The Journal of Rheumatology 2020;47:1541–9
doi:10.3899/jrheum.191075
First Release September 1 2020

The Journal of Rheumatology

Effects of Comorbid Cardiovascular Disease and Diabetes on Hand Osteoarthritis, Pain, and Functional State Transitions: The Johnston County Osteoarthritis Project

Zachary A. Scherzer[1], Carolina Alvarez[2], Jordan B. Renner[3], Louise B. Murphy[4], Todd A. Schwartz[5], Joanne M. Jordan[6], Yvonne M. Golightly[7], and Amanda E. Nelson[8]

ABSTRACT. ***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 timepoints from 845 Johnston County Osteoarthritis Project participants (two-thirds women, one-third African Americans, mean age 60 yrs) with and without HOA, CVD, or DM. A diagnosis of radiographic HOA (rHOA) required a Kellgren-Lawrence severity grade of ≥ 2 in at least 3 joints in each hand. A 4-state progressive model included transitions based on rHOA and pain or function as defined using the Australian/Canadian HOA Index (AUSCAN). Markov multistate models estimated HR (aHR) and 95% CI 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 effect of comorbid CVD and DM on the clinical and radiographic course of HOA. Additional studies are needed to confirm these findings.

Key Indexing Terms: cardiovascular diseases, comorbidity, diabetes mellitus, hand, obesity, osteoarthritis

Hand osteoarthritis (HOA) is a highly prevalent condition, can affect 1 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 an 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) set 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 OA pathology, especially in the knee and hip joints, where it is known to manifest, at least in part, through a body mass index (BMI)-driven mechanical stress on the joint[5]. Obesity is associated with HOA

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 CDC U01DP006266. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

[1]Z.A. Scherzer, BS, Medical Student, Oakland University William Beaumont School of Medicine, Rochester, Missouri, and Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [2]C. Alvarez, MS, Statistician, Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [3]J.B. Renner, MD, Professor of Radiology and Allied Health Sciences, Thurston Arthritis Research Center, and Department of Radiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [4]L.B. Murphy, PhD, Senior Service Fellow/Epidemiologist, Division of Population Health, Centers for Disease Control and Prevention, Atlanta, Georgia; [5]T.A. Schwartz, DrPH, Associate Professor of Biostatistics, Thurston Arthritis Research Center, and Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [6]J.M. Jordan, MD, MPH, Joseph P. Archie, Jr. Eminent Professor of Medicine and Vice Dean for Faculty Affairs and Leadership Development, Thurston Arthritis Research Center, and Department of Medicine, and Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [7]Y.M. Golightly, PT, PhD, Assistant Professor of Epidemiology, Thurston Arthritis Research Center, and Department of Epidemiology, Gillings School of Global Public Health, and Injury Prevention Research Center, and Division of Physical Therapy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [8]A.E. Nelson, MD, MSCR, Associate Professor of Medicine, Thurston Arthritis Research Center, and Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Address correspondence to Dr. A.E. Nelson, University of North Carolina at Chapel Hill, Thurston Arthritis Research Center, 3300 Doc J. Thurston Building, Campus Box 7280, Chapel Hill, NC 27599-7280, USA. Email: aenelson@med.unc.edu.

Accepted for publication January 29, 2020.

as well, although less consistently[6]. Because hand joints are not classified as weight-bearing in character, 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[20,21,22,23,24], coronary heart disease[9], CV events[14,25], and overall CV-related mortality[26]. Regarding DM, some studies have shown no relationship between HOA and type 1 or 2 DM[9,14,27,28,29] or impaired glucose metabolism[30], but 1 cross-sectional study[31] found patients with DM 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.

MATERIALS AND METHODS

Study participants. We used data from the 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 and 1997) cohort and enrichment (baseline data collection between 2003 and 2004) cohort were enrolled and followed about every 6 years. Follow-up data were collected between 1999 and 2003 for the original, and 2006–2011 and 2013–2015 for both the original and enrichment cohorts. At baseline, participants were noninstitutionalized civilian African American (oversampled to equal roughly one-third of the cohort) or white men or women, adults ≥ 45 years of age, residents of 1 of 6 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 our study, we analyzed data from the 3 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# 920583).

