


# BMJ Open Cohort profile: the Halland osteoarthritis (HALLOA) cohort—from knee pain to osteoarthritis: a longitudinal observational study in Sweden

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## ABSTRACT

**Purpose** The overall objective in this study is to investigate the early development of radiographic knee osteoarthritis (OA) and its association with hand or/and knee OA, metabolic diseases, biomarkers, chronic pain, physical function and daily physical activity types.

**Participants** The Halland osteoarthritis (HALLOA) cohort is a longitudinal cohort study that includes individuals with knee pain in the southwest of Sweden. Enrolment took place from 2017 to 2019. The inclusion criteria were current knee pain, with no former known radiographic knee OA and no cruciate ligament rupture or rheumatological disorder. The participants were recruited: (1) when seeking care for knee pain in primary healthcare or (2) by advertisements in local newspapers. There are 306 individuals included in the study, mean age (SD) 51.7 (8.7) years and 69% are women. The baseline and follow-ups include clinical tests, radiographical examinations, blood samples, metabolic measures, pain pressure thresholds, tests of physical functions, daily physical activity types and patient-reported outcomes.

**Findings to date** There were associations between metabolic factors and radiographic knee OA, even in those with normal body mass index at baseline. In addition, clinical hand OA was positively associated with fasting plasma glucose. We also found that modifiable factors as increased visceral fat and total body fat were associated with increased pain sensitivity among individuals with knee pain.

**Future plans** By studying possible pathophysiological mechanisms of OA over time, we aim to provide new insights on OA progression, identify usable preventive measures helping the clinicians in the management of the disease and improve health for the patients. It is also important to study the development of chronic pain in OA, to get tools to identify individuals at risk and to be able to offer them treatment.

**Trial registration number** ClinicalTrials.gov (NCT04928170).

## INTRODUCTION

Osteoarthritis (OA) is the most common musculoskeletal disease and is characterised by cartilage destruction, osteophyte formation, subchondral bone sclerosis and cysts.<sup>1</sup>

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The study has a possibility to detect variations and long-term changes over 5 years.
- ⇒ Causal relationships will be studied.
- ⇒ The large amount of data on people with knee pain will answer a large number of research questions.
- ⇒ The large amount of collected data increases the risk for variables 'lost at follow-up'.
- ⇒ The selection of participants was based on self-interest which may induce bias.

Modern treatment strategies and preventive measures include early detection and knowledge of the early course of the disease. In 97% of cases, knee pain without radiological changes is shown to develop into knee OA with radiological changes.<sup>2</sup> Studies have found an association between OA and metabolic diseases, such as type II diabetes, high blood pressure, lipid disorders, obesity and long-term pain conditions, such as fibromyalgia.<sup>3–5</sup> OA is a heterogeneous disease and a range of phenotypes with different pathophysiological mechanisms are suggested, for example, traumatic, metabolic and ageing phenotype.<sup>3,4</sup>

Obesity is a well-known risk factor for OA and affects the weightbearing joints through increased load and chronic mechanical stress, which induces chondrocytes to use mechanoreceptors to synthesise proinflammatory and cartilage-degrading mediators.<sup>6,7</sup> However, the increased load is probably not the only factor responsible for the link between obesity and OA. For instance, the connection between hand OA and obesity cannot be explained by mechanical stress.<sup>8,9</sup> OA is a disease with low-grade inflammation, which also is seen in metabolic diseases, such as type II diabetes. There are also reports of low-grade inflammation in fibromyalgia.

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An interesting hypothesis is that there is a possible link between OA, generalised pain and metabolic diseases in obesity and the increased amount of adipose tissue,<sup>10</sup> given that obesity is a risk factor in OA, type II diabetes and chronic pain.<sup>8 11–14</sup> Adipose tissue is an endocrine organ with a role in body homeostasis. Adipocytes are metabolically active, synthesising adipokines, regulating appetite, inflammatory and immune functions, glucose and lipid metabolism.<sup>15</sup> Adipokines are proinflammatory and could activate inflammation. Adipokines have also been shown to activate proteases, which could break down cartilage.<sup>16</sup> In addition, other factors are suggested as possible links between type II diabetes and OA, such as oxidative stress and advanced glycation end products accumulation in joint tissues exposed to chronic high glucose concentration.<sup>17</sup>

Pain is the symptom of OA that often leads to disability and inactivity. The association between radiographic knee OA and pain is not unambiguous and not everyone with radiographically verified OA has pain.<sup>18</sup> In individuals with symptomatic knee OA, approximately 30% meet the criteria for chronic widespread pain (CWP),<sup>5</sup> in contrast to about 11% in the general population.<sup>19</sup> Lowered pain thresholds in individuals with knee OA have been reported to be associated with exacerbation of symptoms and increased risk of chronic pain.<sup>20 21</sup>

Connections between knee OA development and mechanical stress in working life, level of physical activity and reduced muscle strength and coordination have also been reported.<sup>22</sup> In Sweden, people with knee OA have an almost twice as high risk of being on sick leave, compared with individuals in the general population, and between 40% and 50% higher risk of being in receipt of disability pension. Approximately 2% of all sick leave days in Sweden are attributed to knee OA.<sup>23 24</sup> Studies have reported a higher incidence of knee OA among individuals in occupations with high physical load, including lifting or carrying heavy loads, frequent stair climbing, climbing ladders, prolonged standing or walking.<sup>25 26</sup> Most studies are based on self-reported information about work patterns, via questionnaires or interviews. To better define how large a dose of each exposure entails a harmful load on the knee joint, prospective studies with repeated objective measurements are needed. Including activity types during both work and leisure entails better understanding about the level of exposure that is harmful. The impact of activities and mechanical load patterns at work and in leisure time are not well studied for the metabolic phenotype of knee OA. The study investigates measured patterns of different activity types in daily life to better understand the effect of mechanical load patterns in a cohort with early OA without cruciate ligament injury, with a focus on metabolic factors. Previous studies have largely been performed on people with established OA and those with traumatic causes of OA. Studies of people with knee pain that is not caused by a major trauma, for example, cruciate ligament injury, or in individuals without radiographic changes, are few, but they are of

great importance to study the early course of knee OA development.

