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The Halland osteoarthritis (HALLOA) cohort – from knee pain to osteoarthritis – study protocol for a five-year observational study

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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 knee osteoarthritis and its association with hand and general osteoarthritis, metabolic diseases, biomarkers, chronic pain, physical function, and mechanical stress patterns.

Participants

The Halland osteoarthritis (HALLOA) cohort is a longitudinal cohort study over five years that includes individuals with knee pain in the southwest of Sweden. Enrolment took place from 2017–2019. The inclusion criteria were current knee pain, with no former known radiographic knee osteoarthritis and no cruciate ligament rupture or rheumatological disorder. The participants were recruited: 1) when seeking care for knee pain in primary health care, 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 and 217 have completed the one-year follow-up. There are annual follow-ups over five years. The baseline and follow-ups include clinical tests, radiographical examinations, blood samples, metabolic measures, pain pressure thresholds, tests of physical functions, mechanical load, and questionnaires.

Findings to date

At baseline there were clear associations between metabolic factors and radiographic knee OA, even in those with normal BMI.. I preliminary results we have found that the only metabolic factor associated with clinical hand OA was fasting plasma glucose. Contrary to other studies, there were no gender differences found. In a study comparing three different criteria for symptomatic knee OA (SKOA) approximately 50-70% of the individuals with knee pain were classified as having SKOA, where EULAR criteria having the lowest prevalence. The knowledge of these classification criteria long term ability capturing early knee OA is scarce. Further longitudinal studies are needed.

Future plans

The study will be following the participants over five years with annual follow-ups and will be ended in December 2024. The study will investigate the early development of knee and hand osteoarthritis in many different perspectives, e.g. associations to metabolic factors, different biomarkers, physical function, and mechanical stress patterns and development of chronic pain over time.

Registration Clinical trial registration: ClinicalTrials.gov NCT04928170

Introduction

Osteoarthritis (OA) is the most common musculoskeletal disease and is characterized by cartilage destruction, osteophyte formation, subchondral bone sclerosis and cysts.[1] 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.[2] Studies have found an association between osteoarthritis and metabolic diseases, such as type II diabetes, high blood pressure, lipid disorders, obesity, and long-term pain conditions, such as fibromyalgia.[3-5] Osteoarthritis is a heterogeneous disease and a range of phenotypes with different pathophysiological mechanisms are suggested e.g., traumatic, metabolic, and aging phenotype.[3 4]

Obesity is a well-known risk factor for OA and affects the weight-bearing joints through increased load and chronic mechanical stress, which induces chondrocytes to utilise mechanoreceptors to synthesize proinflammatory and cartilage-degrading mediators.[6 7] 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.[8 9] Osteoarthritis is a disease with low-grade inflammation, which also is seen in metabolic diseases, such as diabetes type II. There are also reports of low-grade inflammation in fibromyalgia. An interesting hypothesis is that a possible link between osteoarthritis, generalized pain and metabolic diseases is obesity and the increased amount of adipose tissue,[10] given that obesity is a risk factor in osteoarthritis, diabetes type II and chronic pain.[8 11-14] 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.[15] Adipokines are proinflammatory and could activate inflammation. Adipokines have also been shown to activate proteases, which could break down cartilage.[16] In addition, other factors are suggested as possible links between diabetes type II and OA, such as oxidative stress and advanced glycation end products (AGE) accumulation in joint tissues exposed to chronic high glucose concentration.[17]

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 osteoarthritis has pain.[18] In individuals with symptomatic knee osteoarthritis, approximately 30% meet the criteria for chronic widespread pain (CWP),[5] in contrast to about 11% in the general population.[19] Lowered pain thresholds in individuals with knee OA have been reported to be associated with an exacerbation of symptoms and increased risk of chronic pain.[20 21]

Connections between osteoarthritis development and mechanical stress in working life, level of physical activity and reduced muscle strength and coordination have also been reported.[22] In Sweden, people with osteoarthritis have an almost twice as high risk of being on sick leave, compared with individuals in the general population, and between 40-50% higher risk of risk of being in receipt of disability pension. Approximately 2% of all sick leave

days in Sweden are attributed to knee osteoarthritis.[23 24] Studies have reported a higher incidence of knee osteoarthritis among individuals in occupations with high physical load, including lifting or carrying heavy loads, frequent stair climbing, climbing ladders, prolonged standing, or walking.[25 26] 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. No studies have yet looked at stress during leisure time; knowledge of this is required to gain a better understanding about the level of exposure that is harmful. Mechanical stress patterns at work and in leisure time are not well studied for the metabolic phenotype of knee OA. The study investigates mechanical load patterns with an objective assessment 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 osteoarthritis and those with traumatic causes of osteoarthritis. 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 osteoarthritis development.

