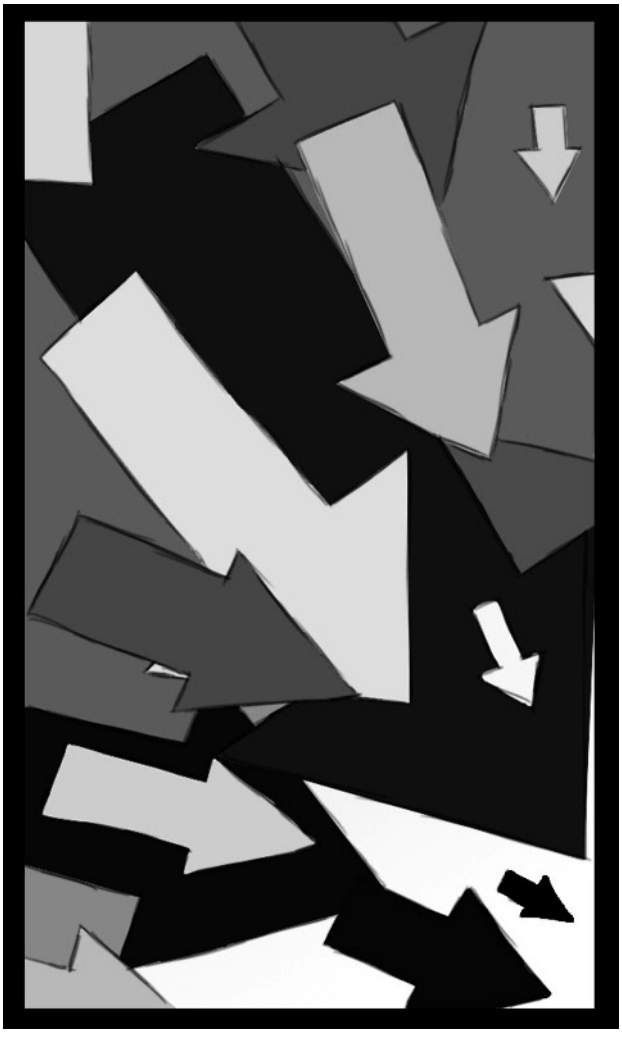
Chapter 1

Introduction to osteoarthritis and its prominent risk factor obesity



1. 1. History

Osteoarthritis (OA) is perhaps the oldest disease of humanity. Throughout history, a condition where cartilage loss presents together with bone features such as osteophytes have been described.[1] The pathology was found in the fossils of our early ancestor Neanderthal man from La-Chapelle-aux-Saints (who lived about 500.000 years B.C.) and seen regularly on radiographs of Egyptian mummies (who lived about more than 3000 years ago). Several terminologies have been used to describe this disease: osteoarthrosis, degenerative joint disease, arthrosis deformans and osteoarthritis. However, it is not until 1890 that the term 'osteoarthritis' is used in its modern sense for the first time by A.E. Garrod.[2]

1. 2. Osteoarthritis is a disorder of the joint

OA should be considered as a joint disorder, which could result from problems in cartilage, subchondral bone, synovium and other tissues in and around the joint.[3] The main reason why someone seeks medical attention for OA is pain related to use.[4] The holy grail in OA research is to find out whether and how this pain originates from the joint structures that are damaged in OA. Other clinical presentations of OA are short-lasting inactivity stiffness, disability, and cracking of joints (crepitus).[3]

OA can be defined by pathology or symptoms.[5] The main method to assess the OA pathology is by using radiographs of the joint. On radiographs, changes in joint structure associated with OA can be visualized. Yet, the changes that can be seen are limited to changes in cartilage and bone. The change in cartilage can only be seen indirectly, and is estimated as joint space narrowing (JSN).[3] For epidemiological studies, the Kellgren and Lawrence (K&L) grading system (table 1.1 and appendix C.1) is the most frequently used radiographic system.[6] To define OA for the knee and hip joint, K&L score is often combined with the presence of clinical findings. This combination is often used by authors of epidemiological studies, such as the American College of Rheumatology (ACR) criteria (table 1.2).

