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

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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 2\(^{nd}\) and 3\(^{rd}\) 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.
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References

1. 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.

2. Kloppenburg M, Kwok WY. Hand osteoarthritis – a heterogeneous disorder. Nat Rev Rheumatol. 2011;22:22-31.

3. Kwok WY, Plevier JW, Rosendaal FR, Huizinga TW, Kloppenburg M. Risk factors for progression in hand osteoarthritis: a systematic review. Arthritis Care Res. 2013;65:552-62.

4. Conaghan PG, Kloppenburg M, Schett G, Bijlsma JW, EULAR osteoarthritis ad hoc committee. Osteoarthritis research priorities: a report from a EULAR ad hoc expert committee. Ann Rheum Dis. 2014;73:1442-5.

5. Yusuf E, Nelissen RG, Ioan-Facsinay A, Stojanovic-Susulic V, DeGroot J, van Osch G, et al. Association between weight or body mass index and hand osteoarthritis: a systematic review. Ann Rheum Dis. 2010;69:761-5.

6. Louati K, Vidal C, Berenbaum F, Sellam J. Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis. RMD Open. 2015;1:e000077.

7. 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.

8. Visser AW, de Mutsert R, le Cessie S, den Heijer M, Rosendaal FR, Kloppenburg M, et al. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. Ann Rheum Dis. 2015;74:1842-7.

9. Tomi AL, Sellam J, Lacombe K, Fellahi S, Sebire M, Rey-Jouvin C, et al. Increased prevalence and severity of radiographic hand osteoarthritis in patients with HIV-1 infection associated with metabolic syndrome: data from the cross-sectional METAFIB-OA study. Ann Rheum Dis. 2016;75:2101-7.

10. Frey N, Huegle T, Jick SS, Meier CR, Spoendlin J. Type II diabetes mellitus and incident osteoarthritis of the hand: a population-based case-control analysis. Osteoarthritis Cartilage. 2016;24:1535-40.

11. Frey N, Hügle T, Jick SS, Meier CR, Spoendlin J. Hyperlipidaemia and incident osteoarthritis of the hand: a population-based case-control study. Osteoarthritis Cartilage. 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. Magnusson K, Slatkowsky-Christensen B, van der Heijde D, Kvien TK, Hagen KB, Haugen IK. Body mass index and progressive hand osteoarthritis: data from the Oslo hand osteoarthritis cohort. Scand J Rheumatol. 2015;44:331-6.

14. Reyes C, Leyland KM, Peat G, Cooper C, Arden NK, Prieto-Alhambra D. Association between overweight and obesity and risk of clinically diagnosed knee, hip, and hand osteoarthritis: a population-based cohort study. Arthritis Rheumatol. 2016;68:1869-75.

15. Yusuf E, Ioan-Facsinay A, Bijsterbosch J, Klein-Wieringa I, Kwekkeboom J, Slagboom PE, et al. Association between leptin, adiponectin and resistin and long-term progression of hand osteoarthritis. Ann Rheum Dis. 2011;70:1282-4.

16. Cvijetic S, Kurtagic N, Ozegovic DD. Osteoarthritis of the hands in the rural population: a follow-up study. Eur J Epidemiol. 2004;19:687-91.

17. Harris PA, Hart DJ, Dacre JE, Huskisson EC, Spector TD. The progression of radiological hand osteoarthritis over ten years: a clinical follow-up study. Osteoarthritis Cartilage. 1994;2:247-52.

18. Grotle M, Hagen HB, Natvig B, Dahl FA, Kvien TK. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. BMC Musculoskeletal Disord. 2008;9:132.

19. Oliveria SA, Felson DT, Cirillo PA, Reed JI,Walkers AM. Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. Epidemiology 1999;10:161-6.

20. Carman WJ, Sowers M, Hawthorne VM, Weissfeld LA. Obesity as a risk factor for osteoarthritis of the hand and wrist: a prospective study. Am J Epidemiol. 1994;139:119-29.

21. Sowers M, Zobel D, Weissfeld L, Hawthorne VM, Carman W. Progression of osteoarthritis of the hand and metacarpal bone loss. A twenty-year followup of incident cases. Arthritis Rheum. 1991;34:36-42.

22. Haugen IK, Magnusson K, Turkiewicz A, Englund M. The prevalence, incidence, and progression of hand osteoarthritis in relation to body mass index, smoking, and alcohol consumption. J Rheumatol. 2017;44:1402-9.
23. 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 (Hoboken). 2017 May 23 [Epub ahead of print].

24. 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. Osteoarthritis Cartilage. 2013;21:1674-84.

