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The association of frontal plane alignment to MRI-defined worsening of patellofemoral osteoarthritis: The MOST study

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E. Macri was involved in conception and design of the present study, conducted analyses, interpreted results, drafted and edited the article, and approved the final version of the manuscript. D. Felson, T. Neogi, J. Torner, C. Lewis and M. Nevitt were involved in original conception and design of the parent study (i.e. MOST study), assisted with interpretation of results, contributed intellectually to manuscript revisions, and approved the final version of the manuscript. M. Ziegler provided guidance for statistical design and analyses, contributed intellectually to manuscript revisions, and approved the final version of the manuscript. T. Cooke conducted data acquisition, assisted in study design and interpretation of results, contributed intellectually to manuscript revisions, and approved the final version of the manuscript. A. Guermazi and F. Roemer were involved in original conception and design of the parent study (i.e., MOST study), conducted data acquisition, assisted with interpretation of results, contributed intellectually to manuscript revisions, and approved the final version of the manuscript. J. Stefanik was involved in conception and design of the present study, conducted analyses, interpreted results, contributed intellectually to manuscript revisions, and approved the final version of the manuscript. J. Stefanik and E. Macri take responsibility for the integrity of the work as a whole.

Conflict of interest:

A Guermazi is the president of Boston Imaging Core Lab (BICL), LLC, and a consultant to Merck Serono, TissueGene, Genzyme, AstraZeneca, OrthoTrophixs, Pfizer and GE Healthcare. F Roemer is CMO and shareholder of BICL. TDV Cooke is the president of OAISYS Inc.

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Abstract

Objective: To determine the sex-specific relation of frontal plane alignment (FPA) to MRI-defined features of patellofemoral osteoarthritis, and also to tibiofemoral osteoarthritis and knee pain.

Method: The Multicenter Osteoarthritis Study is cohort study comprised of individuals with or at risk of knee osteoarthritis. We determined the sex-specific dose-response relation of baseline FPA to MRI-defined patellofemoral and tibiofemoral structural worsening, and incident knee pain, over seven years.

Results: In women only, greater varus alignment was associated with medial patellofemoral osteophytes (risk ratio [RR] 1.7 [95% CI 1.2, 2.6]) and valgus with lateral patellofemoral osteophytes (RR 1.9 [1.0, 3.6]). In men, greater varus increased risk for medial tibiofemoral cartilage worsening (RR 1.7 [1.1, 2.6]), and valgus for lateral tibiofemoral cartilage worsening (RR 1.8 [1.6, 2.2]). In women, findings were similar for tibiofemoral cartilage, but varus also increased risk for medial BMLs (RR 2.2 [1.6, 3.1]) and medial osteophytes (RR 1.8 [1.3, 2.5]), and valgus for lateral BMLs (RR 3.3 [2.2, 4.5]) and osteophytes (RR 2.0 [1.2, 3.2]). Varus increased risk of incident pain in men (RR 1.7 [1.4, 2.2]) and women (RR 1.3 [1.0, 1.6]), valgus did so in men only (RR 1.5 [1.1, 1.9]).

Conclusion: FPA was associated with patellofemoral osteophyte worsening in women, though overall was more strongly associated with tibiofemoral than patellofemoral osteoarthritis feature worsening. FPA in women was more consistently associated with structural worsening, yet men had higher associations with incident pain.

Keywords

alignment; patellofemoral joint; knee osteoarthritis; pain; epidemiology

Introduction:

Patellofemoral osteoarthritis (OA) affects 25%[1] to 50%[2] of the general population, based on radiographic and magnetic resonance imaging (MRI) features, respectively. Knee OA most commonly begins in the patellofemoral joint[3–5] and is an important source of pain[3, 67] Therefore, identifying risk factors for patellofemoral OA is warranted, as this could help identify high risk individuals or guide clinical interventions[8, 9]. Frontal plane alignment has consistently been identified as a risk factor for tibiofemoral OA using both radiographic and MRI-based OA definitions[10–15]. This is believed to occur, in part, via elevated focal joint stress[16] that leads to cartilage damage in either the medial (i.e., with varus alignment) or lateral (i.e., with valgus alignment) tibiofemoral compartment[11]. The association between frontal plane alignment and patellofemoral OA is not as well understood[17–23]. Clarification of the role of alignment in patellofemoral OA may enable detection of risk factors for knee OA in general while potentially shifting focus to earlier detection of OA when it is still isolated to the patellofemoral joint.

Frontal plane alignment may cause patellofemoral OA through a similar mechanism of elevated joint stress by altering the angle of pull on the patella through the extensor mechanism. This could increase lateral patellofemoral joint stress in cases of valgus alignment and vice versa. One study found valgus alignment was associated with higher risk of lateral patellofemoral OA and varus was associated with medial patellofemoral OA[19, 20]. To date, only two relatively small studies have investigated the longitudinal relation of frontal plane alignment to patellofemoral OA[18, 20], with at most 23-months of follow-up. One of these measured radiographic patellofemoral joint space narrowing[20], and the other used MRI to measure change in patellofemoral cartilage volume[18]. Results of these two studies were conflicting in that the former study[20] found baseline alignment predicted joint space narrowing, while the latter study[18] found baseline alignment did not predict loss of cartilage volume, but rather that a change in alignment co-occurred with cartilage volume loss. Moreover, no study has evaluated the association of frontal plane alignment to patellofemoral OA worsening by directly evaluating MRI-defined structural features (e.g., cartilage damage, bone marrow lesions [BMLs], osteophytes). Given that MRI is more sensitive than radiography in detecting early OA lesions[24], the role of frontal plane alignment in patellofemoral OA worsening would be better assessed using MRI for more definitive insights.