Table 1.1 The Kellgren and Lawrence grading system of osteoarthritis.[7]

Grade		Findings
0	None	No features of OA
1	Doubtful	Minute osteophyte, doubtful significance
2	Minimal	Definite osteophyte, unimpaired joint space
3	Moderate	Moderate diminution of joint space
4	Severe	Joint space greatly impaired with sclerosis of subchondral bone

Table 1.2. American College of Rheumatology criteria for OA of the hand, hip and knee.[7]

Sites	Criteria	OA is present if items present are
Hand	Clinical 1. Hand pain, aching or stiffness for most days or prior month 2. Hard tissue enlargement of two or more of ten selected hand joints 3. MCP swelling in two or more joints 4. Hard tissue enlargement of two or more DIP joints 5. Deformity of one or more of ten selected hand joints	1, 2, 3, 4 or 1, 2, 3, 5
Hip	Clinical and radiographic 1. Hip pain for most days of the prior month 2. Erythrocyte sedimentation rate ≤20 mm/h 3. Radiograph femoral and/or acetabular osteophytes 4. Radiograph hip joint-space narrowing	1, 2, 3 or 1, 2, 4 or 1, 3, 4
Knee	Clinical 1. Knee pain for most days of prior month 2. Crepitus on active joint motion 3. Morning stiffness ≤30 minutes in duration 4. Age≥38 years 5. Bony enlargement of the knee on examination Clinical and radiographic 1. Knee pain for most days of prior month 2. Osteophytes at joint margin (radiograph) 3. Synovial fluid typical of OA (laboratory) 4. Age≥40 years 5. Morning stiffness ≤ 30 minutes 6. Crepitus on active joint motion	1,2,3,4 or 1,2,5 or 1,4,5

1.3. Epidemiology

The prevalence of OA varies and depends on the definition used (purely radiographic criteria versus based on clinical findings). In a large population-based radiographic survey in The Netherlands, more than 15 % of men and women older than 60 years

had knee OA, and more than 50 % had hand OA of the distal interphalangeal joint (figure 1.1).[8] It is interesting to compare these data with data from autopsy studies in the 70's that showed that the prevalence of cartilaginous erosions and underlying bony change in the knee ranged between 17 (advanced) to 70 % (mild) of the population who died around the age of 70.[9] When OA is defined purely by history, the prevalence of OA on any site as estimated in Tecumseh Community Health Study in the USA was 17 % in men and 30 % in women older than 60 years.[10]

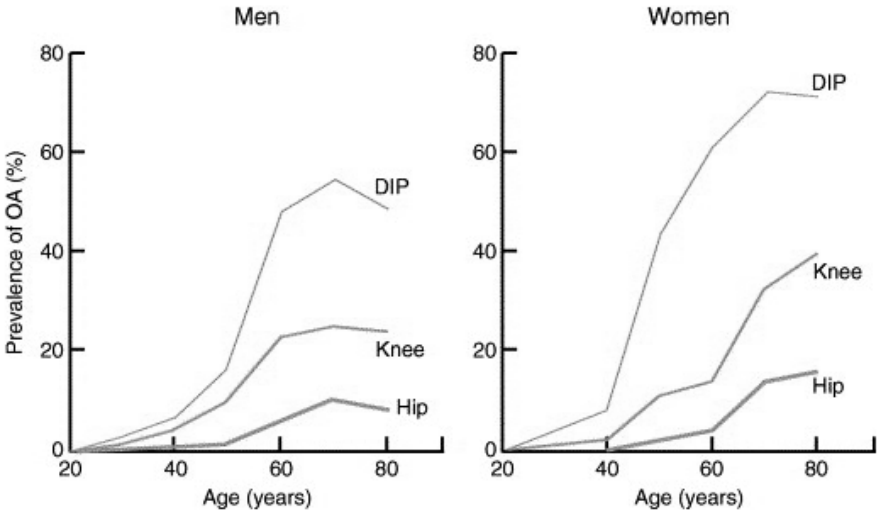


Figure 1.1 Prevalence of radiographic osteoarthritis affecting distal interphalangeal (DIP), knee and hip joints in Zoetermeer study. (From: Van Saase et al. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Annals of Rheumatic Disease 1989).[11]

