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Dynamic and static knee alignment at baseline predict structural abnormalities on MRI associated with medial compartment knee osteoarthritis after 2 years

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Abstract

Background: Dynamic and static varus alignment, both, have been reported as risk factors associated with structural progression of knee osteoarthritis. However the association of none of the static and dynamic alignment with structural, clinical, and functional progression associated with knee osteoarthritis has not been assessed yet in a longitudinal study.

Methods: Forty-seven women with early and established medial knee osteoarthritis were evaluated. Static and dynamic alignment as well as MRI detected structural features, clinical, and functional characteristics of patients were assessed at baseline and at 2 years follow-up. Associations between baseline static and dynamic alignment with structural, functional, and clinical characteristics at the time of entry, as well as the changes over 2 years were evaluated.

Findings: Both static and dynamic varus alignment at baseline were significantly associated with osteoarthritis related tibio-femoral joint structural abnormalities detected on MRI, at the time of entry. Only the magnitude of varus thrust at baseline was predictive of the changes in the presence of meniscal maceration over two years. None of the static or dynamic measures of knee joint alignment were associated with clinical characteristics associated with medial knee osteoarthritis.

Interpretation: The key finding of this study is that both frontal plane dynamic and static alignment, are associated with structural abnormalities in patients with medial knee osteoarthritis.

Keywords: varus alignment, varus thrust, bone marrow lesions, pain, function

1. Introduction

Osteoarthritis (OA) is a chronic joint disease that typically affects weight-bearing joints (1). A report on the global burden of disease indicated knee OA as one of the leading causes of disability (2). The number of knee replacements is small compared to the number of subjects with knee OA (3, 4). Therefore, as suggested by Cooper et al, preventing progression to severe joint damage may offer a more effective public health strategy than attempting to prevent disease incidence (3). Developing strategies to prevent (progression of) knee OA requires a thorough understanding of the factors associated with disease incidence and progression. Several risk factors have been reported to be associated with the incidence of knee OA (3, 5), but the number of studies in which risk factors and incidence of knee OA have been investigated longitudinally, is relatively small.

Knee OA is characterized by symptoms such as pain and functional decline along with structural changes detected on radiography or on MRI such as Bone Marrow Lesions (BMLs), Cartilage Lesions (CL), and Meniscal Injuries (MI) (4). Lesions of bone marrow have been proposed as structural indices for progression of knee OA (6). Especially in the early stages of the disease, these structural changes can be better identified on MRI (7).

The role of mechanical factors, such as knee joint static (mal)alignment, in progression of knee OA has been well-established (8-10). In a study by Hunter et al, it was concluded that the location of BMLs and change in BMLs were mediated by static (mal)alignment (6). On the other hand, evidence exists that *dynamic* knee alignment as measured based on the peak knee adduction angle during walking is a stronger predictor of the knee adduction moment (KAM) (and thus indirect loading) than *static* radiographic (mal)alignment (11). Frontal plane dynamic alignment, and more specifically varus thrust, is defined as an abrupt increase of the knee varus alignment during weight-bearing in gait, and it is one of the newly proposed clinical indices for knee OA (12-14). However, the relation between dynamic knee alignment on one hand, and clinical and structural progression of knee OA on the other, is insufficiently understood.

There is only one single longitudinal study on the association of baseline dynamic alignment, assessed as presence of varus thrust by visual observation, and radiographic progression of knee OA (12). In this study, *the presence of varus* thrust at baseline was associated with a 4-fold increased likelihood of progression of medial knee OA over the next 18 months, as measured with the Kellgren and Lawrence scale (12).

In a recent cross-sectional study, Lo et al. compared two groups of subjects with knee osteoarthritis with and without varus thrust as detected by visual inspection, and reported the association of pain with varus thrust to be stronger compared to its relation with static varus alignment (15). Varus thrust was shown to be associated with KAM (12, 16), which itself is related with a higher prevalence of BMLs in the medial compartment (17). Medial compartment BMLs in turn have been related to pain (18-21). But the relationship between the presence and magnitude of varus thrust with BMLs as well as other structural abnormalities associated with medial knee OA has not yet been investigated. Increased varus thrust can be observed early in the disease process, before signs of an increase in KAM (16).