To comprehensively understand the association of frontal plane alignment with knee OA outcomes, it is important to evaluate the relationship between alignment and patellofemoral OA, but also tibiofemoral OA and knee pain. Understanding whether these associations differ anatomically (patellofemoral vs. tibiofemoral) or by outcome (structure vs. symptoms) may offer insights as to whether certain knee OA phenotypes are at higher risk of worsening, and thus who may benefit from alignment assessment and targeted interventions. Moreover, frontal plane alignment differs by sex[25–27], as do knee OA outcomes in general, though reasons for this sex disparity are unclear. Thus, we have an opportunity to additionally address whether frontal plane alignment accounts for this disparity. Finally, previous studies have used varying cut-points to define varus and valgus malalignment, often without clear biological justification. The use of such cut-points may result in misclassification that could

statistically mask true biological relationships, and more robust methods for determining dose-response patterns exist that can overcome this methodological limitation[28].

We therefore aimed to investigate the sex-specific dose-response relationship of frontal plane alignment to (i) worsening MRI-defined structural features of patellofemoral OA, (ii) worsening MRI-defined structural features of tibiofemoral OA, and (iii) incident frequent knee pain, over seven years.

Methods:

The Multicenter Osteoarthritis Study (MOST) is a NIH-funded prospective cohort study. MOST provides a unique opportunity to assess the longitudinal relation of frontal plane alignment to worsening of MRI-defined features of patellofemoral and tibiofemoral OA in a cohort of individuals with, or at risk for, knee OA. Participants were recruited from Iowa City, Iowa, or Birmingham, Alabama[10, 29, 30]. Ethical approval was provided by the institutional review boards at participating sites and complied with the Helsinki Declaration. Inclusion and exclusion criteria and sample characteristics have been previously described[29, 30].

For the present study, we included data from baseline and 84-month (i.e., seven year) follow-up visits. Of the 3026 participants enrolled in the MOST study, 2933 had bilateral full-limb radiographs at baseline (used to measure frontal plane alignment), and 1101 had MRI acquired and read in one knee at baseline and 84-month visits (Figure 1), making this subsample eligible for structure-related analyses. Pain-related questions were answered at both visits by 2144 participants for at least one knee (most answered questions for both knees separately), and 1862 did not have our primary definition of knee pain at baseline in at least one knee, making this subsample eligible for pain-related analyses.

Frontal plane alignment:

Weight-bearing bilateral full-limb AP radiographs were acquired at baseline using standardized procedures[12, 31]. Hip-knee-ankle (HKA) angle was calculated (to the nearest degree) as the angle formed by the intersection of the femoral line (connecting the centers of the femoral head and intercondylar notch) to the tibial line (connecting the centers of the ankle talus and tibial spines)[11, 31]. Angles less than 180° were in a varus direction, and greater than 180° a valgus direction. The inter-reader intraclass correlation coefficient was 0.995 in a subsample from the MOST cohort (n=200 knees), with a standard error of measure (SEM) of 0.4[32].

MRI-defined features of knee OA:

MRI was acquired at baseline and 84 months using a 1.0-Tesla extremity MRI (OrthOneTM; ONI Medical Systems Wilmington, MA, US) with a phased-array knee coil. Images were acquired using a fast spin echo fat-suppressed proton density-weighted sequence in the sagittal plane (repetition time (TR) ms/echo time (TE) ms 4800/35; slice thickness 3 mm; intersection gap 0 mm; slices 32; matrix 288×192; signals acquired 2; field of view (FOV) 140 mm^2; echo train length 8) and axial plane (TR/TE 4680/13; slice thickness 3 mm; intersection gap 0 mm; slices 20; matrix 288×192; signals acquired 2; FOV 140 mm^2; echo

train length 8), and using a short tau inversion recovery sequence in the coronal plane (TR/TE 6650/15; inversion time 100 ms; slice thickness 3 mm; intersection gap 0 mm; slices 28; matrix 256×192; signals acquired 2; FOV 140 mm^2; echo train length 8).

One randomly-determined knee per participant (n=1101) was read and scored (right knee 55%). Images were scored by two musculoskeletal radiologists (AG, FWR) using the Whole Organ MRI Score (WORMS)[33]. Cartilage damage was scored on a scale from 0 – 6, BMLs from 0 – 3, and osteophytes from 0 – 7. Each feature was assessed in 14 sub-regions of the knee, two of which are relevant to the medial patellofemoral compartment, two to the lateral patellofemoral compartment, five to the medial tibiofemoral compartment, and five to the lateral tibiofemoral compartment. Inter-reader weighted κ coefficients for WORMS scores, based on 30 knees randomly selected and read by both readers, ranged from 0.66 (for BMLs) to 0.78 (for cartilage morphology)[34].

