Females, Overweight and Osteoarthritis: *a complex puzzle*

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Females, Overweight and Osteoarthritis:
a complex puzzle

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een ingewikkelde puzzel

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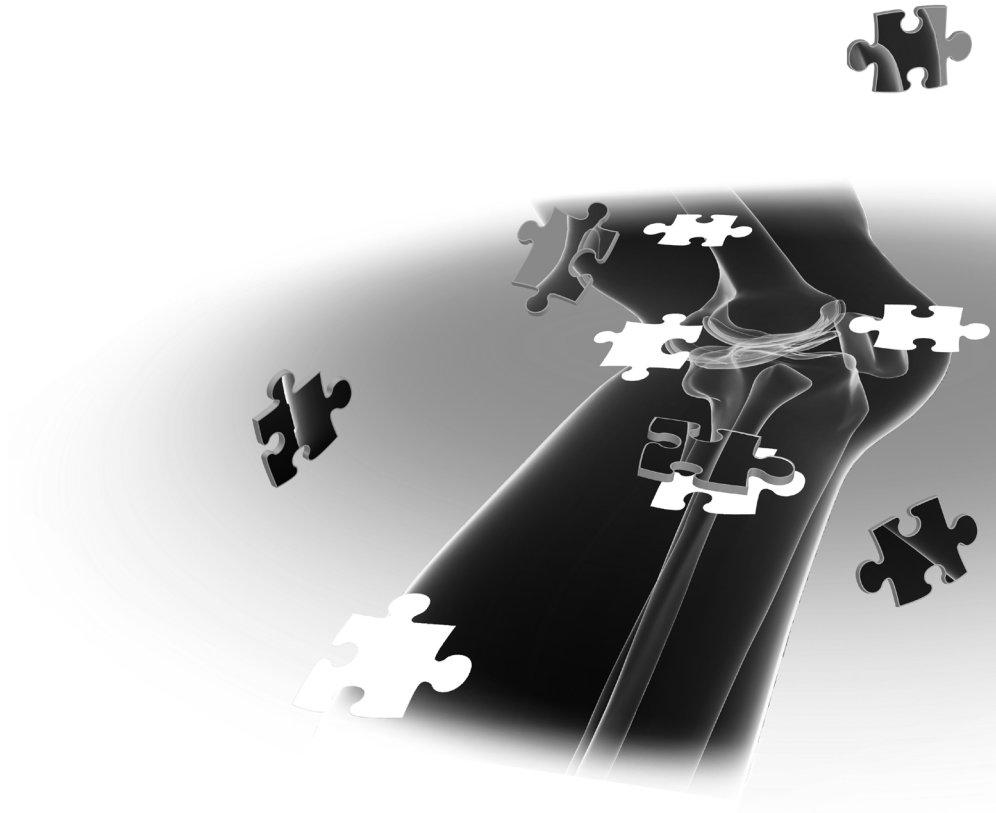
ABBREVIATIONS

AR: attributable risk
BMD: bone mineral density
BMI: body mass index
CMC: carpometacarpal joint
cOA: clinical osteoarthritis
CVD: cardiovascular disease
DBP: diastolic blood pressure
DIP: distal interphalangeal joint
GP: general practitioner
HN: herberden's nodes
HRT: hormone replacement therapy
JSN: joint space narrowing
KL-grade: Kellgren and Lawrence grade
PostMP: post-menopausal
OA: osteoarthritis
OR: odds ratio
PIP: proximal interphalangeal joint
RR: relative risk
rOA: radiological osteoarthritis
RS: Rotterdam study
SPB: systolic blood pressure
THR: total hip replacement
TJR: total joint replacement
TS joint: trapezioscaphoid joint
WHO: World Health Organization
YSM: years since menopause

Chapter 1

General introduction



OSTEOARTHRITIS

Every year many people consult their general practitioner (GP) for complaints related to the musculoskeletal system. Osteoarthritis (OA) is a common progressive joint disease causing pain and disability. This disorder is frequently experienced by middle-aged and older people [1] and generally affects hips, knees and hands. GPs are most often consulted for complaints of the hip and knee joint, with knee joint twice as often as the hip. In middle-aged and elderly people joint complaints are often thought to be caused by OA. With the increase in life expectancy and in the prevalence of obesity (both major risk factors for OA), the prevalence of OA will probably continue to rise [2, 3], as will the associated costs and burden for society.

