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Associations of Comorbid Conditions and Transitions Across States of Knee Osteoarthritis in a Community-Based Cohort

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Objective. To examine relationships between knee osteoarthritis (KOA) and obesity, diabetes mellitus (DM), and cardiovascular disease (CVD).

Methods. Associations of time-dependent obesity, DM, and CVD with KOA transition states over approximately 18 years were examined among 4093 participants from a community-based cohort. Transition states were *1*) no knee symptoms and no radiographic KOA (rKOA; Kellgren-Lawrence grade ≥2 in at least one knee), *2*) asymptomatic rKOA, *3*) knee symptoms only, *4*) symptomatic rKOA (sxKOA; rKOA and symptoms in same knee). Markov multistate models estimated adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for associations between comorbid conditions and transitions across states, adjusting for baseline age, sex, race, education, enrollment cohort, birth year, and time-dependent knee injury history.

Results. At baseline, 40% of participants had obesity, 13% had DM, and 22% had CVD (mean age = 61 years; 34% Black; 37% male). Compared with those without obesity, those with obesity had a higher hazard of worsening from no rKOA/no symptoms to asymptomatic rKOA (aHR = 1.7; 95% CI = 1.3-2.2) and from knee symptoms to sxKOA (aHR = 1.7; 95% CI = 1.3-2.3), as well as a lower hazard of symptom resolution from sxKOA to asymptomatic rKOA (aHR = 0.5 [95% = CI 0.4-0.7]). Compared with those without CVD, those with CVD had a higher hazard of worsening from no rKOA/symptoms to knee symptoms (aHR = 1.5; 95% CI = 1.1-2.1). DM was not associated with transitions of rKOA.

Conclusion. Prevention of obesity and CVD may limit the development or worsening of rKOA and symptoms.

INTRODUCTION

Osteoarthritis (OA), a leading cause of functional disability and the most common type of arthritis, is characterized by a progression in various transitions between radiographic features (ie, osteophytes [bone spurs] and joint space narrowing indicative of cartilage loss), joint pain, or both. Of all the joint sites affected by OA, the knee is one of the most common and consequential. Obesity has been long recognized as a key risk factor for knee OA (KOA) (1), and it also is a significant risk factor for cardiovascular disease (CVD) and a known risk factor for type 2 diabetes mellitus (DM). CVD and DM are frequently comorbid with KOA, and accumulating evidence shows associations between both conditions

and KOA (2–5). Pathophysiological mechanisms, such as chronic inflammation, reduced physical activity, or common metabolic pathways, may link KOA with obesity, CVD, and DM (6). Determining the impact of common comorbid conditions of obesity, CVD, and DM on long-term KOA outcomes may help identify important targeted strategies for OA and disability prevention, possibly well before the occurrence or progression of KOA. The impact of obesity, CVD, and DM, including combinations of these comorbid conditions, on the progression across the different states of KOA is not known.

KOA, obesity, CVD, and DM are common conditions in the population that can differ by sex and race. Compared with men, women are more likely to have KOA (7) and have

a higher prevalence of obesity (8) but are less likely to have CVD and DM (9). Compared with White individuals, Black individuals are more likely to have obesity (10), CVD (11), or DM (12) and are more likely to have both radiographic KOA (rKOA) and symptomatic rKOA (sxKOA) (13). Potentially, relationships of obesity, CVD, and DM with progression of KOA could vary by sex and race.

This study has two purposes. The first purpose was to examine the independent associations of obesity, CVD, and DM, separately and when two conditions were present (ie, obesity and CVD and obesity and DM), with transitions of KOA in a longitudinal cohort with up to 18 years of follow-up time. To achieve this goal, we used Markov multistate models (MSMs) (14–16) rather than a more traditional approach such as the Cox proportional hazards model because the multistate framework has the ability to model multiple event transitions between rKOA and sxKOA, recovery from pain, and death within a single statistical model, while simultaneously allowing covariate effects to vary for each transition. MSMs can address other important issues in longitudinal studies, such as missing data and interval censoring with the event of interest known to occur in the interval between two follow-up visits but with unknown precise timing (17). This capability to model interval-censored events was of particular interest because of the 6-year interval, on average, between visits in our study. The second purpose was to determine associations between these comorbid conditions and the transitions of KOA stratified separately by sex and race (White versus Black). Our hypothesis was that those with each comorbid condition (separately and concomitantly) would have higher hazards for transitions of developing or worsening KOA or symptoms compared with those without the comorbid condition and that these associations would differ by sex and race.

PATIENTS AND METHODS

Study population. The study sample was from the Johnston County OA Project (JoCoOA), a community-based prospective cohort of civilian, noninstitutionalized participants in Johnston County, North Carolina. This study comprises Black and White men and women aged 45 years or older. Baseline data collection occurred from 1991 to 1997 for the original cohort (18) or from 2003 to 2004 for the enrichment cohort (19). Because OA is a slowly developing condition, follow-up data were collected every 6 years, on average, during 1999 to 2003 for the original cohort and during 2006 to 2011 and 2013 to 2015 for both the original and enrichment cohorts. The median follow-up times for the original and enrichment cohorts were 19.3 and 12.1 years, respectively. Using the National Death Index, vital status for all participants was assessed through December 31, 2015. Inclusion criteria were the availability of baseline covariates, knee X-rays, and mortality data, resulting in an initial study sample total of 4093 participants for analysis.

