Insight in the role of lipids and other systemic factors in hand and knee osteoarthritis: lessons from clinical studies

Loef, M.

1

General introduction

Osteoarthritis

"OA is a serious disease with no known cure and no interventions currently available to stop the progression or therapies to manage the pain and loss of mobility with an acceptable benefit:risk profile." – Osteoarthritis: A Serious Disease, OARSI White paper, 2016[1].

Rheumatic musculoskeletal disorders (RMDs) are among the leading causes of disability in middle-aged adults. One of the most prevalent RMDs is osteoarthritis (OA). OA may develop in any joint, but occurs most commonly in hands, knees and hips. Patients with OA suffer from pain, stiffness and an inability to perform day-to-day tasks, and these symptoms can have a tremendous impact on the patients' health-related quality of life (HRQoL)[2,3]. The prevalence and burden of OA has surged in the past decades, affecting approximately 300 million people globally in 2017. This rise in prevalence is accompanied by an increase in years lived with disability of more than 30% since 2007[4]. Most important risk factors for OA are sex, age and obesity[5]. Consequently, OA prevalence is expected to increase even further in the coming years due to ageing of the population and increasing prevalence of obesity. In the Netherlands, the year prevalence of OA is expected to increase with 21% from 2017 to 2030[6]. OA is a heterogeneous disorder, not solely because of the manifestation in multiple joints, but also in its pathophysiology. OA may be classified into different phenotypes, such as post-traumatic, ageing-related and metabolic OA[5,7,8], of which the latter phenotype is the main interest of the research described in this thesis.

Classification

OA can be classified in several ways, which is commonly based on either clinical symptoms alone, or in combination with structural features visualised on imaging. The American College of Rheumatology (ACR) has developed criteria for the classification of hand and knee OA based on clinical and radiographic features[9,10], as listed in **table 1**. The key feature in these classification criteria is the presence of joint pain, co-occurring with typical symptoms and findings during joint examination. For the fulfilment of the radiographic classification criteria, the additional presence of osteophytes is required. Differences in classification methods are important to keep in mind when interpreting study results, especially since clinical symptoms and radiographic findings may not correlate well. Of patients with symptomatic OA, nearly half of patients lack radiological features and vice versa[11,12].

Disease burden

In 2015, osteoarthritis was listed in the top ten of conditions with greatest disease burden in the Netherlands. The prevalence of RMDs is expected to increase based on the predicted demographic developments, which is anticipated to be accompanied by a 17% increase in health expenditure[6]. OA is a chronic disease, and a cure or disease-modifying OA drugs (DMOADs) are currently not available. This limits the adequate treatment of symptoms such as pain and disability, resulting in a further increase in societal and individual burden.

The patients' health status and disease burden can be measured in a standardised way using patient reported outcome measures (PROMs). PROMs may aid shared-decision making and facilitate patient-centred care, as well as structure the monitoring of disease progression or treatment effects[13–15]. Many different outcome measures are being used in OA practise and research, which may be aimed to measure a specific domain, such as pain or function, or give an overall view of the disease, such as quality of life.

Table 1. American College of Rheumatology criteria for hand and knee osteoarthritis

Hand osteoarthritis *Clinical*	**Knee osteoarthritis** *Clinical*	**Knee osteoarthritis** *Clinical and radiographic*
Pain, aching or stiffness +	Pain +	Pain +
≥ 3 of the following:	≥ 3 of the following:	≥ 1 of the following:
- Bony swelling of ≥2 of the 10 selected joints*	- Age >50 years	- Age >50 years
- Bony swelling of ≥2 DIP joints	- Stiffness <30 minutes	- Stiffness <30 minutes
- <3 swollen MCP joints	- Crepitus	- Crepitus +
- Deformity of ≥1 of the 10 selected joints*	- Bony tenderness	Osteophytes
	- Bony enlargement	
	- No palpable warmth	

*Selected joints: bilateral DIP 2 and 3, PIP 2 and 3, bilateral CMC-1 joints

While some PROMs have been specifically developed to evaluate knee or hand OA disease burden, generic PROMs are also frequently used. However, to make optimal use of PROMs data, and interpret them correctly, benchmarks and tools to visually present the results are imperative. Moreover, the clinimetric properties of the instrument need to be kept in mind when selecting the most appropriate measure to use. To improve outcome measurement and facilitate instrument selection, the OMERACT (Outcome Measures in Rheumatology) developed the "OMERACT Filter", which consists of three pillars: truth, discrimination, and feasibility[16]. Selection of an instrument should start by defining the target domain and an evaluation of the applicability of the instrument to the present case (Truth). Also, it should be assessed if the instrument is practical to use, or if is burdensome to the patient (Feasibility). Furthermore, the instrument should be able to discriminate between groups of interest (Discrimination), and needs to produce consistent findings and be able to detect meaningful change over time[17,18].

The Knee injury and Osteoarthritis Outcome Score (KOOS) is an example of a disease-specific PROM that evaluates several aspects of disease burden in patients with knee complaints. The KOOS is a self-administered questionnaire and consists of five subscales, aimed to measure pain, symptoms, function in activities of daily living, function in sport and recreation activities, and quality of life[19]. The KOOS is an extension of the Western Ontario McMaster Universities (WOMAC) questionnaire, which consists of three dimensions: pain, stiffness and limitations in everyday activities. The WOMAC has been extensively evaluated for its clinimetric properties, and is found to be a valid, reliable and responsive measure. The WOMAC is copyrighted, however a request for use may be placed via the website[20]. In contrast to the WOMAC, the KOOS is free of use, and also considered valid, reliable and responsive to change[21].