Overall aim

The overall objective is to study the early development of osteoarthritis of the knee and its association with hand and general osteoarthritis, metabolic diseases, biomarkers, chronic pain, physical function and mechanical stress patterns.

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

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

1A. Relationship between knee OA development and metabolic factors

1B. Relationship between hand OA development and metabolic factors

Research area 2: Biomarkers in knee and hand osteoarthritis – to study cartilage and bone markers that reflect various processes in osteoarthritis development, e.g., inflammation, matrix degradation, both in the short and long term.

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

Research area 4: Physical function and osteoarthritis – to study physical function, physical activity and measured mechanical stress patterns, as well as changes in mechanical stress patterns and the relationship between these and the development of osteoarthritis over time.

Method

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 2017–2019. The participants were recruited: 1) when seeking care for knee pain in primary health care, 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 examined eligible participants to confirm the exclusion criteria of cruciate ligament rupture. The cohort will be followed for five years with yearly follow-ups, figure 1, 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). These individuals will be excluded in the sub-studies if needed.

Clinical outcomes

There will be annual follow-ups over five 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, two and five-year follow-up, there will be clinical examination, measurements of obesity, pain pressure thresholds, and tests of physical function and mechanical load.

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 assessment of knees and fingers are used to classify osteoarthritis of the knees and hands according to Altman.[27 28]

Radiographic examination

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

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.[30 31] Radiographs of the hands will be obtained at two or three years and at five years.

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 LDL cholesterol (mmol/L), HbA1c (mmol/mol) and C-reactive protein (CRP) >1.0 mg/L are measured according to the current laboratory standards in Sweden. CRP below 1.0 mg/L, will be further analysed with a sensitive CRP enzyme-linked immunosorbent assay (ELISA) method (Abnova). Serum-Leptin are analyzed with an ELISA method (Alpco). Serum and plasma are saved in a biobank at -70 degrees Celsius for further analyses.

Raised glucose is classified in accordance with the International Diabetes Federation (IDF) definition as fasting plasma glucose ≥ 5.6 mmol/L, or if the individuals previously are diagnosed with diabetes.[32] Raised triglycerides is classified in accordance with IDF as triglycerides ≥ 1.7 mmol/L or if the individuals have a specific treatment for this lipid abnormality.[32] Reduced HDL-cholesterol is classified according to IDF as HDL-cholesterol < 1.03 mmol/L in males and 1.29 mmol/L in females or if the individuals have a specific treatment for this lipid abnormality.[32]

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 ≥ 94 cm in men and ≥ 80 cm in women.[32] 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.[33] Raised VFA level is classified as having VFA ≥ 100cm2.[34] Blood pressure is measured after five minutes' rest (Omron M3). Raised blood pressure was classified as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or treatment of previously diagnosed hypertension.[32] Metabolic syndrome (MetS) is classified in accordance with IDF definition as central obesity plus any two of the following four factors: raised triglycerides, reduced HDL-cholesterol, raised blood pressure, or raised fasting plasma glucose.[32]

Pain pressure thresholds

The pain pressure thresholds (PPTs) is measured on eight predefined tender points out of the 18 points, as part of the definition of fibromyalgia.[35] 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 mm2 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.[36] Two trials is assessed on each tender point, at a minimum of 30 seconds apart. The pressure gradually increased from 0 to a maximum of 1000 kilopascals (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. [37] The measurement is taken either before physical activity or after 30 minutes of rest.

Tests of physical function

One-leg rise from chair and 30s-chair stand test are assessed three times during the follow-up (at baseline, two and five years) [38-40], test of aerobic capacity is performed according to Åstrand bicycle ergometer test [41] and hand strength is assessed by Grippit.[42]

Mechanical load

Mechanical load is assessed by recurrent or lengthy mechanical stressful postures and activities in work and leisure over seven consecutive days. Through a new type of analysis method of motion (Acti4), where data is 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.[43-45] 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 mechanical load are performed in a sub-sample of the cohort, including 122 individuals.

