HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2017 September 06.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2017 July ; 69(7): 959–965. doi:10.1002/acr.23096.

Longitudinal Changes in Magnetic Resonance Imaging–Based Measures of Femorotibial Cartilage Thickness as a Function of Alignment and Obesity: Data From the Osteoarthritis Initiative

REBECCA MOYER, PT, PhD[1], **WOLFGANG WIRTH, PhD**[2], and **FELIX ECKSTEIN, MD**[2]

[1]Dalhousie University, Halifax, Nova Scotia, Canada

[2]Institute of Anatomy, Paracelsus Medical University Salzburg & Nuremberg, Salzburg, Austria, and Chondrometrics GmbH, Ainring, Germany

Abstract

Objective—To investigate the interaction between malalignment and body mass index (BMI) on cartilage thickness change in patients with knee osteoarthritis (OA).

Methods—Femorotibial cartilage thickness was measured from baseline to 2 years in 558 knees with radiographic OA. Cartilage thickness was determined in the central weight-bearing medial femorotibial cartilage (cMFTC) and lateral (cLFTC) compartments. Femorotibial angle (FTA) was stratified into neutral, minor, and definite malalignment. BMI was stratified using World Health Organization classifications for normal, overweight, and obese. Multivariable linear regression models were used to investigate the interaction between alignment and BMI, adjusting for age, sex, and disease severity.

Results—There was no significant interaction for continuous measures of alignment and BMI ($P = 0.301$ for cMFTC and $P = 0.852$ for cLFTC). Using BMI tertiles, the association between alignment and medial or lateral cartilage thickness loss was not moderated by BMI, despite a significant association of malalignment with greater cartilage thickness loss ($P \leq 0.005$). Using FTA tertiles, the association between BMI and medial cartilage thickness loss was approximately 3 times greater in knees with definite malalignment ($P = 0.149$) and approximately 5 times greater in knees with minor malalignment ($P = 0.006$). Specifically, knees with minor varus significantly modified this relationship ($P = 0.021$).

Conclusion—Malalignment was significantly associated with cartilage thickness loss per degree increase in malalignment, but was not moderated by BMI. BMI was significantly associated with

Address correspondence to Rebecca Moyer, PT, PhD, School of Physiotherapy, Forrest Building, Room 418, 5869 University Avenue, PO Box 15000, Dalhousie University, Halifax, Nova Scotia, Canada, B3H 4R2. rebecca.moyer@dal.ca.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the articleor revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Moyer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Moyer, Wirth, Eckstein.

Acquisition of data .Moyer, Wirth, Eckstein.

Analysis and interpretation of data. Moyer, Wirth, Eckstein.

ADDITIONAL DISCLOSURE

Authors Wirth and Eckstein are employees of Chondrometrics GmbH.

greater rates of medial cartilage thickness loss per unit increase in BMI but only in knees with minor varus malalignment. These findings have implications for better understanding patient subgroups and intervention strategies targeting risk factors for knee OA.

INTRODUCTION

Malalignment and obesity are well-known risk factors for knee osteoarthritis (OA), altering the mechanical environment of the tibiofemoral joint and the distribution of joint loads (1–5). Varus and valgus alignment are strong predictors of the progression of medial and lateral knee OA, respectively, with knees in varus and neutral alignment primarily bearing load through the medial compartment, and knees in valgus alignment primarily bearing load through the lateral compartment (5–9). The individual effects of obesity are less clear, and its relationship with other risk factors, such as malalignment, results in further inconsistencies (10–12).

Obesity is one of the few modifiable, and preventable, risk factors for knee OA, yet approximately 1.9 billion adults worldwide over the age of 18 are overweight, and 600 million of these individuals are obese (13). The multifactorial impact of obesity on knee OA plays a critical role in the local joint environment (14–17), but previous prospective studies are inconsistent about the effects of obesity on disease progression in patients with malalignment (10–12,18). Although body mass index (BMI) has been shown to have a strong relationship with radiographic disease, this relationship was predominantly explained by malalignment mediating the effects of BMI on disease severity (10). Others suggest that a high BMI is associated with an increased risk of radiographic disease progression in knees with moderate malalignment, and not in those with neutral or severe malalignment (11). Additionally, the interaction of BMI and alignment may differ between knees with incident OA versus those with progressive OA (12,19,20). Regardless of alignment severity, individuals who were obese were found to be at an increased risk of incident knee OA (12). Individuals who were obese with neutral alignment had radiographic knee OA progression (12), suggesting that when malalignment is present, BMI may not contribute to knee OA progression.

Most recently, authors have suggested that malalignment and BMI are not additive risk factors (12). Once malalignment is present, BMI may have little additional risk on the progression of knee OA (21). Whether or not an interaction exists between alignment and obesity, when quantitative magnetic resonance imaging (MRI)–based outcomes of cartilage thickness loss are used as a measure of structural progression, is unknown. Furthermore, we are not aware of previous studies investigating whether the same degree of alignment severity impacts cartilage thickness loss similarly in one alignment direction (e.g., varus) compared to another direction (e.g., valgus) in patients who are, and in those who are not, obese.