Our primary outcome was worsening of cartilage morphology, for each subregion, from baseline to 84 months. Worsening encompasses both incidence and progression[35] and is defined as any increase in score from baseline to follow-up. Subregions with the worst possible score at baseline (e.g., grade 6 for cartilage) were excluded from analyses. We defined worsening of BMLs and osteophytes in a similar manner.

Pain:

Participants answered knee-specific pain-related questions at both visits. Participants were asked, “Did you have pain, aching or stiffness on most days of the past month?”[36]. In knees where participants answered ‘yes’ to this question, on two occasions approximately one month apart (a telephone interview prior to the clinic visit, plus the clinic visit), the knee was determined to have consistent frequent knee pain[37]. Knees with consistent frequent knee pain at baseline (or missing data at one or both time points) were excluded from analyses. Knees without consistent frequent knee pain at baseline that developed it by the 84-month visit were determined to have incident consistent frequent knee pain, reflecting new development of knee pain in one or both knees.

Statistical analyses:

As with most health outcome measures[38], there is substantial overlap in frontal plane alignment values in individuals with and without knee OA[27]. Defining malalignment using suggested cut-points[28] can result in statistical masking of true effects, particularly at extreme values of alignment where we would expect risk to be higher[28]. We therefore examined frontal plane alignment as a continuous variable, and evaluated the dose-response pattern between baseline alignment and worsening of MRI features using a multivariable restricted cubic spline mixed effects models[39], with three knots (10^{th}, 50^{th} and 90^{th} percentile). We used mixed effects models to account for the within-person correlations of the multiple subregions for structural outcomes in each compartment[40], and ran separate models for medial and lateral patellofemoral compartments, and medial and lateral tibiofemoral compartments. We used a robust variance estimation, and log link function to obtain risk ratios for each outcome at the 84-month visit based on baseline frontal plane alignment[41].

We included age and BMI in each model, and created separate models for men and women[25, 26]

We estimated risk ratios (95% confidence intervals) of all frontal plane alignment values (i.e., for every degree of alignment) for each outcome, using the median alignment value of the sample (men or women, separately) as the reference[39, 42]. We then plotted line graphs of risk ratios across all frontal plane alignment values to illustrate dose-response patterns. From these results, we extracted risk ratios reflecting + and − 1.96 standard deviations from the mean for men and women separately. This was to aid in interpretation of the dose-response curves, reflecting risk of structural outcomes at the extreme of distribution-based values of varus and valgus. To be clear, these cut-points were not used in the analyses themselves – all models evaluated frontal plane alignment as a continuous variable.

To determine the association between frontal plane alignment and incident consistent frequent knee pain, we created similar models. Up to two knees per person were eligible for inclusion in the analyses depending on baseline presence of pain. The mixed effects model accounted for the correlation between knees within each participant. We included age and BMI as covariates, and also included study site (Alabama or Iowa) in each model to account for possible sociodemographic differences between sites. We ran separate models for men and women. Finally, we performed sensitivity analyses adjusting for the presence of radiographic OA (at least Kellgren and Lawrence Grade 2), recognizing that radiographic OA may influence knee pain. All statistical analyses were done using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results:

We included 1101 participants (1101 knees) in the structural analyses: 690 (62%) women, average age and BMI were 61 (SD 8) years and 29.3 (4.5) kg/m^2, respectively (Table 1). The pain-related analyses (incident consistent frequent knee pain) included 1862 participants (3169 knees): 1107 (59%) women, average age and BMI were 62 (8) years and 30.4 (5.6) kg/m^2, respectively (Table 1). Mean frontal plane alignment was slightly more valgus in women than men. Frontal plane alignment at 1.96 SD from the mean in men was 173° varus and 183° valgus, and in women was 174° varus and 185° valgus.

Patellofemoral compartments:

In women only, greater valgus was associated with lateral patellofemoral osteophyte worsening, and greater varus was associated with medial patellofemoral osteophyte worsening (Figures 2, 3, Table 3).

Tibiofemoral compartments:

Greater valgus was associated with lateral tibiofemoral cartilage worsening in men and women, and lateral tibiofemoral BML and osteophyte worsening in women only (Figures 2, 3, Table 3). Greater valgus was protective against medial tibiofemoral BML worsening in men and women, and medial tibiofemoral osteophyte worsening in men only. Greater varus was associated with medial tibiofemoral cartilage worsening in men and women, and medial

tibiofemoral BML and osteophyte worsening in women only. Greater varus was protective against lateral tibiofemoral cartilage worsening in women only.

Pain:

There was a U-shaped relationship between frontal plane alignment (i.e., both increased valgus and increased varus) and increased risk for incident consistent frequent knee pain in men (Figure 2, Table 3). In women, only increased varus was associated with increased risk for incident consistent frequent knee pain (Figure 3, Table 3). Risk ratios were larger in men than in women.