1.4. Risk factors of OA

Since different joints affected by OA have different biomechanics and different types of injuries, the risk factors of OA are not uniform across the joints. In general, several factors are frequently shown in OA studies to increase the risk of occurrence (i.e. incidence) of OA: obesity, genetic predisposition, malalignment, race, hormonal status, joint trauma, overuse, joint immobilization, age, and gender.[12]

Many of these risk factors for OA development are also recognized as risk factors for the progression of OA.[5] The observation that risk factors for occurrence of OA are not always risk factors for worsening (i.e. progressive) of OA is probably due to limitations in epidemiologic studies.[13] Among the limitations are: conditioning on preexisting knee OA, patients loss to follow-up in observational studies, bias on measurement of effect and ceiling effect.

1.5. Pathophysiology of OA

Each risk factor (A, B, C, D, E, F or G in figure 1.2) could be considered as a component cause in the causal pie model. Combination of the component causes is a sufficient cause. A sufficient cause is sufficient to give a start to a series of processes that are considered as pathophysiological process. Theoretically, there is more than one sufficient cause.

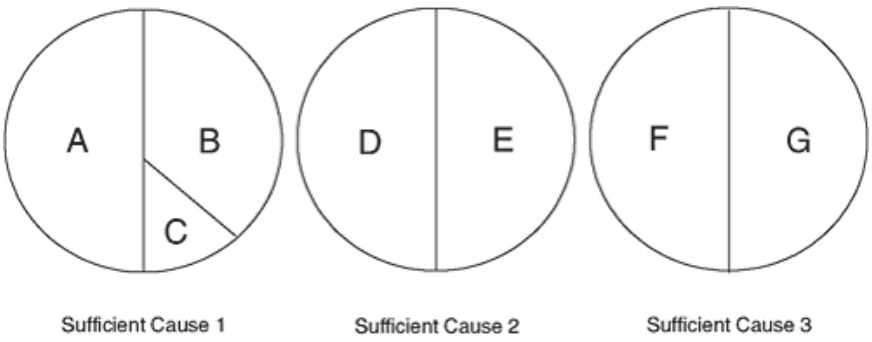


Figure 1.2 Causal pie model. A, B, C, D, E, F, and G are component causes (risk factors). The combination of risk factors could give a sufficient cause to start a disease (osteoarthritis). There is more than one sufficient cause.

In OA, we can consider a synovial joint as having three different levels: the level below cartilage (subchondral bone), at the level of cartilage and the level above cartilage (synovium) (figure 1.3). The sufficient cause can start from any of these levels and the pathophysiological sequence could be considered as a vicious circle (figure 1.4).