The objective of this study was to determine the relative and interactive contributions of malalignment and BMI on longitudinal cartilage thickness loss in patients with radiographic knee OA. Specifically, this study aimed to determine how medial and lateral femorotibial

cartilage loss depends on the stratification of malalignment, independent of and dependent on the direction of alignment (varus or valgus), and clinical classifications of BMI.

PATIENTS AND METHODS

Study participants

Participants were selected from the Osteoarthritis Initiative (OAI), an ongoing multicenter, publicly available cohort, including individuals with or at high risk for knee OA (22). The OAI includes 4,796 participants, with an age range of 25–79 years, and the inclusion and exclusion criteria have been published previously (22,23). The present study sample was derived from 590 OAI participants who had undergone sagittal double-echo steady-state (DESS) acquisitions at baseline and at 2-year followup (23). The included sample was selected from the progression cohort of the OAI with a radiographic diagnosis of knee OA (defined as Kellgren/Lawrence [K/L] grade ≥2) (24), and frequent knee symptoms (defined as pain, aching, or stiffness in or around the knee on most days for at least 1 month in the past 12 months). No knees had undergone replacement within the 2-year followup. Four hips had undergone replacement prior to enrollment and 3 hips had undergone replacement during the 2-year followup. All knees were included in the analysis. MRI-based measures of cartilage thickness loss between baseline and 2-year followup were available from the DESS acquisitions (23). There were 567 knees (of 590) that underwent the sagittal DESS sequence that had definite radiographic knee OA and frequent knee symptoms at baseline. Eight knees did not have a recorded femorotibial angle (FTA) at baseline, and 1 knee did not have a recorded BMI. All 9 knees were excluded, resulting in 558 knees for analysis (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23096/abstract). Twenty-three knees did not have definite radiographic OA (i.e., K/L grade 0–1) based on the central radiographic readings (24) and were thus excluded; however, 19 knees (of 23) had K/L grade 1 and were used for sensitivity analyses.

Radiographic grading

Radiographic knee OA severity was quantified using the K/L grading system (range 0–4) and obtained using the central readings from Boston University (24). Fixed-flexion radiographs were used to quantify FTA at baseline, and each radiograph was read by 2 individuals from Brigham and Women's Hospital (25). Participants were positioned in a fixed-flexion Plexiglas positioning frame (Synaflexer) with the knees positioned at 20–30° of flexion (26). The FTA measurement was defined using a coordinate system for identifying the distal aspect of the femoral condyles, based on anatomic landmarks for establishing a location-specific radiographic joint space width measurement (27,28). Previous work evaluating this method has shown that it is highly correlated with the hip-knee-ankle angle and predicts cartilage loss over 2 years as well as the gold standard (25,29,30). The femoral axis was defined to be perpendicular to the line tangent to the base of the femoral condyles. FTA was defined as the inclusion angle between the femoral axis and the tibial axis, which was centered along the shaft of the tibia, originating at a point 10 cm distal to the tibial plateau. More negative values indicated increased varus alignment. The intra- and

interreader reproducibility of the FTA was high (intraclass correlation coefficient ≥0.98) with good limits of agreement (approximately 1°) (25).

Quantitative measurement of femorotibial cartilage loss

The MRI acquisition protocol included sagittal DESS imaging and has been described previously (23). The medial and lateral femorotibial cartilage was segmented manually, using proprietary software (Chondrometrics GmbH), with readers (WW and FE) blinded to disease severity, alignment, and the order of image acquisition (baseline and 2-year followup) (31). One expert reader (FE), with more than 5 years of MRI-based cartilage segmentation experience, performed quality control readings of all segmentations. The sums of the mean thickness in the medial compartment (central medial tibia and central weight-bearing region of the medial femoral condyle) and lateral compartment (central lateral tibia and central weight-bearing region of the lateral femoral condyle) were used to calculate the cartilage thickness in the central weight-bearing medial (cMFTC) and central lateral femorotibial compartments (cLFTC) (32).

Statistical analysis

All analyses were performed using SPSS, version 23.0. The primary outcome measures were cMFTC and cLFTC. The mean ± SD changes in medial and lateral cartilage thickness between baseline and 2-year followup were determined. Changes were normalized to time (in days) between baseline and followup (mean ± SD 739 ± 35 days [range 506–938 days]). Knee OA progression was defined as cartilage thickness loss exceeding the smallest detectable change (SDC) threshold in MFTC (−111μm) or LFTC (−121μm), respectively (23,31,33). Linear regression models were applied to FTA, adjusting for its varus distribution (25,29).