Therefore, the aim of the present study was to assess both cross-sectionally and longitudinally, the relationship between frontal plane static and dynamic alignment with structural and clinical characteristics of OA in a group of individuals with early and established symptomatic medial knee OA. We hypothesized that higher values of baseline varus thrust magnitude during gait would be associated with structural and clinical abnormalities at the time of entry, as well as with the changes over 2 years.

2. Materials and Methods

Forty-seven patients with medial knee OA participated in this study. The study was approved by the ethical committee for Biomedical Sciences of the KU Leuven in Belgium prior to testing and was conducted in agreement with the principles of the Declaration of Helsinki. All participants were informed about the study procedure and signed informed consent forms.

Participants were recruited during their visit to the University Hospital Leuven. The inclusion criteria for the early OA group were: presence of knee pain, a Kellgren & Lawrence (K&L) grade 0, 1 or 2- (osteophytes only, no joint space narrowing) for the medial compartment on radiography and presence of two of four MRI criteria: (1) ≥ BLOKS grade 2 for size cartilage loss, (2) ≥ BLOKS grade 2 for percentage full-thickness cartilage loss, (3) signs of meniscal degeneration and (4) ≥ BLOKS grade 2 for size of bone marrow lesions (BMLs) in any one compartment (7). Patients with established OA were included in the study based on the slightly adjusted American College of Rheumatology (ACR) classification criteria: knee pain, age above 50, stiffness less than 30 minutes and crepitus (22). Subjects were excluded if they had: higher K&L grade on the lateral than on the medial compartment of the same knee, musculoskeletal disorders other than knee OA in both lower limbs in the last six months, previous surgery of lower extremities and/or low back, neurological disorders, chronic intake of corticosteroids or contra-indications for MRI.

2.1. Assessment of structural OA features and static alignment on radiography

Standard anterior-posterior weight-bearing radiographs in fixed flexed position (Siemens, Siregraph CF, Agfa CR HD5.0 detector 24*30) were taken for each participant. Each radiograph was graded by a single experienced observer (FPL) and the K&L grading system with recent adjustments was used for grading of each tibiofemoral compartment (23).

In addition, an experienced skeletal radiologist assessed the static alignment of the knee joint on full-leg AP weight-bearing plain radiographs of the lower extremities (Oldelft, Triathlon, Agfa ADC M Compact Plus) (8). Knee alignment between -2° and +2° was classified as neutral, while malalignments less than -2 ° or more than +2 ° were categorized as valgus or varus alignment respectively (9, 24).

2.2. Assessment of structural OA features on MRI

All MRI studies were performed with a 3.0 Tesla scanner (Philips Achieva TX, Philips Medical Systems, Best, The Netherlands) with an eight-channel phased array knee coil. Subjects were scanned in a non-weight bearing supine position, as described by Baert et al. (25). The (most) affected side of the subjects, based on radiography, was selected for MRI. Two separate readers (NN, GVDS), using the standardized Boston-Leeds Osteoarthritis Knee Score (BLOKS) scoring system, graded structural features of the tibiofemoral joint (26). The number and amount of BMLs for the tibiofemoral (TF) joint were calculated. For cartilage lesions, cumulative scores for size and % full thickness cartilage loss were calculated for the TF joint. The presence of meniscal extrusion, tear, maceration, or increased signal was also detected.

2.3. Assessment of knee symptoms and function

To evaluate self-reported knee symptoms and function, the Dutch version of Knee Injury and Osteoarthritis Outcome Score (KOOS), was completed by each subject. The validity and reliability of this version for patients with knee OA have been demonstrated in the past (27).

In addition, with the use of two functional tests: The 'Stair Climbing Test' (SCT) and the 'Timed Up & Go test' (TUG), objective physical performance was assessed. An average of three trials for each test was calculated, to determine the final value.

2.4. Assessment of varus thrust

The spatial position of markers on relevant body segments, was recorded using a 3D motion analysis system (Krypton, Metris and Vicon Nexus, Oxford Metrics Group), at 100 samples/s (Figure 1).

