Effects of Comorbid Cardiovascular Disease and Diabetes Mellitus on Hand Osteoarthritis, Pain, and Functional State Transitions

The Johnston County Osteoarthritis Project

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Keywords: Osteoarthritis, Hand, Comorbidity, Cardiovascular Diseases, Diabetes Mellitus, Obesity

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Source of support: Funding was provided in part by the Medical Student Training in Aging Research program through NIA 2-T35-AG038047-08, NIAMS P60 AR049465 and P30 AR072580, and Centers for Disease Control and Prevention U01DP006266.

Conflict of interest: None of the authors has any relevant conflict of interest to report.

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Running head: Comorbidities & Hand Transitions

Objective: The purpose of this study is to examine the course of hand osteoarthritis (HOA) and its relationship with cardiovascular disease (CVD) and diabetes (DM).

Methods: Data were collected at 3 time points from 845 Johnston County Osteoarthritis Project participants (2/3 women, 1/3 African-Americans, mean age 60 years) with and without HOA, CVD, or DM. A diagnosis of radiographic hand osteoarthritis (rHOA) required a Kellgren-Lawrence severity grade of ≥2 in at least 3 joints in each hand. A four-state progressive model included transitions based on rHOA and pain or function as defined using the AUStralian CANadian Osteoarthritis Hand Index (AUSCAN). Markov multi-state models estimated hazard ratios and 95% confidence intervals (aHR [95%]) for associations between DM or CVD and specific state transitions, adjusting for baseline and time-varying covariates.

Results: Participants with DM (vs those without DM) were more likely to experience worsening pain with rHOA. Individuals who had or developed CVD (vs those who did not) were significantly less likely to experience symptomatic improvement, regardless of rHOA status. Those with DM or CVD (vs those without these comorbidities) were less likely to experience improvement in function, although this was statistically significant only for those with DM and no rHOA.

Conclusion: Overall, having or developing DM and/or CVD reduced the likelihood of symptomatic and functional improvement over time, suggesting an impact of comorbid CVD and DM on the clinical and radiographic course of HOA. Additional studies are needed to confirm these findings.

Hand osteoarthritis (HOA) is a highly prevalent condition, can affect one or more joints of the hand, and frequently leads to clinical symptoms and physical limitation (1). Studies of the prevalence of HOA show great variation. For example, in 2011, the Framingham Osteoarthritis Study (2) reported a HOA prevalence of 13% in men and 26% in women >70 years of age, while findings from a study in China showed much lower prevalence values (3.0% of men and 5.8% of women) (3). More recent estimates from the Johnston County Osteoarthritis Project (JoCo OA) have estimated the lifetime risk of developing symptomatic HOA at 40%, further demonstrating the public health significance of this condition (4).

Known risk factors for HOA include advancing age and female sex. Obesity has been implicated with osteoarthritis pathology, especially in the knee and hip joints, where it is known to manifest, at least in part, through a BMI-driven mechanical stress on the joint (5). Obesity is associated with HOA as well, although less consistently (6). As hand joints are not classified as weight-bearing in nature, a more systemic, inflammatory mechanism for HOA has been proposed (7). The relationship between metabolic syndrome (MetS), a condition including hyperglycemia, insulin resistance, obesity, and dyslipidemia, and HOA has been the subject of several studies; some have demonstrated a lack of association between MetS and incident HOA or symptomatic HOA (8,9), while others demonstrate positive relationships between MetS components and HOA (10–17). Additionally, clinical symptoms, physical function, and radiographic changes associated with HOA have been investigated, finding that limitation in physical function correlates with increasing hand pain (18,19).

The association between cardiovascular disease (CVD) and/or diabetes mellitus (DM), and HOA, remains unclear. HOA has been positively associated with higher prevalence of atherosclerosis and endothelial dysfunction (20–24), coronary heart disease (9), cardiovascular

events (14,25), and overall cardiovascular-related mortality (26). Regarding DM, some studies have shown no relationship between HOA and Type 1 or 2 DM (9,14,27–29) or impaired glucose metabolism (30), but one cross-sectional study (31) found DM patients had more than double the odds of hand or knee OA, while another study showed an increased prevalence of hand enthesophytes, or bony spurs associated with HOA, in individuals with DM (32). To date, research in this area has been limited by a lack of standardized methods across studies for assessing DM or CVD presence and measuring and quantifying HOA presence and severity, as well as differences in study populations, sources of participants, duration of follow up, and overall study design.