First, a multivariable linear regression model was created for medial and lateral cartilage thickness to test the hypothesis that a statistical interaction exists between baseline malalignment and BMI on 2-year cartilage thickness change while controlling for other factors suggested to alter cartilage thickness (34). The models included alignment and BMI as continuous variables, their interaction term (FTA × BMI), and additional independent variables, including age, sex, and disease severity (K/L grade). To evaluate clinical classifications, knees were also categorized according to the World Health Organization (WHO) classifications for individuals, as normal (<25 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2) (35). The adjusted FTA was split into tertiles, with the median cutoff used to optimize the sample size in each group, due to the limited number of knees in valgus alignment. Neutral alignment was defined as ± 0–2°, minor malalignment was defined as ± 2–3.5°, and definite malalignment was defined as ± ≥3.5°. Three separate models were tested to determine whether or not the relationship between FTA and cartilage thickness loss varied across BMI classes. Similarly, 3 separate models were tested to determine whether or not the relationship between BMI and cartilage thickness loss varied across tertiles of FTA. Following a significant relationship, FTA tertiles were separated by alignment direction (varus and valgus), and the multivariable linear regression models were repeated. Sensitivity analyses were performed to evaluate the robustness of the models by including knees with K/L grade 1 (19 knees). The significance level was set at P less than 0.05.

RESULTS

There were 558 knees with definite radiographic knee OA included in this study (75 normal, 216 overweight, and 267 obese). There were 238 knees classified as neutral, 154 knees had minor malalignment (111 varus and 43 valgus), and 166 knees had definite malalignment (127 varus and 39 valgus). Demographics and clinical characteristics arranged by malalignment and BMI strata are shown in Table 1. Across all knees, FTA and BMI did not significantly change from baseline to 2 years (−0.08 change in FTA, $P = 0.066$; 0.01 change in BMI, $P = 0.941$). The proportion of knees that exceeded the SDC for medial cartilage thickness loss (i.e., progressors) was lower in neutral knees (normal 28%, overweight 32%, and obese 28%) than in knees with minor malalignment (normal 25%, overweight 50%, and obese 41%) or definite malalignment (normal 25%, overweight 40%, and obese 43%) combined with higher than normal BMI. However, the proportion of knees that exceeded the SDC for lateral cartilage thickness loss was more consistent between neutral knees (normal 23%, overweight 30%, and obese 21%), minor malalignment (normal 46%, overweight 23%, and obese 27%), and definite malalignment (normal 40%, overweight 17%, and obese 36%). The mean ± SD changes for cMFTC and cLFTC are reported in Table 2.

As continuous variables, FTA and BMI were included in the regression models to estimate their relative contributions and the change in cartilage thickness after adjusting for age, sex, and K/L grade. The interaction term (FTA × BMI) was not statistically significant for either model ($P = 0.301$ for cMFTC and $P = 0.852$ for cLFTC). No differences were observed when the analyses were repeated and included K/L grade 1 knees (19 knees). In BMI tertiles, after controlling for other variables in the model, the association between FTA and cartilage thickness loss was shown to remain relatively constant across all BMI classes, suggesting that BMI does not modify the relationship between malalignment and medial or lateral cartilage thickness loss (Table 3). Malalignment did, however, contribute significantly to each model, explaining 18–22% of the variance in the medial compartment and 14–20% of the variance in the lateral compartment.

In FTA tertiles, the association between BMI and medial cartilage thickness loss was approximately 3 times greater in knees with definite malalignment ($P = 0.149$) and approximately 5 times greater in knees with minor malalignment ($P = 0.006$), suggesting that the amount of malalignment may modify the relationship between BMI and cartilage thickness loss (Table 4). Specifically, knees with minor varus significantly modified the relationship between BMI and medial cartilage thickness loss ($P = 0.021$). The association between BMI and lateral cartilage thickness was approximately 1.5 times greater in knees with minor malalignment; however, this was not statistically significant ($P = 0.345$). Knees with minor valgus appeared to modify the relationship between BMI and lateral cartilage thickness loss (approximately 5 times greater than neutral knees) but did not achieve statistical significance ($P = 0.295$).

DISCUSSION

This study is the first to investigate the relative and interactive contributions of malalignment and obesity as risk factors for knee OA progression, using quantitative MRI-based measures

of cartilage thickness loss. Specifically, the association between BMI and cartilage thickness loss may depend on the magnitude of malalignment, with higher associations observed in knees with minor malalignment. For example, in the tertile with minor malalignment, our results suggest an approximate 8μm increase (8% of the mean change) in medial cartilage thickness loss for every 1-unit increase in BMI. Minor varus knees primarily drove this relationship, suggesting an 8.5 μm increase (6% of the mean change) in medial cartilage thickness loss for every 1-unit increase in BMI. In minor valgus knees, a 6 μm increase (4% of the mean change) in lateral cartilage thickness loss for every 1-unit increase in BMI was observed but was not statistically significant.

