Metabolic risk factors and the incidence and progression of radiographic hand osteoarthritis: a population-based cohort study

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Submission category: Original research article - Full-length article

Short running title: Metabolic factors & hand OA progression

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Keywords: Osteoarthritis; hand; incidence; progression; metabolic risk factors; subsets.

Word Count: Main text: 3599/3600

Abstract

Objective: To determine whether selected metabolic factors are associated with greater amounts of radiographic hand osteoarthritis (OA) incidence and progression.

Methods: 706 adults, aged 50-69 years with hand pain and hand radiographs at baseline, were identified from two population-based cohorts. Metabolic factors (body mass index, hypertension, dyslipidaemia, and diabetes) were ascertained at baseline by direct measurement and medical records. Analyses were undertaken following multiple imputation of missing data, and in complete cases (sensitivity analyses). Multivariable regression models estimated associations between metabolic factors and two measures of radiographic change at 7-years for all participants, individuals free of baseline radiographic OA and in baseline hand OA subsets. Estimates were adjusted for baseline values and other covariates.

Results: The most consistent and strong associations observed were between the presence of diabetes and the amount of radiographic progression in individuals with nodal OA (adjusted mean differences in KLsum score of 4.50 (-0.26, 9.25)), generalised OA (3.27 (-2.89, 9.42)), and erosive OA (3.05 (-13.56, 19.67)). The remaining associations were generally weak or inconsistent, although numbers were limited for analyses of incident radiographic OA and erosive OA in particular.

Conclusion: Overall metabolic risk factors were not independently or collectively associated with greater amounts of radiographic hand OA incidence or progression over 7-years, but diabetes was associated with radiographic progression in nodal, and possibly generalised and erosive OA. Diabetes has previously been associated with prevalent but not incident hand OA, further investigation in hand OA subsets using objective measures accounting for disease duration and control is warranted.

Introduction

Symptomatic hand osteoarthritis (OA) is estimated to affect 8.2% of men and 15.9% of women in the general population (1). The course of hand OA is not clear but is thought to be heterogeneous with some individuals experiencing substantial deterioration in structure, pain, and function while others remain stable for many years (2). Currently, there is limited evidence regarding the risk factors for hand OA progression (3), and the need to gain further understanding of the aetiology and course of hand OA has been highlighted as a research priority (4).

Metabolic factors have been associated with hand OA but mainly in cross-sectional studies, systematic reviews have reported associations of obesity and type 2 diabetes with hand OA (5,6), and additional studies have reported associations between metabolic syndrome and hand OA (7-9). These findings suggest systemic metabolic disturbances may play a role in the pathophysiology of hand OA. As the hands are not exposed to the joint loading effects of obesity, they are an ideal site to investigate associations between metabolic factors and OA.

However, the role metabolic factors play in the incidence and progression of hand OA is unclear, as little longitudinal research has been undertaken. Apart from one study that did not find an association between type 2 diabetes and incident hand OA (10), and two studies that examined hyperlipidaemia and incident hand OA with differing results (11,12) most studies have focused on obesity, and conflicting findings have been reported (13-22). The disparity in results could be due to variations in study populations and the definitions of progression used. However, the relationship between obesity and hand OA progression could be confounded or mediated by the presence of hypertension, dyslipidaemia and diabetes and to date, and few analyses have examined metabolic factors independently from each other. Furthermore, the impact of multiple metabolic factors on the course of hand OA has been examined but only in a single study where no association was found between metabolic syndrome and incident and progressive hand OA (23).

There is some evidence that the role of metabolic factors in hand OA pathogenesis varies between subsets of hand OA. Obesity, hypertension, dyslipidaemia and metabolic syndrome occurred more often in community-dwelling individuals with erosive OA compared to other subsets (24). Also, significantly

elevated levels of a serum adipokine adiponectin, which have been associated with obesity, have been found in erosive OA compared to patients with non-erosive hand OA and healthy controls (25). The association between atherosclerosis and hand OA progression was noted to differ by joint group (26). Therefore, the conflicting findings previously reported between obesity and hand OA incidence and progression could also be explained by differing proportions of hand OA subsets within the study populations.

This study sought to determine in population-based older adults whether obesity, diabetes, hypertension and dyslipidaemia and the accumulation of metabolic factors are independently associated with radiographic hand OA incidence and the progression over 7-years as well as progression within different baseline subsets of hand OA.

Materials and methods

Study population & design

Study participants were from a population-based prospective cohort, the Clinical Assessment Studies of the Hand (CASHA)(27). At baseline all adults aged ≥50 years registered with two general practices in North Staffordshire, UK were invited to participate in a two-stage survey. In the UK, 95% of people are registered with general practices thus providing convenient general population sampling frames. Those reporting hand pain or problems in the last year were invited to attend research clinics that included radiographs and assessment of finger nodes in the 2nd and 3rd interphalangeal (IP) joints of each hand by trained assessors. To increase the numbers in each hand OA subset, the sample was enriched with participants from the Clinical Assessment Studies of the Knee (CASK)(28) who were recruited using an identically performed two-stage survey in a similar population of three general practices in the same locality of North Staffordshire. Individuals in this study who reported knee pain in the previous year were invited to attend research clinics, where they also received an identical hand radiographs and assessment of finger nodes to CASHA participants.

All participants included in the current analyses were aged 50-69 years at baseline, had reported hand pain on few days or more in the previous month (29), had hand radiographs, and did not have inflammatory arthritis (n=764). Follow-up was at approximately 7-years with a postal questionnaire and research clinic including hand radiographs. An Index of Multiple Deprivation (IMD)(30), based on a combination of education, employment, income, health, and crime figures in English neighbourhoods, was obtained for each participant using their postcode. UK Local Research Ethics Committees approved these studies (LREC Project No's: 1430, 05/Q2604/72, 06/Q2801/90). All participants provided written informed consent.

Radiographic assessment

Posterior-anterior hand radiographs were taken according to a standardised protocol (27,28). Two trained readers scored twenty hand joints (distal, proximal and thumb IPs and 1st carpometacarpal (1CMC)) for OA using the Kellgren and Lawrence (KL) grading system (0-4) at baseline and 7-years unpaired but with known chronological order (31). A single reader scored the presence of erosive OA using the Verbruggen-Veys Anatomical Phase Progression Score in sixteen IP joints at each time-point (32). Reliability has previously been reported for the presence of OA and erosive OA at baseline (24). At 7-years intra-rater reliability was substantial for OA (unweighted Kappa (K_u)=0.88 & 0.67, percentage agreement (PA)=96% & 93%) and erosive OA (K_u=0.89, PA=99%), and inter-rater reliability was moderate for OA (K_u=0.64, PA=91%) and substantial for erosive OA (K_u=0.84, PA=98%).

Hand OA subsets

The hand OA subsets examined and their definitions were: thumb base OA (KL≥2 in the 1CMCJ in either hand); nodal IPJ OA (KL≥2 in ≥2 IPJs (rays 2-5) & ≥2 nodes (rays 2-3) across either hand); generalised hand OA (KL≥2 in ≥1 distal IPJ & ≥1 proximal IPJ & ≥1 1CMCJ across either hand); and erosive OA (E- or R-phase of the Verbruggen-Veys Anatomical Phase Progression Score in ≥2 IPJ (rays 2-5) across either hand)(24).