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 yrs of education). Covariates treated as time-varying in our analysis, collected at all 3 timepoints, were BMI, symptomatic knee OA (sxKOA) status, nonsteroidal antiinflammatory 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 ≥ 30 kg/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, CVD status was assessed with increasing inclusiveness and specificity (baseline: heart attack, other heart problems, cerebrovascular accident; first follow-up: added angina, congestive heart failure; second 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 timepoint.

Hand symptoms and rHOA assessment. The same radiologist (JBR) assessed each of the 30 joints of both hands on posteroanterior radiographs for signs of rHOA by using a standard OA atlas[34]. Hand radiographs from all 3 timepoints 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] across both hands, involving at least 1 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 0–4 (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 SD 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 1 hand, the following 4 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; and (D) rHOA and high pain (Figure 1). Similar states were defined using AUSCAN functional cutoffs (Figure 2). Types of modeled transitions (i.e., transitions among consecutive visit pairs) can be summarized as follows: 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, and 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 HOA and symptom characteristics, a time-to-event approach was used to allow for (1) study of hand event outcomes with nonexact times of transition (managed as interval-censored) and time-dependent main effects, and (2) multiple hand event states of interest. We used Markov multistate survival models (MSM) for interval-censored outcomes using parametric, piecewise constant exponential distributions to define a 4-state progressive model and transitions of interest (above and Figure 1). MSM 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 MSM were used to estimate HR and 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 through the msm package (R Foundation for Statistical Computing)[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 3). The 2 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 about one-quarter of individuals age 65 years or older. Two-thirds were women and nearly one-third were African American (Table 1A). The average BMI of the study population at baseline (30.9 ± 6.5 kg/m^2) was at the lower end of the obese classification[40], and remained relatively consistent over the study intervals (Table 1A). One in 5 participants self-reported CVD at baseline, increasing to over 40% at the second follow-up. Similarly, about 10% of individuals had DM at baseline, with this percentage increasing to 3-fold by the second follow-up. About 15% of the study population had sxKOA at baseline, increasing to 25% by the second 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 of 3 individuals using NSAID 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 (interquartile range) 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 (Table 1B). Because an individual could contribute or make multiple transitions during follow-up, the number of transitions is not equivalent to the 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