Malalignment, irrespective of severity, was significantly associated with subsequent cartilage loss (Table 3), supporting earlier suggestions that malalignment is associated with structural disease progression (7,8,36,37). However, a linear relationship for increases in the severity of malalignment using location-specific measures of cartilage thickness loss was most evident in knees in the overweight and obese BMI categories, and not in normal knees. These observed changes are consistent with other reports that cMFTC and cLFTC have high sensitivity to change over 1-and 2-year periods (23) and are associated with long-term clinically important outcomes (23,38–40).

In either the medial or lateral compartment, obesity did not appear to moderate the association between malalignment and cartilage thickness loss. Across tertiles of BMI, our results suggest an increase in medial and lateral cartilage thickness loss of up to approximately 14 μm and 19 μm, respectively (approximately 15% and 30% of the mean change) for every 1° increase in varus or valgus alignment. Although knees with malalignment and increasing BMI had larger cartilage thickness loss, the role of BMI as a risk factor for OA progression was less clear (5,15,16). Altering the capacity of articular cartilage to adapt to increasing joint loads associated with obesity would suggest that the greatest cartilage thickness losses should be associated with those in definite malalignment and high BMI. However, BMI appeared most influential in knees with minor malalignment, supporting the mechanism that in more severely malaligned knees, exceeded thresholds for cartilage loss may no longer be affected by additional risk factors (11). Importantly, these findings do not diminish the role of obesity on cartilage disease progression, or the prominence of weight reduction for patients with knee OA. Given the additive loading effects accumulated over the thousands of steps taken per day (41), weight loss for all BMI groups may have a crucial role in protecting cartilage thickness, particularly in patients in minor malalignment.

Previous work suggests that knees with malalignment moderate the effect of obesity on structural disease progression. Felson et al (11) found a significant relationship between obesity and moderate malalignment using measures of radiographic disease progression, such that the odds ratios for progression in knees with neutral, moderate, and severe malalignment were 1.00, 1.23, and 0.93, respectively. Our findings support and complement this work, suggesting a similar pattern of disease progression using quantitative MRI-based measures of cartilage thickness loss. Similarly, these findings also support the suggestion by Sharma et al (10) that an interaction may indeed exist between alignment and BMI on measures of disease progression. However, the relationship between obesity and joint space

narrowing (JSN) on radiographs was mediated by alignment, whereas the relationship between obesity and cartilage thickness loss was moderated by alignment. As a result, the operational definition used to quantify disease progression (i.e., radiographic or quantitative MRI-based outcomes) may influence the mechanism used to explain the mediating or moderating effects of alignment with obesity, which may have implications in future trials evaluating interventions targeting these risk factors.

Importantly, the nonsignificant interaction using continuous measures of BMI and FTA confirms reports by Messier et al (42) suggesting that alignment and BMI influence dynamic knee joint loading via different mechanisms, which may be a reason for the subtle differences observed for changes in cartilage thickness between the medial and lateral compartment. However, despite these novel findings, they must remain speculative and should be interpreted cautiously. Limitations in the present study should be acknowledged when inferring changes in cartilage thickness due to classifications of alignment and obesity at baseline. To detect significant change using quantitative MRI-based outcomes in lieu of radiographic JSN, larger sample sizes among subgroups and further distinction between groups (e.g., mild, moderate, and severe malalignment) may be necessary; however the few knees with baseline valgus alignment limited further stratification of the subgroups. Notably, the clinical significance of a 1–2° alignment difference between groups is uncertain. Semiquantitative measures of disease progression known to be associated with alignment (e.g., meniscal extrusion, bone marrow lesions, and osteophytes) (43) were not adjusted for in the present analysis. Future studies are warranted to evaluate the effects of other MRI structural pathologies and their potential interactive role with malalignment, as well as investigate these relationships over longer followup periods. Further investigations of this relationship may provide additional insight into this interactive model of alignment and obesity on structural disease progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This article was prepared using an Osteoarthritis Initiative (OAI) public-use data set, and its contents do not necessarily reflect the opinions or views of the OAI Study Investigators, the NIH, or the private funding partners of the OAI. The OAI is a public–private partnership between the NIH (contracts N01-AR-2-2258, N01-AR-2-2259, N01-AR-2-2260, N01-AR-2-2261, and N01-AR-2-2262) and private funding partners (Merck Research Laboratories, Novartis Pharmaceuticals, GlaxoSmithKline, and Pfizer) and is conducted by the OAI Study Investigators. Private-sector funding for the OAI is managed by the Foundation for the NIH. The authors of this article are not part of the OAI investigative team. Dr. Moyer's work was supported by the University of Western Ontario Faculty of Health Sciences Postdoctoral Fellowship Program and by the Osteoarthritis Research Society International Collaborative Scholarship.

