

RESEARCH ARTICLE

Age but not BMI Predicts Accelerated Progression of KOA: Data from the Osteoarthritis Initiative

Kyle D. Wallace, MPH¹; Ramzi W. Nahhas, PhD^{2,3}; Andrew W. Froehle, PhD^{4,5}; Naila Khalil, MBBS, MPH, PhD²

¹Public Health – Dayton & Montgomery County, Epidemiology Department, Dayton, OH

²Wright State University Boonshoft School of Medicine, Department of Population and Public Health Sciences, Dayton, OH

³Wright State University Boonshoft School of Medicine, Department of Psychiatry, Dayton, OH

⁴Wright State University College of Education and Human Services, Department of Kinesiology and Health, Dayton, OH

⁵Wright State University Boonshoft School of Medicine, Department of Orthopaedic Surgery, Sports Medicine and Rehabilitation, Dayton, OH

Corresponding Author: Kyle Wallace • 117 S Main St., Dayton, OH 45422 • C (937) 573-9802, W (937) 224-3691 • kwallace@phdmc.org

ABSTRACT

Background/Objectives: Knee osteoarthritis (KOA) accounts for about 35% of the arthritis burden among adults. Most adults with KOA have slowly-progressing, common knee osteoarthritis (CKOA); however, some individuals experience accelerated KOA (AKOA), rapid progression to end-stage disease within 48 months. This study analyzed individuals without radiographic evidence of KOA at baseline to determine which (baseline) characteristics were associated with progression to CKOA and/or AKOA status 48 months later.

Methods Data (n = 1,561) from the Osteoarthritis Initiative (OAI) were utilized. Multinomial logistic regression was employed to determine the magnitude of association between baseline risk factors and 48-month KOA status (AKOA and CKOA, compared to no KOA).

Results Older age (p = 0.032), greater baseline BMI (p < 0.001), female gender (p = 0.009), and greater baseline PASE score (p = 0.036) were significantly associated with CKOA (11.9% of participants) and/or AKOA (3.5% of participants) at 48 months. Age, BMI, and PASE were all more strongly associated with greater risk of AKOA compared to risk of CKOA (Age: OR = 1.59 vs. 0.97; BMI: OR = 1.62 vs. 1.28; PASE: OR = 1.21 vs. 1.08). Of these, only BMI was significantly associated with greater risk of both AKOA and CKOA.

Conclusion Certain factors impact the risk of AKOA and CKOA differently. Age did not increase the risk of CKOA, but among those with CKOA or AKOA, the proportion with AKOA increased with age. Thus, older age at onset is associated with more rapid KOA progression.

Keywords Age; osteoarthritis; accelerated knee osteoarthritis; common knee osteoarthritis

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INTRODUCTION

Osteoarthritis (OA) affects more than 10% of the U.S. (United States) adult population and is the third most significant cause of disability in the U.S.¹ Greater than 35% of adults with OA have knee osteoarthritis (KOA, including common (CKOA) and accelerated KOA (AKOA)), a quite debilitating form of OA.² Typically, CKOA is characterized by slow progression.³ However, recent studies have acknowledged that about 3% to 17% of individuals with KOA rapidly progress from normal knee structure to end-stage KOA within 48 months, classified as AKOA.³

Risk factors distinguishing AKOA from CKOA are not completely understood. However, age, adiposity, and female gender may play a role. Older age is identified as a key risk factor for KOA in general.⁵ The symptoms of KOA include pain, swelling, and stiffness, and among the elderly, KOA is the most significant cause of pain and disability.⁶ Other symptoms such as functional impairments and reduced quality of life, concomitant with pain, are also evident.⁷ KOA symptoms are exacerbated by obesity. Moreover, obesity can accelerate disability and reduce physical activity levels, especially in those with KOA.⁸ Many studies have demonstrated that obesity negatively affects gait speed in individuals with KOA, as measured by the 20-meter walk test.^{7,8,9} These same studies reported similar findings of limited function when measured using a standard repeated chair stand test.

The purpose of this study was to assess baseline differences among individuals being longitudinally followed for different

types of KOA (no KOA, CKOA, AKOA) regarding socio-demographic characteristics (age, ethnicity, gender, income, and education), BMI, physical performance and pain measures, and to determine which baseline characteristics predicted an individual's KOA status (no KOA, CKOA, or AKOA) 48 months later. We hypothesize that there will be a stronger association between AKOA development and older age, female gender, and elevated BMI when compared to no KOA and CKOA.

