



## The relationship of Progressive Osteoarthritis of the Knee and Long-term Progression of Osteoarthritis of the Hand, Hip and Lumbar Spine

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**The relationship of Progressive Osteoarthritis of the Knee and Long-term  
Progression of Osteoarthritis of the Hand, Hip and Lumbar Spine**  
Longitudinal Results from the Chingford Study

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**Objectives:**

Unlike the known association of prevalent knee Osteoarthritis (OA) and OA at other anatomical sites in an individual, the association between progression of knee OA and progression at anatomical sites distant to the knee affected by OA is unclear due to a lack of multi-site longitudinal progression data. We therefore examined the association between radiological progression of knee OA and OA of the hands, hip and lumbar spine in a population based cohort.

**Methods:**

914 women had knee x-rays taken 10 years apart which were read for the presence of osteophytes and joint space narrowing (JSN). Progression status was available for hand, hip and lumbar spine x-rays over the same 8 to 10 years. The association between progression of knee OA and OA at other sites was analysed using odds ratios (OR) and 95% confidence intervals (95% CI) in logistic regression models.

**Results:**

There were 89 of 133 women with progression of knee OA based on osteophytes and 51 of 148 on a JSN definition. Progression of JSN in knee OA was predicted by progression in lumbar spine disc space narrowing (DSN) (OR 2.9, 95% CI 1.2 – 7.5) and hip OA (JSN) (OR 2.0, 95% CI 1.0 – 4.2). No consistent effects were seen for hand OA. The associations remained after adjustment for age and Body Mass Index.

**Conclusions:**

This is the first population-based report on the association between long-term progression of knee OA and OA at other anatomical sites. We have demonstrated that progression of knee OA is associated with progression of lumbar spine and hip OA. This may have implications for DMOAD trial methodology, selection of patients for OA research and in offering advice to patients on prognosis of OA.

The association of Osteoarthritis (OA) at one anatomical site and the presence of OA at another site in an individual has been examined and established in cross-sectional studies [1-4]. The natural history and influence of longitudinal radiographic OA progression has however not been established, although two retrospective studies have suggested the possibility [5;6].

Establishing evidence of an association of radiological progression of OA between anatomical sites could result in disease modifying drugs for osteoarthritis (DMOADs) being tested for efficacy over a range of anatomical sites in the context of prospective intervention studies, clinicians providing risk assessments and preventative advice to patients with multisite OA and providing an important new understanding of OA progression to researchers. We therefore explored knee OA progression in individuals in relation to progression of hand, hip and lumbar spine OA so as to establish a different paradigm for clinical trials and to allow for better identification of individuals at risk of progression.

## **SUBJECTS AND METHODS:**

### **Subjects:**

Subjects were from the Chingford Study population. This study, established in 1988, is a well-described prospective longitudinal cohort of 1003 women seen annually and described in detail previously [7;8]. After ten-years follow up 914 women remained for examination. All the women lived within five miles of the general practice and 98% of the women were white and similar to the United Kingdom general population [9]. Ethics approval for this study was given by the ethics committee of Whipps Cross Hospital, London.

### **Demographic data:**

All women were given a nurse-administered standardised questionnaire. Height was recorded in metres and weight in kilograms, following physical examination. Body mass index (BMI) was calculated as  $\text{kg/m}^2$  and expressed as World Health Organization (WHO) BMI class groups [10]. For all analysis BMI was treated as a categorical variable.

### **Radiographic assessment:**

At baseline, all women had an anteroposterior (AP) radiograph of the hands, a weight bearing AP radiograph of the knee, a supine radiograph of the lateral lumbar spine and an AP supine radiograph of the hip. Follow-up x-rays were taken at variable time points (Year of the Chingford Study) and intervals for each anatomical site (Table 1).