In patients with hand OA, the Australian/Canadian Hand Osteoarthritis Index (AUSCAN) is frequently applied. The AUSCAN is disease-specific PROM developed using the WOMAC as a template, and similarly measures the domains pain, stiffness and function[22]. In addition, the Functional Index for Hand OsteoArthritis (FIHOA) is commonly used for the measurement of hand function in daily activities in patients with hand OA.

Another important domain of disease impact is the health-related quality of life (HRQoL), which is often assessed with the Short Form (SF)-36. The SF-36 is a generic, self-administered, quality of life measure. The SF-36 consists of 36 questions, providing scores for eight health domains, which may be summarised in the physical component summary (PCS) and the mental component summary (MSC) scores. Moreover, the use of norm-based scoring allows

comparison of HRQoL between different conditions and study populations[23].
Specific domains may also be measured with a visual analogue scale (VAS), which is typically a 0-100mm scale. The VAS is an often used measure for the quantification of pain, as well as to get a global assessment of the disease by the patient or physician.

Imaging
Structural OA can be measured with a variety of imaging modalities, of which radiography is the most frequently used in clinical practise and research. The Kellgren-Lawrence (KL) grading system is an often used scoring method, that allows for the assessment of OA severity with a single score from 0 to 4 for each joint. Grade 0 represents no OA, grade 1 doubtful OA, grade 2 definite, but minimal OA, grade 3 moderate OA, and grade 4 represents severe OA[24]. Example radiographs of the distal interphalangeal joint and the knee joint, representing the different grades of OA severity according to the KL system, are depicted in figure 1. In addition, the Osteoarthritis Research Society international (OARSI) developed an atlas to guide the evaluation of individual OA features[25], which has been updated by Altman and Gold[26]. The radiographic OA features included in the atlas differ slightly per joint, but include amongst others: osteophytes, joint space narrowing, malalignment, erosions, subchondral sclerosis and subchondral cysts. Following this atlas, osteophytes and joint space narrowing are scored from 0 to 3, while all other features are scored as absent or present[26].

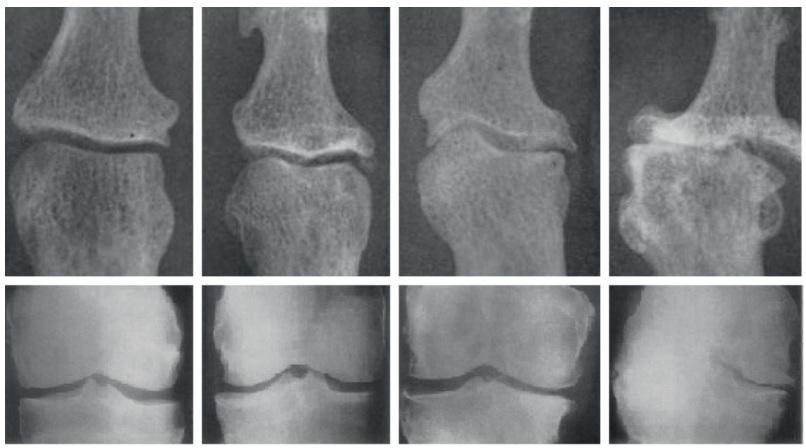

Figure 1. X-ray images of the distal interphalangeal joints (top row) and knee joint (bottom row), graded according to the Kellgren-Lawrence scoring system. *Figure by Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis and Cartilage 2007; 15: A1–56.*

Radiography is commonly used because of the ample experience with this imaging modality, the ease of use, accessibility, and relatively low costs. However, radiography is limited by the visualization of bony structures only. Therefore, magnetic resonance imaging (MRI) is increasingly used in research settings, which has the advantage of assessment of all affected joint tissues including soft tissues. To standardize the scoring of structural OA features on MRI, several scoring systems have been developed. For the assessment of knee OA, the Knee Osteoarthritis Scoring system (KOSS) may be used, which includes in addition to osteophytes and cartilaginous lesions many other OA-related features such as meniscal abnormalities, subchondral cysts, bone marrow lesions (BMLs), effusion and synovitis[27]. Using these features,

the criteria developed by Hunter et al.[28] can be used to determine the presence of structural knee OA. The Oslo Hand Osteoarthritis MRI score was the first scoring system developed to score hand OA features[29]. More recently, the OMERACT Hand OA MRI Scoring System (HOAMRIS) has been developed for the assessment of the distal and proximal interphalangeal joints[30]. Additionally, the OMERACT Thumb Base Osteoarthritis MRI Scoring System (TOMS) was developed, which can be used in a complementary fashion with the HOAMRIS[31].

Metabolic OA: the role of obesity

Obesity has been recognised many years ago as one of the major risk factors for the development of OA[32,33]. However, for long this association was solely ascribed to an increase in mechanical loading. In line with the hypotheses at that time, this association was explained by a cartilage-driven wear-and-tear process, with subsequent degradation of the cartilage[34]. Although mechanical stress due to increased body weight indeed plays a large role in OA risk[35], this does not fully explain the association between obesity and OA, which is apparent from the association between obesity and non-weightbearing joints such as the hand[36,37]. Moreover, OA is a disease of the entire joint. The osteoarthritic process is not only characterised by cartilage degradation, but also by subchondral bone remodelling, formation of osteophytes, degradation of ligaments and synovial inflammation (figure 2)[5,38]. Furthermore, detrimental changes to the periarticular muscles, nerves, bursa and local fat pads may also contribute to OA[38].