METHODS

Data for this analysis were obtained from the publicly available Osteoarthritis Initiative (OAI) database, accessible online (<http://www.oai.ucsf.edu/>). From the database release version 23 the following specific datasets were used: the baseline clinical dataset (0.2.2) and the 48-month clinical dataset (6.2.2).

Setting:

The OAI is a multicenter prospective cohort study of older adults (ages 45 to 79 years) who had existing OA or were at risk of developing OA (n = 4,796). Four clinical sites for this study were Baltimore, Maryland; Pawtucket, Rhode Island; Pittsburgh, Pennsylvania; and Columbus, Ohio. Data collection began in 2004 and participant enrollment was completed in 2006; follow-up visits have been conducted every 12 months since. Institutional review boards at each OAI clinical site and coordinating center approved the study, and all participants provided informed consent.

Design:

The current study employed a prospective cohort design utilizing information from radiographic assessments of KOA to track the disease process and to determine risk factors for CKOA and AKOA. Radiographic assessment of knee degeneration was evaluated using Kellgren-Lawrence (KL) scores (grade 0 to 4) at enrollment (baseline) through 48-month follow-up. Baseline and 48-month bilateral knee radiographs with a standard fixed-flexion posterior-anterior (PA) view were taken for both knees of each participant. To assess KOA severity, two independent reviewers assigned KL scores to each knee. When scores were discrepant, an established adjudication process was employed.¹⁰

Participants:

At baseline of the OAI, 4,796 adults aged 45 to 79 years were enrolled. Our study excluded individuals who had radiographic evidence of KOA at baseline. Included in our study were data from individuals (n = 1,561) free of radiographic KOA (KL < 2) at baseline. These participants were categorized into three disease progression groups based on KL score at 48-month follow-up:

- 1) **No KOA:** no change in KL score in either knee
- 2) **CKOA:** KL score increase in at least one knee from zero to one (0 to 1) or one to two (1 to 2)
- 3) **AKOA:** at least one knee progressed to end-stage KOA; KL grade three (3) or four (4)

Measures/Outcomes:

All study related data were obtained from patient self-reports or measurements based on OAI protocol.¹¹ Demographic, medical, social, and ethnic characteristics of subjects were collected using questionnaires. Baseline age was recorded at the initial screening. Gender was reported as male or female at the initial visit. Race was dichotomized as 'White' or 'All Others' (non-White individuals grouped together due to a small number of individuals in any single other racial group). Education was classified as high school or further education versus less than high school. Annual household income was categorized as \$50,000 or more versus less than \$50,000.

Physical activity levels of study participants were evaluated using the Physical Activity Scale for the Elderly (PASE), a questionnaire assessing leisure-time, household, and occupational activities over the last seven days (scored from 0 to 400 or more; a greater score indicates more physical activity).¹² Participants' self-reported pain was assessed using the Western Ontario and McMaster University OA Index for pain (WOMAC), a five-point Likert scale inquiring about knee pain in the last seven days. The pain measure was the sum of five questions, each scored from zero to four [0 to 4] for a total score of zero to twenty [0 to 20], where a greater score indicates more pain, and was a mean score from the right and left knees.¹³

Measurements included BMI, calculated as weight in kilograms divided by the square of height in meters (kg/m²). We analyzed two different physical activity performance measures: 20-meter walk test and repeated chair stand test. The 20-meter walk test was the average speed (m/sec) at which an individual walked a distance of 20 meters. The repeated chair stand test assessed the ability to stand from a seated position without any aid; measured in the number of stands/sec over a 30-second period.

Statistical Analysis:

Analyses were performed using Statistical Package for the Social Science (SPSS, Version 23.0) and R version 3.3.1.¹⁴ The significance cutoff for hypothesis tests was $\alpha = 0.05$ (two-tailed). The baseline characteristics of study participants by their KOA status at 48 months were compared. Measures of centrality and dispersion included mean and standard deviation for normally distrib-

uted continuous variables and median and interquartile range for non-normally distributed continuous variables. Categorical variables were examined via frequency distributions. For continuous variables, baseline differences between groups (no KOA, CKOA, and AKOA) were tested using Analysis of Variance (ANOVA). When groups had very serious non-normality or very different group variances (determined by Levene's Test for Equality of Variances), the Kruskal-Wallis test (non-parametric alternative to ANOVA) was used. Baseline differences between groups for categorical variables were tested using the chi-square (X^2) test.