25. Filková M, Senolt L, Braun M, Hulejová H, Pavelková A, Slégllová O, et al. Serum hyaluronic acid as a potential marker with predictive value for further radiographic progression of hand osteoarthritis. Osteoarthritis Cartilage. 2009;17:1615-9.

26. 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.

27. Myers H, Nicholls E, Handy J, Peat G, Thomas E, Duncan R, et al. The Clinical Assessment Study of the Hand (CAS-HA): a prospective study of musculoskeletal hand problems in the general population. BMC Musculoskelet Disord. 2007;8:85.

28. Peat G, Thomas E, Handy J, Wood L, Dziedzic K, Myers H, et al. The Knee Clinical Assessment Study - CAS(K). A prospective study of knee pain and knee osteoarthritis in the general population. BMC Musculoskelet Disord. 2004;5:4.

29. Altman R, Alarcón G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum. 1990;33:1601-10.

30. The English Index of Multiple Deprivation (IMD). London (UK): Department of Communities and Local Government; 2015 [cited 2016 Dec 15]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/464430/English_Index_of_Multiple_Deprivation_2015_-_Guidance.pdf

31. Lawrence JS. Osteo-arthritis. In: Lawrence JS, editor. Rheumatism in populations. London (UK): William Heinemann Medical Books; 1977: p. 98-155.
32. Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. Arthritis Rheum. 1996;39:308-20.
33. Bijsterbosch J, van Bemmel JM, Watt I, Meulenbelt I, Rosendaal FR, Huizinga TW, et al. Systemic and local factors are involved in the evolution of erosions in hand osteoarthritis. Ann Rheum Dis. 2011;70:326-30.
34. 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.
35. Harding A, Stuart-Buttle C. The development and role of the Read Codes. J AHIMA. 1998;69(5):34-8.
36. Adult Treatment Panel III. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001;285:2486-97.
37. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol. 2006;59:1087-91.
38. Altman DG. Missing outcomes in randomized trials: addressing the dilemma. Open Med. 2009;3:e51-3.
39. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
40. Klebanoff MA, Cole SR. Use of multiple imputation in the epidemiologic literature. Am J Epidemiol. 2008;168:355-7.
41. Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. Prev Sci. 2007;8:206-13.
42. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30:377–99.
43. Kontopantelis E, White IR, Sperrin M, Buchan I. Outcome-sensitive multiple imputation: a simulation study. BMC Med Res Methodol. 2017;17:2.
44. Janssen KJ, Donders AR, Harrell FE Jr, Vergouwe Y, Chen Q, Grobbee DE, et al. Missing covariate data in medical research: to impute is better than to ignore. J Clin Epidemiol. 2010;63:721-7.
45. Groenwold RH, Donders AR, Roes KC, Harrell FE Jr, Moons KG. Dealing with missing outcome data in randomized trials and observational studies. Am J Epidemiol. 2012;175:210-7

46. Lee KJ, Carlin JB. Multiple imputation for missing data: fully conditional specification versus multivariate normal imputation. Am J Epidemiol. 2010;171:624-32.

47. Van der Heijden GJ, Donders AR, Stijnen T, Moons KG. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. J Clin Epidemiol. 2006;59:1102-9.

48. Rubin DB. Inference and missing data. Biometrika. 1976;63:581-92.

49. Courties A, Gualillo O, Berenbaum F, Sellam J. Metabolic stress-induced joint inflammation and osteoarthritis. Osteoarthritis Cartilage. 2015;23:1955-65.

50. Zhang Y, Neogi T, Hunter D, Roemer F, Niu J. What effect is really being measured? An alternative explanation of paradoxical phenomena in studies of osteoarthritis progression. Arthritis Care Res. 2014;66:658-61.

51. Zhang Y, Niu J, Felson DT, Choi HK, Nevitt M, Neogi T. Methodologic challenges in studying risk factors for progression of knee osteoarthritis. Arthritis Care Res. 2010;62:1527-32.

52. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med. 2010;26:355-69.

