Association between Obesity, Race and Knee Osteoarthritis: The Multicenter Osteoarthritis Study

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Abstract: On the basis of longitudinal Kellgren-Lawrence (KL) grades of knee radiographs obtained from the Multicenter Osteoarthritis Study (MOST), we examine the association of obesity and race with severity of knee osteoarthritis (OA). We use the proportional odds model with mixed effects to conduct the analysis. Repeated KL grades were modeled as ordinal longitudinal measures, and a random effect term was included to adjust for the within-subject correlation among the KL grades over time. We found that African Americans and more obese participants in MOST have a greater risk of developing severe knee OA.

Keywords: Body mass index, Cumulative logits, Kellgren-Lawrence (KL) grade, Knee radiograph, Longitudinal ordinal data, Mixed effects model, Proportional odds model, Risk factors.

INTRODUCTION

Arthritis and rheumatic diseases impact an estimated 46 million individuals in the United States. The grouping includes more than 100 disorders that may affect the joints, tendons, ligaments, bones, and muscles. Some examples include osteoarthritis (OA), rheumatoid arthritis, fibromyalgia, systemic lupus erythematous, gout, psoriatic arthritis, and tendinitis [1]. Osteoarthritis is the most common form of arthritis and contributes greatly to activity limitation and physical disability in the older population. Among US adults, nearly 27 million suffered from OA in 2005 [2]. Globally, OA is identified as one of the ten most disabling diseases in developed countries, and symptomatic OA has been reported in almost 10 percent of men and 20 percent of women aged 60 years and above. Although there is a high prevalence, limited knowledge of the risk factors for the progression of OA is evidenced by the current lack of effective treatments [3].

While OA can occur in almost any peripheral joint, knee OA is the most prevalent symptomatic site and affects more than 10 million Americans [4]. There are several acknowledged risk factors for incident knee OA. The sociodemographic characteristics of age, gender, and race, are often cited in association with developing OA. Aging is a widely accepted risk factor as demonstrated by an increased prevalence of OA beginning at age 45 [5]. It is generally viewed that women develop more knee OA as they age and at a greater rate than men. The predicted lifetime risks for developing symptomatic knee OA are 40% and 47% for men and women, respectively [6]. The biologic basis for gender differences in OA is not fully understood, but it may be attributed to hormonal and biological factors [7]. Prevalence of OA also varies between ethnic groups as knee OA is more commonly found among African Americans and Chinese compared to whites [6].

Obesity is another important factor that is strongly associated with the development of OA. It is estimated that individuals who are obese (BMI ranging from 30 to 34.9 kg/m^2) and very obese (≥ 35 kg/m^2) are at a higher risk for incident knee OA compared to individuals with a normal BMI (< 25 kg/m^2) (Relative Risk (RR)=2.4 with a 95% Confidence Interval (CI): 1.3 – 4.3 and RR=3.2 with a 95% CI: 1.7 – 5.9, respectively); however, there are inconsistent data regarding the association between obesity and the progression of knee OA [8]. Nonetheless, these results are alarming. Taking into consideration the aging US population with increased life expectancy and the current rise in obesity, OA is estimated to affect 67 million Americans aged 18 years or older [9].

Blagojevic *et al.* conducted a systematic review and meta-analysis on additional risk factors for onset of knee OA in older adults [10]. Prior knee injury was reported as the most important risk factor in most studies (14 out of 16). Other risk factors that have been investigated in OA studies include occupational activities, physical activity/exercise, oestrogen use, oral contraceptives, higher bone mineral density (BMD), hysterectomy, and hypertension [10].

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E-ISSN: 1929-6029/14

The objective of this study is to examine how obesity and race are associated with knee OA severity as quantified by ordinal measures of Kellgren-Lawrence (KL) grade using longitudinal data from the Multicenter Osteoarthritis Study (MOST). Analysis of longitudinal ordinal data is a non-trivial matter. We use the cumulative logits based proportional odds model with mixed effects to conduct the analysis [11]. The outcome variable is the repeated KL grade in ordinal measure, and we use a random effect term to adjust for the within-subject correlation among the ordinal KL grades over time.