Assessment of KOA and symptom outcomes. Knee radiographs were collected at each research clinic visit. During 1991 to 1997, anteroposterior (AP) films were obtained with the participant standing with knees fully extended. Because of evidence that posterioanterior (PA) views for OA assessment are superior for reproducibility in research studies (20,21), the knee radiography approach for JoCoOA was changed in 1999 to weight-bearing fixed flexion PA radiographs of both knees using the Synaflexer® positioning device; this method was used for all subsequent study visits. Agreement has been shown to be high between AP and PA reads in the JoCoOA for rKOA (agreement = 89%; κ = 0.73) (22). At all study visits, participants were asked, "On most days, do you have pain, aching, or stiffness in your [right/left] knee?" Knee symptoms were considered present if the response was affirmative. At the participant level, if present in at least one knee, the following were defined: *1*) rKOA based on a Kellgren-Lawrence grade of 2 or more or total knee replacement (TKR); *2*) knee symptoms based on self-report of knee pain, aching, or stiffness on most days; and *3*) sxKOA based on the presence of rKOA or TKR and knee symptoms in the same knee.

Main effects: comorbid conditions. The three comorbidities were assessed at each study visit. Obesity was defined as a measured body mass index (BMI) of 30.0 kg/m^2 or more. Other BMI categories were underweight (<18.5 kg/m^2), normal (18.5 to <25 kg/m^2), and overweight (25 to <30 kg/m^2). DM was based on an affirmative response to a question about whether a doctor, nurse, or health professional had told the participant whether they have now or have ever had "diabetes or high blood sugar." Across the first three data collection time points, assessment of CVD status was consistent with National Health Interview Survey questions, progressively including more specific items with each subsequent study visit. At baseline, CVD was defined based on self-report of heart attack, other heart problems, or cerebrovascular accident. At the first follow-up visit, self-reports of angina and congestive heart failure were added to the CVD questions; by the second follow-up visit, peripheral vascular disease was included. All comorbidity indicators were analyzed as time dependent across visits for all participants; obesity could develop or revert for a participant over time, whereas DM and CVD were conditions that were managed as absent until they were reported by a participant and could not revert once indicated.

Covariates. At baseline, age, sex, race, years of formal education, and birth year were collected via self-report. History of knee injury or fracture was based on an affirmative response to one of two questions, which changed with time to reflect the evolution of these questions in other OA cohorts (23), as follow: "Has a doctor ever told you that you broke or fractured your [right/left] knee?" and "Other than a fracture, have you injured your [right/left] knee enough to require a cane, cast, or crutch for two weeks or longer?"

Statistical analysis. All analyses were conducted at the participant level (ie, individual-specific). The analysis considered intervals between data collected among the baseline and up to three follow-up time points (ie, one to three intervals per participant) or death. All participants, even those who only completed a baseline visit, were included because they could still transition to death. Intervals were analyzed using MSM with the following four transient states: *1)* no rKOA or knee symptoms (state A), *2)* asymptomatic rKOA (ie, rKOA without symptoms in the same knee; state B), *3)* knee symptoms only (state C), and *4)* sxKOA (state D) (Figure 1). The MSM modeled the difference in time from baseline (in years) to a transition event recorded during a follow-up visit; any additional transition event would contribute the added time as the difference from baseline. For example, a participant who starts in state A at baseline and transitions to state B at the first follow-up (5 years from baseline) would be recorded as experiencing this transition event (state A to state B) at 5 years; if they go on to transition again, this time from state B to state D, at the third follow-up visit (17 years from baseline), they would also be recorded as experiencing the state B to state D transition event at 17 years from baseline. If a participant missed an interim follow-up visit, the interval for such a participant was specified as being longer for analysis purposes, not ending until the next visit in which they participated. Death, which is an absorbing (ie, final) state from which no transitions can emerge, was included in models to differentiate being lost to follow-up (censored) versus being physically unable to transition because of death. Follow-up time to the final, absorbing state was calculated from baseline

assessment until censoring, which took place when a participant was lost to follow-up or reached the end of study period (December 31, 2015). These transitions to the absorbing state were not a focus of this study; associations between rKOA, symptoms, CVD, and mortality have been previously reported for the JoCoOA (24). The three types of transitions studied were developing rKOA (either state A to state B or state C to state D), developing knee symptoms (state A to state C or state B to state D), and resolving knee symptoms (state C to state A or state D to state B). Other transitions (eg, diagonal transitions across no rKOA or knee symptoms to sxKOA) were uncommon and were excluded for parsimony. The hazard ratios for a transition from one state to another were estimated on the basis of the Markovian assumptions that a future transition is contingent on the current state and that the risk of the transition is constant. Transitions in KOA and symptoms states are known to differ by age, and, thus, we relaxed the assumption using time-inhomogeneous (time-dependent) MSM piecewise exponential models in which age was partitioned into two intervals (45-64 years and ≥65 years) (25). A constant hazard, with an exponential distribution, was assumed within each of these two separate age intervals, meaning that estimates could change at the cutoff point of age 65. Hence, transition intensities were piecewise constant within these two age intervals. The models were fitted using the msm R package, which allows one to estimate Markov models with interval-censored transition times.