Our study objective was to further assess associations between radiographic changes, pain, and function in HOA and self-reported DM and CVD in a large, longitudinal community-based cohort using standardized assessments and an advanced statistical approach, in a hypothesis-generating manner.

Participants and Methods:

Study Participants

We used data from the Johnston County Osteoarthritis Project (JoCo OA), a large, prospective community-based cohort, well-characterized for a variety of OA-related risk factors and outcomes as well as general health and comorbid conditions. The details of this cohort are described elsewhere (33). In brief, an original (baseline data collection between 1991-1997) cohort and enrichment (baseline data collection between 2003-2004) cohort were enrolled and followed approximately every 6 years such that follow-up data were collected between 1999-2003 for the original and between 2006-2011 and 2013-2015 for both the original and

enrichment cohorts. At baseline, participants were: non-institutionalized civilian African-American (oversampled to equal roughly 1/3 of the cohort) or Caucasian men or women, adults ≥45 years of age, residents of one of six chosen townships of Johnston County, North Carolina, as detailed elsewhere (4,33). HOA symptoms and radiographic measurements were not collected at baseline for the JoCo OA; thus for this study, we analyzed data from the three subsequent study visits (the baseline visit was either the 1999-2003 follow up or the 2003-2004 cohort enrichment). The study has been continuously approved by the University of North Carolina Institutional Review Board (IRB# 92-0583).

Covariates

The JoCo OA protocol consisted of both home interviews and clinic visits. Static covariates included: age, sex, race, and education level (categorized as < 12 or ≥12 years of education). Covariates treated as time-varying in our analysis, collected at all three time points, were: body mass index (BMI), symptomatic knee OA (sxKOA) status, non-steroidal anti-inflammatory drug (NSAID) use, and self-reported DM and CVD status. BMI was derived from height and weight measurements at each clinic visit, with obesity defined as a BMI of ≥ 30kg/m^2. We determined NSAID use (any type) from review of medication lists. SxKOA was defined as 1) a Kellgren-Lawrence score ≥2 in at least 1 knee (by a single, experienced musculoskeletal radiologist [JBR] with high reliability (33)) and 2) in the same knee, an answer of "yes" to the question, "On most days of any one month in the last 12 months, did you have pain, aching or stiffness in your right|left knee?" For defining CVD and DM, participants were read the following statement: "Please tell me which of the following conditions or illnesses a doctor, nurse, or health professional has told you that you have now or have ever had." Self-reported DM status was then elicited through a yes/no answer to "diabetes or high blood sugar." Across

data collection cycles, cardiovascular disease status was assessed with increasing inclusiveness and specificity (baseline: heart attack, other heart problems, cerebrovascular accident; 1st follow-up: added angina, congestive heart failure; 2nd follow-up: added peripheral vascular disease). We assessed each patient's number of clinical comorbidities, for a maximum of 3 (DM, CVD, and obesity), at every time point.

Hand Symptoms and Radiographic HOA Assessment

The same radiologist (JBR) assessed each of the 30 joints of both hands on posteroanterior radiographs for signs of radiographic hand OA (rHOA) by using a standard OA atlas (34). Hand radiographs from all 3 time points were assessed simultaneously in known time order. Reliability of rHOA assessment by the radiologist was previously demonstrated to be good-to-excellent (4). Participants were classified as having rHOA if they met the Genetics of Generalized Osteoarthritis (GOGO) study criteria (35): Kellgren-Lawrence severity grade of 2 or more in at least 3 joints with 2 of these 3 in the same joint group (distal interphalangeal joint [DIP], proximal interphalangeal joint [PIP], and /or carpometacarpal joint [CMC]) across both hands, involving at least one DIP, and with no more than 3 swollen metacarpophalangeal joints (36). For classification purposes, the thumb interphalangeal joint was categorized as a PIP joint (4).

Pain and function were assessed using the AUStralian CANadian Osteoarthritis Hand Index (AUSCAN), a validated self-report measure of hand pain, stiffness, and function with a question response range of 0 to 4 (none to extreme) (37,38). The pain (5-item) and function (9-item) subscales were considered individually for analysis.