DATA AND METHODS

Participants

The Multicenter Osteoarthritis Study (MOST) is a longitudinal, prospective, observational study funded by the National Institute on Aging (NIA) to further osteoarthritis (OA) research in older Americans. The main objective of MOST was to identify possible risk factors (e.g., biomechanical, bone and joint structural and nutritional factors) that may affect the occurrence and progression of radiographic and symptomatic knee OA. MOST enrolled a community-based sample of men and women, aged 50 to 79, who had preexisting OA or were at high risk as indicated by weight, knee symptoms, or a history of knee injuries or operations. Study participants were followed-up five times at 15, 30, 60, 72, and 84 months after baseline. Baseline measurements were conducted at one of two clinical centers (University of Alabama at Birmingham and University of Iowa) along with administration of questionnaires. Follow-up assessments varied with both clinical examinations and telephone interviews. Clinical examinations included knee radiographs, knee imaging, blood and urine specimens, physical performance tests, body composition measurements, knee and hip pain and function, mental health surveys, and evaluations of comorbid conditions [12].

A total of 3,026 participants were recruited for MOST. We excluded 17 participants who had missing values on obesity status, race, age, sex, smoking history, knee injury or unknown Kellgren-Lawrence grades within 60 months since baseline, resulting in a final sample for analysis of 3,009 subjects with up to three follow-up assessments (at 15, 30 and 60 months).

Independent Variables: Obesity Status and Race

The primary independent variable of interest was obesity status which included four categories based on body mass index (BMI): normal (BMI < 25 kg/m^2), overweight (BMI = 25-29.9 kg/m^2), obese (BMI = 30-34.9 kg/m^2), and very obese (BMI ≥ 35 kg/m^2). The other independent variable of interest was race which was categorized into White, Black and other.

Dependent Variable: Kellgren-Lawrence (KL) Grades

Knee OA was assessed and confirmed through radiography. Participants underwent radiological assessment of a bilateral, standing semiflexed posteroanterior view of the tibiofemoral compartments of the knee joint; a unilateral weight-bearing, semiflexed lateral view of the knees; and an x-ray of the full lower limb incorporating the anterior superior iliac crest, hip joint, knee joint, and tibiotalar joint [13]. All films were read by musculoskeletal radiologists. Knee radiographs were graded according to the KL classification scheme for both left and right knees. The severity of OA was considered at five standard levels of KL grade ranging from 0 to 4 [14], which corresponded to tibiofemoral osteoarthritis (TFOA) status (from no TFOA to end stage TFOA). The knee with the higher KL grade (either left or right knee) was selected as the dependent variable. Note that some subjects had a non-standard KL grade of 1.9 indicating a possible incident TFOA. These non-standard cases existed for follow-up visits only. Because of the low frequency of cases with KL grade = 1.9 for either knee (less than 0.01%, 1%, and 2% at 15, 30, and 60 months follow-up, respectively), they were treated as missing and thus excluded from the analytic sample in our regression models.

Statistical Analysis

In addition to descriptive statistics calculated for baseline characteristics of the MOST cohort, we examined the distribution of observed KL grades at each of the assessment times. The association between obesity, race and KL grades was examined using the cumulative logits based proportional odds model with mixed effects, where the KL grades were modeled as ordinal and a random effect term was included to adjust for the within-subject correlation among repeated measures of KL grade over time [11, 15-19]. We included the following covariates as possible confounders in the multivariate regression analyses: KL grade assessment time in years, baseline age in years, gender, smoking history (history of tobacco use, yes/no), and previous knee injury assessed at baseline (whether the participants had ever had an injury to a knee severe enough to limit their ability to walk at least one week).

Let Y_{ij} denote the KL grade and $\mathbf{X}_{ij}$ be a $p\times 1$ vector of covariates for subject i at the j-th assessment time, where $i=1,\cdots,n$ and $j=1,\cdots,4$. The linear predictor of the model is

