

1 **Variations in hip shape are associated with radiographic knee osteoarthritis: cross-sectional and**
2 **longitudinal analyses of the Johnston County Osteoarthritis Project**

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5 **Objective:** Hip shape by statistical shape modeling (SSM) is associated with hip radiographic OA (rOA);
6 we examined associations between hip shape and knee rOA given the biomechanical inter-relationships
7 between these joints.

8 **Methods:** Bilateral baseline hip shape assessments (for those with at least 1 hip with Kellgren-Lawrence
9 grade [KLG] 0 or 1) from the Johnston County Osteoarthritis Project were available. Proximal femur
10 shape was defined on baseline pelvis radiographs and evaluated by SSM, producing mean shape and
11 continuous variables representing independent modes of variation (14 modes=95% of shape variance).
12 Outcomes included prevalent (baseline KLG ≥ 2 or total knee replacement [TKR]), incident (baseline KLG
13 0/1 with follow-up ≥ 2), and progressive (KLG increase of ≥ 1 or TKR) knee rOA. Limb-based logistic
14 regression models for ipsilateral and contralateral comparisons were adjusted for age, sex, race, body
15 mass index (BMI), and hip rOA, accounting for intra-person correlations.

16 **Results:** We evaluated 681 hips and 682 knees from 342 individuals (61% women, 82% white, mean age
17 62 years, BMI 29 kg/m²). Ninety-nine knees (15%) had prevalent rOA (4 knees with TKR). Lower mode 2
18 and 3 scores were associated with ipsilateral prevalent knee rOA; only lower mode 3 scores were
19 associated with contralateral prevalent knee rOA. No statistically significant associations were seen for
20 incident or progressive knee rOA.

21 **Conclusions:** Variations in hip shape were associated with prevalent, but not incident or progressive,
22 knee rOA in this cohort, and may reflect biomechanical differences between limbs, genetic influences, or
23 common factors related to both hip shape and knee rOA.

24 MeSH Keywords: Hip joint, knee osteoarthritis, radiography

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40 **Role of funding source**

41 Funding was provided in part by: NIAMS K23 AR061406 (Nelson); NIH/NIAMS P60AR30701

42 (Jordan/Renner/Schwartz); CDC/ASPH S043 and S3486 (Jordan/Renner); K24-AR04884, P50-AR063043,

43 and P50-AR060752 (Lane); NIH/NCATS KL2TR001109 (Golightly)

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50 Running title: Hip shape & knee OA

51 **Background**

52 Statistical shape modeling (SSM) methods have been used by several groups, including ours, to describe
53 the variability in hip shape in populations. Hip shape by SSM has been found to be a radiographic
54 biomarker for development of osteoarthritis (OA) at the hip, defined as structural disease (radiographic
55 OA [rOA]), clinical/symptomatic OA (rOA with OA symptoms), and/or total hip replacement (1-6).
56 Specifically, our group has found associations between variations in modes 2 (reflecting changes in the
57 width of the femoral neck and size of the trochanters) and 3 (variations in femoral neck length and the
58 width of the greater trochanter) and incident symptomatic hip OA (6).

59 The hip and knee are biomechanically interconnected as part of the kinetic chain, and OA at one of
60 these large joint sites increases risk at the other sites in a non-random fashion. As shown by Shakoor et
61 al (7), in patients requiring a knee replacement after an initial hip replacement, this procedure was much
62 more likely to be done at the contralateral knee and, similarly, for those undergoing initial knee
63 replacement, a subsequent hip replacement was more likely on the contralateral side. Individuals with
64 OA in one of these 4 large joints (right or left, hip or knee) have 40-80% greater odds of having OA in
65 another joint, although the greatest odds were for OA in the contralateral cognate joint (e.g. if the right
66 knee was affected, the odds of left knee OA were dramatically increased)(8). In addition, individuals with
67 developmental dysplasia of the hip are more likely to undergo not only hip but also knee replacement
68 compared with controls (9). Patients with moderate to severe knee OA, compared with controls, also
69 demonstrate differences in biomechanical assessments, not only at the knee, but also at the hip and
70 ankle, including decreased adduction and extension moments at the hip and dorsiflexion moments at
71 the ankle (10). Although the specific biomechanical consequences of variations in joint shape are not yet
72 known, given the above evidence for the inter-relationship between the hip and knee joints, in the
73 current study we sought to assess potential structural associations between hip shape, described

74 quantitatively using modes of variation, and prevalent, incident, and progressive knee rOA in the
75 Johnston County OA Project (JoCo OA).