OA is a disease that affects the whole joint. Not only cartilage degenerates, but also subchondral bone thickens, osteophytes grow and the synovial membrane gets inflamed. All of these symptoms are associated with laxity and decreased muscle strength [4].

Current OA treatment is mainly symptom driven, since no cure is available. Pharmacological treatments commonly used for OA management are often outweighed by their undesired side-effects [5]. Also, disease modification is not yet possible because no effective treatments are currently available. Studies on disease-modifying interventions have had variable results. One problem with such interventions is that they are tested in populations already showing signs of clinically manifest OA.

Treatment with disease-modifying interventions (such as losing weight, exercise therapy or early suppression of pain with medication) might be more effective in an earlier stage of the disease, i.e. in a pre-clinical stage. However, this possibility still needs to be investigated and confirmed in stages of the disease when no structural changes to the joint have occurred.

At the moment it is not possible to determine in an early stage of the disease who will develop OA-related disability in a later stage. Also, it is impossible to identify which persons are at extremely high risk of OA development, or to select those persons already showing early signs of OA.

RISK FACTORS FOR KNEE OSTEOARTHRITIS

OA is widely considered to have a multifactorial cause, but a precise etiology of OA is still lacking. Several important risk factors for knee OA, like age and body mass index, are well established. In 1995, Dieppe [6] introduced a model for joint susceptibility for OA, including local and systemic factors; this is shown in Figure 1.1. However, the way these factors interact with each other in the development of OA remains unclear.

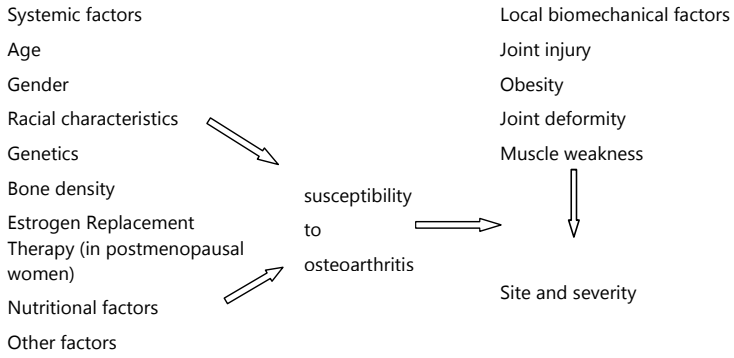


Figure 1.1: Model of osteoarthritis susceptibility according to Dieppe [6].

Obesity

Being overweight or obese is arguably the most important modifiable OA risk factor [7] which affects both the development and progression of the disease [2, 8, 9]. The development of OA can be influenced by obesity in various ways. Local risk factors, such as previous knee trauma [10] and varus alignment [11, 12], may be influenced by overweight through a higher biomechanical loading on the joint. Systemically, high body fat can influence joint health by secretion of inflammatory mediators and estrogen-like substances. Although the exact mechanism has not been fully explained, it is thought to be mechanical ('wear and tear') [13] with an additional systemic role for adipose tissue [14, 15].

Female gender

Female gender is also an acknowledged risk factor for knee OA. Before the age of 50 years OA is more common in men than in women, whereas after age 50 years it is the other way around [16, 17]. Hormonal levels change around the time of menopause, concurrently with an increased incidence of OA in women. This simultaneous occurrence of menopause and increased OA incidence indicates a role for female hormones, which was suggested many years ago [18]; however, the underlying mechanism remains to be elucidated. Although articular tissue has long been considered unresponsive to estrogens, there is increasing evidence that activity of joint tissues is influenced by estrogens through complex pathways [4].