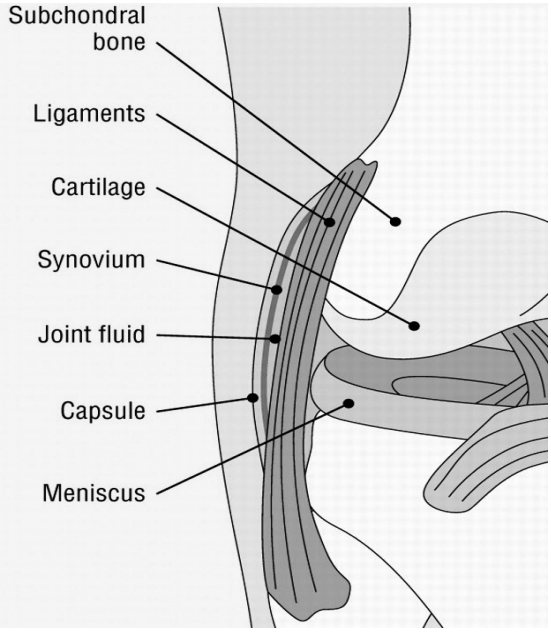


Figure 1.3 Anatomy of a synovial joint (From: Hunter and Felson. Osteoarthritis. BMJ. 2006).[15]

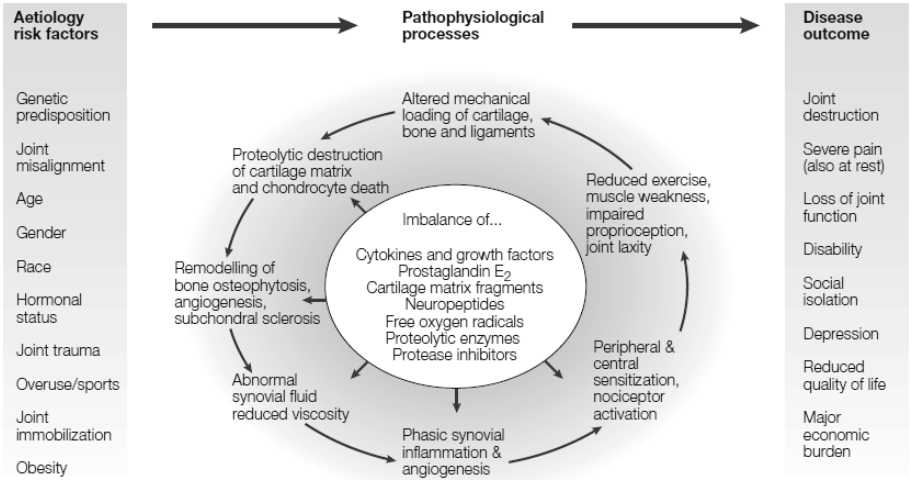


Figure 1.4 The intricate balance between risk factors, pathophysiological process and disease outcome (From: Wieland et al. Osteoarthritis, an untreatable Disease? Nature Reviews Drug Discovery. 2005).[12]

Sufficient cause can lead to subchondral bone damage that consequently resulting in cartilage damage. Following cartilage damage, changes occur in the subchondral bone with the formation of bony outgrowth (osteophytes), and mediators such as cytokines and proteolytic enzymes are produced causing inflammation of synovium (synovitis). Synovitis contributes to more cartilage defects and consequently leads to more subchondral bone damage.

As not only good things come from above (such as cartilage nutrition from the synovium), the presence of the sufficient cause can also start from the level above cartilage (synovitis) instead of from the level below cartilage (subchondral damage). Synovitis can lead to cartilage breakdown. The cartilage breakdown accordingly leads to more synovitis.[14]

The pathophysiological process in OA could ultimately lead to symptoms such as pain. Since cartilage is aneural, intuitively, it is not possible that cartilage damage (a central feature in OA) generates pain.[3] The source of nociceptive stimuli in OA should be sought in other joint structures involved in OA pathology, such as subchondral bone and synovium.[3] As reviewed by Wieland et al., it has been speculated that the invading sensory nerve fibers at the area of bone remodeling in OA could be the source of pain in OA.[12] Synovium is also richly innervated by sensory nerve fibers that can be stimulated by interleukin-1 (IL-1), tumor necrosis factor-alfa (TNF-alfa), PGE-2, histamine and bradykinin. These cytokines are often released from damaged synovium and cartilage.[12]