Discussion:

Our study presents the sex-specific dose-response patterns of frontal plane alignment to risk of worsening of MRI-defined features of knee OA in both the patellofemoral and tibiofemoral compartments, as well as incident knee pain, over seven years. Comparisons of the associations in both patellofemoral and tibiofemoral compartments have not been previously reported. As may be expected, results suggest that frontal plane alignment may be more strongly associated with MRI-detected features of tibiofemoral OA than patellofemoral OA (with the exception of osteophytes, which were similar). In addition, frontal plane alignment was more consistently associated with structural worsening in women than in men, although the association with pain may be larger in men than in women.

Our findings expand on the existing literature by enabling direct comparison of patellofemoral and tibiofemoral compartments as well as incident pain, by comparing sex-specific patterns, and by investigating multiple MRI-defined features of OA (cartilage, BMLs, and osteophytes). Moreover, we applied a statistical approach that enabled exploration of the curvilinear dose-response patterns of frontal plane alignment, rather than categorizing the exposure variable without an underlying biological justification[28]. Importantly, the dose-response curves suggest that there is no threshold effect for malalignment (i.e., no natural biological cut-point exists), but rather that risk for structural worsening and incident pain is graded. The clinician seeking meaningful cut-points for defining malalignment and interpreting associated risk can use the distribution-based cut-points reported in Table 3. Notably, the further beyond these values their patient's alignment is, the higher (or lower) the risk of OA worsening or incident pain (as is illustrated in Figures 2 and 3).

Frontal plane alignment may play a more important role in structural worsening in the tibiofemoral joint than in the patellofemoral joint. This could be explained by the direct influence of frontal plane alignment on load distribution in the frontal plane, and biomechanical studies extend this into a dynamic environment where increased knee adduction moment is seen in those with tibiofemoral OA[43]. However, the relative absence of associations at the patellofemoral joint was unexpected. We found an association in women with osteophyte worsening only. Previous studies reporting associations were most often cross-sectional and used radiographs to define OA[17–23]. Importantly, most of these studies targeted tibiofemoral OA for inclusion into their studies – it is unknown to what extent this

would have influenced study findings. Our results support the findings of one of two longitudinal studies that found baseline frontal plane alignment was not associated with patella cartilage volume loss at 23 months follow up[18]. In the absence of a strong association between frontal plane alignment and patellofemoral OA, it may be that alignment in a different plane (e.g., patella height in the sagittal plane) more directly influences patellofemoral OA worsening[17]. This is supported by biomechanics studies, where in contrast to the frontal plane kinematic changes in tibiofemoral OA, patellofemoral OA seems to be more strongly associated with sagittal plane gait changes[44]. Moreover, while 'dynamic valgus' is associated with patellofemoral pain[45], it is likely that this apparent valgus is comprised largely of femoral internal rotation[46], suggesting axial plane kinematics may influence patellofemoral outcomes more than frontal plane kinematics.

Clinically, patients generally seek care because of pain rather than structural changes. Interestingly, the association between frontal plane alignment and incident knee pain differed by sex in our study. Specifically, in men, incident pain was associated with both varus and valgus alignment. For women, incident pain was generally only associated with varus alignment and the association was not as high as in men. These results could be explained by: a different background rate of pain in men and women, making the relative risk appear higher in men than in women; or due to pain being experienced or reported differently by sex (e.g., due to cultural or other psychosocial reasons, or different central pain processing); or by contributors to pain differing by sex (e.g., different structures as source of pain, loading or activity profiles, or joint stresses due to knee size or shape). Future studies are warranted to clarify the mechanism underlying the sex-related differences in these associations.

Identifying individuals with frontal plane malalignment may help identify those at higher risk of structural knee OA worsening or future pain, and studies are needed to evaluate the predictive accuracy of malalignment with longitudinal outcomes. Malaligned individuals may benefit from targeted mechanical interventions such as knee bracing[47], exercise therapy[48] or gait retraining[49]. However, our study results suggest that associations with structure outcomes may differ from pain outcomes – it may be that certain individuals require a more comprehensive pain management approach that considers multiple mechanical and non-mechanical contributors to pain.

Limitations:

Frontal plane alignment is a static, two-dimensional measure. In reality, the lower extremity is a complex three-dimensional system, thus HKA may only capture a portion of true alignment and its influence on load distribution. Other factors that may influence load distribution and joint stress include bony morphology or geometry[27], joint health, post-traumatic joint instability, quality and types of movements in daily activities, or pain avoidance behaviours.

There are currently no validated, agreed upon criteria for defining patellofemoral or tibiofemoral OA using MRI[50] Further, the extent to which differences in WORMS scores represent meaningful clinical differences is still poorly understood. Nonetheless, we chose to

use MRI for this study because it enables direct evaluation of cartilage, and is more sensitive at identifying OA-related lesions compared to radiographs[51].