Compared to men, women are not only more likely to have knee OA but they also have more severe symptoms, particularly after menopausal age [19]. Again, the mechanisms involved are not clear, and the exact association between female hormonal aspects (such as age at menarche or being postmenopausal) and OA is not yet fully explained.

RADIOLOGICAL OA VERSUS KNEE PAIN

A major problem with OA is that, in many cases, by the time a person starts showing clinical signs like pain and functional limitations, the damage to the joint is already done and cannot be reversed. Degeneration of cartilage is considered a main feature of OA, and cartilage degeneration itself is not a painful process. Cartilage contains no nerves and therefore does not hurt when it is breaking down. Also, since cartilage largely depends on supply by diffusion, instead of via blood vessels, the body has limited ability for repair. Moreover, the cartilage that does grow back slowly is usually of reduced quality. One explanation as to why OA appears to cause pain is that, when cartilage is degenerated to the point that the underlying highly innervated periosteum is exposed, it is too late to stop the process and a total knee replacement may be needed. As stated above, besides cartilage, other joint tissues like ligaments, menisci and bone, are also affected by OA. When patients suffer severely from symptomatic OA, surgery is performed in an earlier stage when cartilage is not yet completely degenerated, suggesting that other pain pathways are also applicable.

However, the situation can become more confusing: not all people with radiological knee OA experience pain and disability and, at the same time, not all people with OA-like knee complaints have OA pathology on X-ray. This discrepancy between the presence of pain and OA pathology on X-ray is well reported [20-22]. Magnetic resonance imaging (MRI) can assess cartilage and other soft joint tissues directly and can visualize early degenerative signs. Therefore, MRI is being advocated as the best available imaging technique currently available for detecting early osteoarthritic changes [23-25] and is increasingly used in epidemiological studies for OA assessment.

Knee complaints are a common reason for consultation in general practice [26]. Especially in elderly persons knee complaints are often thought to be due to OA, but the discrepancy between pain and X-ray pathology makes confirmation of the suspicion of early OA more complex. In daily general practice, the absence of radiological established OA may lead to different patient management [27]. Insight into the predicting factors for development of radiological OA in people with knee complaints, as well as the predicting factors for development of pain, will help general practitioners determine early diagnosis, and will contribute to the formulation of a high-risk profile for those at risk of OA development.

THIS THESIS

Aim

The aim of this thesis is to gain insight into 1) the impact of female gender on OA and its symptoms, 2) the relationship between female hormonal aspects and overweight in OA, and to contribute to the knowledge needed to identify people at high risk of knee OA development in an earlier stage of the disease. For this we focus on a known high-risk group of middle-aged women. In addition, we aim to gain insight into the predicting factors for development of radiological OA in persons with knee complaints, and into factors that predict knee pain in women without knee OA.

Systematic reviews

A systematic review of the literature is the most effective way to summarize available knowledge on a certain subject. Even though female gender is an acknowledged risk factor for OA development, and a relation with the menopause is assumed, the association between OA and female hormonal aspects, or exogenous hormone use, has not yet been thoroughly studied. This thesis addresses all these issues.

Rotterdam study

All original studies in this thesis were written on the basis of data acquired from the Rotterdam Study. The Rotterdam Study is a prospective cohort study, including men and women, which started in 1990 in Ommoord (a suburb of Rotterdam, the Netherlands). The study was designed to investigate chronic diseases in the elderly and collects a variety of data, ranging from blood and urine samples to X-rays of many joints, and from an extensive home interview to fMRI of the brain. This first cohort was named the RS.I cohort and in 2002 the study was extended with the RS.II cohort. In 2010 a design update was published [28].

In 2006 another new cohort was started, including all willing (new) inhabitants of the suburb aged 45 years and over who were not yet included in earlier cohorts. We started our study on OA in this new cohort, named the RS.III cohort. All women in this cohort aged 45-60 years, were invited to participate; those who were willing and gave informed consent, underwent an MRI scan and physical examination of both knees, and were asked to fill out an additional questionnaire with questions related to knee problems. Follow-up will take place about every four years at the research center in Ommoord, with intermediate follow-up questionnaires every two years. A total of 891 women were included in our osteoarthritis study.