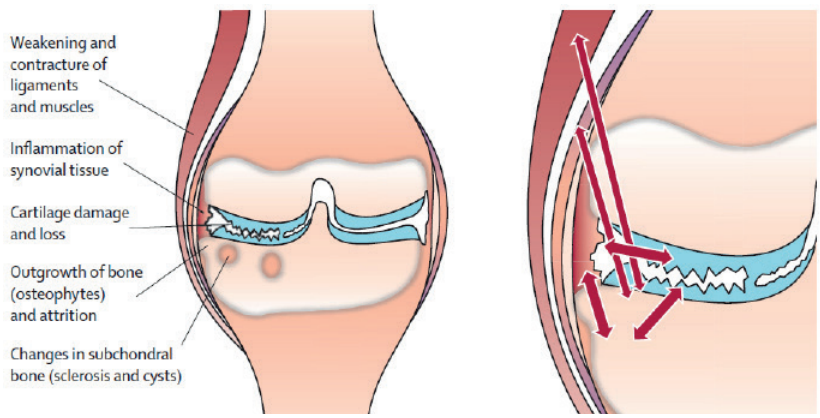

Figure 2. Schematic drawing of the osteoarthritic joint.
Osteoarthritis is a disease of the whole joint (left), and the osteoarthritis processes in the different joint tissues are tightly connected (right). *Figure by Bijlsma, Berenbaum and Lafeber. Osteoarthritis: an update with relevance for clinical practice. Lancet 2011 Jun 18;377(9783):2115-26.*

Obesity is associated with a broad spectrum of systemic effects, which likely are involved in OA, especially in non-weightbearing joints. Obesity is associated with a chronic low-grade inflammation, sometimes also referred to as “metaflammation”, what may lead to metabolic dysregulation and the metabolic syndrome[39]. Components of the metabolic syndrome, such as hypertension, dyslipidaemia and hyperglycaemia, have been previously studied as possible players in OA (figure 3)[40]. However, conflicting results have been reported[41–44]. Furthermore, soluble mediators released by adipose tissue, such as adipokines[45,46] and lipids, could mediate the systemic effects of obesity.

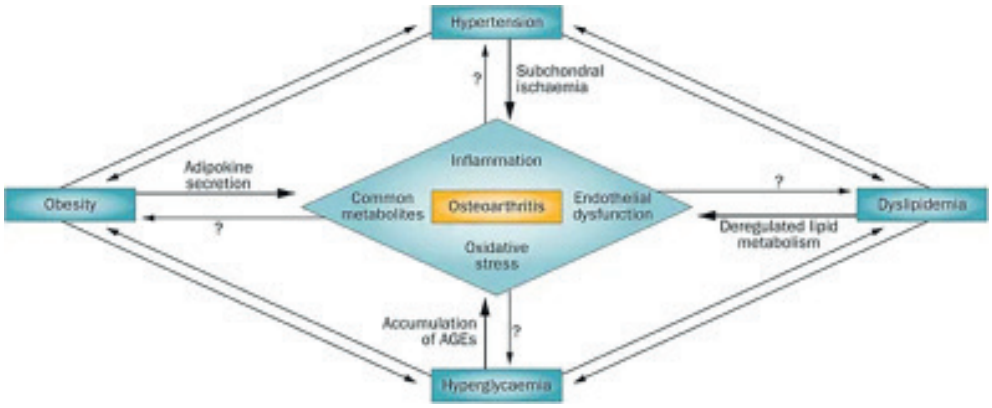

Figure 3. The metabolic syndrome and its components may be associated with osteoarthritis.
AGEs = advanced glycation end-products. *Figure by Zhuo, Yang, Chen and Wang. Metabolic syndrome meets osteoarthritis. Nat Rev Rheumatol. 2012 Dec;8(12):729-3*

Dysregulation of lipid metabolism

Obesity and excessive nutrient intake may exceed the adipose tissues' lipid storage capacity. Subsequently, circulating fatty acid levels will increase, accompanied by ectopic lipid accumulation. The resulting systemic lipotoxicity may be a key driver of the obesity-related metaflammation[47]. Not just the quantity of fat intake plays a role, but also the type of fat may be important[48]. The term lipids comprises many different molecules, such as higher order lipids including, but not limited to, sterols, sphingomyelins and phospholipids, as well as free fatty acids and downstream lipid metabolites. Fatty acids can be categorised depending on their length and degree of saturation into the commonly used subclasses of saturated fatty acids, monounsaturated fatty acids and polyunsaturated fatty acids.

The different fatty acids and lipid metabolites likely have distinct effects on inflammation. For example, while saturated fatty acids and omega-6 polyunsaturated fatty acids have a pro-inflammatory profile, omega-3 polyunsaturated fatty acids have anti-inflammatory effects *in vitro*[49]. These opposing effects have also been observed in preclinical OA research. Saturated fatty acids and omega-6 polyunsaturated fatty acids increased prostaglandin release and upregulate gene expression related to apoptosis and cartilage degradation[50,51], while omega-3 polyunsaturated fatty acids reduced cartilage proteinase mRNA levels and inflammatory cytokines in chondrocyte cultures[52]. However, human epidemiological studies on the association of fatty acids and other lipids on OA are few, inconclusive, and limited to structural knee and hip OA[53–55].

