 0.001$) (Figure 3). Likewise, the deep layer of the lateral compartment exhibited a significantly shorter T2 time within the K&L 0–1 group when compared to the K&L 2–4 group (median 31.8 versus 33.9 ms) ($P < 0.001$) (Figure 3). The superficial layer of the medial and lateral compartment did not exhibit a significant difference between the groups (Medial: $P = 0.12$ Lateral: $P = 0.86$) (Figure 3). Additionally, KL grade and JLCA were moderately positively correlated ($\rho = 0.43$, 95% CI 0.29–0.56, $P < 0.001$).

3.3. Alignment and T2 times correlation in the entire group

For all three aspects of (mal)alignment it was found that varus shapes had higher T2 time (more cartilage degeneration) at the medial compartment compared to the lateral compartment. In line with this, valgus shapes had higher T2 at the lateral compartment (Figure 4).

More specifically in the superficial layer of the medial compartment, a weak but statistically significant correlation was evident between the T2 time and the entire leg (mHKAA) ($\rho = -0.31$, $p < 0.001$). Conversely, a very weak significant correlation was noted between the T2 time and bony alignment ($\rho = -0.19$, $p = 0.04$). Furthermore, a significant, weak correlation was detected between the T2 times and the JLCA derived from weight-bearing radiographs ($\rho = 0.31$, $p < 0.001$). For the superficial layer of the lateral compartment T2 showed very weak correlations with mHKAA ($\rho = 0.11$, $p = 0.59$) and bony deformity ($\rho = 0.10$, $p = 0.35$). Moreover, a correlation of very weak strength was identified between T2 time and the intra-articular alignment (JLCA) ($\rho = -0.05$, $p = 0.62$). See Figure 4 and Table 3.

For the deep layer similar significant correlations were found where again higher T2 times in the medial compartment corresponded with varus deformities for all three aspects of joint (mal)alignment. However, for the bony alignment, no statistically significant correlations were found (medial: $\rho = -0.07$, $p = 0.49$; lateral: $\rho = 0.04$, $p = 0.58$). See Figure 4 and Table 3.

3.4. Alignment and T2 times correlation in the JLCA-normal group

It should be realized that a malalignment of the intra-articular alignment (Figure 4C) already refers to cartilage degeneration, as a high of low JLCA represents cartilage loss in one compartment of the knee joint relative to the other. To assess the pure effects of varus or valgus alignment on T2-related cartilage quality, we examine a subset of participants without intra-articular knee joint deformity. This analysis included 71 participants with normal (straight) joint space, defined by JLCA values between 0° and 2° (Table 1). This enables to analyze the T2 times in medial and lateral compartments with respect to bony alignment only.

In the superficial layer, there was still a weak (non-significant) correlation between the T2 times and bone deformity (medial: $\rho = -0.22$; lateral: $\rho = -0.04$) (Figure 5, Table 4). In the deep layer, this correlation was virtually absent and non-significant (medial: $\rho = -0.03$; lateral: $\rho = -0.05$) (Figure 5 and Table 4).

Table 2
Patient characteristics of the included participants n = 156.

Age (years), mean ± SD	66.7 ± 7.0
Body Mass Index (kg/m^2), mean ± SD	26.8 ± 4.1
Sex (female), n (%)	127 (81.4)
Kellgren and Lawrence, n (%)	
Grade 0	38 (24.4)
Grade 1	41 (26.3)
Grade 2	31 (19.9)
Grade 3	41 (26.3)
Grade 4	5 (3.2)

SD, Standard deviation.