76 **Methods**

77 **Study sample.** Data were from the JoCo OA baseline and first follow-up visit (mean follow-up time 6
78 years [range 4-11 years]); details of the parent project have been described elsewhere (11). The JoCo
79 OA has been continuously approved by the Institutional Review Boards of the University of North
80 Carolina at Chapel Hill and the Centers for Disease Control and Prevention, and all participants
81 completed informed consent. The baseline time point hip shapes used in this analysis were obtained as
82 part of a prior analysis of hip shape and incident symptomatic and radiographic hip OA (6). In brief, of
83 the 1726 individuals with paired radiographic data (anteroposterior [AP] supine pelvis films with the feet
84 in 15 degrees of internal rotation, read blinded to clinical status and chronological order) from both
85 baseline and follow-up time points, 193 hips developed incident rOA, defined as a Kellgren Lawrence
86 grade (KLG) of 0 or 1 at baseline and 2 or more at follow-up. All of these were selected, along with
87 randomly selected control hips (KLG 0 or 1 at both time points) in approximately equal numbers from 4
88 race-by-gender strata (men, women, African American, and white) for a total of 342 individuals.

89 Unlike the previous analysis, which focused on case/control status at the hip (6), for the current analysis
90 baseline hip shape from all hips from all participants (both cases and controls) with suitable radiographs
91 (n=681 hips, Figure 1) were included, such that a small number (77 hips, or 11% of the hips) had
92 evidence of prevalent radiographic hip OA (KLG \geq 2) at baseline (these hips were excluded from the prior
93 study).

94 **Hip Shape Assessment.** A 60-point model of proximal femur shape (2, 6) was defined on the baseline AP
95 pelvis radiographs and evaluated by SSM. Principal components analysis was performed on these 60
96 points; the first fourteen principal components were retained, explaining 95% of the shape variance.

97 These in turn correspond to 14 independent modes of shape variation, which are treated as 14
98 continuous variables in this analysis. Further details on the derivation of these modes have been
99 published previously (6).

100 **Knee OA Assessment.** Bilateral weight-bearing posteroanterior fixed-flexion knee radiographs were
101 obtained for all participants and were read for rOA by a single examiner (JBR; from prior study, weighted
102 kappa for interrater reliability 0.9; kappa for intrarater reliability 0.9, (12)). Knee rOA outcomes were
103 defined as follows: 1) Prevalent knee rOA was defined as a KLG ≥ 2 or total knee replacement (TKR) for
104 OA at baseline; 2) Incident knee rOA was defined as a KLG ≥ 2 at follow-up in a knee having KLG=0 or 1
105 at baseline; 3) Progressive knee rOA was defined as an increase of at least one KLG or progression to TKR
106 between baseline and follow-up, regardless of baseline KLG (to avoid conditioning on an intermediate
107 (13)), and excluding knees with baseline TKR as they could not progress further by definition.

108 **Statistical Analysis.** The 14 baseline hip shape mode scores were simultaneously included in 4 separate
109 limb-based logistic regression models for ipsilateral and contralateral comparisons of knee outcomes (1:
110 right hip/right knee, 2: left hip/left knee, 3: right hip/left knee, and 4: left hip/right knee), adjusted for
111 age, sex, race, body mass index (BMI), and hip rOA (ipsilateral to the mode score in the model),
112 accounting for intra-person correlations (using the cluster option in Stata (14)).

113 **Results**

114 We evaluated 681 hips and 682 knees from 342 individuals (Figure 1); characteristics are shown in Table
115 1. A total of 77 hips (11%) had prevalent radiographic OA at baseline, and prevalent knee rOA was
116 present in 99 knees (15%) at baseline, of which 53 and 46 were right and left knees, respectively.