Independent associations for comorbid conditions with each knee state transition were estimated as adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs), adjusting for the other
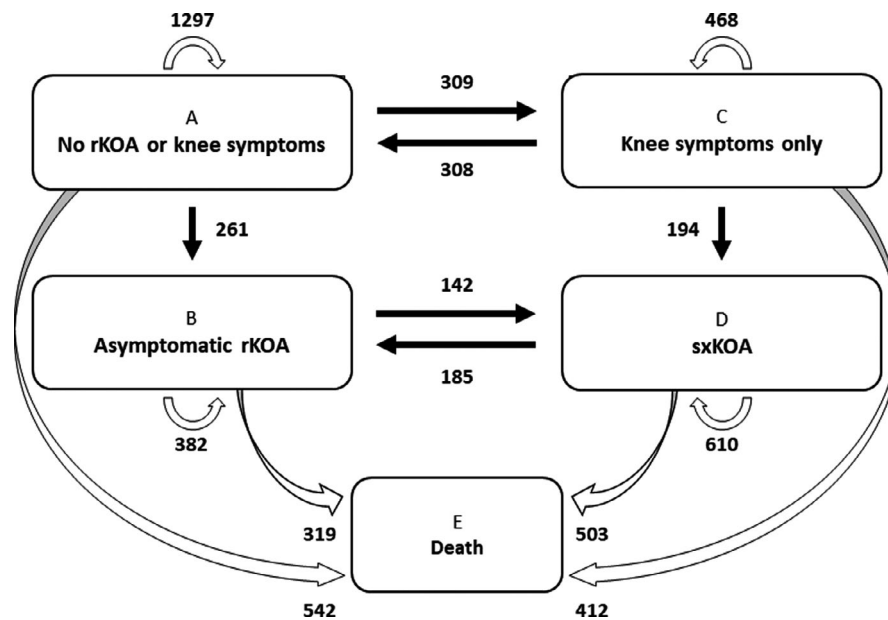
Figure 1. Five-state progressive model for knee status among 4093 study participants. The numbers beside their corresponding transition arrows indicate the number of transition instances, not individuals, over the follow-up period. Transitions to death (the absorbing state) are included in models, but results of main effects on these transitions are not reported because they were not the aim of this study. Diagonal transitions across states were uncommon, and, thus, were excluded for parsimony. The transitions analyzed are in boldface arrows. rKOA, radiographic knee osteoarthritis; A, stage A (no rKOA or knee symptoms); B, stage B (asymptomatic rKOA); C, stage C (knee symptoms only); D, stage D (sxKOA); E, stage E (death); sxKOA, symptomatic rKOA.

two comorbid conditions and seven relevant baseline demographics (continuous age and dichotomous sex, race [African American versus White], and education [<12 years versus ≥12 years], time-dependent history of knee injury or fracture, enrollment cohort [original or enrichment], and mean-centered birth year [to account for calendar effects]). Given the extensive associations involving obesity, the main effects model was conducted with the following two different comparisons for the obesity variable: *1)* obesity versus no obesity (Model 1A) and *2)* overweight versus normal BMI and obesity versus normal BMI (Model 1B). Estimates were calculated for the overall sample and separately by sex and race. Effects by sex and race were analyzed in Model 1A only because Model 1B failed to converge. Finally, because some participants may have more than one comorbid condition, we examined coexisting comorbid conditions involving obesity (ie, obesity plus DM and obesity plus CVD). Both models were adjusted for baseline values of birth year, study cohort, age, sex, race, and education and for time-dependent knee injury. For the model of obesity and DM, we also adjusted for CVD and the grouping on the basis of the cross-classification of BMI status and DM status. For the model of obesity and CVD, we additionally adjusted for DM and the grouping on the basis of the cross-classification of BMI status and CVD status.

RESULTS

From the initial study sample of 4182 participants with knee radiographs and mortality data, 89 (2.1%) were missing at least one baseline covariate (Figure 2). Under complete case analysis considering all relevant covariates of interest, the final analytic sample comprised 4093 participants with baseline and up to three follow-up assessments, which occurred every 6 years, on average. Of those 4093 participants, 1629 (39.8%) did not complete any follow-up visits and were censored at the end of follow-up (December 31, 2015). At baseline, the sample had a mean age of 61 years (SD = 10.5); 37% of participants were men, 34% were Black, and 36% had less than 12 years of education (Table 1). A smaller number of participants completed the final third follow-up visit compared with baseline; approximately one-tenth did not participate, half had died by this visit, and one-quarter belonged to the enrichment cohort, which had not yet completed a third follow-up visit, by study design. Approximately one-fifth of participants reported a knee injury or fracture at baseline, which increased to approximately one-third by the end of the follow-up period. Over the follow-up period, those with a normal BMI range decreased from 23% to 14%, whereas those with obesity increased from 40% to 51%. The frequency of both DM and CVD more than doubled over time (from 13% to 30% for DM and from 22% to 48% for CVD). Proportions of transition states changed from baseline to third follow-up for no rKOA or knee symptoms (45% to 29%), asymptomatic rKOA (10% to 36%), knee symptoms only (27% to 9%), and sxKOA (17% to 26%).