Questionnaires

The questionnaires are all patient-reported and include questions concerning socio-demographics, comorbidities, medical and alternative treatments and the following questionnaires concerning knee and hand function, pain, anxiety and depression, health-related quality of life, 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 (ADL), function in sport and recreation (Sport/Rec) and knee-related quality of life (QOL). KOOS gives a score of 0-100 (worst to best) in each subscale.[46 47]
- The shortened version of the disabilities of the arm, shoulder and hand questionnaire (Quick DASH), 11 items self-administered region-specific outcome instrument developed as a measure of self-rated upper-extremity disability and symptoms ranging from 0-100 (no disability to most severe disability).[48]

- A pain mannequin, with 18 predefined regions (pain regions) where participants mark their painful areas on the pain figure, figure 2, if they have any.[19] There are also questions about pain intensity (numeric 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 out-patient clinic.[49] It contains two 7-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 dimensions, three levels questionnaire to assess health-related quality of life (0-1, worst to best).[50]
- 36-item Short form survey (SF-36), a generic questionnaire, with coherent, and easily administered quality-of-life 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.[51]
- 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).[52] Alcohol habits are assessed by the Alcohol Use Disorders Identification Test – Consumption (AUDIT-C), 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 five points or more, and in women four points or more.[53]
- Psychometric Assessment of the European Health Literacy (HLS-EU-Q16) 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 health care, disease prevention, and health promotion. Scoring varies between 0 and 16, establishing three levels of HL: inadequate (0–8), problematic (9–12), and sufficient (>12).[54 55]

Power calculation

Based on known prevalence of chronic widespread pain (CWP) (30%) and metabolic syndrome (MetS) (14% to 50%) in previous osteoarthritis studies, 300 people would be needed in the study to have at least 40 people with these conditions.[5 56-58]

Findings to date

Preliminary results shows 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 (submitted to BMJ open). 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 [59]. 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 [60]. Preliminary results shows that the test for substitutional patterns (TSP) 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 [61]. In another study we have compared three criteria for symptomatic knee OA (SKOA) and approximately 50-70% of the individuals with knee pain were classified as having SKOA, where EULAR criteria having the lowest prevalence [62].

In a study aimed to (1) investigate pain sensitivity, assessed by pressure pain thresholds (PPTs), among women and men with knee pain and (2) associations with, respectively, radiographic KOA (rKOA), 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 [63].

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 [45].

Strengths and limitations

This is a longitudinal study of individuals with knee pain who are being followed over five 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,[2] but many got radiographically verified knee OA already after five years.[2] The present study is investigating the early disease process in individuals without knee trauma, i.e., 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.[4] This longitudinal study is focusing on the metabolic knee OA phenotype.

A limitation could be the number of included individuals and that the inclusion took two years.

The preferable age range (30-65 years) was chosen with the aim of not including individuals proposed for the aging phenotype (>65 years). [4] The choice of clinical outcomes was based on previous studies of OA, so that the results could be compared with other studies.[64]

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.[65 66]

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.[32] Because BMI has certain weaknesses when it comes to people with large muscle mass and therewith 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 mannequin, frequently used in other studies and NRS scales for pain intensity, and open questions about pain frequency in physical activities and leisure time. The method for measuring pain pressure thresholds was chosen because it is valid;[67] it includes several predefined tender points out of the 18 points, as part of the definition of fibromyalgia.[35]

Tests of physical function applied in this study are commonly used when evaluating knee and hand OA, both in clinical practice and research.[38-42]

The assessment of mechanical load with triaxial accelerometers is a rather new method, which gives the opportunity to measure physical activity and leisure time objectively over seven days. The method has been used previously, but the third accelerometer measuring knee bending has only recently been validated.[44 45] This method has been used in large epidemiological studies, most recently in SCAPIS Uppsala, where approximately 4,500 individuals have carried an accelerometer on their thigh for a week.[68]

The questionnaire includes KOOS, which is an established, validated questionnaire measuring symptoms and physical function in individuals with knee OA.[47 69] 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.[70]

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.[71]

In clinical studies, it is important to assess health-related quality of life. Studies have reported the impact of chronic pain on health-related quality of life.[5 72] 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.[47 69]

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 osteoarthritis 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.

Declarations

Ethics approval and consent to participate

All participants gave their informed consent to participate in the study, which was obtained in accordance with the Helsinki Declaration.[21] The study was approved by the Regional Ethical Review Board, Faculty of Medicine, University of Lund, Sweden (2016-229, 2017/253, 2018/602, 2020-04489, 2020-03866 and 2021-01837).