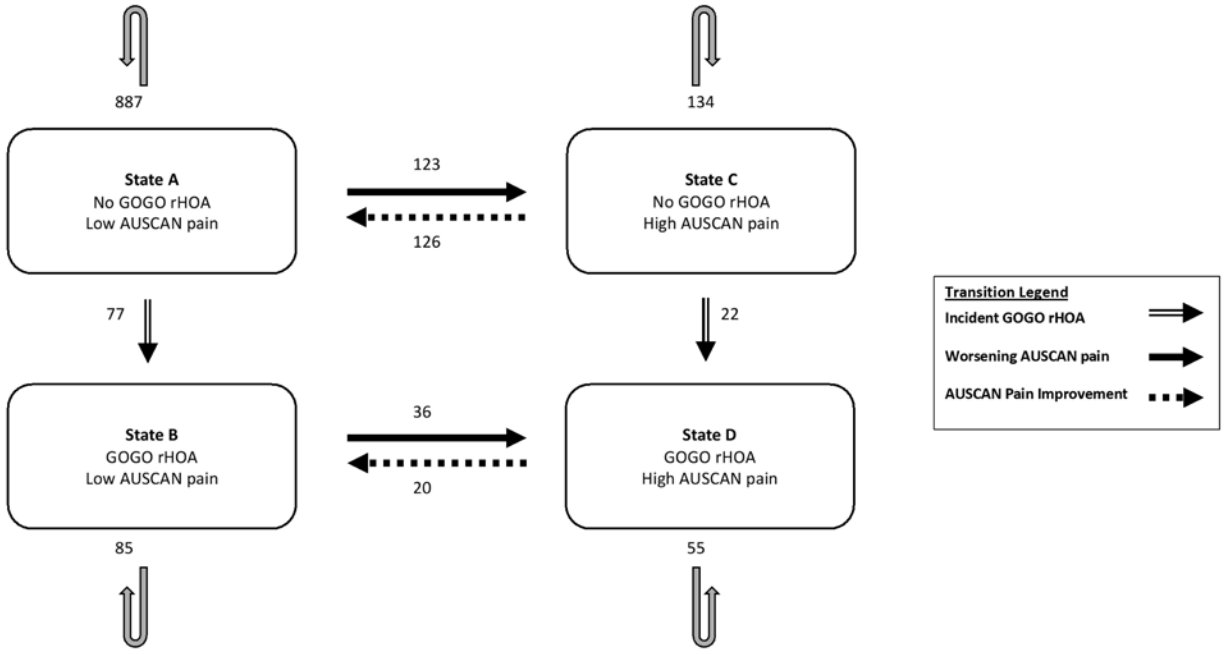

Figure 1. Four-state progressive model for rHOA and AUSCAN pain (cutoff ≤ 6 as low AUSCAN pain or > 6 as high AUSCAN pain); numbers represent transitions among consecutive visit pairs in that a given participant could contribute up to 2 transitions. No change in gray arrow; incident rHOA in double line arrow; worsening symptoms in bold arrow; symptomatic improvement in dashed arrow. AUSCAN: Australian Canadian Osteoarthritis Hand Index; GOGO: Genetics of Generalized Osteoarthritis study; rHOA: radiographic hand osteoarthritis (according to the GOGO definition[35]).

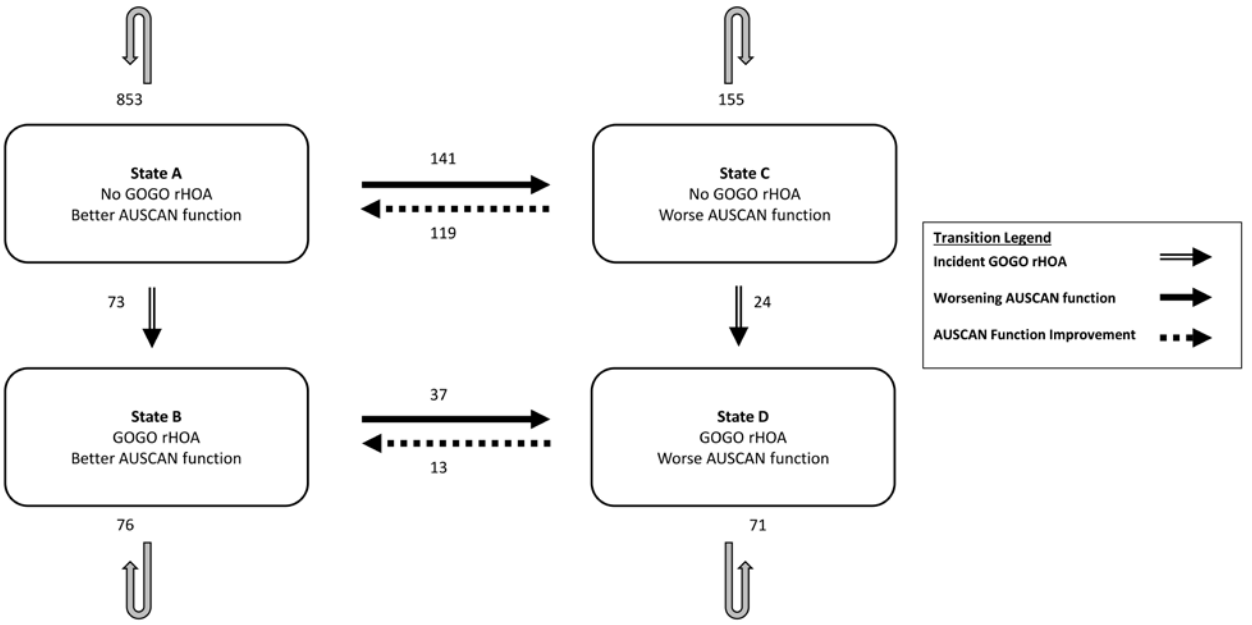

Figure 2. Four-state progressive model for rHOA and AUSCAN function subscore (cutoff ≤ 9 as better AUSCAN function or > 9 as worse AUSCAN function); numbers represent transitions among consecutive visit pairs in that a given participant could contribute up to 2 transitions. No change in gray arrow; incident rHOA in double line arrow; worsening function in bold arrow; functional improvement in dashed arrow. AUSCAN: Australian Canadian Osteoarthritis Hand Index; GOGO: Genetics of Generalized Osteoarthritis study; rHOA: radiographic hand osteoarthritis (according to the GOGO definition[35]).