By use of embedded force plates (Bertec, Ohio, USA and AMTI, MA, USA) in a 12m walkway, ground reaction forces were recorded at a sample rate of 1000 samples/s. Participants were asked to walk naturally at their comfortable speed, until three complete force plate strikes for each foot were recorded. All participants were asked to walk bare-footed (28). The "heel-strike" event was identified as the first sample of vertical ground reaction force that was above 10 N. The "toe-off" event was detected as the first sample at which the vertical ground reaction force was below 10N (29).

The recorded data were low-pass filtered with a fourth-order filter with a cutoff frequency at 25 Hz. The force time series were down-sampled to match the kinematic data. All the analyses were done using Custom-made MATLAB 7.14.0 (The MathWorks, MA) programs. Marker data from Krypton motion analysis system were labeled and smoothed using a spline routine (30). 3D Cardan angles of the knee were calculated using the decomposition order according to Grood & Suntay (31). The gait analysis protocol is described in more details in a previous study of our group (32).

Varus thrust was calculated as the difference between the knee adduction angle at heel strike and the first maximum knee adduction angle during the stance phase of gait (12, 33) (Figure 2).

2.5. Statistical analysis

Statistical calculations were carried out using SPSS software (version 20, Chicago: SPSS Inc) and for all tests, p values less than 0.05 were considered statistically significant. To examine the association of static and dynamic measures of knee alignment (independent variables), with structural features measured <u>at baseline and their changes over 2 years</u> (dependent variables), univariate regression analyses were used for continuous values. For the dichotomous variables (e.g. Presence of meniscal tear), logistic regression analysis was used. Similarly, the association of static and dynamic measures of knee alignment (independent variable) with the clinical features associated with knee OA (pain/symptoms and physical performance) measured <u>at baseline and their changes over 2 years</u> (dependent variables) were determined using univariate regression analyses. As the regression analyses revealed that both static and dynamic alignment were associated with the size of BMLs, at baseline, a final model with standard multiple regression analysis was used to assess the association between the size of BMLs and knee alignment, after checking for multicollinearity.

3. Results

Forty-seven women with a mean BMI of 27.17 (SD = 0.7) kg/m^2 and mean age of 68 (SD = 0.9) years were included in the analysis. Subjects' characteristics are presented in Table 1.

3.1. Cross-sectional association between knee frontal plane alignment and structural features of OA

Details of the regression analyses between measures of static and dynamic (varus thrust magnitude) frontal plane alignment, with MRI features at the time of entry are presented in Table 2. The magnitude of varus thrust was significantly associated with the **cumulative score for size of BMLs in the tibiofemoral joint** (Table 2). Considering static alignment, the **amount and cumulative score for size of BMLs in the tibiofemoral joint,** as well as the **cumulative score for percentage of full-thickness cartilage loss** and **presence of a meniscal maceration** were significantly associated with static varus alignment (Table 2).

A standard multiple regression model, including both varus thrust and static alignment as potential predictors of the cumulative score for size of BMLs in the tibiofemoral joint was made. The Variance Inflation Factor (VIF) to assess multicollinearity of the two independent variables was 1.024 and thus well below the cut-off of 10. Both static alignment and varus thrust remained significantly associated with the **cumulative score for size of BMLs in the tibiofemoral joint** (p = 0.039 and p = 0.049, respectively) and these alignment variables together explained, 20% of its variance.

3.2. Association between knee frontal plane alignment at baseline and changes in structural features over a period of 2 years

The magnitude of varus thrust at baseline was significantly associated with an increase in the score for **presence of meniscal macerations** over two years (Table 2). No other associations were found between baseline varus thrust magnitude and changes in structural features over 2 years (Table 2). Considering frontal plane static alignment no associations were detected between baseline measures and changes in any of the structural feature over 2 years (Table 2).

3.3. Association between knee frontal plane alignment at baseline and clinical characteristics at baseline

No significant associations were found between any of the static or dynamic (varus thrust magnitude) measures of frontal plane knee alignment, and self-reported pain, symptoms and physical function as measured with KOOS subscale ADL (Table 3). Similarly, neither static, nor dynamic alignment showed significant associations with performance-based physical function as measured by the TUG and SCT, (Table 3).