Consent for publication

All participants gave informed consent for publication of results at a group level.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors have no competing interests.

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Authors' contributions

All authors contributed equally to the conception and design of the study. MA drafted the protocol. EH and KA critically revised the protocol. AB and SB read it critically for important intellectual content. MA (maria.andersson@fou-spenshult.se) and SB (stefan.bergman@fou-spenshult.se) is responsibility for the integrity of the study, from inception to finished.

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Tables and Figures

Table

Table 1. Description of the included assessment over five years.

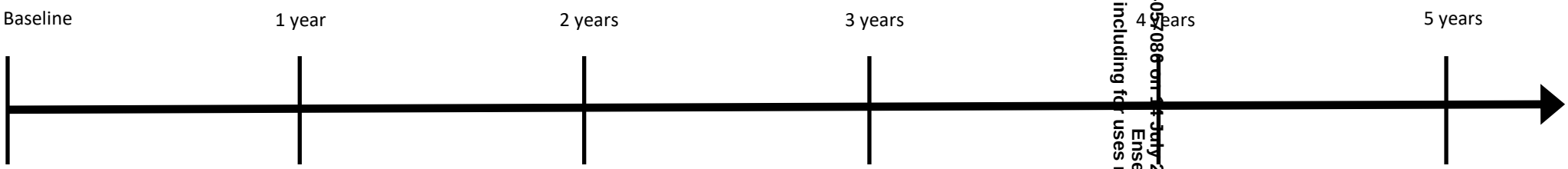
		Inclusion	1 year	2 years	3 years	4 years	5 years
Clinical examination		X		X			X
Radiographic examination	Knees	X	X	X	X	X	X
	Hands			X			X
Blood samples		X	X	X	X	X	X
Metabolic meassures		X		X			X
PPT		X		X			X
Tests of physical function		X		X			X
Mechanical load		X		X			
KOOS		X	X	X	X	X	X
Quick DASH		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

PPT, pain pressure thresholds; KOOS, Knee injury and Osteoarthritis Outcome Score; DASH, disabilities of the arm, shoulder and hand questionnaire; HADS, The Hospital Anxiety and Depression Scale; EQ5D-3L, EuroQol; SF-36, 36-item Short form survey; HLS-EU-Q16, Psychometric Assessment of the European Health Literacy

Figure legends

Figure 1. Flowchart HALLOA study

Figure 2. Pain mannequin



Baseline	1 year	2 years	3 years	4 years	5 years
Clinical examination	Radiographic examination	Clinical examination	Radiographic examination	Radiographic examination	Clinical examination
Radiograhic examination	Blood samples	Radiograhic examination	Blood samples	Blood samples	Radiograhic examination
Blood samples	Questionnaire	Blood samples	Questionnaires	Questionnaires	Blood samples
Obesity meassures		Obesity meassures			Obesity meassures
Pain pressure thresholds		Pain pressure thresholds			Pain pressure thresholds
Tests of physical function		Test of physical function			Test of physical function
Mechanical load		Mechanical load			Mechanical load
Questionnaires		Questionnaires			Questionnaires

Clinical examination—Clinical examination of knee and hands, blood preassure

Radiographic examination—Knees yearly and hands at 2 -and 5 years

Blood samples—Triglycerides, Cholesterol (total, LDL and HDL), fasting glucose, HbA1c, CRP and for saving in a biobank

Obesity meassures—Waist and hip circumference, height, lenght, body composition (Inbody 770)

Pain pressure thresholds—measured on eight predefined tender points by algometer

Tests of physical function—-one leg-rise, chair-stand test, quadriceps strength with dynamometer, hand strenght, postural control (at baseline) and fitness at 2– and 5 years

Mechanical load—Movement behavior measured with a triaxle accelerometer at work and leisure for 7 days

Questionnaire—including pain assessment with EVAS (Visual Analog Scale), pain drawing, KOOS, SF36, EQ5D, quickDASH and questions about lifestyle