Multinomial logistic regression (R software package `nnet`)¹⁵ was used to determine the magnitude of association between baseline risk factors and 48-month KOA status (AKOA and CKOA, compared to no KOA). Each continuous variable was divided by a factor to make odds ratios (OR) more interpretable. Reported ORs correspond to a 10-year difference in age, a five kg/m² difference in BMI, a 50-unit difference in PASE, a 0.25 m/sec difference in 20-meter walk test, 0.25 stands/sec difference in repeated chair stand test, and a 4-unit difference in WOMAC scores. These selected factors did not alter significance of statistical tests and were chosen as values that represent meaningful differences in risk factors.

All risk factors were included in the regression model simultaneously, and missing data was handled using multiple imputation (MI) via the `aregImpute` function in the `Hmisc` package in R.¹⁶⁻²¹ MI assumes that missing values of a variable can be predicted from the observed values of that variable and the other risk factors.

RESULTS

Baseline Differences in Risk Factors:

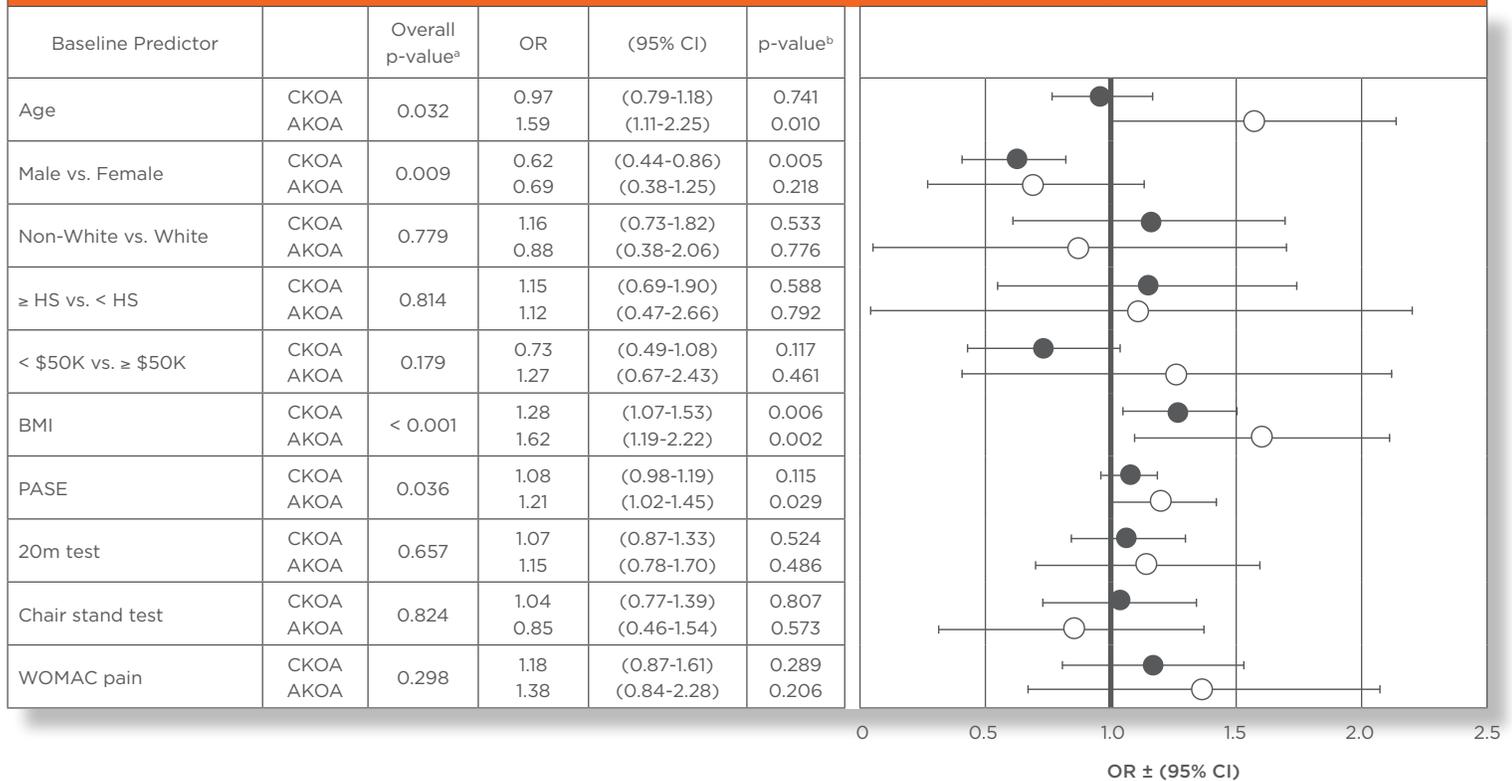
The baseline characteristics of study participants by 48-month KOA status are presented in Table 1. At 48 months, 11.9% and 3.5% of the sample had developed CKOA and AKOA, respectively. Significant group differences were observed in mean age ($p = 0.032$), BMI ($p = 0.001$), and WOMAC pain score ($p = 0.034$). On average, individuals (at 48 months) with AKOA compared to those with CKOA and no KOA were (at baseline) older (63 years vs. 56 years and 58 years, respectively), had a higher BMI (28.89 vs. 27.92 and 27.04, respectively), and reported more pain (1.50 vs. 1.00 and 0.50, respectively). Across increasing severity of 48-month KOA status, an upward trend in BMI was observed. A similar trend was observed in WOMAC pain score; increasing KOA severity was associated with greater pain.

