Clinical Study Protocol

Study protocol for the follow-up examination of the Nor-Hand study: A hospital-based observational cohort study exploring pain and biomarkers in people with hand osteoarthritis

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ABSTRACT

Objective: This study aims to increase the understanding of pain mechanisms in hand OA and explore potential risk factors for pain development or worsening in a biopsychosocial framework. Another important aim is to validate potential soluble and imaging OA biomarkers.

Design: The follow-up examination of the Nor-Hand hospital-based observational cohort study started in October 2019 and was completed in May 2021. In total, 212 of the 300 participants with hand OA who were examined at baseline attended the follow-up study. The participants underwent clinical joint examinations, medical and functional assessments, quantitative sensory testing, fluorescence optical imaging, ultrasound of the hands, acromioclavicular joints, feet, knees and hips, conventional radiographs of the hands and feet and magnetic resonance imaging of the dominant hand. Blood and urine samples were collected, and all participants answered questions about demographic factors and OA-related questionnaires. Associations between disease variables and symptoms will be examined in cross-sectional and longitudinal analyses. Longitudinal analyses will be performed to assess the predictive value of baseline variables on hand OA outcomes.

Conclusion: Current knowledge about predictors for disease progression in hand OA is limited, but with longitudinal data we will be able to explore the predictive value of baseline variables on hand OA outcomes, such as changes in patient-reported outcomes or changes in soluble and imaging biomarkers. This provides a unique opportunity to gain more knowledge about the natural disease course of hand OA.

1. Introduction

1.1. Osteoarthritis

Hand osteoarthritis (OA) is a common condition that might lead to pain, disability and reduced health-related quality of life [1]. There are different phenotypes based on joint affection or radiographic and clinical presentations, such as interphalangeal vs. thumb base OA and erosive vs. non-erosive hand OA [2]. There are few longitudinal hand OA studies, making it challenging to study the natural disease course.

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1.2. Pain and pain sensitization

Pain in hand OA is complex and multifactorial, but different pain phenotypes based on pain characteristics or drivers of pain have not yet been established in people with hand OA. Other factors than OA may affect the pain experience, such as previous life events, hereditary factors, mood, coping strategies, comorbidities and sociocultural factors [3]. Thus, studies of pain should be performed with a biopsychosocial perspective. Peripheral and central pain sensitization may cause an increased pain response to both painful and normally non-painful stimuli. With longitudinal data, we have opportunities to explore the predictive value of measurements of peripheral and central sensitization with regards to development and worsening of pain.

1.3. Imaging modalities

Conventional radiography is the most frequently used method to evaluate structural hand OA progression, but is hampered by visualization of bony changes only, and only indirectly showing the cartilage as the joint space. Magnetic Resonance Imaging (MRI) is the only imaging modality that can visualize the whole joint [4]. Currently, there is no evidence that MRI is more sensitive to change than conventional radiography [5], and assessment of progression using MRI of good quality is needed. Ultrasound can visualize osteophytes and synovitis in hand OA [4], but further knowledge about its validity is needed. Fluorescence optical imaging (FOI) demonstrates enhanced microcirculation around finger joints as a sign of inflammation, and its role in hand OA is currently unclear due to limited data on validity [6]. With longitudinal data, we will be able to examine the predictive value and the sensitivity to change of different imaging modalities.

1.4. Soluble biomarkers

Systemic inflammation, cartilage degeneration/reduced synthesis and bone resorption can be measured in plasma/serum/urine. Most hand OA studies to date have been small and cross-sectional [7–9]. The Nor-Hand study will provide novel information with regards to disease activity, prognosis and sensitivity to change, which is needed before soluble biomarkers can be used as surrogates for clinical outcomes in hand OA trials.

1.5. Project aims and objectives

- To explore different phenotypes of hand OA, and examine whether the natural disease course differs between groups.
- To assess risk factors for pain development or worsening in a biopsychosocial framework.
- To validate OA biomarkers, including imaging and soluble biomarkers (e.g. compare their sensitivity to change, their predictive value with regards to disease progression and the associations with patient-reported outcomes).