Associations between KOA state transitions and individual comorbidities. Results of each comorbid condition's (ie, obesity, DM, and CVD) main effect on the transitions between states of KOA are given in Table 2, shown separately
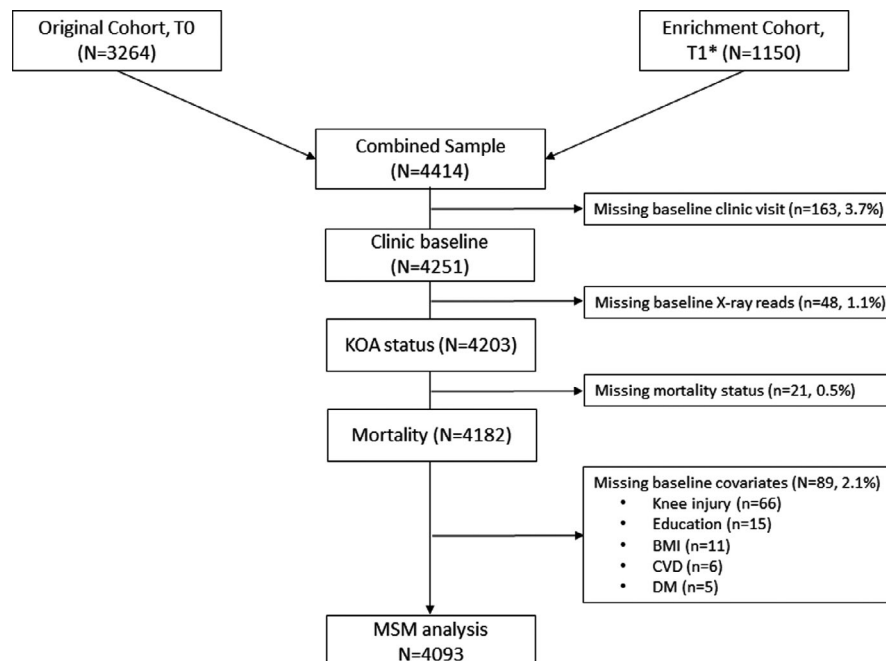
Figure 2. Johnston County Osteoarthritis Project participants with data available for analyses (n = 4093). BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; KOA, knee osteoarthritis; MSM, Markov multistate model; T0, baseline time point for Original Cohort; T1*, baseline time point for Enrichment Cohort.

Table 1. Descriptive characteristics of 4093 Johnston County Osteoarthritis Project participants with complete data

Characteristics	Study Visit			
	Baseline (1991-1997 or 2003-2004; n = 4093)	First Follow-Up (1999-2003 or 2006-2011; (n = 2421; 6.0 ± 1.2 Years From Baseline)	Second Follow-Up (2006-2011 or 2013-2015; n = 1436; 12.2 ± 1.5 Years From Baseline)	Third Follow-Up (2013-2015; n = 552; 18.4 ± 1.5 Years From Baseline)[a]
Demographic/clinical				
1991-1997 cohort, n (%)	3060 (74.8)	1829 (75.6)	1104 (76.9)	552 (100)
Age, years, mean ± SD	61.0 ± 10.5	65.8 ± 9.8	69.9 ± 8.4	73.3 ± 7.0
Male sex, n (%)	1501 (36.7)	815 (33.7)	465 (32.4)	186 (33.7)
Black, n (%)	1402 (34.3)	770 (31.8)	439 (30.6)	156 (28.3)
<12 years education, n (%)	1459 (35.6)	727 (30.0)	311 (21.7)	80 (14.5)
Knee injury, n (%)	776 (19.0)	666 (27.5)	422 (29.4)	176 (31.9)
Comorbid conditions, n (%)				
BMI categories (kg/m^2)				
Underweight (BMI < 18.5 kg/m^2)	41 (1.0)	18 (0.7)	10 (0.7)	2 (0.4)
Normal (18.5 ≤BMI<25.0)	925 (22.6)	433 (17.9)	210 (14.6)	78 (14.1)
Overweight (25.0≤BMI<30.0)	1487 (36.3)	846 (34.9)	482 (33.6)	191 (34.6)
Obese (BMI ≥ 30.0 kg/m^2)	1640 (40.1)	1124 (46.4)	734 (51.1)	281 (50.9)
DM	538 (13.1)	459 (19.0)	366 (25.5)	163 (29.5)
CVD	899 (22.0)	787 (32.5)	599 (41.7)	263 (47.6)
Transition states, n (%)				
KOA and symptoms				
No rKOA or symptoms	1852 (45.2)	940 (38.8)	505 (35.2)	160 (29.0)
Asymptomatic rKOA	417 (10.2)	373 (15.4)	376 (26.2)	196 (35.5)
Knee symptoms only	1115 (27.2)	547 (22.6)	178 (12.4)	52 (9.4)
sxKOA	709 (17.3)	561 (23.2)	377 (26.3)	144 (26.1)

Abbreviation: BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; KOA, knee osteoarthritis; rKOA, radiographic KOA; sxKOA, symptomatic KOA.
[a] All third follow-up visits are from the original cohort (1991-1997) because the enrichment cohort could not have had their third follow-up visit by December 31, 2015.

as comparisons of obesity versus no obesity (normal BMI and overweight; Model 1A) and overweight versus normal and obesity versus normal (Model 1B), respectively.