X-rays of the knees were standardised with the back of the knees in contact with the cassette, the patella centralized over the lower end of the femur, and the beam centered 2.5cm below the apex of the patella, with the tube-to-film distance of 100 cm. Repeat AP extended-view weight bearing knee radiographs were taken 10 yrs later by the same technician using the same equipment and methods as at baseline in order to maximise standardisation. Paired films were read side by side by a trained examiner (DH) for the presence of knee osteophytes and JSN for each compartment using a validated atlas on a 0-3 scale of severity [11]. X-rays of the hands were graded 0-3 for the presence of osteophytes and JSN using the same validated atlas at the distal interphalangeal joints (DIP) and the carpometacarpal joints (CMC) by a trained examiner (GH). Lateral lumbar spine x-rays were taken centered on the L3 vertebrae with the subjects in the left lateral recumbent position by the same radiographer at

both time-points. A single trained observer (GH) blinded to patient identification and chronological order, read all the lumbar spine radiographs. Each lateral lumbar spine x-ray was graded 0-3 for the individual features of disc space narrowing (DSN) and anterior osteophyte (AO) formation, using the semi-quantitative method reported by Lane *et al*, summarized as Grade 0=normal; Grade 1=mild; Grade 2=moderate; Grade 3=severe [12]. Supine x-rays of the hips were taken using the Bucky screen technique using the same equipment and methods. The beam was centred in the midline half way between the level of the anterior superior iliac spines and the symphysis pubis, with the tube-to-film distance of 100 cm and 15° of internal rotation. Landmarks for the site of maximal JSN were marked out on the paired films in advance of reading the films as recommended by Auleley *et al* [13]. A millimetre reticule reading at the site of maximal hip JSN was obtained and the presence of osteophytes and JSN was graded 0-3 using a validated atlas [11].

### **Definitions of OA Progression:**

Definitions of progression were based on radiographic assessments. Knee OA at baseline was defined as the presence of a grade 1+ osteophyte or JSN in at least one of the four knee compartments (lateral or medial, right or left knee). Subjects were classified as knee OA progressors if they developed an increased grade  $\geq 1$  from baseline or developed a new compartmental grade 1+ osteophyte or JSN. Baseline hand radiographs were graded for OA at the DIP and CMC joints. Subjects were classified as having DIP OA at baseline for the presence of a grade 1+ osteophyte or JSN in at least 2 DIP joints of either hand: and progression if they developed an increased grade  $\geq 1$  from baseline or developed a new grade 1+ osteophyte or JSN in an unaffected baseline DIP joint. CMC OA was defined at baseline by the presence of a grade 1+ osteophyte or JSN in either the right or left CMC joints and progression as an increase in grade  $\geq 1$  from baseline or development of a grade 1+ osteophyte or JSN in an unaffected baseline CMC joint. Hand OA was defined as the presence of either DIP OA or CMC OA at baseline with progression at either the DIP or CMC joint as defined above. Hip OA at baseline was defined as the presence of a grade 1+ osteophyte (acetabular or femoral) or JSN in either the right or left hip. Progression was defined as an increased grade  $\geq 1$  from baseline or developing a grade 1+ osteophyte or JSN in the contra-lateral hip. Analysis of our intra-observer limits of agreement for hip JSN measurement in millimetres (mm) at the site of maximal JSN was  $-0.23$  to  $0.25$ mm and therefore we defined progression as at least twice this value ( $\geq 0.5$ mm decrease in joint space width (JSW)) at that site from baseline. Lumbar spine OA was defined using thresholds of AO or DSN grade 1+ in at least one or more vertebrae (L1-5) within a subject. Progression was defined as an increase in grade in an affected Year 1 vertebra or developing an AO or DSN grade 1+ affected vertebrae [14]. For all anatomical sites a subject was defined as having OA based on either osteophytes or JSN as mutually exclusive case definitions.

### **Reproducibility of grading:**

Reproducibility for change in longitudinal knee radiographs in the Chingford Cohort has yielded intra-observer agreement of  $\kappa = 0.79$  for osteophytes and  $\kappa = 0.70$  for joint space narrowing [15]. The within-observer reproducibility (kappa) of radiographic assessment of the hip and hand x-rays was  $>0.70$ , and  $0.78-0.89$  for the lumbar spine [11;14]. Less than 3% of subjects appeared to regress radiographically and these subjects were excluded from the analysis.

**Statistical analysis:**

Odds ratios (OR) and 95% confidence intervals (95% CI) were derived for the radiographic progression at other sites on the progression of knee OA adjusting for age and BMI within subjects, using logistic regression models. The statistical package (STATA) was used for all analysis.