Radiographic change

The amount of radiographic change was assessed by two outcomes using continuous measures to avoid loss of information and inflation of type 2 errors (13,25,33,34):

i) the KL summed (KLsum) score for 20 hand joints at 7-years (0-80) adjusted for the baseline KLsum score (0-80)(providing a composite measure of change that combines the amount of within-joint change and the number of joints changing)

ii) the number of joints with KL≥2 at 7-years (0-20) adjusted for baseline number of joints with KL≥2 (0-20)(change represents the number of joints newly classed as having definite radiographic disease)

Incident radiographic OA was investigated in participants free of radiographic OA (KL<2) at baseline whereas the term progression was used to collectively refer to radiographic worsening in participants with and without baseline radiographic OA.

Participants with maximum scores at baseline were excluded from analyses, as they could not undergo further progression.

Risk factors

Metabolic risk factors included body mass index (BMI), determined from height and weight measured at the baseline research clinics and used as a continuous variable. Consultations and/or diagnoses of hypertension, dyslipidaemia and type 2 diabetes/impaired fasting glucose (IFG) in the 2 years before and 2 years after the baseline research clinics were obtained from primary care medical records for those participants providing permission (94%, n=660) and used as dichotomous variables. Consultations and diagnoses in the UK are coded using a hierarchical method of standardised Read Codes (35). The validity of using the Read Codes for type 2 diabetes and hypertension was examined against individuals self-reporting having diabetes and raised blood pressure and was found to be 95% and 87% respectively. The validity of having a Read Code for type 2 diabetes was further checked against prescriptions records. All individuals prescribed a diabetic drug in the 2 years before and after baseline had a Read Code for diabetes in the same period.

The collective influence of multiple metabolic factors was examined using the number of metabolic risk factors (0-4), and the presence of metabolic syndrome (adapted from the NCEP/ATPIII definition)(36),

which was classed as three or more of the following: BMI ≥30, hypertension, dyslipidaemia and diabetes type 2/IFG.

Statistical analysis

Descriptive characteristics for all baseline participants, those followed-up at 7-years by postal questionnaire and at the 7-year research clinics were compared.

Baseline scores were plotted against 7-year scores to investigate the amount of radiographic change for the two outcomes, stratified by sex. Adjusted mean estimates and 95%CIs were determined at 7-years for both outcomes using analysis of covariance. Analyses were stratified by sex and adjusted for baseline value of the outcome, cohort (CASK or CASHA), age, and time to follow-up.

The independent associations between metabolic factors and incidence and progression of radiographic hand OA at 7-years were estimated using analysis of covariance (KLsum, number of joints) using three models: 1) BMI, hypertension, dyslipidaemia, diabetes type 2/IFG; 2) metabolic syndrome; 3) number of metabolic factors. All models were adjusted for the following potential confounders: baseline radiographic score, sex, baseline age, cohort, time to follow-up, baseline smoking status (never, ex, current) and IMD. This analysis was undertaken in all study participants, stratified by baseline hand OA subset and in those with no baseline hand OA (KL≤2).

Analyses that exclude individuals with missing data are acknowledged to produce biased estimates and reduced power and precision compared to those including all individuals (37,38). Multiple Imputation (MI) is recognised as an appropriate statistical method for handling missing data and overcoming the aforementioned limitations through addressing the uncertainty around missing values by generating imputes in multiple datasets (39). Therefore MI was undertaken using chained equations (MICE) in all eligible individuals. Primary analyses were undertaken in the imputed datasets, with complete cases analyses undertaken for sensitivity purposes (40). Data were imputed for missing 7-year outcome scores (45.0%) and for missing baseline data (BMI 0.3%; Index of Multiple Deprivation 0.3%; baseline smoking status 1.3% and metabolic factors 6.5% in those not consenting to medical record review). Fifty imputed

datasets were generated (41,42). A relatively large amount of outcome data was imputed, but research has shown that models still perform well in these situations (39,43-45). The distribution of variables in the imputed datasets were checked ensuring plausible values had been imputed, and model assumptions were verified. MI relies on variables being missing completely at random or missing at random (37,46). Missing data were associated with a number of baseline variables and therefore assumed to be missing at random. The imputation model included these baseline variables as well as the metabolic factors and 7-year outcomes to increase the power and precision of the imputation model (Supplementary Table 1)(47). Data could still be missing due to other unaccounted variables, but our participants were well-characterised with an extensive range of descriptive, sociodemographic, hand symptoms, general, physical and mental health, and self-reported comorbidities. Rubin's rules were used to combine estimates from imputed datasets (48). Analyses were performed using SPSS v21.0 (IBM Corporation, Armonk, NY, USA).

Results

Study population

Of 764 eligible individuals at baseline, after 58 exclusions (deaths or untraced departures from GP practice (31), severe ill health or terminal illness (21), address unknown (6)), 552 of the 706 were followed up at 7-years (adjusted response 78%)(Figure 1). Those lost to follow-up were mainly due to failure to renew consent to further contact at the interim 3-year follow-up (105). Some respondents at 7-years were unwilling to attend the 7-year research clinic (157); therefore a total of 388 had hand radiographs at baseline and follow-up with a mean follow-up time of 83 months (SD 6.7).

Compared with all eligible participants at baseline, those followed up with hand radiographs at 7-years were less likely to be a current or ex-smoker, have type 2 diabetes/IFG, and had slightly lower anxiety & depression scores. The distribution of other baseline variables was similar (Table 1).

One individual was excluded from the analyses examining the progression of the number of hand joints with KL≥2 due to having the maximum number of 20 joints affected at baseline, where applicable this is indicated in the relevant results tables.

Radiographic change

Scatterplots indicate positive linear trends between the baseline and 7-year scores for both hand OA outcomes in the imputed data and were similar for men and women (Figure 2). Overall, in the imputed data the amount of radiographic change at 7 years was significantly lower in men compared to women for each outcome (Table 2). Compared to the overall estimates of radiographic change at 7-years, those who were free of radiographic OA at baseline on average underwent less change, whereas those who had thumb base, nodal, generalised and erosive OA at baseline experienced more change (Table 2). Results were comparable in the complete case analysis although the amount of radiographic change was slightly lower for the no baseline hand OA group (Supplementary Figure 1, Supplementary Table 2).

Association between metabolic factors and hand OA progression

Overall in all participants, generally non-significant weak associations were found between each of the metabolic factors and the amount of radiographic change for both of the outcomes at 7-years, with adjusted mean differences over 7-years of less than 1 point for the KLsum score or 1 joint affected with OA (Table 3). These findings were replicated in the complete case analysis (Table 3).

Association between metabolic factors and progression in hand OA subsets

For the nodal, generalised and erosive hand OA subsets adjusted mean differences in the KLsum score at 7-years were consistently higher in individuals with diabetes type 2/IFG compared to those without diabetes/IFG in the imputed data with the adjusted mean differences ranging from 3.05 (-13.56, 19.67) for erosive OA to 4.50 (-0.26, 9.25) for nodal IPJ OA (Table 3). In individuals with nodal OA, the number of affected hand joints at 7 years was also greater in those with diabetes/IFG compared to those without diabetes/IFG (adjusted mean difference 2.06 (0.25, 3.87) (Table 3). Results for erosive OA were similar, although estimates were much less precise due to the small number in this subset.