2. Materials and methods

2.1. Design and setting

Nor-Hand is a hospital-based observational cohort study of people with hand OA recruited from the rheumatology outpatient clinic or a one-day multidisciplinary OA education program organized by the Division of Rheumatology and Research at Diakonhjemmet Hospital (Fig. 1). A minority of participants were included after contacting the project coordinator or project leader directly. The baseline examination of 300 participants was performed in 2016–2017, while the follow-up examination takes place in 2019–2021. The questionnaires were completed by 212 participants, of whom 205 attended the clinical examination visit in 2019–2021.

2.2. Participants

The inclusion and exclusion criteria have been previously described [10]. Participants were 40–70 years of age at screening and had hand OA by clinical examination or ultrasound, and no evidence of systemic inflammatory joint disease, psoriasis or hemochromatosis. Before the follow-up examination, all participants were asked by the project coordinator about development of systemic inflammatory joint diseases and skin psoriasis. If such conditions had evolved, the participant was excluded from further participation.

2.3. Timelines

Data collection in the Nor-Hand follow-up study took place between October 2019 and May 2021. Weekly test evenings with up to nine participants were arranged with the exception of holidays and periods with unavailable personnel. Due to the Covid-19 pandemic, the data collection was closed in March 2020. With strict rules for infection prevention, the data collection continued in May–June 2020 with fewer participants and study personnel per evening. No data collection was performed between July 2020 and January 2021 because the project coordinator and project leader were unavailable. The remaining data collection continued in February–May 2021.

Fig. 1. Flowchart.
2.4. Patient and public involvement

A user representative was involved at an early stage in planning the study. She was involved in the study design, primarily to plan the selection of questionnaires and examinations, and to assess the burden of the investigations and the time required to participate.

2.5. Assessments

One afternoon every week (with exceptions as explained in the "timelines" section), participants were invited to a test evening with a duration of approximately 4 h. Most assessments, except conventional radiographs and MRI, were performed during these test evenings. Several trained medical students (and a few students in the master program of clinical nutrition) and physicians at Diakonhjemmet Hospital performed the examinations blinded to the results of the examinations performed by other study personnel. In addition, participants answered questions about demographic factors and lifestyle, and OA-specific questionnaires prior to or at the test evening. Conventional radiography and MRI were performed prior to or in most cases after the test evening.

2.5.1. Questionnaires

The participants received questions about demographic factors, lifestyle, fertility-menopause (women only), shoe wear, previous injuries or treatment, pain threshold and general health status (Table 1). With few exceptions, these questionnaires were completed prior to the test evening. Patient-reported outcome measures administered at the test evening include questionnaires assessing health-related quality of life, pain, stiffness, physical function, self-efficacy, pain catastrophizing and illness perception (Table 2). The translated versions of the Michigan Hand Outcome Questionnaire (MHOQ) and the Foot Function Index (FFI) were completed twice by 44 and 45 participants, respectively, to evaluate the reliability.

2.5.2. Medical assessments

The examinations from baseline were repeated at the follow-up examination. A trained medical student measured the height (centimeters, one decimal) in standing position without shoes and weight (kilograms, one decimal) of the participants with light clothing and no shoes. Waist and hip circumferences were measured (centimeters, one decimal). Blood pressure was measured in a sitting position after 5 min of rest in supine position. The measurements were repeated until two consecutive systolic and diastolic pressures differed 5 mmHg or less. The medical student recorded the last two measurements of blood pressure and heart rate.

The participants responded to a self-administered comorbidity questionnaire, whilst supervised by the student [11]. In addition, all participants brought a list of medications.

2.5.3. Functional assessments

The functional assessments of the hands included the Moberg Pick-up test and grip strength measurements [12,13], as explained in the protocol for the baseline examination [10]. Both the dominant and non-dominant hand were tested. Additionally, tests assessing the function in lower extremities were added to the follow-up examination. During the Chair stand test, the participants were instructed to stand completely up from a seated position and sit completely back down on a chair without armrest. The procedure was repeated for as many times as possible in 30 s. For the 40 m fast paced walk test, the participants were instructed to walk as quickly, but safely as possible, without running on a 10-m walkway and turn around the cones in the beginning and the end (4×10 m). All tests were supervised by a trained medical student.