## Overall aim

The overall objective is to study the early development of radiographic OA of the knee and its association with hand OA and/or knee OA, metabolic diseases, biomarkers, chronic pain, physical function and daily physical activity types.

The project includes four different research areas that are studied with the help of several smaller substudies:

Research area 1: metabolic OA—to study the links between metabolic factors and OA development in the knee and hand.

1A. Relationship between knee OA development and metabolic factors

► Which metabolic factors are associated with knee OA development?

1B. Relationship between hand OA development and metabolic factors

► Which metabolic factors are associated with hand OA development?

Research area 2: biomarkers in knee and hand OA—to study cartilage and bone biomarkers that reflect various processes in radiographic knee and/or hand OA development, for example, inflammation, matrix degradation, both in the short and long term.

► Which cartilage and/or bone biomarkers are reflecting the processes in knee and/or hand OA development?

Research area 3: pain and knee OA—to study pain development and pain pressure thresholds (PPTs) in relation to lifestyle, depression and health-related quality of life (HRQoL) in individuals with symptomatic knee OA.

► How do radiographic progress, lifestyle habits, depression, and HRQoL relate to chronic pain and PPTs in individuals with symptomatic knee OA?

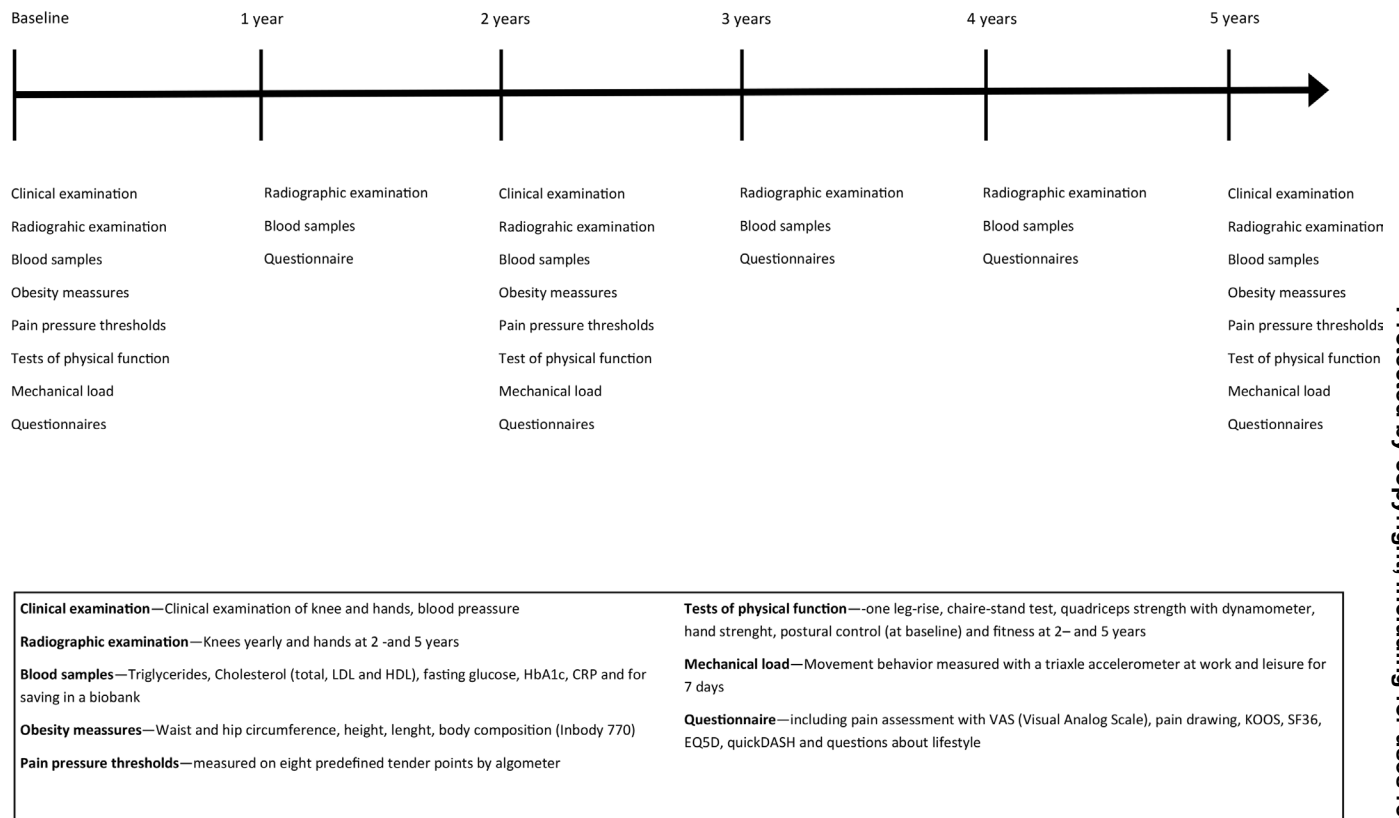
Research area 4: physical function and knee OA—to study physical function, daily physical activity types, as well as changes in daily physical activity types and the relationship between these and the development of radiographic knee OA over time.

► How do physical function and physical activity type during work and leisure time associate with knee OA progress over time?

## COHORT DESCRIPTION

### Study design

This is a longitudinal cohort study that includes individuals with knee pain in the southwest of Sweden, called the Halland osteoarthritis (HALLOA) cohort. The enrolment took place from 2017 to 2019. The participants were recruited: (1) when seeking care for knee pain in primary healthcare or (2) by advertisements in local newspapers. The inclusion criteria were current knee pain, with no former known radiographic knee OA and no cruciate ligament rupture or rheumatological disorder, with a preferable age of 30–65 years. A general practitioner



**Figure 1** Flow chart of HALLOA Study. CRP, C reactive protein; DASH, Disabilities of the Arm, Shoulder and Hand Questionnaire; EQ5D, EuroQol five-dimension questionnaire; HALLOA, Halland osteoarthritis; HbA1c, Hemoglobin A1c; HDL, high-density lipoprotein; KOOS, Knee injury and Osteoarthritis Outcome Score; LDL, low-density lipoprotein; SF-36, 36-item Short Form survey.

examined eligible participants to confirm the exclusion criteria of cruciate ligament rupture. The cohort will be followed for 5 years with yearly follow-ups (figure 1 and table 1).