We acknowledge that previously published studies reporting the association of varus and valgus with incident tibiofemoral cartilage damage uses the same MOST cohort as in the present study[10, 11]. However, the present study builds on these previous works by evaluating both the patellofemoral and tibiofemoral compartments, by evaluating incident pain, by evaluating sex-specific patterns, by including worsening using MRI-defined OA including BMLs and osteophytes in addition to cartilage morphology, by evaluating over a seven year period, and by evaluating dose-response patterns across the range of frontal plane alignment values without explicitly categorizing alignment into varus or valgus based on cut-points.

Finally, the MOST cohort represents an enriched sample of older individuals who were selected for the parent study based on risk factors other than frontal plane alignment. This may have resulted in biased estimates of the associations between frontal plane alignment and structural and symptomatic outcomes. This could result in conservative estimates in our study, since individuals with no other risk factors for OA who developed OA because of frontal plane alignment may not have been included in the cohort.

Conclusions:

Frontal plane alignment was associated with patellofemoral joint osteophyte worsening in women, though overall was more strongly associated with tibiofemoral than patellofemoral compartment OA feature worsening. Alignment was also more consistently associated with structural worsening in women than in men. Both varus and valgus alignment were associated with incident knee pain in men, while only varus was associated with incident pain in women. Identifying individuals with frontal plane malalignment may help identify those at higher risk of knee OA worsening or pain, and those who may benefit from targeted interventions.

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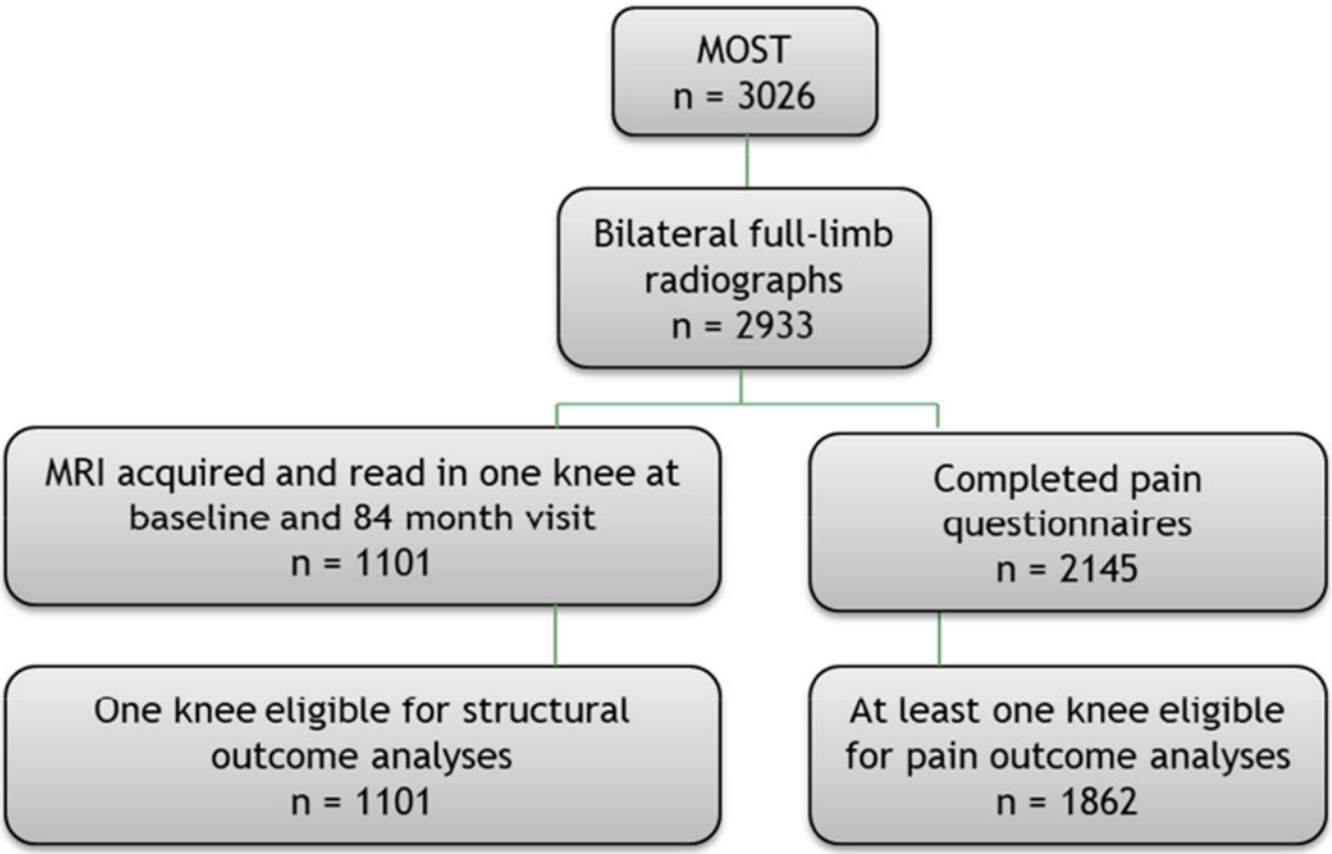

Figure 1.
Flow chart for eligibility for analyses for structural outcomes (n=1101) and pain outcomes (n=1862).

