Title: Prevalence and distribution of ultrasound detected hand synovial abnormalities in a middle-aged and older population

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ABSTRACT

Objective

Synovial abnormalities are modifiable targets for hand pain and osteoarthritis. We examined the prevalence and distribution of ultrasound-detected hand synovial abnormalities in a community-derived sample of older people in China.

Methods

Within the community-based Xiangya Osteoarthritis Study, we assessed synovial hypertrophy (SH), joint effusion, and Power Doppler signal (PDS) on all fingers and thumbs of both hands using standardized ultrasound examinations (score: 0-3). We assessed distribution patterns of SH and effusion using the χ^2-test and interrelationships of SH and effusion in different joints and hands by generalized estimating equations.

Results

Among 3,623 participants (mean age: 64.4 years; women: 58.1%), the prevalence of SH, effusion, and PDS were 85.5%, 87.3%, and 1.5%, respectively. Prevalence of SH, effusion and PDS increased with age, was higher in the right hand than in the left hand, and was more common in proximal than distal hand joints. SH and effusion often occurred in multiple joints ($P < 0.001$). SH in one joint was strongly associated with the presence of SH in the same joint of the opposite hand (odds ratio [OR]= 6.60, 95% confidence interval [CI]: 6.19-7.03) followed by SH in other joints in the same row, (OR=5.70, 95%CI: 5.32-6.11), and then other joints in the same ray of the same hand (OR=1.49, 95%CI: 1.39-1.60). Similar patterns were observed for effusion.

Conclusion

Hand synovial abnormalities are common among older people, often affect multiple hand joints and present a unique pattern. These findings suggest that both systemic and mechanical factors play roles in their occurrence.

Key words: Synovial abnormalities; Hand; Prevalence; Distribution; Ultrasonography; General population

INTRODUCTION

Hand pain is common in the middle-aged and older population, with prevalence ranging from 14% to 60%[1-4]. Pain from hand osteoarthritis (OA) causes significant disability, functional limitation, and reduced quality of life[2, 5, 6]. Previous studies have demonstrated that synovial abnormality, a potentially modifiable pathological process[7, 8], highly correlates with hand pain[4], and thus has been recommended as an intervention target[7-9]. However, the etiology of hand synovial abnormalities is not fully understood, which hinders the development of effective prevention and treatment strategies.

Systemic factors, such as systemic inflammation, genetic, metabolic and neurogenic factors, have been postulated to play important roles in the pathogenesis of common chronic hand diseases[10-12]. Studies of patterns of joint involvement of disease in the hands may shed light on our understanding of the etiology. For example, the symmetry pattern of hand OA was considered to represent systemic factors, whereas clustering pattern OA by row and by ray may suggest local biomechanical factors[13]. To date, few, if any studies, have studied patterns of imaging-detected hand synovial abnormalities in the general population. Such data are of importance to epidemiology and might help understand the etiology and in developing management strategies.

In the present study, we described the prevalence of hand synovial abnormalities using ultrasound and examined joint-involvement patterns of synovial abnormalities in

a large population sample.

METHODS

Study design and population

Participants were from the Xiangya Osteoarthritis Study, a population-based longitudinal study of the natural history and risk factors for OA. Participants were a randomly selected sample of residents aged 50 years or older from rural mountainous villages of Longshan County in Hunan Province, China. Besides age, there were no other exclusion criteria for residents to participate in the study. In brief, we adopted a probability proportionate to size sampling method to select 14 towns. All villages in the selected towns were listed in random order. Village-to-village recruitment began from the first village in the first town until the number of participants in that town met the pre-determined proportion in sex and the age stratum (50-60, 60-70, ≥70 years) according to the Sixth National Census Data of Longshan County (2010).