**RESULTS:**

Paired radiographs were available for analysis in 796 women for the lumbar spine, 704 for the hands, 800 for the hips and 914 for the knees (Table 1). The numbers of films available varied due to losses at follow up and a recruitment drive during the tenth year to re-contact all those women who had previously dropped out. Of the women with paired knee x-rays, 133 (14.6%) had baseline knee OA defined by osteophytes and 148 (16.2%) defined by JSN and were therefore studied for analysis of progression.

**Table 1: Year of Chingford Study and Duration of follow-up for the X-rays available by Anatomical Site**

X-ray site	Reader	No of x-rays	Year of Study	Duration of Follow-up (yrs)	Score	Kappa's
<b>Lumbar Spine</b>	GH*	796	1, 9	9	OS	$\kappa = 0.89$
					DSN	$\kappa = 0.78$
<b>Hand</b>	GH*	704	1,11	11	OS JSN	$\kappa > 0.70$
<b>Hip</b>	GH*	800	2, 8	7	OS JSN	$\kappa > 0.70$
<b>Knee</b>	DH#	914	1,10	10	OS	$\kappa = 0.79$
					JSN	$\kappa = 0.70$

**Legend:** \*G Hassett; # D J Hart

**Baseline characteristics:**

Table 2 shows the baseline characteristics of the 914 women with paired radiographs available, and those with knee OA based on osteophyte and JSN progressor status. The mean  $\pm$  SD age of the group at baseline was  $54.1 \pm 6.0$  years; after 10-year follow-up it was  $64.1 \pm 6.0$  years. Women with knee OA progression defined by osteophytes were older, but had similar BMI's compared to non-progressors. Women with knee OA progression defined by JSN were younger and had non-significant differences in BMI's compared to non-progressors.

**Table 2: Characteristics of study group at baseline\***

Parameter	Study group				
	Overall (n=914)	Knee OA – OS progressors (n=89)	Knee OA – OS non- progressors (n=44)	Knee OA – JSN progressors (n= 51)	Knee OA – JSN non- progressors (n= 97)
Age, years	54.1 ± 6.0	57.6 ± 5.3	56.1 ± 6.2	55.2 ± 5.5	53.9 ± 6.5
BMI, kg/m <sup>2</sup>	25.6 ± 4.2	27.7 ± 4.2	27.8 ± 5.5	26.4 ± 4.6	26.0 ± 4.2

\*Values are the mean ± SD. BMI = Body Mass Index; OA = osteoarthritis; OS = osteophytes; JSN = joint space narrowing.

### Rates of Progression:

Tables 3 and 4 show the frequency of baseline OA at all sites and progression of knee OA defined by osteophytes or JSN respectively by progression of OA at the hip, lumbar spine and hand. Of the women with baseline knee OA, 67% (n = 89/133) progressed by an osteophyte definition and 35% (n = 51/148) progressed by a worsening of JSN grade over a ten year period. Progression rates per annum can be calculated from the Tables 3 and 4. For knee and hand OA progression rates per annum ranged from 3.5% to 6.7% according to the definition of OA, with similar rates of osteophyte progression seen at both sites. Lumbar spine OA progression rates were 3.9% for anterior osteophytes and 3.2% for DSN with rates of 4.5% and 7.4% for osteophytic and JSN progression at the hip. Progression in the knee and hand occurred in 58.9% (n = 30/51) of women with baseline osteophytes at the two anatomical sites, and in 23.8% (n = 15/63) of those with baseline JSN. Progression in the knee and lumbar spine occurred in 31.6% (n = 30/95) of women with baseline osteophytes at the two anatomical sites, and in 15.1% (n = 16/106) of those with baseline JSN and DSN respectively. In the Chingford Cohort the prevalence of radiographic hip OA defined by JSN semiquantitative grade at baseline is low (n = 29) and therefore there were only a small number of women with JSN at the hip and knee at baseline (n = 7), resulting in progression data in this subgroup being difficult to interpret and univariate and multivariate analysis unable to be performed. Hip OA JSN progression defined by a ≥ 0.5mm decrease in JSW from baseline in the hip resulted in larger numbers of affected women and the data was therefore available for subgroup analysis. Osteophytosis of the hip, although less diagnostic, was more common. Progression in the knee and hip occurred in 40% (n = 14/35) of women with baseline osteophytes at the two anatomical sites.