$g(E(Y_{ij}))=\eta_{ij}=\mathbf{X}_{ij}{}^{T}\boldsymbol{\beta}+u_i$ where $\boldsymbol{\beta}$ is a $p\times 1$ vector of regression coefficients representing the covariate effects on the KL grade and u_i is a random effect which follows a normal distribution with mean zero and variance σ^2. Under the proportional odds model, the odds ratio (OR) of making the KL grade response $\geq k$ at $\mathbf{X}_{ij}$ as compared to $\mathbf{X}_{i^*j}$ can be calculated as

$$\frac{P(Y_{ij}\geq k\mid \mathbf{X}_{ij}) \Big/ P(Y_{ij}< k\mid \mathbf{X}_{ij})}{P(Y_{i^*j}\geq k\mid \mathbf{X}_{i^*j}) \Big/ P(Y_{i^*j}< k\mid \mathbf{X}_{i^*j})}=\exp\left[\left(\mathbf{X}_{i^*j}-\mathbf{X}_{ij}\right)^{T}\boldsymbol{\beta}\right] \quad (1)$$

for any $k=1,2,3,4$ and $i\neq i^*$. An odds ratio of cumulative probabilities in (1) is called a cumulative odds ratio [11, 16]. The derivation of the OR as defined in (1) is described in the Appendix. All analyses including fitting the mixed effects proportional odds models were performed with Stata 13 (StataCorp LP, College Station, TX).

RESULTS

Participant Characteristics

Table **1** shows the baseline characteristics of the MOST participants by obesity status, race, age, gender, smoking history, and previous knee injury. The mean age of the study sample was 62.5 years. Over 80% (n=2,506) of the participants were White. There were 60.1% (n=1,807) females, 46.9% (n=1,412) who reported having a history of tobacco use, and 37.0% (n=1,113) who had a knee injury severe enough to limit their ability to walk at least one week. Among all participants, 14.8% (n=445) had normal weights, 36.1% (n=1,087) were overweight, 29.7% (n=893) were obese, and 19.4% (n=584) were considered to be very obese. For obesity status, smoking history, and previous knee injury, there were significant differences between females and males. A higher proportion of

Table 1: Baseline Sample Characteristics of the MOST Participants

	Total N=3,009	Female n=1,807	Male n=1,202	P-value
Obesity status (n, %)				<0.001[a]
Normal	445 (14.79)	306 (16.93)	139 (11.56)	
Overweight	1,087 (36.12)	600 (33.20)	487 (40.52)	
Obese	893 (29.68)	506 (28.00)	387 (32.20)	
Very obese	584 (19.41)	395 (21.86)	189 (15.72)	
Race (n, %)				0.056[a]
White	2,506 (83.28)	1,491 (82.51)	1,015 (84.44)	
Black	460 (15.29)	295 (16.33)	165 (13.73)	
Other	43 (1.43)	21 (1.16)	22 (1.83)	
Age (median [Q1 – Q3])	62 [55 – 69]	62 [56 – 69]	62 [54 – 69]	0.146[b]
Smoking history (n, %)				<0.001[a]
No	1,597 (53.07)	1,128 (62.42)	469 (39.02)	
Yes	1,412 (46.93)	679 (37.58)	733 (60.98)	
Previous knee injury (n, %)				<0.001[a]
No	1,896 (63.01)	1,248 (69.06)	648 (53.91)	
Yes	1,113 (36.99)	559 (30.94)	554 (46.09)	

[a]Based on the chi-square test.
[b]Based on the Wilcoxon rank-sum test.

Table 2: Distribution of the Observed KL Grade Over Time

	Baseline	Follow-up visits		
		15 months	30 months	60 months
	n=3,009	n=290	n=2,637	n=2,081
KL grade (n, %)				
0	977 (32.47)	79 (27.24)	857 (32.50)	614 (29.51)
1	465 (15.45)	32 (11.03)	322 (12.21)	307 (14.75)
2	555 (18.44)	66 (22.76)	497 (18.85)	424 (20.37)
3	644 (21.40)	74 (25.52)	589 (22.34)	558 (26.81)
4	368 (12.23)	39 (13.45)	372 (14.11)	178 (8.55)

males had a smoking history and previous knee injury compared to females.

KL Grade Distribution

The distribution of the observed KL grades at baseline and three follow-up assessment times is shown in Table **2**.