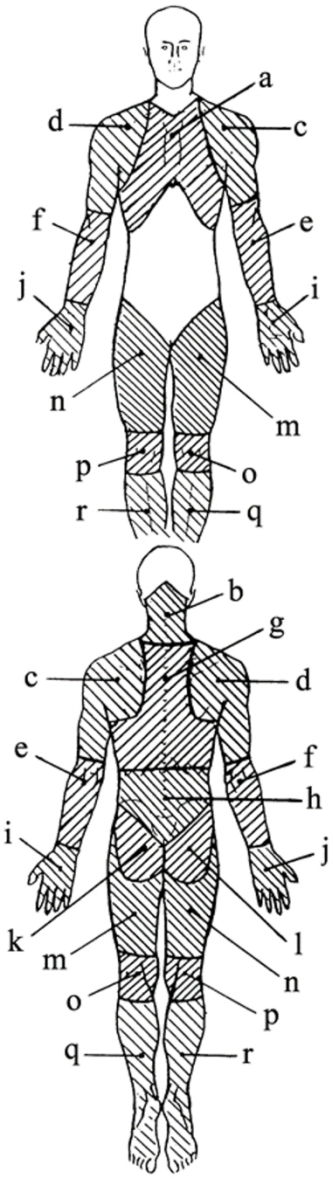


Figure 2. Pain mannequin

125x435mm (149 x 149 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the **study's design** with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4
Methods			
Study design	4	Present key elements of study design early in the paper	Method, page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Method, page 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Method page 5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	page 5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*page5-8*
Bias	9	Describe any efforts to address potential sources of bias.	
Study size	10	Explain how the study size was arrived at	page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	page 5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	NA
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed.	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 5
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	Page 5
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 9-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Cohort profile: The Halland osteoarthritis (HALLOA) cohort – from knee pain to osteoarthritis – a longitudinal observational study in Sweden

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Secondary Subject Heading:	Epidemiology, Diabetes and endocrinology, General practice / Family practice
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, GENERAL MEDICINE (see Internal Medicine), Rheumatology < INTERNAL MEDICINE

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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 2017–2019. 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 health care, 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 BMI at baseline. In addition, clinical hand OA was positively associated to 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.

Registration Clinical trial registration: ClinicalTrials.gov NCT04928170

Strengths and limitations of this study

- The study has a possibility to detect variations and long-term changes over five 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

Introduction

Osteoarthritis (OA) is the most common musculoskeletal disease and is characterized by cartilage destruction, osteophyte formation, subchondral bone sclerosis and cysts.[1] 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.[2] 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.[3-5] OA is a heterogeneous disease and a range of phenotypes with different pathophysiological mechanisms are suggested e.g., traumatic, metabolic, and aging phenotype.[3 4]

Obesity is a well-known risk factor for OA and affects the weight-bearing joints through increased load and chronic mechanical stress, which induces chondrocytes to utilise mechanoreceptors to synthesize proinflammatory and cartilage-degrading mediators.[6 7] 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.[8 9] OAis a disease with low-grade inflammation, which also is seen in metabolic diseases, such as diabetes type II. There are also reports of low-grade inflammation in fibromyalgia. An interesting hypothesis is that a possible link between OA, generalized pain and metabolic diseases is obesity and the increased amount of adipose tissue,[10] given that obesity is a risk factor in OA, diabetes type II and chronic pain.[8 11-14] 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.[15] Adipokines are proinflammatory and could activate inflammation. Adipokines have also been shown to activate proteases, which could break down cartilage.[16] In addition, other factors are suggested as possible links between diabetes type II and OA, such as oxidative stress and advanced glycation end products (AGE) accumulation in joint tissues exposed to chronic high glucose concentration.[17]

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 osteoarthritis has pain.[18] In individuals with symptomatic knee OA, approximately 30% meet the criteria for chronic widespread pain (CWP),[5] in contrast to about 11% in the general population.[19] Lowered pain thresholds in individuals with knee OA have been reported to be associated with an exacerbation of symptoms and increased risk of chronic pain.[20 21]

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.[22] 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 40-50% higher risk of risk of being in receipt of disability pension. Approximately 2% of all sick leave days in Sweden are attributed to knee OA.[23 24] 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.[25 26] 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, daily physical activity types.

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

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 to knee OA development?

1B. Relationship between hand OA development and metabolic factors

- Which metabolic factors are associated to hand OA development?

Research area 2: Biomarkers in knee and hand osteoarthritis – to study cartilage and bone biomarkers that reflect various processes in radiographic knee and /or hand OA development, e.g., 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 in relation to lifestyle, depression, and health-related quality of life (HRQoL) in individuals with symptomatic knee osteoarthritis.