1.6. Monitoring the OA progression

OA is often detected when the symptoms are experienced. Clinical trials on therapies to prevent the development of OA symptoms are therefore difficult or impossible to perform. Lengthy trials are needed to follow patients since the presence of the pathologic features until the symptoms present. Due to this practical limitation, trials on preventing the progression of OA are more feasible than trials preventing the incidence of symptomatic OA. However, until now, no effective methods for modifying OA progression is available.[12] One of the possible explanations why trials

on novel drugs to modify OA failed, is because the heterogeneity between OA patients. Not every patient with OA will show progression. When clinical trials are 'contaminated' with patients who are not prone to disease progression, this could lead to underestimation of the effect. Therefore, to optimize clinical trial efficiency, it is important to know at baseline which patients are at risk for progression.

The most common method used to monitor the progression of OA in epidemiologic studies is radiography.[16,17] The preferred method to assess progression on radiographs is measuring joint space narrowing (JSN) since this is an estimation of cartilage thinning.[18,19] The knee joints with OA are placed in a positioning frame to facilitate uniform alignment of the knees, and radiographs are made at baseline and at follow-up. Progression is measured as increase in JSN above a predefined threshold, or above the smallest detectable change (SDC). SDC is a statistical method to define real change, i.e. change above measurement error.[20] Another imaging technique that is increasingly used to monitor the progression of OA is Magnetic Resonance Imaging (MRI).[21,22] The major advantage of MRI over radiographs is that MRI can depict all components of the joint; not only cartilage but also synovium, bone contours and bone marrow. Yet, at present, the change of other features of OA beside cartilage is not commonly used. Increased cartilage volume loss (quantitative measure) and increased cartilage defect (semi-quantitative) are currently the most commonly used ways to monitor OA progression on MRI.[21,23,24]

A promising way to monitor the change in OA pathology is by using biomarkers. Biomarkers are objective measures that can be derived from body fluid such as blood or urine.[16] Interestingly, several biomarkers have been developed not only to monitor change in cartilage, but also to monitor change in bone and inflammation.[25] Among the biomarkers that have been developed to monitor cartilage processes are urinary excretion of β-isomerized terminal cross-linking telopeptide of collagen type II (uCTX-II), serum N propeptide of collagen type IIA (sPIIANP) and serum cartilage oligomeric matrix protein (sCOMP). Among biomarkers that could be used to monitor bone turnover are uCTX-I and serum total osteocalcin. Examples of biomarkers to monitor synovitis and inflammation are Glc-Gal-PYD and high sensitivity C-Reactive Protein (hsCRP).

From a patient perspective, the most important measure for OA progression is not imaging and biomarkers, but clinical progression. However, clinical progression is difficult to define. This may be the underlying reason why data on clinical progression are lacking compared to data on radiological progression. At this moment, there is no consensus on a clinical definition of knee and hip OA progression.

1.7. Obesity

1.7.1. Why is obesity important in OA?

Among the risk factors for occurrence and progression of OA, obesity is the most appealing for several reasons. Firstly, obesity is a strong risk factor [26] that is consistently reported to be associated with OA.[9,27,28] Secondly, obesity is a factor that can be modified. Having more knowledge on how obesity is involved in pathophysiology of OA will consequently lead to better measures to prevent the occurrence and the progression of OA on an individual level. When it seems to be difficult to stop the global epidemic in obesity [29] , individual approaches tailored for OA might be more efficient.

1.7.2. Body Mass Index (BMI) and the epidemiology of obesity

Obesity should be considered as excess of fat. The most popular way to asses fatness is by measuring body mass index (BMI).[30] Due to its widespread use, it is sometimes forgotten that BMI is just a proxy of human body fat.[31] It was not invented to study obesity but to define the characteristics of a 'normal man'. In 1832, 2 years after the independence of Belgium from The Netherlands, Adolphe Jacques Quetelet (1796-1874), who was the president of the Belgian Royal Academic of Science, concluded that weight increases as the square of height. This was known as Quetelet Index until the term BMI was coined in 1972 by Ancel Keys (1904-2004).[32] Despite the fact that it is just a vague measurement of adiposity, it correlates well with body fat mass.[30] According to the World Health Organization (WHO), adults with a BMI between 25 and 30 kg/m^2 are considered to be overweight and those with BMI > 30 kg/m^2 are considered to be obese.[33]

