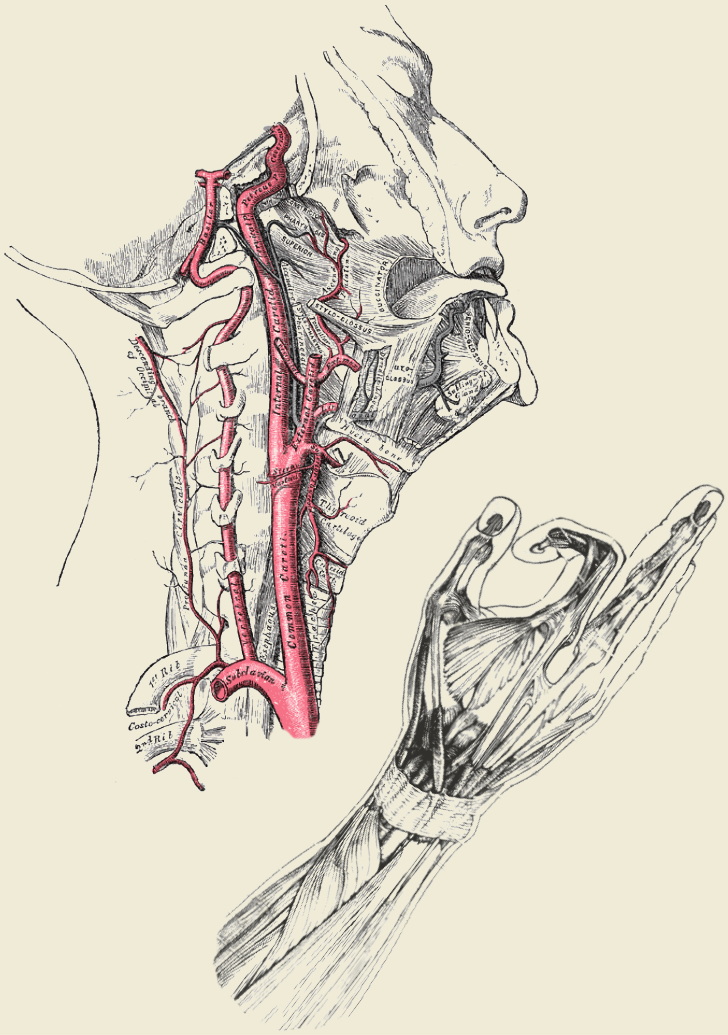
Vascular pathology and osteoarthritis

Population-based studies

Theun Hoeven



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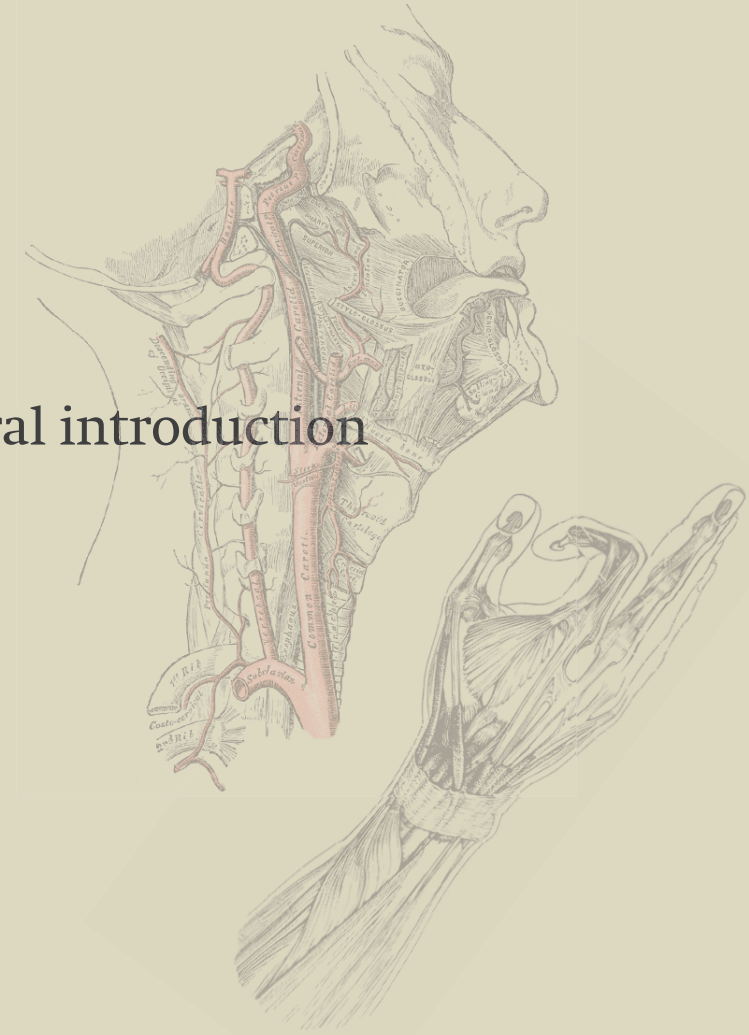
General introduction



Osteoarthritis

Osteoarthritis (OA) is the most frequent joint disorder worldwide and causes a considerable burden of pain, disability, and ever increasing costs to society.[1] Due to rapid ageing and the epidemic of obesity in western populations, prevalence of OA is expected to increase even more, by approximately 20% in the next 10 years. This will make OA the fourth leading cause of disability.[2]

OA can occur in every synovial joint, but is most common in the hips, knees, hands, feet and spine.[3] Histologically, it is characterized by loss of cartilage structure, subchondral bone sclerosis, synovial inflammation and osteophyte formation, with affection of the whole joint (i.e. joint failure).[4] (**Figure 1)**

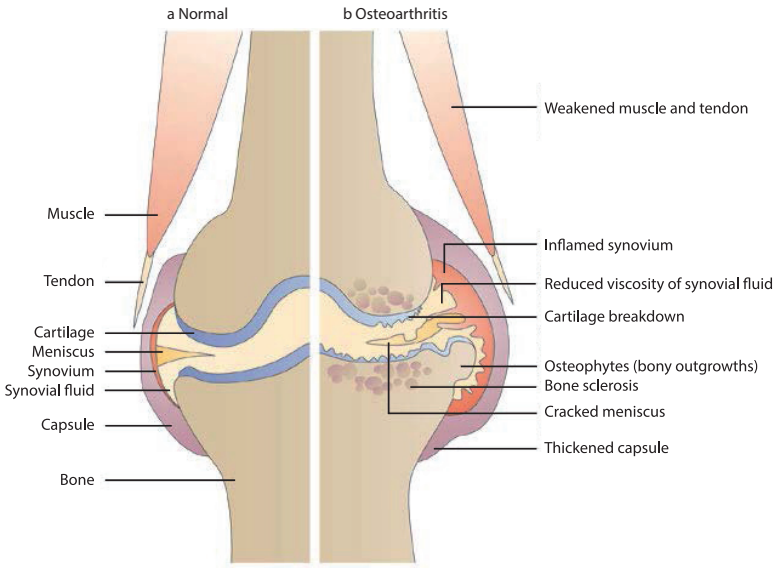


Figure 1. Overview of joint tissues involved in the osteoarthritic disease process.

OA is considered to be a multifactorial disease and its aetiology involves biomechanical, genetic, inflammatory and hormonal factors. Over the last decades, interactions between these risk factors have been identified in epidemiological and experimental studies, adding to our understanding of the complexity of this chronic progressive disorder. For instance, the effect of obesity on knee osteoarthritis is amplified if hypertension is present, which might reflect an accumulative effect of cardiovascular risk factors.[5] Furthermore, malalignment of the knee seems to be a risk factor for knee OA only among obese individuals.[6,7] In addition to the interaction between risk factors, different risk factors are related to OA in different joints.[8]

OA might be seen as a result of a common pathway secondary to many predisposing factors (**Figure 2**). Although the mechanism leading to the initiation and progression of OA remains largely unknown, it is well known that the disease process ultimately leads to pain or disability.[9] For more than a decade, much effort has been made in OA research to find disease-modifying drugs, mainly targeting the cartilage. Unfortunately, at present only symptomatic treatment for OA is available, with minor effectiveness.[10]

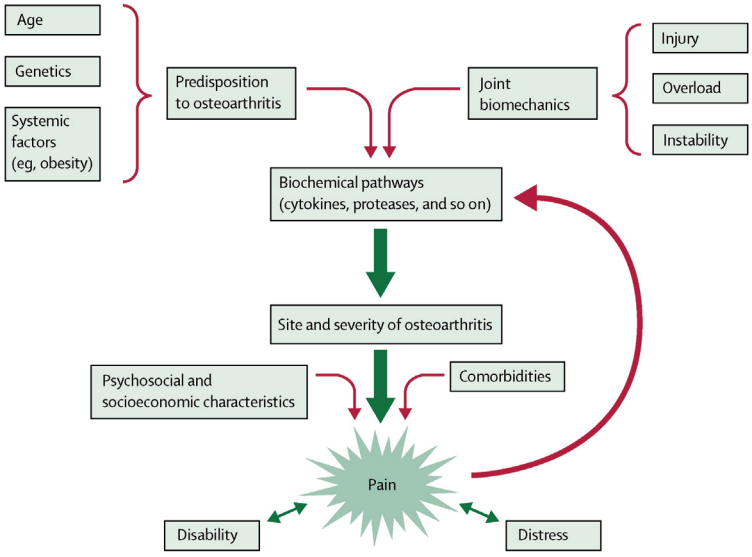


Figure 2. Risk factors involved in the aetiology of OA and its consequences as presented by Dieppe and Lohmander.[9]

Several epidemiological studies have identified age, female sex and obesity as key risk factors for OA. The involvement of other potential risk factors such as diabetes[11], menopause[12,13], and cholesterol[14] in the disease process suggests that OA could be part of the metabolic syndrome[15], a condition with as its main characteristic systemic inflammation caused by visceral adipose tissue.[16] An important clinical manifestation of the metabolic syndrome is atherosclerosis. In this thesis, we will focus on the chronic inflammatory process of atherosclerosis and its relation to osteoarthritis in a population-based setting, since several epidemiological studies have indicated a relation between subclinical measures of atherosclerosis and OA.[17-19]

Vascular pathology

Atherosclerosis is the underlying cause of 50% of all deaths in western societies.[20] In short, it is a multifactorial progressive condition characterized by the accumulation of lipids and fibrous elements in the arterial walls. The accumulation of lipids in the arteries over time can be viewed as a 'response to injury' caused by an unhealthy environment, genetic susceptibility or other risk factors as the injurious agents.[20-22] **Figure 3** shows the inflammatory pathway of atherosclerosis three-dimensionally on a gliding scale and reflects its complex aetiology. Interaction between risk factors (similar to the aetiology of OA) adds to this complexity. Eventually, accumulation of risk factors or 'injuries' in the chronic inflammatory process of atherosclerosis results in an acute clinical event (such as a myocardial infarction or stroke) by plaque rupture and thrombosis (see also **figure 3**).[20] The exact trigger for a clinical event remains an area of debate.

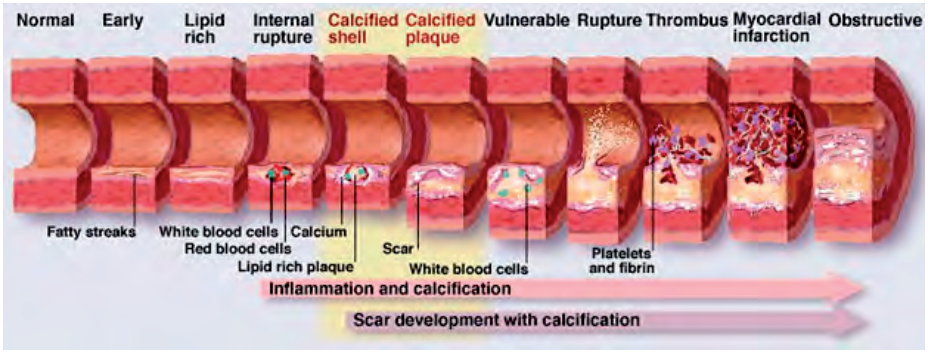


Figure 3. Pathophysiology of atherosclerosis.

Vascular Pathology and osteoarthritis

An association between cardiovascular events and OA has been reported repeatedly.[23-25] Cerhan et al.[26] showed overall cardiovascular mortality to be directly proportional to the extent of radiographic evidence of OA, implying a dose-response relationship. Several explanations have been suggested for these associations; the common treatment of OA with non-steroidal anti-inflammatory drugs (NSAIDs), which increase the risk for myocardial events, as well as a lack of exercise due to the presence of OA.[27] However, a Finnish study showed that OA in any finger joint predicted cardiovascular death[28], a type of OA for which long term NSAID use is not common and that hardly causes inactivity. Another explanation focuses on the shared association with obesity. Poor

fetal growth, or an altered lipid metabolism has also been suggested as a potential shared causal mechanism.[27,29,30]

Recently, Saleh et al.[19] showed an association between arterial stiffness and hand OA. In addition, Jonsson et al.[18] showed that carotid and coronary atherosclerosis were associated with hand OA, in women but not in men. Both studies were cross-sectional in design. Saleh et al.[19] proposed that this relationship arises from an accumulation of advanced glycation end-products in both cartilage and arteries, or alternatively from oxidative stress in both cartilage and arteries. Hence, atherosclerosis and OA could be **concurrent diseases** with a shared aetiology. However, Jonsson et al. suggested that atherosclerosis plays an **initiating role** in OA; circulatory disturbances in the synovial membrane and subchondral bone could contribute to the cartilage destruction and the pathophysiological process of osteoarthritis.[18] This may occur through mechanical changes of the subchondral bone, or more directly through bone-derived cytokines causing degradation of the cartilage.

There already is convincing evidence that areas of bone marrow edema in the subchondral bone predict OA progression[31-33] and that these are present early on in the disease.[34] Histologically, bone marrow edema is an area of necrosis and remodeling[35] and may represent ischaemic areas in the bone similar to those in avascular necrosis.[36] Conaghan et al.[27] argued that atherosclerosis might be of even more importance for the **progression** of OA than for the initiation of OA and postulated that the subchondral bone ischaemia theory is the most likely one to explain that link.

Taken together, atherosclerosis and OA might be associated but it is still unclear whether these diseases are concurrent diseases or whether vascular pathology plays a causal role in OA. Several hypotheses have been formulated to explain the apparent link, but longitudinal population-based studies are lacking.

Overall aim of the thesis

The goal of this thesis is to investigate whether atherosclerosis and OA are concurrent conditions with shared pathophysiological mechanisms or rather that atherosclerosis acts as a risk factor for OA. This knowledge may be crucial: if atherosclerosis turns out to play an important role in the initiation of OA, this may stimulate a new way of thinking about OA pathology, with new alternatives for disease modifying treatment or even the prevention of OA as a result.

Our primary research questions are:

1. Are subclinical measures of atherosclerosis detected by imaging or in serum associated with prevalent radiographic hand OA, hip OA, or knee OA?

2. Do subclinical measures of atherosclerosis detected by imaging or in serum predict the development and progression of radiographic hand OA, hip OA, or knee OA?
3. Are subclinical measures of atherosclerosis detected by imaging associated with subchondral bone marrow edema (anearly feature of knee OA) in women without radiographic knee OA?

Our secondary research questions are:

4. If the association between atherosclerosis and OA is more pronounced in women, is this related to years since menopause?
5. Is OA an additional risk factor for incident cardiovascular disease?

In order to answer our research questions, we obtained data from a longitudinal population-based cohort study; the Rotterdam Study. All studies in this thesis were part of the project "vascular pathology and osteoarthritis", supported by a grant from the Reumafonds (Dutch Arthritis Foundation).

Study population

The Rotterdam Study was set up in 1989 to investigate the occurrence and determinants of diseases in middle-aged and elderly populations. Inclusion of participants is visualized in **figure 4**. In short, all 10,275 inhabitants aged 55 years and older who had been living for at least 1 year in the Ommoord district of the city of Rotterdam were invited to participate (cohort RS-I-1) at the beginning of the study. The response rate was 78%, meaning that 7,983 subjects responded. In 2000, 3,011 participants (out of 4,472 invitees) who had become 55 years of age or had moved into the study district since the start of the study were added to the cohort (RS-II-1). In 2006, a further extension of the cohort was initiated in which 3,932 subjects were included, aged 45-54 years, out of 6,057 invited (RS-III-1). Therefore, by the end of 2008 the Rotterdam Study comprised 14,926 subjects aged 45 years or over.[37] All participants take part in extensive examinations, including blood sampling, interviews, physical examinations, ultrasounds and X-rays, among other. Follow-up takes place every 4-5 years and the study base is digitally linked to medical records of general practitioners and a pharmacy in the Ommoord area.