- How do radiographic progress, lifestyle habits, depression, and health-related quality of life (HRQoL) relate to chronic pain and pain pressure thresholds in individuals with symptomatic knee osteoarthritis?

Research area 4: Physical function and knee OA – to study physical function, daily physical activity types, as well as changes 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 2017–2019. The participants were recruited: 1) when seeking care for knee pain in primary health care, 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 examined eligible participants to confirm the exclusion criteria of cruciate ligament rupture. The cohort will be followed for five years with yearly follow-ups, figure 1, 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). These individuals will be excluded in the sub-studies if needed.

Clinical outcomes

There will be annual follow-ups over five 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, two and five-year follow-up, there will be clinical examination, measurements of obesity, pain pressure thresholds, 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 assessment of knees and fingers are used to classify OA of the knees and hands according to Altman.[27 28]

Radiographic examination

The radiographs of the knees are obtained in a skyline view of patellofemoral (PF) joints, and posteroanterior radiographs of both the tibiofemoral (TF) joints were obtained in weightbearing position with flexed knees. Radiographic knee OA was initially defined

according to Ahlbäck,[29] as having Ahlbäck grade I or more in at least one knee. The radiographs will also be scored according to Kellgren and Lawrence.[30]

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.[30 31] Radiographs of the hands will be obtained at two or three years and at five years. In this cohort study, radiographic knee and/or hand OA are considered as the end point 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 LDL cholesterol (mmol/L), HbA1c (mmol/mol) and C-reactive protein (CRP) >1.0 mg/L are measured according to the current laboratory standards in Sweden. CRP below 1.0 mg/L, will be further analysed with a sensitive CRP enzyme-linked immunosorbent assay (ELISA) method (Abnova). Serum-Leptin are analyzed with an ELISA method (Alpco). Serum and plasma are saved in a biobank at -70 degrees Celsius for further analyses.

Raised glucose is classified in accordance with the International Diabetes Federation (IDF) definition as fasting plasma glucose ≥ 5.6 mmol/L, or if the individuals previously are diagnosed with diabetes.[32] Raised triglycerides is classified in accordance with IDF as triglycerides ≥ 1.7 mmol/L or if the individuals have a specific treatment for this lipid abnormality.[32] Reduced HDL-cholesterol is classified according to IDF as HDL-cholesterol < 1.03 mmol/L in males and 1.29 mmol/L in females or if the individuals have a specific treatment for this lipid abnormality.[32]

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 ≥ 94 cm in men and ≥ 80 cm in women.[32] 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.[33] Raised VFA level is classified as having VFA ≥ 100cm2.[34] Blood pressure is measured after five minutes' rest (Omron M3). Raised blood pressure was classified as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or treatment of previously diagnosed hypertension.[32] Metabolic syndrome (MetS) is classified in accordance with IDF definition as central obesity plus any two of the following four factors: raised triglycerides, reduced HDL-cholesterol, raised blood pressure, or raised fasting plasma glucose.[32]

Pain pressure thresholds

The pain pressure thresholds (PPTs) is measured on eight predefined tender points out of the 18 points, as part of the definition of fibromyalgia.[35] 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 mm2 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.[36] Two trials is assessed on each tender point, at a minimum of 30 seconds apart. The pressure gradually increased from 0 to a maximum of 1000 kilopascals (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.[37] The measurement is taken either before physical activity or after 30 minutes of rest.

Tests of physical function

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

Daily physical activity types

Daily physical activity types are assessed by recurrent or lengthy mechanical stressful postures and activities in work and leisure over seven consecutive days. Through a new type of analysis method of motion (Acti4), where data is 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.[45-47] 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 sub-sample of the cohort, including 122 individuals.

Questionnaires

The questionnaires are all patient-reported and include questions concerning socio-demographics, comorbidities, medical and alternative treatments and the following questionnaires concerning knee and hand function, pain, anxiety and depression, health-related quality of life, 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 (ADL), function in sport and recreation (Sport/Rec) and knee-related quality of life (QOL). KOOS gives a score of 0-100 (worst to best) in each subscale.[48 49]