Using this WHO definition, a survey in 2007-2008 showed that more than 30% of people in the US are obese.[29] In the UK, this number is 23% in 2004.[30] Data from the Dutch National Institute for Public Health and the Environment showed that 11% of the Dutch population are obese.[34] Despite the awareness that obesity is a danger to health, the number of people with obesity has increased compared with one decade earlier.[29] Increasing consumption of fatty food in combination with more sedentary lifestyle are factors that contribute to the obesity epidemic. Several public health measures have been taken to fight against the epidemic of obesity. However, these measures have to overcome several problems. Since the number of obese subjects in the population is high, any public health measure will be quite expensive. Another complicating factor is that we have no idea yet how to reverse the obesogenic environment (availability of fat food and sedentary life style).

1.7.3. Why fat is dangerous for the joint health

The real interest in fat and its health effect began just after the second world war.[35] In a paper in Science, Gofman used a newly invented technique to separate plasma lipoprotein and showed that this lipoprotein was related to atherosclerotic disease.[36] At the same time Ancilla Keys, who coined the term BMI, also published several papers on dietary fat and mortality due to cardiac disease.[35] The first studies on the association between obesity and OA were also published in the fifties of the last century by Lewis-Fanning (1946) and Kellgren and Lawrence (1958).[37] Probably because the gross damage in OA is easier to assess in larger joints than in smaller joints, research on the effect of obesity in OA focused mainly on knee and hip joints. This might also be the reason why the effect of obesity has been regarded simply as a consequence of the added mechanical load to articular damage and bone.[38] However, several studies have shown that obesity is also associated with the presence of OA in non weight-bearing joints such as hand joints.[39,40] These observations challenge the view that the mechanical explanation is the sole explanation for the involvement of excess of fat in the pathophysiology of OA.

Until recently, adipose tissue was considered as a passive store of energy.[41] In 1994, due the discovery of leptin, a 16 kDa protein produced by the obese gene (ob), adipose tissue came to be considered as an endocrine organ.[42] At present, at least 50 cytokines and other molecules are produced by fat.[42] Adipokines is the term coined to describe biologically active substances found in the adipose tissue. It is noteworthy to mention that these substances could also be made by tissues other than fat.[42] Adipokines include a variety of pro-inflammatory peptides, such as IL-1 and TNF-alfa and peptide hormones, such as leptin, adiponectin and resisitin. Interestingly, these adipokines are also shown to be involved in inflammatory and immune responses and therefore are not only of interest in OA but also in rheumatoid arthritis (RA).

1.8. Outline of this thesis

The research projects described in this thesis are aimed to give more insight into how obesity links with the development and progression of OA. The knowledge derived from the investigations in this thesis will shed more light on the pathophysiology of obesity in OA. When more is known about the role of obesity in OA in the future, effective personalized strategies to treat OA can be pursued. These individual measures are needed besides public health measures to reduce obesity since public health measures seem to struggle in stopping the global epidemic of obesity.

This thesis starts with three chapters aimed at increasing insight into OA. To treat OA in the future, knowledge on the structures involved in OA and knowledge on the progression of OA are needed. The development of new treatments for OA (novel drugs or novel conservative therapies) warrants better methods of monitoring OA progression and of stratifying patients (i.e. to differentiate patients who will have progression and who will not have progression in the future) at an early stage. Knowing how to monitor OA progression and how to stratify patients will lead to more effective clinical trials in OA.