The burden of atherosclerosis is visualized in the Rotterdam Study by noninvasive methods. Ultrafast computerized tomography and extravascular ultrasound assess coronary artery calcification (RS-I-3), carotid intima-media thickness, and carotid plaque (RS-I-1/RS-III-1). These subclinical measures of atherosclerosis reflect changes in the vascular wall over time and are strong predictors of coronary heart disease and cardiovascular events.[38-41] Another way to diagnose atherosclerosis is to use more inva-

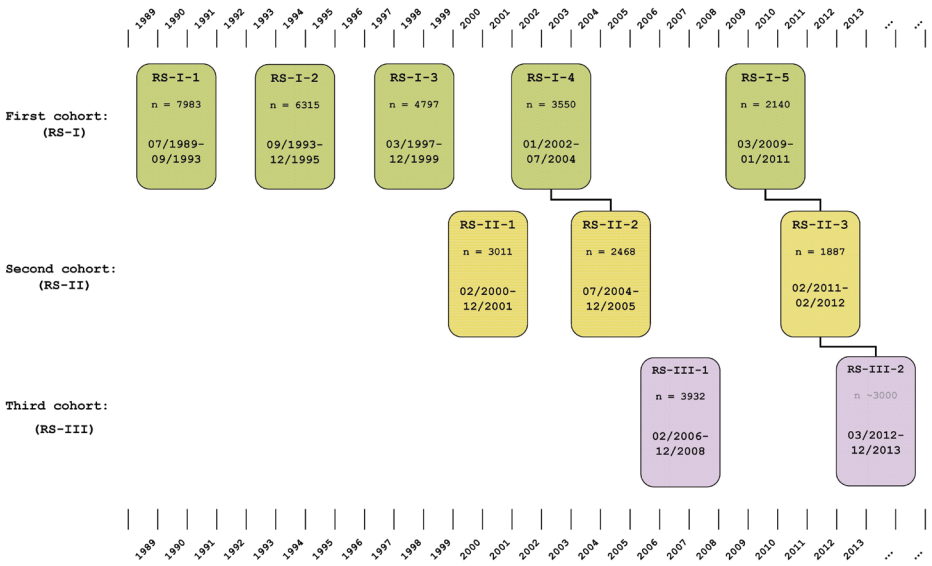


Figure 4. Design of the Rotterdam Study.

sive measures. Catherization is the gold standard, but undesirable for financial reasons and because of significant risks. Certain biochemical markers for the disease, such as vascular cell adhesion molecule and vascular endothelial growth factor are considered more useful[42,43] and were available in cohort RS-I-3.

To define OA, radiographs, symptoms, and magnetic resonance imaging (MRI) are used. Half a century ago, Kellgren & Lawrence (K&L) composed a 5-point (0-4) grading scale using radiographic changes that is still widely used and recommended for the proper determination of radiographic OA today. Within the Rotterdam Study, a grade 5 for total joint replacements was added to the K&L scale. Radiographs were available in cohorts RS-I-1, RS-I-3, RS-I-4, RS-II-1, and RS-III-1. We defined clinical OA as a K&L grade≥2 and reported pain in the same joint in the past month, similar to the definition developed for scientific studies by the American College of Rheumatology.[44] This was done in cohort RS-I-1. MRI has the advantage of providing a three-dimensional view of the (mainly knee) joint and can detect more subtle structural abnormalities in an earlier phase of the OA disease process than radiographs. MRIs of the knees were available in a nested cohort of almost 900 randomly selected women in RS-III-1.

To summarize, the Rotterdam Study, comprising a huge data set of an adult population with prospective data on a large number of objective measurements of atherosclerosis, confounding factors, and features of local and widespread OA over a ten year period, gives us the unique opportunity to disentangle the mechanism of interaction between atherosclerosis and OA.

Outline of this thesis

Chapter 2 describes subclinical measures of atherosclerosis and their relation with the presence and progression of osteoarthritis of the knee, hip, and the different hand joints in the first cohort of the Rotterdam Study (Questions 1, 2, and 4). The same cohort, only older, is investigated in **Chapter 3**. Additional markers of early and late atherosclerosis in relation to the presence and progression of knee osteoarthritis are presented and evaluated. **Chapter 4** reports on the association between carotid atherosclerosis and early features of knee osteoarthritis in middle-aged women (Questions 3 and 4). These first chapters discuss atherosclerosis and OA as concurrent diseases and atherosclerosis as an initiator or progressor of OA. The association between clinical manifestations of the metabolic syndrome and OA is complex, and prone to confounding factors, which hampers interpretation when classical epidemiological methods are used. In **chapter 5**, we therefore explored Mendelian randomisation (instrumental-variable-approach), which uses genetic variation as a surrogate marker for a risk factor. In contrast to atherosclerosis and OA, many single nucleotide polymorphisms are known for glycemic traits with moderate to large effect sizes. We investigated whether genetically defined elevated levels of fasting glucose and fasting insulin were associated with OA. **Chapter 6** provides evidence on the relation between osteoarthritis and cardiovascular events (Question 5). Is it an additional risk factor for incident cardiovascular disease or not? Finally, **Chapter 7** reflects on the main findings of the preceding chapters, as well as their limitations. Furthermore, implications for future research and clinical practice are discussed.

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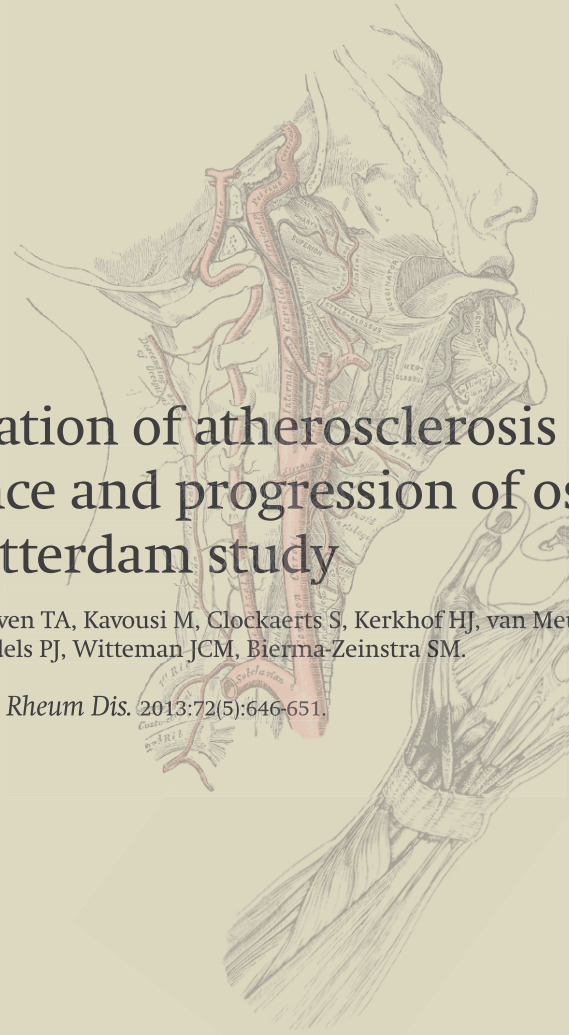

02
Association of atherosclerosis with presence and progression of osteoarthritis: the Rotterdam study

Hoeven TA, Kavousi M, Clockaerts S, Kerkhof HJ, van Meurs JB, Franco OH, Hofman A, Bindels PJ, Witteman JCM, Bierma-Zeinstra SM.

Ann Rheum Dis. 2013:72(5):646-651.

Abstract

Objective

We examined whether vascular alterations are associated with the presence and progression of osteoarthritis (OA) of the knee, the hip, and the different hand joints in a large prospective cohort study.

Methods

In this population-based study involving participants aged 55 years and older (Rotterdam Study-I), men (n=2,372) and women (n=3,278) were analyzed separately. We scored X-rays of the knee, hip and hand using the Kellgren & Lawrence (K&L) score for OA at baseline, after 6.6 years and 10 years. Measures of atherosclerosis (carotid intima media thickness (IMT) and carotid plaque) and data on covariates (age, body mass index, hypertension, cholesterol ratio, diabetes mellitus and smoking) were collected at baseline. Multivariate logistic regression models with generalized estimated equations were used to calculate odds ratios and corresponding 95% confidence intervals. Secondary multiple comparisons adjustment resulted in a significance level of $p<0.0021$.

Results

In women, IMT showed an independent association with prevalence of knee OA (adjusted odds ratio (aOR) 1.7 (1.1 - 2.7)), and carotid plaque with distal interphalangeal (DIP) OA (aOR 1.4 (1.2 - 1.7)) and with metacarpophalangeal (MCP) OA (aOR 1.5 (1.1 - 2.2)). An independent association for IMT with progression of MCP OA was found in women (aOR 2.9 (1.18 - 6.93). Additional adjustment for multiple testing yielded a significant association between carotid plaque and DIP OA in women ($p<0.001$).

Conclusions

This study showed independent associations of atherosclerosis with OA of the knee and hand joints in women. The evidence was most solid for a relation with DIP OA. More research is needed to confirm the associations and examine the differential association with various joints.

Introduction

Osteoarthritis (OA) is a highly prevalent joint disorder that causes a huge burden of pain and disability [1]. It is characterized by loss of cartilage structure, subchondral bone sclerosis, synovial inflammation and osteophyte formation, with affection of the whole joint (i.e. joint failure) [2]. Different risk factors have been suggested for OA, among these age, female gender and obesity are the key ones. The involvement of other potential risk factors like diabetes [3], menopause [4,5], and cholesterol [6] in the disease process suggest that OA could be part of or linked to the metabolic syndrome [7]. In addition, a higher risk of cardiovascular death has been reported for patients with knee or hip OA [8].

Atherosclerosis is an important feature of cardio-metabolic disorders. Although some studies have indicated that atherosclerosis is associated with OA, they are few in number, often lack sufficient power and are cross-sectional only. As a result, it is unclear whether atherosclerosis and OA are associated, either as concurrent diseases due to a common aetiology or causally related. Furthermore, whether there are differences in association with vascular diseases between joints affected by OA remains undetermined.

Therefore, using data from a large longitudinal population-based study, we investigated the role that atherosclerosis might play in the prevalence, but also in the incidence and progression of OA and examined whether this association might vary by types of joints, gender and other key factors.

Methods

Study Population

The Rotterdam Study is a prospective population-based cohort study that was set up in 1989 to investigate the occurrence and determinants of diseases in middle age and elderly populations [9]. All 10.275 inhabitants aged 55 years and older who had been living for at least 1 year in the Ommoord district of the city of Rotterdam were invited to participate. The response rate was 78%, meaning that 7983 subjects responded. All participants gave written informed consent and the study was approved by the ethics committee of the Erasmus University Medical Centre, Rotterdam. Baseline measurements were obtained from 1990 to 1993 and consisted of a home interview and visits to the research centre for physical examinations. Follow-up data were collected during follow-up visits from 1997 to 2000 and from 2002 to 2005. In 2011, we included participants for whom radiographs of knees, hips or hands at baseline and follow-up were available and had been scored.

Measures of atherosclerosis

A 7.5-MHz linear array transducer with a Duplex scanner (ATL UltraMark IV) was used for ultrasonography of both carotid arteries. On a longitudinal two-dimensional ultrasound image of the carotid artery, the near and far walls of the carotid artery were displayed as two bright white lines separated by a hypoechogenic space. The distance from the leading edge of the first bright line of the far wall (lumen-intima interface) to the leading edge of the second bright line (media-adventitia interface) indicated the intima media thickness (IMT). Data on IMT was available for 3369 women and 2275 men. Reproducibility assessed by the intraclass correlation coefficient was 0.74 [10].

The presence of plaques in the carotid artery was assessed by examining the ultrasonographic images of the common, internal, and bifurcation sites of the carotid artery for presence of atherosclerotic lesions. Plaques were defined as a focal widening relative to adjacent segments, with protrusion into the lumen composed of either only calcified deposits or a combination of calcified and noncalcified material [11,12]. Data on presence of plaque was available for 2665 women and 1808 men. Readers of the ultrasound images were unaware of the case status of the subject.

Assessment of OA

Standard anteroposterior radiographs of both hands were scored by three trained assessors. Each joint was graded for overall radiographic OA using a Kellgren-Lawrence (K&L) grade scaled 0-4 (see supplementary table S1). Radiographic OA was defined as a K&L grade ≥2. DIPs, PIPs, MCPs and CMC/TS groups were defined as positive if the K&L score in at least one joint in the group was ≥2. Interobserver reliability of K&L score of 2 or more as a dichotomous variable expressed by the intraclass correlation coefficient was as follows: DIPs; 0.69, PIPs; 0.74, MCPs; 0.70, CMC/TS (base of thumb); 0.84. After consultation of an expert, we excluded hand X-rays with signs of rheumatoid arthritis or fractures. X-rays of the hand were available at baseline for 3210 women and 2428 men and after 10 years of follow-up for 1385 women and 1057 men. Progression of hand OA was defined as 1 grade increase in the K&L scale. This was done for each of the handjoint groups separately (Kerkhof HJM, 2011, unpublished data).

Knee and hip X-rays were taken and scored with a K&L grade scaled 0-4 (see supplementary table S1). Radiographs of the pelvis were obtained when both feet were rotated 10° inward and the X-ray beam was centred on the umbilicus and knee radiographs were taken with the knee extended and the patella in a central position. The intraclass correlation coefficient was 0.71 for the knee and 0.74 for the hip [13,14]. Knee and hip OA progression were defined as an increase in the K&L score between baseline and follow-up of 1 or more [15]. X-rays of the knee and hip were available at baseline for 3278 women and 2372 men, after 6.6 years for 2449 women and 1232 men, and after 10 years for 1149 women and 941 men. If X-rays were available after 6.6 years, but not

after 10 years of follow-up, data was forwarded. Assessment of OA was done blinded for clinical and demographic data.

Co-factors

Trained interviewers gathered information on medical history and risk factors for chronic diseases. Participants were invited to visit the research centre for clinical examinations and laboratory assessments. The following information was collected: age; body mass index (BMI; weight (kg)/height (m^2)); total cholesterol/high density lipoprotein (HDL) ratio (serum total cholesterol determined by an enzymatic procedure; HDL measured after precipitation of non-HDL cholesterol); current smoking (self-reported); diabetes mellitus (use of glucose lowering medication or non-fasting random or post load glucose levels exceeding 11.0 mmol/liter); and arterial hypertension (systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher, or use of antihypertensive drugs for hypertension).

Statistical analysis

We analyzed the association between atherosclerosis and the presence of osteoarthritis using multivariate logistic regression models in which IMT and plaque were included separately for the calculation of odds ratios and 95% confidence intervals. Thickness of the common carotid arteries (IMT) was analyzed continuously. Presence of plaque was treated as a binary variable in the analysis. Different models were built to provide insight in how the link between atherosclerosis and OA might be driven (non-adjusted, age adjusted, age and BMI adjusted, and fully adjusted). The inclusion of potential confounding variables such as age, body mass index, total cholesterol/HDL ratio, diabetes, hypertension and smoking was based on existing literature about risk factors for cardiovascular disease and OA and following initial univariate evaluation. In addition, adjustments for follow-up time and baseline K&L score were made for the multivariate analyses on progression of OA. We used generalized estimating equations (GEE), a mixed logistic regression model, to adjust for correlations between the right and left extremity in each individual and to increase discriminative ability. Because the definition of progression implies that participants are conditioned by the baseline presence of OA the estimates of an effect of exposure (atherosclerosis) on outcome (OA) might be biased. We therefore again included all potential confounders in the model to minimize conditioning by baseline [16]. Subjects with missing values were excluded from the analysis. Stratification by sex was based on previous studies [17,18]. Our a priori p-value threshold was set at $P \leq 0.05$. However, due to multiple comparisons for the different joint groups, the two measures of atherosclerosis, and both genders we further examined the associations in a second analysis for the more rigorous p-value of $p<0.0021$ ($\alpha/24$). We performed all analyses with the Statistical Package for Social Sciences (SPSS) version 17.0.

Results

General characteristics

Of the total 7983 participants, 3278 women and 2372 men were included in this study. Because they did not have X-rays taken at baseline, 2333 participants were excluded. **Table 1** shows the baseline characteristics of the study population, overall and stratified by sex. The mean age of the population at baseline was 68.2 years; 58% were female. In this study, women were slightly older (68.6 years vs. 67.5 years), had a higher BMI (26.8 kg/m² vs. 25.7 kg/m²), and more of them reported a history of hypertension (58% vs. 53%) compared to men. However, there were more men with carotid plaques (66% vs. 55%). In men, carotid intima media thickness was higher (1.1mm vs. 1.0mm), they smoked more (29% vs. 19%), and had a higher total cholesterol/HDL ratio (5.5 vs. 5.1). The commonest OA sites in women were distal interphalangeal (DIP) joints (39%), carpometacarpal/trapezoscaphoid (CMC/TS) joints (33%) and knee joints (20%). In men, osteoarthritis in the distal interphalangeal (DIP) joints was commonest (25%), followed by carpometacarpal/trapezoscaphoid (CMC/TS) joints (19%). The prevalence of OA was significantly higher in women for all joint groups.