- The shortened version of the disabilities of the arm, shoulder and hand questionnaire (Quick DASH), 11 items self-administered region-specific outcome instrument developed as a measure of self-rated upper-extremity disability and symptoms ranging from 0-100 (no disability to most severe disability).[50]
- A pain mannequin, with 18 predefined regions (pain regions) where participants mark their painful areas on the pain figure, figure 2, if they have any.[19] There are also questions about pain intensity (numeric 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 out-patient clinic.[51] It contains two 7-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 dimensions, three levels questionnaire to assess health-related quality of life (0-1, worst to best).[52]
- 36-item Short form survey (SF-36), a generic questionnaire, with coherent, and easily administered quality-of-life 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.[53]
- 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).[54] Alcohol habits are assessed by the Alcohol Use Disorders Identification Test – Consumption (AUDIT-C), 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 five points or more, and in women four points or more.[55]
- Psychometric Assessment of the European Health Literacy (HLS-EU-Q16) 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 health care, disease prevention, and health promotion. Scoring varies between 0 and 16, establishing three levels of HL: inadequate (0–8), problematic (9–12), and sufficient (>12).[56 57]

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 (COMP) [58].

Research area 3 - Based on known prevalence of chronic widespread pain (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.[5]

Research area 4 – To be able to show a difference of 3.3 (minimal detectable change = 3.3) in 30s-chairstands test, effect size of 0.5 and a power of 80%, a double-sided test requires a sample size of 198 individuals. [59]

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 shows 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 [60]. 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 [61]. Preliminary results shows that the test for substitutional patterns (TSP) 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 [62]. 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 EULAR criteria having the lowest prevalence [63].

In a study aimed to (1) investigate pain sensitivity, assessed by pressure pain thresholds (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 [64].

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 [47].

Strengths and limitations

This is a longitudinal study of individuals with knee pain who are being followed over five 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,[2] but many got radiographically verified knee OA already after five years.[2] The present study is investigating the early disease process in individuals without knee trauma, i.e., 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.[4] 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 generalizability.

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

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.[66 67]

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.[32] Because BMI has certain weaknesses when it comes to people with large muscle mass and therewith 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 mannequin, frequently used in other studies and NRS scales for pain intensity, and open questions about pain frequency in physical activities and leisure time. The method for measuring pain pressure thresholds was chosen because it is valid;[68] it

includes several predefined tender points out of the 18 points, as part of the definition of fibromyalgia.[35]

Tests of physical function applied in this study are commonly used when evaluating knee and hand OA, both in clinical practice and research.[38-40 43 44]

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 seven days. The method has been used previously, but the third accelerometer measuring knee bending has only recently been validated.[46 47] This method has been used in previously large epidemiological studies.[69]

The questionnaire includes KOOS, which is an established, validated questionnaire measuring symptoms and physical function in individuals with knee OA.[49 70] 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.[71]

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.[72]

In clinical studies, it is important to assess health-related quality of life. Studies have reported the impact of chronic pain on health-related quality of life.[5 73] 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.[49 70]

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.

Declarations

Ethics approval and consent to participate

All participants gave their informed consent to participate in the study, which was obtained in accordance with the Helsinki Declaration.[21] The study was approved by the Regional Ethical Review Board, Faculty of Medicine, University of Lund, Sweden (2016-229, 2017/253, 2018/602, 2020-04489, 2020-03866 and 2021-01837).

Consent for publication

All participants gave informed consent for publication of results at a group level.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors have no competing interests.

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Authors' contributions

All authors contributed equally to the conception and design of the study. MA drafted the protocol. EH and KA critically revised the protocol. AB and SB read it critically for important intellectual content. MA (maria.andersson@fou-spenshult.se) and SB (stefan.bergman@fou-spenshult.se) has responsibility for the integrity of the study, from inception to finished.

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Tables and Figures

Table

Table 1. Description of the included assessment over five years.

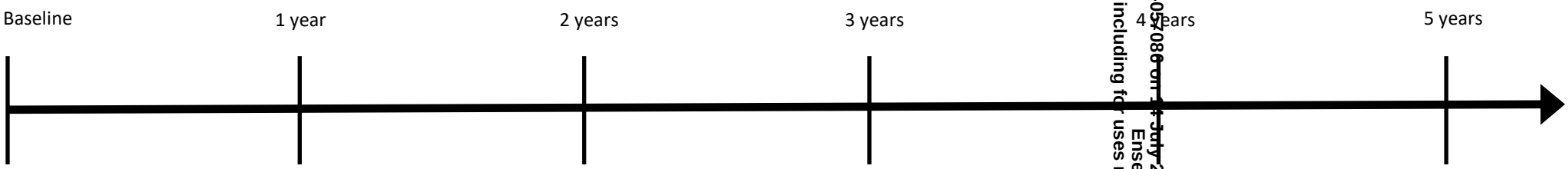
		Inclusion	1 year	2 years	3 years	4 years	5 years
Clinical examination		X		X			X
Radiographic examination	Knees	X	X	X	X	X	X
	Hands			X			X
Blood samples		X	X	X	X	X	X
Metabolic meassures		X		X			X
PPT		X		X			X
Tests of physical function		X		X			X
Daily physical activity types		X		X			
KOOS		X	X	X	X	X	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