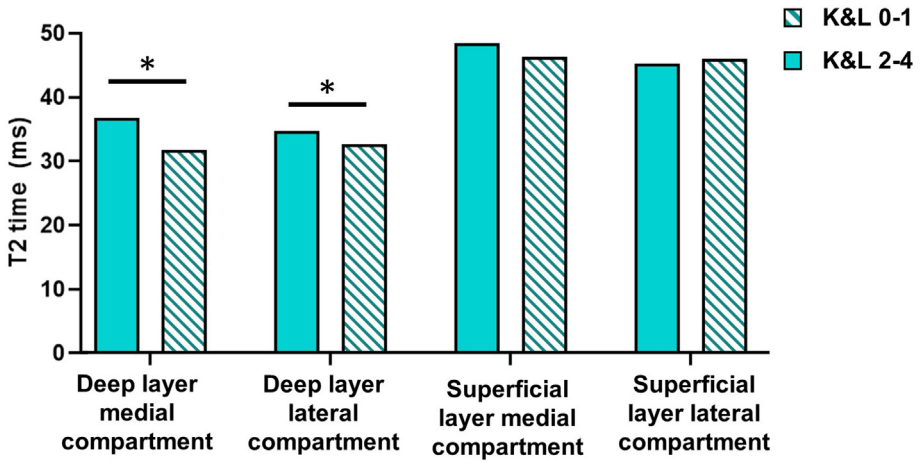

Figure 3. Comparison of T2 time across different knee compartments and layers between two groups (K&L 0–1 and K&L 2–4). Asterisks indicate significant differences ($p < 0.05$) between the groups for the specified compartments.

4. Discussion

This study examined the association between knee cartilage quality, assessed by T2 mapping, and lower limb malalignment. Prolonged T2 times, indicating lower cartilage quality, were generally observed in participants with higher K&L scores. This is a finding that confirmed previous work [5,7,33]. We evaluated entire leg alignment (mHKAA), bony alignment (reflecting tibial and femoral bowing), and intra-articular alignment (JLCA). All three measures were associated with reduced cartilage quality in the superficial layer of the medial compartment in varus knees and the lateral compartment in valgus knees. The strongest correlations with T2 values were observed for JLCA, while correlations with bony alignment were minimal. This suggests that the association between mHKAA and cartilage quality is primarily driven by intra-articular alignment, as mHKAA reflects both components. These findings highlight the need to distinguish between bony and intra-articular deformities in future osteotomy studies and clinical decision-making. In medial KOA with bony malalignment, osteotomy is generally effective. However, when malalignment is intra-articular only, surgical outcomes are less predictable [34]. Therefore, surgical planning should not rely solely on mHKAA; bony and intra-articular alignment must be assessed separately.

Furthermore, cartilage quality was also assessed in individuals with constitutional joint malalignment—defined by bony varus or valgus alignment without intra-articular deformity—to isolate the effect of limb alignment on T2 values. MRI T2 mapping was used to evaluate cartilage quality and potentially identifying those at elevated risk for unicompartmental KOA. In this subgroup, varus bone bowing was associated with higher T2 times in the medial compartment, but only in the superficial cartilage layer, while no such association was found for valgus alignment. The correlation between constitutional varus and elevated T2 times was weak and not statistically significant, likely due to insufficient statistical power (46%, $\rho = 0.22$, $\alpha = 0.05$, $N = 71$) of this subgroup analysis [32]. Nonetheless, a correlation of 0.3 is insufficient to reliably indicate reduced cartilage quality at the individual patient level. We hoped that T2 mapping could serve as a radiological biomarker to identify participants with constitutional malalignment and elevated T2 values, who may be at increased risk for developing KOA in the future. However, this hypothesis remains unconfirmed due to the absence of longitudinal T2, radiographic, and CT data in the IMI-APPROACH cohort. Moreover, the IMI-APPROACH cohort includes patients with symptomatic KOA, thereby excluding individuals with asymptomatic constitutional malalignment.

Regarding the mHKAA, a significant correlation was found only for varus malalignment in the superficial and deep layers of the medial compartment. This may be due to the fact that, in a neutral stance, approximately 70% of knee load passes through the medial compartment [12]. Varus alignment increases this load, leading to overload and cartilage degeneration, while valgus alignment distributes the load more evenly. These results align with Sharma et al. [12], who reported an association between malalignment and cartilage damage but did not distinguish between mHKAA, bony, and intra-articular alignment. Additionally, the higher prevalence of intra-articular varus compared to valgus (Table 2) may partly explain the observed correlation, given that mHKAA reflects both bony (mMPTA, mLDFA) and intra-articular (JLCA) deformities.