**Table 3: Relationship of the presence of Baseline and Progressive Knee OA defined by osteophytes and OA at other anatomical sites\***

OA other anatomical sites	Baseline Knee OA (OS) (n=133)	Knee OS progressors (n=89)	Knee OS non-progressors (n=44)
Baseline Hand OA (OS) (n=222)	51	36	15
Hand OS progressors (n=161)	40	30	10
Hand OS non-progressors(n=61)	11	6	5
Baseline Hand OA (JSN) (n=308)	44	33	11
Hand JSN progressors (n=197)	32	25	7
Hand JSN non-progressors (n=111)	12	8	4
Baseline Lumbar Spine AO (n=714)	95	66	29
Lumbar Spine AO progressors (n=248)	41	30	11
Lumbar Spine AO non-progressors (n=466)	54	36	18
Baseline Lumbar Spine DSN (n=514)	72	53	19
Lumbar Spine DSN progressors (n=148)	33	29	4
Lumbar spine DSN non-progressors (n=366)	39	24	15
Baseline Hip OA (OS) (n=201)	35	24	11
Hip OS progressors (n= 101)	21	14	7
Hip OS non-progressors (n=100)	14	10	4
Baseline Hip OA (JSN (grade)) (n=29)	10	9	1
Hip JSN (grade) progressors (n=15)	5	5	0
Hip JSN (grade) non-progressors (n=14)	5	4	1
Hip JSN (mm) progressors (n=490)	49	33	16
Hip JSN (mm) non-progressors (n=301)	55	38	17

\*Except where otherwise indicated, values are the number. BMI = Body Mass Index: OA = osteoarthritis: OS = osteophytes: JSN = joint space narrowing: CMC = Carpometacarpal: DIP = Distal Interphalangeal: PIP = Proximal Interphalangeal: DSN = Disc Space Narrowing: AO = Anterior Osteophytes.

**Table 4: Relationship of the presence of Baseline and Progressive Knee OA defined by joint space narrowing and OA at other anatomical sites\***

OA other anatomical sites	Baseline Knee OA (JSN) (n=148)	Knee JSN progressors (n=51)	Knee JSN non-progressors (n=97)
Baseline Hand OA (OS) (n=222)	45	14	31
Hand OS progressors (n=161)	35	10	25
Hand OS non-progressors (n=61)	10	4	6
Baseline Hand OA (JSN) (n=308)	63	28	35
Hand JSN progressors (n=197)	41	15	26
Hand JSN non-progressors (n=111)	22	13	9
Baseline Lumbar Spine AO (n=714)	106	43	63
Lumbar Spine AO progressors (n=248)	32	16	16
Lumbar Spine AO non-progressors (n=466)	74	27	47
Baseline Lumbar Spine DSN (n=514)	77	29	48
Lumbar Spine DSN progressors (n=148)	27	17	10
Lumbar spine DSN non-progressors (n=366)	60	22	38
Baseline Hip OA (OS) (n=201)	34	15	19
Hip OS progressors (n= 101)	14	8	6
Hip OS non-progressors (n=100)	20	7	13
Baseline Hip OA (JSN) (n=29)	7	3	4
Hip JSN progressors (n=15)	2	1	1
Hip JSN non-progressors (n=14)	5	2	3
Hip JSN (mm) progressors (n=490)	49	24	25
Hip JSN (mm) non-progressors (n=301)	74	24	50

\*Except where otherwise indicated, values are the number. BMI = Body Mass Index; OA = osteoarthritis; OS = osteophytes; JSN = joint space narrowing; CMC = Carpometacarpal; DIP = Distal Interphalangeal; PIP = Proximal Interphalangeal; DSN = Disc Space Narrowing; AO = Anterior Osteophytes.