The complete case analysis showed similar results but additionally, dyslipidaemia was positively associated with higher KL summed score and an increase in hand joints affected with KL≥2 at 7-years in those with

thumb base OA, nodal OA and generalised OA, although this association was statistically significant only for the number of joints affected in thumb base OA (Table 3).

Association between metabolic factors and incident hand OA

In those free of radiographic OA at baseline, weak non-significant associations were found between the metabolic factors and the amount of radiographic change for the two outcomes at 7-years, adjusted for baseline score and other potential confounders (Table 4). Findings were comparable in the complete case analysis (Table 4).

Discussion

Adjusted for baseline values and other covariates the amount of radiographic change for each outcome at 7-years varied by gender and by baseline hand OA subset, with females and those with nodal, generalised and erosive OA undergoing greater amounts of progression. Overall, obesity, hypertension, dyslipidaemia and diabetes type 2/IFG, were not found to be associated, either independently or collectively, with the amount of radiographic incidence or progression over 7-years in people with hand symptoms. Trends in the data indicated that the association between metabolic factors and progression might vary by hand OA subset. Diabetes was associated with greater amounts of radiographic progression in those with nodal OA at baseline and possibly implicated in those with generalised and erosive OA.

In this population-based prospective cohort study, descriptive analysis of individuals followed-up with hand radiographs at 7-years compared to those lost to follow-up suggest the possibility of attrition bias. As missing data from loss to follow-up could have affected estimates of the associations between metabolic factors and incidence and progression of radiographic hand OA, MI was undertaken for missing data (37,46). Therefore, discrepancies between the results of the complete case analysis and the imputed data are likely to be due to selective loss to follow-up, as was noted in the differences in baseline characteristics, and estimates obtained in the MI data given more credence.

A meta-analysis of cross-sectional studies found an association between the presence of diabetes and OA (6). Hyperglycaemia has been associated with elevated reactive oxygen species and advanced glycation end products that are thought to lead to low-grade inflammation and oxidative stress, which is believed to damage the chondrocytes (49). We believe this is the first study to examine diabetes as a risk factor for hand OA progression, and find an association in nodal OA. There were also non-significant patterns for increased progression in generalised and erosive OA, though this could be due to the small numbers in the erosive and generalised OA subsets affecting the precision of the estimates. The consistently higher mean differences in the KLsum score at 7-years of between 3 and 5 points in individuals with diabetes compared to those without suggests that diabetes may contribute to progression in specific hand OA subsets, particularly nodal OA. Further examination of the effects of diabetes and the other metabolic risk factors on hand OA progression across different hand OA subsets is required.

While inconsistent findings have been reported in the relation between obesity and hand OA progression (15-17), these early studies were at risk of collider bias due to conditioning on the presence of baseline radiographic hand OA (13,50,51). Restricting participants to only those with existing hand OA, could lead to biased estimates of the relationship between potential risk factors and hand OA progression. The weak non-significant association between BMI and hand OA progression in the current study is consistent with the results of the Oslo Hand OA Cohort (13). These concordant findings were despite differences in the study population settings (primary versus secondary care), the severity of hand OA at baseline (mean baseline KLsum score 7.8 versus 21.0 respectively) and adjustment for the presence of other metabolic factors in the current study. Risk factors for hand OA could vary for different stages of disease (52) as associations have been reported between obesity and diabetes, and incident hand OA (10,18-21), but the current work did not find an association between obesity or diabetes and incident OA over 7-years. This lack of association could be due to the relatively small numbers available in the incident analyses, the small amounts of change that were seen in KLsum score and number of joints with KL≥2 over 7-years in this group and because while individuals were free of radiographic OA, they had hand pain and could have had clinical or pre-radiographic OA.

The lack of association between metabolic factors and the amount of hand OA progression does not necessarily mean that no association exists. The presence of an association is likely to be affected by the time it takes for an exposure to affect the structure of a joint and the amount of exposure that is required to induce change.

This study used a large well-characterised cohort through which selective loss to follow-up was determined and overcome using MI. Attempts were also made to overcome collider bias, which is thought to have been a limitation of previous research (15-17), by including all participants in the analysis, so there was no conditioning for the presence of existing radiographic hand OA, an approach taken by others (13,53). Associations between metabolic factors and radiographic change were also examined in the subgroup of individuals who were free of OA at baseline, but the findings were unchanged. We, therefore, accept there is a risk of collider bias if the aim is to estimate the total effect of metabolic factors (the pre-baseline and the baseline status) on disease incidence and progression. However, we feel our study still makes a useful contribution as our findings highlight that it is unlikely that the change in radiographic OA between baseline and 7-years would be affected by the status of metabolic factors at baseline in a population of mid to later adulthood. Of course, it is still possible that the prevention of these metabolic risk factors would have some effect on radiographic OA change.

There are some limitations that should be acknowledged. Participants were from two studies, but both were general population samples from the same locality, the same data collection was used, and follow-up rates were comparable. It was not possible to differentiate between recently diagnosed and long-standing exposures as we only had consent to access individuals' medical records for the period 2 years prior and post baseline recruitment. Furthermore, objective exposure measurements could not be used as not all individuals had values entered in their medical records. More precise information might reveal differences in risk in those who are more severely affected compared to those individuals just above the threshold for diagnoses. Additionally, our analysis did not allow us to differentiate between the presence of a risk factor that is optimally managed and those that are not, which could affect the relation between metabolic factors and hand OA incidence and progression. Finally, while the presence of nodes on rays 2 to 5 was

collected in the CASHA cohort, nodes were only determined on rays 2 and 3 in the CASK cohort to fulfil ACR criteria, which could have led to nodal incidence and progression being underestimated.

Overall metabolic risk factors were not independently or collectively associated with greater amounts of radiographic hand OA incidence and progression over 7-years. Potential variation was found between the baseline hand OA subsets; with diabetes being a risk factor for radiographic hand OA progression in individuals with nodal, and possibly generalised and erosive OA. Further research is needed to explore differences between hand OA subsets, using objective measures to assess metabolic factors, taking account of the duration of exposures and to what extent metabolic factors are controlled.

Acknowledgements

The authors would like to acknowledge the contributions of Professor Peter Croft, Professor Elaine Hay, Dr Laurence Wood, Dr Elaine Thomas, June Handy, Charlotte Purcell, Catherine Tyson, Professor Chris Buckland–Wright and Professor Iain McCall for aspects of the conception and design of the study and the acquisition of data. Dr Jacqueline Saklatvala, Carole Jackson, Julia Matheson and the radiographers from the Department of Radiography at the Haywood Hospital, have contributed specifically to the acquisition of radiographs. We also wish to acknowledge June Handy and Abigail Gibson for their assistance in grading the CASK study radiographs at baseline and 7-years respectively, and Wing-Yee Kwok for grading the CASK & CASHA radiographs at erosive OA baseline. This project was undertaken with the support of Keele Clinical Trials Unit, Keele University, UK. The authors would also like to thank the staff and patients of the participating general practices.