While previous studies on T2 mapping have focused on demographic and early OA indicators [7,29], our study specifically examined lower limb alignment. Our findings suggest that intra-articular malalignment may affect cartilage quality; however, due to the cross-sectional design of this study, causal interferences cannot be drawn. As abnormal JLCA can be detected on conventional radiographs, the added value of T2 mapping in symptomatic knees may be limited to a theoretical value. In participants with constitutional varus, elevated T2 values were observed in the medial compartment, though not statistically significant. This subgroup likely includes individuals with limited cartilage degeneration, as no severe bony varus or valgus deformities were present. Participants with such deformities may already exhibit cartilage loss and/or meniscal extrusion,

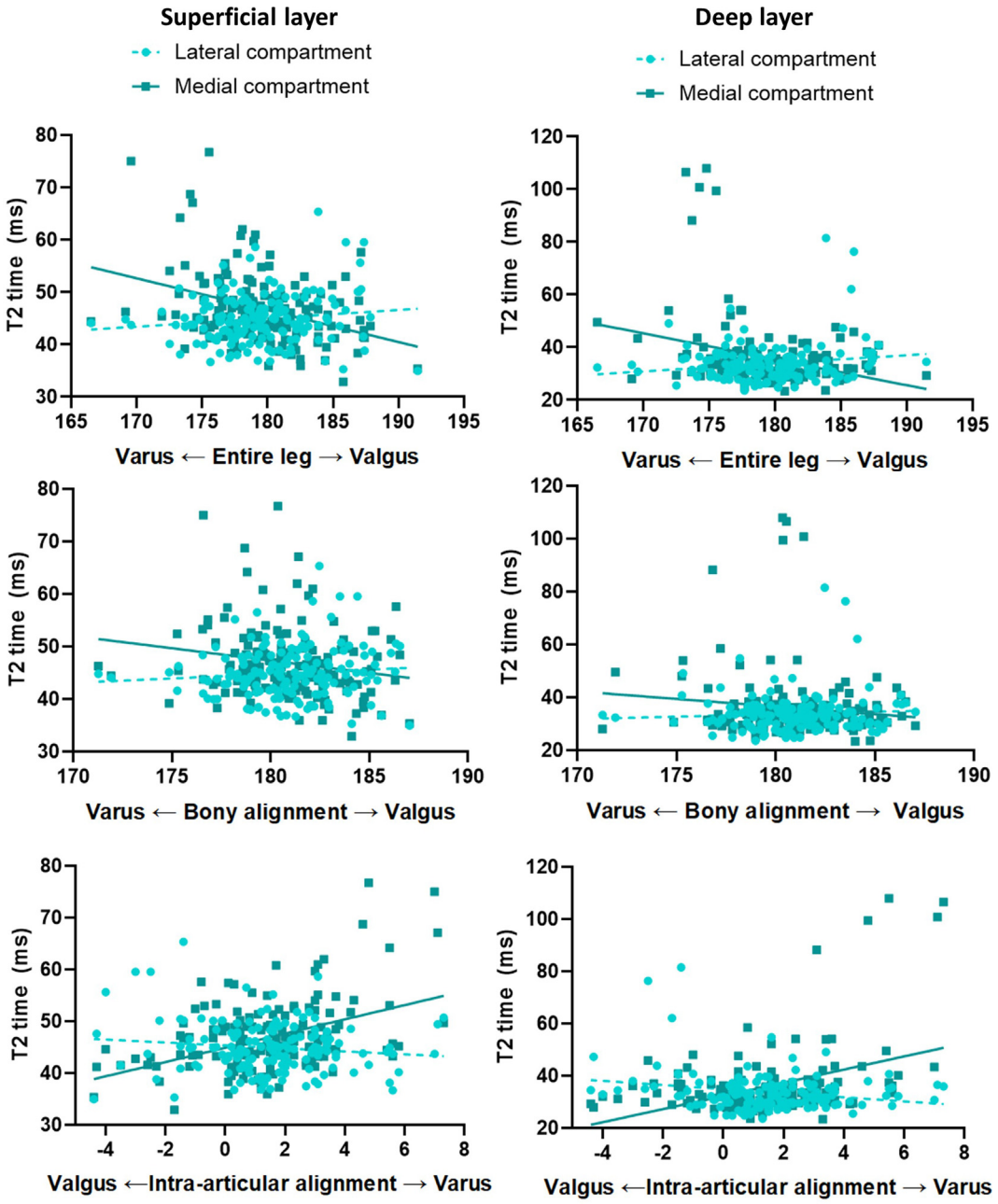

Figure 4. Correlation between T2 time and the various aspects of alignment: entire leg alignment (mHKAA) (A), bony alignment (B), and intra-articular alignment (JLCA) (C) for the superficial layer and deep layer of the medial and lateral compartment. *Correlation is considered statistically significant.

resulting in an abnormal JLCA and their exclusion from the constitutional malalignment group. Additionally, we assessed both cartilage layers and found, consistent with previous research [35], that the superficial layer showed greater sensitivity to mechanical load, reflected by higher T2 values in participants with mild intra-articular malalignment.