Table 1. Baseline characteristics of the study population.

Variable	All (n = 5650)	Men (n = 2372)	Women (n = 3278)
Age, years	68.2 ± 8.0	67.5 ± 7.6	68.6 ± 8.3
Male, %	42		
Body Mass Index, kg/m2	26.3 ± 3.6	25.7± 3.0	26.8 ± 4.0
Diabetes, %	10	10	10
Smoking, %	24	29	19
Hypertension, %	56	53	58
Total cholesterol/HDL ratio	5.2 ± 1.6	5.5 ± 1.6	5.1 ± 1.6
Intima media thickness, mm	1.0 ± 0.2	1.1 ± 0.2	1.0 ± 0.2
Plaque present, %	59	66	55
Prevalence of OA			
Knee, %	15	9	20
Hip, %	6	5	7
DIP, %	33	25	39
PIP, %	12	9	16
MCP, %	5	4	7
CMC/TS, %	27	19	33

Categorical variables are presented as percentage. Continuous variables are expressed as mean ± SD.

OA = osteoarthritis; DIP = distal interphalangeal; PIP = proximal interphalangeal; MCP = metacarpophalangeal; CMC/TS = carpometacarpal/trapezoscaphoid

Association of atherosclerosis with OA

Table 2 shows the association between IMT, carotid plaques and presence of knee and hip OA in the different models by gender. After full adjustment IMT showed an association with prevalence of knee OA (fully adjusted odds ratio (aOR) 1.7 (1.1 - 2.7)) at a p-value <0.05 in women. Associations between IMT and carotid plaque with hand OA by gender are presented in **Table 3.** After full adjustment, carotid plaque showed an association with distal interphalangeal (DIP) OA (aOR 1.4 (1.2 - 1.7) and with metacarpophalangeal (MCP) OA (aOR 1.5 (1.1 -2.2)) in women. No independent associations existed between measures of atherosclerosis and hip OA, PIP and CMC/TS OA. Comparison of the crude and adjusted models in **Table 2** and **Table 3** shows that the associations between IMT and plaque with presence of knee, hip, or hand OA are largely attenuated by age adjustment.

Table 2. Analysis of vascular variables in relation to the presence of knee OA and hip OA.

Men(n=2372)		Crude	Age adjusted	Age+BMI adjusted	Fully adjusted[a]
KneeOA	IMT	2.5 (1.48 to 4.08)**	1.5 (0.82 to 2.64)	0.9 (0.62 to 1.18)	1.3 (0.68 to 2.36)
	Plaque	1.0 (0.76 to 1.42)	1.2 (0.64 to 2.17)	0.9 (0.61 to 1.18)	0.9 (0.60 to 1.19)
HipOA	IMT	1.5 (0.87 to 2.82)	1.0 (0.48 to 1.91)	0.9 (0.59 to 1.28)	1.0 (0.48 to 2.03)
	Plaque	1.1 (0.73 to 1.58)	0.9 (0.44 to 1.85)	0.9 (0.60 to 1.31)	0.9 (0.70 to 1.63)
Women(n=3278)					
KneeOA	IMT	3.8 (2.54 to 5.52)***	1.7 (1.10 to 2.52)*	1.7 (1.07 to 2.51)*	1.7 (1.10 to 2.73)*
	Plaque	1.2 (1.02 to1.49)*	0.9 (0.77 to 1.15)	1.0 (0.79 to 1.19)	1.0 (0.81 to 1.24)
HipOA	IMT	2.6 (1.59 to 4.38)**	1.3 (0.69 to 2.37)	1.3 (0.68 to 2.41)	1.4 (0.71 to 2.60)
	Plaque	0.9 (0.73 to 1.26)	0.7 (0.54 to 0.99)*	0.7 (0.54 to 0.99)	0.8 (0.55 to 1.06)

Unless otherwise indicated, values are odds ratios (95% CI)
IMT= intima media thickness, OA= osteoarthritis
[a]Adjusted for age, body mass index (BMI), diabetes, hypertension, cholesterol/HDL and smoking
*p<0.05 **p<0.01 ***p<0.001

The relationship between vascular variables and overall progression of OA (**Table 4**) showed a fully adjusted association between IMT and overall progression of MCP OA (aOR 2.9 (1.18 - 6.93) at a p-value of <0.05 in women. In men, no fully adjusted significant associations were observed between IMT or plaque and presence (**Table 2** and **Table 3**) or overall progression of OA (data not shown).

In a second step, we tested our results conservatively by using rigorous correction for multiple testing at p<0.0021 ($\alpha/24$). This showed that the association between carotid plaque and DIP OA prevalence remained (aOR 1.4 (1.2 - 1.7)).

Table 3. Analysis of vascular variables in relation to the presence of hand OA.

Men(n=2410)		Crude	Age adjusted	Age+BMI adjusted	Fully adjusted[a]
DIPOA	IMT	1.7 (1.12 to 2.44) *	1.1 (0.73 to 1.70)	1.0 (0.65 to 1.51)	1.1 (0.67 to 1.64)
	Plaque	1.0 (0.84 to 1.27)	0.9 (0.74 to 1.14)	0.9 (0.74 to 1.14)	1.0 (0.76 to 1.18)
PIPOA	IMT	1.3 (0.78 to 2.23)	0.8 (0.45 to 1.52)	0.7 (0.39 to 1.35)	0.8 (0.40 to 1.40)
	Plaque	1.0 (0.74 to 1.35)	0.9 (0.66 to 1.23)	0.9 (0.65 to 1.22)	0.9 (0.66 to 1.24)
MCPOA	IMT	2.8 (1.61 to 5.00)***	1.2 (0.56 to 2.47)	1.1 (0.51 to 2.25)	1.0 (0.46 to 2.06)
	Plaque	1.6 (1.00 to 2.65)*	1.3 (0.79 to 2.18)	1.3 (0.79 to 2.16)	1.3 (0.78 to 1.80)
CMC/TSOA	IMT	1.7 (1.13 to 2.63)*	0.9 (0.56 to 2.47)	0.9 (0.53 to 1.38)	0.9 (0.56 to 1.54)
	Plaque	1.2 (0.98 to 1.56)	1.0 (0.80 to 1.29)	1.0 (0.79 to 1.27)	1.0 (0.78 to 1.28)
Women(n=3204)					
DIPOA	IMT	2.4 (1.68 to 3.42)***	1.3 (0.89 to 1.91)	1.3 (0.85 to 1.83)	1.4 (0.93 to 2.10)
	Plaque	1.5 (1.27 to 1.71)***	1.3 (1.09 to 1.50)**	1.3 (1.10 to 1.52)**	1.4 (1.19 to 1.65)***
PIPOA	IMT	2.9 (1.92 to 4.27)***	1.5 (0.97 to 2.36)	1.5 (0.92 to 2.28)	1.3 (0.81 to 2.22)
	Plaque	1.3 (1.06 to 1.59)*	1.1 (0.86 to 1.31)	1.1 (0.87 to 1.33)	1.1 (0.90 to 1.40)
MCPOA	IMT	3.9 (2.38 to 6.40)***	1.6 (0.88 to 2.78)	1.5 (0.81 to 2.67)	1.6 (0.84 to 2.94)
	Plaque	2.0 (1.45 to 2.73)***	1.5 (1.04 to 2.01)*	1.4 (1.04 to 2.00)*	1.5 (1.09 to 2.18)*
CMC/TSOA	IMT	2.1 (1.45 to 3.00)***	1.1 (0.72 to 1.63)	1.0 (0.86 to 1.22)	1.0 (0.68 to 1.59)
	Plaque	1.2 (1.04 to 1.43)*	1.1 (0.71 to 1.62)	1.0 (0.86 to 1.22)	1.0 (0.88 to 1.24)

Unless otherwise indicated, values are odds ratios (95% CI)
IMT= intima media thickness, OA= osteoarthritis,
[a]Adjusted for age, body mass index (BMI), diabetes, hypertension, total cholesterol/HDL and smoking
*p<0.05 **p<0.01 ***p<0.001

Discussion

In the present study independent correlations between measures of atherosclerosis with knee and hand OA prevalence were found in women after adjustment for cardiovascular risk factors. The same applied for progression of hand OA. In the next four subheadings we will discuss the most important findings.

Gender differences

This study showed an independent association between atherosclerosis and OA of the DIP, MCP and knee joints in women, whereas this was not the case for men. Jonsson et al. previously demonstrated that hand OA and atherosclerosis were associated in older women [18] and hypothesized that circulatory disturbances in the synovial membrane and subchondral bone might contribute to the cartilage destruction and to the pathophysiological process of osteoarthritis; we confirmed their results in this study. Our results might indicate that due to hormonal changes during menopause, women are more at risk for developing vascular disease and OA. However, a systematic review

Table 4. Analysis of vascular variables in relation to the overall progression of OA in women.

		No.of progressors (%)	Crude	Adjusted [a]
Progression Knee OA	IMT	228 (19)	2.4 (1.19 to 5.00)*	1.9 (0.83 to 4.39)
	Plaque	180 (18)	1.3 (0.98 to 1.66)	1.3 (0.97 to 1.67)
Progression Hip OA	IMT	131 (8)	0.9 (0.36 to 1.99)	0.5 (0.17 to 1.17)
	Plaque	108 (8)	0.8 (0.59 to 1.11)	0.7 (0.53 to 1.02)
Progression DIP OA	IMT	530 (47)	1.0 (0.54 to 1.85)	1.3 (0.65 to 2.66)
	Plaque	445 (47)	1.0 (0.82 to 1.25)	1.1 (0.86 to 1.34)
Progression PIP OA	IMT	292 (26)	0.6 (0.27 to 1.24)	0.6 (0.26 to 1.34)
	Plaque	246 (26)	1.0 (0.75 to 1.21)	1.0 (0.77 to 1.29)
Progression MCP OA	IMT	202 (18)	3.2 (1.49 to 6.87)**	2.9 (1.18 to 6.93)*
	Plaque	158 (17)	1.0 (0.72 to 1.27)	0.9 (0.67 to 1.22)
Progression CMC/TS OA	IMT	352 (31)	0.9 (0.44 to 1.77)	0.6 (0.25 to 1.27)
	Plaque	285 (30)	1.0 (0.75 to 1.21)	0.9 (0.68 to 1.13)

Unless otherwise indicated, values are odds ratios (95% CI).
OA= osteoarthritis, IMT= intima-media-thickness. DIP= distal interphalangeal, PIP= proximal interphalangeal, MCP= metacarpophalangeal, CMC/TS= carpometacarpal/trapezioscaphoideal
[a] Adjusted for age, body mass index, diabetes mellitus, hypertension, total cholesterol/HDL, smoking, months between baseline and follow-up visit and K&L score at baseline.
*$p<0.05$ **$p<0.01$

found no clear association between female hormonal aspects and OA [19]. Furthermore, effect modification by years since menopause was not present in our study. Recently, Gast el al.[20] showed that women with vasomotor menopausal symptoms are at risk for coronary heart disease. We studied a population of women aged ≥55 and detailed data on the perimenopausal period were not available. It is probable that the relation between menopause, atherosclerosis and OA is complex and cannot be shown in our study population. Younger perimenopausal women with early signs of OA manifest a greater metabolic component and research focussing on this group might elucidate why vascular disease and OA are associated in women, but not in men.

Knee OA, DIP OA and MCP OA

We showed associations between atherosclerosis and OA in several joints in women, but not with CMC OA or osteoarthritis of the hip. In the same way, Dahaghin et al [21] showed that BMI was associated with OA of DIP, PIP and MCP joints, but not with OA of the thumb base (CMCOA). CMC OA might be regarded a subset of hand OA and aetiologically different from DIP, PIP and MCP OA [22]. Various studies support a different pathogenesis between hip OA and knee OA as well [23-25]. Systemic factors such as disordered glucose metabolism, lipid metabolism and atherosclerosis, all related to the metabolic syndrome, seem to be more related to knee OA than hip OA. For example, BMI is highly associated with knee OA, but not or to a lesser degree with hip OA [23,24].

Cardiometabolic disorders and OA

The metabolic syndrome is a multiplex cardiovascular risk factor. Besides atherosclerosis, obesity, diabetes mellitus and dyslipidemia are listed as part of the metabolic syndrome. The main characteristic is the presence of systemic inflammation caused by visceral adipose tissue that secretes proinflammatory cytokines and adipokines [26]. These inflammatory processes are involved in the aetiopathogenesis of atherosclerosis, but also in rheumatic diseases such as psoriasis arthritis. There is increasing evidence that chronic systemic inflammation in patients with the metabolic syndrome might also initiate or stimulate the OA disease process [7]. We studied vascular variables that not only reflect generalized atherosclerosis, but are typically increased in individuals with the metabolic syndrome, or cardiometabolic disorders in general, as well [27,28]. Based on our results, osteoarthritis of the DIP joints may be linked to cardiometabolic disorders in women. Additional investigations to test this hypothesis are warranted.

Progression of OA

We noticed a tendency for an association between IMT and progression of MCP OA and knee OA in women. However, also indications for contradictory estimates were found for the association of vascular variables with overall progression of hip OA in women. We can't give a clear explanation for these results, different relations between overall progression of knee and hip OA have been reported previously [15]. In addition, because the reasons for total hip replacements were not always clear, overall progression of hip OA remained a complex variable to analyze, although we adjusted for hip fractures as well. Furthermore, the very limited power for hip progression can give spurious results.

Overall progression of osteoarthritis was defined as the combination of the incidence and the progression of existing OA at baseline [15]. When we analyzed incidence or progression separately as previously described in hands [29], or in knees and hips [25] we found similar results (data not shown). However, associations between vascular variables and incidence of knee OA in women were stronger than with true progression of knee OA. These results do not fully agree with the hypothesis proposed by Conaghan et al. [30] that by causing subchondral bone ischemia, atheromatous vascular disease contributes more to the progression of OA than to its initiation. The mechanism leading to the initiation and progression of OA still remains largely unknown [31].

Strengths and limitations

The major strength of this study is its size. We used a large population-cohort study, the Rotterdam Study, in which all relevant clinical and radiographic data were collected from a population at risk for osteoarthritis and cardiovascular disease. Detailed cardiovascular data, reflecting generalized atherosclerosis were available [10,11] and in the adjusted models we included potential confounders that could influence the associa-

tion between atherosclerosis and osteoarthritis. Furthermore, we adjusted for baseline presence of osteoarthritis in our analyses of progression [16]. Due to the longitudinal nature of the Rotterdam study, we had the opportunity to analyze both prevalence and overall progression of OA.

Although our joint-specific analyses were hypothesis based, we tested our results conservatively by using rigorous adjustment for multiple testing in a second step. Some other hand joints as well as the knee joint showed effect estimates of similar magnitude in the same direction in both crude and adjusted analyses, but they did not reach statistical significance after these rigorous adjustments, possibly because of the lower prevalence of OA in these joints. Therefore we believe that our findings are supportive of an association between atherosclerosis and hand OA and knee OA in women, as found in previous studies [17,18].

The selection of our participants, based on the availability of radiographs, might have introduced a healthy-workers-effect, since these participants survived the follow-up period and were fit enough to visit the research centre. We selected a younger and healthier sample and the incidence and progression of OA in these participants will be lower than in a population-based sample, so we can assume that if this healthy-workers-effect would have influenced the associations we found, it would underestimate the true effect. In addition, data on overall progression of osteoarthritis was available for a small number of participants, which has limited our power to detect these associations. Unfortunately, we did not have information on activity levels. As a result, residual confounding cannot be totally ruled out.

Future research

This study is the first large-scale prospective population-based cohort study that addresses the association between measures of atherosclerosis and OA. Our study can therefore be viewed as one of the first steps to unravel the link between these two conditions. Many of the covariates are characteristics of a cardiovascular and metabolic profile [6,32,33]. The associations between measures of atherosclerosis and OA were highly driven by age and additional links seem to exist in certain joint types. We do not know which risk factors are specific for OA. We do know, however, that chronic inflammation plays an important role in both diseases. The accumulation of glycation end-products (AGEs) in cartilage and arteries, or alternatively from oxidative stress in cartilage and arteries indicates a shared aetiology in vascular disease and OA [34]. However, additional replication in other studies is recommended and more detailed research is necessary to identify the exact underlying mechanisms for the association between cardiovascular disease and OA. A better understanding of how inflammatory activity in OA and atherosclerosis in women interacts with other recognized risk factors such as increasing age, menopause, diabetes and genetics might lead to improved

treatment strategies in women. In addition, reverse causation in which for example painful knee or hip OA leads to a sedentary life style and a cardiometabolic syndrome might exist.

Conclusions

This study showed independent associations of atherosclerosis with OA of the knee and hand joints in women. The evidence was most solid for a relation with DIP OA. More research is needed to confirm the associations and examine the differential association with various joints.