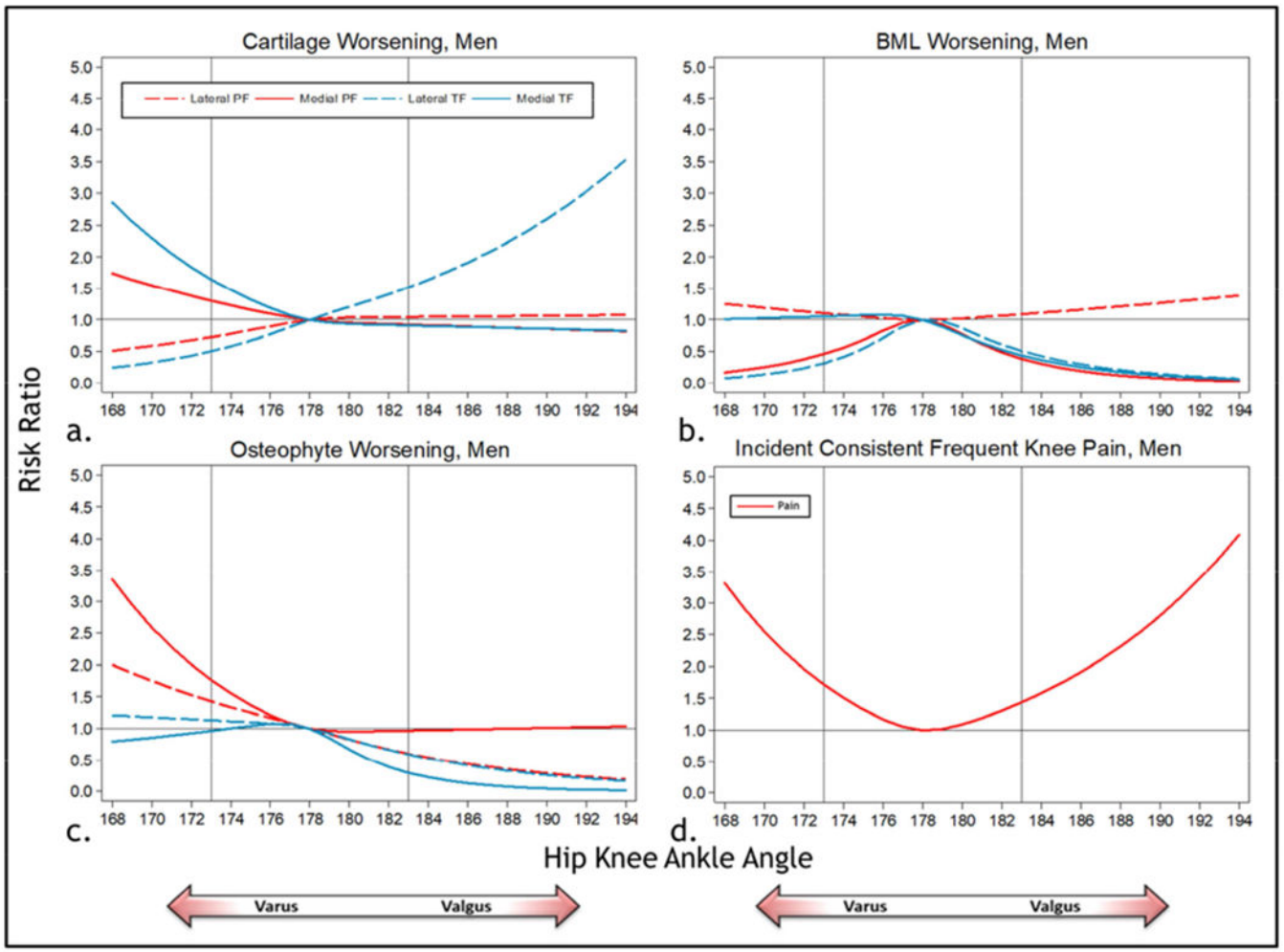

Figure 2.

Risk Ratio dose-response patterns, in men, across frontal plane alignment values for: cartilage worsening (a.); BML worsening (b.); osteophyte worsening (c.); and incident consistent frequent knee pain (d.). Vertical lines represent 1.96 standard deviations below (i.e. varus) and above (i.e. valgus) mean frontal plane alignment in men (173°, 183°) – risk ratios at these values are reported in Table 3.