Inflammation

Despite that not always all of the classical clinical features of inflammation, *rubor, calor, dolor* and *tumour*, can be observed in OA, a chronic, low-grade local and systemic inflammation is present. The role of inflammation in the development of OA has only been given full consideration since the last decades, but is now accepted as having a pivotal role in OA pathogenesis. This paradigm shift occurred following advances in molecular biology, showing the involvement of soluble inflammatory mediators.

Serum levels of various proinflammatory cytokines are increased in OA patients, which is believed to be produced by inflamed synovium and activated chondrocytes. Breakdown products of the extracellular matrix may act as damage-associated molecular patterns (DAMPs). DAMPs, as well as intracellular proteins, or "alarmins" , may activate the innate immune system, resulting in upregulation of proinflammatory cytokines and catabolic mediators such as metalloproteinases (MMPs) and disintegrin and metalloproteinase with thrombospondin-1 domains (ADAMTS)[56–58]. In particular, cytokines from the interleukin (IL) family, as well as tumour necrosis factor alpha (TNFα) have been extensively investigated[59]. In addition to stimulating MMPs and ADAMTS proteinases, these cytokines stimulate the expression of COX-2, increasing the synthesis of prostaglandins, and upregulate the production of nitric oxide. Moreover, IL-1β and TNFα may induce other proinflammatory cytokines[58], further enhancing the inflammatory response.

Additionally, the involvement of inflammation is overtly apparent from imaging studies. Inflammatory signs such as gray-scale synovitis and power Doppler signals on ultrasonography[60,61], as well as synovitis and BMLs on MRI scans[62], are often present in patients with OA. Importantly, structural inflammatory features are not merely a reflection of damage but likely contribute to the OA process. Inflammatory features detected by ultrasound, were associated with the development of joint erosions in patients with hand OA[63]. In addition, in patients with knee OA synovitis and BMLs have been associated with cartilage deterioration[64,65]. Moreover, synovial inflammation and BMLs were associated with commonly reported symptoms such as pain in both hand and knee OA[60–62,66].

Treatment

There is a high unmet need for disease modifying drugs for the treatment of OA. Current guidelines recommend, in addition to non-pharmacological interventions such as (supervised) exercise and self-management programs, the use of oral or topical nonsteroidal anti-inflammatory drugs[67]. In addition, intra-articular injections with glucocorticoids may be considered[67,68].

At the moment, treatment options are limited to approaches aimed to reduce symptoms. The role of inflammation in OA and its association with structural progression and clinical outcomes has piqued an interest for targeting inflammation in therapeutic research. However, research investigating the use of biologics have been disappointing so far[69]. Possibly, potential treatment effects have been obscured by too short follow-up in the studies, small cohort sizes[70], or the inclusion of a heterogeneous study population. Conceivably, treatment effects may be observed in studies with a sufficiently long study duration, as OA often progresses slowly. Alternatively, study designs allowing the selection of patients with a high likelihood of fast progression or evident inflammatory disease may show different outcomes. In addition, the majority of available findings results from studies in patients with knee OA, and few studies have investigate soluble biomarkers in hand OA[70]. Another explanation may be that previous studies have targeted systemic effects with a relatively small role in OA pathogenesis. Increasing our understanding of OA pathogenesis may reveal potential new systemic treatment targets.

Aim of thesis

This thesis aimed to:

1. Increase our understanding of the role of inflammation-related systemic factors in the aetiology of OA, by focusing on the association of lipids with hand and knee OA.
2. Assess the disease burden associated with hand and knee OA in the general population as well as in secondary care patient populations, with a specific focus on improvement of the interpretation of PROMs.

Study populations

The research described in this thesis has been performed with data of several study populations, which enabled us to study OA in various stages of the disease, in differing settings, as well as multiple OA phenotypes. The main characteristics of the included study populations are briefly introduced below.

NEO study

The Netherlands Epidemiology of Obesity (NEO) study is a prospective population-based cohort study, which was designed to investigate pathways that lead to obesity-related diseases and conditions. In this thesis, we performed cross-sectional analyses of baseline measurements, for which individuals between 45 and 65 years of age were recruited between 2008 and 2012. Prior to the study visit, participants completed questionnaires on demographic and clinical information. The HRQoL was measured with the SF-36. In addition, participants completed the KOOS[19] and the AUSCAN[71], giving insight in OA specific disease burden of the knees and hands, respectively. At the study centre, blood samples were obtained after an overnight fast. Subsequently, a standardised liquid mixed-meal was consumed, and after 150 minutes postprandial blood samples were drawn. These blood samples were analysed for the quantification of lipid and metabolite measures. Furthermore, an extensive physical examination was performed, including measurement of body weight and total body fat by bioelectrical impedance analysis. In addition, a standardised examination of the hands and knees allowed us to define a clinical hand and knee phenotype according to the ACR classification criteria[9,10]. A subset of the population underwent an MRI of the right knee, on which OA features were scored using the KOSS[27], and a structural knee phenotype was defined according to modified criteria by Hunter et al.[28]. We investigated the association of several obesity-related factors with clinical hand and knee OA, as well as structural knee OA, in the general middle-aged Dutch population. In addition, we developed percentile curves for the KOOS questionnaire, to provide benchmarks to aid interpretation of KOOS subscale scores, and investigated differences in HRQoL of participants with and without hand OA.