Content

In **Chapters 2 and 3** the available literature on the associations between OA of the hand, hip and knee with exogenous hormone use, and OA with female hormonal aspects, was systematically reviewed. For the remaining studies data were used from the Rotterdam Study (from the RS.I or RS.III cohorts). The study in **Chapter 4** aimed to gain insight into where the damage in the knee joint is first manifest in the high-risk group of disease-free middle-aged women, in other words which tissue is visually affected first. **Chapter 5** describes our study on interactions between body mass index and other known risk factors for, and symptoms of, knee OA. The aim of **Chapter 6** was to explore the best prognostic determinants for development of radiological OA (rOA) in the knee in elderly people with knee complaints but no current rOA in the painful joint. In **Chapter 7** we went a further step back in the process of early identification and investigated the best prognostic determinants for development of knee pain in a high-risk group of middle-aged women. Finally, **Chapter 8** discusses the main results of the studies and their implications for future research and clinical practice.

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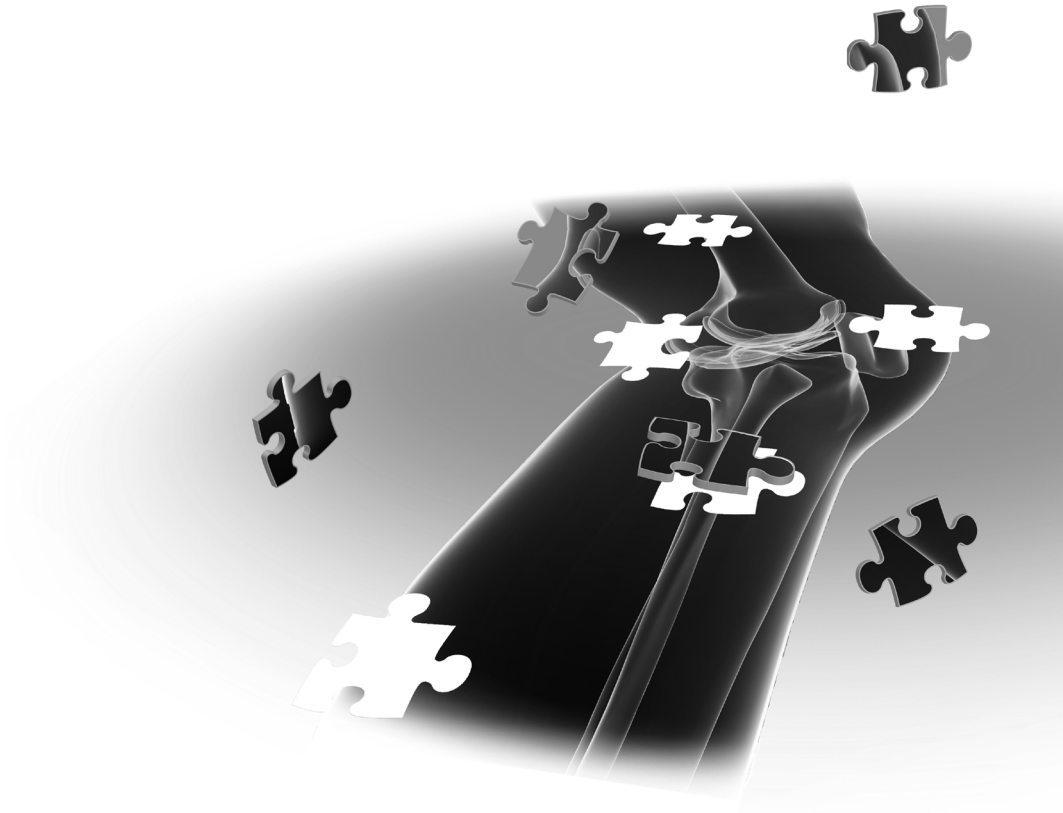
Chapter 2

Limited evidence for a protective effect of unopposed estrogen therapy for osteoarthritis of the hip: a systematic review

de Klerk BM, Schiphof D, Groeneveld FPMJ, Koes BW, van Osch GJVM, van Meurs JBJ, Bierma-Zeinstra SMA

Rheumatology 2009;48(2):104–112



ABSTRACT

Objectives

Above age 50 the incidence of osteoarthritis (OA) rises steeply in women but less in men, suggesting an association with changes in female hormone levels in the menopause. This systematic review summarizes the evidence on the assumed association between exogenous hormone use and OA.