## Participants

There are 306 individuals included in the study; the mean age (SD) is 51.7 (8.7) years and 69% are women. There are five individuals older than 65 (two are 66, two are 67 and one is 73) and two individuals younger than 30 (29 and 24) years. These individuals will be excluded in the substudies if needed.

## Clinical outcomes

There will be annual follow-ups over 5 years (figure 1). Each year, there will be radiographic examination of the knees, blood samples will be taken, and questionnaires will be handed out or sent by post. At baseline, 2-year and 5-year follow-up, there will be clinical examination, measurements of obesity, PPTs, and tests of physical function and daily physical activity types.

## Clinical examination

The clinical examination includes measurement of the active range of motion in flexion and extension of the knee and foot, palpation of the knee and finger joints to evaluate bony enlargement and crepitation, and assessment of alignment. The assessments of knees and fingers

are used to classify OA of the knees and hands according to Altman *et al.*<sup>27 28</sup>

## Radiographic examination

The radiographs of the knees are obtained in a skyline view of patellofemoral joints, and posteroanterior radiographs of both the tibiofemoral joints were obtained in weightbearing position with flexed knees. Radiographic knee OA was initially defined according to Ahlback,<sup>29</sup> as having Ahlback grade I or more in at least one knee. The radiographs will also be scored according to Kellgren and Lawrence.<sup>30</sup>

The radiographs of the hands were performed in a skyline view of the dorsal side of the hands. Radiographic hand OA will be defined according to Kellgren and Lawrence.<sup>30 31</sup> Radiographs of the hands will be obtained at 2 or 3 years and at 5 years. In this cohort study, radiographic knee and/or hand OA is considered as the endpoint measure.

## Blood samples

Venous blood samples are drawn, and fasting plasma glucose (mmol/L), triglycerides (TG) (mmol/L), total cholesterol (mmol/L), high-density lipoprotein (HDL) and low-density lipoprotein cholesterol (LDL) (mmol/L), HemoglobinA1c (HbA1c) (mmol/mol) and C reactive protein (CRP) >1.0 mg/L are measured according to

**Table 1** Description of the included assessment over 5 years

		Inclusion	1 year	2 years	3 years	4 years	5 years
Clinical examination		X		X			X
Radiographic examination	Knees	X	X	X	X	X	X
	Hands			X			X
Blood samples		X	X	X	X	X	X
Metabolic measures		X		X			X
PPT		X		X			X
Tests of physical function		X		X			X
Daily physical activity types		X		X			
KOOS		X	X	X	X	X	X
Quick DASH		X	X	X	X	X	X
Pain questions		X	X	X	X	X	X
HADS		X	X	X	X	X	X
EQ5D-3L		X	X	X	X	X	X
SF-36		X	X	X	X	X	X
Lifestyle habits		X	X	X	X	X	X
HLS-EU-Q16				X	X	X	X

DASH, Disabilities of the Arm, Shoulder and Hand Questionnaire; EQ5D-3L, EuroQol five-dimension, three-level questionnaire; HADS, Hospital Anxiety and Depression Scale; HLS-EU-Q16, Psychometric Assessment of the European Health Literacy; KOOS, Knee injury and Osteoarthritis Outcome Score; PPT, pain pressure threshold; SF-36, 36-item Short Form survey.

the current laboratory standards in Sweden. CRP below 1.0 mg/L will be further analysed with a sensitive CRP ELISA method (Abnova). Serum leptin is analysed with an ELISA method (Alpco). Serum and plasma are saved in a biobank at  $-70^{\circ}\text{C}$  for further analyses.

Raised glucose is classified in accordance with the International Diabetes Federation (IDF) definition as fasting plasma glucose  $\geq 5.6$  mmol/L, or if the individuals previously are diagnosed with diabetes.<sup>32</sup> Raised TG is classified in accordance with IDF as TG  $\geq 1.7$  mmol/L or if the individuals have a specific treatment for this lipid abnormality.<sup>32</sup> Reduced HDL-cholesterol is classified according to IDF as HDL-cholesterol  $< 1.03$  mmol/L in men and 1.29 mmol/L in women, or if the individuals have a specific treatment for this lipid abnormality.<sup>32</sup>

#### Metabolic measures

Waist circumference is manually assessed with a measuring tape (cm) around the waist at the height of the navel. Central obesity is classified in accordance with IDF as waist circumference  $\geq 94$  cm in men and  $\geq 80$  cm in women.<sup>32</sup> Body length and weight were measured, and body mass index (BMI) is calculated. Proportion of fat and visceral fat area (VFA) are assessed by Inbody 770 (Seoul, Korea).<sup>33</sup> Raised VFA level is classified as having VFA  $\geq 100$  cm<sup>2</sup>.<sup>34</sup> Blood pressure is measured after 5-minute rest (Omron M3). Raised blood pressure was classified as systolic blood pressure  $\geq 130$  mm Hg or diastolic blood pressure  $\geq 85$  mm Hg or treatment of previously diagnosed hypertension.<sup>32</sup> Metabolic syndrome (MetS) is classified in accordance with IDF definition as central obesity plus

any two of the following four factors: raised TG, reduced HDL-cholesterol, raised blood pressure or raised fasting plasma glucose.<sup>32</sup>