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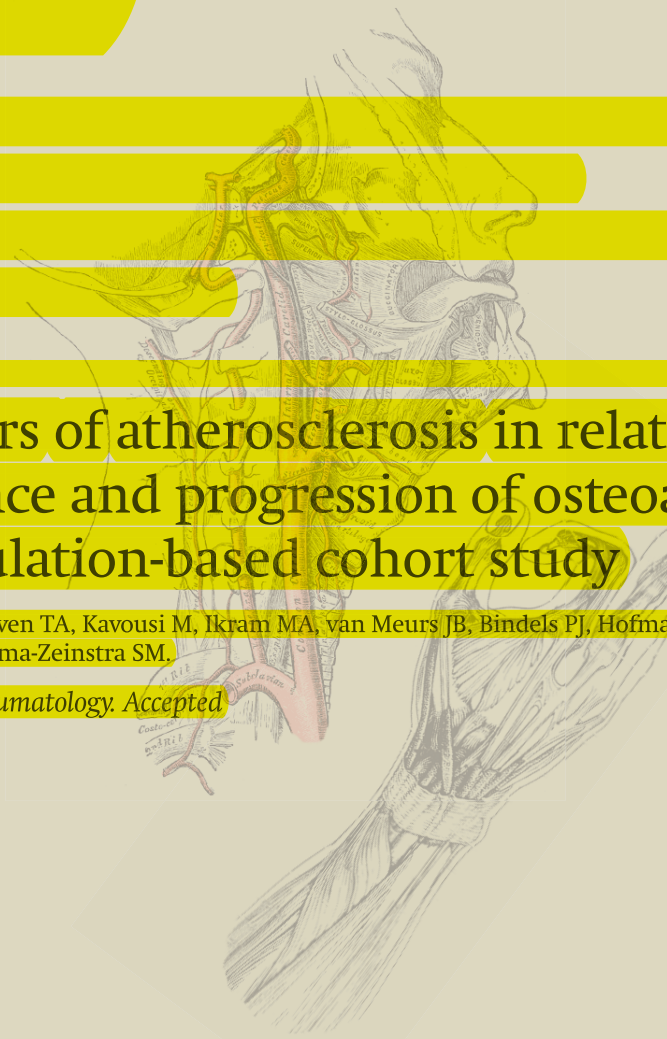
Supplementary table S1.

Definition of the Kellgren-Lawrence radiographic grades.

Grade		Knee	Hip	Hand
0	No osteoarthritis	No features of osteoarthritis	No features of osteoarthritis	No features of osteoarthritis
1	Doubtful	Doubtful narrowing of joint space and possible osteophytic lipping	Possible narrowing of joint space medially and possible osteophytes around the femoral head; or osteophytes alone	Minute osteophytes, doubtful significance
2	Mild	Definite osteophytes and possible narrowing of joint space	Definite narrowing of joint space inferiorly, definite osteophytes, and slight sclerosis	Definite osteophytes, unimpaired joint space
3	Moderate	Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends	Marked narrowing of joint space, definite osteophytes, some sclerosis and cyst formation, and deformity of the femoral head and acetabulum	Diminution of joint space
4	Severe	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends	Gross loss of joint space with sclerosis and cysts, marked deformity of femoral head and acetabulum and large osteophytes	Joint space impaired with sclerosis or subchondral bone

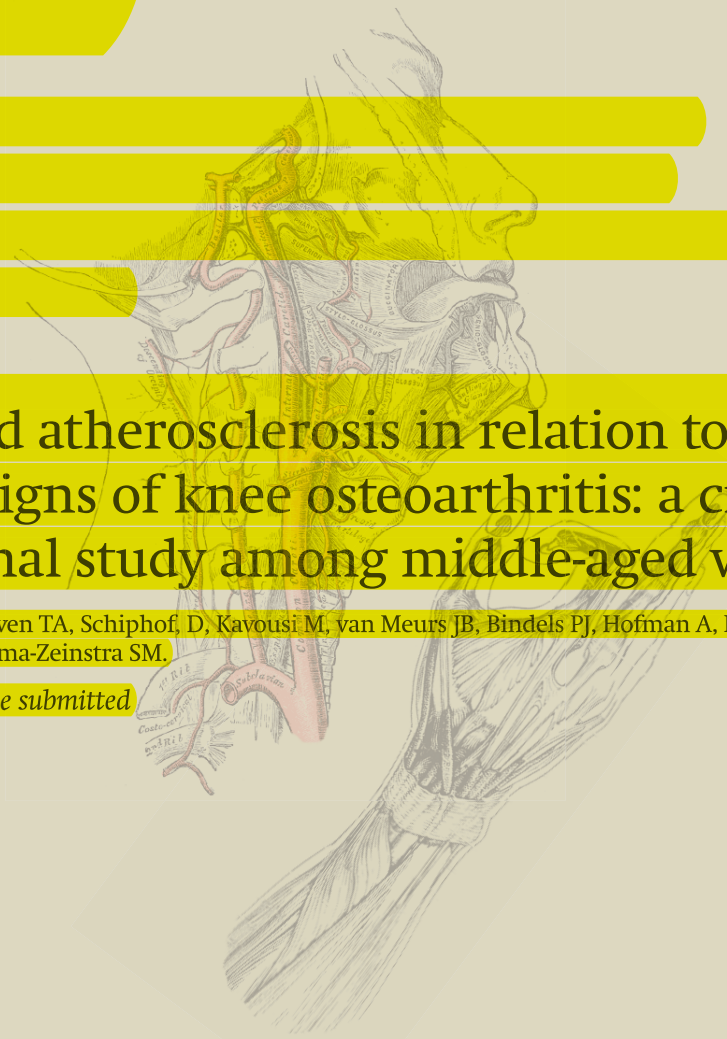


03

Markers of atherosclerosis in relation to presence and progression of osteoarthritis: a population-based cohort study

Hoeven TA, Kavousi M, Ikram MA, van Meurs JB, Bindels PJ, Hofman A, Franco OH, Bierma-Zeinstra SM.

Rheumatology. Accepted

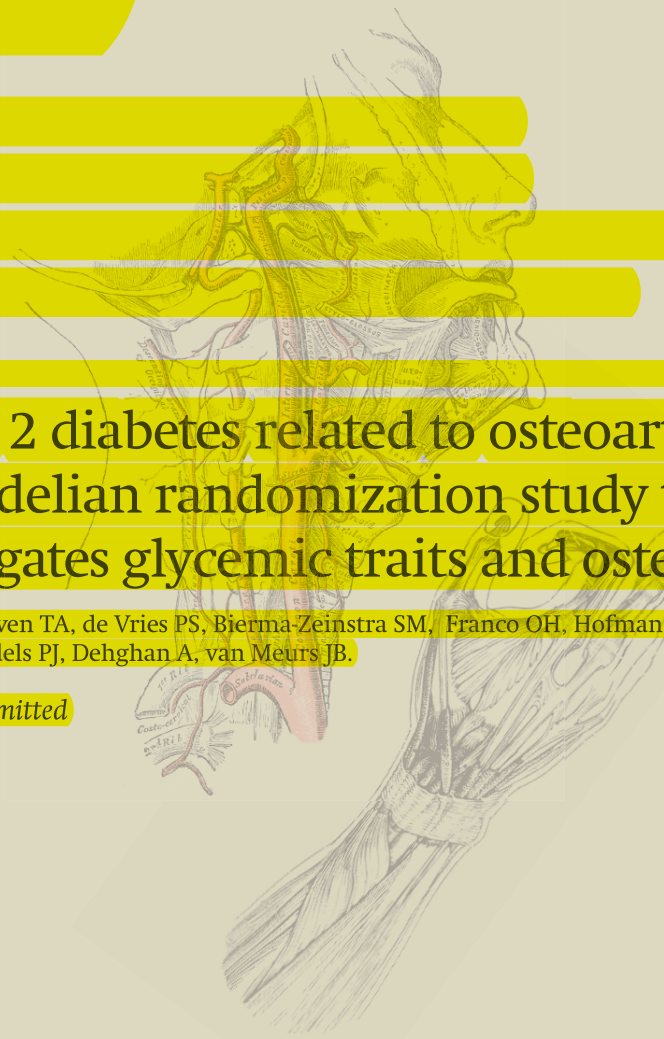


04

Carotid atherosclerosis in relation to early signs of knee osteoarthritis: a cross-sectional study among middle-aged women

Hoeven TA, Schiphof, D, Kavousi M, van Meurs JB, Bindels PJ, Hofman A, Franco OH, Bierma-Zeinstra SM.

To be submitted

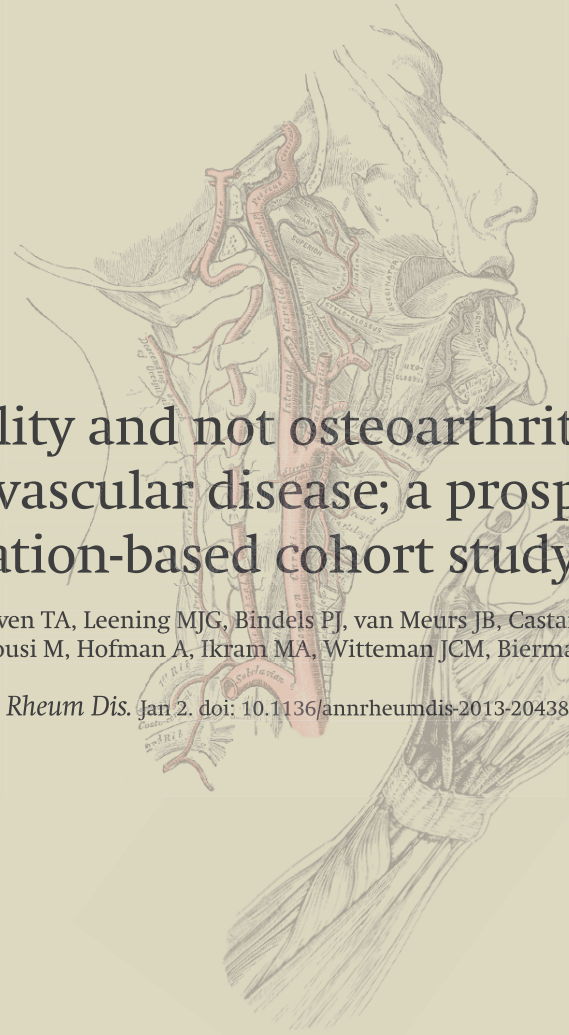


05

Is type 2 diabetes related to osteoarthritis? A Mendelian randomization study that investigates glycemic traits and osteoarthritis

Hoeven TA, de Vries PS, Bierma-Zeinstra SM, Franco OH, Hofman A, Uitterlinden AG, Bindels PJ, Dehghan A, van Meurs JB.

Submitted



06

Disability and not osteoarthritis predicts cardiovascular disease; a prospective population-based cohort study

Hoeven TA, Leening MJG, Bindels PJ, van Meurs JB, Castano-Betancourt M, Franco OH, Kavousi M, Hofman A, Ikram MA, Witteman JCM, Bierma-Zeinstra SM.

Ann Rheum Dis. Jan 2. doi: 10.1136/annrheumdis-2013-204388

Abstract

Objectives

Previous studies found an association between osteoarthritis (OA) and risk of cardiovascular disease (CVD) and therefore suggested intensive treatment of cardiovascular risk factors in OA patients. However, prospective population-based data is lacking. We investigated the association between OA and CVD longitudinally in a general population and additionally examined the role of disability in this association.

Methods

This study was embedded in The Rotterdam Study, a prospective population-based cohort study in Rotterdam, the Netherlands that started in 1989. At baseline 4,648 persons aged ≥55, free of CVD were classified into those with and those without radiographic or clinical OA. Hazard ratios (HRs) adjusted for traditional cardiovascular risk factors for developing CVD (a composite of fatal and nonfatal coronary heart disease and stroke) were calculated.

Results

During a median follow-up of 14.4 years 1,230 cardiovascular events occurred, of which 101 in the participants with clinical OA. Presence of radiographic OA at baseline was not related to future CVD (HR 0.99, 95%CI 0.86-1.15), neither was presence of clinical OA (HR 1.09, 95%CI 0.88-1.34). However, persons with increasing disability were more likely to suffer a cardiovascular event compared with non-disabled persons (HR 1.26, 95%CI 1.12-1.42); this was independent of the presence of OA.

Conclusions

In this large population-based study, participants with OA were not at increased risk of CVD. The close relation between disability and osteoarthritis may explain previous findings. Further studies are required in order to clarify whether OA patients need more intensive treatment of their cardiovascular risk factors.

Introduction

Osteoarthritis (OA) is the most frequent joint disorder in the elderly and causes a considerable burden of pain, disability, and ever increasing costs to society [1]. Several cross-sectional [2, 3] and disease-specific mortality [4-6] studies suggest an association between OA and cardiovascular disease (CVD). The strongest body of evidence comes from a recent study comparing CVD mortality of selected OA patients with mortality statistics from the general population [6]. Therefore more intensive treatment of cardiovascular risk factors has been proposed to prevent premature CVD in OA patients, similar to conditions like rheumatoid arthritis or gout [7-9]. Before implementing OA as another red flag into guidelines critical assessment of such claims are warranted, especially if robust prospective population-based comparisons are lacking.

Previous studies were hampered by methodological issues [6,10], such as small or selected patient groups, performed in occupational settings, or included reference groups based on data from national statistics. These study designs may thus be liable to mechanisms that increase the possibility of false positive results.

In the large ongoing Rotterdam Study, an unselected population, we studied the association between various definitions of OA and long-term risk of CVD. We additionally examined the role of disability in explaining the apparent association between OA and CVD occurrence.

Methods

Study design, setting, and population

The Rotterdam Study is a prospective population-based cohort study that started in 1990 to investigate the occurrence and determinants of diseases in a middle age and elderly population [11]. All 10,275 inhabitants aged 55 years and older who had been living for at least 1 year in the Ommoord district of the city of Rotterdam were invited to participate, of which 7,983 agreed. Trained interviewers obtained information at home on current health status, medical history, activities of daily living, joint complaints, and cardiovascular risk factors. Subsequently, all participants were invited to visit the research center for clinical examinations, laboratory assessments, and radiographs, regardless of their health status.

For this study, 1,428 participants with known CVD (defined as a history of myocardial infarction, surgical or percutaneous coronary revascularisation, or stroke) at baseline were excluded. Furthermore, 1,907 persons who either did not visit the research centre or had no radiographs taken due to logistic or technical problems were excluded,

which left us with a total population for analyses of 4,648 persons of whom we assessed CVD at follow-up.

All people provided written informed consent to participate in the Rotterdam Study and to obtain information from their treating physicians, separately. The study was approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam, the Netherlands.

Assessment of OA

In total, 3 definitions of OA were formulated for knees, hips, and hands separately. The first one, radiographic OA (K&L graded score greater or equal to 2), as described in appendix 1. Secondly, we defined clinical OA as the presence of radiographic OA and reported complaints of the same joint in the last month. Finally, we analysed self-reported OA (verified by trained interviewers; "Did you suffer from joint complaints last month which were attributed to OA by a physician?") as a potential phenotype of OA. Since knee OA is highly prevalent and most clearly defined, we decided to show results with this phenotype in the analyses. However, we also analysed hand and hip OA, see Appendix 2.

Assessment of disability

For the assessment of disability the Stanford Health Assessment Questionnaire (HAQ) was used [12]. The HAQ measures disability in eight fields (dressing and grooming, rising, reach, hygiene, eating, walking, grip and activity). Each field comprises two to four items. Per item the status of the respondent is scored as able to do without difficulty (0), with some (1) or much (2) difficulty or unable to do with or without assistance (3). The highest item score determines the final field score. The mean score of all fields constitutes the disability index ranging from 0.00 to 3.00 [13]. In the present study we dichotomised disability as having any disability present in one of the eight fields versus none, irrespective of the presence of OA. In addition, we similarly analysed lower limb disability involving the fields rising and walking only. All values given in our analyses refer to the dichotomised disability variable.

Assessment of covariates

Data on medication use and smoking habits were obtained during the home interview. Smoking was classified as never, former, or current smoking. Established cardiovascular risk factors were measured at the research centre. Body mass index was computed as weight divided by height squared. Blood pressure was measured at the right upper arm using a random-zero sphygmomanometer. We used the average of two measurements measured on one occasion and defined hypertension as a systolic blood pressure of 140 mmHg higher, a diastolic blood pressure of 90 mmHg or higher, or the use

of blood pressure lowering medication for the indication of hypertension. Diabetes mellitus was defined as the use of antidiabetic medication or a non-fasting or post-load serum glucose level exceeding 11.0 mmol/L. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol were determined by means of an automated enzymatic procedure in non-fasting blood samples.