Findings from Mixed Effects Proportional Odds Models

Table **3** presents the results of the mixed effects proportional odds models that were used to examine the unadjusted and adjusted associations between KL grade and obesity status, race, and other covariates. Factors including obesity status, race, assessment time since baseline, age, and previous knee injury were all significantly associated with KL grades with or without adjusting for other covariates. Those belonging to higher obesity categories were found to have less favorable OA assessment results. Compared to participants with normal weights, the odds of having more severe OA was much higher for those who were overweight (aOR=1.88; 95% CI: 1.35 – 2.63), those who were obese (aOR=4.43; 95% CI: 2.98 – 6.57), and those who were very obese (aOR=17.48; 95% CI: 10.97 – 27.86). For African Americans, the odds of having more severe OA was almost 10 times that for whites (aOR=9.92; 95% CI: 5.20 – 18.91). Therefore, participants who were more obese and African Americans had a greater risk of developing severe OA. Furthermore, the odds of having severe OA was significantly higher for older participants (aOR=1.27; 95% CI: 1.23 – 1.31) and those with previous knee injury (aOR=5.48; 95% CI: 3.46 – 8.68). Overall, the odds of having more severe OA tended to increase over time (aOR=1.29; 95% CI: 1.25 – 1.33) for this MOST cohort. The interaction effect between obesity status and race was no significant (p=0.572) and thus was not included in the multivariate proportional odds model.

DISCUSSION

Overall, African Americans and more obese persons were observed to have a greater risk of developing severe knee OA. Prior studies also support the finding that those with elevated BMI are at a greater risk of having severe knee OA [10, 20]. The Rotterdam Study, a prospective cohort study of men and women aged 55 years and older conducted in the Netherlands, also found that high BMI (> 27.5 kg/m^2 as compared to ≤ 25 kg/m^2) at baseline is associated with incident knee OA as defined by baseline KL grade ≤ 1 and follow-up KL grade ≥ 2 (OR=3.3; 95% CI: 2.1 – 5.3) and with progression of knee OA as defined by a joint space narrowing of at least 1.5 mm at follow-up (OR=3.2; 95% CI: 1.1 – 9.7) [21].

There are other variables that may be associated with knee OA that were not included in this analysis including previous knee surgery and physical activity. Inclusion of these additional variables could have helped to better elucidate the association between obesity status, race and knee OA. A meta-analysis of knee OA related studies found that those with a history of knee surgery and those who exercise more regularly/intensely are at an increased risk of knee OA [10]. As for race, Anderson and Felson examined the factors associated with knee OA in the First National Health and Nutrition Examination Survey (NHANES I) and found black women had an increased risk of knee OA (OR=2.12; 95% CI: 1.39 − 3.23) after controlling for age and weight, although black men did not [22]. On the basis of data from the Johnston County Osteoarthritis Project conducted in North Carolina, Jordan *et al.* reported that African Americans had a slightly higher prevalence of radiographic and

Table 3: Association between KL Grade and Obesity Status, Race, and Other Covariates

	Unadjusted OR[a]		Multivariate-adjusted OR[a,b]	
	OR	95% CI	aOR	95% CI
Obesity status				
Normal	REF		REF	
Overweight	1.83	(1.32, 2.53)	1.88	(1.35, 2.63)
Obese	3.77	(2.57, 5.52)	4.43	(2.98, 6.57)
Very obese	14.39	(9.15, 22.64)	17.48	(10.97, 27.86)
Race				
White	REF		REF	
Black	5.65	(2.89, 11.05)	9.92	(5.20, 18.91)
Other	0.18	(0.04, 0.90)	0.57	(0.11, 2.85)
Time since baseline (in years)	1.31	(1.27, 1.35)	1.29	(1.25, 1.33)
Age (in years)	1.22	(1.18, 1.25)	1.27	(1.23, 1.31)
Gender				
Female	REF		REF	
Male	0.73	(0.46, 1.14)	0.72	(0.46, 1.13)
Smoking history				
No	REF		REF	
Yes	1.05	(0.67, 1.63)	0.86	(0.56, 1.33)
Previous knee injury				
No	REF		REF	
Yes	2.77	(1.74, 4.39)	5.48	(3.46, 8.68)

[a]Odds of having more severe OA (i.e., KL≥4 vs. KL<4; KL≥3 vs. KL<3; KL≥2 vs. KL<2; and KL≥1 vs. KL<1).
[b]Based on the multivariate model with obesity status, race, assessment time, age, gender, smoking history, and previous knee injury.

symptomatic knee OA and a significantly higher prevalence of severe radiographic knee OA as compared to Caucasians [23]. This discrepancy may be due to differences in covariates examined as well as differences in the age range of participants. The NHANES I study and the Johnston County Osteoarthritis Project consisted of study participants aged 35 to 74 years and at least 45 years, respectively; while the MOST study included older participants aged 50 to 79 years.