3.4. Association between knee frontal plane alignment at baseline and changes in clinical characteristics over a period of 2 years

Neither the magnitude of varus thrust nor frontal plane static alignment at baseline showed any significant associations with the changes in any of the self-reported pain, symptom, and physical function, as measured with the KOOS subscales over 2 years follow-up (Table 3). Identical results were found for the baseline static alignment and varus thrust at baseline, with 2-years changes in measures of physical function, as measured with TUG and SCT (Table 3).

4. Discussion

To the best of our knowledge, this is the first study to assess the associations between the magnitude of varus thrust and static alignment, both, with structural features associated with medial knee OA detected on MRI both cross-sectionally and longitudinally. The main findings of the present study were that both static and dynamic alignment in the frontal plane were significantly associated with OA related tibiofemoral joint structural abnormalities detected on MRI, at the time of entry. Only the magnitude of varus thrust at baseline was predictive of the changes in the presence of meniscal maceration over two years. In contrast, none of the static and dynamic measures of knee joint alignment were associated with any clinical or functional characteristics of the subjects.

The role of static varus alignment in the incident and progression of knee OA have been reported before (9, 34). In a study on the effect of baseline static alignment on progression of knee OA, in a group of patients with established medial knee OA, varus alignment at baseline was reported to be associated with a 4-fold increase in the odds of medial progression (8). Also, regarding dynamic alignment, a previous report suggests an association between presence of thrust during walking, with structural progression of knee OA detected on plain radiographs (12). During walking, even in a neutrally aligned knee, the transmission of load is in favor of the medial compartment, due to the ground reaction force passing medial to the knee joint (35, 36). An increase in (static/dynamic) varus alignment of the knee, further increases the total load passing medial to the joint, during walking (37). Varus thrust results in a shift of the GRF towards the medial compartment of the knee, with each step. As a result a shift in loading occurs, and an extra load will be exerted on (medial) regions in the cartilage that have not been adapted to the high loads that occur at heel strike (13). Previous reports showed positive associations between magnitude of varus thrust and KAM in a group of subjects with and without symptomatic knee OA (33), as well as in a group of subjects with early and established medial knee OA (16). It has been demonstrated that those with elevated KAM showed higher prevalence of BMLs in the medial compartment, a feature that has also been associated with knee pain (17-21). Previous reports illustrated that BMLs increased the risk of joint space loss (38). This suggests that BMLs could be a strong indicator of the structural deterioration related to knee OA, and that their relationship to disease progression could be explained, to some extent, by their association with limb static and dynamic (mal)alignment (38). The relationship between varus thrust and BMLs shows its possible indirect effect on development of joint space narrowing after 2 years, considering the strong association between BMLs and joint space loss on radiographs (38). In a diseased knee this may result in meniscal macerations. The main finding of the current study that higher values of baseline varus thrust and varus static alignment were significantly associated with larger size of BMLs in the tibiofemoral joint, confirms the role of dynamic and static (mal)alignment in the structural abnormalities associated with knee OA.

Previous reports showed higher values of knee pain in subjects with varus thrust as detected by visual observation, but the present study could not confirm these results (15). Lo et al, reported significantly higher knee pain, especially during weight-bearing and standing, in a group of subjects “with definite varus thrust” compared to a group of “without definite varus thrust” (15). A possible explanation for this controversy might be related to differences in methodology. In the current study, participants were restricted to women with medial tibiofemoral knee OA only, but in the study by Lo et al, both male and female subjects were tested, which might affect the results as they reported higher number of males in the group of subjects with definite varus thrust (15).

In the present study, we did not find significant associations between the magnitude of varus thrust at baseline with physical function, as measured by KOOS, TUG, and the SCT at baseline and their changes over 2 years follow-up. Similarly, in a study by Chang et al, the presence of varus thrust at baseline, as detected by observation, did not significantly predict poor physical function, as assessed using the WOMAC scale for physical function and the chair-stand performance (12). The current study, adds to the existing literature by showing that varus thrust, apart from its effect on KAM, is directly associated with increased BMLs.