Our study has several limitations. First, the additional analysis lacked statistical power due to the small number of participants with a JLCA within the normal range, which may explain the non-significant correlation between bony varus and increased medial T2 times. Only 30 participants (42.3%) showed constitutional malalignment, indicating a limited sample size of constitutional varus or valgus in our cohort. Moreover, there was a predominance of varus lower limb malalignment compared with valgus, which may further explain why no significant correlation was found between valgus malalignment and increased T2 times in the lateral compartment. Second, CT scans were acquired in a supine position rather than weight-bearing, which may have affected the accuracy of bony alignment assessment. However, Roth et al. [36] found minimal dif-

Table 3
T2 times correlated to the entire leg alignment, bony alignment and intra-articular alignment.

	Spearman's rho	Confidence interval	P-value[a]
Entire leg alignment			
Deep layer of lateral compartment	0.05	[−0.11; 0.21]	0.59
Superficial layer of lateral compartment	0.11	[−0.05; 0.27]	0.34
Deep layer of medial compartment	−0.23	[−0.37;−0.06]	**0.02**
Superficial layer of medial compartment	−0.31	[−0.45; −0.15]	**< 0.001**
Bony alignment			
Deep layer of lateral compartment	0.04	[−0.12; 0.21]	0.58
Superficial layer of lateral compartment	0.10	[−0.06; 0.26]	0.35
Deep layer of medial compartment	−0.07	[−0.23; 0.09]	0.49
Superficial layer of medial compartment	−0.19	[−0.35; −0.03]	**0.04**
Intra-articular alignment			
Deep layer of lateral compartment	−0.10	[−0.26; 0.06]	0.32
Superficial layer of lateral compartment	−0.05	[−0.21; 0.11]	0.62
Deep layer of medial compartment	0.26	[0.10; 0.40]	**0.004**
Superficial layer of medial compartment	0.31	[0.16; 0.45]	**<0.001**

[a] *p* values corrected for multiple testing using the Benjamini–Hochberg. The bold *p* values were considered statistically significant.

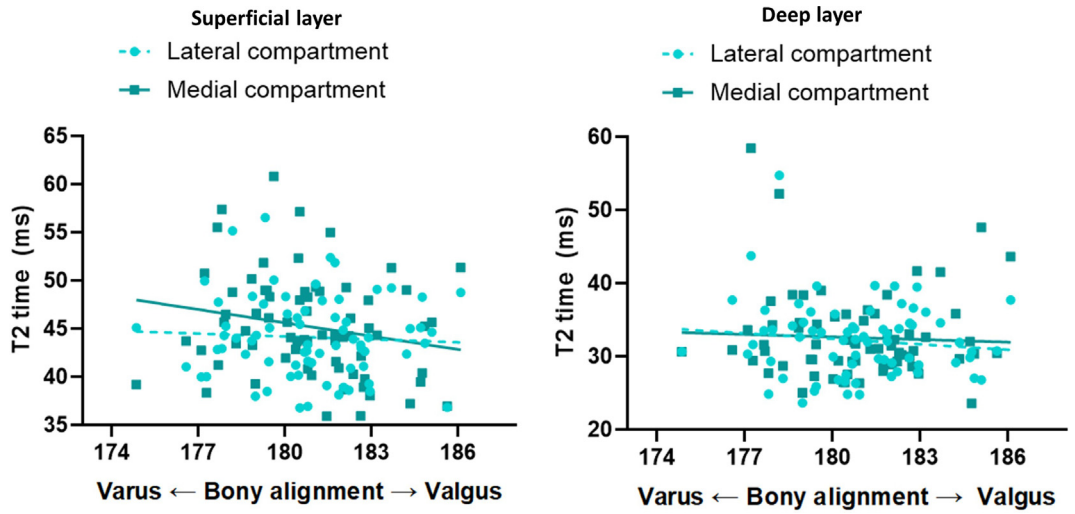

Figure 5. Correlation between T2 time bony alignment of the 71 participants with JLCA values within the normal range for the superficial layer and deep layer of the medial and lateral compartment.