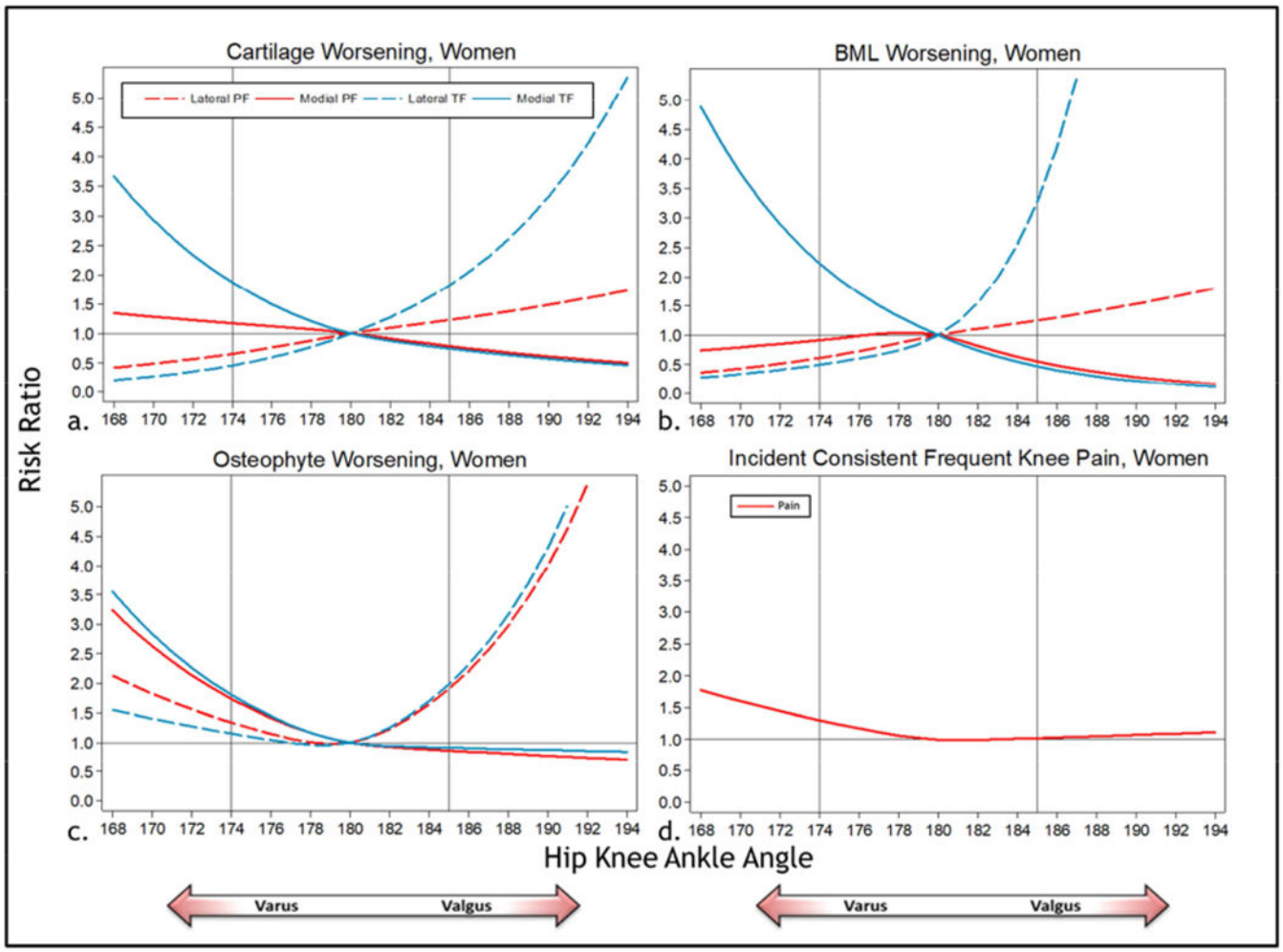

Figure 3.

Risk Ratio dose-response patterns, in women, across frontal plane alignment values for: cartilage worsening (a.); BML worsening (b.); osteophyte worsening (c.); and incident consistent frequent knee pain (d.). Vertical lines represent 1.96 standard deviations below (i.e. varus) and above (i.e. valgus) mean frontal plane alignment in women (174°, 185°) – risk ratios at these values are reported in Table 3.

Table 1.

Baseline participant characteristics in (i) subsample with MRI images scored at baseline and 84 months (n=1101) – left two columns; and (ii) subsample with pain questions answered (n=1862) – right two columns.

	Structural worsening subsample		Incident consistent frequent knee pain subsample	
	Women (n=690)	**Men (n=411)**	**Women (n=1107)**	**Men (n=755)**
Age (y)	61.5 (7.5)	60.4 (7.6)	62.1 (7.7)	61.6 (7.9)
BMI (kg/m^2)	29.0 (4.8)	29.8 (4.0)	30.4 (6.1)	30.3 (4.8)
Hip-Knee-Ankle angle * ()	179.5 (2.8)	178.1 (2.7)	179.3 (3.2)	177.8 (3.2)
Site n (%)				
Alabama	-	-	478 (43.2)	337 (44.6)
Iowa	-	-	629 (56.8)	418 (55.4)

All values are mean (SD) unless otherwise noted.

* Varus-directed is <180°, valgus-directed is >180°; nb MRI-knee is reported in structural subsample (55% right knee), and all eligible knees (i.e. all knees without pain at baseline) are reported in pain subsample

Table 2.

Unadjusted prevalence of outcomes: structural worsening of subregions within each knee compartment, and two definitions of incident knee pain.