117 *Prevalent knee rOA: Ipsilateral Associations*

118 The odds of having prevalent rOA in the right knee were increased by 74% for every 1-SD reduction in
119 mode 2 at the right hip in analyses adjusted for age, sex, race, BMI, and right hip rOA (Table 2). The
120 associations between left hip mode 2 score and prevalent left knee rOA were not statistically significant.
121 In adjusted analyses, for every 1-SD lower score for mode 3 at the right hip, the odds of right knee rOA
122 were increased by 46%; for every 1-SD reduction in mode 3 score at the left hip, the odds of left knee
123 rOA were increased by 50%. As shown in Table 2, there were also statistically significant associations for
124 a 1-SD lower score for modes 8 and 14 at the left hip and prevalent left knee OA, although these modes
125 account for only 2.3% and 0.6% of total shape variance, respectively.

126 *Prevalent knee rOA: Contralateral Associations*

127 For mode 2, none of the contralateral associations between hip shape modes and prevalent knee rOA
128 were statistically significant. However, a 35% increase in the odds of right knee rOA for every 1-SD
129 reduction in mode 2 score at the left hip was noteworthy and approached statistical significance (aOR
130 1.35, 95% CI [0.96, 1.91], Table 2). For every 1-SD reduction in mode 3 score at the left hip, there was a
131 statistically significant 78% increase in the odds of prevalent right knee rOA in adjusted analyses.
132 Associations between mode 3 at the right hip and left knee rOA were not statistically significant.

133 *Incident knee rOA*

134 Of 579 eligible knees (99 had prevalent rOA, 4 lacked follow-up films), 94 (16%) developed incident rOA
135 at follow-up, of which 50 and 44 were right and left knees, respectively. There were no statistically
136 significant associations between modes and incident knee rOA (Table 3). Of potential interest, although
137 not statistically significant, were suggestive associations between right hip shape and incident right
138 knee rOA (34% higher odds for every 1-SD lower score on mode 9), and between right hip shape and
139 incident left knee rOA (38% higher odds for every 1-SD reduction in mode 7 score, and 39% higher odds
140 per 1-SD higher score for mode 8, Table 3).

141 *Progressive knee rOA*

142 Of 672 eligible knees (4 had baseline TKR, 6 lacked follow-up films), 219 (33%) met the definition of
143 progressive knee rOA, of which 118 and 101 were right and left knees, respectively. There were no
144 significant associations between modes and progressive knee rOA (Table 4). Associations approaching
145 statistical significance, though not formally so, were seen in adjusted analyses between right hip shape
146 and progressive right knee rOA (28% higher odds for every 1-SD reduction in mode 9 score) and
147 between right hip shape and progressive left knee rOA (23% lower odds for every 1-SD lower mode 11
148 score, Table 4).

149 **Discussion**

150 Variations in the shape of the hip (particularly modes 2 and 3) were related to the baseline prevalence
151 of knee rOA in this cohort, although the relationships varied among ipsilateral and contralateral joint
152 pairings. Our findings for the ipsilateral hip shape-knee rOA association are supported by a study of the
153 Osteoarthritis Initiative cohort that reported an association between prevalent knee OA (lateral and
154 medial compartments) with ipsilateral proximal femur shapes (15). In our study, Mode 2 reflects
155 differences in the width of the femoral neck and size of the trochanters, while mode 3 is suggestive of
156 variation in the width of the greater trochanter and femoral neck length (6). Our prior work shows
157 associations between modes 2 and 3 (explaining 16% and 13% of total shape variance respectively,
158 shown in Figure 2 as mean shape \pm 2SD for illustrative purposes) with incident symptomatic hip OA.
159 There was a likely, yet not statistically significant, relationship between mode 9 at the right hip and both
160 incident and progressive right knee rOA that was not seen with other joint combinations. Associations
161 with modes 7, 8, and 11 were inconsistent, and these modes explained little of the total shape variance.
162 Therefore, this analysis suggests that radiographic hip shape by SSM represents a modest, independent
163 risk factor for prevalent knee rOA.