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 0.58, 95% CI 0.36–0.92; state D to state B: aHR 0.13, 95% CI 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; Figure 2). 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; Figure 2). Compared to individuals without DM, those with DM and no rHOA had a 42% lower rate of improvement of hand function (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 1 or 2 comorbidities compared to those with none had about half the hazard of improvement in pain in the absence of rHOA [state C to state 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, 95% CI 0.13–0.88). Those with 1 or 2 comorbidities, compared with none, also had a reduced hazard for improvement in function without rHOA [state C to state 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 4 times the hazard of developing worsening function in the setting of rHOA [state B to state 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 our 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

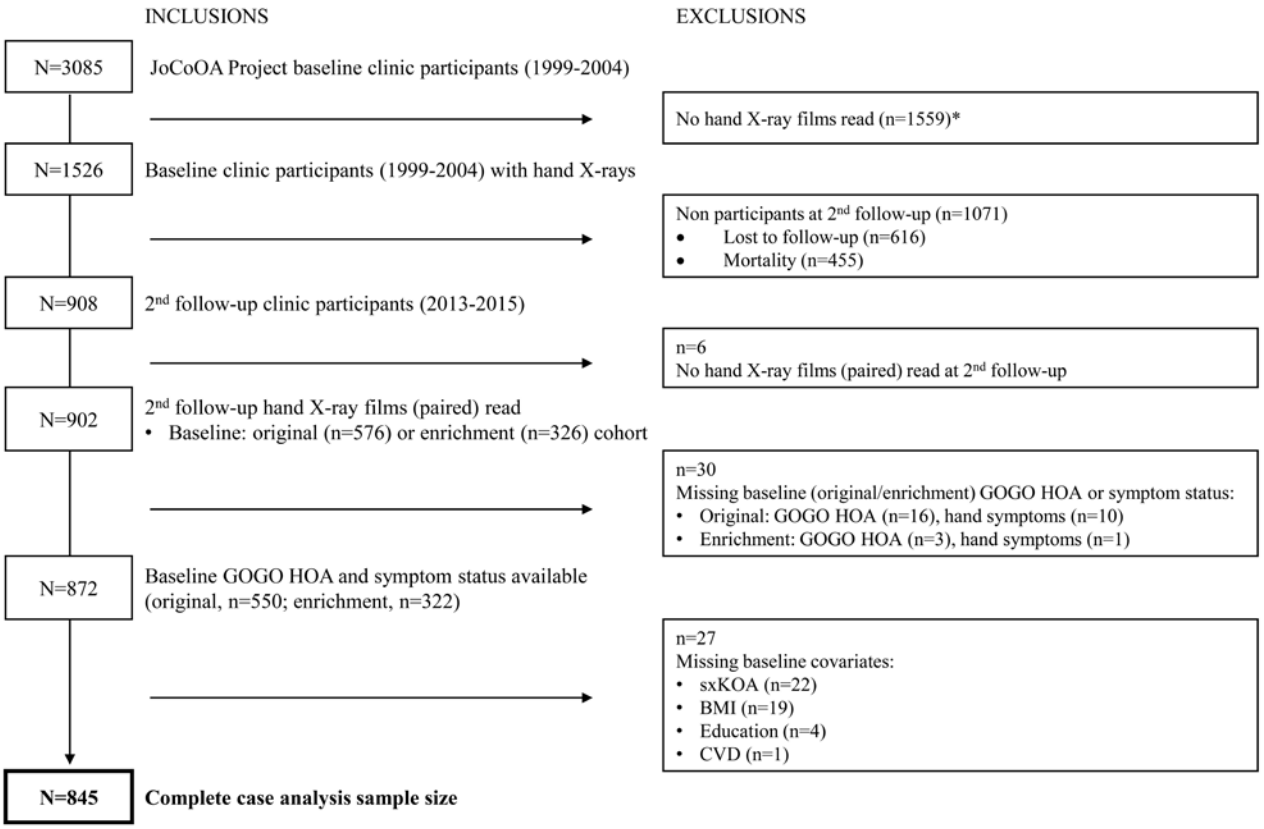

Figure 3. Distribution of participants in the hand OA study sample from the Johnston County Osteoarthritis Project. Baseline participants are shown at the top with detailed inclusion/exclusion criteria leading to the complete case sample. Note that radiographs from individuals at baseline who did not follow up have not been read (for priority reasons). BMI: body mass index; CVD: cardiovascular disease; GOGO: Genetics of Generalized OA study; HOA: hand osteoarthritis; JoCo OA: Johnston County OA Project; sxKOA: symptomatic knee OA.

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 1 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 6 years[19]. Another study demonstrated that progression of pain and functional limitation can occur in many HOA patients over just 2 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 patients with type 1 DM 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; the NEO study was cross-sectional[6]. 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

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

Characteristics	Baseline (n = 852)		Study Visit 1st Follow-up 6.4 ± 0.8 yrs (n = 815)		2nd Follow-up 12.0 ± 1.2 yrs (n = 845)	
	n or Mean	% or ± SD	n or Mean	% or ± SD	n or Mean	% or ± SD
Static covariates						
Age, yrs, mean ± SD	59.5	± 7.4	66.1	± 7.5	71.4	± 7.7
Age ≥ 65 yrs	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 yrs education	118	14.0	115	14.1	118	14.0