Structural worsening *	**Women (n=690)**	**Men (n=411)**
Medial PF (2 subregions)		
Cartilage damage worsening	251/1312 (19.1%)	110/794 (13.9%)
BML worsening	135/945 (14.3%)	48/593 (8.1%)
Osteophyte worsening	133/920 (14.5%)	54/578 (9.3%)
Lateral PF (2 subregions)		
Cartilage damage worsening	225/1278 (17.6%)	109/786 (13.9%)
BML worsening	141/947 (14.9%)	71/594 (12.0%)
Osteophyte worsening	93/918 (10.1%)	34/578 (5.9%)
Medial TF (5 subregions)		
Cartilage damage worsening	548/3414 (16.1%)	329/2041 (16.1%)
BML worsening	234/2437 (9.6%)	162/1525 (10.6%)
Osteophyte worsening	473/2337 (20.2%)	197/1463 (13.5%)
Lateral TF (5 subregions)		
Cartilage damage worsening	455/3441 (13.2%)	168/2050 (8.2%)
BML worsening	144/2440 (5.9%)	34/1521 (2.2%)
Osteophyte worsening	273/2337 (11.7%)	82/1465 (5.6%)
Incident pain ^	**Women (n=1107)**	**Men (n=755)**
Incident consistent frequent knee pain	337/1848 (18.2%)	191/1321 (14.5%)

* Denominators for structural outcomes are equivalent to the sample size times the number of subregions, minus missing subregions, maximal scores at baseline, or missing covariates. Note, cartilage scores were read in all participants but BMLs and osteophytes were scored in a smaller subsample.

^ Denominators for pain take into account sample size, number of knees without frequent knee pain at baseline minus missing covariates.

Table 3.

Estimated risk ratios (95% confidence intervals) for structural and pain outcomes, at 1.96 standard deviations below (i.e., varus) and above (i.e., valgus) mean alignment values for men (left two columns) and women (right two columns).

		Men		Women	
		Varus (173°)	**Valgus (183°)**	**Varus (174°)**	**Valgus (185°)**
Cartilage *	PF	0.73	1.05	0.66	1.23
	lateral	(0.40, 1.32)	(0.60, 1.82)	(0.39, 1.11)	(0.80, 1.90)
	PF	1.30	0.92	1.17	0.79
	medial	(0.74, 2.28)	(0.46, 1.84)	(0.77, 1.79)	(0.50, 1.25)
	TF	0.50	**1.84**	**0.46**	**1.83**
	lateral	(0.24, 1.04)	(1.56, 2.17)	(0.27, 0.78)	(1.35, 2.48)
	TF	**1.65**	0.91	**1.87**	0.75
	medial	(1.06, 2.56)	(0.63, 1.31)	(1.38, 2.55)	(0.49, 1.13)
BMLs	PF	1.11	1.09	0.61	1.25
	lateral	(0.51, 2.42)	(0.61, 1.95)	(0.31, 1.20)	(0.70, 2.24)
	PF	0.46	0.39	0.92	0.55
	medial	(0.15, 1.42)	(0.10, 1.47)	(0.53, 1.60)	(0.27, 1.12)
	TF	0.31	0.51	0.50	**3.26**
	lateral	(0.02, 4.04)	(0.11, 2.40)	(0.17, 1.43)	(2.23, 4.78)
	TF	1.06	**0.44**	**2.23**	**0.47**
	medial	(0.34, 3.23)	(0.21, 0.93)	(1.59, 3.13)	(0.26, 0.85)
Osteophytes	PF	1.43	0.60	1.34	**1.90**
	lateral	(0.48, 4.21)	(0.15, 2.36)	(0.53, 3.43)	(1.01, 3.57)
	PF	1.77	0.96	**1.74**	0.87
	medial	(0.70, 4.47)	(0.33, 2.85)	(1.15, 2.64)	(0.45, 1.66)
	TF	1.13	0.59	1.15	1.98
	lateral	(0.29, 4.40)	(0.23, 1.50)	(0.62, 2.15)	(1.22, 3.22)
	TF	0.96	**0.29**	**1.81**	0.91
	medial	(0.36, 2.54)	(0.11, 0.78)	(1.30, 2.52)	(0.60, 1.40)
Incident consistent frequent knee pain		**1.74**	**1.46**	**1.29**	1.02
		(1.40, 2.16)	(1.13, 1.88)	(1.03, 1.60)	(0.73, 1.43)
		1.31^	**1.32**^	1.07^	0.92^
		(1.02, 1.68)	(1.06, 1.64)	(0.85, 1.34)	(0.66, 1.28)

PF = patellofemoral joint; TF = tibiofemoral joint

Note, bold indicates statistically significant. Risk ratios have been calculated for every value (degree) of frontal plane alignment relative to the median reference value, however only the risk ratio for two values (men 173° and 183°, women 174° and 185°) are reported here to simplify interpretation. Risk will increase or decrease at values beyond those reported here - dose-response patterns can be seen in Figures 2 and 3.

*Structural worsening models all include age and BMI as covariates; incident pain models include age, BMI, depression, pain catastrophizing, and study site as covariates (radiographic OA see below)

^ORs for models with radiographic OA presence (at least KL Grade 2) included as a covariate