Statistical Analysis

Descriptive statistics were calculated as frequencies and percentages for categorical variables, and as means and standard deviations for continuous variables. The AUSCAN pain subscore values were dichotomized using upper and lower quartile cutoffs (at the 75th percentile, or a numeric score of 6), as noted in previous literature (18) and supported by close correspondence between these quartile values and a calculated pain subscore based on all "mild" responses. An AUSCAN pain subscore<=6 was defined as "low pain" and an AUSCAN pain subscore>6 was defined as "high pain." This same method was used in assessing functional limitation and establishing a cutoff value for the 9-question AUSCAN physical function subscale (at the 75th percentile, or a score of 9). An AUSCAN function subscore<=9 was defined as "better function" and an AUSCAN function subscore>9 was defined as "worse function."

At the participant level, and if present in at least one hand, the following four GOGO rHOA and AUSCAN pain states were defined: A) No rHOA with low pain; B) rHOA with low pain; C) No rHOA and high pain; D) rHOA and high pain, **Figure 1**). Similar states were defined using AUSCAN functional cutoffs (shown in Figure 3). Types of modeled transitions (i.e., transitions among consecutive visit pairs) can be summarized as: incident rHOA (State A to State B, and State C to State D), worsening pain/function (State A to State C, and State B to State D, and improvement in pain/function (State C to State A, and State D to State B). Transitions from a state of rHOA to no rHOA (State B to State A, State D to State C) were not modeled (not a common or clinically relevant change).

To assess the independent association of comorbid conditions with changes in hand OA and symptom characteristics, a time-to-event approach was used to allow for: 1) study of hand event outcomes with non-exact times of transition (managed as interval-censored) and time-dependent main effects and 2) multiple hand event states of interest. We used Markov multi-state survival

models (MSMs) for interval-censored outcomes using parametric, piecewise constant exponential distributions to define a four-state progressive model and transitions of interest (above and Figure 1). MSMs use the theory of stochastic processes (a set of random variables representing the evolution of a process over time) to assess transitions between states in continuous time. Under the Markov assumption, future transitions were assumed to depend only on the current state, independent of time. The MSMs were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for each comorbid condition and the 6 transitions simultaneously. All models were person-based and adjusted for aforementioned static covariates (e.g., sex), or time-dependent covariates which were allowed to change at observed times (e.g., BMI). Each comorbid condition was examined individually in an overall model. In a separate model, a count variable of comorbid conditions of DM, CVD, and obesity, ranging from 0 to 3, was assessed for its association with HOA states. All MSM analysis was conducted using R software via the **msm** package (39).

Results

A total of 845 participants from the JoCo OA longitudinal cohort had all baseline covariates and comprised the complete case analysis sample (**Figure 2**). The two study follow-ups were at a mean ± SD of 6.4 ± 0.8 and 12.0 ± 1.2 years from baseline, respectively. At baseline, the mean age was 60 ± 7.4 years, with approximately one-quarter of individuals age 65 years or older. Two-thirds were women and nearly one-third were African American (**Table 1**). The average BMI of the study population at baseline (30.9 ± 6.5kg/m^2) was at the lower end of the obese classification (40), and remained relatively consistent over the study intervals (**Table 1**). One in five participants self-reported CVD at baseline, increasing to over 40% at the 2nd

follow-up. Similarly, about 10% of individuals had DM at baseline, with this percentage increasing to be three-fold by the 2nd follow-up. Approximately 15% of the study population had symptomatic knee OA (sxKOA) at baseline, increasing to 25% by the 2nd follow-up. Finally, NSAID use (any, regardless of type, purpose, or duration) was reported by almost half of study participants at baseline with over 2/3 of individuals using NSAIDs by the final data collection cycle. For the outcomes, 24% of the participants had high hand pain and 8% had rHOA at baseline. At baseline, median (IQR) was 0 (0-6) for AUSCAN pain and 1 (0-9) for AUSCAN function.

Transitions defined by rHOA and AUSCAN Pain subscores

The majority of individuals remained in State A without rHOA and low pain. As an individual could contribute or make multiple transitions during follow-up, the number of transitions is not equivalent to number of participants (**Figure 1**).

For incident rHOA, there were 77 transitions to incident rHOA while maintaining low pain (State A to State B) and 22 transitions to incident rHOA while maintaining high pain (State C to State D). No significant associations were seen between DM or CVD and the transition to incident rHOA, although some comparisons were limited by small numbers (**Table 2**).

For worsening pain (from low to high pain), there were 123 transitions in those without rHOA (State A to State C) and 36 in those with rHOA (State B to State D). No significant associations were seen between CVD and worsening of AUSCAN pain subscore (**Table 2**). However, there was a statistically significant association between having or developing DM and worsening pain in individuals with rHOA [State B to State D; **Table 2**].