Methods

Medline was searched up to March 2008. Articles assessing associations between OA of hand, hip or knee and menopause-related aspects. Methodological quality of the studies was assessed systematically. The results were summarized in a best-evidence synthesis.

Results

19 studies on exogenous hormone use are included. Limited evidence was seen for a protective effect of unopposed estrogen use for incidence of total hip / joint (hip or knee) replacements and a protective trend for incident radiological OA (rOA) of the knee. In prevalence studies conflicting evidence was observed for Hormone Replacement Therapy (HRT) use with DIP rOA and 'any joint OA', and estrogen use with clinical knee OA. We found limited evidence for a significantly increased risk by using HRT for clinical hip OA and a significant protective effect of long term HRT use for hip rOA. For all other relations studied no associations were found.

Limitations

Heterogeneity between the hormones used and outcome measurements made statistical data pooling impossible.

Conclusion

The assumed relationship between the exogenous hormone use and OA was not clearly observed in this review. The relationship is perhaps too complex, or other aspects, yet to be determined, play a role in the increased incidence in women aged over 50 years.

INTRODUCTION

Osteoarthritis is a growing problem among the elderly in western societies and causes pain and disability. In addition to the burden of physical discomfort, the enormous costs for society [1-3] are expected to keep rising due to increasing life expectancy [4,5]. Prevalence of osteoarthritis (OA) is higher in women than in men [6] and incidence rises with age.

The increase of OA incidence is higher in women than in men after the age of 50 [7], which is puzzling. As early as 1925 Cecil and Archer [8] reported an apparent close connection between OA and the menopause based on a study of 50 female cases. Estrogen levels are lower in menopausal women than normal menstruating women, which suggests that estrogen may be an important regulator of OA [9]. Results of studies on the possible association between OA and menopausal aspects and exogenous hormone use are not consistent, and a complete overview on the present level of knowledge on this relationship is lacking. Insight in the association between OA and exogenous hormone use may contribute to the formulation of a high-risk profile for OA development and a better understanding of OA aetiology.

The aim of this systematic review is to gain insight in the current stage of knowledge on the association between OA and exogenous hormone use.

METHODS

Identification of studies

The articles were identified by systematically searching the database of Medline up to March 2008. Osteoarthritis, estrogen, hormone replacement therapy (HRT), menopause, and equivalents of these words were used as keywords (Appendix I). The search was extended by screening the reference lists of all included studies and relevant reviews.

A study was included when all the following criteria were fulfilled: 1) the article presents original data on a human study population, 2) disease of interest is incident or prevalent osteoarthritis of the hand, hip or knee (tibiofemoral OA), 3) women with and without OA are compared in the study, 4) the study reports on exogenous hormone use related to OA presenting odds ratios, relative risks, p-values or data extended enough for one of these to be calculated, 5) studies on genetics of menopause-related determinants are excluded, 6) the article was written in English, Dutch, German, African, Norwegian, Danish or Swedish, 7) the full text article was available. Two independent researchers checked the abstracts on the above-mentioned criteria.

Methodological quality

The methodological quality of the included articles was assessed using a scoring list based on the scoring list used by Scholten-Peeters et al. [10] and Lievense et al. [11] (Appendix II, with specifications in Appendix III). The list was modified to cover the topic of our review and concerns both the internal validity and informativeness of the article. If type of HRT used (unopposed estrogen or opposed estrogen (this is a combination therapy of estrogen plus progesteron)) is mentioned in the article, then this is reported in the results section. If not mentioned the terms HRT or estrogen are used.

All articles were scored independently by two reviewers (BMdK and DS). In case of disagreement, consensus was aimed for. If consensus was not achieved a third reviewer (SMABZ) gave final judgement.