There are some limitations of this study that should be taken into account. First, in the current study barefoot walking has been chosen in order to obtain a better tracking of the markers of the motion analysis system, however this limits generalization of the results. Second, as only women were included in this study, generalization of the current results to men should be treated with care. Finally, thrust as observed, may be different from thrust as measured as it is hard to distinguish actual thrust from a combined flexion rotation movement. To the best of our knowledge no study to date specifically addressed this issue in knee OA population, despite disagreements between biomechanists and clinicians. At the same time, this phenomenon seems to happen and it could still be clinically relevant.

5. Conclusion

The present study showed that both static and dynamic alignment in the frontal plane were significantly associated with OA related tibiofemoral joint structural abnormalities detected on MRI. But, only the dynamic measure magnitude of varus thrust at baseline was predictive of the changes in the presence of meniscal maceration over two years. In previous studies of our group, we reported that the magnitude of varus thrust was already significantly higher in a group of women with early knee OA, compared to a group of controls (14). After adjustment for static alignment, the differences between the early OA and the control group were still significant (14). The presence of varus thrust might be present and clinically detectable, even before the development of (static) radiographic varus (mal)alignment. Thus, the association of thrust with MRI lesions presents an opportunity to identify those at risk for developing established OA, or at the early stages of radiographic knee OA. Results from the current study highlight the role of frontal plane static and dynamic alignment in the disease process and hence, suggested that attempts for therapy are probably more successful when efforts are made to correct alignment, as well.

Author contributions

AM, IB, FL, and SV contributed to the conception and design of this study. AM, IB and FL contributed to the collection of the data. AM contributed to the analysis of the data with expertise of JvD, JB, and GF. AM, IB, JvD, SB, FL, GF and SV contributed to the interpretation of the data. Article drafts were written by AM and SV and critically revised by all authors. The final version of the article was approved by all authors. AM takes responsibility for the integrity of the work as a whole (armaghan.mahmoudian@faber.kuleuven.be).

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Competing interest statement

The authors declare that they have no conflicts of interest.

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References

1. Felson D. The course of osteoarthritis and factors that affect it. Rheumatic diseases clinics of North America 1993;19:607-15.
2. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Annals of the rheumatic diseases 2014:annrheumdis-2013-204763.
3. Cooper C, Snow S, McAlindon TE, Kellingray S, Stuart B, Coggon D, et al. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis & Rheumatism 2000;43:995-1000.
4. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman BN, Aliabadi P, et al. The incidence and natural history of knee osteoarthritis in the elderly, the framingham osteoarthritis study. Arthritis & Rheumatism 1995;38:1500-5.
5. Corti MC, Rigon C. Epidemiology of osteoarthritis: prevalence, risk factors and functional impact. Aging clinical and experimental research 2003;15:359-63.
6. Hunter DJ, Zhang Y, Niu J, Goggins J, Amin S, LaValley MP, et al. Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. Arthritis & Rheumatism 2006;54:1529-35.
7. Luyten FP, Denti M, Filardo G, Kon E, Engebretsen L. Definition and classification of early osteoarthritis of the knee. Knee Surgery, Sports Traumatology, Arthroscopy 2012;20:401-6.
8. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. Jama 2001;286:188-95.
9. Brouwer G, Van Tol A, Bergink A, Belo J, Bernsen R, Reijman M, et al. Association between valgus and varus alignment and the development and progression of radiographic osteoarthritis of the knee. Arthritis & Rheumatism 2007;56:1204-11.
10. Tanamas S, Hanna FS, Cicuttini FM, Wluka AE, Berry P, Urquhart DM. Does knee malalignment increase the risk of development and progression of knee osteoarthritis? A systematic review. Arthritis care & research 2009;61:459-67.
11. Barrios JA, Royer TD, Davis IS. Dynamic versus radiographic alignment in relation to medial knee loading in symptomatic osteoarthritis. J Appl Biomech 2012;28:551-9.
12. Chang A, Hayes K, Dunlop D, Hurwitz D, Song J, Genge R, et al. Thrust during ambulation and the progression of knee osteoarthritis. Arthritis & Rheumatism 2004;50:3897-903.
13. Andriacchi TP, Mündermann A, Smith RL, Alexander EJ, Dyrby CO, Koo S. A framework for the in vivo pathomechanics of osteoarthritis at the knee. Annals of biomedical engineering 2004;32:447-57.