Time-varying covariates						
NSAID	396	46.9	538	66.0	582	68.9
sxKOA	129	15.3	171	21.0	214	25.3
BMI, kg/m^2, mean ± SD	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

Table 1B. Transition states of the study population at baseline and over the 2 follow-up cycles.

Transition States	Baseline (n = 852)		Study Visit 1st Follow-up 6.4 ± 0.8 yrs (n = 815)		2nd Follow-up 12.0 ± 1.2 yrs (n = 845)	
	n or mean	% or ± SD	n or mean	% or ± SD	n or mean	% or ± SD
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

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. AUSCAN: Australian Canadian Osteoarthritis Hand Index, pain and function subscales; BMI: body mass index; CVD: cardiovascular disease; DM: diabetes mellitus; GOGO rHOA: radiographic hand osteoarthritis according to the Genetics of Generalized Osteoarthritis (GOGO) study[35]; NSAID: nonsteroidal antiinflammatory drugs; sxKOA: symptomatic knee OA.

comorbidities have been closely linked to symptomatic HOA[14] and even proposed as independent risk factors 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

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

Arrows indicate transition from 1 state to another. Each transition type (column 1) shows 2 state transitions. * Adjusted for static (age, sex, race, education level) and time-varying (BMI, sxKOA, NSAID use) covariates. † aHR and 95% CI not estimable because of small sample size. ‡ Statistically significant. Low AUSCAN pain = AUSCAN pain score ≤ 6; high AUSCAN pain = AUSCAN pain score > 6. aHR: adjusted HR; AUSCAN: Australian Canadian Osteoarthritis Hand Index; GOGO rHOA: radiographic hand osteoarthritis according to the Genetics of Generalized Osteoarthritis (GOGO) study[35].

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

Arrows indicate transition from 1 state to another. Each transition type (column 1) shows 2 state transitions. * Adjusted for static (age, sex, race, education level) and time-varying (BMI, sxKOA, NSAID use) covariates. † aHR and 95% CI not estimable because of small sample size. ‡ Statistically significant. Better AUSCAN function = AUSCAN function score ≤ 9; worse AUSCAN function = AUSCAN function score > 9. aHR: adjusted HR; AUSCAN: Australian Canadian Osteoarthritis Hand Index; BMI: body mass index; GOGO rHOA: radiographic hand osteoarthritis according to the Genetics of Generalized Osteoarthritis (GOGO) study[35]; NSAID: nonsteroidal antiinflammatory drug; sxKOA: symptomatic knee OA.