**Risk of knee progression by alternate joint site:**

For knee OA osteophyte progression, there was an approximate 4-fold increased risk of progression if DSN progression occurred at the lumbar spine (OR 4.5, 95% CI: 1.3 – 15.5) (Table 5), with non-significant increased risks seen for lumbar spine osteophytosis alone (OR 1.4, 95% CI: 0.6 – 3.3), for hand osteophytic OA (OR 2.5, 95% CI: 0.6 – 10.0) or hand JSN OA (OR 1.8, 95% CI: 0.4 – 7.7) and no difference seen with radiographic hip OA.

There was a 2-3 fold increased risk of knee JSN progression if there was DSN progression (OR 2.9, 95% CI: 1.2 – 7.5) or anterior osteophyte progression (OR 1.7, 95% CI: 0.8 – 4.0). Hip progression defined by a  $\geq 0.5$ mm change in JSW increased the risk 2 fold (OR 2.0, 95% CI: 1.0 – 4.2). Whilst a similar increase in risk was seen with progression of hip osteophytes (OR 2.5, 95% CI: 0.6 – 10.0), the number of women was small (n=14) and the confidence intervals wide. A non-significant risk reduction of 40-60% for progression was demonstrated for progression of hand OA osteophytes (OR 0.6, 95% CI: 0.1 – 2.6) and JSN (OR 0.4, 95% CI: 0.1 – 1.2).

**Table 5: Univariate Analysis of the association of Knee OA Progression and Progression of OA at other anatomical sites\***

Progressors at other anatomical sites of OA	Knee Osteoarthritis					
	Knee OS progressors	Knee OS non-progressors	OR (95% CI)	Knee JSN progressors	Knee JSN non-progressors	OR (95% CI)
Hand Osteophytes	30	10	2.5 (0.6 – 10.0)	10	25	0.6 (0.1 – 2.6)
Hand JSN	25	7	1.8 (0.4 – 7.7)	15	26	0.4 (0.1 – 1.2)
Hip Osteophytes	14	7	0.8 (0.2 – 3.5)	8	6	2.5 (0.6 – 10.0)
Hip JSN (mm)	33	16	0.9 (0.4 – 2.1)	24	25	2.0 (1.0 – 4.2)
Lumbar Spine AO	30	11	1.4 (0.6 – 3.3)	16	16	1.7 (0.8 – 4.0)
Lumbar Spine DSN	29	4	4.5 (1.3 – 15.5)	17	10	2.9 (1.2 – 7.5)

\*Except where otherwise indicated, values are the number. BMI = Body Mass Index; OA = osteoarthritis; OS = osteophytes; JSN = joint space narrowing; CMC = Carpometacarpal; DIP = Distal Interphalangeal; PIP = Proximal Interphalangeal; DSN = Disc Space Narrowing; AO = Anterior Osteophytes.

Table 6, shows the adjusted odds ratios for knee OA progression risk by progression of OA at the hip, lumbar spine and hand. We adjusted for age and BMI, two well-established risk factors for knee OA. Estimates of the magnitude of risk for progression of knee OA stratified for progression of OA at other anatomical sites were not altered by adjustment for age or BMI except for the odds ratio for knee OA JSN progressors which increased for those women who were also hip JSN progressors.

**Table 6: Multivariate Analysis of the association of Knee OA Progression and Progression of OA at other anatomical sites\***

Progressors at other anatomical sites of OA	Knee Osteoarthritis	
	Knee OS progressors OR (95% CI)*	Knee JSN progressors OR (95% CI)*
Hand Osteophytes	2.0 (0.5 – 8.5)	0.5 (0.1 – 2.5)
Hand JSN	1.6 (0.3 – 7.5)	0.4 (0.1 – 1.4)
Hip Osteophytes	0.9 (0.2 – 4.4)	2.1 (0.4 – 9.7)
Hip JSN (mm)	0.9 (0.4 – 2.1)	2.7 (1.2 – 6.3)
Lumbar Spine AO	1.3 (0.5 – 3.2)	1.5 (0.6 – 3.7)
Lumbar Spine DSN	6.8 (1.8 – 26.7)	3.7 (1.2 – 11.1)

\*All OR adjusted for age (yrs) and BMI (kg/m<sup>2</sup>). BMI = Body Mass Index: OA = osteoarthritis: OS = osteophytes: JSN = joint space narrowing: CMC = Carpometacarpal: DIP = Distal Interphalangeal: PIP = Proximal Interphalangeal: DSN = Disc Space Narrowing: AO = Anterior Osteophytes.