Associations between Baseline Risk Factors and 48-month KOA Status:

Multivariate multinomial logistic regression results are presented in Table 2 and as a forest plot in Figure 1. Age was significantly associated with overall KOA status ($p = 0.032$) (Table 2). However, older age was associated with a significantly greater risk of AKOA only (OR = 1.59, $p = 0.010$; OR near 1 for CKOA vs. no KOA). Also, a significant association between gender and KOA status was observed ($p = 0.009$). Being male was protective against CKOA (OR = 0.62, $p = 0.005$) compared to no KOA; although the OR for males was similar for AKOA (OR = 0.69, $p = 0.218$), the ratio was not significant, possibly due to the smaller sample size of this group. Baseline BMI was significantly associated with 48-month KOA status overall ($p < 0.001$). Higher BMI was associated with a greater risk of CKOA and AKOA compared to no KOA; however, the magnitude of association was stronger for AKOA (OR = 1.62, $p = 0.002$) compared to CKOA (OR = 1.28, $p = 0.006$). PASE score was significantly associated with KOA status overall ($p = 0.036$); however, higher PASE score was associated with a significantly greater risk of AKOA only (OR = 1.21, $p = 0.029$) (OR near 1 for CKOA vs. no KOA). Figure 1 forest plot illustrates the point estimates of the ORs (and 95% confidence intervals) for CKOA and AKOA as compared to no KOA for each predictor.

Table 1. Results from Multivariable Multinomial Logistic Regression					
Baseline Predictor	Overall p-value ^a	KOA Status at 48 Months	OR	(95% CI)	p-value ^b
Age	0.032	No KOAc	1.00	—	—
		CKOA	0.97	(0.79-1.18)	0.741
		AKOA	1.59	(1.11-2.25)	0.010
Male vs. Female	0.009	No KOAc	1.00	—	—
		CKOA	0.62	(0.44-0.86)	0.005
		AKOA	0.69	(0.38-1.25)	0.218
Non-White vs. White	0.779	No KOAc	1.00	—	—
		CKOA	1.16	(0.73-1.82)	0.533
		AKOA	0.88	(0.38-2.06)	0.776
≥ High School vs. < High School	0.814	No KOAc	1.00	—	—
		CKOA	1.15	(0.69-1.90)	0.588
		AKOA	1.12	(0.47-2.66)	0.792
< \$50K vs. ≥ \$50K	0.179	No KOAc	1.00	—	—
		CKOA	0.73	(0.49-1.08)	0.117
		AKOA	1.27	(0.67-2.43)	0.461
BMI	< 0.001	No KOAc	1.00	—	—
		CKOA	1.28	(1.07-1.53)	0.006
		AKOA	1.62	(1.19-2.22)	0.002
PASE	0.036	No KOAc	1.00	—	—
		CKOA	1.08	(0.98-1.19)	0.115
		AKOA	1.21	(1.02-1.45)	0.029
20m test	0.657	No KOAc	1.00	—	—
		CKOA	1.07	(0.87-1.33)	0.524
		AKOA	1.15	(0.78-1.70)	0.486
Chair stand test	0.824	No KOAc	1.00	—	—
		CKOA	1.04	(0.77-1.39)	0.807
		AKOA	0.85	(0.46-1.54)	0.573
WOMAC pain	0.298	No KOAc	1.00	—	—
		CKOA	1.18	(0.87-1.61)	0.289
		AKOA	1.38	(0.84-2.28)	0.206

