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Brief Report

The ageing joint-standard age- and sex-related values of bone erosions and osteophytes in the hand joints of healthy individuals

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SUMMARY

Objective: To analyze the age-related changes of the physiological hand joint architecture.
Method: To address this concept, healthy individuals (each 10 women and 10 men in six different age decades spanning from 21 to 80 years) were recruited through a field campaign, investigated for the absence of rheumatic diseases and other comorbidities and received high-resolution quantitative computed tomography (HR-pQCT) examination of the hand joints. Number and extent of erosions and osteophytes were quantified across the ages and different sexes.
Results: Bone erosions [median (Q1–Q3), 1 (0–2)] and osteophytes [2 (1–4)] were found in healthy women and men with no significant sex differences. Structural changes however accumulated with age: the overall incidence rate ratio (IRR) for the number of erosions and osteophytes per age were 1.04 (95% CI: erosions 1.03–1.06; osteophytes: 1.03–1.05). This means a 4% increase in the number of erosions and osteophytes per year. Using third decade as reference, healthy individuals in the age decades from 50 years had higher IRR for erosion numbers (sixth, seventh, eigth decade: 4.87 (2.20–11.75), 6.81 (3.08–16.46) and 6.92 (3.11–16.79)) compared to younger subjects (fourth, fifth decade: 1.80 (0.69–4.87), 1.53 (0.59–4.10)). The IRRs of osteophytes also indicate a gradual increase after the fifth decade, with IRRs of 2.32 (1.32–4.17), 4.17 (2.38–7.49) and 6.86 (3.97–12.20) for the sixth, seventh and eigth decades, respectively.
Conclusions: Structural changes in the hand joints of healthy individuals are age dependent. While being rare under 50 years of age, erosions and osteophytes accumulate above the age of 50, suggesting that the threshold between "normal" and "pathological" is shifted with the increase of age.

Introduction

The "normal" skeletal architecture of the joint is characterized by a smooth and intact cortical bone surface, which separates the bone marrow cavity from the synovial space. Arthritis is typically associated with changes of this architecture leading to breaks in the cortical lining, termed erosions, or local bone appositions, termed osteophytes or enthesiophytes, dependent on their anatomical localization[1,2]. Hence, in diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and osteoarthritis (OA) the "normal" skeletal architecture of the joint is changed.

"Normal" however, has not been defined with respect to joint architecture and may not stay the same during the course of life. Though such "physiological" age-related changes of the hand joints may be milder than those found in arthritis, they define the baseline age-adjusted appearance of the "healthy" joint. With conventional radiography, such age-related changes may stay under the detection threshold, however, if using more sensitive bone imaging, these changes may become detectable and define the specific skeletal architecture of the normal joint during a certain age[3]. Definition of such standard age-related values has not been accomplished so far.

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Herein, we prospectively recruited 120 healthy women and men (21–80 years) and quantified their erosive and osteophytic bone changes by high-resolution quantitative computed tomography (HR-pQCT) aiming to define the standard age-related structural changes in the hand joints of healthy individuals.

Patients and methods

Subjects

Healthy subjects aged 21–80 years were recruited through a field campaign. The recruitment was prospective aiming for each 10 females and 10 males in six different decades (21–30, 31–40, 41–50, 51–60, 61–70 and 71–80 years). A detailed history taking and clinical examination was done in all subjects by skilled rheumatologists (AH/AK/JR/SF) to rule out tenderness, stiffness, swelling and bony swelling. Individuals must have been free of present or past signs of rheumatic disease. Subjects with a history of osteoporosis, pathological fractures, recent trauma (<1 year) or those having received glucocorticoids or bisphosphonates were not included. Subjects needed to be free of cancer, diabetes mellitus, cardiovascular disease (angina, myocardial infarction, stroke) as well as chronic renal, gastrointestinal and hepatic disease. Subjects had to be tested negative for rheumatoid factor or anti-cyclic citrullinated protein antibodies (ACPA). Presence of psoriasis or a positive family history was also not allowed. Smoking status, alcohol intake, body mass index (BMI) and health assessment questionnaire (HAQ-DI) were recorded. All subjects gave informed consent. The ethical committee of the University Clinic of Erlangen and the National Radiation Safety Agency approved the study.