164 This study is unique in that it considers the impact of hip shape on OA at joints other than the hip in a
165 community-based cohort of African American and White men and women. The question then is, how to
166 explain this association? Arguably the most obvious mechanism is biomechanical; the shape of the hip,
167 whether assessed using SSM or geometric measures, may influence loading and forces generated at the
168 knee and in the rest of the lower extremity kinetic chain (i.e. lumbar spine, ankle, foot), although a
169 mechanism has yet to be elucidated given the complexity of the needed analyses. Alternatively, there
170 may be common factors underlying both the shape of the hip and the development of knee OA, such as
171 genetics or lifestyle factors, that may explain their relationship. A necessary part of future research will
172 be to examine biomechanics, genetics, and other potentially shared risk factors for these conditions.

173 The associations between hip shape and knee rOA varied between ipsilateral and contralateral
174 relationships. Consistent with prior research (16-18), we found a higher frequency of knee rOA on the
175 right versus the left side. Kopec et al reported moderate associations between prevalent hip and knee
176 rOA but these did not vary by side (18). Shakoore et al, in addition to demonstrating nonrandom
177 distribution of joint replacement (7), also found higher joint loads in contralateral knees of patients
178 undergoing unilateral hip replacement, even after surgery (19). Overall, in the current analysis,
179 ipsilateral associations between hip shape and knee rOA were stronger than contralateral ones; that the
180 strongest associations identified were those between right hip shape variation and right sided prevalent
181 knee rOA may be consistent with greater right leg dominance in the participants. These findings may
182 reflect biomechanical differences between limbs, but the present study lacked comprehensive
183 biomechanical assessments to test this hypothesis.

184 Unlike prevalent knee rOA, we did not see any associations reach statistical significance between hip
185 shape and incident and progressive knee rOA. This may be in part due to the older age of our cohort,
186 since variation in hip shape is likely primarily genetically determined, and is present throughout life in

187 the absence of pathologic changes (such as those that occur with OA). Therefore, variation in hip shape
188 may primarily be a risk factor for early onset or rapidly progressive knee rOA, and may not be associated
189 with later incident or progressive disease in this population, though it would still be associated with
190 prevalent disease. Alternatively, 6 years of follow-up may be insufficient to allow incident and
191 progressive knee outcomes to develop. Additionally, although our study design was longitudinal, we
192 were not able to conclusively evaluate the causal relationship; it is conceivable that hip joint shape may
193 lead to altered knee joint mechanics and therefore to a greater risk of knee OA, or equally reasonably,
194 that knee OA could result in remodeling at the hip altering its shape, or potentially even a combination
195 of these. A next step in this research is to examine the clinically relevant association of hip shape with
196 symptomatic knee OA.

197 This study has several strengths, including the assessment of multiple joints on participants in this well-
198 characterized cohort, the ability to conduct longitudinal analyses, and the standardized radiographs read
199 with high reliability for KLG and for hip shape. The limitations of this work include the relatively small
200 sample size precluding sub-group analyses (such as stratification by sex or race), the use of a single
201 cohort which may limit generalizability, and the lack of long-limb radiographs for assessment of
202 alignment.

203 **Conclusions**

204 Radiographic hip shape is a modest risk factor for prevalent knee rOA independent of age, sex, race,
205 body mass index, and baseline hip rOA. Future studies should examine the role of biomechanical factors
206 in this relationship, as well as assessment of multiple lower-body joint OA over a longer follow-up time.

207 **List of Abbreviations**

208 BMI: body mass index

209 JoCo OA: Johnston County Osteoarthritis Project

210 KLG: Kellgren-Lawrence grade

211 OA: osteoarthritis

212 rOA: radiographic osteoarthritis

213 SSM: Statistical shape modeling

214 TKR: total knee replacement

215 **Competing interests**

216 The authors report no competing interests in relation to this work.

217 **Acknowledgments**

218 We would like to thank our funding sources, as well as the staff and participants in the Johnston County
219 Osteoarthritis Project, without whom this work would not be possible.

220

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277 **Figure 1. Flowchart of included participants and joints.**

278

279 **Figure 2. Hip shape modes associated with prevalent radiographic knee OA (mean: black solid lines;**

280 **+2SD: dark dashed lines; -2SD: light dashed lines). Figure based on the same data as figure 2 in**

281 **reference (6); a lower mode score (similar to -2SD line) was associated with incident symptomatic hip**

282 **OA in reference (6).**