14. Mahmoudian A, van Dieen JH, Bruijn SM, Baert IA, Faber GS, Luyten FP, et al. Varus thrust in women with early medial knee osteoarthritis and its relation with the external knee adduction moment. Clinical Biomechanics 2016;39:109-14.
15. Lo GH, Harvey WF, McAlindon TE. Associations of varus thrust and alignment with pain in knee osteoarthritis. Arthritis & Rheumatism 2012;64:2252-9.
16. Mahmoudian A, van Dieen J, Bruijn SM, Baert I, Faber G, Luyten F, et al. Varus thrust in women with early medial knee osteoarthritis and its relation with the external knee adduction moment. Manuscript sumbitted for publication 2016.
17. Bennell KL, Creaby MW, Wrigley TV, Bowles K-A, Hinman RS, Cicuttini F, et al. Bone marrow lesions are related to dynamic knee loading in medial knee osteoarthritis. Annals of the rheumatic diseases 2010;69:1151-4.
18. Felson DT, Chaisson CE, Hill CL, Totterman SM, Gale ME, Skinner KM, et al. The association of bone marrow lesions with pain in knee osteoarthritis. Annals of internal medicine 2001;134:541-9.
19. Felson DT, Niu J, Guermazi A, Roemer F, Aliabadi P, Clancy M, et al. Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. Arthritis & Rheumatism 2007;56:2986-92.
20. Torres L, Dunlop D, Peterfy C, Guermazi A, Prasad P, Hayes K, et al. The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. Osteoarthritis and cartilage 2006;14:1033-40.
21. Lo GH, McAlindon T, Niu J, Zhang Y, Beals C, Dabrowski C, et al. Bone marrow lesions and joint effusion are strongly and independently associated with weight-bearing pain in knee osteoarthritis: data from the osteoarthritis initiative. Osteoarthritis and Cartilage 2009;17:1562-9.
22. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis & Rheumatism 2011;63:573-86.
23. Felson DT, Niu J, Guermazi A, Sack B, Aliabadi P. Defining radiographic incidence and progression of knee osteoarthritis: suggested modifications of the Kellgren and Lawrence scale. Annals of the rheumatic diseases 2011;70:1884-6.
24. Moreland JR, Bassett L, Hanker G. Radiographic analysis of the axial alignment of the lower extremity. The Journal of Bone & Joint Surgery 1987;69:745-9.
25. Baert IA, Staes F, Truijen S, Mahmoudian A, Noppe N, Vanderschueren G, et al. Weak associations between structural changes on MRI and symptoms, function and muscle strength in relation to knee osteoarthritis. Knee Surgery, Sports Traumatology, Arthroscopy 2013:1-13.
26. Hunter D, Lo G, Gale D, Grainger A, Guermazi A, Conaghan P. The reliability of a new scoring system for knee osteoarthritis MRI and the validity of bone marrow lesion assessment: BLOKS (Boston–Leeds Osteoarthritis Knee Score). Annals of the rheumatic diseases 2008;67:206-11.
27. de Groot I, Favejee M, Reijman M, Verhaar J, Terwee C. The Dutch version of the Knee Injury and Osteoarthritis Outcome Score: a validation study. Health and quality of life outcomes 2008;6:16.
28. Shakoor N, Block JA. Walking barefoot decreases loading on the lower extremity joints in knee osteoarthritis. Arthritis & Rheumatism 2006;54:2923-7.
29. Hansen AH, Childress DS, Meier MR. A simple method for determination of gait events. Journal of Biomechanics 2002;35:135-8.
30. Woltring HJ. A FORTRAN package for generalized, cross-validatory spline smoothing and differentiation. Advances in Engineering Software (1978) 1986;8:104-13.
31. Grood ES, Suntay WJ. A joint coordinate system for the clinical description of three-dimensional motions: application to the knee. Journal of biomechanical engineering 1983;105:136-44.