2.5.4. Joint assessment

The joint assessment of the hands was identical to the joint assessment that was performed at the baseline examination [10]. One rheumatologist (BSC) (alternatively a rheumatology resident when BSC is not available) examined all hand joints for bony enlargement, soft tissue swelling and tenderness using the Doyle index [14,15]. The physician-based hand OA disease activity was reported on an NRS (0–10). The rheumatologist assessed whether the participants fulfilled the ACR hand, hip and knee OA criteria [16–18] (Table 3). The clinical foot examination that was performed at baseline was not repeated at the follow-up examination.

2.5.5. Quantitative sensory testing

The quantitative sensory testing was performed by a trained physician (MG) or a trained medical student. Training was provided according to a detailed pre-defined protocol, and the physician and medical student had three training sessions before the first test evening to ensure that the tests are being similarly performed. Training was also repeated during the study. The examinations that were performed at baseline were repeated at the follow-up examination, with the exception of the light touch tests with the von Frey filaments.

Temporal summation (TS) at the left distal radioulnar joint was measured at the beginning of this session as previously explained [10]. While the TS test was performed once at baseline, the test was repeated after 3 min at the follow-up examination.

Pressure pain thresholds (PPT) were tested at the same joints as at baseline: Two interphalangeal joints of the hand (one painful and one non-painful at baseline), the left distal radioulnar joint and mid-portions of the trapezius and tibialis anterior muscles. Before the examination, the examiner asked the participants whether the interphalangeal joints that

| Topic                  | Measure                                                                 |
|------------------------|-------------------------------------------------------------------------|
| Demographics           | Relationship status                                                     |
|                        | Employment                                                              |
|                        | Personal economy                                                       |
|                        | Social network                                                          |
| Lifestyle              | Physical activity: How often do you exercise? (e.g. walking, skiing, swimming or other activities) What is the intensity of your exercise? What is the average duration of a workout session? |
|                        | Use of alcohol (AUDIT-C): How often do you have a drink containing alcohol? How many drinks containing alcohol do you have on a typical day when you are drinking? How often do you have six or more drinks on one occasion? |
|                        | Smoking: current or previous smoker, daily or non-daily smoker, smoking pack years |
| Fertility/ menopause   | Age at menarche                                                         |
| (women only)           | Age at menopause (if applicable)                                        |
|                        | Regularity of menstrual cycles                                         |
|                        | Longer periods without menstrual bleedings                              |
|                        | Previous gynecological surgery                                          |
|                        | Previous use of contraceptive pills                                    |
|                        | Previous present use of estrogen therapy                                |
|                        | Previous pregnancies and births                                         |
|                        | Duration of breastfeeding                                               |
|                        | Fertility problems                                                      |
| Shoe wear              | Use of different shoe wear in a typical week in each decade of their adult life (including the shape of the forefoot and the shoe heel) |
| Injuries/treatment     | Previous hand/wrist injuries                                            |
|                        | Previous steroid injections in the finger joints or thumb base joints   |
|                        | Use of hand orthosis                                                    |
|                        | Use of customized aids                                                  |
|                        | Previous joint replacement surgery                                      |
|                        | Use of alternative therapies due to joint pain                          |
| Pain threshold         | Self-reported pain threshold: “like most others”, “higher than others” or “lower than others” |
| General health status  | Self-reported health status: How will you rate your general health today? (0–100 scale) |

AUDIT-C, Alcohol Use Disorder Identification Test- Consumption.
Table 2
Questions/questionnaires administered to the participants at the test evening.