HOSTAS study

The Hand OSTeoArthritis in Secondary care (HOSTAS) is an observational cohort study aimed to investigate determinants of disease outcome and the utility of clinimetric instruments in patients with primary hand OA. HOSTAS included consecutive patients from the LUMC rheumatology outpatient clinic between 2009 and 2015, based on the rheumatologist's diagnosis of primary hand OA and absence of other rheumatic diseases or secondary OA. The LUMC serves both as a secondary and tertiary referral centre for rheumatic diseases, enabling

inclusion of patients with primary hand OA in all disease stages. In the HOSTAS study, we assessed HRQoL in patients with primary hand OA, and compared differences with patients with concurrent knee OA. Moreover, we made an indirect comparison with individuals with hand OA in the general population (NEO study).

HOPE study

The Hand Osteoarthritis Prednisolone Efficacy (HOPE) study is a double-blind, randomised placebo-controlled trial, designed to investigate the efficacy and safety of short-term prednisolone treatment in patients with symptomatic, inflammatory hand OA. Patients were randomly assigned (1:1) to receive 10mg prednisolone or placebo daily for six weeks, followed by a two-week tapering schedule and six-week follow-up without study medication. Detailed description of the HOPE study, including the primary endpoint results, can be read elsewhere[72]. Briefly, patients with symptomatic hand OA, fulfilling the ACR criteria[9], and signs of inflammation on ultrasound were included. At baseline and week 6, patients filled in a visual analogue scale (VAS) for finger pain and VAS global assessment on a 0-100mm scale, and the AUSCAN pain and function subscales. At week 6, fulfilment of the OMERACT-OARSI responder criteria was assessed[73]. Blood samples were obtained non-fasted at baseline, 6 and 14 weeks, for the measurement of a large array of higher order lipids and fatty acids with the exploratory lipidomics platform Lipidyzer™, and measurement of oxylipins with an in-house developed LC-MS/MS platform. We developed a standardised procedure for the pre-processing of Lipidyzer™ data, and compared the reproducibility of Lipidyzer™ measurements over 6 weeks' time in commonly used plasma samples, with potentially more stable erythrocyte samples. In addition, we investigated the predictive value of baseline lipid levels for the response to prednisolone treatment after 6 weeks. Furthermore, we assessed if treatment with prednisolone alters lipid concentrations.

APPROACH study

The Applied Public-Private Research enabling OsteoArthritis Clinical Headway (APPROACH) is an exploratory, 2-year, prospective multi-centre cohort study, which started in 2018. The APPROACH study included patients with knee OA fulfilling the clinical ACR criteria[10] from five hospitals in four European countries: The Netherlands (University Medical Centre Utrecht, Leiden University Medical Center), Norway (Diakonhjemmet Hospital, Oslo), France (Assistance Public Hôpitaux de Paris) and Spain (Servizo Galego de Saúde, A Coruña). Patients were selected using machine learning models, developed on data from a previous OA cohort, to display a high likelihood of structural and/or pain progression. At baseline, participants completed an extensive booklet of questionnaires, among which the KOOS and the FIHOA[74,75] for assessment of knee and hand OA-specific disease burden, respectively. Radiographic knee and hand OA was measured according to the KL grading system[24]. Blood samples were drawn fasted, and plasma samples were used for measurements with the Lipidyzer™ platform, and measurement of oxylipin metabolites with an in-house developed LC-MS/MS platform. The research described in this thesis used baseline measurements to investigate the association of higher order lipid levels and downstream lipid metabolites, with radiographic knee and hand OA severity, as well as knee and hand pain and function.

LOAS study

The Longitudinal Leiden Orthopeadics Outcomes of Osteo-Arthritis study (LOAS) started in 2012, and is an ongoing, multi-centre, longitudinal prospective cohort study designed to

determine long-term outcomes of total knee arthroplasty (TKA) and total hip arthroplasty. Patients scheduled for primary or revision arthroplasty were recruited from seven hospitals in the Netherlands, as described previously[76]. For the present analyses, we aimed to validate the KOOS percentile curves developed in the general population (NEO study). Therefore, we included patients undergoing primary TKA between 45 and 65 years of age. KOOS subscale scores were obtained preoperatively and 6, 12 and 24 months after TKA. Preoperative knee radiographs were assessed according to the KL grading system[24] in a subset of patients (37%). We plotted the median population-level KOOS scores on the population-based KOOS percentile curves.

Outline of thesis

Part 1 – Lipids and other metabolic factors in osteoarthritis
In part one we aimed to increase our insight in OA pathogenesis, by investigating the association between inflammation-related systemic factors and OA, with a specific focus on the association of lipids with hand and knee OA.