#### Pain pressure thresholds

The PPT is measured on eight predefined tender points out of the 18 points, as part of the definition of fibromyalgia.<sup>35</sup> The locations of the eight tender points is: trapezius (bilateral, midpoint of the upper border); second rib (right side, at the second costochondral junctions, just lateral to the junctions on the upper surfaces); lateral epicondyle (right side, 2 cm distal to the epicondyles); knees (bilateral, at the medial fat pad proximal to the joint line); and gluteal (bilateral, in upper outer quadrants of the buttocks in the anterior fold of the gluteus maximus muscle). A hand-held pressure algometer with a 10 mm<sup>2</sup> rubber probe is used, together with a computer interface with an assistant linear response to force application (AlgoMed, Medoc, Ramat Yishai, Israel). A constant rate of force has been shown to have the highest reliability.<sup>36</sup> Two trials are assessed on each tender point, at a minimum of 30 s apart. The pressure gradually increased from 0 to a maximum of 1000 kPa, at a rate of approximately 40 kPa/s, or until the participant pressed the stop button. The pressure gradually increased from 0 to a maximum of 1000 kPa, at a rate of approximately 40 kPa/s, or until the participant pressed the stop button. The participants were informed that the aim of the test was to measure the pain thresholds and not pain tolerance level and received the following instruction: 'Press the button when you feel the first sensation of pressure shifting to pain'. During the measurements, the fact that physical activity can affect PPT measurements is



taken into account.<sup>37</sup> The measurement is taken either before physical activity or after 30 min of rest.

### Tests of physical function

One-leg rise from chair and 30-second chair stand test are assessed three times during the follow-up (at baseline, 2 and 5 years),<sup>38–40</sup> isometric strength of the knee extensor is measured with a hand-held dynamometer,<sup>41 42</sup> test of aerobic capacity is performed according to Åstrand bicycle ergometer test<sup>43</sup> and hand strength is assessed by Grippit.<sup>44</sup>

### Daily physical activity types

Daily physical activity types are assessed by recurrent or lengthy mechanical stressful postures and activities in work and leisure over 7 consecutive days. Through a new type of analysis method of motion (Acti4), where data are collected with three triaxial accelerometers (Axivity AX3), it is possible to get an objective measure of how much (%) of their working and leisure time the individual walks, runs, cycles, stands, climbs stairs, sits, lies down, squats and kneels.<sup>45–47</sup> The previously validated method (Acti4) registers acceleration and angle in relation to the vertical. The accelerometers are attached with skin-friendly tape to the right thigh, right calf and upper back (C7-TH1). Measurements of daily physical activity types are performed in a subsample of the cohort, including 122 individuals.

### Questionnaires

The questionnaires are all patient reported and include questions concerning sociodemographics, comorbidities, medical and alternative treatments and the following questionnaires concerning knee and hand function, pain, anxiety and depression, HRQoL, lifestyle habits and health literacy:

- ▶ Knee injury and Osteoarthritis Outcome Score (KOOS), an instrument to assess the patient's opinion about their knee and associated problems, which consists of five subscales: pain, other symptoms, function in daily living, function in sport and recreation and knee-related quality of life (QOL). KOOS gives a score of 0–100 (worst to best) in each subscale.<sup>48 49</sup>
- ▶ The shortened version of the Disabilities of the Arm, Shoulder and Hand Questionnaire (Quick DASH), an 11-item self-administered region-specific outcome instrument, was developed as a measure of self-rated upper extremity disability and symptoms ranging from 0 to 100 (no disability to most severe disability).<sup>50</sup>
- ▶ A pain manikin, with 18 predefined regions (pain regions) where participants mark their painful areas on the pain figure (figure 2), if they have any.<sup>19</sup> There are also questions about pain intensity (Numerical Rating Scale (NRS) 0–10, best to worst), duration and diurnal variation of pain.
- ▶ The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-report screening scale that was originally developed to indicate the possible presence of anxiety

and depressive states in the setting of a medical outpatient clinic.<sup>51</sup> It contains two seven-item scales: one for anxiety and one for depression, both with a score range of 0–21 (best to worst).

- ▶ EuroQol (EQ5D-3L), a five-dimension, three-level questionnaire to assess HRQoL (0–1, worst to best).<sup>52</sup>
- ▶ 36-item Short Form survey (SF-36), a generic questionnaire, with coherent, and easily administered QOL measures in eight items: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health. Each item is scored 0–100 (worst to best).<sup>53</sup>
- ▶ Lifestyle habits (smoking habits, diet and physical activity) are assessed by questions that had been used previously in a national patient survey in Sweden (Health on Equal Terms).<sup>54</sup> Alcohol habits are assessed by the Alcohol Use Disorders Identification Test–Consumption, an alcohol screening questionnaire that can help identify patients who are hazardous drinkers or have active alcohol use disorders (including alcohol abuse or dependence). The cut-off for hazardous drinking in men is 5 points or more, and in women 4 points or more.<sup>55</sup>
- ▶ Psychometric Assessment of the European Health Literacy is a questionnaire containing 16 items that address self-reported difficulties in accessing, understanding, appraising and applying information to tasks related to making decisions in healthcare, disease prevention and health promotion. Scoring varies between 0 and 16, establishing three levels of health literacy: inadequate (0–8), problematic (9–12) and sufficient (>12).<sup>56 57</sup>