Assessment of CVD

Persons were followed for the occurrence of a first coronary or cerebrovascular event, including myocardial infarction, surgical or percutaneous coronary revascularisations, coronary death, and stroke (both ischaemic and hemorrhagic) confirmed by one of the patients' treating physicians. Methods of data collection and adjudication of events have been described previously in detail [14, 15]. In short, Rotterdam Study participants are followed-up continuously through direct digital linkage of the study base with medical files from the general practitioners working in the research area. Moreover, the entire medical record of each participant is checked on a regular basis for diagnoses of interest. All available information, such as discharge reports, ECGs, and neuroimaging results are copied from the medical records or are obtained from the hospitals. Subsequently each potential CVD event is adjudicated according to standardised definitions by two independent research physicians and either an experienced cardiologist or neurologist.

Statistical analysis

Baseline characteristics are summarized as percentages for categorical data. Continuous data are presented as mean values and standard deviations.

We used eighteen Cox proportional hazard models to estimate the association between OA and risk of incident CVD. All models met the proportional hazards assumption. In the first model, we estimated the association of radiographic knee OA with the occurrence of CVD adjusted for age and gender. In the second model, we additionally adjusted for the following cardiovascular risk factors: hypertension, smoking status, body mass index, diabetes, and total cholesterol to HDL-cholesterol ratio. Likewise, clinical knee OA, and self-reported OA were analysed as different phenotypes of OA. Next, we checked whether there was evidence of effect modification by gender, since previous studies have described associations between OA and subclinical atherosclerosis in women only [2, 16]. This was done by assessing the interaction terms between gender and OA status.

Since a recent study reported an association between walking disability and risk of CVD within OA patients [6] we ran similar Cox models as described above to estimate the association between overall disability and CVD and lower limb disability and CVD; this was done independent of the presence of OA. Last, in order to reduce the potential

diluting effects of misclassification of the outcome we performed a sensitivity analysis restricted to hard atherosclerotic CVD outcomes: myocardial infarction, ischaemic stroke, and coronary death.

Persons free of radiographic knee OA, free of clinical knee OA, and those without self-reported OA were reference categories, respectively. All analyses were performed for hip OA and hand OA as well in an identical manner. Persons were censored at the date of noncoronary or noncerebrovascular death, loss to follow-up, or the end of the study period defined as the last date of follow-up. Approximately 1% of our study population had missing values for one or more cardiovascular covariates. These missing values were handled by single imputation using an expectation-maximisation algorithm [17]. All measures of association are presented with 95% confidence intervals. We used the level of significance of $p<0.05$ for all statistical analyses and the data were analysed using PASW statistical package, version 17.0.2 (SPSS Inc., Chicago, Ill., USA).

Results

Characteristics of the study population

Baseline characteristics of the study population free of CVD at baseline are summarised in table 1. The mean age of the 4,648 persons in this study was 67.6 years, and 61% were women. During a median follow-up time of 14.4 years (interquartile range 7.6 years) a total of 1,230 CVD events occurred, of which 101 in the participants with clinical knee OA. These events consisted of 304 myocardial infarctions, 64 coronary artery bypass

Table 1. Baseline characteristics of the study population.

Variable	All (n=4648)	Knee OA* (n=336)	Hip OA* (n=134)	Hand OA* (n=339)
Age, years	67,6 ± 7,9	71,0 ± 8,2	72,0 ± 7,7	69,8 ± 7,6
Male gender, %	39	21	15	13
Body mass index, kg/m2	26,3 ± 3,6	28,2 ± 4,1	27,4 ± 3,9	27,2 ± 4,1
Cholesterol/HDL ratio	5,2 ± 1,6	5,1 ± 1,6	5,1 ± 1,5	5,1 ± 1,5
Diabetes, %	9	9	11	11
Current smoking, %	24	17	19	16
Hypertension, %	53	63	55	61
Disability, %	57	85	90	75
Radiographic Knee OA†, %	21	100	19	53
Self-reported OA , %	18	56	63	19

Categorical variables are presented as percentages. Continuous variables are expressed as means and corresponding standard deviations. HDL = high density lipoprotein, OA = osteoarthritis
† Kellgren-Lawrence score ≥2 in at least one joint.
* Radiographic OA and reported complaints of the same joint during the last month.

grafts, 69 percutaneous coronary interventions, 215 other fatal coronary heart disease events, and 578 strokes (of which 60 confirmed haemorrhagic). Only 41 (<1%) persons were lost to follow-up.

Osteoarthritis and cardiovascular disease

The associations between OA of the knees and incident CVD are shown in table 2. After adjustment for age and gender, we found no association between radiographic knee OA and incident CVD (HR 0.99, CI 0.86 to 1.15), neither between clinical knee OA and CVD (HR 1.08, CI 0.88 to 1.33), or between self-reported OA and CVD (HR 1.08, CI 0.93 to 1.24). Further adjustment for cardiovascular risk factors did not change the results. Interaction by gender could not be demonstrated (p=0.34) and the sensitivity analyses with hard CVD only did not alter the results. We performed identical analyses for hand and hip OA; the corresponding results are presented in appendix 2. Results for hand OA or hip OA were not different from those for knee OA.

Table 2. Knee osteoarthritis and risk of incident cardiovascular disease.

		Hazard ratio (95%CI)	P-value	Hazard ratio (95%CI)	P-value
		Total CVD (n=1230)		Hard CVD (n=889)	
Radiographic OA†	Model 1*	1.00 (0.87 to 1.15)	0.96	1.03 (0.88 to 1.21)	0.72
	Model 2**	0.99 (0.86 to 1.15)	0.92	0.99 (0.84 to 1.17)	0.91
Clinical OA ‡	Model 1*	1.08 (0.88 to 1.33)	0.45	0.99 (0.77 to 1.28)	0.95
	Model 2**	1.09 (0.88 to 1.34)	0.43	0.96 (0.75 to 1.24)	0.76
Self-reported OA	Model 1*	1.08 (0.93 to 1.24)	0.32	1.07 (0.94 to 1.21)	0.33
	Model 2**	1.09 (0.94 to 1.26)	0.26	1.09 (0.95 to 1.24)	0.24

CI = confidence interval, OA = osteoarthritis, CVD = cardiovascular disease
Total CVD = myocardial infarction, surgical or percutaneous coronary revascularisation, coronary mortality and stroke (ischaemic and hemorrhagic)
Hard CVD = myocardial infarction, ischaemic stroke, and coronary mortality
† Kellgren-Lawrence score ≥2 in at least one joint, ‡Kellgren-Lawrence score ≥2 and complaints in the same joint during the last month
* adjusted for age and sex
** adjusted for age, sex, body mass index, diabetes, hypertension, total cholesterol/HDL cholesterol ratio, and smoking

Disability and cardiovascular disease

After adjustment for age and gender, disability was strongly associated with incident CVD (HR 1.30, CI 1.15 to 1.46). Full adjustment for body mass index, diabetes mellitus, hypertension, total cholesterol/HDL cholesterol ratio, and smoking slightly attenuated the association somewhat (HR 1.26, CI 1.12 to 1.42). Sensitivity analyses with lower limb disability only were not substantially different from overall disability. This is demonstrated in table 3. Age and gender adjusted survival curves according to disability status,

stratified on the presence of clinical knee OA, are shown in figures 1a and 1b. There was no evidence for interaction between disability and clinical knee OA status (p=0.89).

Table 3. Disability and risk of incident cardiovascular disease.

		Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
		Total CVD (n=1230)		Hard CVD (n=889)	
Disability	Model 1*	1.30 (1.15 to 1.46)	<0.001	1.29 (1.12 to 1.49)	0.001
	Model 2**	1.26 (1.12 to 1.42)	<0.001	1.22 (1.06 to 1.41)	0.007
LL disability	Model 1*	1.22 (1.08 to 1.38)	0.002	1.26 (1.09 to 1.45)	0.002
	Model 2**	1.19 (1.05 to 1.34)	0.008	1.18 (1.02 to 1.37)	0.03

CI = confidence interval, CVD = cardiovascular disease, LL = lower limb.
Total CVD = myocardial infarction, surgical or percutaneous coronary revascularisation, coronary mortality and stroke (ischaemic and hemorrhagic)
Hard CVD = myocardial infarction, ischaemic stroke, and coronary mortality.
* adjusted for age and sex
** adjusted for age, sex, body mass index, diabetes, hypertension, total cholesterol/HDL cholesterol ratio, and smoking

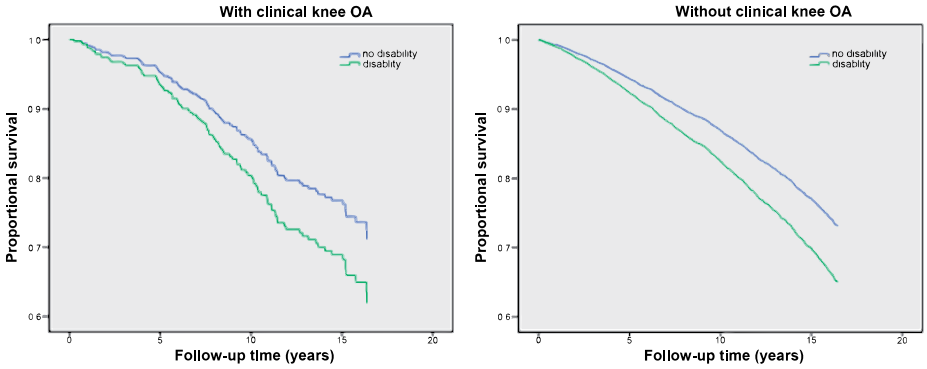


Figure 1. Age and gender adjusted CVD-free survival curves for non-disabled and disabled participants in A) participants with clinical knee OA, and B) participants free of clinical knee OA.

Discussion

In the present study, we examined the association of different phenotypes of OA with the long-term risk of CVD in a prospective population-based cohort. We showed that the presence of OA is not related to incident CVD in adults aged 55 years and older. However, overall and lower limb disabilities are risk factors for CVD, independent of OA status.

Context

Our study was prompted by the recent report by Nüesch et al [6] who found that OA patients were at higher risk of cardiovascular death compared with their age and gender matched peers. This study was performed in a group of OA patients compared to national statistics where data on covariates were not available. As a result, they could not correct for significant confounding variables such as comorbidities or disability. Furthermore, selection of diseased patients into their study may have led to inflated estimates. This is referred to as the sick-person-effect [18].

We used a population-based cohort with detailed data on cardiovascular covariates and disability, also for persons without OA, and were thereby able to provide a less biased estimate of the association. Given that we did not find an association between several phenotypes of OA and cardiovascular endpoints in our study population, we also investigated other phenotypes. When we analysed summed K&L scores of the knees, hands or hips separately or included all total joint replacements due to OA as markers of severity of OA the results did not alter. This was also the case when we compared participants with generalized OA (at least two out of three joint groups affected) to participants without any OA. Moreover, the association of OA with the various components of the composite CVD outcome (coronary heart disease and stroke) analysed separately did not change our results (data not shown). In the present study disability – defined by the HAQ questionnaire – strongly predicted CVD independent of clinical OA status. Our results therefore support the view that disability, and not OA, predicts CVD [19]. Disability might represent a marker of the general health status rather than a representation of specific underlying chronic diseases such as OA. Further studies are needed to investigate whether HAQ disability contributes to improved cardiovascular risk stratification in the population at large and to identify underlying causes of disability in order to ameliorate excess cardiovascular risk.

Implications

The relation between OA and increased risk of future CVD mortality, as found by Nuesch et al suggested intensive treatment of cardiovascular risk factors in OA patients [6]. Before implementing OA as another red flag into CVD prevention guidelines, we considered it necessary to critically assess this claim in a robust population-based study. In contrast to Nuesch et al, we excluded persons with known CVD at baseline to investigate whether OA patients were at high risk of CVD. We demonstrated that OA is not an independent risk factor for the development of incident CVD in a population-based setting.

Strengths and limitations

The major strengths of the present study are its vast size, the long-term highly detailed follow-up, the community-based setting, and moreover the use of an internal reference population for comparing people with OA to those free of OA. A substantial number of people with OA – defined both by radiographs, and by symptoms – were included and the median follow-up time was 14.4 years.

However, residual confounding has to be considered. As we did not measure physical fitness and had no reliable information on medication use without a prescription, additional confounders might exist. In addition, participation bias, occurring in all studies requiring active participation, may have influenced our results.

The main aim of this study was to investigate whether physicians should consider OA patients at high risk of CVD. Our study population comprised persons aged 55 years and older and we were thereby unable to look into the association between OA and CVD in younger individuals. A cardiometabolic phenotype of OA [20] in younger women characterized by low-grade inflammation by visceral adipose tissue [21] might exist. Although both conditions share aetiological features [3, 16] and risk factors, we did not focus on a common pathophysiology by investigating subclinical measures of atherosclerosis. This complex and promising field of research merits further elucidation and will be investigated in depth in future studies with currently gathered data from younger women [11].

Conclusions

In this population-based study, persons with OA were not at increased risk of developing CVD compared to those without OA. The close relation between disability and OA may explain earlier findings of a relation between OA and risk of CVD. Further studies are required to clarify whether younger OA patients than in the present study benefit from more intensive treatment of their cardiovascular risk factors.

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Appendix 1.

Knee, hand, and hip radiographs were taken and scored with a Kellgren-Lawrence grade scaled 0-4. Radiographs of the pelvis were obtained with both feet rotated 10° inward and the X-ray beam centred on the umbilicus and knee radiographs were taken with the knee extended and the patella in a central position. Assessment was done blinded for clinical data. The intraclass correlation coefficient was 0.71 for the knee and 0.74 for the hip [16,22,23]. Radiographic knee and hip OA were defined as a K&L score of 2 or higher present in at least one joint. Persons with total joint replacements (knees; n=10, hips; n=113) at baseline were excluded from the analyses. The hand joints were divided into distal interphalangeal (DIP), proximal interphalangeal (PIP), and first carpometacarpal/trapezioscaphoid (CMC1/TS, base of thumb) joint groups where OA was considered present if at least one joint of the group scored a K&L grade of 2 or higher. Radiographic hand OA was defined according to the Rotterdam definition: present if at least 2 out of 3 hand joint groups (DIP/PIP/CMC1 or TS) had a K&L score of 2 or higher in at least one hand [24]. For the handjoints the intraclass correlation coefficient was as follows: DIPs; 0.69, PIPs; 0.74, CMC1/TS (base of thumb); 0.84.

Appendix 2.

Hand osteoarthritis and risk of incident cardiovascular disease.

		Hazard ratio (95% CI)	Hazard ratio (95% CI)
		Total CVD (n=1239)	Hard CVD (n=804)
Radiographic OA †	Model 1*	0.91 (0.80 to 1.03)	0.97 (0.83 to 1.13)
	Model 2**	0.93 (0.82 to 1.06)	0.97 (0.83 to 1.14)
Clinical OA ‡	Model 1*	1.04 (0.84 to 1.29)	1.22 (0.94 to 1.57)
	Model 2**	1.08 (0.87 to 1.34)	1.25 (0.97 to 1.61)
Self reported OA	Model 1*	1.08 (0.94 to 1.25)	1.09 (0.91 to 1.31)
	Model 2**	1.09 (0.94 to 1.26)	1.08 (0.90 to 1.30)

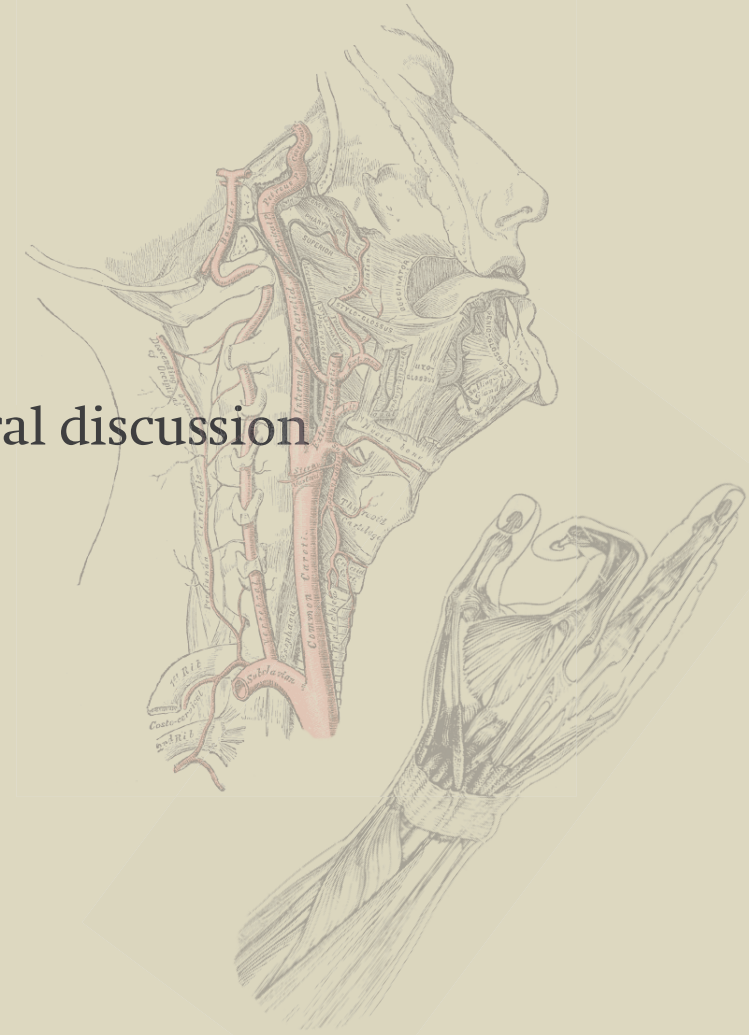
CI = confidence interval, OA = osteoarthritis, CVD = cardiovascular disease
Total CVD = myocardial infarction, surgical or percutaneous coronary revascularisation, coronary mortality and stroke (ischaemic and haemorrhagic)
Hard CVD = myocardial infarction, ischaemic stroke, and coronary mortality.
*adjusted for age and sex
** adjusted for age, sex, body mass index, diabetes, hypertension, total cholesterol/HDL cholesterol ratio, and smoking
† At least 2 out of 3 hand joint groups Kellgren-Lawrence score ≥ 2 in at least one hand
‡ At least 2 out of 3 hand joint groups Kellgren-Lawrence score ≥ 2 in at least one hand, and joint complaints

Hip osteoarthritis and risk of incident cardiovascular disease.