For improvement in pain (from high to low pain), there were 126 transitions in those without rHOA (State C to State A) and 20 in those with rHOA (State D to State B, **Figure 1**). As

shown in Table 2, individuals who had or developed CVD during the course of the study, versus those who did not, had a significantly lower hazard of improvement in pain regardless of rHOA status [(State C to State A), aHR (95% CI): 0.58 (0.36, 0.92); (State D to State B), aHR (95% CI): 0.13 (0.02, 0.77)].

Transitions defined by rHOA and AUSCAN Function subscores

For incident rHOA, there were 73 transitions to incident rHOA while maintaining a better functional status (State A to State B) and 24 transitions to incident rHOA while maintaining a worse functional status (State C to State D). No significant associations were seen between DM or CVD and the transition to incident rHOA (**Table 3**).

For worsening function (from better to worse function), there were 141 transitions in those without rHOA (State A to State C) and 37 transitions in those with rHOA (State B to State D). No significant associations were seen between DM or CVD and worsening function, regardless of rHOA status (**Table 3**), although there was a borderline association between having or developing CVD and risk of worsening function in the setting of rHOA (State B to State D, aHR 3.55, 95% CI [0.88, 14.3]).

For improvement of function (from worse to better function), there were 119 transitions in those without rHOA (State C to State A) and 13 transitions in those with rHOA (State D to State B). Compared to individuals without DM, those with DM and no rHOA had a 42% lower rate of improvement of hand function in (State C to State A, **Table 3**). Those with CVD and no rHOA, compared to those without CVD, also showed a borderline significant reduced hazard for improvement in AUSCAN function subscore (State C to State A, **Table 3**).

When a count of comorbidities (obesity, DM, and CVD) was used, those with one or two comorbidities compared to those with none had about half the hazard of improvement in pain in

the absence of rHOA (State C to A, aHR for 1 [95%CI]: 0.53 [0.32, 0.89]; aHR for 2: 0.57 [0.31, 1.04]). Those with all 3 comorbidities had over 60% reduced hazard for improvement in pain (aHR: 0.34 [0.13, 0.88]). Those with one or two comorbidities, compared with none, also had a reduced hazard for improvement in function without rHOA (State C to A, aHR for 1 [95%CI]: 0.60 [0.36, 1.02]; aHR for 2: 0.55 [0.30, 1.01]). Additionally, those with 1-2 comorbidites had about four times the hazard of developing worsening function in the setting of rHOA (State B to D, aHR for 1: 4.05 [1.52, 10.84]; aHR for 2: 3.98 [1.07, 14.85]). This was not seen in the AUSCAN function model for those with 3 comorbidities.

Discussion

In this study, we examined the effects of DM and CVD on the radiographic, symptomatic, and functional transitions of HOA. We found that comorbid DM increased the odds of worsening AUSCAN pain among those with rHOA, while comorbid CVD significantly reduced the chance of AUSCAN pain score improvement in those with and without rHOA. Improvement in hand function was less likely in those with DM or CVD, compared to those without these comorbidities. Finally, the concurrence of multiple comorbidities (obesity, DM, and CVD) was associated with 1) less likely improvement in pain or functional status in those with rHOA and 2) more likely worsening function in the presence of rHOA.

The imperfect concordance between hand pain/disability and the presence of rHOA (19) suggests a need for further investigation into other determinants (e.g., CVD or DM) of the HOA disease process (41). Pain can influence the course of OA, acting as a mediator in the loss of hand function (18). Patients reporting high levels of pain at baseline in one study exhibited greater functional limitation and worse pain outcomes in the long term, with only a quarter of

individuals experiencing an improvement in HOA symptoms over six years (19). Another study demonstrated that progression of pain and functional limitation can occur in a many HOA patients over just two years (42).

In our study, HOA patients with comorbid DM experienced an increased hazard for worsening pain in the presence of radiographic changes. There is a lack of consensus regarding the association between DM and HOA, due to differences in definitions and cohorts. An increased prevalence of hand pain, disability, and stiffness not explained by radiographic changes or peripheral neuropathy in a group of Type 1 DM patients was seen in the Dialong Hand Study (27). DM was significantly associated with an increased prevalence of symptomatic HOA in a Chinese Han population (20). On the other hand, findings from the Netherlands Epidemiology of Obesity study demonstrated no connection between DM and AUSCAN pain in cross-sectional analysis of all participants (30). A systematic review (43) on DM as a risk factor for HOA revealed no studies that indicated DM as an independent risk factor for HOA. Study designs differ, as the NEO study was cross-sectional, Courties et al (9) incorporated a 3-year longitudinal follow-up of only rHOA patients, compared to our 6- and 12-year follow-up of individuals including those without rHOA. Several studies have demonstrated a relationship between DM and erosive HOA, a more progressive and severe form of the disease (27,30,44).