For Model 1A, those with obesity or those who developed obesity (compared with those without obesity) had a higher hazard of developing rKOA, regardless of whether symptoms were already present (onset of asymptomatic rKOA among those who were previously without symptoms or rKOA [state A to state B: aHR = 1.71; 95% CI = 1.33-2.18] and onset of symptomatic rKOA among those with knee symptoms only [state C to state D: aHR = 1.71; 95% CI = 1.28-2.27]). Individuals with obesity also had a lower hazard of resolving knee symptoms if rKOA was already present (state D to state B: aHR = 0.50; 95% CI = 0.35-0.70). Having or developing DM was not associated with any of the modeled transitions. Those with CVD or those who developed CVD (compared with those without CVD) had a higher hazard of developing knee symptoms (onset of knee symptoms only [state A to state C: aHR = 1.53; 95% CI = 1.12-2.09]).

For Model 1B, obesity effects on the hazard of the previously mentioned transitions were stronger when compared with those with a normal BMI. Those with obesity (compared with those with a normal BMI) had a higher hazard of developing asymptomatic rKOA among those without rKOA or knee symptoms (state A to state B: aHR = 2.17; 95% CI = 1.58-2.99) and a higher hazard

of developing sxKOA among those with knee symptoms already present (state C to state D: aHR = 3.68; 95% CI = 2.00-6.76). Those who were overweight (compared with those with a normal BMI) also had an increased hazard of developing rKOA whether or not knee symptoms were already present (state A to state B and state C to state D). Among those without rKOA (compared with those with normal BMI), those with obesity had a significantly lower hazard (aHR = 0.64; 95% CI = 0.45-0.91) of resolving knee symptoms (state C to state A). Similar to Model 1A, having or developing DM was not associated with any of the transitions, and those who had or developed CVD (compared with those without CVD) had a significantly higher hazard of developing knee symptoms (state A to state C: aHR = 1.52; 95% CI = 1.12-2.08).

Associations between KOA state transitions and individual comorbidities by sex and race. Results stratified by sex are shown in Table 3. The result of obesity increasing the hazard of developing rKOA with (state A to state B) or without (state C to state D) knee symptoms present was statistically significant among women. The lower hazard of resolving knee symptoms with rKOA already present (state D to state B) for individuals with obesity was similar among women and men. For both sexes, no associations were observed between having or developing DM and any of the modeled transitions. The result of CVD increasing

Table 2. aHRs and 95% CIs for each comorbid condition main effect on modeled transition states, comparing obesity with no obesity (model 1A) and obesity or overweight with normal BMI (model 1B[b]) (n = 4093)

Type of Transition	State Transitions	Model 1A [n (Vs n) for Transitions; aHR (95% CI)][a]			Model 1B [n (Vs n) for Transitions; aHR (95% CI)][b]			
		Obesity (Vs No Obesity)	DM (vs No DM)	CVD (Vs No CVD)	Overweight (Vs Normal)	Obesity (Vs Normal)	DM (Vs No DM)	CVD (Vs No CVD)
Developing rKOA	No rKOA or knee symptoms → asymptomatic rKOA	117 (vs 144); 1.71 (1.33-2.18)	57 (vs 204); 0.94 (0.64-1.37)	79 (vs 182); 1.04 (0.77-1.40)	108 (vs 36); 1.46 (1.06-2.01)	117 (vs 36); 2.17 (1.58-2.99)	57 (vs 204); 0.94 (0.65-1.36)	79 (vs 182); 1.02 (0.75-1.37)
	Knee symptoms only → sxKOA	135 (vs 59); 1.71 (1.28-2.27)	45 (vs 149); 0.70 (0.45-1.07)	76 (vs 118); 0.73 (0.54-1.00)	52 (vs 7); 2.81 (1.50-5.27)	135 (vs 7); 3.68 (2.00-6.76)	45 (vs 149); 0.67 (0.44-1.02)	76 (vs 118); 0.77 (0.57-1.06)
Developing knee symptoms	No rKOA or knee symptoms → knee symptoms only	143 (vs 166); 1.30 (0.98-1.71)	50 (vs 259); 0.91 (0.60-1.39)	115 (vs 194); 1.53 (1.12-2.09)	114 (vs 52); 1.17 (0.83-1.66)	143 (vs 52); 1.39 (0.97-2.00)	50 (vs 259); 0.91 (0.60-1.39)	115 (vs 194); 1.52 (1.12-2.08)
	Asymptomatic rKOA → sxKOA	88 (vs 54); 0.90 (0.62-1.32)	36 (vs 106); 0.91 (0.55-1.51)	61 (vs 81); 1.01 (0.67-1.51)	43 (vs 11); 0.92 (0.66-2.45)	88 (vs 11); 1.11 (0.63-1.98)	36 (vs 106); 0.89 (0.54-1.47)	61 (vs 81); 1.00 (0.67-1.50)
Resolving knee symptoms	Knee symptoms only → no rKOA or knee symptoms	139 (vs 169); 0.77 (0.58-1.01)	72 (vs 236); 0.89 (0.61-1.32)	116 (vs 192); 0.93 (0.69-1.25)	116 (vs 53); 0.76 (0.54-1.08)	139 (vs 53); 0.64 (0.45-0.91)	72 (vs 236); 0.91 (0.61-1.34)	116 (vs 192); 0.91 (0.68-1.23)
	sxKOA → asymptomatic rKOA	119 (vs 66); 0.50 (0.35-0.70)	50 (vs 135); 0.79 (0.50-1.23)	79 (vs 106); 1.22 (0.85-1.74)	51 (vs 15); 1.38 (0.72-2.64)	119 (vs 15); 0.64 (0.34-1.21)	50 (vs 135); 0.78 (0.50-1.21)	79 (vs 106); 1.22 (0.85-1.74)