Firstly, **chapter 2** summarizes the available preclinical and clinical evidence on the association between fatty acids and OA, showing clear gaps in our knowledge regarding fatty acids in OA. Observational human study results are few, and limited to structural OA. To advance this knowledge, we investigated the association between plasma fatty acids and clinical hand and knee OA, as well as structural knee OA, in the NEO study in **chapter 3**. In the human body, the majority of fatty acids is bound to carrier molecules to form higher order lipids species. In addition, fatty acids are metabolised to bioactive oxylipins. Lipidomics comprises the measurement of lipid species and their metabolites, and may be valuable in understanding the pathogenesis of diseases, as well as to predict treatment responses. However, biomarker discovery starts by being able to obtain reliable and reproducible measurements. Therefore, in **chapter 4** we investigated the reproducibility of lipid measurements in different sample types obtained by the standardised and commercially available Lipidyzer™ platform. Furthermore, we present a standardised method to pre-process the Lipidyzer™ data, to guide future biomarker research. In **chapter 5** we described the association of lipidomics with the severity of radiographic hand and knee OA, as well as hand and knee pain, using data from the APPROACH study. In addition, we explored the use of lipidomics for the prediction of prednisolone treatment response in **chapter 6**, and the influence of prednisolone treatment on lipid levels in **chapter 7**, in patients with inflammatory hand OA.

Lipid dysregulation also affects other conditions, such as cardiovascular disease. Moreover, associations between cardiovascular disease and OA have previously been reported. However, to which extent cardiovascular disease markers may explain the well-known association between obesity and OA, has not been investigated. Therefore, in **chapter 8** we assessed if the previously established association between obesity and OA is mediated by blood pressure, arterial stiffness and subclinical atherosclerosis.

Part 2 – Osteoarthritis disease burden

In part two we focussed on several PROMs, with a specific interest for epidemiological and methodological aspects. Disease burden can be measured in many ways, among which are quality of life, pain and function.

In **chapter 9** we investigated the association between OA and HRQoL in different study populations with hand OA. Firstly, we assessed the impact of hand OA in a population-based cohort, the NEO study. Furthermore, we examined this question in a secondary and tertiary care cohort with primary hand OA patients, the HOSTAS study.

OA symptoms, such as pain and functional impairment, may influence a patients' physical activity levels. Since physical activity is known to positivity influence disease burden, it presents a potential target for intervention. Therefore, it is essential to have insight in the relation between OA and physical activity. In **chapter** 10, we investigated the association of physical activity levels with clinical and structural knee OA, as well as the association between physical activity and several PROMs.

As a lack of benchmarks hinders adequate interpretation of PROMs, we explored in **chapter 11** factors that may influence KOOS scores, and developed percentile curves in the general Dutch population. Subsequently, we investigated the applicability of these curves by applying them on real-world clinical data of patients undergoing TKA included in the LOAS study, which is described in **chapter 12**.

To conclude, a summary and general discussion of the findings of this thesis, along with a research agenda for future investigations is provided in **chapter 13**. **Chapter 14** summarizes the main points raised in this thesis in Dutch.

References

1 OARSI White Paper- OA as a Serious Disease. Osteoarthritis Research Society International. 2018; published online April 16. https://www.oarsi.org/education/oarsi-resources/oarsi-white-paper-oa-serious-disease (accessed April 9, 2020).

2 Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. *Nat Rev Rheumatol* 2014; 10: 437–41.

3 Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet* 2019; 393: 1745–59.

4 GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392: 1789–858.

5 Bijlsma JWJ, Berenbaum F, Lafeber FPJG. Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011; 377: 2115–26.

6 Eysink PED, Poos M, Gijsen R, Kommer GJ, van Gool CH. Epidemiologische data van Ziekten van het botspierstelsel en bindweefsel: Achtergrondrapport voor Programma Zinnige Zorg. *Epidemiological data of disorders of the musculoskeletal system and connective tissue : Background report from 'Zinnige Zorg' Programme* 2019; published online Oct 3. DOI:10.21945/RIVM-2019-0180.

7 Dell'Isola A, Allan R, Smith SL, Marreiros SSP, Steultjens M. Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. *BMC Musculoskelet Disord* 2016; 17: 425.

8 Sellam J, Berenbaum F. Is osteoarthritis a metabolic disease? *Joint Bone Spine* 2013; 80: 568–73.

9 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.

10 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.

11 Altman RD. Criteria for classification of clinical osteoarthritis. *J Rheumatol Suppl* 1991; 27: 10–2.

12 Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. *J Rheumatol* 2000; 27: 1513–7.

13 Yang LY, Manhas DS, Howard AF, Olson RA. Patient-reported outcome use in oncology: a systematic review of the impact on patient-clinician communication. *Support Care Cancer* 2018; 26: 41–60.

14 Appleby J, Poteliakhoff E, Shah K, Devlin N. Using patient-reported outcome measures to estimate cost-effectiveness of hip replacements in English hospitals. *J R Soc Med* 2013; 106: 323–31.

15 Devlin NJ, Appleby J. Getting the most out of PROMs: putting health outcomes at the heart of NHS decision-making. London: King's Fund, 2010.

16 Boers M, Brooks P, Strand CV, Tugwell P. The OMERACT filter for Outcome Measures in Rheumatology. *J Rheumatol* 1998; 25: 198–9.

17 Kianifard F. Evaluation of Clinimetric Scales: Basic Principles and Methods. *Journal of the Royal Statistical Society Series D (The Statistician)* 1994; 43: 475–82.

18 de Vet HCW, Terwee CB, Bouter LM. Current challenges in clinimetrics. *J Clin Epidemiol* 2003; 56: 1137–41.

19 Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther* 1998; 28: 88–96.

20 WOMAC Osteoarthritis Index- WOMAC 3.1 - Knee and Hip Osteoarthritis. http://www.womac.com/womac/index.htm (accessed April 30, 2020).