32. Mahmoudian A, van Dieen J, Baert I, Bruijn SM, Faber G, Luyten F, et al. Changes in gait characteristics of women with early and established medial knee OA: results from a 2-years longitudinal study. Manuscript submitted for publication 2016.
33. Kuroyanagi Y, Nagura T, Kiriyama Y, Matsumoto H, Otani T, Toyama Y, et al. A quantitative assessment of varus thrust in patients with medial knee osteoarthritis. The Knee 2012;19:130-4.
34. Sharma L, Song J, Dunlop D, Felson D, Lewis CE, Segal N, et al. Varus and valgus alignment and incident and progressive knee osteoarthritis. Annals of the rheumatic diseases 2010;69:1940-5.
35. Andriacchi TP. Dynamics of knee malalignment. The Orthopedic clinics of North America 1994;25:395-403.
36. Morrison J. The mechanics of the knee joint in relation to normal walking. Journal of biomechanics 1970;3:51-61.
37. HSU RW, HIMENO S, COVENTRY MB, CHAO EY. Normal axial alignment of the lower extremity and load-bearing distribution at the knee. Clinical orthopaedics and related research 1990;255:215-27.
38. Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale ME, Totterman S, et al. Bone marrow edema and its relation to progression of knee osteoarthritis. Annals of internal medicine 2003;139:330-6.

Table 1. Characteristics of the study population (n = 47)

	Mean (SD)[a] or Median (IQR)[b] or n (%)[c]	Range	95% CI of the mean
Weight (kg)	70.64 (1.8)[a]	51.2 – 98.1	66.92 – 74.36
BMI (kg/m²)	27.17 (0.7)[b]	20.52 – 35.6	25.74 – 28.59
Height (m)	1.61 (0.01)[a]	1.47 – 1.77	1.59 – 1.63
Age (years)	68.00 (0.9)[a]	57 - 83	66.23 – 6
K&L score (MC)			
K&L 0	10 (22%)[c]		
K&L 1	16 (36%)[c]		
K&L 2^-	1 (2%)[c]		
K&L 2^+	12 (27%)[c]		
K&L 3	6 (13%)[c]		
Static alignment			
Neutral	27 (60%)[c]		
Valgus	5 (11%)[c]		
Varus	13 (29%)[c]		

SD = Standard Deviation; IQR = Inter Quartile Range; CI = Confidence Interval; BMI = Body Mass Index; MC = Medial Compartment; K&L = Kellgren & Lawrence (range 0-4).

Table 2. Associations between knee joint frontal plane (static and dynamic) alignment and structural features on MRI

	Independent variables							
	with structural features at baseline				***with changes in structural features over 2 years***			
	Varus thrust		**Static alignment**		**Varus thrust**		**Static alignment**	
Dependent variables **Structural MRI features**	***β***	***P***	***β***	***P***	***β***	***P***	***β***	***P***
Bone Marrow Lesions and cysts								
Amount of BMLs	0.194	0.206	**0.368**	**0.012†**	0.2	0.216	0.141	0.373
Cum score for size of BMLs	**0.34**	**0.024†**	**0.352**	**0.016†**	0.004	0.983	0.014	0.93
Cartilage lesions								
Amount of cartilage lesions	0.061	0.693	0.182	0.226	0.049	0.762	0.03	0.85
Cum score for size of cartilage loss	0.087	0.575	0.212	0.157	0.011	0.946	-0.047	0.769
Cum score for % full-thickness cartilage loss	-0.002	0.992	**0.302**	**0.042†**	-0.004	0.979	0.068	0.671
Meniscal lesions								
Presence of extrusion	0.035	0.823	0.156	0.301	0.005	0.976	-0.208	0.187
Presence of increased signal	0.042	0.801	-0.191	0.231	-0.09	0.58	0.032	0.842
Presence of tear	0.192	0.213	0.138	0.359	-0.196	0.228	-0.119	0.453
Presence of maceration	0.117	0.448	**0.443**	**0.002†**	**0.504**	**0.001†**	0.236	0.132
Synovitis and effusion								
Score for size of effusion (score 0-3)	0.062	0.691	0.105	0.489	0.277	0.083	0.008	0.962
Cum score for presence of synovitis + size effusion (0-6)	-0.012	0.943	0.242	0.123	0.17	0.295	-0.035	0.824
Score for presence of synovitis and/or effusion (0-2)	0.038	0.807	0.162	0.281	0.11	0.5	-0.047	0.766