Funding: This work was supported by Programme Grants awarded by the Medical Research Council, UK (Grant Code: G9900220) and Arthritis Research UK (Grant Code: 18174) and NHS service support costs were provided by Support for Sciences funding secured from North Staffordshire Primary Care Consortium. DvdW is a member of PROGRESS; Medical Research Council Prognosis Research Strategy (PROGRESS) Partnership (G0902393/99558).

Role of funding source: The funders did not contribute to data collection, analysis or interpretation of the data, manuscript preparation or submission.

Conflicts of interests: The authors have no conflicts of interests to declare.

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Table 1. Characteristics of study participants overall, those followed-up at 7-years and those with hand radiographs at baseline and 7-years

Baseline Characteristics	Participants (n=706)	Participants followed-up by questionnaire at 7-years (n=522)	Participants who attended research clinic and had hand radiographs at 7-years (n=388)
% Female (n)	62.0 (438)	60.9 (318)	60.1 (233)
Age, mean (SD)	60.5 (5.2)	60.3 (5.3)	60.5 (5.2)
% CASHA Study (n)	51.4 (363)	54.6 (285)	51.5 (200)
Index of multiple deprivation, mean (SD)	14971 (7425)	15524 (7390)	15316 (7509)
% White ethnicity (n)	99.7 (693)	99.8 (512)	99.7 (381)
% Smoking (n)			
Never	48.4 (338)	51.8 (268)	54.4 (210)
Ex	41.4 (289)	39.7 (205)	38.6 (149)
Current	10.2 (71)	8.5 (44)	7.0 (27)
% Hand pain on most or all days in the last month (n)	44.7 (315)	44.4 (232)	45.4 (176)
AUSCAN pain, mean (SD)	6.7 (4.2)	6.5 (4.1)	6.5 (4.1)
AUSCAN function, mean (SD)	10.0 (8.1)	9.6 (7.9)	9.6 (7.9)
AUSCAN stiffness, mean (SD)	1.2 (1.0)	1.2 (1.0)	1.2 (0.9)
% Radiographic hand OA (KL≥2 in ≥1 joints) (n)	68.7 (485)	68.1 (356)	67.5 (262)
Baseline summed KL score (0-80), mean (SD) median (IQR)	8.2 (9.6) 5 (2, 11)	7.9 (9.2)	7.8 (9.1)
Baseline number of joints KL≥2 (0-20), mean (SD) median (IQR)	2.8 (3.4) 2 (0, 4)	2.7 (3.3) 2 (0, 4)	2.7 (3.3) 2 (0, 4)
% Thumb base OA (KL≥2 in either 1CMCJ) (n)	42.9 (303)	43.1 (225)	43.6 (169)
% Nodal IPJ OA (KL≥2 in ≥2 IPJs (rays 2-5) & ≥2 nodes (rays 2-3) across either hand) (n)	21.5 (152)	21.3 (111)	21.9 (85)
% Generalised hand OA (KL≥2 in ≥1 distal IPJ & ≥1 proximal IPJ & ≥1 1CMCJ across either hand) (n)	11.8 (83)	10.9 (57)	11.6 (45)
% Erosive OA (E or R phase in ≥2 IPJ (rays 2-5) across either hand) (n)	3.1 (22)	3.3 (17)	2.8 (11)
Metabolic factors			
BMI, mean (SD)	29.2 (5.2)	28.9 (4.9)	28.9 (4.9)
% Hypertension (n)	36.4 (240)	36.7 (180)	36.6 (234)
% Diabetes type 2 or impaired fasting glucose (n)	10.8 (71)	8.6 (42)	9.8 (36)
% Dyslipidaemia (n)	30.8 (203)	31.4 (154)	31.2 (115)
No. metabolic factors, mean (SD)	1.1 (1.0)	1.1 (1.0)	1.1 (1.1)
% Metabolic Syndrome (n)	11.2 (74)	10.0 (49)	11.4 (42)
SF12 Physical Component Score, mean (SD)	39.2 (12.1)	39.9 (11.9)	40.0 (12.0)
SF12 Mental Component Score, mean (SD)	49.9 (11.0)	50.8 (10.6)	51.1 (10.6)
HADS Anxiety scale, mean (SD)	7.2 (4.2)	6.8 (4.1)	6.6 (4.1)
HADS Depression scale, mean (SD)	4.7 (3.6)	4.4 (3.5)	4.3 (3.4)
SF36 Physical functioning scale, mean (SD)	60.6 (28.4)	63.0 (27.8)	62.6 (28.3)

SD, Standard deviation; AUSCAN, Australian Canadian Hand Osteoarthritis Index; KL, Kellgren Lawrence; IPJ, Interphalangeal Joint; 1CMC, First Carpometacarpal joint; BMI, Body Mass Index

Table 2. The amount of radiographic change at 7-years overall, for those free of radiographic OA at baseline, and also separately for baseline hand OA subsets, stratified by sex in the imputed data (n=706)

	Females			Males		
Outcome = Kellgren-Lawrence summed score (0-80)						
	n	Adjusted mean*	(95%CI)	n	Adjusted mean*	(95%CI)
Total	438	17.0	(15.8, 18.2)	268	12.5	(11.2, 13.8)
No baseline hand OA	123	9.0	(7.1, 10.9)	98	6.8	(4.7, 8.8)
Thumb base OA	199	21.0	(19.6, 22.5)	104	16.1	(14.0, 18.1)
Nodal IPJ OA	115	26.6	(23.6, 29.5)	37	21.5	(17.7, 25.4)
Generalised hand OA	61	31.6	(28.0, 35.2)	22	27.6	(21.5, 33.7)
Erosive OA	19	40.1	(34.9, 45.3)	3	-	-
Outcome = Number of hand joints with Kellgren-Lawrence Grade≥2 (0-20) †						
	n	Adjusted mean*	(95%CI)	n	Adjusted mean*	(95%CI)
Total	437	6.7	(6.2, 7.2)	268	5.3	(4.7, 5.8)
No baseline hand OA	123	3.6	(2.9, 4.4)	98	2.8	(2.0, 3.7)
Thumb base OA	198	8.2	(7.7, 8.8)	104	6.6	(5.8, 7.4)
Nodal IPJ OA	114	10.5	(9.3, 11.7)	37	9.4	(7.9, 11.0)
Generalised hand OA	60	12.1	(10.7, 13.4)	22	10.8	(8.9, 12.8)
Erosive OA	18	13.5	(11.6, 15.4)	3	-	-

*95% CI, 95% Confidence interval; * adjusted for baseline value of outcome measure, cohort, age, time to follow-up; † One individual excluded due to maximum number of joints affected at baseline (n=20); - unable to calculate due to small numbers.*
No hand OA = KL<2 in all hand joints; Nodal IPJ OA = KL≥2 in ≥2 IPJs (rays 2-5) & ≥2 nodes (rays 2-3) across either hand; Thumb base OA = KL≥2 in the 1CMCJ in either hand; Generalised hand OA = KL≥2 in ≥1 distal IPJ & ≥1 proximal IPJ & ≥1 1CMCJ across either hand; Erosive OA (≥2 IPJ (rays 2-5)) across either hand.