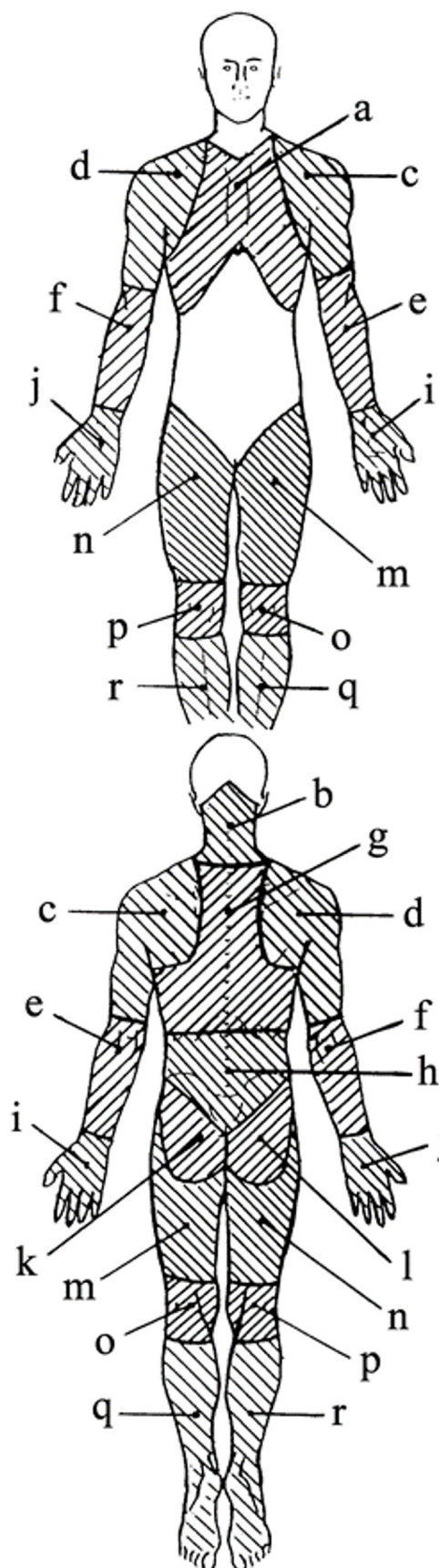
### Power calculation

Research area 1: to be able to show a difference in glucose levels of 0.2 mmol/L between groups, SD 0.5 (an effect size of 0.4), with a significance level of 5% and 80% power, a double-sided test requires 200 individuals. To be able to show a difference in waist circumference levels of 6 cm between groups, SD 12 cm, an effect size of 0.5, a significance level of 5%, a double-sided test requires 195 individuals for a power of at least 80%.

Research area 2: experience from previous studies of knee OA, with the same inclusion criteria, shows that 300 individuals are sufficient to find differences in biomarkers such as cartilage oligomeric matrix protein.<sup>58</sup>

Research area 3: based on known prevalence of CWP (30%) in previous knee OA studies, 300 people would be needed in the study to find about 90 people with CWP, which should be sufficient to detect differences.<sup>5</sup>

Research area 4: to be able to show a difference of 3.3 (minimal detectable change=3.3) in 30-second chair stand test, effect size of 0.5 and a power of 80%, a double-sided test requires a sample size of 198 individuals.<sup>59</sup>



**Figure 2** Pain manikin. The predefined areas a, the front of the chest; b, neck; c, left shoulder/upper arm; d, right shoulder/upper arm; e, left elbow/forearm; f, right elbow/forearm; g, thoracic spine; h, lumbar/lumbar spine; i, left hand/wrist; j, right hand/wrist; k, left buttock; l, right buttock; m, left hip/thigh; n, right hip/thigh; o, left knee; p, right knee; q, left lower leg/foot; r, right lower leg/foot

## Patient and public involvement

A patient research partner, educated by the Swedish Rheumatism organisation, took part in the development and design of the study. Patients were not involved in the recruitment of participants or conduct of the study. The participants will be able to take part of the results through lectures, both physical and digital.

## FINDINGS TO DATE

Preliminary results show that there were clear associations between metabolic factors and radiographic knee OA at baseline, even in those with normal BMI, which supports the link between visceral fat and radiographic knee OA. At baseline, the only metabolic factor associated with clinical hand OA was fasting plasma glucose. Contrary to other studies, there were no gender differences found.<sup>60</sup> We have also found that knee pain affects gait symmetry (GS) negatively and that lower extremity muscle function is an important feature for symmetry and dynamic joint stability in this group of patients. We also found that pain in one leg is related to less GS while bilateral knee pain is more symmetrical and will need healthy controls for comparison to better understand the negative impact of the disease early knee OA.<sup>61</sup> Preliminary results show that the test for substitutional patterns could be used as a functional test to detect early signs of knee OA as altered knee alignment and assist the physiotherapist in the decision-making in the rehabilitation of individuals with symptomatic knee OA.<sup>62</sup> In another study, we have compared three criteria for symptomatic knee OA and approximately 50%–70% of the individuals with knee pain were classified as having symptomatic knee OA, where European Alliance of Associations for Rheumatology criteria having the lowest prevalence.<sup>63</sup>

In a study aimed to (1) investigate pain sensitivity, assessed by PPTs, among women and men with knee pain and (2) associations with, respectively, radiographic knee OA, CWP and overweight/obesity, we found that modifiable factors, increased VFA and body fat could be associated with increased pain sensitivity among individuals with knee pain. Longitudinal studies are needed to further investigate the associations.<sup>64</sup>

In a study of baseline data with the aim to refine and assess the validity of an algorithm to detect lying down from raw data of thigh-worn accelerometers, we have found that the refined algorithm can be used to estimate lying time in studies using different accelerometer brands.<sup>47</sup>

## STRENGTHS AND LIMITATIONS

This is a longitudinal study of individuals with knee pain who are being followed over 5 years, with yearly follow-ups. Previous studies of individuals with knee pain report that almost all individuals with knee pain developed radiographically verified knee OA after 12 years,<sup>2</sup> but many got radiographically verified knee OA already

after 5 years.<sup>2</sup> The present study is investigating the early disease process in individuals without knee trauma, that is, cruciate ligament rupture. Most studies on the disease process in knee OA include individuals with cruciate ligament rupture. However, a range of phenotypes in knee OA have been proposed, which could have different pathophysiological mechanisms.<sup>4</sup> This longitudinal study is focusing on the metabolic knee OA phenotype.

A limitation could be the number of included individuals and the longitudinal design, which could increase the risk of individuals 'lost to follow-up' and have an impact on the power in the study. The large amount of data collected could also increase the risk of variables 'lost to follow-up'. Possible confounders will be adjusted for in the statistical analysis. Missing data and attrition could be handled statistically with basic imputation techniques, as imputation with a constant value or imputation using the statistics (mean, median, mode), if needed. The selection of participants was based on self-interest which may have an impact on generalisability.