Abbreviation: aHR, adjusted hazard ratio; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; rKOA, radiographic knee osteoarthritis; sxKOA, symptomatic knee osteoarthritis; vs, versus.
[a] Model 1A is adjusted for baseline values of birth year, study cohort, age, sex, race, and education and time-dependent obesity, DM, CVD, and knee injury.
[b] Model 1B is adjusted for baseline values of birth year, study cohort, age, sex, race, and education and time-dependent underweight, overweight, obesity, DM, CVD, and knee injury.

Table 3. aHRs and 95% CIs for comorbid conditions, individually, on modeled transition states comparing obesity with no obesity over the full Follow-up period, by sex (n = 4093)

Type of Transition	State Transitions	Obesity (Vs No obesity) [n (Vs n) for Transitions; aHR (95% CI)][a]	DM (Vs No DM) [n (Vs n) for Transitions; aHR (95% CI)][a]	CVD (Vs No CVD) [n (Vs n) for Transitions; aHR (95% CI)][a]
Women				
Developing rKOA	No rKOA or knee symptoms → asymptomatic rKOA	74 (vs 79); 2.02 (1.45-2.80)	32 (vs 121); 0.98 (0.61-1.57)	51 (vs 102); 1.17 (0.80-1.72)
	Knee symptoms only → sxKOA	98 (vs 36); 1.81 (1.28-2.58)	30 (vs 104); 0.67 (0.39-1.15)	60 (vs 74); 0.77 (0.53-1.11)
Developing knee symptoms	No rKOA or knee symptoms → Knee symptoms only	107 (vs 118); 1.29 (0.92-1.82)	41 (vs 184); 1.12 (0.68-1.86)	80 (vs 145); 1.33 (0.91-1.95)
	Asymptomatic rKOA → sxKOA	65 (vs 38); 0.96 (0.60-1.53)	29 (vs 74); 0.97 (0.55-1.73)	51 (vs 52); 1.10 (0.69-1.73)
Resolving knee symptoms	Knee symptoms only → no rKOA or knee symptoms	95 (vs 123); 0.75 (0.53-1.06)	51 (vs 167); 1.00 (0.59-1.67)	78 (vs 140); 0.80 (0.55-1.15)
	sxKOA → asymptomatic rKOA	84 (vs 40); 0.47 (0.31-0.71)	35 (vs 89); 0.78 (0.45-1.35)	56 (vs 68); 1.26 (0.83-1.91)
Men				
Developing rKOA	No rKOA or knee symptoms → asymptomatic rKOA	43 (vs 65); 1.36 (0.93-1.99)	25 (vs 83); 0.92 (0.50-1.66)	28 (vs 80); 0.83 (0.48-1.44)
	Knee symptoms only → sxKOA	37 (vs 23); 1.27 (0.78-2.07)	15 (vs 45); 0.63 (0.31-1.29)	16 (vs 44); 0.65 (0.35-1.20)
Developing knee symptoms	No rKOA or knee symptoms → knee symptoms only	36 (vs 48); 1.17 (0.72-1.90)	9 (vs 75); 0.39 (0.13-1.12)	35 (vs 49); 2.17 (1.24-3.81)
	Asymptomatic rKOA → sxKOA	23 (vs 16); 0.84 (0.44-1.61)	7 (vs 32); 0.87 (0.33-2.31)	10 (vs 29); 0.72 (0.27-1.94)
Resolving knee symptoms	Knee symptoms only → no rKOA or knee symptoms	44 (vs 46); 0.82 (0.51-1.32)	21 (vs 69); 0.85 (0.47-1.55)	38 (vs 52); 1.29 (0.76-2.18)
	sxKOA → asymptomatic rKOA	35 (vs 26); 0.58 (0.33-1.00)	15 (vs 46); 0.85 (0.40-1.82)	23 (vs 38); 1.12 (0.57-2.19)

Abbreviation: aHR, adjusted hazard ratio; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; rKOA, radiographic knee osteoarthritis; sxKOA, symptomatic knee osteoarthritis; vs, versus.
[a] Model is adjusted for baseline values of birth year, study cohort, age, race, and education and time-dependent obesity, DM, CVD, and knee injury.

the hazard of only developing knee symptoms (state A to state C) was statistically significant among men.