Acquisition of HR-pQCT data

HR-pQCT of the second and third metacarpophalangeal (MCP) and proximal inter-phalangeal (PIP) joints of the dominant hand was performed using the XtremeCT I scanner (Scanco). Measurements of the MCP joints were performed as previously described using 322 slices[4]. In the PIP joints, 111 slices in the distal and proximal direction were done using the apex of the third PIP head as reference point. Radiation exposure for three stacks (MCP joints) was 9 μSV for two Stacks (PIP) six μSV. Gray scale images (Image Sequence data ISQ) were transformed into DICOM images on the workstation (μCT Evaluation program Version 6). Images were assessed using the DICOM viewer OsiriX (version 6.5).

Assessment of erosions and osteophytes in the hand joints

Two independent readers assessed osteophytes and erosions (DS, AB). Erosions were defined as juxta-articular breaks of the cortical shell, traceable in two successive slices and in two vertical planes[5]. An osteophyte was defined as a bony outgrowth occurring adjacent to the joint. Osteophytes and erosions were assessed in number, size and localization. Though all osteophytes/erosions were counted, only the biggest osteophyte/erosion per quadrant was assessed for size: Osteophytes size was defined as the distance between the highest surface of the lesion and the original surface of the cortical bone[6]. Erosions volume was assessed by Medical Image Analysis Framework (MIAF), an image analysis software that allows a full 3D segmentation of erosions[7].

Statistical analysis

Continuous and count data were summarized using medians and first to third quartile intervals (Q1-Q3) or means and standard deviations as appropriate. We visually explored the relationship between number of osteophytes, number of erosions, size of erosions and age with scatterplots and empirical cumulative probability plots stratified by age decades. We utilized negative binomial regression to model counts by age (continuous and in decades) and gender as explanatory variables and reported incidence rate ratios (IRR) with 95% confidence intervals. Relationship between age and erosion size was analyzed with a gamma hurdle model. Maximum osteophyte size was readily explained by the number of osteophytes ($r^2 = 0.89$) and not separately analyzed. In order to define normal ranges we used an empirical bootstrap method to determine a 95% confidence interval for the median and a point estimate for the ninety fifth percentile of erosion and osteophyte counts for each age decade. We calculated intra-class correlation coefficients (ICC) to determine the image reading agreement. Data analyses were performed using the open-source R software V 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographic characteristics of the subjects

Demographic data of the 120 healthy individuals are shown in Table I. Subjects were lean (BMI 24.7 ± 3.7), smoking was rare (6.7%) and hypertension found only in a minority of subjects ($N = 19$; 15.8%). Functional state of the subjects was very good (HAQ 0.005 ± 0.04).

Bone erosions in healthy individuals' hand joints

Overall 168 erosions were detected in MCP and PIP joints of the 120 subjects. 65 (56.0%) subjects showed at least one erosion. Most (67.8%) of the erosions were found at the radial side of MCPs ($N = 70$) and PIPs ($N = 44$), respectively (Fig. 1). The MCP/PIP erosion ratio was 1.1. The number of erosions ranged from 0 to 12 with a median (Q1-Q3) of 1 (0–2). The median erosion volume was 7.23 mm^3 (2.07–20.39). The observed values and distributions of erosion counts by age categories are depicted in Fig. 2(A). Median and interquartile ranges are provided in Table S1.

Osteophytes in healthy individuals' hand joints

347 osteophytes were detected. 100 healthy subjects showed at least one osteophyte. The MCP/PIP osteophyte ratio was 1.4. The median number of osteophytes was 2 (1–4). Most of the bony proliferations were found at the dorsal or palmar sides (Fig. 1). Inter-observer agreement for osteophytes (ICC 0.96; [95% CI] 0.92, 0.98) and erosions (0.76; [95% CI] 062, 0.86) was high (also see Fig. 2(B)/Table S1).