21 Knee injury and Osteoarthritis Outcome Score. http://www.koos.nu/ (accessed April 30, 2020).

22 Bellamy N, Campbell J, Haraoui B, *et al.* Dimensionality and clinical importance of pain and disability in hand osteoarthritis: Development of the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index. *Osteoarthr Cartil* 2002; 10: 855–62.

23 Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30: 473–83.

24 Kellgren JH, Lawrence JS. Radiological Assessment of Osteo-Arthrosis. *Annals of the Rheumatic Diseases* 1957; 16: 494–502.

25 Altman RD, Hochberg M, Murphy WA, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. *Osteoarthr Cartil* 1995; 3 Suppl A: 3–70.

26 Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis and Cartilage* 2007; 15: A1–56.

27 Kornaat PR, Ceulemans RYT, Kroon HM, *et al.* MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS)--inter-observer and intra-observer reproducibility of a compartment-based scoring system. *Skeletal Radiol* 2005; 34: 95–102.

28 Hunter DJ, Arden N, Conaghan PG, *et al.* Definition of osteoarthritis on MRI: results of a Delphi exercise. *Osteoarthritis Cartilage* 2011; 19: 963–9.

29 Haugen IK, Lillegraven S, Slatkowsky-Christensen B, *et al.* Hand osteoarthritis and MRI: development and first validation step of the proposed Oslo Hand Osteoarthritis MRI score. *Annals of the Rheumatic Diseases* 2011; 70: 1033–8.

30 Haugen IK, Ostergaard M, Eshed I, *et al.* Iterative development and reliability of the OMERACT hand osteoarthritis MRI scoring system. *J Rheumatol*

2014; 41: 386–91.
31 Kroon FPB, Conaghan PG, Foltz V, *et al.* Development and Reliability of the OMERACT Thumb Base Osteoarthritis Magnetic Resonance Imaging Scoring System. *J Rheumatol* 2017; 44: 1694–8.
32 Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham Study. *Ann Intern Med* 1988; 109: 18–24.
33 Davis MA, Ettinger WH, Neuhaus JM. Obesity and osteoarthritis of the knee: evidence from the National Health and Nutrition Examination Survey (NHANES I). *Semin Arthritis Rheum* 1990; 20: 34–41.
34 Radin EL, Paul IL, Rose RM. Role of mechanical factors in pathogenesis of primary osteoarthritis. *Lancet* 1972; 1: 519–22.
35 Visser AW, de Mutsert R, le Cessie S, *et al.* The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. *Ann Rheum Dis* 2015; 74: 1842–7.
36 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.
37 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.
38 Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum* 2012; 64: 1697–707.
39 Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. *Nature* 2017; 542: 177–85.
40 Zhuo Q, Yang W, Chen J, Wang Y. Metabolic syndrome meets osteoarthritis. *Nat Rev Rheumatol* 2012; 8: 729–37.
41 Monira Hussain S, Wang Y, Cicuttini FM, *et al.* Incidence of total knee and hip replacement for osteoarthritis in relation to the metabolic syndrome and its components: a prospective cohort study. *Semin Arthritis Rheum* 2014; 43: 429–36.
42 Yoshimura N, Muraki S, Oka H, *et al.* Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. *Osteoarthr Cartil* 2012; 20: 1217–26.
43 Dahaghin S, Bierma-Zeinstra SMA, Koes BW, Hazes JMW, Pols H a. P. Do metabolic factors add to the effect of overweight on hand osteoarthritis? The Rotterdam Study. *Ann Rheum Dis* 2007; 66: 916–20.
44 Garessus EDG, de Mutsert R, Visser AW, Rosendaal FR, Kloppenburg M. No association between impaired glucose metabolism and osteoarthritis. *Osteoarthr Cartil* 2016; 24: 1541–7.
45 Richter M, Trzeciak T, Owecki M, Pucher A, Kaczmarczyk J. The role of adipocytokines in the pathogenesis of knee joint osteoarthritis. *Int Orthop* 2015; 39: 1211–7.
46 Kroon FPB, Veenbrink AI, de Mutsert R, *et al.* The role of leptin and adiponectin as mediators in the relationship between adiposity and hand and knee osteoarthritis. *Osteoarthr Cartil* 2019; 27: 1761–7.
47 Ertunc ME, Hotamisligil GS. Lipid signaling and lipotoxicity in metaflammation: indications for metabolic disease pathogenesis and treatment. *J Lipid Res* 2016; 57: 2099–114.
48 Cordain L, Eaton SB, Sebastian A, *et al.* Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr* 2005; 81: 341–54.
49 Bagga D, Wang L, Farias-Eisner R, Glaspy JA, Reddy ST. Differential effects of prostaglandin derived from omega-6 and omega-3 polyunsaturated fatty acids on COX-2 expression and IL-6 secretion. *Proc Natl Acad Sci USA* 2003; 100: 1751–6.
50 Bastiaansen-Jenniskens YM, Siawash M, van de Lest CHA, *et al.* Monounsaturated and Saturated, but Not n-6 Polyunsaturated Fatty Acids Decrease Cartilage Destruction under Inflammatory Conditions: A Preliminary Study. *Cartilage* 2013; 4: 321–8.
51 Alvarez-Garcia O, Rogers NH, Smith RG, Lotz MK. Palmitate has proapoptotic and proinflammatory effects on articular cartilage and synergizes with interleukin-1. *Arthritis Rheumatol* 2014; 66: 1779–88.
52 Zainal Z, Longman AJ, Hurst S, *et al.* Relative efficacies of omega-3 polyunsaturated fatty acids in reducing expression of key proteins in a model system for studying osteoarthritis. *Osteoarthr Cartil* 2009; 17: 896–905.
53 Baker KR, Matthan NR, Lichtenstein AH, *et al.* Association of plasma n-6 and n-3 polyunsaturated fatty acids with synovitis in the knee: the MOST study. *Osteoarthr Cartil* 2012; 20: 382–7.
54 Hill CL, March LM, Aitken D, *et al.* Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose. *Ann Rheum Dis* 2016; 75: 23–9.
55 Castro-Perez JM, Kamphorst J, DeGroot J, *et al.* Comprehensive LC-MS E lipidomic analysis using a shotgun approach and its application to biomarker detection and identification in osteoarthritis patients. *J Proteome Res* 2010; 9: 2377–89.
56 Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. *Ther Adv Musculoskelet Dis* 2013; 5: 77–94.
57 Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). *Osteoarthr Cartil* 2013; 21: 16–21.
58 Goldring MB, Otero M. Inflammation in osteoarthritis. *Curr Opin Rheumatol* 2011; 23: 471–8.
59 Rahmati M, Mobasheri A, Mozafari M. Inflammatory mediators in osteoarthritis: A critical review of the state-of-the-art, current prospects, and future challenges. *Bone* 2016; 85: 81–90.
60 Kortekaas MC, Kwok W-Y, Reijnierse M, Watt I, Huizinga TWJ, Kloppenburg M. Pain in hand osteoarthritis is associated with inflammation: the