The study consists of three sub-cohorts (i.e., Sub-cohorts I, II, and III). In total, 4,080 (response rate 86.04%) from 25 villages consented to participate at baseline. Sub-cohort I was recruited in 2015 when 1,469 individuals completed their interviews and clinical examinations. Of these 1,207 and 1,181 participants attended Year 1 (2016) and Year 2 (2017) follow-ups, respectively. To obtain a more accurate estimate of the prevalence and incidence of osteoarthritis, we expanded the original study by recruiting two additional cohorts: i.e., Sub-cohort II in the Year 2018 (n=1,271) and Sub-cohort

III in the Year 2019 (n=1,340), respectively, using the same sampling methods described above. The current study population included individuals who were eligible to participate in 2017 (the second-year follow-up of Sub-cohort I), 2018 (baseline of Sub-cohort II), and 2019 (baseline of Sub-cohort III) with hand ultrasound examination.

Since the Xiangya Osteoarthritis Study is an observational study, no intervention, such as treatment or behavioral counseling, was implemented in the study. The study was approved by the Research Ethical Committee of Xiangya Hospital, Central South University (201510506), and all participants provided written informed consent before participating in the study.

Assessment of ultrasound

Bilateral hand ultrasound was performed for participants in Sub-cohort 1 in 2017 (i.e., the second year of follow-up visit), Sub-cohort 2 in 2018 (baseline) and Sub-cohort 3 in 2019 (baseline) (**Supplemental Figure S1**). One trained sonographer, with over ten years' experience in musculoskeletal ultrasonography, performed all ultrasound examinations using a Philips CX30 ultrasound machine with a 7-15 MHz linear transducer. A pulse repetition frequency of 400 Hz was used for PD examination, the gain being adjusted until the background signal was removed. The sonographer was blinded to the results of other assessments.

As Outcome Measures in Rheumatology (OMERACT) recommended[14, 15],

bilateral 1st carpometacarpal joint (CMC1), metacarpophalangeal joints 1-5 (MCP1-5), proximal interphalangeal joints 1-5 (PIP1-5) and distal interphalangeal joints 2-5 (DIP2-5) were scanned. Synovial hypertrophy (SH), joint effusion and Power Doppler signals (PDS) were assessed on extended joints by longitudinal scanning with swiping of the probe from side to side of the dorsal aspect of MCP, PIP and DIP joints and at the radiopalmar side of CMC1 joints. Additional transverse scanning was undertaken when the presence of pathology was uncertain. SH and effusion were assessed using OMERACT-7 definitions[16], and PDS was defined as flow signal detected within areas of synovial hypertrophy[15, 17, 18]. Each single component (i.e., SH, effusion and PDS) was scored separately using a validated semiquantitative (0-3) grading scale (**Supplemental Figure S2-4 and Supplemental Table S1**) [19, 20]. A joint was defined as having SH, effusion, or PDS if the feature was scored ≥1. A participant was defined as having hand synovial abnormalities if the synovial feature was scored ≥1 in at least one hand joint.

Intra-rater reliability was evaluated by scanning 60 randomly selected individuals (120 hands) on two separate days within a 14 day. To assess inter-rater reliability, another reader (a trained orthopedic surgeon with more than three years' experience in musculoskeletal ultrasound) scored a randomly selected subset of grey-scale and PD US examinations (42 individuals, 84 hands) independently and consecutively on the same day. As shown in **Supplemental Table S2**, the weighted Kappa for intra-rater reliability was 0.74 (95%CI: 0.69 to 0.78) for SH and 0.65 (95%CI: 0.60 to 0.71) for

effusion, respectively. The corresponding weighted Kappa for inter-rater reliability was 0.64 (95%CI: 0.57 to 0.70) and 0.61 (95%CI: 0.54 to 0.68). We did not evaluate the intra- and inter-rater reliability for PDS because prevalence of PDS was very low (only one participant had PDS of grade 1 in the reliability sample).

Assessment of covariates

Sociodemographic and anthropometric data (i.e., age, sex, smoking, alcohol drinking, occupation, education, and hand injury history) and medication usage were collected face-to-face by trained health professionals via interview, and the following parameters were included in the standard questionnaires which were used during the interview: age (50-59, 60-69, ≥ 70 years), smoking status (non-smoker, ex-smoker and current smoker), alcohol drinking (non-drinker, ex-drinker and current drinker), education (non-educated and educated), and hand injury history (yes or no). Educated was defined as primary school or above. Hand injury history was defined as a history of hand injury severely restricting function for at least one week. The history of autoimmune diseases was ascertained based on the self-reported physician diagnosis. Height and weight were measured, and body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2). We grouped BMI into two categories: normal (BMI: < 25 kg/m^2) and overweight (BMI: ≥ 25 kg/m^2).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical

variables were expressed as percentage. We estimated the prevalence of SH, effusion and PDS, at both the person and the joint level and examined the relation of age and sex to the prevalence of synovial abnormalities.