Table 3. The association between baseline metabolic factors and hand OA progression at 7-years for all participants and stratified by baseline hand OA subset

	All participants (n=706)	Thumb base OA (n=303)	Nodal IPJ OA (n=152)	Generalised OA (n=83)	Erosive OA (n=22)
ANALYSIS BASED ON MULTIPLY IMPUTED DATA					
Outcome = Kellgren-Lawrence summed score (0-80)					
Adjusted mean difference (95%CI)*					
BMI, kg/m^2 †	-0.01 (-0.15, 0.13)	-0.11 (-0.33, 0.10)	-0.10 (-0.40, 0.20)	-0.37 (-0.87, 0.13)	-0.47 (-2.13, 1.19)
Hypertension	0.45 (-1.12, 2.03)	0.33 (-2.13, 2.78)	1.82 (-1.59, 5.24)	-0.36 (-6.04, 5.32)	2.49 (-9.26, 14.24)
Diabetes type 2/IFG	0.76 (-1.62, 3.13)	1.50 (-1.75, 4.75)	4.50 (-0.26, 9.25)	3.27 (-2.89, 9.42)	3.05 (-13.56, 19.67)
Dyslipidaemia	0.07 (-1.51, 1.66)	0.72 (-1.61, 3.04)	1.40 (-2.09, 4.89)	1.81 (-3.83, 7.45)	-6.55 (-19.58, 6.47)
No. of metabolic factors (0-4) †	0.02 (-0.57, 0.62)	0.06 (-0.81, 0.93)	0.75 (-0.72, 2.22)	-0.46 (-2.54, 1.62)	-2.09 (-7.94, 3.77)
Metabolic syndrome ‡	0.50 (-1.39, 2.40)	0.87 (-1.90, 3.64)	1.97 (-2.61, 6.54)	-0.81 (-7.85, 6.23)	-0.88 (-17.21, 15.44)
Outcome = Number of hand joints with Kellgren-Lawrence Grade≥2 (0-20) §					
Adjusted mean difference (95%CI)*					
BMI, kg/m^2†	0.01 (-0.05, 0.06)	-0.05 (-0.13, 0.03)	0.01 (-0.11, 0.12)	-0.11 (-0.29, 0.06)	-0.15 (-0.87, 0.57)
Hypertension	-0.01 (-0.63, 0.60)	-0.12 (-1.04, 0.80)	0.34 (-0.92, 1.61)	-0.61 (-2.59, 1.36)	0.34 (-4.58, 5.25)
Diabetes type 2/IFG	0.35 (-0.58, 1.28)	0.67 (-0.58, 1.93)	2.06 (0.25, 3.87)	1.42 (-0.71, 3.56)	2.02 (-6.02, 10.07)
Dyslipidaemia	0.21 (-0.41, 0.83)	0.53 (-0.36, 1.41)	0.67 (-0.60, 1.95)	1.09 (-0.89, 3.08)	-1.02 (-5.65, 3.62)
No. of metabolic factors (0-4) †	-0.01 (-0.25, 0.25)	0.02 (-0.31, 0.35)	0.41 (-0.15, 0.98)	-0.04 (-0.78, 0.70)	-0.50 (-2.76, 1.77)
Metabolic syndrome ‡	0.42 (-0.37, 1.22)	0.68 (-0.38, 1.73)	1.70 (-0.09, 3.50)	0.47 (-1.99, 2.93)	0.25 (-6.05, 6.54)
COMPLETE CASE ANALYSIS					
	All participants (n=365)	**Thumb base OA (n=169)**	**Nodal IPJ OA (n=85)**	**Generalised OA (n=45)**	**Erosive OA (n=11)**
Outcome = Kellgren-Lawrence summed score (0-80)					
Adjusted mean difference (95%CI)*					
BMI, kg/m^2 †	0.02 (-0.14, 0.19)	-0.17 (-0.45, 0.11)	-0.14 (-0.55, 0.27)	-0.92 (-2.00, 0.15)	-
Hypertension	0.80 (-0.85, 2.44)	0.38 (-2.57, 3.33)	2.15 (-2.65, 6.94)	-4.5 (-15.24, 6.15)	-
Diabetes type 2/IFG	-0.25 (-2.91, 2.41)	0.56 (-3.73, 4.84)	7.78 (1.13, 14.43)	9.46 (-1.98, 20.90)	-
Dyslipidaemia	0.15 (-1.53, 1.83)	1.59 (-1.29, 4.47)	2.34 (-2.56, 7.24)	4.93 (-4.98, 14.85)	-
No. of metabolic factors (0-4) †	0.10 (-0.61, 0.81)	0.08 (-1.02, 1.18)	1.49 (-0.46, 3.44)	0.01 (-3.83, 3.9)	1.12 (-4.59, 6.84)
Metabolic syndrome ‡	0.82 (-1.47, 3.11)	0.82 (-2.75, 4.39)	2.39 (-4.13, 8.92)	-3.60 (-17.06, 9.87)	3.88 (-15.43, 23.18)
Outcome = Number of hand joints with Kellgren-Lawrence Grade≥2 (0-20) §					
Adjusted mean difference (95%CI)*					
BMI, kg/m^2†	0.01 (-0.06, 0.07)	-0.08 (-0.17, 0.02)	-0.01 (-0.15, 0.13)	-0.25 (-0.55, 0.04)	-
Hypertension	0.09 (-0.56, 0.75)	-0.28 (-1.31, 0.76)	0.28 (-1.37, 1.92)	-2.08 (-4.97, 0.81)	-
Diabetes type 2/IFG	-0.24 (-1.30, 0.83)	-0.20 (-1.70, 1.30)	3.35 (1.08, 5.62)	2.94 (-0.13, 6.00)	-
Dyslipidaemia	0.27 (-0.40, 0.94)	1.18 (0.16, 2.19)	1.27 (-0.41, 2.98)	2.44 (-0.33, 5.21)	-
No. of metabolic factors (0-4) †	-0.01 (-0.29, 0.28)	0.02 (-0.38, 0.42)	0.70 (-0.01, 1.39)	0.34 (-0.83, 1.50)	0.04 (-1.54, 1.62)
Metabolic syndrome ‡	0.41 (-0.50, 1.33)	0.39 (-0.90, 1.67)	2.19 (-0.09, 4.48)	-0.29 (-4.36, 3.78)	-1.02 (-5.04, 3.00)

*95% CI, 95% Confidence interval; BMI, Body Mass Index; IFG, Impaired Fasting Glucose; * estimated from analysis of covariance adjusted for baseline value of outcome measure, cohort, time to follow-up, sex, age, Index of Multiple Deprivation, smoking status; † per unit increase (all other factors are classed present/absent); ‡ Any three of BMI≥30kg/m^2, diabetes type 2/IFG, hypertension, dyslipidaemia; § One individual excluded due to maximum number of joints affected at baseline; - unable to calculate due to small numbers. Thumb base OA = KL≥2 in the 1CMCJ in either hand; Nodal IPJ OA = KL≥2 in ≥2 IPJs (rays 2-5) & ≥2 nodes (rays 2-3) across either hand; Generalised hand OA = KL≥2 in ≥1 distal IPJ & ≥1 proximal IPJ & ≥1 1CMCJ across either hand; Erosive OA = ≥2 IPJ (rays 2-5) across either hand.*

Table 4. The association between baseline metabolic factors and incident hand OA at 7-years in those free of radiographic hand OA at baseline