Dr. Wirth is employed part time by and co-owner of Chondrometrics GmbH. Dr. Eckstein has received consulting fees from Mariel Therapeutics, Merck Serono, Servier, and Snyarc (less than $10,000 each), has received fees from Medtronic for the provision of educational sessions (less than $10,000), and is the chief executive officer and co-owner of Chondrometrics GmbH.

References

1. Morrison JB. The mechanics of the knee joint in relation to normal walking. J Biomech. 1970; 3:51–61. [PubMed: 5521530]
2. Johnson F, Leitl S, Waugh W. The distribution of load across the knee: a comparison of static and dynamic measurements. J Bone Joint Surg Br. 1980; 62:346–9. [PubMed: 7410467]
3. Andriacchi TP. Dynamics of knee malalignment. Orthop Clin North Am. 1994; 25:395–403. [PubMed: 8028883]
4. 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. [PubMed: 11448282]
5. 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 Rheum. 2000; 43:995–1000. [PubMed: 10817551]
6. Cicuttini F, Wluka A, Hankin J, Wang Y. Longitudinal study of the relationship between knee angle and tibiofemoral cartilage volume in subjects with knee osteoarthritis. Rheumatology (Oxford). 2004; 43:321–4. [PubMed: 14963201]
7. Brouwer GM, van Tol AW, Bergink AP, Belo JN, Bernsen RM, Reijman M, et al. Association between valgus and varus alignment and the development and progression of radiographic osteoarthritis of the knee. Arthritis Rheum. 2007; 56:1204–11. [PubMed: 17393449]
8. Eckstein F, Wirth W, Hudelmaier M, Stein V, Lengfelder V, Cahue S, et al. Patterns of femorotibial cartilage loss in knees with neutral, varus, and valgus alignment. Arthritis Rheum. 2008; 59:1563–70. [PubMed: 18975356]
9. Teichtahl AJ, Davies-Tuck ML, Wluka AE, Jones G, Cicuttini FM. Change in knee angle influences the rate of medial tibial cartilage volume loss in knee osteoarthritis. Osteoarthritis Cartilage. 2009; 17:8–11. [PubMed: 18590972]
10. Sharma L, Lou C, Cahue S, Dunlop DD. The mechanism of the effect of obesity in knee osteoarthritis: the mediating role of malalignment. Arthritis Rheum. 2000; 43:568–75. [PubMed: 10728750]
11. Felson DT, Goggins J, Niu J, Zhang Y, Hunter DJ. The effect of body weight on progression of knee osteoarthritis is dependent on alignment. Arthritis Rheum. 2004; 50:3904–9. [PubMed: 15593215]
12. Niu J, Zhang YQ, Torner J, Nevitt M, Lewis CE, Aliabadi P, et al. Is obesity a risk factor for progressive radiographic knee osteoarthritis? Arthritis Rheum. 2009; 61:329–35. [PubMed: 19248122]
13. World Health Organization. Obesity and overweight fact sheet from the WHO. 2011. URL: http://www.thehealthwell.info/node/82914
14. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis: the Framingham Study. Ann Intern Med. 1988; 109:18–24. [PubMed: 3377350]
15. Spector TD, Hart DJ, Doyle DV. Incidence and progression of osteoarthritis in women with unilateral knee disease in the general population: the effect of obesity. Ann Rheum Dis. 1994; 53:565–8. [PubMed: 7979593]
16. Reijman M, Pols HA, Bergink AP, Hazes JM, Belo JN, Lievense AM, et al. Body mass index associated with onset and progression of osteoarthritis of the knee but not of the hip: the Rotterdam Study. Ann Rheum Dis. 2007; 66:158–62. [PubMed: 16837490]
17. Lohmander LS, de Verdier MG, Rollof J, Nilsson PM, Engström G. Incidence of severe knee and hip osteoarthritis in relation to different measures of body mass: a population-based prospective cohort study. Ann Rheum Dis. 2009; 68:490–6. [PubMed: 18467514]
18. Moyer RF, Birmingham TB, Chesworth BM, Kean CO, Giffin JR. Alignment, body mass and their interaction on dynamic knee joint load in patients with knee osteoarthritis. Osteoarthritis Cartilage. 2010; 18:888–93. [PubMed: 20417288]
19. Spector TD, Dacre JE, Harris PA, Huskisson EC. Radiological progression of osteoarthritis: an 11-year follow up study of the knee. Ann Rheum Dis. 1992; 51:1107–10. [PubMed: 1444622]