Effect of age and sex on erosions in hand joints

The IRR for number of erosions and volume per year of age was estimated at 1.04 (95% CI: 1.03–1.06; 1.01–1.07), namely a 4% increase in the number of erosions and volume of erosions with each year. An inspection of empirical cumulative probability plots in age categories however suggest that number and volume distribution of erosions show two clusters in individuals below and above 50 years of age (Fig. S1). Using third decade as the reference, IRRs for the fourth and fifth decades were 1.80 and 1.53 respectively with largely overlapping confidence intervals that included unity, whereas the IRRs for the sixth, seventh and eighth decades were 4.87, 6.81 and 6.92 respectively, with largely overlapping confidence intervals that excluded both unity and the point estimates for the fourth and fifth decades [Fig. 2(C)]. Bootstrapped confidence intervals for age specific medians and point estimates for the ninety fifth percentile for

Table I
Demographic characteristics and bone changes in the joints of healthy subjects

A. Demographic characteristics	
N	120
Age, years	49.2 ± 17.0
Females, N (%)	61 (50.1)
Body mass index	24.7 ± 3.7
Current smokers, N (%)	8 (6.7)
Previous smokers, N (%)	0
Never smokers, N (%)	112 (93.3)
Alcohol use, N (%)*	114 (95.0)
Hypertension, N (%)	19 (15.8)
HAQ-DI	0.005 ± 0.04

B. Bootstrap CI and ninety fifth percentiles for erosion and osteophyte counts

Age group	Erosions		Osteophytes	
	Median (95% CI)	Ninety fifth percentile	Median (95% CI)	Ninety fifth percentile
21–30	0 (0–1)	1	1 (0–2)	2
31–40	0 (0–1)	3	2 (1–2)	5
41–50	0 (0–1)	2	1 (0–2)	4
51–60	1 (0–2)	5	3 (1–3)	6
61–70	2 (2–4)	5	3 (3–4)	13
71–80	2 (1–3)	6	6 (6–9)	15

CI, confidence interval.
* low to moderate alcohol consumption; values indicate means ± SD.

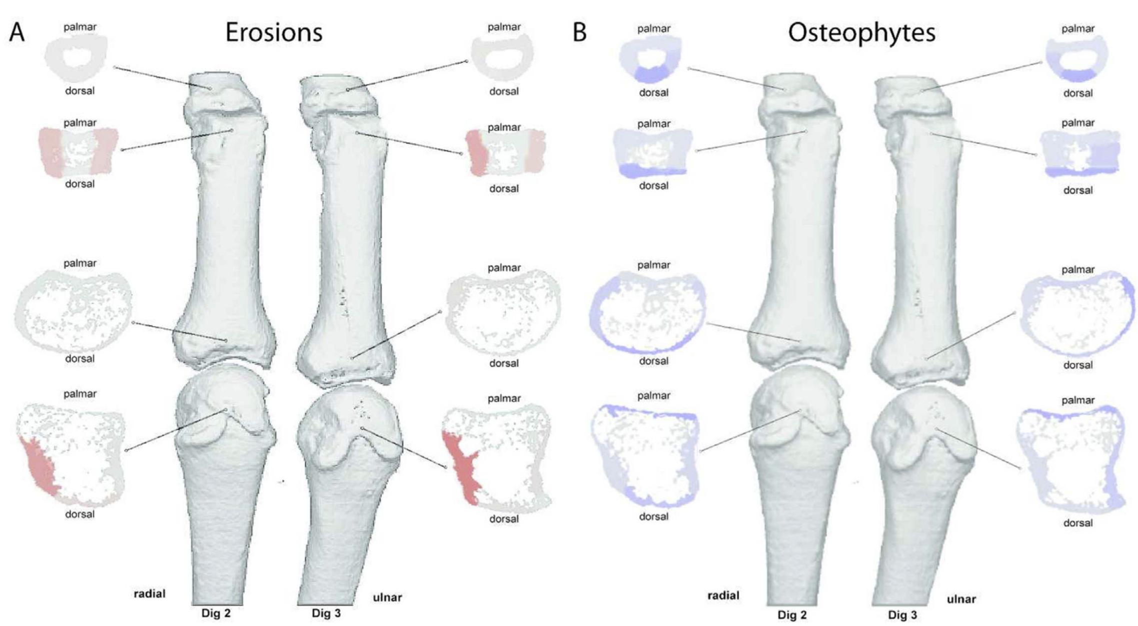

Fig. 1. Distribution of erosions and osteophytes in healthy subjects. Distribution of erosions is shown in A, distribution of osteophytes in B. The more intense the colour, the higher the number of erosions (hatched in red) or osteophytes (hatched in blue). Erosions are mostly found at the radial sides of MCP and proximal interphalangeal joints, osteophytes mostly at the dorsal or palmar sides.