ANALYSIS BASED ON MULTIPLY IMPUTED DATA	
Participants free of hand OA at baseline (n=221)	
Outcome = Kellgren-Lawrence summed score (0-80)	
	Adjusted mean difference* (95%CI)
BMI, kg/m^2 †	0.05 (-0.18, 0.28)
Hypertension	-0.26 (-2.70, 2.18)
Diabetes type 2/IFG	0.66 (-3.25, 4.57)
Dyslipidaemia	-0.22 (-2.83, 2.40)
No. of metabolic factors (0-4) †	-0.36 (-1.40, 0.68)
Metabolic syndrome ‡	-0.15 (-3.53, 3.22)
Outcome = Number of hand joints with Kellgren-Lawrence Grade≥2 (0-20) *§*	
	Adjusted mean difference* (95%CI)
BMI, kg/m^2 †	0.02 (-0.08, 0.12)
Hypertension	-0.20 (-1.19, 0.79)
Diabetes type 2/IFG	0.04 (-1.48, 1.55)
Dyslipidaemia	0.16 (-0.92, 1.23)
No. of metabolic factors (0-4) †	-0.15 (-0.59, 0.28)
Metabolic syndrome ‡	-0.07 (-1.52, 1.39)
COMPLETE CASE ANALYSIS	
Participants free of hand OA at baseline (n=126)	
Outcome = Kellgren-Lawrence summed score (0-80)	
	Adjusted mean difference* (95%CI)
BMI, kg/m^2 †	0.10 (-0.12, 0.33)
Hypertension	-0.34 (-2.45, 1.78)
Diabetes type 2/IFG	-0.25 (-3.78, 3.29)
Dyslipidaemia	0.04 (-2.35, 2.43)
No. of metabolic factors (0-4) †	-0.16 (-1.13, 0.81)
Metabolic syndrome ‡	-0.15 (-3.26, 2.96)
Outcome = Number of hand joints with Kellgren-Lawrence Grade≥2 (0-20) *§*	
	Adjusted mean difference* (95%CI)
BMI, kg/m^2 †	0.02 (-0.08, 0.11)
Hypertension	-0.19 (-1.12, 0.74)
Diabetes type 2/IFG	-0.42 (-1.98, 1.13)
Dyslipidaemia	0.08 (-0.98, 1.13)
No. of metabolic factors (0-4) †	-0.16 (-0.59, 0.27)
Metabolic syndrome ‡	-0.11 (-1.47, 1.26)

*95% CI, 95% Confidence interval; BMI, Body Mass Index; IFG, Impaired Fasting Glucose; * estimated from analysis of covariance adjusted for baseline value of outcome measure, cohort, time to follow-up, sex, age, Index of Multiple Deprivation, smoking status; † per unit increase (all other factors are classed present/absent); ‡ Any three of BMI≥30kg/m^2, diabetes type 2/IFG, hypertension, dyslipidaemia; § One individual excluded due to maximum number of joints affected at baseline.*

Figure 1. Flow diagram of study participants

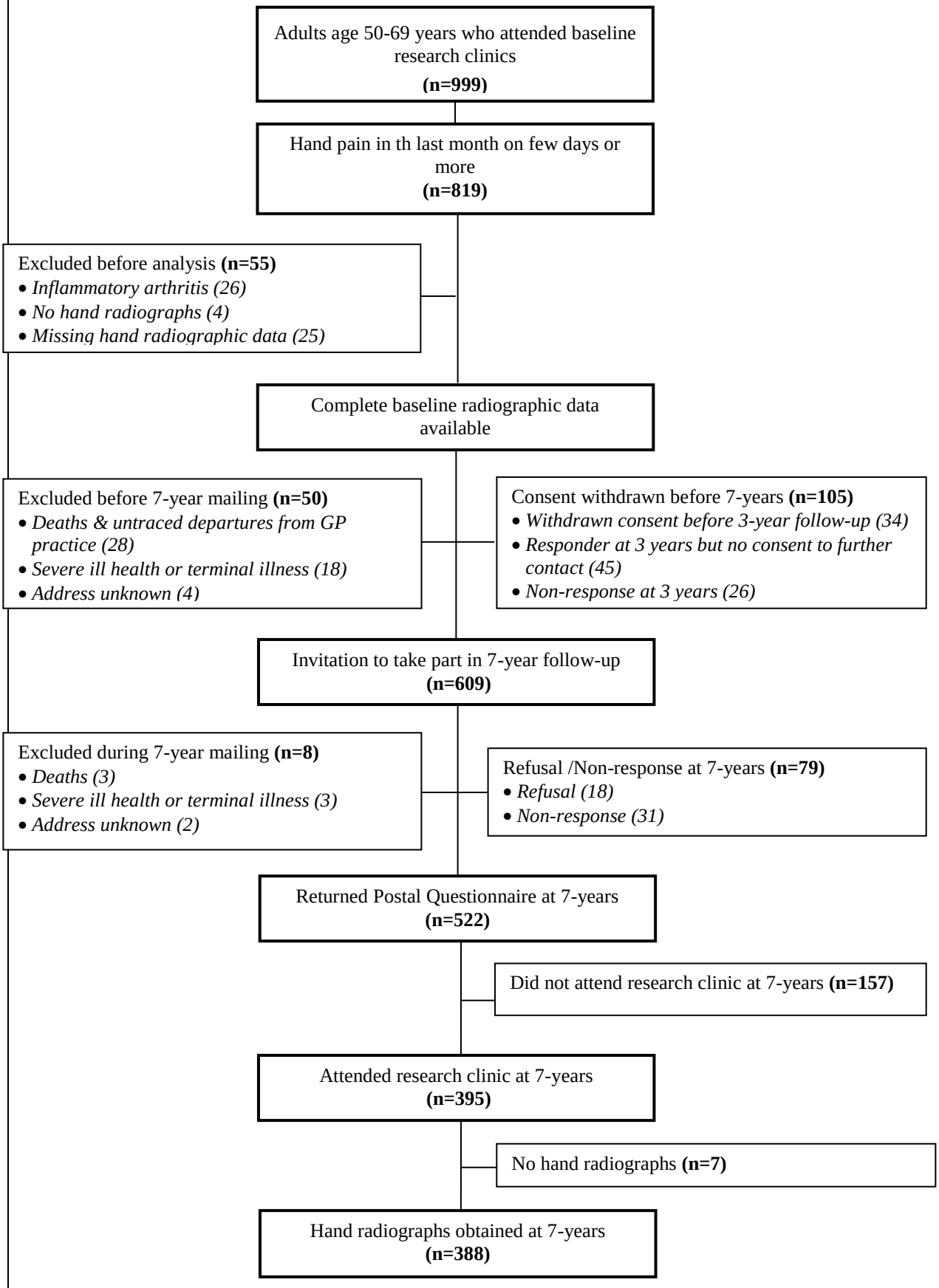
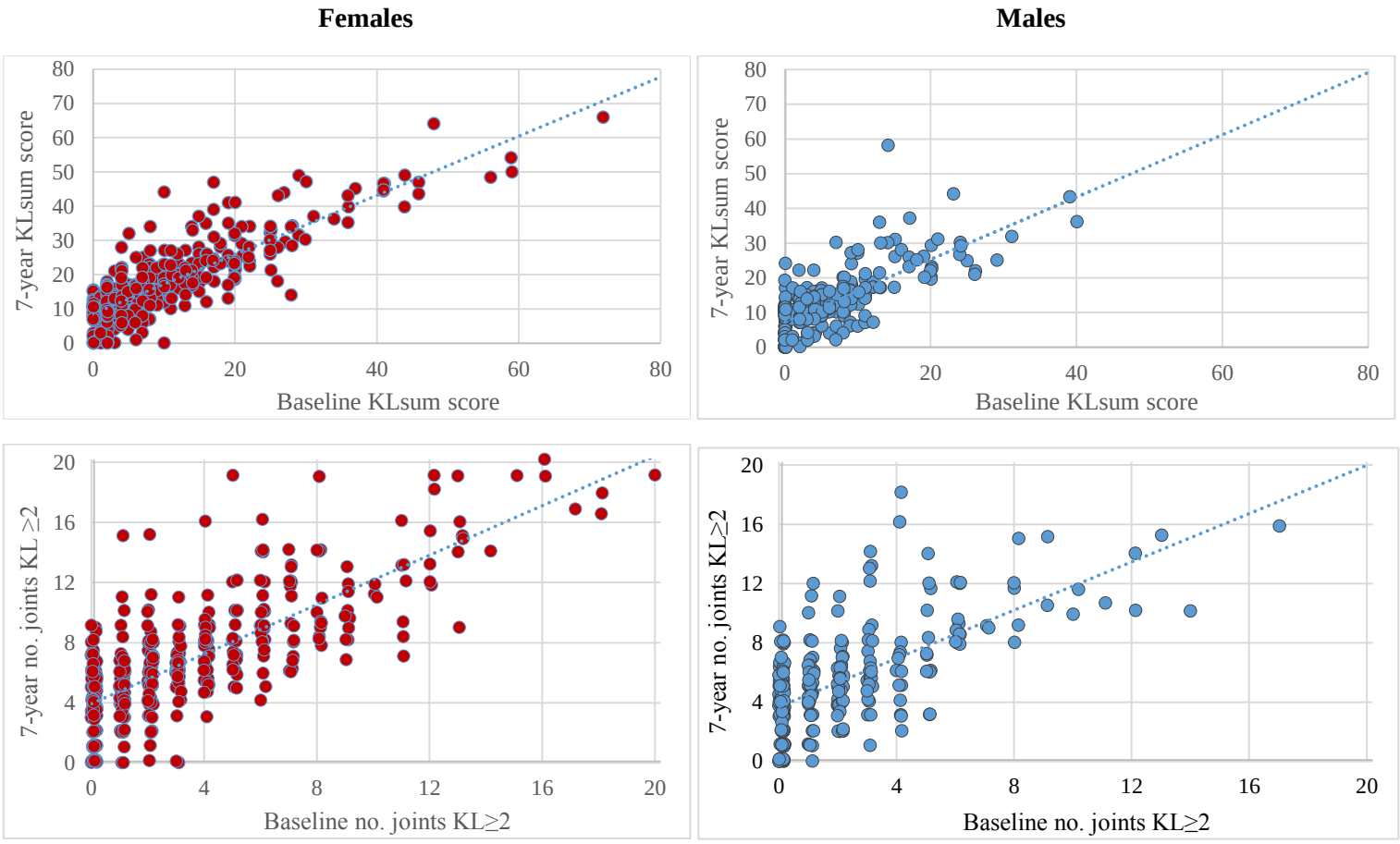