		Hazard ratio (95% CI)	Hazard ratio (95% CI)
		Total CVD (n=1172)	Hard CVD (n=745)
Radiographic OA †	Model 1*	0.98 (0.79 to 1.22)	0.93 (0.70 to 1.22)
	Model 2**	0.97 (0.77 to 1.21)	0.91 (0.69 to 1.21)
Clinical OA ‡	Model 1*	1.03 (0.67 to 1.58)	1.04 (0.61 to 1.76)
	Model 2**	1.01 (0.65 to 1.57)	1.10 (0.65 to 1.87)
Self reported OA	Model 1*	1.09 (0.94 to 1.27)	1.13 (0.94 to 1.36)
	Model 2**	1.08 (0.93 to 1.26)	1.11 (0.92 to 1.34)

CI = confidence interval, OA = osteoarthritis, CVD = cardiovascular disease
Total CVD = myocardial infarction, surgical or percutaneous coronary revascularisation, coronary mortality and stroke (ischaemic and haemorrhagic)
Hard CVD = myocardial infarction, ischaemic stroke, and coronary mortality.
* adjusted for age and sex
** adjusted for age, sex, body mass index, diabetes, hypertension, total cholesterol/HDL cholesterol ratio, and smoking
† Kellgren-Lawrence score ≥2 in at least one side
‡ Kellgren-Lawrence score ≥2 and joint complaints during the last month

07
General discussion



Introduction

The objective of this thesis was to gain insight into the relation between vascular pathology and osteoarthritis (OA). We could not show an association between atherosclerosis and the incidence or progression of OA and could therefore not confirm an initiating role for atherosclerosis in the development of OA. Furthermore, OA was not a risk factor for incident cardiovascular disease. On the other hand, atherosclerosis was associated with prevalent OA of the knee and hand joints among women. Also, plasma levels of biomarkers of early atherosclerosis (CD40L and VCAM-1) were higher in women with knee OA than in those without. The same did not hold for men. These findings are in line with the hypothesis that atherosclerosis and OA are concurrent diseases with a shared aetiology, possibly systemic low-grade inflammation, among women. In this chapter, I first summarize and review the main findings in the context of current knowledge. Because additional cardiovascular risk factors might confound the association between atherosclerosis and OA, the focus will also be on a common precursor of cardiovascular risk factors, namely obesity, in relation to OA. Next, methodological issues are discussed and finally I will reflect on the clinical implications of the reported studies and make suggestions for possible directions of future research.

Atherosclerosis, hand OA and knee OA

In the Rotterdam Study, we found cross-sectional associations between carotid atherosclerosis and knee and hand OA among women aged ≥55 years, after adjustment for potential confounders (**chapter 2**). The evidence was most solid for a relation with distal interphalangeal (DIP) OA of the hands. Several other studies have found associations between subclinical measures of atherosclerosis and OA, suggesting either a local effect, a systemic effect, or both.[1-4]

A possible systemic effect is most pronounced in the aetiology of hand OA. Saleh et al.[1] previously reported a relation between arterial stiffness and hand OA that was largely confounded by age. In addition, Jonsson and colleagues[2] demonstrated that atherosclerosis and OA of this non-weight bearing joint were associated among older women (mean age 76 years); both carotid plaques and coronary artery calcifications showed a linear trend with hand OA severity. Analyses were adjusted for age, body mass index (BMI) and other cardiovascular risk factors. These findings were confirmed in another large cohort among elderly women (mean age 69 years) in **chapter 2**. Moreover, OA in any finger joint predicted cardiovascular death in a Finnish study.[5]

It is remarkable that an association between atherosclerosis and hand OA is mainly found among older women. Assuming that this relation exists based on the evidence

described above, what underlying mechanism is most probable? In menopause, production of estrogen diminishes and the incidence of both cardiovascular disease and OA rises faster compared to men in the same age-bracket.[6-9] The menopausal transition also induces a rapid increase in fat mass and redistribution of fat to the abdomen.[10] Furthermore, women generally have a higher fat percentage and more fatmass compared to men.[11] Possibly, an inflammatory effect of adipose tissue, also known as metabolic syndrome, contributes to the development of both atherosclerosis and hand OA among women.[12] It is known that adipose tissue is not inert and actively contributes to systemic inflammation through the secretion of inflammatory cells; abdominal fat especially is believed to act as an inflammatory mediator.[13,14] However, additional investigation is warranted to test this hypothesis. Whether similar mechanisms play a role in men remains to be determined. Also, genetics and residual confounding cannot be ruled out in the apparent association between atherosclerosis and hand OA among women. These issues will be further discussed in the methodological considerations paragraph.

Previous studies on atherosclerosis and knee OA are inconclusive. Reported associations are consistent neither for different measures of atherosclerosis, nor for early features of knee OA. For instance, Davies-Tuck et al.[3] found that increased retinal vascular diameters were associated with early features of knee OA detected with magnetic resonance imaging (MRI) among 289 women with no knee symptoms. Analyses were adjusted for age and BMI. By contrast, no association was reported between aortic stiffness and bone marrow lesions (early features of knee OA) among 208 individuals with symptomatic knee OA.[15] Also, we could not show a relation between carotid atherosclerosis and similar signs of early knee OA (**chapter 4**). Our study population and methodology were similar to the study that investigated the retinal vasculature. We don't have a clear explanation for these discrepancies. Microvascular pathology (as reflected in the retina) might be more important in the pathogenesis of knee OA than large artery atherosclerosis. Visual impairments and OA are indeed a common comorbid pair.[16] Studies focused on the retinal vasculature as a reflection of OA activity are therefore needed.

Interestingly, recent studies showed that a local effect of atherosclerosis might contribute to development of knee OA. Increased popliteal arterial wall thickness was associated with symptomatic knee OA[4] and predicted adverse changes in knee structure (reduced medial tibial cartilage volume and BML deterioration) two years later in a population without clinical knee OA (n = 254). It remains unclear whether increased wall thickness of the popliteal artery near the knee is a localized or generalized medium-sized artery phenomenon. Locally, a reduced blood flow by popliteal atherosclerosis near the knee might affect the subchondral bone, thereby initiating the knee OA disease process. Yet, a recent study found no reduced blood flow in the main vessels supplying the knee joints in 39 female bilateral knee OA patients compared

to 30 healthy controls.[17] Unfortunately, OA patients with hypertension and diabetes were excluded, and knee OA was defined through radiographs. Additional longitudinal studies are warranted to examine a possible causal effect of local atherosclerosis on knee OA development.

To summarize, our findings suggest that systemic processes associated with atherosclerosis contribute most in the aetiology of hand OA.[18] Regarding knee OA, we found less evidence for a systemic effect. Similar differences in the contribution of systemic processes associated with atherosclerosis to OA development of non-weight bearing and weight-bearing joints have been reported in other large cohorts as well.[19,20]

Possible pathways between atherosclerosis and OA

Generalized atherosclerosis (as measured in the carotids, coronary arteries and by serum markers) was not associated with the initiation or progression of OA of the hands, knees, or hips (**chapter 2 and 3**). We therefore did not find evidence to support the theory that atherosclerosis precedes OA. The studies in this thesis are the first large-scale prospective population-based cohort studies that address the association between different measures of atherosclerosis and the initiation or progression of OA and can therefore be viewed as one of the first steps to uncover the link between these two conditions. Unfortunately, the power to analyse progression of OA was limited and definitions of the incidence and progression of OA were based on radiographs that might be unable to detect subtle structural changes within the joints involved. In addition, we did not investigate the thickness of the popliteal artery wall.

In the course of the last decade, several theories on how atherosclerosis contributes to OA have been postulated. We will shortly highlight two hypotheses and add a third one, focused on knee OA.

Possibly, atheromatous disease of the artery disturbs cartilage homeostasis by a reduced blood flow to the synovial membrane and subchondral bone, thereby initiating the OA process[2,21], as shortly mentioned above with regard to the popliteal artery and knee OA. This might occur through mechanical changes of the subchondral bone or pro-inflammatory cells that mediate degradation of the cartilage. Alternatively, the OA disease process could be accelerated instead of initiated by atheromatous disease. It could alter the subchondral bone through direct ischaemic effects (e.g. bone marrow edema). Histologically, bone marrow edema is an area of necrosis and remodeling[22] and may represent ischaemic areas in the bone similar to those in avascular necrosis.[23] Bone marrow edema in the subchondral bone strongly predicts knee OA progres-

sion.[24-26] Hence, atherosclerosis could be more important in the progression to severe joint damage than in the initiation of OA.[27]

We hypothesize that a local effect of adipokines secreted by adipose tissue[28,29] adds to the influence of atherosclerosis on knee OA. Among women, painful knees (early signs of knee OA) are related to a greater inter-muscular fat mass in the thighs. An additional tissue could therefore be involved in the initiation or progression of knee OA, namely adipose tissue in the thigh. We theorize that a cumulative effect of local adipokines[30] released by the fat mass in the thigh (and possibly also the infrapatellar fat pad) exists that deteriorates the knee joint. On a molecular level, adipokines are capable of modulating cross-talk between T-cells and chondrocytes.

However, all these complex theories remain speculative. Hitherto, observational studies have focussed on atherosclerosis and early features of knee OA and were mainly cross-sectional in design. Additional longitudinal and experimental studies are needed to elucidate if and how atherosclerosis and adipose tissue localized near the knee contribute to knee OA development. Also, whether the mechanisms described play a role in hand or hip OA development remains to be determined. Longitudinal magnetic resonance imaging (MRI) knee data from the Rotterdam Study with detailed information on structures involved in KOA development will become available in the next year and might offer additional insights on the role of atherosclerosis and adipose tissue surrounding the knee as initiators or progressors of knee OA.

The role of obesity

Both vascular atheromatous disease and OA are slow progressive disorders that co-occur with many other chronic conditions, which makes their mutual relation complex to analyze and easy to confound. For instance, cardiovascular risk factors such as hypertension, dyslipidemia, and increased glucose levels might influence both atherosclerosis and OA separately. Furthermore, it is not known how these risk factors interact, neither for the initiation, nor for the progression of the OA disease process. For these reasons and because we found evidence for a relation between atherosclerosis and OA that can be explained by a common underlying effect of adipose tissue, we will now shortly focus on the common precursor of cardiovascular risk factors, namely **obesity**, in relation to OA.

Obesity influences the development of OA in various ways. Being overweight obviously increases mechanical forces across weight-bearing joints.[31,32] In addition to loading, systemic factors associated with obesity also play a role.[33] Adipose tissue secretes inflammatory mediators (adipokines) that might increase the incidence and progression

of OA.[34] Mainly visceral fat seems to be important in this process. A strong body of evidence has demonstrated a relation between obesity and hand OA[35,36], thereby suggesting that systemic factors associated with obesity are involved in the development of OA; after all, 'obese people do not walk on their hands'.[37] An excess of adipose tissue might cause a state of permanent low-grade, systemic inflammation[13], also known as metabolic syndrome. Biochemically, the main characteristic of metabolic syndrome is a systemic inflammation caused by visceral adipose tissue that secretes proinflammatory cytokines and adipokines.[14] In clinical practice, metabolic syndrome can be seen as a multiplex cardiovascular risk factor including obesity, diabetes mellitus, hypertension, and dyslipidemia. However, it is unknown whether the concept of a clinical syndrome improves individual cardiovascular risk prediction compared to independent cardiovascular risk factors; a potential accumulative effect of the components of metabolic syndrome remains an area of debate.

Figure 1 schematically highlights obesity in relation to several known and lesser-known processes that are involved in OA development. I focus on the grey rectangle, but it might be clinically relevant to study areas such as pain and comorbidity in relation to OA development as well.

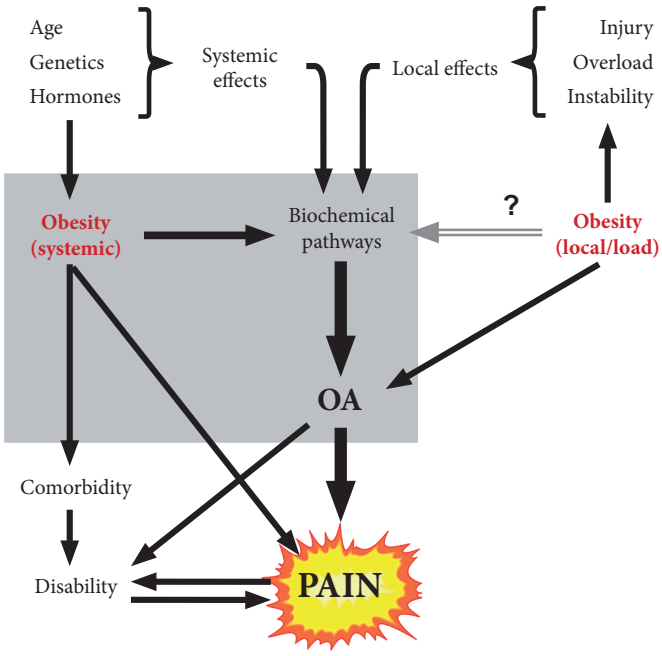


Figure 1. Simplified model of pathways involved in OA pathogenesis. The figure is a modification of the schematic representation of relations between environmental and endogenous risk factors for OA and its consequences as proposed by Dieppe and Lohmander. (see general introduction, figure 2)

A metabolic OA phenotype?

As visualized in figure 1, OA is a complex multifactorial disease that can be seen as a final common pathway to many predisposing factors, age, gender, genetics, trauma, and mechanical load being the key ones. Anything that can be intervened with within these pathophysiological processes is a potential phenotype of OA. In one individual, several different OA phenotypes might co-exist and interact, which complicates this area of research. Therefore, observational studies probably cannot prove phenotypes of OA. Nonetheless, suggestions for phenotypes of OA have increased in number in the last decade[38-41] and have led to an intense debate. This is understandable, because every phenotype is a potential target for randomized clinical trials[40] and is in essence therapeutically different. No disease-modifying treatment for any subgroup of OA exists just yet. We attempt to add to the discussion by proposing a combination of a joint-based and pathophysiology-based model.

It is well-known that knee OA is a strong predictor for hand OA[42,43] and vice versa.[44] They share several risk factors, and inflammatory mediators (adipokines) released by adipose tissue might influence both phenotypes[36,45,46], albeit more pronounced in hand OA. Based on a review of the scientific literature of the last 5 years, a clinical OA phenotype was proposed recently among obese women aged 45-65 years affecting mainly hand and knee joints.[41] In the Rotterdam Study, atherosclerosis and OA of the hand and knee joints were also associated among women (mean age 68.6 years) (**chapter 2**), which supports the proposed metabolic phenotype. Among middle-aged women similar measures of generalized atherosclerosis were not associated with early features of knee OA (**chapter 4**), but the power was limited.

Taken together, there is evidence suggesting a clinical metabolic OA phenotype of the hand and knee joints that might be restricted to women. Inflammatory mediators released by adipose tissue could be a specific therapeutic target, next to weight loss.[41] Although this potential phenotype is not yet fully characterized, it might provide a starting point for further research and discussion. OA pathogenesis might proceed via unique gender-specified pathways based on underlying hormonal and anatomic differences. In our search for a better understanding of metabolic contributions to OA, it is important to evaluate potential gender-differences.[47] Particularly the metabolic effects of menopause deserve more attention.