Figure 1. Results from Multivariable Multinomial Logistic Regression Side-by-Side Results and Forest Plot from Multivariable Multinomial Logistic Regression



Note: ORs for continuous predictors compare odds (risk) of CKOA or AKOA vs. no KOA for a 10-year difference in age, a 5 kg/m² difference in BMI, a 50-unit difference in PASE, a 0.25 m/s difference in the 20m walk test, a 0.25 stands/s difference in the chair stand test, and a 4-unit difference in WOMAC pain scores.

^a Overall p-value for predictor.

^b p-value of OR for each individual KOA status group vs. reference group.

^c No KOA was treated as the reference group in determining CKOA and AKOA ORs.

Figure 2. Estimated Proportions of 48-month KOA Status By Baseline Age and BMI

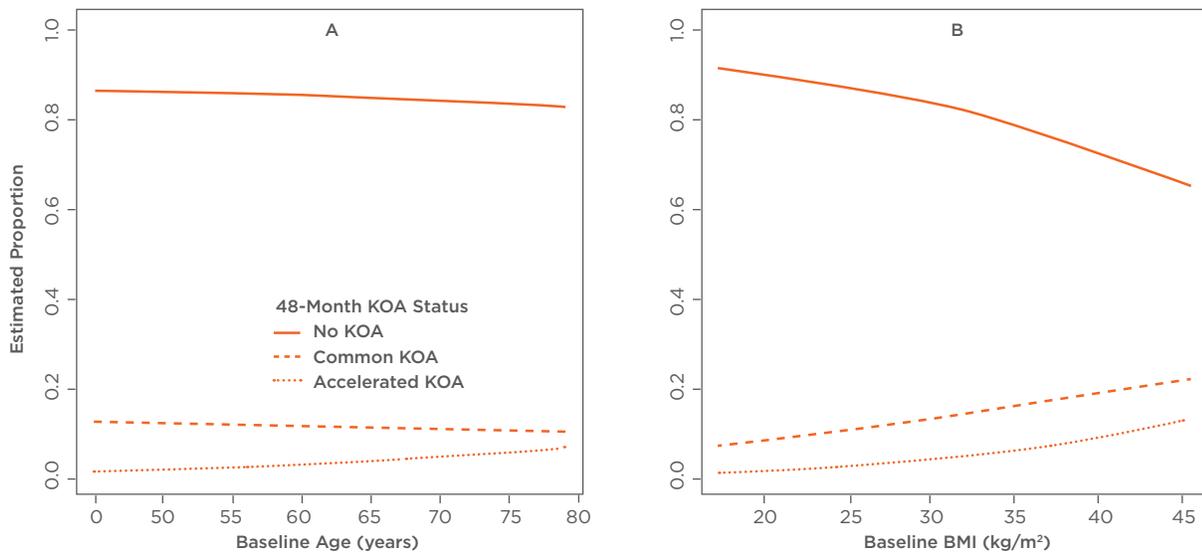


Figure 2 displays the estimated proportions of individuals at each 48-month KOA status vs. baseline age (panel A) and baseline BMI (panel B), holding all other baseline variables fixed at their observed mean values. The figure panels A and B, show that older age and BMI at onset are associated with more rapid AKOA progression.

DISCUSSION

This analysis revealed that, at baseline, individuals who developed AKOA 48 months later tended to be older, and had higher BMI compared to those who developed CKOA and no KOA. At baseline, individuals who developed AKOA 48 months later reported higher levels of pain than those who developed CKOA. These differences in pain that occur before evidence of disease progression may be due to cartilage damage, bone marrow lesions, and/or meniscal pathology – knee abnormalities that are often present within individuals who later develop AKOA.⁴ These results are similar to existing research assessing the differences in KOA symptoms by KOA severity.^{4,22} Our results also suggest that KOA is associated with gender; and that being male was protective against CKOA and AKOA (though not significantly so for the smaller AKOA group). KOA prevalence is higher among women compared to men; it is thought that low estrogen levels among postmenopausal women increase the risk of KOA.²³ Since our cohort of study participants is older (mean age 56, 63 in CKOA, AKOA, respectively), the majority of women are likely post-menopausal, and thus at greater risk of KOA.