20. Dieppe PA, Cushnaghan J, Shepstone L. The Bristol “OA500” study: progression of osteoarthritis (OA) over 3 years and the relationship between clinical and radiographic changes at the knee joint. Osteoarthritis Cartilage. 1997; 5:87–97. [PubMed: 9135820]
21. Wolfe F, Lane NE. The long-term outcome of osteoarthritis: rates and predictors of joint space narrowing in symptomatic patients with knee osteoarthritis. J Rheumatol. 2002; 29:139–46. [PubMed: 11824950]
22. Nevitt, MC., Felson, DT., Lester, G. The Osteoarthritis Initiative: protocol for the cohort study. URL: http://oai.epi-ucsf.org/datarelease/docs/StudyDesignProtocol.pdf
23. Eckstein F, Wirth W, Nevitt MC. Recent advances in osteoarthritis imaging: the Osteoarthritis Initiative. Nat Rev Rheumatol. 2012; 8:622–30. [PubMed: 22782003]
24. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis. 1957; 16:494–502. [PubMed: 13498604]
25. Iranpour-Boroujeni T, Li J, Lynch JA, Nevitt M, Duryea J, Osteoarthritis Initiative Investigators. A new method to measure anatomic knee alignment for large studies of OA: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage. 2014; 22:1668–74. [PubMed: 25278076]
26. Radiographic procedure manual for examinations of the knee, hand, pelvis and lower limbs. Osteoarthritis Initiative: a knee health study. 2006. Version 2.1URL: http://oai.epi-ucsf.org/datarelease/operationsmanuals/radiographicmanual.pdf.
27. Duryea J, Neumann G, Niu J, Totterman S, Tamez J, Dabrowski C, et al. Comparison of radiographic joint space width with magnetic resonance imaging cartilage morphometry: analysis of longitudinal data from the Osteoarthritis Initiative. Arthritis Care Res (Hoboken). 2010; 62:932–7. [PubMed: 20589702]
28. Neumann G, Hunter D, Nevitt M, Chibnik LB, Kwoc K, Chen H, et al. for the Health ABC Study. Location-specific radiographic joint space width for osteoarthritis progression. Osteoarthritis Cartilage. 2009; 17:761–5. [PubMed: 19073368]
29. Moyer R, Wirth W, Eckstein F. Sensitivity of different measures of frontal plane alignment to medial and lateral joint space narrowing: from the osteoarthritis initiative. Semin Arthritis Rheum. 2015; 45:268–74. [PubMed: 26250956]
30. Moyer R, Wirth W, Duryea J, Eckstein F. Anatomical alignment, but not goniometry, predicts femorotibial cartilage loss as well as mechanical alignment: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage. 2016; 24:254–61. [PubMed: 26382108]
31. Wirth W, Nevitt M, Hellio Le Graverand MP, Benichou O, Dreher D, Davies RY, et al. Sensitivity to change of cartilage morphometry using coronal FLASH, sagittal DESS, and coronal MPR DESS protocols: comparative data from the Osteoarthritis Initiative (OAI). Osteoarthritis Cartilage. 2010; 18:547–54. [PubMed: 20060948]
32. Eckstein F, Ateshian G, Burgkart R, Burstein D, Cicuttini F, Dardzinski B, et al. Proposal for a nomenclature for magnetic resonance imaging based measures of articular cartilage in osteoarthritis. Osteoarthritis Cartilage. 2006; 14:974–83. [PubMed: 16730462]
33. Bruynesteyn K, Boers M, Kostense P, van der Leeuwen S, van der Heijde D. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. Ann Rheum Dis. 2005; 64:179–82. [PubMed: 15286006]
34. Kleinbaum, DG., Kupper, L., Muller, KE. Applied regression analysis and other multivariable methods. 2nd. Boston: PWS-Kent Publishing Company; 1988. p. 718
35. World Health Organization. Obesity: preventing and managing the global epidemic. Geneva: World Health Organization; 2000. Report of a WHO Consultation. WHO Technical Report Series 894
36. Sharma L, Eckstein F, Song J, Guermazi A, Prasad P, Kapoor D, et al. Relationship of meniscal damage, meniscal extrusion, malalignment, and joint laxity to subsequent cartilage loss in osteoarthritis knees. Arthritis Rheum. 2008; 58:1716–26. [PubMed: 18512777]
37. Moisio K, Chang A, Eckstein F, Chmiel JS, Wirth W, Almagor O, et al. Varus–valgus alignment: reduced risk of subsequent cartilage loss in the less loaded compartment. Arthritis Rheum. 2011; 63:1002–9. [PubMed: 21225680]
38. Eckstein F, Collins JE, Nevitt MC, Lynch JA, Kraus VB, Katz JN, et al. Cartilage thickness change as an imaging biomarker of knee osteoarthritis progression: data from the Foundation for the

National Institutes of Health Osteoarthritis Biomarkers Consortium. Arthritis Rheumatol. 2015; 67:3184–9. [PubMed: 26316262]