Not all items were applicable for every study design and the number of relevant determinants differs between studies. For example, for a prospective cohort study specifications on loss to follow-up should be described, while this item is not applicable in a retrospective case-control or cross-sectional study. Therefore the maximum score of each study (100%) was based on the number of items applicable for that particular study. All other items were scored identical for all study designs, scoring positive (+), negative (-) or not given (?). Positive scores were summed up to indicate an overall internal validity score.

Evidence synthesis

Evidence from homogeneous studies outcomes was pooled. In case of heterogeneity, we refrained from statistical pooling and performed a 'best-evidence synthesis' [11-14].

The studies are divided into subgroups according to the study design. A study was considered to be of high quality if the methodological score was ≥60%. The best evidence synthesis was performed using the following levels of evidence [14,15]:

- *Strong evidence*: Consistent findings (>75%) in multiple high-quality studies
- *Moderate evidence:* Consistent findings (>75%) in: one high-quality study and some other low-quality studies or multiple low-quality studies
- *Limited evidence:* Only one high-quality study
- *Conflicting evidence:* Inconsistent findings in several studies of equal quality
- *Insufficient evidence:* No high-quality study and at most one low-quality study available
- *No evidence*: Provided when no studies could be found

In case of a sufficient number of included studies (N=10) a sensitivity analysis (binary logistic regression analysis (SPSS-11.0.1)) was performed. In case of an insufficient number of included articles, differences were screened by eyeballing method

Data extraction

Two researchers (BMdK and DS) independently collected characteristics of the included studies. The characteristics covered the study design, study population, determinants and type and severity of OA. Relative risks (RR) or odds ratios (OR) were extracted. The following definitions were applied for dichotomous outcomes:

- 95% Confidence Interval (CI) does not include 1.00: significant outcomes: association present

OR > 1.00: significantly increased risk;

OR < 1.00: significant protective effect.

- 95% CI includes 1.00: non-significant (NS) outcomes: no association present

OR < 0.5; 95% CI includes 1.00: NS protective;

OR > 2.0 95% CI includes 1.00: NS increased risk;

0.5 < OR < 2.0; 95% CI includes 1.00: No relation.

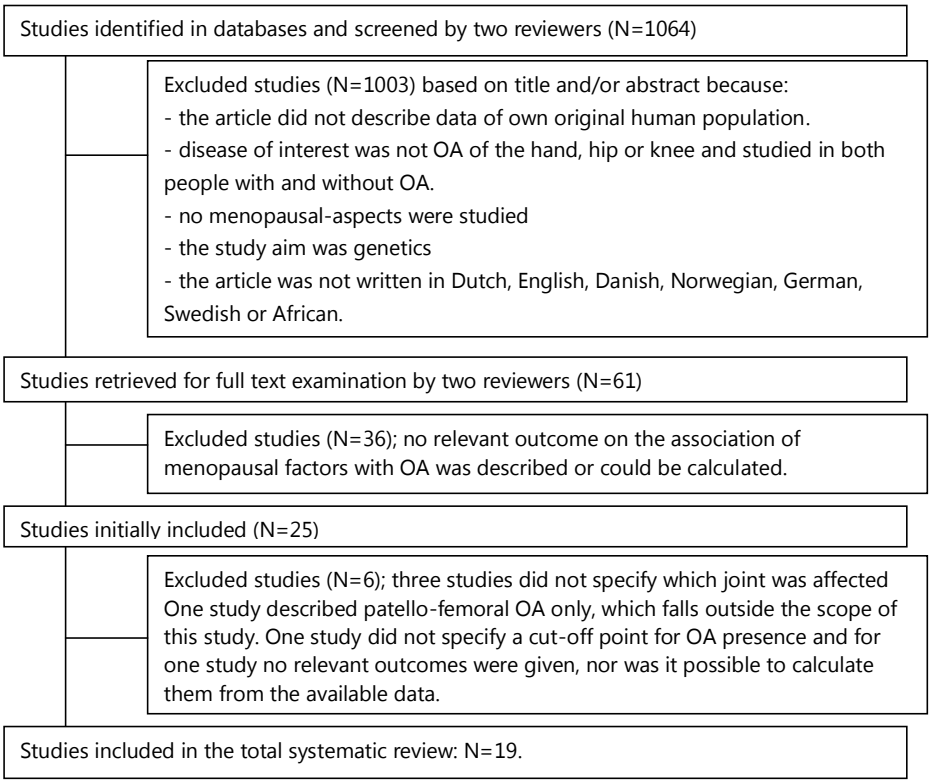


Figure 2.1: Flow chart of the selection process.