Menopause

In menopause, production of estrogen diminishes and the incidence of both cardiovascular disease and OA rises faster compared to men in the same age-bracket.[6-9] This

sudden increase might be due to the loss of a protective effect of estrogen. However, in a large prospective cohort study hormone replacement therapy did not improve cardiovascular outcome in postmenopausal women.[48] In addition, a recent systematic review found no clear association between female hormonal aspects and the development of OA.[49] Investigations of hormonal aspects of menopause are complicated by the production of estrogen by body fat and the fact that estrogen levels in premenopausal women change almost daily. Maybe, the role of female hormones is more complex than can be shown by population-based association studies.

Unfortunately, in vivo and in vitro studies on female hormones and OA add to this complexity. A systematic review showed considerable evidence for a relation between ovariectomy (female hormone depletion) and cartilage degeneration in mature animals.[50] However, evidence for the effect of estrogen suppletion on cartilage and subchondral bone was inconclusive or conflicting. For example, intra-articular high-dose estradiol injections administered to rabbits led to detrimental effects on cartilage tissue[51], whereas in ovariectomized mice estradiol injections had a beneficial effect on cartilage and subchondral cortical thinning.[52] Such discrepancies might be due to large variations in experimental setup, but also reflect the difficulties in epidemiological and experimental research focused on estrogens and OA. Estrogens affect numerous articular tissues in the human body through direct and indirect mechanisms that are not fully understood.[53,54] Several reviews suggest that estrogens have the ability to interact with known and unknown inflammatory cytokines released by chondrocytes, and that next to estrogen receptor (ER) upregulation other processes (free radical scavengers) can be involved in estradiol-induced cartilage damage.[55]

With regard to the pathway between estrogens, menopause and cardiovascular disease, questions remain as well. On a molecular level, estrogens might reduce atherosclerosis by binding to estrogen receptors (ER). Mainly ERα seems to be important in altering gene expression and thereby vascular cell function. ERα expression is strongly related to endothelial dilatation and is reported to be more than 30% lower in postmenopausal women than in premenopausal women.[56] However, many aspects of these complex signaling ER pathways remain unknown and they are strongly influenced by disease and age.[57] On a population level, Gast et al.[58] recently demonstrated that women with menopausal symptoms (night sweats) have an increased risk of coronary heart disease, which cannot be totally explained by the levels of cardiovascular risk factors. Furthermore, data from the Framingham Heart Study suggest that a harmful cardiovascular risk profile may be more cause than consequence of age at menopause.

The pathway between menopause, cardiovascular disease, and osteoarthritis seems to be highly complex and much remains to be discovered.

It is possible that the risks imposed by menopause, metabolic syndrome and atherosclerosis somehow depend on each other, which might explain some of the complexities in OA aetiology that are not well understood. A study also analyzing data from the large Rotterdam cohort suggests that menopause as a risk factor for OA depends on body mass index. Menopause was related to both osteophytes and bone marrow lesions, but only among obese women (de Klerk, preliminary data). Following this reasoning, menopausal status might act as a moderator of the influence of metabolic syndrome on the development of OA. Alternatively, menopausal status could influence OA indirectly, by influencing metabolic syndrome (**figure 2**). Whether similar mechanisms hold true for the thickness of the arteries above a certain cut-off remains to be determined.

In summary, atherosclerosis, metabolic syndrome, menopause and OA are all slow and complex processes that are prone to interacting factors. The pathway of atherosclerosis (or metabolic syndrome) to OA and the moderating effect of menopause herein merit further research.

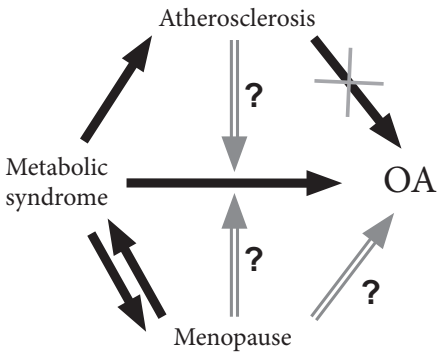


Figure 2. Schematic representation of the complex relation between metabolic syndrome, atherosclerosis, menopause and OA. Arrows indicate causal pathways.

Methodological considerations

All studies described in this thesis were part of the Rotterdam Study, a prospective population-based study.[59] Unfortunately, population-based studies are scarce worldwide, probably due to high costs (large sample sizes, many measurements and long follow-up periods) and logistical challenges. Yet, I advocate conducting population-based cohort studies with clinical outcome measures. They provide a wide range of exposure-disease associations in an unselected population. Another advantage is the external validity – that is, the applicability of results to a defined population.[60]

Observational studies such as the Rotterdam Study are used to study the incidence and causes of disease. The 'Ommoord cohort', comprising a huge data set of an adult

population with prospective data on, among others, measurements of atherosclerosis (including both imaging and serum markers), features of local and widespread OA (radiographic imaging, MRI), and potential confounders over a ten-year period, has given us the opportunity to investigate the mechanism of action of vascular pathology in OA. However, cohort studies may be subject to data dredging and bias.[61] Although we have tried to minimize these issues by high response rates, minimal loss to follow-up, pre-defined hypotheses, and adjustment for known confounders, bias can never be totally ruled out. For instance, there are many serum markers of atherosclerosis; which ones reflect atherosclerosis best remains area of debate. Originally, we planned to look at von Willebrandfactor as a serum marker of atherosclerosis as well. However, based on discussions with experts in cardiovascular epidemiology and a consultation of the scientific literature[62,63] we chose vascular cell adhesion molecule, CD40 ligand, and vascular endothelial growth factor.

Karasik et al.[64] showed in the Framingham Heart Study that hand osteophytes were not associated with abdominal aortic calcification, after adjustment for age, sex, body mass index, smoking, alcohol consumption, physical activity, systolic blood pressure, total cholesterol level, diabetes, and estrogen replacement therapy. Unfortunately, we did not have reliable information on activity levels and were unable to adjust for this potential confounder. Being physically inactive is a key risk factor for OA, disability, and cardiovascular disease and might thus be a significant "hidden" confounder that explains the association found between atherosclerosis and OA. In addition, vascular pathology and osteoarthritis are slow and complex disorders, often accompanied by other diseases.[65,66] Analyses are always complicated by bio-psychosocial factors including lifestyle and mental health (residual confounding). Residual confounding also hampered the interpretation of classical epidemiological methods in this thesis (**chapters 2, 3, and 4**).

In a Mendelian randomization study, we therefore investigated whether genetically defined elevated levels of glycemic traits were associated with the presence of OA of the knee, hip and hand (**chapter 5**). The random assortment of alleles at the time of gamete formation results in population distributions of genetic variants that are generally independent of behavioral factors that confound epidemiological associations.[67] Single nucleotide polymorphisms (SNPs) that are genome-wide significant are used to construct genetic risk scores (GRS) for chronic diseases such as diabetes and OA. In other words, GRS identify persons at increased risk for a chronic disease based on their genetic profile. In contrast to atherosclerosis and OA, many SNPs are known for glycemic traits with moderate to large effect sizes. In our case, we chose genetically defined elevated glucose levels, but other components of the metabolic syndrome, such as higher cholesterol levels, could be another field of research. A recent study using a similar Mendelian randomisation approach clearly showed that body mass index plays

a causal role in the development of OA. It might also identify other independent risk factors for OA and provide further insights into the biological processes that underlie OA susceptibility.[68]

Generalized estimating equations (GEE), taking into account both extremities, were used to adjust for correlations between the right and left extremity in each individual and to increase discriminative ability (**chapter 2, 3, and 4**). However, atherosclerosis is most likely a systemic condition and adjustment for the correlation between both extremities might not be essential and could theoretically distort the association. We therefore also constructed several logistic regression models on a person level to provide additional insight into how the link between atherosclerosis and OA might be driven. These models showed similar results as the GEE models. Because GEE increases power and discriminative ability, we prefer GEE-based analyses in OA research.

In a mediation analysis (Sobel-test) we found that OA precedes disability (**chapter 6**). This is not new evidence[69], but studying if and how OA causes disability remains a challenge.[70] There are other chronic diseases that co-exist with OA and that might cause disability.[71,72] **(figure 3).** Interestingly, Reeuwijk et al[73] recently investigated which co-existing disorders are disabling among hip or knee OA patients in order to eventually develop functional exercise therapy. They found that chronic back pain, diabetes, hearing impairment, visual impairment, dizziness in combination with falling, hand OA, and especially being overweight, were associated with disability. Unfortunately, OA patients were recruited from hospitals and rehabilitation centers. It might be worthwhile to start a similar study in a general population suffering from OA as well. Questionnaires or medical record review could be used to determine comorbidities, disability and for instance pain.

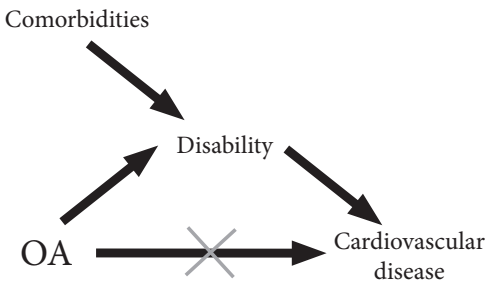


Figure 3. Schematic representation of the relation between OA, disability, and cardiovascular disease. Arrows indicate causal pathways.

Clinical implications

The main objective of **Chapter 6** was to investigate whether physicians should consider OA patients at high risk of cardiovascular disease (CVD). Before including OA as another red flag in CVD prevention guidelines similar to conditions such as rheumatoid arthritis or gout[74,75], as proposed by the British Medical Journal[76,77], we considered it necessary to critically assess this claim in a robust population-based study. In contrast to previous studies, we excluded persons with known CVD at baseline to investigate whether OA patients were at high risk of CVD. We demonstrated that OA is not an independent risk factor for the development of incident CVD in a population-based setting. Our recommendation is therefore not to include OA into CVD prevention guidelines.

Disability, however, was a risk factor for CVD, independent of OA status. Even minimal activity limitations as defined by the Stanford Health Assessment Questionnaire (for instance being unable to stand up from a straight chair) already led to a higher risk of cardiovascular disease.

Because several studies have shown that obesity is causal in both disability and OA we stress the need for the prevention of overweight in vulnerable periods in life, for example during menopause and young adulthood.[78] This suggestion for the prevention of overweight is not derived directly from our findings, but it is clinically relevant, at least in western industrialized countries; due to rapid aging the prevalence of chronic conditions such as obesity will rise. In addition, campaigning for healthy eating, weight control and exercise in younger populations is likely to be more cost-effective than the treatment of the pain and disability that result from overweight later in life.[79] Although aggressive marketing strategies by food companies and a long lag period between weight gain and clinical OA or disability complicate successful intervention, there are strong indications from observational studies that avoiding weight gain reduces the odds of developing OA.[79-81] Also obese patients with knee OA could benefit on a functional and structural level taking into account the following 'lifestyle-rules'[82-84]:

1. Lose weight when overweight or obese.
2. Be as physically active as possible.
3. Replace sedentary time with light activity.

Generally, the self-awareness of health and identification of risk factors needs more attention, which should also result in a better prevention of cardiovascular events.[85]

OA is a disease with a high rate of comorbidities (68-85%).[86,87] Hypertension, diabetes type II, dyslipidemia, and obesity are most often mentioned as comorbid disorders in prevalence studies.[88,89] OA can thus also be seen as a multimorbid disorder. The concept of multimorbidity (i.e. coexistence of 2 or more chronic conditions) needs further consideration. Disorders not seen as the primary condition are often undertreated[90] and there are patterns of multimorbidity beyond chance.[91] Visual impairment in particular

deserves more attention. It often co-exists with OA[16,73], leads to activity limitations and might reflect a burden of vascular disease that has accumulated over time. Also, obesity is underexposed, but plays a central role in many conditions.

In a few medical specialties, attempts at paradigm shifts are being made. Recently, the American college of cardiology strongly suggested to change current treatment strategies in cardiac care by involving comorbidities such as chronic obstructive pulmonary disease.[92] We support adding comorbidities to current treatment guidelines; especially chronic diseases that influence physical functioning deserve extra attention. Sooner or later, multimorbidity will lead to disability, poor quality of life and an elevated risk of dying.[93] We found indications for this pathway in **chapter 6**. We therefore also advocate a more generalistic view of health, transcending medical specialties. A first step could be to adjust current treatment guidelines for comorbid disorders. Altogether, the management of multiple diseases in particularly the elderly requires complex therapy and care, and remains an important challenge in health care. General practitioners might be the ones best equipped to provide this complex form of care, also because the majority of people is treated within primary care facilities.

Future research

Although epidemiological studies on atheromatous vascular disease and OA – by us and others – have contributed to our understanding of the aetiology of both atherosclerosis and OA, many aspects remain unclear. Several unanswered questions have already been mentioned throughout this chapter and are shortly repeated below.

A metabolic OA phenotype might exist that affects knee and especially hand joints among women. Inflammatory mediators secreted by adipose tissue could be the most important actors, explaining the co-occurrence of vascular disease and OA (multimorbidity). Therefore, OA as a multimorbid disorder on the whole might be a direction for future research. Unselected general populations are a promising source of information to gain insight into patterns of multimorbidity. In addition, the complex relation between obesity, menopause and OA needs to be studied more extensively. The possible moderating effect of menopause on the association between obesity and OA could be investigated by a structural equation modeling approach taking latent variables into account. Finally, the role of popliteal atheromatous disease and surrounding adipose tissues in the development of knee OA needs further consideration, similar to the retinal vasculature as a reflection of OA activity.

I have stressed the importance of large population-based studies for studying incidence and determinants of chronic disease in this thesis. However, to understand the underlying pathophysiology of atherosclerosis and OA, we have to combine the

knowledge derived from epidemiological studies with discoveries in the field of basic immunology and human genetics, i.e. interdisciplinary research. The implications of insights for clinical practice can be addressed in appropriate clinical trials.

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Summary

Osteoarthritis (OA) is the most frequent joint disorder worldwide and causes a considerable burden of pain, disability, and ever increasing costs to society. OA is considered to be a multifactorial disease and its aetiology involves biomechanical, genetic, inflammatory and hormonal factors. Several studies have identified age, female sex and obesity as key risk factors for OA. The involvement of other potential risk factors such as diabetes, menopause, and cholesterol in the disease process suggests that OA could be part of the metabolic syndrome, a condition with as its main characteristic systemic inflammation caused by visceral adipose tissue. An important clinical manifestation of the metabolic syndrome is atherosclerosis.

Atherosclerosis is the underlying cause of 50% of all deaths in western societies. It is a multifactorial progressive condition characterized by the accumulation of lipids and fibrous elements in the arterial walls. Eventually, accumulation of risk factors (age, hypertension, diabetes mellitus, obesity) leads to an acute clinical event (such as a myocardial infarction or stroke) as a result of plaque rupture and thrombosis.

Because several epidemiological studies indicated a relation between subclinical measures of atherosclerosis and OA, we examined OA as a risk factor for cardiovascular disease and focused on the chronic inflammatory process of atherosclerosis and its relation with osteoarthritis in a population-based setting. Previous studies hypothesized that atherosclerosis and OA could either be **concurrent diseases** with a shared aetiology or that atherosclerosis could play an **initiating role** in OA; circulatory disturbances in the synovial membrane and subchondral bone could contribute to the cartilage destruction and the pathophysiological process of osteoarthritis. This may occur through mechanical changes of the subchondral bone, or more directly through bone-derived cytokines causing degradation of the cartilage.

The overall goal of this thesis was to investigate whether atherosclerosis and OA are concurrent conditions with shared pathophysiological mechanisms or rather that atherosclerosis acts as a risk factor for OA. All studies were performed within the framework of the large population-based Rotterdam Study, comprising a huge data set of an adult population with prospective data on a large number of objective measurements of atherosclerosis, confounding factors as well as on features of local and widespread OA over a ten-year period. **Chapter 2, 3, and 4** report on atherosclerosis and OA as concurrent diseases and atherosclerosis as an initiator or progressor of OA.

In **chapter 2,** we examined whether vascular alterations (carotid intima media thickness and carotid plaque) were associated with the presence and progression of OA of the knee, the hip, and the different hand joints among 2,372 men and 3,278 women in the first cohort of the Rotterdam Study. Independent associations between subclinical atherosclerosis and prevalent OA of the knee and hand joints were found among women. The evidence was most solid for a relation with distal interphalangeal OA of the hands. The same cohort, only older was investigated in **chapter 3.** Additional markers of early and late atherosclerosis in relation to presence and progression of knee osteoarthritis were evaluated. Serum levels of biomarkers of early atherosclerosis (CD40L and VCAM-1) were higher in women with knee OA than in those without. The same did not hold for men. These findings are in line with the hypothesis that atherosclerosis and OA are concurrent diseases with a shared aetiology, possibly systemic low-grade inflammation, among women. However, in **chapter 4**, cross-sectional associations between subclinical atherosclerosis and OA could not be replicated among younger middle-aged women (third cohort of the Rotterdam Study) and early features of knee osteoarthritis detected with sensitive magnetic resonance imaging. In addition, we could not show an association between atherosclerosis and incidence or progression of OA (**chapter 2 and 3**) and could thereby not confirm an initiating role for atherosclerosis in the development of OA.