To describe the joint-involvement pattern of synovial SH, we first compared the prevalence of each synovial abnormalities (i.e., SH, effusion and PDS) between the right hand and the left hand using the Generalized Estimate Equation (GEE) with logit link. To evaluate whether the clustering of synovial hypertrophy and joint effusion is not a random phenomenon, based on the binomial distribution, we first calculated the number of subjects expected to have 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10+ joints with synovial hypertrophy and joint effusion. For instance, assuming the probability of a joint with synovial hypertrophy was 0.144, the probability of seeing exactly 1 joint with synovial hypertrophy in a total of 30 hand joints was $f(1,30,0.144) = \binom{30}{1}0.144^1(1-0.144)^{30-1}$ =0.0476, and the number of subjects expected to have 1 joint with synovial hypertrophy was 3,623*0.0476=172. Then, we compared this expected number with the actual observed number of subjects with 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10+ joints with synovial hypertrophy and joint effusion using a χ^2-test. If the P<0.05, we may conclude that the distribution of synovial hypertrophy and joint effusion is not a random phenomenon. The method has been done in the evaluation of other diseases, such as osteoarthritis [13] and gout [21]. To assess the symmetrical pattern of presence of synovial abnormalities in hand joints, we examined the association between the presence of SH and effusion in a particular joint and the presence of that abnormality

in the same joint of the opposite hand, the joints in the same row of the same hand, and the joints in the same ray of the same hand, respectively, using the Generalized Estimating Equations with logit link. In the multivariable regression we adjusted for age, sex, BMI, smoking status, alcohol consumption, education level, and hand injury history. We further did sensitivity analyses based on the exclusion of participants with autoimmune diseases and medication usage of glucocorticoids, immunosuppressants, and painkillers such as nonsteroidal anti-inflammatory drugs. The joint-involvement pattern of synovial PDS was not analyzed because of the small number of participants with PDS.

All *P* values were 2-sided and $P < 0.05$ was considered significant. All statistical analyses were conducted using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Characteristics of the population

Among 3,792 participants 169 (4.5%) were excluded from the current analyses because of mutilated hand (n=93), fusion of hand joint (n=13), current severe hand injury (n=16), severe hand deformity (n=9), poor (n=5) or no (n=33) ultrasound image. Of the remaining 3,623 participants, 58.1% were women, the mean age was 64.4 (SD: 9.3) years, and the average BMI was 24.0 kg/m^2 (**Supplemental Table S3**). 95% the participants were farmers.

Prevalence of hand synovial abnormalities at person and joint level

As shown in **Table 1**, 85.5%, 87.3% and 1.5% participants had at least one joint with SH, effusion and PDS, respectively. The prevalence of hand synovial abnormalities increased with age (**Figure 1**, all *P* for trend < 0.05), but no such a difference was observed between men and women (*P*=0.407 for SH, *P*=0.906 for effusion, and *P*=0.828 for PD).

The prevalence of synovial abnormalities in individual joints is shown in **Figure 2 and Supplemental Table S4**. The prevalence of SH and effusion at DIP joints, ranging from 17.4 to 36.0% and 20.9 to 38.6%, was much higher than that in other joints (i.e., PIP joints, MCP joints and CMC1 joints), ranging from 2.8% to 19.0% and 2.3% to 18.9%, respectively. Distal hand joints were more likely to have SH and effusion than proximal joints. However, no such pattern was observed in thumbs. Prevalence of PDS was very low, ranging from 0 to 0.4% for different hand joints.