39. Eckstein F, Kwoh CK, Boudreau RM, Wang Z, Hannon MJ, Cotofana S, et al. Quantitative MRI measures of cartilage predict knee replacement: a case–control study from the Osteoarthritis Initiative. Ann Rheum Dis. 2013; 72:707–14. [PubMed: 22730370]
40. Eckstein F, Guermazi A, Gold G, Duryea J, Le Graverand MP, Wirth W, et al. Imaging of cartilage and bone: promises and pitfalls in clinical trials of osteoarthritis. Osteoarthritis Cartilage. 2014; 22:1516–32. [PubMed: 25278061]
41. Messier SP, Gutekunst DJ, Davis C, DeVita P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. Arthritis Rheum. 2005; 52:2026–32. [PubMed: 15986358]
42. Messier SP, Pater M, Beavers DP, Legault C, Loeser RF, Hunter DJ, et al. Influences of alignment and obesity on knee joint loading in osteoarthritis gait. Osteoarthritis Cartilage. 2014; 22:912–7. [PubMed: 24857973]
43. Hunter DJ, Zhang Y, Niu J, Tu X, Amin S, Goggins J, et al. Structural factors associated with malalignment in knee osteoarthritis: the Boston osteoarthritis knee study. J Rheumatol. 2005; 32:2192–9. [PubMed: 16265702]

Significance & Innovations

- This is the first study to use magnetic resonance imaging–based quantitative measures of cartilage thickness to investigate the interaction between malalignment and obesity on knee osteoarthritis (OA) progression.
- Malalignment is a stronger risk factor for structural OA progression than obesity.
- The association between alignment and cartilage thickness loss was not moderated by body mass index.
- Malalignment moderates the association between obesity and cartilage thickness loss, and this relationship may differ between knees with varus and valgus malalignment.

Table 1

Demographics and clinical characteristics (n = 558)*

	Varus			Valgus	
	Definite (n=127)	**Minor (n=111)**	**Neutral (n=238)**	**Minor (n=43)**	**Definite (n=39)**
Normal BMI					
Age, years	60 ± 8	63 ± 11	61 ± 9	64 ± 11	69 ± 8
Male, no. (%)	11 (79)	8 (62)	3 (9)	2 (20)	1 (20)
BMI, kg/m^2†	23.3 ± 0.9	23.0 ± 1.6	22.6 ± 1.7	22.9 ± 1.6	23.2 ± 0.7
K/L grade 2, no. (%)	4 (29)	7 (54)	24 (73)	4 (40)	1 (20)
K/L grade 3, no. (%)	10 (71)	5 (39)	8 (24)	6 (60)	4 (80)
K/L grade 4, no. (%)	0 (0)	1 (7)	1 (3)	0 (0)	0 (0)
Unadjusted FTA	−8.5 ± 0.8	−6.9 ± 0.9	−4.7 ± 1.4	−1.8 ± 0.8	1.0 ± 1.6
Adjusted FTA‡	−4.5 ± 0.7	−2.8 ± 0.4	−2.7 ± 0.4	2.6 ± 0.5	5.4 ± 1.8
Overweight					
Age, years	61 ± 10	64 ± 9	61 ± 9	63 ± 10	66 ± 9
Male, no. (%)	45 (78)	26 (58)	37 (42)	6 (67)	3 (20)
BMI, kg/m^2†	26.7 ± 2.1	26.8 ± 2.5	26.2 ± 2.7	24.7± 2.4	26.3 ± 2.2
K/L grade 2, no. (%)	16 (28)	16 (36)	58 (65)	1 (11)	6 (40)
K/L grade 3, no. (%)	41 (70)	29 (64)	31 (35)	8 (89)	9 (60)
K/L grade 4, no. (%)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Unadjusted FTA	−8.7 ± 1.2	−6.8 ± 0.8	−4.6 ± 1.4	−1.4 ± 0.9	0.3 ± 1.5
Adjusted FTA‡	−4.7 ± 1.0	−2.7 ± 0.4	−0.2 ± 1.1	2.6 ± 0.5	4.7 ± 1.3
Obese					
Age, years	58 ± 9	61 ± 8	60 ± 8	59 ± 6	65 ± 9
Male, no. (%)	35 (28)	26 (26)	26 (12)	2 (5)	3 (8)
BMI, kg/m^2†	33.8 ± 3.1	34.9 ± 3.4	34.4 ± 3.9	34.8 ± 3.5	33.1 ± 3.0
K/L grade 2, no. (%)	6 (11)	24 (44)	87 (72)	15 (62)	1 (5)
K/L grade 3, no. (%)	48 (87)	29 (56)	31 (28)	9 (38)	17 (90)
K/L grade 4, no. (%)	1 (2)	0 (0)	0 (0)	0 (0)	1 (5)
Unadjusted FTA	−9.3 ± 1.4	−6.9 ± 0.9	−4.9 ± 1.3	−2.2 ± 0.8	0.7 ± 1.8

	Varus			Valgus	
	Definite (n=127)	Minor (n=111)	Neutral (n=238)	Minor (n=43)	Definite (n=39)
Adjusted FTA[‡]	−5.1 ± 1.5	−2.7 ± 0.4	−0.4 ± 1.1	2.5 ± 0.4	5.2 ± 1.5

[*] Values are the mean ± SD unless otherwise indicated. BMI = body mass index; K/L = Kellgren/Lawrence; FTA = femorotibial angle.