Research into the co-occurrence of CVD and HOA in patients has also given inconsistent results. CVD-related comorbidities have been closely linked to symptomatic HOA (14) and even proposed to be an independent risk factor for HOA development (45); symptomatic HOA was also associated with an increased prevalence of coronary heart disease in the Framingham Heart Study (25). Other studies have found no association (13,46,47). Atherosclerosis and resultant coronary heart disease has been associated with rHOA severity (22), contrary to our study

findings; however, previous associations with increased AUSCAN pain score and deterioration of Functional Index of Hand Osteoarthritis score (9) concur with our results. Several pathophysiological mechanisms have been proposed. It is known, for example, that in patients with OA, inflammatory mediators are released from the joint into systemic circulation, thereby rendering a low-grade inflammation thought to induce atherosclerosis (48). Given the many connections and proposed mechanisms, and the complex relationship between HOA and CVD, this is an area in need of further research.

As little is known about the clinical course and progression of pain and functional limitation in HOA patients (42), the longitudinal design of our study, and the relatively large sample size, stands out when compared to many of the prior longitudinal and cross-sectional investigations. The JoCo OA study design also allowed for analysis of time-varying covariates at each time point, thus providing a more complete picture of the interplay between comorbidities and clinical and radiological course of HOA. However, this work also has limitations. Despite our overall large sample, small numbers were seen for several of the transition states, complicating analysis and interpretation of the findings and leading to large confidence intervals; as such the study is hypothesis-generating. The self-reported nature of the comorbid conditions and the medication lists (generic or brand name) also could be a limitation, although likely less so for DM (where positive and negative predictive values compared to medical records in prior studies have been >80% (49)) than for CVD (where under-reporting and specific diagnosis reporting can be an issue, (50) although better results are seen for more inclusive, composite categories). Those classified as using NSAIDs for HOA symptom and pain management may have been using low-dose aspirin for CVD prevention, which could account for the counter-intuitive CVD findings. We used stringent definitions of rHOA (via the GOGO criteria) and

AUSCAN thresholds that reflect a more severe phenotype and may not be generalizable to milder disease. Finally, while a strength of this community-based study is that findings may be extended to the general population, the lower-income, semirural southern US population of the JoCo OA may limit generalizability.

Conclusion

Overall, DM and CVD were common comorbidities in this cohort, in line with trends in the general population, and having or developing either condition alone or in combination tended to result in a reduced likelihood of symptomatic and functional improvement and an increased likelihood for worsening in both outcomes with regard to the hands over time. With an aging population and growing presence of multi-morbidity among middle age and older adults, the relationships among common chronic diseases, such as OA, DM and CVD, are of interest and warrant further research.

Acknowledgements

We would like to thank the staff and participants in the Johnston County Osteoarthritis Project without whom this work would not be possible.

Funding was provided in part by: Medical Student Training in Aging Research program through NIA 2-T35-AG038047-08, NIAMS P60 AR049465 and P30 AR072580 and Centers for Disease Control and Prevention U01DP006266.

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Figure Legends

Figure 1. Four-state progressive model for radiographic hand OA and AUSCAN pain (cutoff ≤6 as Low AUSCAN pain or > 6 as High AUSCAN pain); numbers represent transitions among consecutive visit pairs in that a given participant could contribute up to two transitions. OA=osteoarthritis, rHOA=radiographic hand OA (according to the Genetics of Generalized Osteoarthritis [GOGO] definition (35)); AUSCAN = AUStralian CANadian Osteoarthritis Hand Index.

Legend text (visual on figure): No change in gray arrow; incident rHOA in double line arrow; worsening symptoms in bold arrow; symptomatic improvement in dashed arrow.

Figure 2. Distribution of participants in the hand OA study sample from the Johnston County Osteoarthritis Project. Baseline participants are shown at the top with detailed inclusion/exclusion criteria leading to the complete case sample. Note that x-rays from individuals at baseline who did not follow up have not been read (for priority reasons).