Figure 2. Scatter plots showing the relation between baseline and 7-year radiographic cores, stratified by sex in the imputed data (n=706)



KL, Kellgren Lawrence. Jittering has been used to allow better visualisation of overlapping markers.

Supplementary Table 1. Variables included in the multiple imputation model

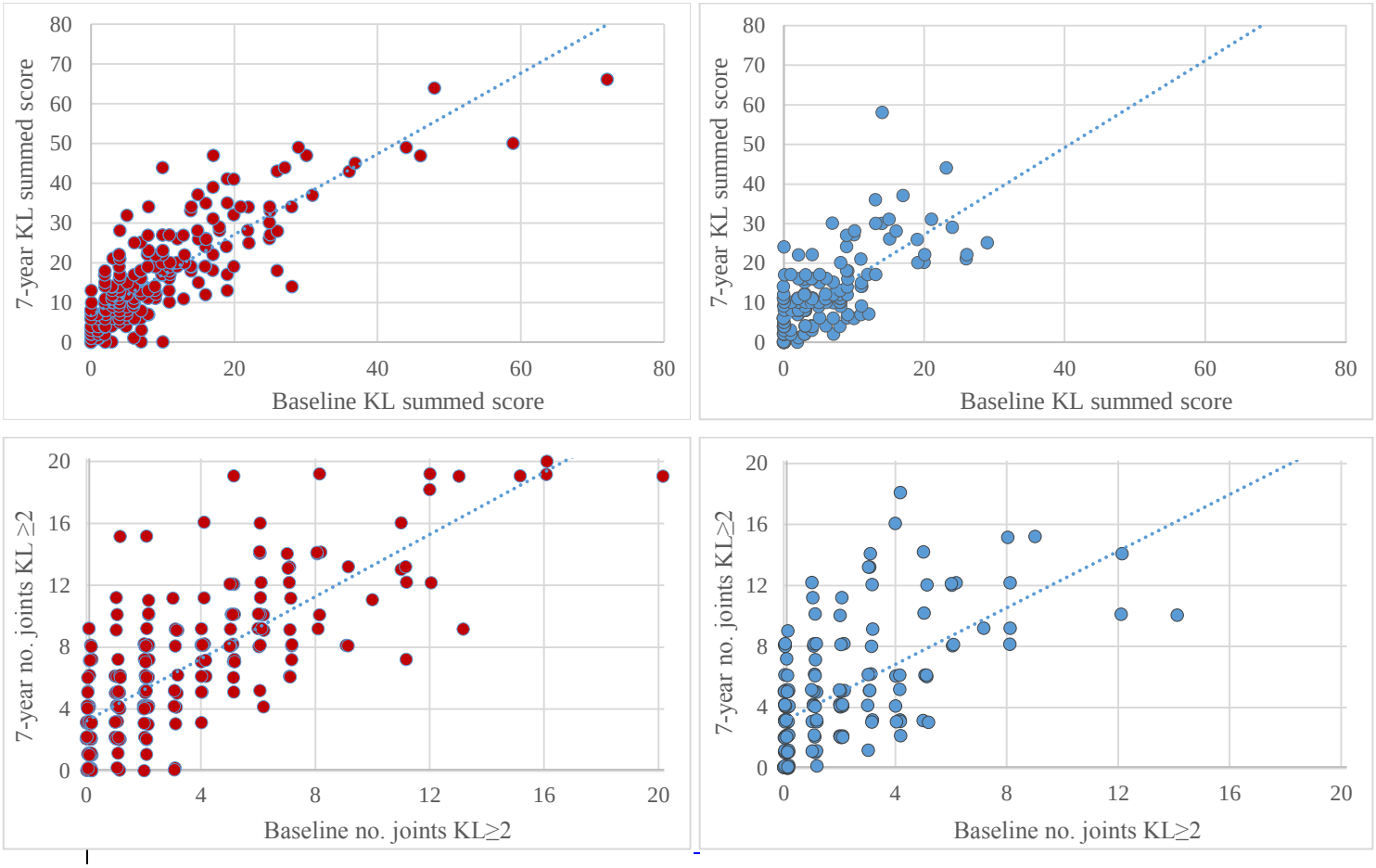
Concept	Measurement	Baseline	7-years	Included in subsequent analysis
Descriptive & sociodemographic	Sex (Female, Males)	•		•
	Age (years)	•		•
	Cohort (CASHA, CASK)	•		•
	Follow-up time (months)		•	•
	Smoking status (Never, Ex, Current)	I = 0.3%		•
	Index of Multiple Deprivation	I = 0.3%		•
	Further education (Yes, No)	•		
	Socioeconomic status[Office for National Statistics 2000]	•		
Metabolic factors (2 years before and after baseline)	BMI	I = 0.3%		•
	Hypertension (Present, Absent)	I = 6.5%		•
	Diabetes type 2 or impaired fasting glucose (Present, Absent)	I = 6.5%		•
	Dyslipidaemia (Present, Absent)	I = 6.5%		•
	No. metabolic factors (0-4)	I = 6.5%		•
	Metabolic Syndrome (Present, Absent) †	I = 6.5%		•
	No. days statins prescribed	I = 6.5%		
Radiographic OA	KLsum score (0-80)	•	I = 45.0%	•
	No. joints with OA (KL≥2) (0-20)	•	I = 45.0%	•
Hand characteristics and symptoms	Hand problem in the past 12 months (Yes, No)	•	•	
	Hand pain in the past 12 months (Yes, No)	•	•	
	Side of pain in past 12 months (Right, Left, Both)	•	•	
	Duration of hand problem (months)	•		
	Duration of pain in past 12 months (<7 days, 1-4 weeks, 1-3 months, >3 months)	•	•	
	Frequency of pain in past 1 month (no, few, some, most, all days)	•	•	
	AUSCAN pain, function & stiffness subscales[Bellamy 2002] (0-20; 0-36; 0-4 respectively)	•	•	
	Thumb base OA (Present, Absent)	•	•	•
	Nodal OA (Present, Absent)	•	•	•
	Generalised OA (Present, Absent)	•	•	•
	Erosive OA (Present, Absent)	•	•	•
General, physical and mental health	SF12 physical and mental component scores[Ware 1996] (0-100 each)	•		
	SF36 physical functioning scale[Ware & Sherborne 1992] (0-100)	•		
	HADS anxiety and depression subscales[Zigmond & Snaith 1983] (0-21 each)	•		
Self-reported comorbidities and health problems	Raised blood pressure (Present, Absent)	•		
	Diabetes (Present, Absent)	•		
	Chest problems (Present, Absent)	•		
	Heart problems (Present, Absent)	•		
	Deafness (Present, Absent)	•		
	Problems with eyesight (Present, Absent)	•		
	A fall or falls (Present, Absent)	•		
	Difficulty remembering things (Present, Absent)	•		
	Cough with spit (Present, Absent)	•		
	Breathless when walking (Present, Absent)	•		
	Dizziness or unsteadiness (Present, Absent)	•		
	Weakness in an arm or leg (Present, Absent)	•		