| Question/questionnaire                                                                 | Dimensions                                                                 |
|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Use of analgesics                                                                       | Have you taken any analgesics today? If yes, please specify.                 |
| Numeric Rating Scales (NRS) (0–10)                                                      | Joint pain in general during the last 24 h                                   |
|                                                                                       | Hand pain during the last 24 h                                              |
|                                                                                       | Hand pain during the last 48 h                                              |
|                                                                                       | Hand pain during the last week                                               |
|                                                                                       | Feet pain during the last 24 h                                              |
|                                                                                       | Global disease activity during the last 24 h                                 |
|                                                                                       | General quality of health during the last 24 h                              |
| Homunculi, hand and foot diagrams                                                      | Localization of pain during the last 24 h                                   |
|                                                                                       | and 6 weeks in the neck, upper, middle and lower back, bilateral shoulders, |
|                                                                                       | elbows, wrists, hips, knees and ankles.                                     |
|                                                                                       | Localization of pain during the last 24 h                                   |
|                                                                                       | and 6 weeks in bilateral 2nd-5th DIP, 2nd-5th PIP, 1st IP, 1st-5th MCP and  |
|                                                                                       | thumb base joints.                                                          |
|                                                                                       | Localization of pain during the last 24 h                                   |
|                                                                                       | and 6 weeks in the bilateral 1st-5th MTP joints.                            |
|                                                                                       |                                                                        |
| The Australian/Canadian (AUSCAN) Osteoarthritis Hand Index [28,29]                     | Hand pain during the last 48 h (5 questions)                                 |
|                                                                                       | Hand stiffness during the last 48 h (1 question)                             |
|                                                                                       | Hand function during the last 48 h (9 questions)                            |
|                                                                                       | Knee/hip pain during the last 48 h (5 questions)                            |
|                                                                                       | Knee/hip stiffness during the last 48 h (2 questions)                       |
|                                                                                       | Physical function during the last 48 h (17 questions)                       |
| PainDETECT (a modified version to measure possible neuropathic-like pain in the hands) | Pain course pattern (1 question)                                            |
|                                                                                       | Gradation of pain (7 questions)                                             |
|                                                                                       | Radiating pain (1 question)                                                 |
|                                                                                       | Pain intensity ratings of different situations in daily life (17 questions) |
|                                                                                       | Widespread pain index                                                       |
|                                                                                       | Symptom severity scale score: Fatigue, waking unrefreshed and cognitive     |
|                                                                                       | symptoms during the last week.                                              |
|                                                                                       | Headaches, pain or cramps in lower abdomen and depression during the       |
|                                                                                       | previous 6 months.                                                         |
|                                                                                       |                                                                        |
| The Western Ontario and McMaster Universities Arthritis Index (WOMAC) [30]             | Widespread pain index                                                       |
|                                                                                       | Symptom severity scale score: Fatigue, waking unrefreshed and cognitive     |
|                                                                                       | symptoms during the last week.                                              |
|                                                                                       | Headaches, pain or cramps in lower abdomen and depression during the       |
|                                                                                       | previous 6 months.                                                         |
| Pain Sensitivity Questionnaire [32]                                                    | Widespread pain index                                                       |
|                                                                                       | Symptom severity scale score: Fatigue, waking unrefreshed and cognitive     |
|                                                                                       | symptoms during the last week.                                              |
|                                                                                       | Headaches, pain or cramps in lower abdomen and depression during the       |
|                                                                                       | previous 6 months.                                                         |
| ACR criteria for fibromyalgia [33]                                                     | Widespread pain index                                                       |
|                                                                                       | Symptom severity scale score: Fatigue, waking unrefreshed and cognitive     |
|                                                                                       | symptoms during the last week.                                              |
|                                                                                       | Headaches, pain or cramps in lower abdomen and depression during the       |
|                                                                                       | previous 6 months.                                                         |
|                                                                                       |                                                                        |
| EuroQol 5 dimensions 3 levels (EQ-5D-3L) [34]                                          | Mobility (1 question)                                                       |
|                                                                                       | Self-care (1 question)                                                      |
|                                                                                       | Main activity (e.g., work, studies, housework) (1 question)                 |
|                                                                                       | Pain/discomfort (1 question)                                                |
|                                                                                       | Anxiety/depression (1 question)                                             |
| Sleep disturbances                                                                     | 1 question (5 response options ranging from 0 – normal sleep to 4 – severe |
|                                                                                       | sleep disturbances)                                                        |
| Short form (SF) 12 [35]                                                               | Energy during the last 4 weeks (1 question)                                 |
| Hospital Anxiety and Depression Scale (HADS) [36]                                      | Anxiety (7 questions)                                                       |
|                                                                                       | Depression (7 questions)                                                    |
| The arthritis self-efficacy scale (ASRS) [37]                                         | Pain subscale (5 questions)                                                 |
| The pain catastrophizing scale (PCS) [38]                                              | Rumination (4 questions)                                                    |
|                                                                                       | Magnification (3 questions)                                                 |
|                                                                                       | Helplessness (6 questions)                                                  |
| The Brief Illness Perception Questionnaire (BIPQ) [39]                                 | 9 items assessing different dimensions of illness perception: Consequences, |
|                                                                                       | timeline, personal control, treatment control, identity, coherence, concern, |
|                                                                                       | emotional response and causes                                               |
| The Michigan Hand Outcomes Questionnaire (MHOQ) [40]                                   | Overall hand function (5 questions about right hand and 5 questions about left hand) |