Figure 3. Four-state progressive model for radiographic hand OA and AUSCAN function subscore (cutoff ≤9 as better AUSCAN function or > 9 as worse AUSCAN function); numbers represent transitions among consecutive visit pairs in that a given participant could contribute up to two transitions. OA=osteoarthritis, r rHOA=radiographic hand OA (according to the Genetics of Generalized Osteoarthritis [GOGO] definition (35)); AUSCAN = AUStralian CANadian Osteoarthritis Hand Index.

Legend text (visual on figure): No change in gray arrow; incident rHOA in double line arrow; worsening function in bold arrow; functional improvement in dashed arrow.

Table 1. Sociodemographic and clinical characteristics of the study population at baseline and time-varying characteristics over the 2 follow-up cycles.

Characteristics	Study Visit					
	Baseline (n=852)		1st Follow-Up 6.4 ± 0.8 years (n=815)		2nd Follow-Up 12.0 ± 1.2 years (n=845)	
	n or mean	% or ± SD	n or mean	% or ± SD	n or mean	% or ± SD
Static Covariates						
Age, mean ± SD years	59.5	± 7.4	66.1	± 7.5	71.4	± 7.7
Age ≥ 65	202	23.9	413	50.7	669	79.2
Women	574	67.9	555	68.1	574	67.9
African American	277	32.8	258	31.7	277	32.8
<12 years education	118	14.0	115	14.1	118	14.0
Time-Varying Covariates						
NSAIDs	396	46.9	538	66.0	582	68.9
sxKOA	129	15.3	171	21.0	214	25.3
BMI, mean ± SD kg/m^2	30.9	± 6.5	31.7	± 6.5	30.9	± 6.4
Obesity (BMI≥30 kg/m^2)	408	48.3	443	54.4	424	50.2
CVD	158	18.7	265	32.5	365	43.2
DM	94	11.1	165	20.2	251	29.7
Obesity, DM, and CVD Count						
0	340	40.2	248	30.4	212	25.1
1	367	43.4	317	38.9	308	36.4
2	121	14.3	194	23.8	243	28.8
3	17	2.0	56	6.9	82	9.7
Transition States						
Four states (GOGO rHOA and AUSCAN pain)						
(missing)	*3*	*0.4*	*5*	*0.6*	*11*	*1.3*
(A) No GOGO rHOA, low AUSCAN pain	604	71.5	545	66.9	502	59.4
(B) GOGO rHOA, low AUSCAN pain	37	4.4	85	10.4	112	13.3
(C) No GOGO rHOA, high AUSCAN pain	174	20.6	131	16.1	132	15.6
(D) GOGO rHOA, high AUSCAN pain	27	3.2	49	6.0	88	10.4
Four states (GOGO rHOA and AUSCAN function)						

(missing)	*2*	*0.2*	*5*	*0.6*	*12*	*1.4*
(A) No GOGO rHOA, better AUSCAN function	594	70.3	540	66.3	462	54.7
(B) GOGO rHOA, better AUSCAN function	37	4.4	77	9.4	98	11.6
(C) No GOGO rHOA, worse AUSCAN function	185	21.9	136	16.7	171	20.2
(D) GOGO rHOA, worse AUSCAN function	27	3.2	57	7.0	102	12.1

*SD = standard deviation; NSAIDs = Non-steroidal anti-inflammatory drugs; sxKOA = symptomatic knee osteoarthritis; BMI = Body mass index; CVD = cardiovascular disease; DM = diabetes mellitus; rHOA = radiographic hand osteoarthritis according to the Genetics of Generalized Osteoarthritis (GOGO) study (35); AUSCAN = AUStralian CANadian Osteoarthritis Hand Index, pain and function subscales; Low AUSCAN pain = AUSCAN pain score ≤6; High AUSCAN pain = AUSCAN pain score >6; Better AUSCAN function= AUSCAN function score ≤9; Worse AUSCAN function = AUSCAN function score >9.