Patterns of synovial SH and effusion in hand joints

Hand synovial abnormalities was more common in the right hand than in the left hand. The odds ratios of SH, effusion and PDS for right hand vs. left hand were 1.69 (95%CI 1.59 to 1.80), 1.55 (1.46 to 1.66) and 3.45 (1.40 to 8.53), respectively. SH was more likely to occur in multiple hand joints than that by chance alone (*P*<0.001) (**Table 2**). Assuming prevalent SH in hand joints followed a binomial distribution, we would expect that 26 individuals would have SH in 10 or more joints; however, we observed

that 414 individuals had SH in 10 or more joints, suggesting SH at hand joints was more likely to occur in a subset of individuals. The interrelationships of the presence of synovial SH and effusion in hand joints are presented in **Table 3**. After adjusting for age, sex, BMI, smoking status, alcohol consumption, education level, and hand injury history, the presence of SH at a given joint was most strongly associated with the presence of SH of the same joint of the opposite hand (ORs=6.60, 95%CI: 6.19 to 7.03), followed by the presence of synovial SH or effusion in the joints in the same row of the same hand (OR=5.70 95%CI 5.32 to 6.11), then by the other joints in the same ray of the same hand (OR=1.49 95%CI 1.39 to 1.60), all $P<0.001$. Similar patterns were also observed for effusion. Such patterns were not changed materially after excluding participants with autoimmune diseases and oral medication usage of glucocorticoids, immunosuppressants, and painkillers such as nonsteroidal anti-inflammatory drugs. (**Supplemental Table S5**).

DISCUSSION

In this large community-based study, ultrasound-detected SH and effusion, but not PDS, were common in hand joints of older people. The ultrasound-detected synovial abnormalities were likely to occur in multiple hand joints, more prevalent in distal joints than in proximal joints, and more common in the right hand than in the left hand. The presence of SH and effusion at a particular joint was most strongly associated with the same abnormality at the same joint of the contralateral hand, followed by other joints in the same row of the same hand, then by other joints in the same ray of the same hand.

These findings suggest that both systemic and mechanical factors may play roles in the pathology of synovial abnormalities.

Previous MRI studies have described low-grade synovitis-like changes in MCP joints and tenosynovitis of hand joints of healthy individuals [22, 23]. To date, there was a paucity data on population-based prevalence of image-detected hand synovial abnormalities and its joint involvement pattern. The results from Tasmanian older adult cohort [TASOAC] study found that hand synovial abnormalities were very common: almost all participant had ultrasound detected grey-scale synovitis (≥ grade 1) and 33% had PD synovitis (≥ grade 1) [4]; However, the study did not describe the joint involvement patterns of synovial abnormalities. Similarly, we also observed that hand synovial abnormalities were prevalent although the mean age (64.4 years) in our study was younger than TASOAC study (72.1 years).

The unique joint involvement pattern of synovial abnormalities in hand suggests that both systemic and mechanical factors may play roles in the pathology of synovial abnormalities. Some systemic factors, such as age-related inflammation[24, 25], neurogenic factors[12] and migration of synovial fibroblasts[26] might contribute to the symmetrical pattern of synovial abnormalities in hand. The role of other essential and recognized systematic factors, such as genetics and metabolism et al., in the etiology of synovial abnormalities is worthy of investigation in the future. On the other hand, more prevalent synovial hypertrophy and joint effusion in the right hand may

imply that mechanical factors play roles in the occurrence of synovitis. Indeed, in most people, the right hand is the dominant hand, and the joint load is likely to be greater in the dominant hand than that in the contralateral hand, which could lead to a higher prevalence of synovial abnormalities in the right hand[27-29]. In addition, our findings that the high prevalence of SH and effusion but very low prevalence of PDS may suggest that these synovial changes are more of part of low-grade systemic inflammation or an adaptive response to joint insult with attempted repair (i.e., typical of OA) than a primary aggressive synovitis as seen in rheumatoid and seronegative spondyloarthritis[25, 30, 31].