Results stratified by race are shown in Table 4. Having obesity increased the hazard of only developing knee symptoms (state A to state C) among White individuals but not Black individuals. Similarly, for both races, having obesity increased the hazard of developing rKOA with (state A to state B) or without (state C to state D) knee symptoms present and decreased the hazard of resolving

Table 4. aHRs and 95% CIs for comorbid conditions, individually, on modeled transition states comparing obesity with no obesity over the full follow-up period, by race (n = 4093)

Type of Transition	State Transitions	Obesity(Vs No Obesity) [n (Vs n) for Transitions; aHR (95% CI)][a]	DM(Vs No DM) [n (Vs n) for Transitions; aHR (95% CI)][a]	CVD(Vs No CVD) [n (Vs n) for Transitions; aHR (95% CI)][a]
White				
Developing rKOA	No rKOA or knee symptoms → asymptomatic rKOA	74 (vs 116); 1.64 (1.22-2.19)	39 (vs 151); 1.11 (0.70-1.75)	57 (vs 133); 1.03 (0.71-1.50)
	Knee symptoms only → sxKOA	88 (vs 47); 1.63 (1.18-2.26)	24 (vs 111); 0.86 (0.50-1.48)	48 (vs 87); 0.67 (0.45-1.00)
Developing knee symptoms	No rKOA or knee symptoms → knee symptoms only	103 (vs 128); 1.47 (1.07-2.01)	31 (vs 200); 0.95 (0.55-1.62)	86 (vs 145); 1.72 (1.20-2.47)
	Asymptomatic rKOA → sxKOA	53 (vs 38); 1.05 (0.66-1.65)	21 (vs 70); 0.74 (0.38-1.45)	38 (vs 53); 1.23 (0.73-2.07)
Resolving knee symptoms	Knee symptoms only → (A) no rKOA or knee symptoms	89 (vs 123); 0.76 (0.54-1.06)	44 (vs 168); 1.05 (0.63-1.75)	78 (vs 134); 1.03 (0.71-1.48)
	sxKOA → asymptomatic rKOA	72 (vs 51); 0.54 (0.36-0.80)	29 (vs 94); 0.69 (0.39-1.23)	50 (vs 73); 1.26 (0.80-1.98)
Black				
Developing rKOA	No rKOA or knee symptoms → asymptomatic rKOA	43 (vs 28); 1.79 (1.13-2.85)	18 (vs 53); 0.68 (0.36-1.30)	22 (vs 49); 1.14 (0.67-1.92)
	Knee symptoms only → sxKOA	47 (vs 12); 2.05 (1.07-3.92)	21 (vs 38); 0.57 (0.30-1.11)	31 (vs 28); 0.84 (0.48-1.47)
Developing knee symptoms	No rKOA or knee symptoms → knee symptoms only	40 (vs 38); 0.86 (0.49-1.51)	19 (vs 59); 0.84 (0.42-1.67)	29 (vs 49); 0.99 (0.52-1.91)
	Asymptomatic rKOA → sxKOA	35 (vs 16); 0.66 (0.34-1.25)	15 (vs 36); 1.16 (0.54-2.47)	23 (vs 28); 0.80 (0.41-1.54)
Resolving knee symptoms	Knee symptoms only → no rKOA or knee symptoms	50 (vs 46); 0.70 (0.41-1.17)	28 (vs 68); 0.75 (0.41-1.38)	38 (vs 58); 0.73 (0.44-1.21)
	sxKOA → asymptomatic rKOA	47 (vs 15); 0.46 (0.24-0.90)	21 (vs 41); 0.99 (0.49-2.03)	29 (vs 33); 1.21 (0.67-2.19)

Abbreviation: aHR, adjusted hazard ratio; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; rKOA, radiographic knee osteoarthritis; sxKOA, symptomatic knee osteoarthritis; vs, versus.
[a] Model is adjusted for baseline values of birth year, study cohort, age, sex, and education and time-dependent obesity, DM, CVD, and knee injury.

knee symptoms with rKOA already present (state D to state B). For either racial group, having or developing DM was not associated with any transitions. The presence of CVD increased the hazard of developing knee symptoms (state A to state C) among White participants but not Black participants.

Associations between KOA state transitions and coexisting comorbidities. Finally, coexisting comorbid conditions involving obesity were considered (Supplementary Table). The combination of obesity and DM was associated with the hazard of developing asymptomatic rKOA (state A to state B). Notably, those with both obesity and DM had a lower hazard (aHR = 0.42; 95% CI = 0.19-0.93) of resolving knee symptoms with rKOA already present (state D to state B). Having both obesity and CVD (compared with those without CVD and a normal BMI) was associated with developing rKOA (state A to state B and state C to state D) and both developing (state A to state C) and resolving knee symptoms without rKOA (state C to state A).

DISCUSSION

In this longitudinal analysis of a community-based cohort, multivariable results suggest several relationships between obesity and CVD and knee state transitions that were independent of relevant demographic and clinical factors. Associations were not observed for DM and transitions of KOA. This study provides novel findings of differences in the associations by sex and race as well as the combined impact of two comorbidities (obesity and DM or obesity and CVD) on knee state transitions. Additionally, this research adds to our understanding of comorbid conditions and state transitions at joint sites, which we previously reported for the hip (26) and hand (27).

Specifically, both obesity and an overweight status were associated with worsening of rKOA, which aligns with extensive evidence of a higher BMI, principally obesity, being a major risk factor for KOA (28–32). By examining state transitions in KOA and symptoms, the present study extends prior knowledge by showing a link of obesity and overweight status with a worsening of rKOA, irrespective of the presence of baseline knee symptoms. Associations were attenuated and not statistically significant for obesity and overweight status with developing knee symptoms. These results suggest that a higher BMI may have more of an influence on the joint structure than pain mechanisms at the knee; potentially, obesity and overweight status contribute to articular changes at the knee, either by mechanical overload or by metabolic factors (33). Although obesity played less of a role in developing knee symptoms than in developing rKOA, resolving knee symptoms was inversely associated with obesity, suggesting that individuals with obesity are much less likely to experience an improvement in knee symptoms compared with those who have a normal weight. Maintaining a normal weight may be advantageous for resolving knee symptoms, which could subsequently improve other knee-related factors associated with symptoms such as physical function and quality of life.