## DISCUSSION:

Clinicians are often asked by their patients what risk they have of their knee OA progressing and or the risk of progressing or developing OA at distant anatomical sites. To date we have not had the prospective longitudinal x-ray data to answer these questions regarding multi-site OA progression [16-19]. Therefore the association between knee OA progression and OA progression at anatomical sites distant to the knee is important to establish. In addition if OA progression is correlated between anatomical sites, then perhaps the results of recent DMOAD trials in knee OA can be extrapolated to other sites. However, it is still to be established if the same biological processes are determining progression at each site of OA and the generalizability of DMOAD knee OA trial results would need to be tested and confirmed in the context of prospective OA intervention studies.

Disc space narrowing progression in the lumbar spine was associated with knee OA progression both due to osteophytes and JSN, although the relationship was stronger for JSN progression at the knee with a 4 fold increase in risk. The association of knee OA with lumbar spine OA may suggest a common mechanism through obesity or mechanical forces (e.g. occupation and physical activity) although it remained after adjustment for BMI. Occupational activity and physical activity have however previously not been shown to be risk factors for lumbar spine OA progression in the Chingford Cohort [14]. A recent family based study suggested a genetic relationship between generalised osteoarthritis and disc degeneration, which may in part explain the correlation of progression between lumbar spine OA and knee OA [20]. Anterior osteophytes of the lumbar spine did not show a significant association with knee OA progression, which may in part be due to the high prevalence of anterior osteophytes by age 50 (60-80%) with onset and progression of these osteophytes occurring in subjects at a younger age than that for knee OA [14].

Radiographic hand OA progression demonstrated inconsistent and non-significant results with similar results seen when we analysed radiographic progression at the CMC and the DIP joints separately (data not shown). This may in part be due to JSN at the hand not being a useful predictor [21]. Our study tentatively suggests an association between hand osteophytes and knee osteophytes although not with knee JSN which may indicate that JSN at the knee is not a good indicator of multi-site OA or that the mechanisms driving osteophyte production are different to the mechanisms at work in the knee that lead to loss of cartilage and JSW.

Hip JSN (mm) and osteophyte progression were associated with a 2-fold increase in the risk of knee OA JSN progression although the results were not significant for osteophytes which may reflect the small numbers of women in this subgroup analysis. Given the low prevalence rates of hip OA as defined by semi-quantitative measures for osteophytes and JSN due to the older age of onset of hip OA and the relatively young age of the women in the Chingford cohort, we cannot make any firm conclusions regarding the association of hip OA progression and knee OA progression in the younger age group, but the relationship should be explored in an older population group given our findings using a JSN (mm) definition of hip OA progression which has detected an association in the younger subjects of this study. We acknowledge that using a threshold change in a hip JSW  $\geq 0.5$ mm to define hip JSN (mm) OA could represent age related change rather than progression in a pre-osteoarthritic hip. Nevertheless given the low prevalence rates of hip JSN  $\leq 2.5$ mm we felt it was a marker of more rapid change and could have validity in some cases where hip OA occurred early.