erosion counts are presented in Table S1. The case for the volume of erosions was similar with respect to unity however the confidence intervals were wide. The IRR of erosion counts for female sex was 0.69 (95% CI 0.45–1.05) showing a 31% lower incidence of erosions in females in comparison to males however a null effect cannot be excluded with good certainty.

Effect of age and sex on osteophytes in hand joints

The IRR of osteophyte counts for age was 1.04 (95% CI 1.03–1.05) indicating a 4% increase per age similar to erosion counts. The cumulative probability plots and IRRs for age categories suggest a gradual increase in the number of osteophytes after the fifth decade with IRRs of 2.32, 4.17 and 6.86 all with partially overlapping confidence intervals that exclude unity [Fig. 2(D)]. Bootstrapped confidence intervals for age specific medians and point estimates for the ninety fifth percentile for osteophyte counts are presented in Table S1. The IRR for female sex was 0.88 (95% CI 0.64–1.22) and did not suggest a significant association of gender with the number of osteophytes.

Discussion

Our data show that both erosive as well as osteophytic changes in hand joints significantly increase with age in healthy individuals. The study hence provides first data on the normal age- and sex-related values for bone structure in the hand joints. The high resolution of HR-pQCT allows meticulous assessment of articular bone

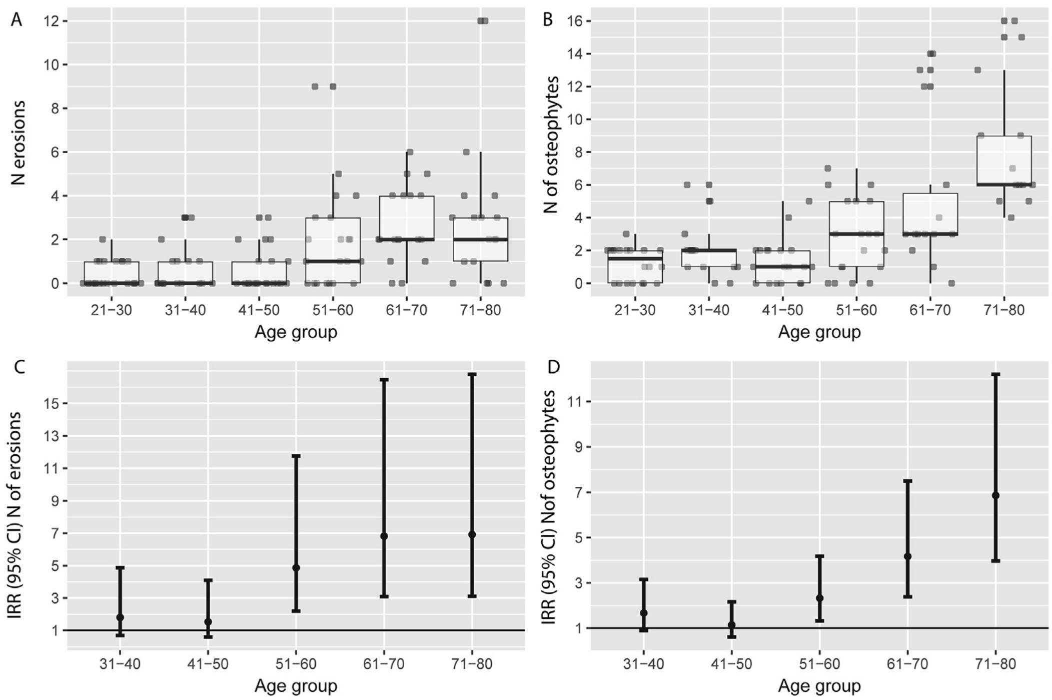

Fig. 2. Number and IRR of erosions and osteophytes in healthy subjects by age decades. The first row presents the distribution of number of erosions (D) and osteophytes (E) by six different age decades. Second row depicts the IRR for erosions (F) and osteophytes (G).

and has been used to quantify erosions[8,9], bony proliferations[6,10] and intra-/peri-articular bone loss[4,11] in different forms of arthritis. It has also allowed discovering new structural features such as cortical micro-channels (CoMiCs)[12].