Our findings from the MOST data also show disproportionate burden of severe knee OA on African Americans. Future studies should investigate tailored prevention and treatment strategies for racial and ethnic subpopulations. The potential public health impact of these suggested tailored interventions to prevent severe knee OA conditions can be substantial.

ACKNOWLEDGEMENT

We thank the Editor and two referees for their helpful comments and suggestions, which greatly improved the paper. This project was supported in part by the University of Maryland Center of Excellence in Health IT Research Seed Grant (He, Lee and Hochberg).

APPENDIX: DERIVATION OF THE OR AS DEFINED IN (1)

The proportional odds model uses all cumulative logits [11, 15, 16]. Under the proportional odds model, the conditional probabilities of the ordered KL grade responses can be written as

$$P(Y_{ij}=0\,|\,\mathbf{X}_{ij})=\frac{1}{1+\exp[-(c+\eta_{ij})]}\ ,$$

$$P(Y_{ij}=1\,|\,\mathbf{X}_{ij})=\frac{1}{1+\exp[-(c+d_1+\eta_{ij})]}-\frac{1}{1+\exp[-(c+\eta_{ij})]}\ ,$$

$$P(Y_{ij}=2\,|\,\mathbf{X}_{ij})=\frac{1}{1+\exp[-(c+d_1+d_2+\eta_{ij})]}-\frac{1}{1+\exp[-(c+d_1+\eta_{ij})]},$$

$$P(Y_{ij}=3\mid \mathbf{X}_{ij})=\frac{1}{1+\exp[-(c+d_1+d_2+d_3+\eta_{ij})]}-\frac{1}{1+\exp[-(c+d_1+d_2+\eta_{ij})]},$$

$$P(Y_{ij}=4\mid \mathbf{X}_{ij})=1-\frac{1}{1+\exp[-(c+d_1+d_2+d_3+\eta_{ij})]},$$

where the cut-points (thresholds) c, $c+d_1$, $c+d_1+d_2$ and $c+d_1+d_2+d_3$ are unknown parameters satisfying the condition $d_1\geq 0$, $d_2\geq 0$, and $d_3\geq 0$. The odds of making the KL grade response $\geq k$ ($k=1,2,3,4$) is given by

$$\frac{P(Y_{ij}\geq 1\mid \mathbf{X}_{ij})}{P(Y_{ij}<1\mid \mathbf{X}_{ij})}=\exp\left[-(\mathrm{c}+\eta_{ij})\right],$$

$$\frac{P(Y_{ij}\geq 2\mid \mathbf{X}_{ij})}{P(Y_{ij}<2\mid \mathbf{X}_{ij})}=\exp\left[-(\mathrm{c}+d_1+\eta_{ij})\right],$$

$$\frac{P(Y_{ij}\geq 3\mid \mathbf{X}_{ij})}{P(Y_{ij}<3\mid \mathbf{X}_{ij})}=\exp\left[-(\mathrm{c}+d_1+d_2+\eta_{ij})\right],$$

and

$$\frac{P(Y_{ij}\geq 4\mid \mathbf{X}_{ij})}{P(Y_{ij}<4\mid \mathbf{X}_{ij})}=\exp\left[-(\mathrm{c}+d_1+d_2+d_3+\eta_{ij})\right].$$

Therefore, the odds ratio (OR) of making the KL grade response $\geq k$ at $\mathbf{X}_{ij}$ as compared to $\mathbf{X}_{i^*j}$ can be calculated as

$$\frac{P(Y_{ij}\geq k\mid \mathbf{X}_{ij})\Big/P(Y_{ij}<k\mid \mathbf{X}_{ij})}{P(Y_{i^*j}\geq k\mid \mathbf{X}_{i^*j})\Big/P(Y_{i^*j}<k\mid \mathbf{X}_{i^*j})}=\exp\left[\left(\mathbf{X}_{i^*j}-\mathbf{X}_{ij}\right)^T\boldsymbol{\beta}\right]$$

for any $k=1,2,3,4$ and $i\neq i^*$.

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Received on 10-06-2014 Accepted on 18-07-2014 Published on 05-08-2014

http://dx.doi.org/10.6000/1929-6029.2014.03.03.2