Table 2. Adjusted* hazard ratios with 95% confidence intervals of radiographic and AUSCAN pain state transitions in participants with diabetes mellitus (DM) or cardiovascular disease (CVD) compared to those without DM or CVD

Type of Transition	State Transition	DM vs. no DM	CVD vs. no CVD
		n1 [DM])/n2 [no DM] aHR (CI 95%)	*n1[CVD])/ n2 [no CVD]* aHR (CI 95%)
Incident GOGO rHOA	(A) No GOGO rHOA and low AUSCAN Pain → (B) GOGO rHOA and low AUSCAN Pain	*14/63* 1.01 (0.51, 1.99)	*20/57* 0.76 (0.45, 1.26)
	(C) No GOGO rHOA and high AUSCAN Pain → (D) GOGO rHOA and high AUSCAN Pain	*2/20* †	*13/9* 1.58 (0.64, 3.93)
Worsening AUSCAN pain	(A) No GOGO rHOA and low AUSCAN Pain → (C) No GOGO rHOA and high AUSCAN Pain	*36/87* 0.97 (0.55, 1.71)	*52/71* 0.99 (0.63, 1.55)
	(B) GOGO rHOA and low AUSCAN Pain → (D) GOGO rHOA and high AUSCAN Pain	*11/25* **5.08 (1.38, 18.77) ‡**	*13/23* 1.08 (0.39, 3.01)
Improvement in AUSCAN pain	(C) No GOGO rHOA and high AUSCAN Pain → (A) No GOGO rHOA and low AUSCAN Pain	*34/92* 0.87 (0.53, 1.41)	*54/72* **0.58 (0.36, 0.92) ‡**
	(D) GOGO rHOA and high AUSCAN Pain → (B) GOGO rHOA and low AUSCAN Pain	*7/13* 4.48 (0.92, 21.89)	*6/14* **0.13 (0.02, 0.77) ‡**

DM = diabetes mellitus; CVD = cardiovascular disease; aHR = adjusted hazard ratio; rHOA = radiographic hand osteoarthritis according to the Genetics of Generalized Osteoarthritis (GOGO) study (35); AUSCAN = AUStralian CANadian Osteoarthritis Hand Index; Low AUSCAN pain = AUSCAN pain score ≤6; High AUSCAN pain = AUSCAN pain score >6

* Adjusted for static (age, sex, race, education level) and time-varying (BMI, sxKOA, NSAID use) covariates

† aHR and 95% CI not estimable due to small sample size

‡ Statistically significant

Table 3. Adjusted* hazard ratios with 95% confidence intervals of radiographic and AUSCAN function state transitions in participants with diabetes mellitus (DM) or cardiovascular disease (CVD) compared to those without DM or CVD

Type of Transition	State Transition	DM vs. no DM *n1 [DM])/n2 [no DM]* aHR (CI 95%)	CVD vs. no CVD *n1[CVD])/ n2 [no CVD]* aHR (CI 95%)
Incident GOGO rHOA	(A) No GOGO rHOA and better AUSCAN Function → (B) GOGO rHOA and better AUSCAN Function	*18/55* 0.64 (0.24, 1.70)	*17/56* 0.77 (0.43, 1.40)
	(C) No GOGO rHOA and worse AUSCAN function → (D) GOGO rHOA and worse AUSCAN Function	*6/18* 0.53 (0.15, 1.89)	*12/12* 1.18 (0.46, 3.04)
Worsening AUSCAN function	(A) No GOGO rHOA and better AUSCAN function → (C) No GOGO rHOA and worse AUSCAN function	*42/99* 0.88 (0.52, 1.50)	*65/76* 1.15 (0.74, 1.78)
	(B) GOGO rHOA and better AUSCAN function → (D) GOGO rHOA and worse AUSCAN function	*12/25* †	*17/20* 3.55 (0.88, 14.3)
Improvement in AUSCAN function	(C) No GOGO rHOA and worse AUSCAN function → (A) No GOGO rHOA and better AUSCAN function	*37/82* **0.58 (0.34, 0.98) ‡**	*49/70* 0.66 (0.41, 1.06)
	(D) GOGO rHOA and worse AUSCAN function → (B) GOGO rHOA and better AUSCAN function	*3/10* †	*4/9* 0.69 (0.09, 5.43)

DM = diabetes mellitus; CVD = cardiovascular disease; aHR = adjusted hazard ratio; GOGO rHOA = radiographic hand osteoarthritis according to the Genetics of Generalized Osteoarthritis (GOGO) study (35); AUSCAN = AUStralian CANadian Osteoarthritis Hand Index; Better AUSCAN function= AUSCAN function score ≤9; Worse AUSCAN function = AUSCAN function score >9.