Classical observational studies into the causal relation between a risk factor and a disease can result in contradictory findings due to confounding factors. For osteoarthritis this might be the case with type 2 diabetes. A solution is to conduct a Mendelian randomisation (MR) analysis, which uses genetic variation as a surrogate marker for the risk factor (Instrumental-variable-approach). We explored this method in chapter 5 and found that persons with genetically defined elevated levels of fasting glucose and fasting insulin were not at higher risk of OA. However, the power of a MR analysis depends on the fraction of total variance explained, which was relatively low (0.9% and 0.4%). Therefore, similar analyses should be done when further genetic associations with glycemic traits are discovered, and in a larger context.

The main objective of **Chapter 6** was to examine whether physicians should consider OA patients at high risk of cardiovascular disease (CVD). Previous studies found an association between OA and risk of CVD and therefore suggested intensive treatment of cardiovascular risk factors in OA patients, similar to conditions such as rheumatoid arthritis or gout. Yet, prospective population-based data was lacking. Before implementing OA as another red flag into CVD prevention guidelines, we considered it necessary to critically assess this claim in a robust population-based study. We demonstrated that OA is not an independent risk factor for the development of incident CVD in a

population-based setting. Our recommendation is therefore not to include OA into CVD prevention guidelines.

Chapter 7 reflects on the main findings of this thesis. We could not show an association between atherosclerosis and the incidence or progression of OA and could thereby not confirm an initiating role for atherosclerosis in the development of OA. Furthermore, OA was not a risk factor for incident cardiovascular disease. On the other hand, atherosclerosis was associated with prevalent OA of the knee and hand joints among women. A metabolic OA phenotype might exist that affects knee and especially hand joints among women. Inflammatory mediators secreted by adipose tissue could be the most important actors, explaining the co-occurrence of vascular disease and OA (multimorbidity). Therefore, OA as a multimorbid disorder on the whole might be a direction for future research.

Nederlandse samenvatting

Artrose is wereldwijd de meest voorkomende gewrichtsaandoening en leidt tot pijn, fysieke beperkingen, en almaar stijgende kosten voor de samenleving. De ziekte wordt gezien als een multifactoriële aandoening en is het eindresultaat van biomechanische, genetische, inflammatoire en hormonale oorzaken. Verschillende studies laten zien dat leeftijd, het vrouwelijke geslacht en obesitas belangrijke risicofactoren zijn voor het krijgen van artrose. De invloed van andere potentiële risicofactoren zoals diabetes, de menopauze, en cholesterol suggereert dat artrose deel uitmaakt van het zogenaamde metabool syndroom. Een syndroom met als belangrijkste kenmerk systemische ontsteking, mogelijk als gevolg van visceraal vetweefsel. Een belangrijke klinische uiting van het metabool syndroom is atherosclerose.

Atherosclerose is de onderliggende oorzaak van 50% van alle sterfgevallen in westerse samenlevingen. Het is een progressieve, multifactoriële aandoening die gekenmerkt wordt door de opbouw van lipiden en vezelachtige elementen in de arteriële wand (plaque-vorming). Uiteindelijk leidt een combinatie en opeenstapeling van risicofactoren (leeftijd, hypertensie, diabetes mellitus, obesitas) tot een plaque ruptuur en trombosering of afsluiting van een arterie. Deze indrukwekkende consequentie van het atherosclerotisch proces worden in de klinische setting ook wel acuut cerebrovasculair accident (beroerte) of myocardiaal infarct (een hartaanval) genoemd.

Omdat een aantal epidemiologische studies een relatie lieten zien tussen subklinische maten van atherosclerose en artrose, hebben we onderzocht of artrose een onafhankelijke risicofactor is voor hart- en vaatziekten. Ook hebben we ons gericht op het chronische inflammatoire proces van atherosclerose en de relatie met artrose in een open-populatiestudie. Eerdere studies postuleerden dat atherosclerose en artrose ofwel gelijktijdige ziekten met een gedeelde etiologie waren of dat atherosclerose een initierende rol speelde bij artrose; doorbloedingsstoornissen in de synoviale membraan en het subchondrale bot zouden kunnen bijdragen aan destructie van kraakbeen en het pathofysiologische proces van artrose. Mechanische veranderingen van het subchondrale bot of van het bot afkomstige cytokinen zouden verantwoordelijk kunnen zijn voor deze afname van kraakbeen.

Het doel van dit proefschrift was om te onderzoeken of atherosclerose en artrose gelijktijdig optredende ziektes zijn met overeenkomstige pathofysiologische mechanismen of dat atherosclerose juist een risicofactor is voor het ontwikkelen van artrose. Alle studies zijn uitgevoerd binnen het raamwerk van de ERGO-studie, een grote open-populatie studie met een enorme hoeveelheid data van een volwassen populatie. We

beschikten daarmee over prospectieve data van zowel objectieve atherosclerose maten, verstorende factoren (confounders), als artrosekenmerken. **Hoofdstuk 2, 3, en 4** gaan over atherosclerose en artrose als gelijktijdig voorkomende ziektes en atherosclerose als een initiator of progressor van artrose.

In **hoofdstuk 2** onderzochten we bij 2372 mannen en 3278 vrouwen in het eerste cohort van de ERGO-studie of vaatveranderingen (intima-media-dikte en plaque vorming in de arteria carotis) geassocieerd waren met de aanwezigheid en progressie van artrose van de knie, heup, en handgewrichten. Bij alleen de vrouwen werden onafhankelijke associaties tussen de bovengenoemde atherosclerose-maten en prevalente artrose van de knie en handgewrichten gevonden. Het bewijs was het meest robuust voor een relatie met distale interphalangeale artrose van de handen. Hetzelfde cohort, alleen ouder, werd onderzocht in **hoofdstuk 3**. Additionele markers van vroege en late atherosclerose werden onderzocht in relatie met de aanwezigheid en progressie van knie-artrose. Biomarkers van vroege atherosclerose (CD40L en VCAM-1) waren meer aanwezig in het plasma van vrouwen met knie-artrose vergeleken met het plasma van vrouwen zonder knie-artrose. Bij mannen werd dit verschil niet teruggevonden. Deze bevindingen komen overeen met de hypothese dat atherosclerose en artrose bij vrouwen gelijktijdig optredende aandoeningen zijn met een gedeeld pathofysiologisch mechanisme, mogelijk systemische laaggradige inflammatie. Echter, in **hoofdstuk 4** konden de cross-sectionele associaties tussen subklinische atherosclerose en artrose niet worden gerepliceerd in een cohort met jongere vrouwen. Bij deze jongere vrouwen (derde cohort van de ERGO-studie) beschikten we over de magnetische resonantie techniek die kenmerken van knie artrose in een vroeg stadium kunnen afbeelden. Daarnaast vonden we geen associatie tussen atherosclerose en de ontwikkeling (incidentie en progressie) van artrose (**hoofdstuk 2 en hoofdstuk 3**) en konden we een initiërende rol voor atherosclerose bij de ontwikkeling van artrose daarom niet bevestigen.

Klassieke observationele studies naar de causale relatie tussen een risicofactor en een ziekte kunnen resulteren in tegenstrijdige bevindingen door verstorende factoren (confounding). Dit lijkt ook het geval bij diabetes mellitus type II als risicofactor voor artrose. Een mogelijke oplossing is een analyse op basis van Mendeliaanse randomisatie, waarin genetische variatie als surrogaat-marker voor een risicofactor voor een ziekte wordt gebruikt (Instrumentele-variabele-analyse). We onderzochten deze methode in **Hoofdstuk 5** en vonden dat personen met genetisch verhoogde nuchtere glucose en insulinewaarden geen hoger risico op artrose hadden. Echter, de verklaarde variantie van de nuchtere glucose en insulinewaarden was laag en vergelijkbare analyses in een grotere context moeten worden uitgevoerd om uitspraken te doen over diabetes mellitus type II als risicofactor voor artrose.

In **hoofdstuk 6** onderzochten we artrose als rode vlag voor hart-en vaatziekten (HVZ). Voorgaande studies vonden namelijk een relatie tussen artrose en een verhoogd risico op HVZ en adviseerden een meer intensieve behandeling van cardiovasculaire risicofactoren bij artrose patiënten. Helaas ontbrak het aan prospectieve data uit grote open-populaties bij deze studies. We vonden het daarom nodig om deze aanbeveling kritisch te onderzoeken in een robuuste open-populatie studie, vóór implementatie van artrose als additionele onafhankelijke risicofactor in de klinische praktijk. We lieten zien dat artrose geen rode vlag is voor de ontwikkeling van incidente HVZ. Onze aanbeveling is daarom om artrose niet toe te voegen aan richtlijnen voor preventie van hart-en vaatziekten.

Hoofdstuk 7 reflecteert op de belangrijkste bevindingen in dit proefschrift. We vonden geen relatie tussen atherosclerose en incidentie of progressie van artrose en konden daarom niet bevestigen dat atherosclerose een initiërende rol heeft in de ontwikkeling van artrose. Daarnaast was artrose geen risicofactor voor hart-en vaatziekten. Echter, subklinische atherosclerose was wel geassocieerd met de aanwezigheid van knie- en handartrose bij vrouwen. Er zou een metabool artrose fenotype kunnen bestaan dat de knie- en vooral de handgewrichten aantast bij vrouwen. Door het vetweefsel uitgescheiden cytokines kunnen tot een chronische ontstekingsreactie leiden en zouden een verklaring kunnen zijn voor het gelijktijdig voorkomen van atherosclerose en artrose (multimorbiditeit). Toekomstig onderzoek zal dit moeten uitwijzen.

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Collega's van de (cardiovasculaire) epidemiologie; ik sluit me volledig aan bij het commentaar van meerdere reviewers, namelijk dat jullie een excellente groep zijn: wat een kwaliteit! Maarten, met jou heb ik het stuk geschreven waar ik het meest trots

op ben, bedankt voor het meedenken en je uitzonderlijke methodologische kennis. Ik hoop voor je dat Feyenoord nog een keer kampioen wordt. Maryam, ik herinner me naast de methodologische discussies en dilemmas ook de waardevolle gesprekken over onderwijs en opvoeding. Succes in je ongetwijfeld succesvolle verdere wetenschappelijke loopbaan. Paul, je hebt me bij de laatste loodjes enorm geholpen, het waren fijne gesprekken, heb veel van je geleerd op genetisch gebied. Abbas, Symen, Frank, Arfan, Renée, Klodian en Sanaz, jullie ook bedankt.

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Beseffende dat ik ongetwijfeld nog veel mensen vergeten ben, wil ik het hierbij laten.

Curriculum vitae

Theun Antonius Hoeven is op 7 juli 1983 geboren te Breda. Daar combineerde hij het Stedelijk Gymnasium met een opleiding tot professioneel voetballer (N.A.C.). Na het VWO diploma woonde hij een jaar in Barcelona om Spaans te leren en te voetballen. In 2001 begon hij aan de studie Geneeskunde in Rotterdam, waar hij als lid van STOLA (Stages in Ontwikkelingslanden) de Tropencursus organiseerde. In het tweede studiejaar werd hij uitgenodigd om de Master of Science in Clinical Epidemiology te volgen bij het Netherlands Institute of Health Sciences. Hierdoor kreeg hij de mogelijkheid om verschillende methodologische cursussen te volgen aan internationaal gerenommeerde opleidingsinstituten (o.a. Harvard University (VS), Cambridge University (UK) en Erasmus University (NL)). Lepra onderzoek in Bangladesh resulteerde in een internationale publicatie waarmee deze Master of Science werd afgerond. In 2008 behaalde hij ook zijn artsenbul en na een korte periode werkzaam te zijn geweest in de psychogeriatrie (Stadzicht Rotterdam) begon hij in 2009 aan de huisartsopleiding. Als AIOTHO (Arts-in-opleiding-tot-huisarts-en-onderzoeker) is hij sinds 2010 onderdeel van de afdeling huisartsgeneeskunde in het Erasmus Medisch Centrum. Momenteel is hij bezig met het laatste jaar van de huisartsopleiding bij praktijk Havenbogen te Schiedam.

Theun woont met zijn vrouw Jona, en dochters Line en Jade op Katendrecht, in Rotterdam.

List of publications

This thesis

Hoeven TA, Kavousi M, Clockaerts S, et al. Association of atherosclerosis with presence and progression of osteoarthritis: The Rotterdam study. *Ann Rheum Dis*. 2013;72(5):646-651.

Hoeven TA, Leening MJ, Bindels PJ, et al. Disability and not osteoarthritis predicts cardiovascular disease: a prospective population-based cohort study. *Ann Rheum Dis*. 2014. Jan 2. doi: 10.1136/annrheumdis-2013-204388.

Hoeven TA, Kavousi M, Ikram MA, et al. Markers of atherosclerosis in relation to presence and progression of knee osteoarthritis: a population-based cohort study. *Rheumatology*. Accepted

Hoeven TA, de Vries PS, Bierma-Zeinstra SM, et al. Is type 2 diabetes related to osteoarthritis? A Mendelian randomization study that investigates glycemic traits and osteoarthritis. Submitted.

Other Publications

T. Hoeven, P.Bindels, S. Bierma-Zeinstra. Atherosclerosis and osteoarthritis; insights from the Rotterdam Study. http://www.athero.org/commentaries/comm1157.asp Editorial *International Atherosclerosis Society*.

T. Hoeven. Laymen summary for the non-clinician: Are osteoarthritis and atherosclerosis linked? *Annals of the Rheumatic Diseases. http://ard.bmj.com/content/72/5/646/suppl/DC2*

T.A. Hoeven, E.A.J. Fischer, D. Pahan, J.H. Richardus. Social distance and spatial distance are not the same, observations on the use of GIS in leprosy epidemiology (2008), *Epidemiology and Infection*, **136**: 1624-1627.

T.A. Hoeven en E.F. van Beeck. Onderzoek Evaluatie Richtlijnen Werkgroep Infectie Preventie (WIP) 2007, Afdeling Maatschappelijke Gezondheidszorg, Erasmus MC.

Hoeven TA, de Vos BC. Weight loss in a commercial setting. *Lancet*. 2012;379(9820):1003; author reply 1003.

PHD Portfolio

	Year	Workload
Courses		
Biomedical English writing and communication	*2011*	*4 ECTS*
Conceptual foundation of epidemiologic study design	*2011*	*20 hours*
Cohort studies	*2011*	*20 hours*
Heuvellandcursus, Maastricht University	*2013*	*1 ECTS*
Presentations		
Oral		
NAPCRG, New Orleans	*2012*	*1 ECTS*
NAPCRG, Ottawa	*2013*	*1 ECTS*
BMJD, Bruxelles, **under 34 competition winner**	*2013*	*1 ECTS*
OARSI, Philadelphia	*2013*	*1 ECTS*
NHG Wetenschapsdag, Leiden	*2013*	*1 ECTS*
Poster		
OARSI, Barcelona	*2012*	*1 ECTS*
ESC, Amsterdam, **best moderated poster award**	*2013*	*1 ECTS*
OARSI, Paris	*2014*	*1 ECTS*
NAPCRG, New York, **distinguished trainee award**	*2014*	*1 ECTS*
Workshops/seminars/conferences		
OARSI, San Diego	*2011*	*1 ECTS*
AIOTHO-dagen, the Netherlands	*2011-14*	*30 hours*
COEUR lezingen ErasmusMC, Rotterdam	*2011-14*	*20 hours*
PhD-day; defend your thesis	*2013*	*20 hours*
Other activities		
Kritisch lezen Huisarts-afdeling	*2011*	*30 hours*
ERGO-medical practitioner	*2012*	*90 hours*
Coding cardiovascular events	*2013*	*60 hours*

Vascular pathology and osteoarthritis

Population-based studies

Theun Hoeven

Vascular pathology and osteoarthritis are highly prevalent disorders that often co-occur and they have a large impact on quality of life. Focus in this thesis is on atherosclerosis (chronic inflammatory condition of the arterial wall) and its relation with osteoarthritis, a widespread joint disease (i.e. joint failure). Does atherosclerosis preceed osteoarthritis, or are they concurrent diseases with shared aetiological features, for instance systemic inflammatory effects of adipose tissue?

This thesis aims to answer these and other questions surrounding osteoarthritis and vascular disease. All studies derived from the Rotterdam Elderly Study, a prospective population-based cohort study in the Ommoord district in the city of Rotterdam, the Netherlands.

The author was born on july 7th 1983 in Breda, the Netherlands. At the Erasmus medical center in Rotterdam, he was trained as a medical doctor and obtained a Master of Science degree in Clinical Epidemiology (Leprosy research). He started with the PhD project the role of vascular pathology in the development and progression of osteoarthritis in 2011 and is currently in his final year of a general practitioner traineeship.