The preferable age range (30–65 years) was chosen with the aim of not including individuals proposed for the ageing phenotype (>65 years).<sup>4</sup> The choice of clinical outcomes was based on previous studies of OA, so that the results could be compared with other studies.<sup>65</sup>

The radiographs of the knees and hands will be assessed in accordance with Ahlbäck and Kellgren and Lawrence for knee OA and Kellgren and Lawrence for hand OA, as many studies use one of these methods to assess radiographic changes in knee and hand OA.<sup>66 67</sup>

The specific analyses of the blood samples were selected to show metabolic factors, such as glucose and lipid levels included in the criteria for MetS and a commonly used marker for inflammation. Serum and EDTA plasma are saved and stored in a biobank for further analysis.

For the obesity assessment, we are using three different methods: BMI, which was chosen to enable comparison with other studies, given that it is the most common method. Waist circumference, assessed with a measuring tape, was chosen because it is also well used and a criterion for metabolic syndrome.<sup>32</sup> Because BMI has certain weaknesses when it comes to people with large muscle mass and with a higher weight, we also chose to use bioimpedance to assess obesity, visceral fat and fat mass.

Pain is assessed both with patient-reported methods and with an algometer measuring PPTs. The questionnaire contains a pain manikin, frequently used in other studies and NRS for pain intensity, and open questions about pain frequency in physical activities and leisure time. The method for measuring PPTs was chosen because it is valid<sup>68</sup>; it includes several predefined tender points out of the 18 points, as part of the definition of fibromyalgia.<sup>35</sup>

Tests of physical function applied in this study are commonly used when evaluating knee and hand OA, both in clinical practice and research.<sup>38–40 43 44</sup>

The assessment of daily physical activity types with triaxial accelerometers is a rather new method, which gives the opportunity to measure physical activity and



leisure time objectively over 7 days. The method has been used previously, but the third accelerometer measuring knee bending has only recently been validated.<sup>46 47</sup> This method has been used in previously large epidemiological studies.<sup>69</sup>

The questionnaire includes KOOS, which is an established, validated questionnaire, measuring symptoms and physical function in individuals with knee OA.<sup>49 70</sup> Quick DASH is also a well-established, validated questionnaire measuring symptoms and function of the shoulder, arm and hand, and is used when evaluating hand OA.<sup>71</sup>

Depression and anxiety are often seen in individuals with pain, and we wanted to evaluate this aspect, also in individuals with knee pain. We chose HADS, as it is a patient-reported validated outcome widely used to assess psychological distress.<sup>72</sup>

In clinical studies, it is important to assess HRQoL. Studies have reported the impact of chronic pain on HRQoL.<sup>5 73</sup> We decided to use EQ5D-3L and SF-36 to assess this aspect, since they are widely used generic instruments when assessing HRQoL. KOOS has also an item measuring HRQoL in the aspect of knee OA.<sup>49 70</sup>

OA has an impact on many aspects of life. In this study, we have tried to capture as many as we think is possible to get as broad a perspective as possible on OA and life with OA. It is important to study possible pathophysiological mechanisms of OA to be able to prevent and treat the disease. It is possible that there are several different pathophysiological mechanisms involved in OA development and, by identifying them, one can adapt both the treatment and preventive measures. It is also important to study the development of chronic pain in OA, to get tools to identify individuals at risk and to be able to offer them treatment.

## COLLABORATION

We are positive to collaborations, and they will be considered on reasonable request to the corresponding author.

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**Contributors** All authors contributed equally to the conception and design of the study. MLEA drafted the protocol. EH and KA critically revised the protocol. AB and

SB read it critically for important intellectual content. MLEA (maria.andersson@fou-spenshult.se) and SB (stefan.bergman@fou-spenshult.se) have the responsibility for the integrity of the study, from inception to finished. MLEA is the guarantor of the study and the principal investigator.

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## REFERENCES

- 1 Kloppenburg M, Berenbaum F. Osteoarthritis year in review 2019: epidemiology and therapy. *Osteoarthritis Cartilage* 2020;28:242–8.
- 2 Thorstensson CA, Andersson MLE, Jönsson H, et al. Natural course of knee osteoarthritis in middle-aged subjects with knee pain: 12-year follow-up using clinical and radiographic criteria. *Ann Rheum Dis* 2009;68:1890–3.
- 3 Berenbaum F, Walker C. Osteoarthritis and inflammation: a serious disease with overlapping phenotypic patterns. *Postgrad Med* 2020;132:377–84.
- 4 Sellam J, Berenbaum F. Is osteoarthritis a metabolic disease? *Joint Bone Spine* 2013;80:568–73.
- 5 Bergman S, Thorstensson C, Andersson MLE. Chronic widespread pain and its associations with quality of life and function at a 20-year follow-up of individuals with chronic knee pain at inclusion. *BMC Musculoskelet Disord* 2019;20:592.
- 6 Gosset M, Berenbaum F, Levy A, et al. Mechanical stress and prostaglandin E2 synthesis in cartilage. *Biorheology* 2008;45:301–20.
- 7 Stürmer T, Günther KP, Brenner H. Obesity, overweight and patterns of osteoarthritis: the ULM osteoarthritis study. *J Clin Epidemiol* 2000;53:307–13.