Table 3
ACR criteria for osteoarthritis in hands, hips and knees (clinical criteria).

| Question/questionnaire                                                                 | Dimensions                                                                 |
|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Hand osteoarthritis                                                                   | Pain in the hip<sup>a</sup>                                                  |
|                                                                                       | Pain in the knee<sup>a</sup>                                                 |
| AND 3 of the following:                                                              | AND 1 or 2                                                                |
| Hard tissue enlargement of 2 or more joints<sup>b</sup>                               | 1. Internal hip rotation <15° and ESR ≤ 45 mm/h (or hip flexion <115° if ESR is unavailable) |
| Hard tissue enlargement of 2 or more DIP joints                                      | 2. Internal hip rotation ≥15°, pain associated with internal hip rotation, morning stiffness of the hip ≤60 min and age >50 years |
| Less than 3 swollen MCP joints                                                       | Morning stiffness of the knee <30 min                                        |
| Deformity of at least one joint<sup>b</sup>                                           | Crepitus on active motion                                                  |
|                                                                                       | Bony tenderness                                                            |
|                                                                                       | Bony enlargement                                                           |
|                                                                                       | No palpable warmth of synovium                                              |

<sup>a</sup> On most days of the previous month.

<sup>b</sup> 2<sup>nd</sup> and 3<sup>rd</sup> distal interphalangeal, 2<sup>nd</sup> and 3<sup>rd</sup> proximal interphalangeal and the 1<sup>st</sup> carpometacarpal joints of both hands.

were tested were painful or not at the moment. PPT was assessed with a digital hand-held algometer (FPIX25 with a 1 cm<sup>2</sup> flat rubber probe, Wagner instruments, or alternatively FPX50 if values > 10 kg/cm<sup>2</sup> were measured) with the same procedure as at the baseline examination [10]. PPT at each location was computed as the average of three measurements.

Conditioned pain modulation (CPM) was tested using an inflated blood pressure cuff around the right upper arm as the conditioning stimulus [10]. Three PPT measurements at the left distal radioulnar joint (post-CPM PPT) were repeated with the blood pressure cuff still being inflated.

2.5.6. Blood tests/Biobank
To ensure that it was safe for the participants to undergo contrast-enhanced MRI and FOI, blood samples were collected less than 3 months before the examinations, including creatinine, glomerular filtration rate (GFR), alanine amino transferase (ALAT), aspartate amino transferase (ASAT) and thyroid status with fT4 and thyroid-stimulating hormone (TSH). In addition, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured. At the test evening, a trained student collected whole-blood, plasma and serum, as well as a urine sample, from all participants. The samples were prepared and stored in a
freezer with a temperature of $\sim -80 \degree C$.

2.5.7. Ultrasound

An ultrasound examination of the bilateral hands, acromioclavicular joints, hips, knees and feet were performed. Two trained physicians (OM, PSP) performed the ultrasound examinations. AM performed the ultrasound assessment in case of absent physicians. Before the first test evening, the physicians had three 90-min sessions where they were instructed in detail on how to perform the ultrasound assessments by two experienced ultrasonographers (HHB, AM). A still-image reliability exercise of osteophytes (grade 0–3) of 150 finger joints between AM, HBH, OM and PSP showed substantial to perfect reliability (weighted kappa for all pairs >0.60). An additional still-image reliability exercise of the lower extremities was done by OM and PSP (45 images of osteophytes in hips, knees and feet, 35 images of synovitis in knees and feet and 10 images of power Doppler signals in feet) showed substantial inter-reader reliability (weighted kappa >0.60).

To facilitate a standardized ultrasound examination, the same machines (GE Logic E9 or GE Logic E10) and fixed settings were used throughout the follow-up study. Due to feasibility and concerns about the reliability, the ultrasound examination was compressed compared with the baseline examination, focusing on osteophytes in all examined joints and assessment of grey-scale synovitis and power Doppler activity in hands only. Furthermore, fewer joints in the feet were examined.