value of ultrasound. *Ann Rheum Dis* 2010; 69: 1367–9.
61 Keen HI, Wakefield RJ, Grainger AJ, Hensor EMA, Emery P, Conaghan PG. An ultrasonographic study of osteoarthritis of the hand: synovitis and its relationship to structural pathology and symptoms. *Arthritis Rheum* 2008; 59: 1756–63.
62 Haugen IK, Christensen BS, Boyesen P, Sesseng S, van der Heijde D, Kvien TK. Increasing synovitis and bone marrow lesions are associated with incident joint tenderness in hand osteoarthritis. *Annals of the Rheumatic Diseases* 2016; 75: 702–8.
63 Kortekaas MC, Kwok W-Y, Reijnierse M, Stijnen T, Kloppenburg M. Brief Report: Association of Inflammation With Development of Erosions in Patients With Hand Osteoarthritis: A Prospective Ultrasonography Study. *Arthritis & Rheumatology (Hoboken, NJ)* 2016; 68: 392–7.
64 de Lange-Brokaar BJ, Bijsterbosch J, Kornaat PR, *et al.* Radiographic progression of knee osteoarthritis is associated with MRI abnormalities in both the patellofemoral and tibiofemoral joint. *Osteoarthritis Cartilage* 2016; 24: 473–9.
65 Roemer FW, Guermazi A, Javaid MK, *et al.* Change in MRI-detected subchondral bone marrow lesions is associated with cartilage loss: the MOST Study. A longitudinal multicentre study of knee osteoarthritis. *Ann Rheum Dis* 2009; 68: 1461–5.
66 Torres L, Dunlop DD, Peterfy C, *et al.* The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. *Osteoarthritis and Cartilage* 2006; 14: 1033–40.
67 Kolasinski SL, Neogi T, Hochberg MC, *et al.* 2019 American College of Rheumatology/ Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Care Res (Hoboken)* 2020; 72: 149–62.
68 Kloppenburg M, Kroon FP, Blanco FJ, *et al.* 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Ann Rheum Dis* 2019; 78: 16–24.
69 Chevalier X, Eymard F, Richette P. Biologic agents in osteoarthritis: hopes and disappointments. *Nat Rev Rheumatol* 2013; 9: 400–10.
70 van Spil WE, Szilagyi IA. Osteoarthritis year in review 2019: biomarkers (biochemical markers). *Osteoarthr Cartil* 2020; 28: 296–315.
71 Bellamy N, Campbell J, Haraoui B, *et al.* Dimensionality and clinical importance of pain and disability in hand osteoarthritis: Development of the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index. *Osteoarthr Cartil* 2002; 10: 855–62.
72 Kroon FPB, Kortekaas MC, Boonen A, *et al.* Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial. *The Lancet* 2019; 394: 1993–2001.
73 Pham T, van der Heijde D, Altman RD, *et al.* OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthr Cartil* 2004; 12: 389–99.
74 Wittoek R, Vander Cruyssen B, Maheu E, Verbruggen G. Cross-cultural adaptation of the Dutch version of the Functional Index for Hand Osteoarthritis (FIHOA) and a study on its construct validity. *Osteoarthritis and Cartilage* 2009; 17: 607–12.
75 Dreiser RL, Maheu E, Guillou GB, Caspard H, Grouin JM. Validation of an algofunctional index for osteoarthritis of the hand. *Rev Rhum Engl Ed* 1995; 62: 43S-53S.
76 Leichtenberg CS, Meesters JJL, Kroon HM, *et al.* No associations between self-reported knee joint instability and radiographic features in knee osteoarthritis patients prior to Total Knee Arthroplasty: A cross-sectional analysis of the Longitudinal Leiden Orthopaedics Outcomes of Osteo-Arthritis study (LOAS) data. *The Knee* 2017; 24: 816–23.
77 Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, *et al.* Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007; 146: 406–15.