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† aHR and 95% CI not estimable due to small sample size

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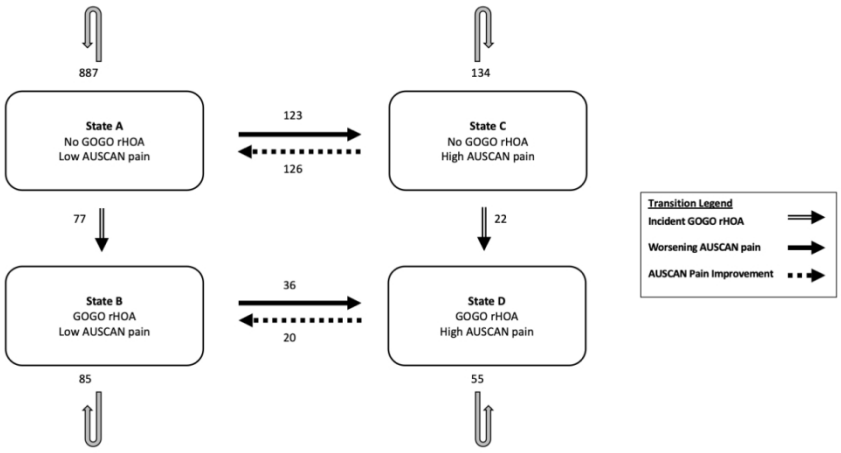

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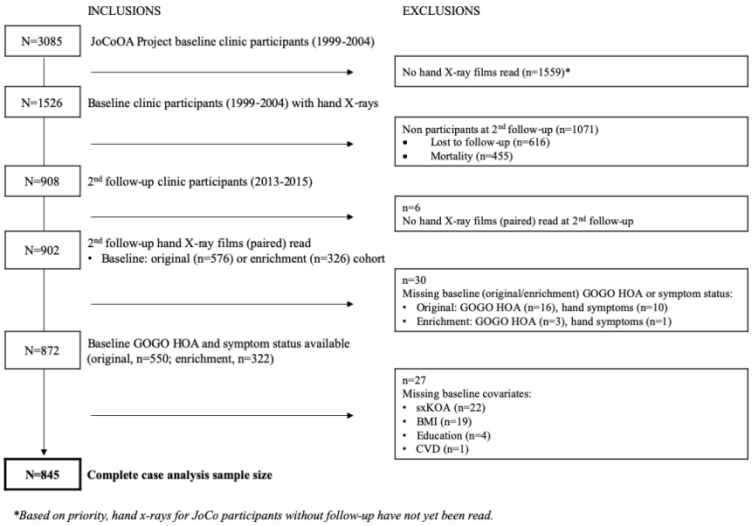

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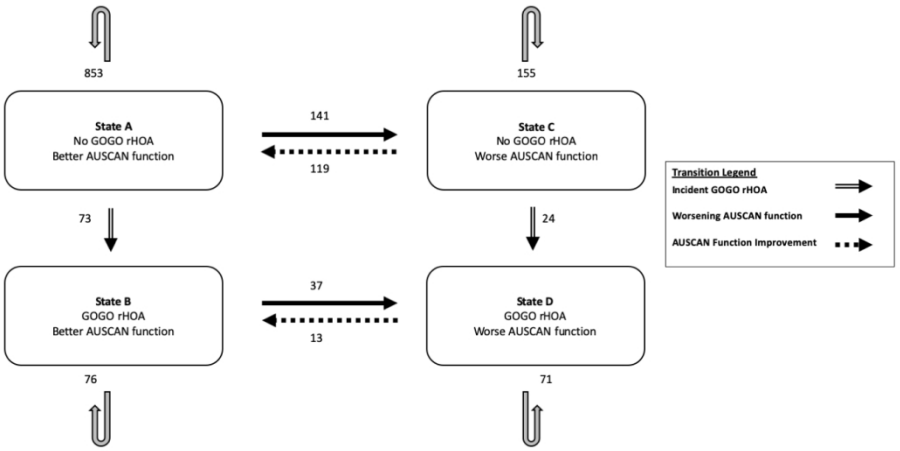

Figure 3. Four-state progressive model for radiographic hand OA and AUSCAN function subscore (cutoff ≤9 as better AUSCAN function or > 9 as worse AUSCAN function); numbers represent transitions among consecutive visit pairs in that a given participant could contribute up to two transitions. OA=osteoarthritis, r rHOA=radiographic hand OA (according to the Genetics of Generalized Osteoarthritis [GOGO] definition (35)); AUSCAN = AUStralian CANadian Osteoarthritis Hand Index.

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