The results of this study suggest that the "normal" state of the hand joint varies with age. While erosions and osteophytes are rare in younger subjects, they steeply increase with age. In healthy subjects over 50 years the incidence of erosions has almost quadrupled compared to subjects younger than 50 years. The incidence of osteophytes also rises sharply from this age group onwards, with patients over 70 years of age having an almost seven-fold increase compared to healthy subjects under 50 years of age. Remarkably, their distribution is not different from erosive changes found in RA and osteophytic changes found in primary or secondary OA, albeit their severity is much milder[6,8,13]. The distribution of erosive changes in the HR-pQCT is very similar to that found by Mangnus[14] and Boeters[15] investigating healthy subjects by magnetic resonance imaging (MRI)[14] as well as Fodor assessing healthy hand joints by ultrasound[16]. This conserved distribution pattern at the bare areas of the radial sites of the hand joints has also been supported by histologic studies by McGonagle[17] and HR-pQCT studies by Stach[8] in RA joints. The data are in line with the localization of the recently discovered cortical bone micro-channels[18], which increase with age especially at the radial sites of the hand joints[12].

It can be speculated that the age-related increase of structural bone changes in healthy individuals is based on the accrual of mechanical damage during life. The somewhat stronger increase of erosions and osteophytes in males seems to support this theory. Such wear-and-tear concept may comprise spurious inflammatory responses that induce erosions and related tissue responses that trigger osteophytes. In support, previous radiographic studies showed that bone changes resembling features of OA accumulate with age[19,20]. Our data now quantify these changes in hand joints and suggest that the physiological joint architecture is substantially different in aged compared to young individuals. However, we would not term such lesions "osteoarthritis", since they are clinically silent and the term "osteoarthritis" is reserved for a disease rather than physiological age-related change. Nonetheless, the generation of erosive and osteophytic changes in aged healthy individuals may still follow similar mechanically-induced processes that can be found in OA. Since OA is an insidious disease, it may be possible that the subjects in our study have a gradually progressive pathological process that has not reached a threshold sufficient to cause clinical symptoms. However, longitudinal investigations are required for the conclusive proof of causality.

Limitations of these findings in hand joints are the relatively small number of exclusively Caucasian subjects. Therefore it is not clear at present, whether these values may also apply for other populations and other joints.

In summary, our data show that erosions and osteophytes in hand joints steeply increase above the age of 50 years. This phenomenon somehow resembles the well-known physiological age-related change of bone mass during life, where absolute values describing bone mass in relation to young individuals (T-score) as well as age-adjusted values (Z-score) are in use since a long time. A similar concept seems to be relevant for describing the normal joint architecture. Diseases such as arthritis further damage the joint and accrue damage on top of the baseline physiological changes. Hence, the amount of damage seen in diseases such as arthritis is the sum of physiological and disease-specific changes, with physiological changes gaining higher relevance in the aged individual.

Contribution statement

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Schett had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: AB, AK, DS, GS. Acquisition of data: AB, DS, AH, JR, SF, AK. Analysis and interpretation of data: AB, AK, DS, KT, GS. Writing of

manuscript: AK and GS. The present work was performed in (partial) fulfillment of the requirements for obtaining the degree "Dr. med." for Andreas Berlin.

Competing interest

The authors have no competing or conflicts of interest.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2019.01.019.