PPT, pain pressure thresholds; KOOS, Knee injury and Osteoarthritis Outcome Score; DASH, disabilities of the arm, shoulder and hand questionnaire; HADS, The Hospital Anxiety and Depression Scale; EQ5D-3L, EuroQol; SF-36, 36-item Short form survey; HLS-EU-Q16, Psychometric Assessment of the European Health Literacy

Figure legends

Figure 1. Flowchart HALLOA study

Figure 2. Pain mannequin



Baseline	1 year	2 years	3 years	4 years	5 years
Clinical examination	Radiographic examination	Clinical examination	Radiographic examination	Radiographic examination	Clinical examination
Radiograhic examination	Blood samples	Radiograhic examination	Blood samples	Blood samples	Radiograhic examination
Blood samples	Questionnaire	Blood samples	Questionnaires	Questionnaires	Blood samples
Obesity meassures		Obesity meassures			Obesity meassures
Pain pressure thresholds		Pain pressure thresholds			Pain pressure thresholds
Tests of physical function		Test of physical function			Test of physical function
Mechanical load		Mechanical load			Mechanical load
Questionnaires		Questionnaires			Questionnaires

Clinical examination—Clinical examination of knee and hands, blood preassure

Radiographic examination—Knees yearly and hands at 2 -and 5 years

Blood samples—Triglycerides, Cholesterol (total, LDL and HDL), fasting glucose, HbA1c, CRP and for saving in a biobank

Obesity meassures—Waist and hip circumference, height, lenght, body composition (Inbody 770)

Pain pressure thresholds—measured on eight predefined tender points by algometer

Tests of physical function—-one leg-rise, chair-stand test, quadriceps strength with dynamometer, hand strenght, postural control (at baseline) and fitness at 2– and 5 years

Mechanical load—Movement behavior measured with a triaxle accelerometer at work and leisure for 7 days

Questionnaire—including pain assessment with EVAS (Visual Analog Scale), pain drawing, KOOS, SF36, EQ5D, quickDASH and questions about lifestyle

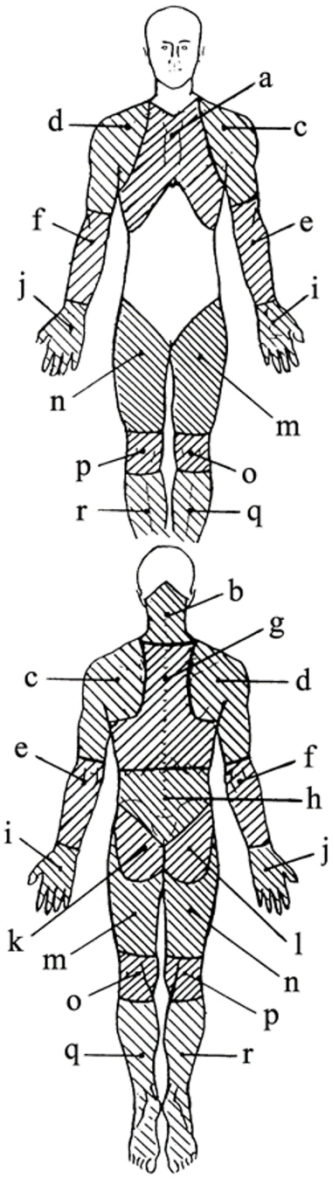


Figure 2. Pain mannequin

125x435mm (149 x 149 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the **study's design** with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4
Methods			
Study design	4	Present key elements of study design early in the paper	Method, page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Method, page 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Method page 5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	page 5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*page5-8*
Bias	9	Describe any efforts to address potential sources of bias.	
Study size	10	Explain how the study size was arrived at	page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	page 5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	NA
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed.	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 5
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	Page 5
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 9-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.