The patterns of joint involvement of synovial abnormalities in the current study are consistent with the pattern in OA. A previous study demonstrated that the presence of symptomatic OA at a particular joint was strongly associated with symptomatic OA in the same joint of the opposite hand, followed by other joints in the same row of the same hand, and then other joints in the same ray of the same hand [13]. These finding suggest that either both conditions may share the same risk factors or synovial abnormalities may be part of the OA features. Since synovial abnormalities are modifiable, any novel treatment that could reduce synovial inflammation would be an important breakthrough for management of hand OA.

There are several strengths to our study. To our knowledge, this is the first study that described joint-involvement patterns of hand synovial abnormalities in the general

311 population. The sample is relatively large (n=3,623), and the participation rate was high.
312 Furthermore, all ultrasound examinations were performed by a single experienced
313 musculoskeletal sonographer; thus, reducing inter-observer variability. In addition, we
314 used a semiquantitative (0–3) grading scale to assess each synovial abnormality, thus
315 the results can be compared with other studies that used the same method to assess
316 synovial abnormalities.
317
318 Our study has some limitations. First, participants were residents in rural areas of
319 China; thus, the prevalence of synovial abnormalities in our study may not represent
320 that in urban or suburban populations in China, or in other countries. Second, while
321 each single synovial feature was scored separately using a validated semiquantitative
322 (0-3) grading scale, there has not been a uniform agreement on which grade, 1 or 2,
323 should be used to define the abnormality. We defined a joint as having a specific
324 abnormality if the feature was scored ≥1 as one previous study did[32]. Nevertheless,
325 when we used >1 as a cut point, similar joint-involvement patterns of synovial
326 abnormalities were also observed (**Supplemental Table S6 and S7**), indicating the
327 robustness of our study findings. Third, the assessment of the function of hand joints
328 were not performed for all the included participant, thus, we could not adjust for
329 dexterity during the analyses. Finally, because this is a cross-sectional study, we did not
330 examine specific risk factors, both systemic and local, for synovial abnormalities.
331 Prospective studies are required to examine risk factors for incident synovial
332 abnormalities in the hands as well as sequalae of synovial changes, such as pain and

OA.

CONCLUSION

In conclusion, hand synovial abnormalities are common among middle aged and elderly. SH and effusion often affected multiple joints, were more prevalent in the right than in the left hand and tended to show a symmetrical pattern. The findings may shed light on our understanding of potential pathophysiology of hand OA.

Declaration of interests

All authors report no competing interests.

References:

1. Dahaghin S, Bierma-Zeinstra SM, Reijman M et al. Prevalence and determinants of one month hand pain and hand related disability in the elderly (Rotterdam study). Ann Rheum Dis 2005; 64: 99-104. DOI: 10.1136/ard.2003.017087
2. Dziedzic K, Thomas E, Hill S et al. The impact of musculoskeletal hand problems in older adults: findings from the North Staffordshire Osteoarthritis Project (NorStOP). Rheumatology (Oxford) 2007; 46: 963-967. DOI: 10.1093/rheumatology/kem005
3. Cole A, Gill TK, Taylor AW et al. Prevalence and associations of hand pain in the community: results from a population-based study. Scand J Rheumatol 2011; 40: 145-149. DOI: 10.3109/03009742.2010.508467
4. Mattap SM, Laslett LL, Squibb K et al. Hand examination, ultrasound and its association with hand pain and function in community-based older adults. Arthritis Care Res (Hoboken) 2019. DOI: 10.1002/acr.24128
5. Thomas E, Croft PR, Dziedzic KS. Hand problems in community-dwelling older adults: onset and effect on global physical function over a 3-year period. Rheumatology (Oxford) 2009; 48: 183-187. DOI: 10.1093/rheumatology/ken452
6. Zhang Y, Niu J, Kelly-Hayes M et al. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. Am J Epidemiol 2002; 156: 1021-1027. DOI: 10.1093/aje/kwf141
7. Karim Z, Quinn MA, Wakefield RJ et al. Response to intramuscular methyl prednisolone in inflammatory hand pain: evidence for a targeted clinical, ultrasonographic and therapeutic approach. Ann Rheum Dis 2007; 66: 690-692. DOI: 10.1136/ard.2006.061861
8. Kroon FPB, Kortekaas MC, Boonen A et al. Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial. Lancet 2019; 394: 1993-2001. DOI: 10.1016/S0140-6736(19)32489-4
9. Conaghan PG, Cook AD, Hamilton JA et al. Therapeutic options for targeting inflammatory osteoarthritis pain. Nat Rev Rheumatol 2019; 15: 355-363. DOI: 10.1038/s41584-019-0221-y
10. Visser AW, de Mutsert R, le Cessie S et al. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. Ann Rheum Dis 2015; 74: 1842-1847. DOI: 10.1136/annrheumdis-2013-205012
11. Spector TD, Cicuttini F, Baker J et al. Genetic influences on osteoarthritis in women: a twin study. BMJ 1996; 312: 940-943. DOI: 10.1136/bmj.312.7036.940
12. Kidd BL, Mapp PI, Gibson SJ et al. A neurogenic mechanism for symmetrical arthritis. Lancet 1989; 2: 1128-1130. DOI: 10.1016/s0140-6736(89)91491-8
13. Niu J, Zhang Y, LaValley M et al. Symmetry and clustering of symptomatic hand osteoarthritis in elderly men and women: the Framingham Study. Rheumatology (Oxford) 2003; 42: 343-348. DOI: 10.1093/rheumatology/keg110
14. Hammer HB, Iagnocco A, Mathiessen A et al. Global ultrasound assessment of structural lesions in osteoarthritis: a reliability study by the OMERACT ultrasonography group on scoring cartilage and osteophytes in finger joints. Ann Rheum Dis 2016; 75: 402-407. DOI: 10.1136/annrheumdis-2014-206289
15. Mathiessen A, Hammer HB, Terslev L et al. Ultrasonography of Inflammatory and Structural Lesions in Hand Osteoarthritis: An OMERACT Agreement and Reliability Study. Arthritis Care Res (Hoboken) 2021. DOI: 10.1002/acr.24734

16. Wakefield RJ, Balint PV, Szkudlarek M et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol 2005; 32: 2485-2487.
17. Koski JM, Saarakkala S, Helle M et al. Power Doppler ultrasonography and synovitis: correlating ultrasound imaging with histopathological findings and evaluating the performance of ultrasound equipments. Ann Rheum Dis 2006; 65: 1590-1595. DOI: 10.1136/ard.2005.051235
18. D'Agostino MA, Terslev L, Aegerter P et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce-Part 1: definition and development of a standardised, consensus-based scoring system. RMD Open 2017; 3: e000428. DOI: 10.1136/rmdopen-2016-000428
19. Szkudlarek M, Court-Payen M, Jacobsen S et al. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum 2003; 48: 955-962. DOI: 10.1002/art.10877
20. Mathiessen A, Hammer HB, Terslev L et al. Ultrasonography of Inflammatory and Structural Lesions in Hand Osteoarthritis: An Outcome Measures in Rheumatology Agreement and Reliability Study. Arthritis Care Res (Hoboken) 2022; 74: 2005-2012. DOI: 10.1002/acr.24734
21. Yokose C, Dalbeth N, Wei J et al. Radiologic evidence of symmetric and polyarticular monosodium urate crystal deposition in gout - A cluster pattern analysis of dual-energy CT. Semin Arthritis Rheum 2020; 50: 54-58. DOI: 10.1016/j.semarthrit.2019.07.002
22. Ejbjerg B, Narvestad E, Rostrup E et al. Magnetic resonance imaging of wrist and finger joints in healthy subjects occasionally shows changes resembling erosions and synovitis as seen in rheumatoid arthritis. Arthritis Rheum 2004; 50: 1097-1106. DOI: 10.1002/art.20135
23. Parodi M, Silvestri E, Garlaschi G et al. How normal are the hands of normal controls? A study with dedicated magnetic resonance imaging. Clin Exp Rheumatol 2006; 24: 134-141.
24. Sarkar D, Fisher PB. Molecular mechanisms of aging-associated inflammation. Cancer Lett 2006; 236: 13-23. DOI: 10.1016/j.canlet.2005.04.009
25. Saboury B, Parsons MA, Moghbel M et al. Quantification of aging effects upon global knee inflammation by 18F-FDG-PET. Nucl Med Commun 2016; 37: 254-258. DOI: 10.1097/MNM.0000000000000430
26. Lefevre S, Knedla A, Tennie C et al. Synovial fibroblasts spread rheumatoid arthritis to unaffected joints. Nat Med 2009; 15: 1414-1420. DOI: 10.1038/nm.2050
27. Schett G, Tohidast-Akrad M, Steiner G et al. The stressed synovium. Arthritis Res 2001; 3: 80-86. DOI: 10.1186/ar144
28. Shay AK, Bliven ML, Scampoli DN et al. Effects of exercise on synovium and cartilage from normal and inflamed knees. Rheumatol Int 1995; 14: 183-189. DOI: 10.1007/BF00262296
29. Jamal J, Roebuck MM, Lee SY et al. Modulation of the mechanical responses of synovial fibroblasts by osteoarthritis-associated inflammatory stressors. Int J Biochem Cell Biol 2020; 126: 105800. DOI: 10.1016/j.biocel.2020.105800
30. Wood MJ, Leckenby A, Reynolds G et al. Macrophage proliferation distinguishes 2 subgroups of knee osteoarthritis patients. JCI Insight 2019; 4. DOI: 10.1172/jci.insight.125325
31. Pratt AG, Siebert S, Cole M et al. Targeting synovial fibroblast proliferation in rheumatoid arthritis (TRAFIC): an open-label, dose-finding, phase 1b trial. Lancet Rheumatol 2021; 3: e337-e346. DOI: 10.1016/S2665-9913(21)00061-8
32. Padovano I, Costantino F, Breban M et al. Prevalence of ultrasound synovial inflammatory findings in healthy subjects. Ann Rheum Dis 2016; 75: 1819-1823. DOI: 10.1136/annrheumdis-2015-208103