References

1. Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. Nat Rev Rheumatol 2012;8:656–64.
2. Schett G, Lories RJ, D'Agostino MA, Elewaut D, Kirkham B, Soriano ER, *et al*. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol 2017;13:731–41.
3. Geusens P, Chapurlat R, Schett G, Ghasem-Zadeh A, Seeman E, de Jong J, *et al*. High-resolution in vivo imaging of bone and joints: a window to microarchitecture. Nat Rev Rheumatol 2014;10:304–13.
4. Simon D, Kleyer A, Stemmler F, Simon C, Berlin A, Hueber AJ, *et al*. Age- and sex-dependent changes of intra-articular cortical and trabecular bone structure and the effects of rheumatoid arthritis. J Bone Miner Res 2017;32:722–30.
5. Barnabe C, Toepfer D, Marotte H, Hauge EM, Scharmga A, Kocijan R, *et al*. Definition for rheumatoid arthritis erosions imaged with high resolution peripheral quantitative computed tomography and interreader reliability for detection and measurement. J Rheumatol 2016;43:1935–40.
6. Figueiredo CP, Simon D, Englbrecht M, Haschka J, Kleyer A, Bayat S, *et al*. Quantification and impact of secondary osteoarthritis in patients with anti-citrullinated protein antibody-positive rheumatoid arthritis. Arthritis Rheumatol 2016;68:2114–21.
7. Figueiredo CP, Kleyer A, Simon D, Stemmler F, d'Oliveira I, Weissenfels A, *et al*. Methods for segmentation of rheumatoid arthritis bone erosions in high-resolution peripheral quantitative computed tomography (HR-pQCT). Semin Arthritis Rheum 2018;47:611–8.
8. Stach CM, Bauerle M, Englbrecht M, Kronke G, Engelke K, Manger B, *et al*. Periarticular bone structure in rheumatoid arthritis patients and healthy individuals assessed by high-resolution computed tomography. Arthritis Rheum 2010;62:330–9.
9. Albrecht A, Finzel S, Englbrecht M, Rech J, Hueber A, Schlechtweg P, *et al*. The structural basis of MRI bone erosions: an assessment by microCT. Ann Rheum Dis 2013;72:1351–7.
10. Finzel S, Sahinbegovic E, Kocijan R, Engelke K, Englbrecht M, Schett G. Inflammatory bone spur formation in psoriatic arthritis is different from bone spur formation in hand osteoarthritis. Arthritis Rheumatol 2014;66:2968–75.
11. Boutroy S, Bouxsein ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. J Clin Endocrinol Metab 2005;90:6508–15.
12. Werner D, Simon D, Englbrecht M, Stemmler F, Simon C, Berlin A, *et al*. Early changes of the cortical micro-channel system in the bare area of the joints of patients with rheumatoid arthritis. Arthritis Rheumatol 2017;69:1580–7.
13. Finzel S, Englbrecht M, Engelke K, Stach C, Schett G. A comparative study of periarticular bone lesions in rheumatoid arthritis and psoriatic arthritis. Ann Rheum Dis 2011;70:122–7.
14. Mangnus L, van Steenbergen HW, Reijnierse M, van der Helm-van Mil AH. Magnetic resonance imaging-detected features of inflammation and erosions in symptom-free persons from the general population. Arthritis Rheumatol 2016;68:2593–602.
15. Boeters DM, Nieuwenhuis WP, van Steenbergen HW, Reijnierse M, Landewe RBM, van der Helm-van Mil AHM. Are MRI-detected erosions specific for RA? A large explorative cross-sectional study. Ann Rheum Dis 2018;77:861–8.
16. Fodor D, Felea I, Popescu D, Motei A, Ene P, Serban O, *et al*. Ultrasonography of the metacarpophalangeal joints in healthy subjects using an 18 MHz transducer. Med Ultrason 2015;17:185–91.
17. McGonagle D, Tan AL, Moller Dohn U, Ostergaard M, Benjamin M. Microanatomic studies to define predictive factors for the topography of periarticular erosion formation in inflammatory arthritis. Arthritis Rheum 2009;60:1042–51.
18. Scharmga A, Keller KK, Peters M, van Tubergen A, van den Bergh JP, van Rietbergen B, *et al*. Vascular channels in metacarpophalangeal joints: a comparative histologic and high-resolution imaging study. Sci Rep 2017;7:8966.
19. van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis 1989;48:271–80.
20. 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.