- 8 Visser AW, Ioan-Facsinay A, de Mutsert R, *et al.* Adiposity and hand osteoarthritis: the Netherlands epidemiology of obesity study. *Arthritis Res Ther* 2014;16:R19.
- 9 Yusuf E, Nelissen RG, Ioan-Facsinay A, *et al.* Association between weight or body mass index and hand osteoarthritis: a systematic review. *Ann Rheum Dis* 2010;69:761–5.
- 10 Ursini F, Naty S, Grembale RD. Fibromyalgia and obesity: the hidden link. *Rheumatol Int* 2011;31:1403–8.
- 11 Sowers MR, Karvonen-Gutierrez CA. The evolving role of obesity in knee osteoarthritis. *Curr Opin Rheumatol* 2010;22:533–7.
- 12 Yunus MB, Arslan S, Aldag JC. Relationship between body mass index and fibromyalgia features. *Scand J Rheumatol* 2002;31:27–31.
- 13 Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006;444:840–6.
- 14 Pan F, Tian J, Cicuttini F, *et al.* Metabolic syndrome and trajectory of knee pain in older adults. *Osteoarthritis Cartilage* 2020;28:45–52.
- 15 Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. *Mol Cell Endocrinol* 2010;316:129–39.
- 16 Funcke J-B, Scherer PE. Beyond adiponectin and leptin: adipose tissue-derived mediators of inter-organ communication. *J Lipid Res* 2019;60:1648–84.
- 17 Courties A, Sellam J. Osteoarthritis and type 2 diabetes mellitus: what are the links? *Diabetes Res Clin Pract* 2016;122:198–206.
- 18 Wang Y, Teichtahl AJ, Abram F, *et al.* Knee pain as a predictor of structural progression over 4 years: data from the osteoarthritis initiative, a prospective cohort study. *Arthritis Res Ther* 2018;20:250.
- 19 Bergman S, Herrström P, Högström K, *et al.* Chronic musculoskeletal pain, prevalence rates, and sociodemographic associations in a swedish population study. *J Rheumatol* 2001;28:1369–77.
- 20 Carlesso LC, Neogi T. Identifying pain susceptibility phenotypes in knee osteoarthritis. *Clin Exp Rheumatol* 2019;37 Suppl 120:96–9.
- 21 Fingleton C, Smart K, Moloney N, *et al.* Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2015;23:1043–56.
- 22 Ezzat AM, Li LC, . Occupational physical loading tasks and knee osteoarthritis: a review of the evidence. *Physiother Can* 2014;66:91–107.
- 23 Hubertsson J, Petersson IF, Thorstensson CA, *et al.* Risk of sick leave and disability pension in working-age women and men with knee osteoarthritis. *Ann Rheum Dis* 2013;72:401–5.
- 24 Hubertsson J, Turkiewicz A, Petersson IF, *et al.* Understanding occupation, sick leave, and disability pension due to knee and hip osteoarthritis from a sex perspective. *Arthritis Care Res* 2017;69:226–33.
- 25 Allen KD, Chen J-C, Callahan LF, *et al.* Associations of occupational tasks with knee and hip osteoarthritis: the Johnston county osteoarthritis project. *J Rheumatol* 2010;37:842–50.
- 26 McWilliams DF, Leeb BF, Muthuri SG, *et al.* Occupational risk factors for osteoarthritis of the knee: a meta-analysis. *Osteoarthritis Cartilage* 2011;19:829–39.
- 27 Altman R, Alarcón G, Appelrouth D, *et al.* The American college of rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601–10.
- 28 Altman R, Asch E, Bloch D, *et al.* Development of criteria for the classification and reporting of osteoarthritis. classification of osteoarthritis of the knee. diagnostic and therapeutic criteria committee of the American rheumatism association. *Arthritis Rheum* 1986;29:1039–49.
- 29 Ahlback S. Osteoarthrosis of the knee. a radiographic investigation. *Acta Radiol Diagn* 1968;277:7–72.
- 30 Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. *Ann Rheum Dis* 1957;16:494–502.
- 31 Marshall M, Dziedzic KS, van der Windt DA, *et al.* A systematic search and narrative review of radiographic definitions of hand osteoarthritis in population-based studies. *Osteoarthritis Cartilage* 2008;16:219–26.
- 32 Federation ID. The IDF consensus worldwide definition of the metabolic syndrome; 2006.
- 33 Lahav Y, Goldstein N, Gepner Y. Comparison of body composition assessment across body mass index categories by two multifrequency bioelectrical impedance analysis devices and dual-energy X-ray absorptiometry in clinical settings. *Eur J Clin Nutr* 2021;75:1275–82.
- 34 Examination Committee of Criteria for 'Obesity Disease' in Japan, Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J* 2002;66:987–92.
- 35 Wolfe F, Smythe HA, Yunus MB, *et al.* The American College of rheumatology 1990 criteria for the classification of fibromyalgia. report of the multicenter criteria committee. *Arthritis Rheum* 1990;33:160–72.
- 36 Jensen K, Andersen Henrik Ørbaek, Olesen J, *et al.* Pressure-pain threshold in human temporal region. evaluation of a new pressure algometer. *Pain* 1986;25:313–23.
- 37 Vaegter HB. Exercising non-painful muscles can induce hypoalgesia in individuals with chronic pain. *Scand J Pain* 2017;15:60–1.
- 38 Dobson F, Hinman RS, Hall M, *et al.* Reliability and measurement error of the osteoarthritis research society international (OARSI) recommended performance-based tests of physical function in people with hip and knee osteoarthritis. *Osteoarthritis Cartilage* 2017;25:1792–6.
- 39 Thorstensson CA, Henriksson M, von Porat A, *et al.* The effect of eight weeks of exercise on knee adduction moment in early knee osteoarthritis—a pilot study. *Osteoarthritis Cartilage* 2007;15:1163–70.
- 40 Thorstensson CA, Petersson IF, Jacobsson LTH, *et al.* Reduced functional performance in the lower extremity predicted radiographic knee osteoarthritis five years later. *Ann Rheum Dis* 2004;63:402–7.
- 41 Hirano M, Katoh M, Gomi M, *et al.* Validity and reliability of isometric knee extension muscle strength measurements using a belt-stabilized hand-held dynamometer: a comparison with the measurement using an isokinetic dynamometer in a sitting posture. *J Phys Ther Sci* 2020;32:120–4.
- 42 Koblbauer IFH, Lambrecht Y, van der Hulst MLM, *et al.* Reliability of maximal isometric knee strength testing with modified hand-held dynamometry in patients awaiting total knee arthroplasty: useful in research and individual patient settings? a reliability study. *BMC Musculoskelet Disord* 2011;12:249.
- 43 Astrand I. Aerobic work capacity in men and women with special reference to age. *Acta Physiol Scand Suppl* 1960;49:1–92.
- 44 Nordenskiöld UM, Grimby G. Grip force in patients with rheumatoid arthritis and fibromyalgia and in healthy subjects. a study with the grippit instrument. *Scand J Rheumatol* 1993;22:14–19.
- 45 Skotte J, Korshøj M, Kristiansen J, *et al.* Detection of physical activity types using triaxial accelerometers. *J Phys Act Health* 2014;11:76–84.
- 46 Stenlund I, Ingebrigtsen J, Christiansen CS, *et al.* Validity of the Acti4 method for detection of physical activity types in free-living settings: comparison with video analysis. *Ergonomics* 2015;58:953–65.
- 47 Hettiarachchi P, Aili K, Holtermann A, *et al.* Validity of a non-proprietary algorithm for identifying lying down using raw data from thigh-worn triaxial accelerometers. *Sensors* 2021;21. doi:10.3390/s21030904. [Epub ahead of print: 29 Jan 2021].
- 48 Roos EM, Klässbo M, Lohmander LS. WOMAC osteoarthritis index. reliability, validity, and responsiveness in patients with arthroscopically assessed osteoarthritis. Western Ontario and McMaster universities. *Scand J Rheumatol* 1999;28:210–5.
- 49 Roos EM, Roos HP, Ekdahl C, *et al.* Knee injury and osteoarthritis outcome Score (KOOS)—validation of a Swedish version. *Scand J Med Sci Sports* 1998;8:439–48.
- 50 Gummesson C, Ward MM, Atroshi I. The shortened disabilities of the arm, shoulder and hand questionnaire (QuickDASH): validity and reliability based on responses within the full-length DASH. *BMC Musculoskelet Disord* 2006;7:44.
- 51 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
- 52 EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
- 53 Sullivan M, Karlsson J, Ware JE. The Swedish SF-36 health survey—I. evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. *Soc Sci Med* 1995;41:1349–58.
- 54 Sweden TPHAo. National public health survey, health on equal terms; 2016.
- 55 Bush K, Kivlahan DR, McDonnell MB, *et al.* The audit alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. ambulatory care quality improvement project (ACQUIP). alcohol use disorders identification test. *Arch Intern Med* 1998;158:1789–95.
- 56 Sørensen K, Van den Broucke S, Pelikan JM, *et al.* Measuring health literacy in populations: illuminating the design and development process of the European health literacy survey questionnaire (HLS-EU-Q). *BMC Public Health* 2013;13:948.
- 57 Wangdahl JM, Dahlberg K, Jaensson M, *et al.* Psychometric validation of Swedish and arabic versions of two health literacy questionnaires, eHEALS and HLS-EU-Q16, for use in a Swedish context: a study protocol. *BMJ Open* 2019;9:e029668.
- 58 Petersson IF, Boegård T, Svensson B, *et al.* Changes in cartilage and bone metabolism identified by serum markers in early osteoarthritis of the knee joint. *Br J Rheumatol* 1998;37:46–50.