The physician performed an ultrasound examination of the hand joints (bilateral scaphotrapezial, 1st carpometacarpal, 1st-5th metacarpophalangeal, 1st interphalangeal, 2nd-5th proximal and distal interphalangeal joints). Synovial hypertrophy and/or effusion, power Doppler signals and osteophytes were scored on 0–3 scales. Osteophytes in the acromioclavicular, hip, knee (four compartments) and 1st metatarsophalangeal joints were scored on 0–3 scales.

An atlas of pathology in hand joints and an atlas of normal foot joints were actively used by the physicians during scoring. Atlas-images of the knee were presented to the physicians before the test-evenings to ensure reliability [22].

2.5.8. Fluorescence optical imaging

The FOI examination was performed by a trained medical student with the same Xiralite® scanner (Xiralite GmbH) that was used at the baseline examination. We added hand wash (37 $\degree C$ for 60 s) of all participants prior to the scanning at the follow-up examination. Nail polish was removed prior to the examination. A photograph of the hands was obtained in order to document any wounds, scars or rashes. The FOI examination was otherwise performed as explained in the baseline protocol [10]. An intravenous fluorescent dye (Indocyanine green, 0.1 mg/kg of the body weight) was injected. Participants with liver affection (transaminases above twice the upper reference limit), poor renal function (GFR below 40 mL/min), untreated hyperthyroidism (T4 above 21 pmol/L and TSH below 0.5 mIE/L), pregnancy or breast-feeding or allergy to radiocontrast agents, iodine or indocyanine did not perform FOI.

FOI enhancement in finger joints on paired images from baseline and follow-up will be scored according to the FOI activity score by a trained reader [6].

2.5.9. Conventional radiographs

Radiographs of the hands and feet were obtained at the Department of Radiology at Diakonhjemmet Hospital with the same protocol that was used at baseline [10]. A trained reader (IKH) will read the paired longitudinal hand radiographs with known time sequence according to validated scoring systems [23–25]. The paired foot radiographs will be scored by a trained reader using the Kellgren-Lawrence scale or other available scoring systems for the foot.

2.5.10. MRI

At the baseline examination, the MRI scans were obtained at a private imaging center, while the scans were obtained at the Department of Radiology at Diakonhjemmet Hospital at the follow-up examination. Importantly, the acquisition was performed with the same type of scanner (Siemens Aera 1.5T MRI scanner, Germany) and a 16-channel hand/wrist coil with a field of view which extended over both the interphalangeal and thumb base joints. We used the same protocol as we did at the baseline examination with minor adjustments to optimize the images (Table 4).

Participants received intravenous contrast (Clariscan 0.5 mmol/mL, 0.2 mL/kg body weight) unless contraindications, like GFR < 40 mL/min or previous allergic reactions. Paired longitudinal MRIs will be scored by a trained reader supervised by a radiologist according to validated scoring systems [26,27].

2.6. Statistical analyses

We will perform cross-sectional analyses of the follow-up data and longitudinal analyses of the baseline and follow-up data combined. Parametric and non-parametric statistical analyses will be performed, as appropriate.

Intra- and/or inter-observer reliability of the assessments will be evaluated with e.g., intraclass correlation coefficients and kappa values. Using regression analyses on the cross-sectional data from the follow-up examination we will for example explore whether OA biomarkers and pain sensitization are associated with clinical and patient-reported outcomes. The predictive value of baseline variables on for example changes in OA biomarkers or changes in patient-reported outcomes will be assessed in longitudinal analyses. The inter-relationship between changes in OA biomarkers and changes in patient-reported outcomes will be evaluated. The sensitivity to change will be assessed, and we will compare the disease course of different hand OA or pain phenotypes. Missing data will be handled by complete case analyses or imputation, depending on the character of missing data. In cases where a change in outcome is unlikely, the baseline variable can be used instead of the variable from the follow-up examination.

2.7. Ethics and dissemination

Prior to the baseline examination, all participants gave their consent to be contacted again for a follow-up examination. The follow-up examination has been approved by the Norwegian Regional Committee for Medical and Health Research Ethics (Ref. no: 2019/363) and the data protection officer at Diakonhjemmet Hospital. The procedures followed were in accordance with their ethical standards and with the Helsinki Declaration. The Nor-Hand study is registered at https://clinicaltrials.gov (Ref. no: NCT03083548).