Table 4
T2 times correlated to the bony alignment of the 71 participants with normal JLCA values.

	Spearman's rho	Confidence interval	P-value[a]
Bony alignment			
Deep layer of lateral compartment	−0.05	[−0.29; 0.19]	1.00
Superficial layer of lateral compartment	−0.04	[−0.28; 0.20]	0.97
Deep layer of medial compartment	−0.03	[−0.27; 0.21]	0.81
Superficial layer of medial compartment	−0.22	[−0.43; 0.03]	0.28

[a] *p* values corrected for multiple testing using the Benjamini–Hochberg.

ferences in bone deformities between weight-bearing and non-weight-bearing scans, while mHKAA and JLCA showed significant variation. Therefore, we used JLCA from weight-bearing radiographs to capture intra-articular alignment, and calculated mHKAA as the sum of non-weight-bearing bony alignment (from CT) and weight-bearing JLCA (from radiographs). Future improvements may include weight-bearing CT scanning [37], EOS imaging [38], or simulated standing CT reconstructions [39]. Third, interobserver variability of the K&L score is another limitation [40]. Further research may consider utilizing

the JLCA as a measure of KOA instead of the K&L score. Fourth, we assessed only superficial and deep cartilage layers using T2 mapping and did not evaluate the subchondral bone that may also contribute to early cartilage pathology [41,42]. Lastly, although JLCA reflects intra-articular KOA severity through compartmental differences in cartilage loss or meniscal extrusion [14,15], our study did not include direct measures of these features. A varus or valgus JLCA already suggests the presence of cartilage loss and/or meniscal extrusion, both features of KOA.

5. Conclusion

This study demonstrates a significant relationship between lower limb alignment and cartilage quality, with alignment assessed in terms of whole-leg, bony, and intra-articular alignment. Our findings support the hypothesis that varus lower limb malalignment was associated with reduced cartilage quality in the medial compartment, whereas, contrary to our hypothesis, valgus lower limb malalignment was not associated with reduced cartilage quality in the lateral compartment. The, strongest correlations were observed for intra-articular alignment. Therefore, future research should distinguish between bony and intra-articular malalignment when evaluating knee alignment. While varus bone bowing in our subgroup analysis showed a trend toward increased T2 values in the medial compartment, this finding was not statistically significant, likely due to the small sample size. Further studies are needed to determine whether bony malalignment plays a role in initiating cartilage degeneration and OA progression.

Ethics statement

All procedures performed in the IMI-Approach study were conducted in compliance with the protocol, Good Clinical Practice (GCP), the Declaration of Helsinki, and the applicable ethical and legal regulatory requirements (for all countries involved), and is registered under clinic altrials.gov identifier: NCT03883568. Informed consent was obtained from all individual participants included in the study.

CRediT authorship contribution statement

Eva A. Bax: Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Joost A.J. Kerkhof:** Writing – original draft, Project administration, Investigation, Formal analysis. **Nienke van Egmond:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Ruurd J.A. Kuiper:** Writing – review & editing, Software, Data curation. **Hassan Rayegan:** Writing – review & editing, Software, Data curation, Conceptualization. **Margreet Kloppenburg:** Writing – review & editing, Resources, Funding acquisition, Data curation. **Francisco J Blanco:** Writing – review & editing, Resources, Funding acquisition, Data curation. **Ida K. Haugen:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Francis Berenbaum:** Writing – review & editing, Resources, Funding acquisition, Data curation. **Simon C. Mastbergen:** Writing – review & editing, Resources, Funding acquisition, Data curation. **Felix Eckstein:** Writing – review & editing, Software, Resources, Data curation. **Wolfgang Wirth:** Writing – review & editing, Software, Resources, Data curation. **Frank W. Roemer:** Writing – review & editing, Software, Resources, Data curation. **Moyo C. Kruyt:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Harrie Weinans:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Roel J.H. Custers:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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