The likelihood of progression of knee OA has previously been shown to be increased in those subjects with prevalent OA at other sites [16-19]. To our knowledge no previous studies have examined the longitudinal relationships at different sites. Previously the cross-sectional prevalence of lumbar spine disc degeneration has been reported as higher in those with generalised OA at other sites, and in women with Heberden's nodes [20;22;23]. Therefore we included lumbar spine disc degeneration as one of the 3 potential anatomical sites of radiographic OA progression. A number of non-population based studies have examined subjects with end-stage lower limb OA and the relationship in these subjects to the presence of OA in other joints [24;25]. Gunther *et al*, demonstrated in 640 subjects with advanced symptomatic hip and knee OA requiring joint replacement that most had bilateral disease and 26.8% of all patients had polyarticular disease with the prevalence of GOA in the knee group (34.9%) higher than in the hip group (19.3%) [25]. Chitnavis *et al*, demonstrated in a retrospective cohort of n=402 Caucasian subjects that around a third undergoing a total hip or knee replacement had bilateral replacements [24]. The percentage of women with nodal hand osteophytic OA undergoing THR and TKR were very similar. Cooper *et al*, demonstrated in a study of 5.1 years mean duration follow-up, a non-significant trend for the presence of Heberden's nodes in those with osteophyte formation in knee OA based on the Kellgren and Lawrence (K&L) grading system (OR 2.0, 95% CI: 0.7 – 5.7), but not for JSN [18]. Over a mean follow-up of 2 years, Ledingham *et al* having defined knee OA progression as an increase in K&L grade from a baseline of K&L grade 2+, found a weak association (OR 1.8, 95% CI: 1.1 – 3.1) with the presence of baseline nodal OA [19]. A follow-up study by Shakoor *et al* found a high rate of 2<sup>nd</sup> TJR, which was twice as likely to be in a contra-lateral as the ipsilateral hip or knee joint [6] and suggested that subjects with advanced hip OA may undergo prolonged gait adaptations [26]. A potential limitation

of this kind of study is that the order of TJR surgery does not necessarily reflect the order in which OA develops, and it is difficult to separate cause and or effect.

Limitations of the study need to be discussed. Obesity is reported to be a risk factor for knee OA progression but even after adjusting for BMI our results did not change except for hip JSN (mm) progressors. Biomechanical factors, including abnormal static and dynamic joint loading may play a role in the progression of lower limb OA, which may explain in part the relationship of hip and knee OA progression [26]. We however did not have any data on alignment or mechanical forces through the knee or hip to explore this. Racial variations in OA prevalence exist [27-30]. Therefore, although there are no data on racial differences in OA progression, our data may not be applicable to other races or males. We used for progression a grade 1+ definition for the presence of baseline OA at all 4 anatomical sites and a change in grade of  $\geq 1$  or a new grade 1+ in an unaffected anatomical compartment of a joint or disc space, in keeping with traditional definitions of progression [18]. The definitions of progression are however problematic given lack of standard accepted or validated definitions and the multi-compartment joint and disc space levels; of the knee, hand and lumbar spine respectively. Moreover it is not possible to have a standardised system for each joint site that can be combined that reflects similar sensitivities, relation to symptoms and observer-error. In general however these factors would act against us finding associations and indeed some of the non-significant trends found may be under-estimates of the true association. Precise minimum joint space measurements for the knee were not possible due to the use in the Chingford cohort of the traditional fully extended knee view as opposed to the current semi-flexed views of the knee, which make this measurement and semiquantitative assessment easier, although still with methodological concerns. Although most subjects had mild disease, we could make no allowance for OA treatments or treatment of diseases that may influence the progression of OA. The time to follow-up for the x-rays ranged from a minimum of 7 years to a maximum of 11 years. The long time intervals and the absence of intermediate measures, means that we may have missed important time points or intervals at which progression occurs – but radiation doses make more intensive study impossible. Lumbar facet joints were not examined, as they are not easily or consistently visualized on lateral lumbar spine x-rays. DSN may however be a surrogate for associated facet joint OA for when DSN occurs there is posterior displacement of the vertebral body and subsequent subluxation of the apophyseal joint that may lead to osteoarthritis at this site [31;32].

Our study has a number of potential implications for both clinicians managing and discussing prognosis with patients with OA, researchers involved in basic science and epidemiological studies of OA and investigators of DMOADs in clinical trials. The utility of biochemical markers may be in separating those with generalised progression versus non-progressors, rather than as markers of progression in individual joints. DMOADs may have greater impact on the burden of OA disease if progressors with knee OA are likely to be progressing at other anatomical sites. Clinicians may also encourage patients with known OA progression at the lumbar spine, hip, or knee to protect their joints at other anatomical sites and use potential DMOAD drugs.

In conclusion, this is the first population based longitudinal multi-site study to examine the relationship of knee OA progression to longitudinal progression of hand, hip and lumbar spine OA. We have shown that in subjects with knee OA, progression in the knee is not an isolated evolution of disease but that progression of lumbar spine, hand and or hip OA is often occurring in the same individual.

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**COMPETING INTEREST STATEMENT:**

We the authors have no competing interests to declare.

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