The project coordinator (HG) contacted the participants who were enrolled at baseline by phone. All participants received oral information and were asked if they were willing to participate. If so, a new informed consent form with written information about the study was signed. The participants could withdraw the consent at any time without further explanation.

All collected data will be plotted in an electronic case form (eREG) Data will be de-identified before it is stored safely on the research server at Diakonhjemmet Hospital. A code list with ID numbers, names and birth dates is kept separate from the data files. Results will be presented as abstracts at national and international conferences, and manuscripts will be submitted to peer-reviewed international rheumatology journals and social media platforms from 2022.

3. Discussion

One of our main aims is to increase understanding of pain mechanisms and pain experience in hand OA, which will be explored in a biopsychosocial framework. Longitudinal data will give us unique opportunities to explore risk factors for development of pain sensitization.
and whether pain sensitization predict poorer outcomes. Such knowledge will be important for the prevention of pain sensitization in clinical practice.

Another important aim is to validate OA biomarkers, including soluble and imaging markers. The Nor-Hand study is the largest hand OA study to date, with such a broad data collection with regards to imaging. Longitudinal data will allow us to explore biomarkers that potentially can be used as outcome measures also in clinical trials. Investigation of soluble biomarkers can lead to increased knowledge about disease processes and inflammatory pathways in hand OA.

The follow-up examination of the Nor-Hand study will contribute with knowledge about the natural disease course, risk factors for disease progression, pain characteristics, pain sensitization, detection of new biomarkers and validation of more established biomarkers in people with hand OA. We strongly believe that longitudinal results from our data collection have the potential to influence future clinical trials, as well as clinical management of hand OA.

Declaration of competing interest

Hilde Berner Hammer reports speaker honorarium from AbbVie, Novartis and Lilly, outside the submitted work during the past 36 months. Tore Kristian Kvien reports grants from AbbVie, grants from Amgen, grants from BMS, grants from MSD, grants from Novartis, grants from Pfizer and grants from UCB, outside the submitted work during the past 36 months. Ida Kristin Haugen reports grants from Pfizer, related to the conduct of the study, and consulting fees from Novartis, outside the submitted work during the past 36 months. Marthe Glaeser, Pernille Steen Pettersen, Øystein Maugesten, Elisabeth Mulrooney, Alexander Mathiessen, Heidi Gammelsrud, Tuhina Neogi, Sarah Ohrndorf, Karwan Faraj, Dag Sjølie and Barbara Slatkowsky-Christensen have nothing to disclose.

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Author contributions

MG: Substantial contributions to acquisition of data, drafting the manuscript and final approval of the version of the manuscript to be submitted.

PSP: Substantial contributions to acquisition of data, drafting the manuscript and final approval of the version of the manuscript to be submitted.

OØM: Substantial contributions to acquisition of data, drafting the manuscript and final approval of the version of the manuscript to be submitted.

EM: Substantial contributions to acquisition of data, drafting the manuscript and final approval of the version of the manuscript to be submitted.

AM: Substantial contributions to study design (ultrasound), critical revision and final approval of the version of the manuscript to be submitted.

HG: Substantial contributions to acquisition of data (project coordinator), critical revision and final approval of the version of the manuscript to be submitted.

HBH: Substantial contributions to study design (ultrasound), critical revision and final approval of the version of the manuscript to be submitted.

TN: Substantial contributions to study design (quantitative sensory testing), critical revision and final approval of the version of the manuscript to be submitted.

SO: Substantial contributions to study design (fluorescence optical imaging), critical revision and final approval of the version of the manuscript to be submitted.

KF: Substantial contributions to study design (conventional radiographs), critical revision and final approval of the version of the manuscript to be submitted.

DS: Substantial contributions to study design (MRI), critical revision and final approval of the version of the manuscript to be submitted.

BSC: Substantial contributions to acquisition of data, critical revision and final approval of the version of the manuscript to be submitted.

TKK: Substantial contributions to study design, critical revision and final approval of the version of the manuscript to be submitted.

IKH: Substantial contributions to study design, drafting the manuscript and final approval of the version of the manuscript to be submitted. MG and IKH take responsibility for the integrity of the work as a whole, from inception to finished article.

Role of the funding source

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Appendix A: Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2021.100198.

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