53. Roemer FW, Felson DT, Wang K, Crema MD, Neogi T, Zhang Y, et al. Co-localisation of non-cartilaginous articular pathology increases risk of cartilage loss in the tibiofemoral joint--the MOST study. Ann Rheum Dis. 2013;72:942-8.
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)                   | 8.2 (9.6)           | 7.9 (9.2)                                                     | 7.8 (9.1)                                                                            |
| median (IQR)                                                  | 5 (2, 11)           |                                                               |                                                                                      |
| Baseline number of joints KL≥2 (0-20), mean (SD) median (IQR)| 2.8 (3.4)           | 2.7 (3.3)                                                     | 2.7 (3.3)                                                                            |
| % 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 |                   |                   |
|----------------|---------|-------------------|-------------------|-------|-------------------|-------------------|
|                | n       | Adjusted mean*    | (95%CI)           | n     | Adjusted mean*    | (95%CI)           |
| Outcome = Kellgren-Lawrence summed score (0-80) |         |                   |                   |       |                   |                   |
| 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) †  |         |                   |                   |       |                   |                   |
| 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

| ANALYSIS BASED ON MULTIPLY IMPUTED DATA | All participants (n=706) | Thumb base OA (n=303) | Nodal IPJ OA (n=152) | Generalised OA (n=83) | Erosive OA (n=22) |
|----------------------------------------|--------------------------|-----------------------|----------------------|-----------------------|-------------------|
| **Outcome = Kellgren-Lawrence summed score (0-80)** | | | | | |
| **Outcome** | | | | | |
| **BMI, kg/m² †** | -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) |

| COMPLETE CASE ANALYSIS | | | | | |
| **Outcome = Kellgren-Lawrence summed score (0-80)** | | | | | |
| **Adjusted mean difference (95%CI)*** | | | | | |
| **BMI, kg/m² †** | 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) |

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/m², 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 1CMIJ in either hand; Nodal IPJ OA = KL≤2 in ≥2 IPJ/s (rays 2-5) & ≥2 nodes (rays 2-3) across either hand; Generalised hand OA = KL≥2 in ≥1 distal IPJ & ≥1 proximal IPJ & ≥1 1CMIJ 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/m² †                           | 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/m² †                                                   | 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/m² †           | 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/m² †                                                              | 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/m², 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

Adults age 50-69 years who attended baseline research clinics
(n=999)

Hand pain in the last month on few days or more
(n=819)

Excluded before analysis (n=55)
- Inflammatory arthritis (26)
- No hand radiographs (4)
- Missing hand radiographic data (25)

Complete baseline radiographic data available

Excluded before 7-year mailing (n=50)
- Deaths & un traced departures from GP practice (28)
- Severe ill health or terminal illness (18)
- Address unknown (4)

Invitation to take part in 7-year follow-up
(n=609)

Consent withdrawn before 7-years (n=105)
- Withdrawn consent before 3-year follow-up (34)
- Responder at 3 years but no consent to further contact (45)
- Non-response at 3 years (26)

Refusal /Non-response at 7-years (n=79)
- Refusal (18)
- Non-response (31)

Returned Postal Questionnaire at 7-years
(n=522)

Did not attend research clinic at 7-years (n=157)

Attended research clinic at 7-years
(n=395)

No hand radiographs (n=7)

Hand radiographs obtained at 7-years
(n=388)

Excluded during 7-year mailing (n=8)
- Deaths (3)
- Severe ill health or terminal illness (3)
- Address unknown (2)

Excluded before analysis (n=55)
- Deaths (3)
- Severe ill health or terminal illness (3)
- Address unknown (2)

Hand pain in the last month on few days or more
(n=819)

Complete baseline radiographic data available

Excluded before analysis (n=55)
- Inflammatory arthritis (26)
- No hand radiographs (4)
- Missing hand radiographic data (25)

Excluded before 7-year mailing (n=50)
- Deaths & un traced departures from GP practice (28)
- Severe ill health or terminal illness (18)
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Invitation to take part in 7-year follow-up
(n=609)

Consent withdrawn before 7-years (n=105)
- Withdrawn consent before 3-year follow-up (34)
- Responder at 3 years but no consent to further contact (45)
- Non-response at 3 years (26)

Refusal /Non-response at 7-years (n=79)
- Refusal (18)
- Non-response (31)

Returned Postal Questionnaire at 7-years
(n=522)

Did not attend research clinic at 7-years (n=157)

Attended research clinic at 7-years
(n=395)

No hand radiographs (n=7)

Hand radiographs obtained at 7-years
(n=388)
Figure 2. Scatter plots showing the relation between baseline and 7-year radiographic cores, stratified by sex in the imputed data (n=706)

Females

Males

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 | ● | ● |  |
| 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* (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 1994) (0-100 each) | ● | ● |  |
| | SF36 physical functioning scale† (Ware 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) | ● | ● |  |

*BMIs, 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/m², 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 JE 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)

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 |                   |
|--------------------------|---------|-------------------|-------|-------------------|
|                          | n       | Adjusted mean*    | (95%CI)| n                | Adjusted mean*    | (95%CI) |
| **Outcome = Kellgren-Lawrence summed score (0-80)** |         |                   |       |                   |                   |
| 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)** |     |                   |       |                   |
| 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.