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.

Because little is known about the clinical course and progression of pain and functional limitation in patients with HOA[42], the longitudinal design of our study, and the relatively large sample size, stand 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 timepoint, 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 CI; therefore, the study is hypothesis-generating. The self-reported aspect 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 underreporting and specific diagnosis reporting can be an issue[50], although better results are seen for more inclusive, composite categories). Those classified as using NSAID for HOA symptom and pain management may have been using low-dose aspirin for CVD prevention, which could account for the counterintuitive CVD findings. We used stringent definitions of rHOA (through 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.

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 regarding the hands over time. With an aging population and growing presence of multimorbidity 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.

ACKNOWLEDGMENT

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

REFERENCES

1. Leung GJ, Rainsford KD, Kean WF. Osteoarthritis of the hand I: aetiology and pathogenesis, risk factors, investigation and diagnosis. J Pharm Pharmacol 2014;66:339-46.
2. Haugen IK, Englund M, Aliabadi P, Niu J, Clancy M, Kvien TK, et al. Prevalence, incidence and progression of hand osteoarthritis in the general population: the Framingham Osteoarthritis Study. Ann Rheum Dis 2011;70:1581-6.
3. Zhang Y, Xu L, Nevitt MC, Niu J, Goggins JP, Aliabadi P, et al. Lower prevalence of hand osteoarthritis among Chinese subjects in Beijing compared with white subjects in the United States: The Beijing Osteoarthritis Study. Arthritis Rheum 2003;48:1034-40.
4. Qin J, Barbour KE, Murphy LB, Nelson AE, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic hand osteoarthritis: The Johnston County Osteoarthritis Project. Arthritis Rheumatol 2017;69:1204-12.
5. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med 2010;26:355-69.
6. Visser AW, Ioan-Facsinay A, de Mutsert R, Widya RL, Loef M, de Roos A, et al; NEO Study Group. Adiposity and hand osteoarthritis: the Netherlands Epidemiology of Obesity study. Arthritis Res Ther 2014;16:R19.
7. Jiang L, Xie X, Wang Y, Wang Y, Lu Y, Tian T, et al. Body mass index and hand osteoarthritis susceptibility: an updated meta-analysis. Int J Rheum Dis 2016;19:1244-54.
8. Strand MP, Neogi T, Niu J, Felson DT, Haugen IK. Association between metabolic syndrome and radiographic hand osteoarthritis: data from a community-based longitudinal cohort study. Arthritis Care Res 2018;70:469-74.
9. Courties A, Sellam J, Maheu E, Cadet C, Barthe Y, Carrat F, et al. Coronary heart disease is associated with a worse clinical outcome of hand osteoarthritis: a cross-sectional and longitudinal study. RMD Open 2017;3:e000344.
10. Baudart P, Louati K, Marcelli C, Berenbaum F, Sellam J. Association between osteoarthritis and dyslipidaemia: a systematic literature review and meta-analysis. RMD open 2017;3:e000442.