[†] BMI values are significantly different between groups, within each FTA category ($P < 0.05$).

[‡] FTA values are significantly different between groups, within each BMI category ($P < 0.05$).

Table 2

Mean ± SD changes in cartilage thickness (μm) for all knees, and for subgroups of knees based on FTA and BMI categories, with negative values representing cartilage thickness loss*

		Varus/Valgus		Varus		Valgus	
	Neutral	**Minor**	**Definite**	**Minor**	**Definite**	**Minor**	**Definite**
cMFTC							
Normal	−42 ± 123	−43 ± 141	−32 ± 89	−62 ± 176	−48 ± 96	1.6 ± 50	12 ± 63
Overweight	−53 ± 103	−111 ± 170	−120 ± 190	−129 ± 173	−150 ± 197	−12 ± 134	−4 ± 94
Obese	−62 ± 158	−117 ± 202	−133 ± 192	−168 ± 216	−170 ± 200	−9 ± 106	−28 ± 122
cLFTC							
Normal	−43 ± 93	−75 ± 135	−66 ± 135	−43 ± 116	−24 ± 104	−116 ± 152	−183 ± 153
Overweight	−64 ± 143	−39 ± 101	−61 ± 131	−33 ± 94	−27 ± 78	−68 ± 133	−193 ± 199
Obese	−38 ± 127	−72 ± 166	−59 ± 143	−26 ± 91	−13 ± 94	−175 ± 237	−195 ± 175

*BMI categories defined as normal <25 kg/m^2, overweight 25–30 kg/m^2, and obese >30 kg/m^2. FTA = femorotibial angle; BMI = body mass index; cMFTC = central weight-bearing medial femorotibial compartment; cLFTC = central weight-bearing lateral femorotibial compartment.

Table 3

Regression coefficients for FTA and the proportion of variance in each model for cMFTC and cLFTC for BMI tertiles*

	Model R^2, %	β (95% CI)	*P*
cMFTC			
Normal	22.2	14.3 (14.4, 24.3)	0.005
Overweight	19.8	13.3 (6.2, 20.5)	< 0.001
Obese	17.5	14.4 (7.0, 22.0)	< 0.001
cLFTC			
Normal	19.8	−15.4 (−25.0, −5.8)	0.002
Overweight	11.7	−16.1 (−22.3, −9.8)	<0.001
Obese	13.9	−18.9 (−24.9, −12.9)	< 0.001

*Positive beta coefficients indicate cartilage thinning per unit increase toward varus. Negative beta coefficients indicate cartilage thinning per unit increase toward valgus. FTA = femorotibial angle; cMFTC = central weight-bearing medial femorotibial compartment; cLFTC = central weight-bearing lateral femorotibial compartment; BMI = body mass index; 95% CI = 95% confidence interval.

Table 4

Regression coefficients for BMI and the proportion of variance in each model for cMFTC and cLFTC for tertiles and quintiles of FTA*

	Model R^2, %	β (95% CI)	*P*
FTA tertiles			
cMFTC			
Neutral (± 0–2°)	9.1	−1.6 (−4.8, 1.6)	0.314
Minor malalignment (± 2–3.5°)	13.3	−7.7 (−13.2, −2.2)	0.006
Definite malalignment (± ≥3.5°)	14.2	−4.6 (−10.9, 1.7)	0.149
cLFTC			
Neutral (± 0–2°)	9.8	1.3 (−1.7, 4.3)	0.398
Minor malalignment (± 2–3.5°)	1.0	−2.2 (−6.6, 2.3)	0.345
Definite malalignment (± ≥3.5°)	9.6	1.7 (−3.1, 6.5)	0.486
FTA quintiles			
cMFTC			
Definite varus (≤ −3.5°)	13.6	−3.6 (−11.2, 4.0)	0.352
Minor varus (−3.5 to −2°)	16.2	−8.4 (−15.5, −1.3)	0.021
Neutral (± 0–2°)	9.1	−1.6 (−4.8, 1.5)	0.314
cLFTC			
Definite valgus (≥3.5°)	12.6	2.6 (−11.1, 16.3)	0.706
Minor valgus (2–3.5°)	6.4	−6.1 (−17.9, 5.6)	0.295
Neutral (± 0–2°)	9.8	1.3 (−1.7, 4.3)	0.398

*Negative beta coefficients indicate cartilage thinning per unit increase in BMI. Positive beta coefficients indicate cartilage thickening per unit increase in BMI. BMI = body mass index; cMFTC = central weight-bearing medial femorotibial compartment; cLFTC = central weight-bearing lateral femorotibial compartment; FTA = femorotibial angle; 95% CI = 95% confidence interval.