Table 1. Prevalence of hand synovial abnormalities on ultrasound at participant level

	Overall	Men	Women	P value
Synovial hypertrophy, %	85.5	86.1	85.1	0.407
Grade 1	62.3	62.2	62.4	
Grade 2	20.0	20.5	19.7	
Grade 3	3.2	3.4	3.0	
Joint effusion, %	87.3	87.2	87.3	0.906
Grade 1	71.0	69.9	71.8	
Grade 2	14.4	15.3	13.7	
Grade 3	1.9	1.9	1.8	
Power Doppler signal*, %	1.8	1.7	1.8	0.828
Grade 1	1.5	1.4	1.6	
Grade 2	0.3	0.3	0.2	
Any synovial abnormality, %	90.0	90.2	89.9	0.783

***** We did not detect grade 3 PDS in the hand joints of participants of our study.

Table 2. Observed and expected number of participants with synovial abnormalities in hands

Number of Sites	Observed	Expected	χ^2	P value
Synovial hypertrophy			1402.34	<0.001
0	526	34		
1	493	172		
2	469	419		
3	398	659		
4	358	749		
5	288	656		
6	215	460		
7	198	266		
8	147	129		
9	117	53		
≥10	414	26		
Joint effusion			1204.73	<0.001
0	462	39		
1	515	191		
2	476	451		
3	425	687		
4	389	756		
5	290	640		
6	245	435		
7	195	243		
8	161	114		
9	112	45		
≥10	353	22		

438 **Table 3. Clustering patterns of hand synovial abnormalities**

	Synovial hypertrophy	Joint effusion
Same joint, other side		
OR (95% CI) *	6.60 (6.19, 7.03)	6.29 (5.91, 6.69)
P value	<0.001	<0.001
Same row, same hand		
OR (95% CI) *	5.70 (5.32, 6.11)	5.88 (5.49, 6.29)
P value	<0.001	<0.001
Same ray, same hand		
OR (95% CI) *	1.49 (1.39, 1.60)	1.26 (1.18, 1.35)
P value	<0.001	<0.001

439 OR, odds ratio; CI, confidence interval.

440 * OR were adjusted for age, sex, BMI, smoking status, alcohol consumption, education level and hand
441 injury history.