In **Chapter 2**, we perform a systematic review to investigate the possible joint structures visible on MRI that could be the source of pain in knee OA. Not long ago, the only way to assess pathology was radiography.[4] On radiographs, the presence

of cartilage damage is assessed indirectly as the narrowing of the space between two bones that formed a synovial joint. It might sound strange, but the presence of cartilage is not strongly associated, let alone pathognomonic for the presence of joint pain. Many people with JSN do not have joint pain, and vice versa. The pathology in OA can also be assessed by modern imaging techniques such as MRI. MRI has several advantages above radiography. Firstly, it visualizes cartilage itself. Secondly, it can visualize more structures such as bones and synovium. Due to these advantages, MRI has been used in research investigating the possible source of pain in OA. When a tissue is shown to be associated with pain in OA, it could be investigated more deeply to understand its pathology and to test treatment aimed to recover this tissue. Such treatment might reduce pain, the reason why patients with OA seek medical help.

In **Chapter 3**, we select patients with either clinical knee or clinical hip OA, and investigate factors that are associated with the clinical progression (worsening) and the good prognosis of lower limb OA. The choice for the population and outcomes is motivated by several reasons. We combine patients with either knee or hip OA in our study because knee and hip OA often occurs simultaneously.[43,44] Moreover, validated questionnaires on OA symptoms consist of questions on pain related to daily activities involving all lower limb joints, such as climbing the stairs. We assess clinical progression because this is relevant for the patient.

OA is a progressive disease and thus as a consequence, methods are needed to monitor its progression. In **Chapter 4**, we investigate the possible use of several biomarkers as a predictor of progression or as a sensitive measurement of OA change at multiple sites. These biomarkers are developed to represent several processes in tissues involved in OA such as cartilage, bone and inflammation. Using biomarkers for these purposes has several possible advantages above the radiographs (the present widespread method to asses OA progression). Firstly, biomarkers are more sensitive to change in the disease process. For example, it is not necessary to wait until the cumulative effect of cartilage damage is seen on radiographs to get information about the actual OA state. Secondly, biomarkers give more information about tissues involved in OA, not only on cartilage loss but also tissues such as bone and

synovium. The study presented in this chapter was unique because we used multiple measurements of biomarkers. Multiple measurements might be more informative than a single measurement. Moreover, we assessed multiple instead of separate joints. We did this because all joints could contribute to the measured biomarkers.

The following three chapters of this thesis try to answer several questions on how obesity influences the development and progression of OA.

In **chapter 5**, we perform a systematic review on the association between obesity and the development of hand OA. This to provide a 'proof of principal' that obesity leads to OA not simply by added mechanical force. Since we do not walk on our hands, it could be suggested, when such a 'proof' is established, that metabolic factors associated with fat might also play a role in OA.

Consequently, in **chapter 6**, we investigate the association between the products of fat tissue (adipokines) and the progression of radiographic hand OA. We investigate the following adipokines: leptin, adiponectin, and resistin. In this study, the hand is investigated instead of weight bearing joints such as the knee or hip joint because we want to investigate the metabolic effect and exclude the mechanical effect.

In **chapter 7,** we investigate the association between obesity and pain in patients who are visiting orthopedic surgeons to discuss the possibility of having joint prosthesis. Since obesity has been shown to be associated with chronic pain, fibromyalgia, abdominal pain and migraine [45] it is thus reasonable to hypothesize that obesity could also cause joint pain independent of structural damage in an OA joint. Therefore, in this study we also investigate the role of the radiographic severity of OA on the association between BMI and pain. Since the mechanical effect of obesity differs on hip and knee, we also investigate the difference in the association between obesity and indication to perform total hip and total knee replacement.

In **chapter 8**, we investigate the possible interaction between obesity and another strong risk factor of OA, i.e. malignment in 'causing' the progression of knee OA. Arguably, when the two forces—overweight and malalignment—are present together in one knee, the chance of having knee OA progression will increase.

Finally, we present our conclusions and discuss possible future researches on obesity and OA in **chapter 9** and in **chapter 10** (in Dutch).

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