- 59 Alfonso-Rosa RM, Del Pozo-Cruz B, Del Pozo-Cruz J, *et al.* Test-retest reliability and minimal detectable change scores for fitness assessment in older adults with type 2 diabetes. *Rehabil Nurs* 2014;39:260–8.
- 60 Andersson M, Haglund E, Aili K, *et al.* AB0854 Metabolic factors associated to clinical hand osteoarthritis in individuals with knee pain. *Ann Rheum Dis* 2020;79:1734.1–1734.
- 61 Haglund E, Sant'Anna A, Andersson MLE. Dynamic joint stability measured as gait symmetry in people with symptomatic knee osteoarthritis. *Ann Rheum Dis* 2019;78(Supplement 2):1458.
- 62 Tornblom M, Andersson MLE, Trulsson A. Validation of the Test for Substitution Patterns - in individuals with symptomatic knee osteoarthritis. *Ann Rheum Dis* 2019;78(Supplement 2):712.
- 63 Törnblom M, Bremander A, Aili K, *et al.* AB0586 prevalence of early symptomatic knee osteoarthritis according to three clinical classification criteria. *Ann Rheum Dis* 2021;80:1330
- 64 Sylwander C, Larsson I, Haglund E, *et al.* Pressure pain thresholds in individuals with knee pain: a cross-sectional study. *BMC Musculoskelet Disord* 2021;22:516.
- 65 Bijlsma JWW, Berenbaum F, Lafeber FPJG. Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011;377:2115–26.
- 66 Luyten FP, Bierma-Zeinstra S, Dell'Accio F, *et al.* Toward classification criteria for early osteoarthritis of the knee. *Semin Arthritis Rheum* 2018;47:457–63.
- 67 Visser AW, Bøyesen P, Haugen IK, *et al.* Radiographic scoring methods in hand osteoarthritis--a systematic literature search and descriptive review. *Osteoarthritis Cartilage* 2014;22:1710–23.
- 68 Kinser AM, Sands WA, Stone MH. Reliability and validity of a pressure algometer. *J Strength Cond Res* 2009;23:312–4.
- 69 Ekblom-Bak E, Olsson G, Ekblom Örjan, *et al.* The daily movement pattern and Fulfilment of physical activity recommendations in Swedish middle-aged adults: the SCAPIS pilot study. *PLoS One* 2015;10:e0126336.
- 70 Roos EM, Roos HP, Lohmander LS, *et al.* Knee injury and osteoarthritis outcome score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther* 1998;28:88–96.
- 71 Lutsky K, Kim N, Medina J, *et al.* Hand dominance and common hand conditions. *Orthopedics* 2016;39:e444–8.
- 72 Bjelland I, Dahl AA, Haug TT, *et al.* The validity of the hospital anxiety and depression scale. an updated literature review. *J Psychosom Res* 2002;52:69–77.
- 73 Vitaloni M, Botto-van Bemden A, Sciortino Contreras RM, *et al.* Global management of patients with knee osteoarthritis begins with quality of life assessment: a systematic review. *BMC Musculoskelet Disord* 2019;20:493.