11. Frey N, Hügle T, Jick SS, Meier CR, Spoendlin J. Hyperlipidaemia and incident osteoarthritis of the hand: a population-based case-control study. Osteoarthr Cartil 2017;25:1040-5.
12. Garcia-Gil M, Reyes C, Ramos R, Sanchez-Santos MT, Prieto-Alhambra D, Spector TD, et al. Serum lipid levels and risk of hand osteoarthritis: The Chingford prospective cohort study. Sci Rep 2017;7:3147.
13. Addimanda O, Mancarella L, Dolzani P, Ramonda R, Fioravanti A, Brusi V, et al. Clinical associations in patients with hand osteoarthritis. Scand J Rheumatol 2012;41:310-3.
14. Calvet J, Orellana C, Larrosa M, Navarro N, Chillaron JJ, Pedro-Botet J, et al. High prevalence of cardiovascular co-morbidities in patients with symptomatic knee or hand osteoarthritis. Scand J Rheumatol 2016;45:41-4.
15. Kluzek S, Newton JL, Arden NK. Is osteoarthritis a metabolic disorder? Br Med Bull 2015;115:111-21.
16. Dahaghin S, Bierma-Zeinstra SM, Koes BW, Hazes JM, Pols HA. Do metabolic factors add to the effect of overweight on hand osteoarthritis? The Rotterdam study. Ann Rheum Dis 2007; 66:916-20.
17. Visser AW, de Mutsert R, le Cessie S, den Heijer M, Rosendaal FR, Kloppenburg M; NEO Study Group. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. Ann Rheum Dis 2015;74:1842-7.
18. Siviero P, Zambon S, Limongi F, Castell MV, Cooper C, Deeg DJ, et al; EPOSA Research Group. How hand osteoarthritis, comorbidity, and pain interact to determine functional limitation in older people: observations from the European Project on OSteoArthritis Study. Arthritis Rheumatol 2016;68:2662-70.
19. Bijsterbosch J, Watt I, Meulenbelt I, Rosendaal FR, Huizinga TW, Kloppenburg M. Clinical and radiographic disease course of hand osteoarthritis and determinants of outcome after 6 years. Ann Rheum Dis 2011;70:68-73.
20. Wang F, Shi L, Xue QY. Association of metabolic factors with symptomatic hand osteoarthritis in the Chinese Han population aged 40 years and above. Chin Med J 2016;129:2301-7.
21. Koutroumpas A, Giannoukas A, Zintzaras E, Exarchou E, Baliakos A, Makaritsis K, et al. Erosive hand osteoarthritis is associated with subclinical atherosclerosis and endothelial dysfunction. Int J Biomed Sci 2013;9:217-23.
22. Cemeroglu O, Aydin HI, Yasar ZS, Bozduman F, Saglam M, Selcoki Y, et al. Hand and heart, hand in hand: is radiological hand osteoarthritis associated with atherosclerosis? Int J Rheum Dis 2014;17:299-303.
23. Hoeven TA, Kavousi M, Clockaerts S, Kerkhof HJ, van Meurs JB, Franco O, et al. Association of atherosclerosis with presence and progression of osteoarthritis: the Rotterdam Study. Ann Rheum Dis 2013;72:646-51.
24. Jonsson H, Helgadottir GP, Aspelund T, Eiriksdottir G, Sigurdsson S, Ingvarsson T, et al. Hand osteoarthritis in older women is associated with carotid and coronary atherosclerosis: the AGES Reykjavik study. Ann Rheum Dis 2009;68:1696-700.
25. Haugen IK, Ramachandran VS, Misra D, Neogi T, Niu J, Yang T, et al. Hand osteoarthritis in relation to mortality and incidence of cardiovascular disease: data from the Framingham heart study. Ann Rheum Dis 2015;74:74-81.
26. Haara M, Manninen P, Kroger H, Arokoski JP, Karkkainen A,