BMI, Body Mass Index; KL, Kellgren Lawrence; AUSCAN, Australian-Canadian Hand Osteoarthritis Index; SF12, Short Form 12; HADS, Hospital Anxiety and Depression Scale; SF36, Short Form 36; I, Data that was imputed and the proportion. † Metabolic Syndrome = Any three of BMI≥30kg/m^2, diabetes type 2/IFG, hypertension, dyslipidaemia. Thumb base OA = KL≥2 in the 1CMCJ in either hand; Nodal IPJ OA = KL≥2 in ≥2 IPJs (rays 2-5) & ≥2 nodes (rays 2-3) across either hand; Generalised hand OA = KL≥2 in ≥1 distal IPJ & ≥1 proximal IPJ & ≥1 1CMCJ across either hand; Erosive OA = E or R phase in ≥2 IPJ (rays 2-5) across either hand.

References: Bellamy N, et al. Dimensionality and clinical importance of pain and disability in hand osteoarthritis: Development of the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index. Osteoarthritis Cartilage 2002;10:855-62. Office for National Statistics (ONS). The National Statistics Socioeconomic Classification User Manual (version 1). London: Office for National Statistics. 2002. Ware J Jr, et al. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220-33. Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-83. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.

Supplementary Figure 1. Scatter plots showing the relation between baseline and 7-year radiographic scores, stratified by sex in the complete case analysis (n=388)

Females **Males**



KL, Kellgren Lawrence. Jittering has been used to allow better visualisation of overlapping markers.

Supplementary Table 2. The amount of radiographic change at 7-years overall, for those free of radiographic OA at baseline, and also separately for baseline hand OA subsets, stratified by sex in the complete case analysis

	Females			Males		
	Outcome = Kellgren-Lawrence summed score (0-80)					
	n	Adjusted mean*	(95%CI)	n	Adjusted mean*	(95%CI)
Total	233	16.5	(15.5, 17.5)	155	11.1	(10.0, 12.1)
No baseline hand OA	62	5.6	(4.1, 7.2)	64	4.0	(2.5, 5.6)
Thumb base OA	115	21.3	(19.9, 22.8)	54	16.1	(13.4, 18.9)
Nodal IPJ OA	62	27.9	(24.2, 31.6)	23	20.7	(15.9, 25.5)
Generalised hand OA	32	33.0	(28.5, 37.5)	13	27.2	(14.9, 39.4)
Erosive OA	10	42.8	(38.3, 47.3)	1	-	-
	Outcome = Number of hand joints with Kellgren-Lawrence Grade≥2 (0-20) †					
	n	Adjusted mean*	(95%CI)	n	Adjusted mean*	(95%CI)
Total	232	6.5	(6.1, 6.9)	155	4.8	(4.3, 5.2)
No baseline hand OA	62	2.4	(1.7, 3.0)	64	1.7	(1.0, 2.5)
Thumb base OA	114	8.4	(7.8, 8.9)	52	6.8	(5.8, 7.7)
Nodal IPJ OA	61	11.1	(9.9, 12.3)	23	9.2	(7.3, 11.1)
Generalised hand OA	31	12.7	(11.2, 14.1)	13	11.0	(7.7, 14.4)
Erosive OA	9	13.3	(11.5, 15.0)	1	-	-

*95% CI, 95% Confidence interval; * adjusted for baseline value of outcome measure, cohort, age, time to follow-up; † One individual excluded due to maximum number of joints affected at baseline (n=20). No hand OA = KL<2 in all hand joints; Nodal IPJ OA = KL≥2 in ≥2 IPJs (rays 2-5) & ≥2 nodes (rays 2-3) across either hand; Thumb base OA = KL≥2 in the 1CMCJ in either hand; Generalised hand OA = KL≥2 in ≥1 distal IPJ & ≥1 proximal IPJ & ≥1 1CMCJ across either hand; Erosive OA = ≥2 IPJ (rays 2-5) across either hand.*