Results from our analysis suggest that, prospectively, older age is associated with a greater risk of AKOA, even after controlling for covariates. Age is a known risk factor for KOA, but evidence has shown that individuals who develop AKOA are older than those with CKOA and no KOA.⁵ Our results also depict a trend in baseline BMI that increases with severity of KOA at 48 months. According to our results, individuals with an elevated BMI were at an increased risk of CKOA and AKOA development; however, BMI was a stronger risk factor for AKOA (OR = 1.62) than it was for CKOA (OR = 1.28) showing a dose-response association.

In terms of absolute risk however, age of KOA onset appears to be critical in predicting disease progression. With older baseline age, the proportion of people with AKOA at 48 months demonstrated an upward trend, with a concomitant decrease in the proportions of people with CKOA or no KOA. Since participants were free of KOA at baseline, this suggests that an older age at onset is associated with an increased likelihood of rapid disease

progression toward end-stage KOA. In contrast, younger age at onset appears to be associated with slower disease progression, at least over the course of 48 months.

The pattern of absolute KOA risk for increasing BMI was different from that of age. In general, and unsurprisingly, at higher values of baseline BMI a greater proportion of the sample had some form of KOA. In terms of disease progression, however, the upward trends for CKOA and AKOA with higher baseline BMI were similar. For both CKOA and AKOA, the proportion of the sample with either disease type at 48 months increased by roughly 10% between the low and high ends of the sample's BMI range (from ~20 to 45 kg/m²). This suggests that relative to normal BMI, being extremely overweight does not increase the proportion of people with AKOA anymore than it does the proportion of people with CKOA. This finding may indicate that while BMI is a major risk factor for development of KOA in general, it is not an important determinant of accelerated disease progression.

Our study offers insight into the public health implications of KOA, and more specifically, differentiates AKOA from CKOA. However, there are some limitations to be considered. First, we observed only a small proportion of individuals with AKOA (3.5%). Our ability to identify significant associations may be limited by this small sample size. Despite this, however, we found significant associations between AKOA and age, BMI, and PASE.

Another limitation could be recall bias associated with self-reported study measures (i.e., PASE and WOMAC scores). There may also be residual confounding even after adjusting for covariates in the multivariable model. For example, there is potential for confounding with comorbidity scores and previous joint injuries, not included, which may bias our results. Data on previous knee injuries and knee surgeries (potential sources of confounding) are available in the OAI database but were not incorporated in our study for the sake of simplicity. One finding from our study differing from the literature is the association between higher PASE score (indicating more physical activity) and greater risk of AKOA (OR = 1.21). Regular physical activity is a known protective factor for several chronic diseases including KOA.⁹ We found it to be anomalous that a higher PASE score was a risk factor for AKOA compared to no KOA. A potential explanation is that the observed greater risk of AKOA associated with greater physical activity is limited to those with higher BMI, however a post-hoc test of the BMI x PASE interaction was not significant with ORs near 1. Aside from this counterintuitive result, our findings agree with the literature and provide further insight into the different risk factor implications of AKOA versus CKOA.

PUBLIC HEALTH IMPLICATIONS

KOA is a debilitating disease, common among the older population and known to reduce quality of life, thus an important public health and clinical concern. These implications not only apply to individuals with KOA but those with other forms of OA and arthritis as well. In Ohio, an estimated 30.5% (approximately 2.7 million Ohioans) of adults have been diagnosed with some form of arthritis.²⁵ The estimated percentage of adults ages 65 years and older reporting a diagnosis of some form of arthritis is nearly 57% (approximately 1.1 million elderly Ohioans).²⁵ KOA is one of the most common forms of arthritis, and even though these estimates include other types of arthritis, the burden of KOA still likely affects a considerable proportion of the adult and more specifically the older adult population in Ohio. Thus, the findings from our study are relevant to public health in Ohio and should be considered by practitioners. In general, KOA deserves significant research attention and AKOA even more so due to its aggressive nature. Among individuals at risk of KOA, especially the elderly, maintaining a normal BMI will preserve a higher quality of life and protect against AKOA.

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