BML=Bone Marrow Lesion; Cum = Cumulative.
†Significant association based on regression analysis ($P < 0.05$)

Table 3. Associations between knee joint frontal plane (static and dynamic) alignment and clinical and functional characteristics

	Independent variables							
	with structural features at baseline				***with changes in structural features over 2 years***			
	Varus thrust		**Static alignment**		**Varus thrust**		**Static alignment**	
Dependent variables	***β***	***P***	***β***	***P***	***β***	***P***	***β***	***P***
Pain and other symptoms								
KOOS pain	0.017	0.91	0.046	0.763	-0.014	0.927	-0.111	0.469
KOOS symptoms	-0.001	0.997	0.132	0.381	0.015	0.923	-0.049	0.748
Physical performance								
KOOS ADL	0.069	0.657	0.072	0.636	-0.08	0.62	-0.141	0.366
TUG	-0.031	0.844	-0.093	0.539	-0.077	0.622	0.102	0.506
SCT	-0.03	0.846	-0.087	0.567	-0.09	0.569	0.072	0.642

OA=osteoarthritis; KOOS = Knee injury and Osteoarthritis Outcome Score; ADL = Activities of Daily Living; TUG = Timed Up and Go; SCT = Stair Climbing Test.
†Significant association based on regression analysis ($P < 0.05$)

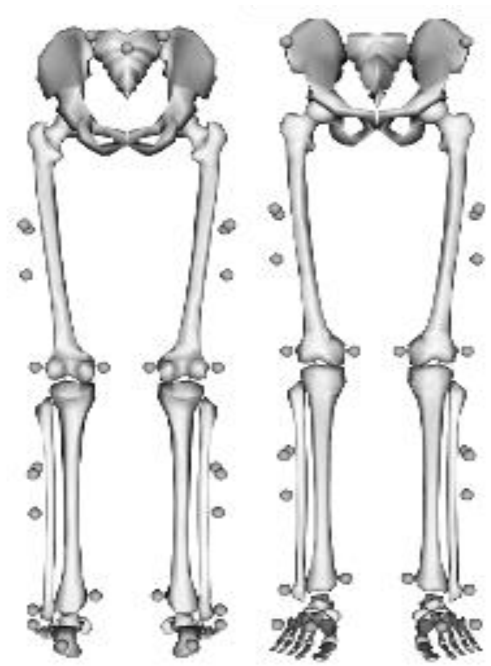

Figure 1. Marker set used for motion capture.

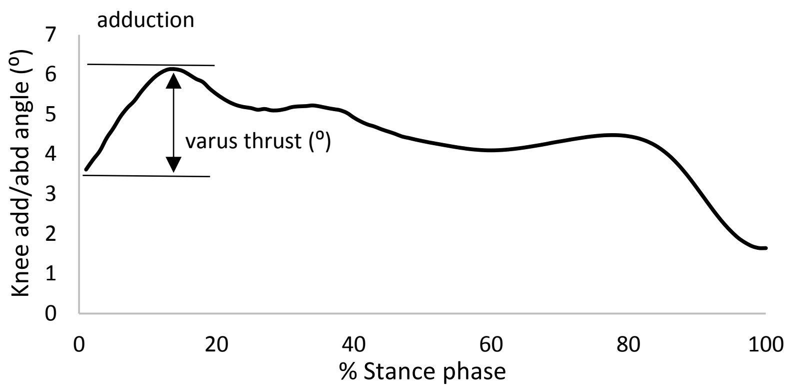

Figure 2. Varus thrust magnitude calculated as the difference between the knee adduction angle at heel strike and the first maximum knee adduction angle during the stance phase of gait.