Knekt P, et al. Osteoarthritis of finger joints in Finns aged 30 or over: prevalence, determinants, and association with mortality. Ann Rheum Dis 2003;62:151-8.
27. Magnusson K, Bech Holte K, Juel NG, Brox JI, Hagen KB, Haugen IK, et al. Long term type 1 diabetes is associated with hand pain, disability and stiffness but not with structural hand osteoarthritis features - The Dialong hand study. PLoS One 2017;12:e0177118.
28. Frey N, Hugle T, Jick SS, Meier CR, Spoendlin J. Type II diabetes mellitus and incident osteoarthritis of the hand: a population-based case-control analysis. Osteoarthr Cartil 2016;24:1535-40.
29. Siviero P, Tonin P, Maggi S. Functional limitations of upper limbs in older diabetic individuals. The Italian longitudinal study on aging. Aging Clin Exp Res 2009;21:458-62.
30. Garessus EDG, de Mutsert R, Visser AW, Rosendaal FR, Kloppenburg M. No association between impaired glucose metabolism and osteoarthritis. Osteoarthr Cartil 2016;24:1541-7.
31. Nieves-Plaza M, Castro-Santana LE, Font YM, Mayor AM, Vila LM. Association of hand or knee osteoarthritis with diabetes mellitus in a population of Hispanics from Puerto Rico. J Clin Rheumatol 2013;19:1-6.
32. Gibson N, Guermazi A, Clancy M, Niu J, Grayson P, Aliabadi P, et al. Relation of hand enthesophytes with knee enthesopathy: is osteoarthritis related to a systemic enthesopathy? J Rheumatol 2012;39:359-64.
33. Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol 2007;34:172-80.
34. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16: 494-502.
35. Kraus VB, Jordan JM, Doherty M, Wilson AG, Moskowitz R, Hochberg M, et al. The Genetics of Generalized Osteoarthritis (GOGO) study: study design and evaluation of osteoarthritis phenotypes. Osteoarthr Cartil 2007;15:120-7.
36. Nelson AE, Golightly YM, Renner JB, Schwartz TA, Kraus VB, Helmick CG, et al. Brief report: differences in multijoint symptomatic osteoarthritis phenotypes by race and sex: the Johnston County Osteoarthritis Project. Arthritis Rheum 2013;65:373-7.
37. Bellamy N, Campbell J, Haraoui B, Gerecz-Simon E, Buchbinder R, Hobby K, et al. Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. Osteoarthr Cartil 2002;10:863-9.
38. Allen KD, DeVellis RF, Renner JB, Kraus VB, Jordan JM. Validity and factor structure of the AUSCAN Osteoarthritis Hand Index in a community-based sample. Osteoarthr Cartil 2007;15:830–6.
39. Jackson CH. Multi-state models for panel data: The msm package for R. J Stat Softw 2011;38:1-28.
40. National Heart, Lung, and Blood Institute. Classification of overweight and obesity by BMI, waist circumference, and associated disease risks. [Internet. Accessed July 22, 2020.] Available from: www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi_dis.htm
41. Dahaghin S, Bierma-Zeinstra SM, Reijman M, Pols HA, Hazes JM, Koes BW. Prevalence and determinants of one month hand pain and hand related disability in the elderly (Rotterdam study). Ann Rheum Dis 2005;64:99-104.
42. Botha-Scheepers S, Riyazi N, Watt I, Rosendaal FR, Slagboom E, Bellamy N, et al. Progression of hand osteoarthritis over 2 years: a clinical and radiological follow-up study. Ann Rheum Dis 2009;68:1260-4.
43. Dawson LP, Fairley JL, Papandony MC, Hussain SM, Cicuttini FM, Wluka AE. Is abnormal glucose tolerance or diabetes a risk factor for knee, hip, or hand osteoarthritis? A systematic review. Semin Arthritis Rheum 2018;48:176-89.
44. Marshall M, Peat G, Nicholls E, van der Windt D, Myers H, Dziedzic K. Subsets of symptomatic hand osteoarthritis in community-dwelling older adults in the United Kingdom: prevalence, inter-relationships, risk factor profiles and clinical characteristics at baseline and 3-years. Osteoarthr Cartil 2013;21:1674-84.
45. Zhang JF, Song LH, Wei JN, Zhang AL, Dong HY, Wen HY, et al. Prevalence of and risk factors for the occurrence of symptomatic osteoarthritis in rural regions of Shanxi Province, China. Int J Rheum Dis 2016;19:781-9.
46. Nielen MM, van Sijl AM, Peters MJ, Verheij RA, Schellevis FG, Nurmohamed MT. Cardiovascular disease prevalence in patients with inflammatory arthritis, diabetes mellitus and osteoarthritis: a cross-sectional study in primary care. BMC Musculoskelet Disord 2012;13:150.
47. Kendzerska T, Juni P, King LK, Croxford R, Stanaitis I, Hawker GA. The longitudinal relationship between hand, hip and knee osteoarthritis and cardiovascular events: a population-based cohort study. Osteoarthr Cartil 2017;25:1771-80.
48. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthr Cartil 2013; 21:16-21.
49. Jackson JM, DeFor TA, Crain AL, Kerby TJ, Strayer LS, Lewis CE, et al. Validity of diabetes self-reports in the Women's Health Initiative. Menopause 2014;21:861-8.
50. Dey AK, Alyass A, Muir RT, Black SE, Swartz RH, Murray BJ, et al. Validity of self-report of cardiovascular risk factors in a population at high risk for stroke. J Stroke Cerebrovasc Dis 2015;24:2860-5.