In analyses of other comorbid conditions, DM was not independently related to knee transitions, whereas CVD was independently associated with developing knee symptoms among those without rKOA at baseline. Of note, CVD was not associated with developing rKOA (asymptomatic or symptomatic). Collectively, prior studies and the present results may indicate a complex interrelationship of obesity, CVD, and knee pain/OA, which may be driven by low physical activity and disability. This study demonstrated the effects of these conditions on KOA, but KOA also may influence these conditions directly or indirectly via reduced physical activity. In models with two coexisting comorbid conditions (ie, obesity and DM and obesity and CVD), effects were generally stronger; these associations were likely driven by obesity, but the presence of DM or CVD also contributed. Largely, these results support interventions to prevent or manage comorbid conditions to mitigate the development of knee symptoms and OA, which could ultimately impact mobility and other health outcomes.

Considering the paradoxical protective association of obesity and progression of KOA in observational studies due to collider bias, we considered whether this bias may be present in the results of our study. If we were not observing an effect from obesity or overweight status on most of the transitions, we would be concerned about the potential for collider bias. However, our results demonstrate an effect. Considering that our analyses may be prone to attenuating the BMI effect, we noted that we continue to observe an effect of BMI even after adjusting for DM or CVD, which may indicate that collider bias is doubtful. Additionally, post hoc directed acyclic graphs showed that obesity could be on the causal pathway to developing DM or CVD, but KOA leading to DM or CVD is questionable, further suggesting that collider bias is unlikely.

In analyses stratified by sex, obesity was statistically associated with a higher hazard of developing rKOA regardless of knee symptom presence in women, but the estimate was lower and not statistically significant in men. Among men, CVD was associated with a higher hazard of developing knee symptoms without rKOA. Overall, differences by race were few. For both White and Black participants, obesity was associated with a higher hazard of developing rKOA and a lower hazard of resolving knee symptoms. The only dissimilarity was that obesity and CVD were both associated with a higher hazard of developing knee symptoms among White participants but not Black participants. Because a larger percentage of Black participants had baseline knee symptoms compared with White participants, the sample available for knee symptom transitions was smaller, which may partly explain the differences between groups and the less precise estimates among Black participants.

Strengths of this study include the credible assessment of rKOA and joint symptoms, long (up to 18 years) follow-up, community basis, inclusion of Black as well as White men and women, and use of a relatively novel analytical approach that can model

several transitions and accommodate the cohort's interval censoring. There were several limitations as well. First, there was self-report of two conditions (CVD and DM), although, compared with the medical record, self-report of DM has high positive predictive values, and self-report of some CVD risk factors has shown moderate to good sensitivity (34,35). Second, there was a limited sample size for analyses by sex and race. Stratified analyses of the sex and race subgroups (ie, White women, White men, Black women, and Black men) were not conducted because of smaller sample sizes, particularly among Black men. Third, sample sizes were too small to conduct analyses of coexisting comorbid conditions (ie, obesity and DM and obesity and CVD) by sex and race. Fourth, comprehensive data on all aspects of treatment strategies (eg, diet, exercise interventions, rehabilitation, and medications) were not available for all participants at all follow-up points and were not included in the models. Fifth, analyses were conducted at the person level, and thus examinations of unilateral/bilateral disease or Kellgren-Lawrence grade severity were not conducted, as they require a different analytical approach at the joint level. Also, this analysis examined structure and pain but did not include function, another important aspect of KOA. Examining KOA transition states in physical function will be a topic of future study in the JoCoOA. Finally, there was some cohort attrition, with an approximately 30% loss to follow-up after their baseline visits that was not attributed to mortality. Although some participants could not be contacted (17%) or declined to continue participation in the study (44%), many of those lost to follow-up had moved out of the study area (20%) or became physically or mentally unable to participate (18%). Given the possibility of unobservable characteristics contributing to this missingness, these data could be missing not at random. Because of the extreme complexity in simultaneously implementing both the MSM methods using the msm R package and advanced imputation methods assuming a missing-not-at-random mechanism for multiple variables, estimates in this report are based on data with complete case information.

In summary, our results suggest that obesity and CVD are risk factors associated with transitions across rKOA and knee symptom states that are independent of relevant demographic and clinical factors. Despite simultaneous adjustment of all three comorbidities, these associations persisted, which suggests independent effects of these conditions on KOA and knee symptom state transitions. Potential differences by sex and race require further examination in additional populations. For public health messaging and clinical care, these study results support advising individuals with obesity and who are overweight to modify weight, particularly among those with other comorbid conditions such as DM and CVD, in order to prevent the development of KOA and knee symptoms and perhaps to encourage knee symptom resolution.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Golightly 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. Golightly, Alvarez, Arbeeva, Cleveland, Schwartz, Renner, Murphy, Callahan, Jordan, Nelson.
Acquisition of data. Renner, Jordan.
Analysis and interpretation of data. Golightly, Alvarez, Arbeeva, Cleveland, Schwartz, Renner, Murphy, Callahan, Jordan, Nelson.

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