Table 2.1: Characteristics of the included studies

Reference	Study design	N	Age: mean years (range)	Joint	OA assessment	Definition cases (=OA+) / population
INCIDENCE STUDIES: High quality						
Zhang [23]	Cohort, 8 year follow-up	551	71 (63-91)	Knee	Radiographic	Females participating in Framingham study. Cases had no OA grade 4 at baseline measurement. (incidence + prevalence study)
Cirillo [24]	RCT, 7.1 year follow-up	10272[1] 16049[2]	50-79	Hip Knee	THR TKR	Community dwelling women from the Women's Health Initiative two placebo-controlled, double-blind randomized trials. 7 years follow-up. One trial with hysterectomized women (1), other: non-hysterectomized women(2)
Hart [22]	Cohort, 4 year follow-up	715	54 (49-60)	Knee	Radiographic	Females participating in Chingford study. None of the participants had OA at baseline. 14 year follow-up period.
Oliveria* [25]	Nested CC	268	(20-89)	Hand Hip Knee	Radiographic Symptomatic	Continuous female members of Fallon Community Health Plan. None of the participants had OA at baseline
INCIDENCE STUDIES: Low quality						
Oliveria* [37]	Nested CC	120	60	Hip Knee	Radiographic Symptomatic	Pre- and Postmenopausal females Continuous female members of Fallon Community Health Plan. None of the participants had OA at baseline
Lane [36]	Cohort, 8.3 year follow-up	4933	78.3	Hip	Radiographic THR	All females participating in SOF study who had undergone their 5th measurement. Only hips without OA at baseline were included in analysis.
PREVALENCE STUDIES: High quality						
Cooley [26]	CS	348	Cases: 79 Controls: 51 (40-85)	Hand	Radiographic Symptomatic	All Tasmanian females with hand OA and a history of at least one living relative with hand OA were invited to take part. with their families (both affected and unaffected) Cases recruited from records of rheumatology practice.
Carbone [30]	Nested CS	666	74 (69-81)	Knee	Radiographic Symptomatic	All females participating in Health ABC study reporting knee pain for the first time. Women included with and without pain, aching and stiffness of the knee (WOMAC).
Spector [29]	Nested CS	1003	54.2 (45-64)	Hand Knee	Radiographic	Postmenopausal females participating in Chingford study
Von Muhlen [31]	Nested CS	1001	72 (43-97)	Hand Hip Knee	Symptomatic	Postmenopausal females participating in Rancho Bernardo study

Table 2.1: Characteristics of the included studies

Reference	Study design	N	Age: mean years (range)	Joint	OA assessment	Definition cases (=OA+) / population
Cicuttini [32]	CS	325	58.6	Knee	Radiographic	Females from general population participating in twin study; only one twin included
Hannan [33]	Nested CS	615	73 (63-93)	Knee	Radiographic Symptomatic	Females participating in Framingham study
Sowers [27]	Nested CS	573	37 (24-45)	Hand Knee	Radiographic	Pre- and peri-menopausal females participating in Michigan Bone Health study (MBHS) in 1992 (recruited from general population). X-rays of dominant hand and knees were examined
Nevitt [28]	Nested CS	4366	72	Hip	Radiographic Symptomatic	All females participating in Study of Osteoporotic Fractures study
Sandmark [34]	CC	548	56-74	Knee	TKR	Females who had undergone total knee replacement between 1991-1993 (Age: 55-70 at the time of surgery) due to clinically significant primary tibio-femoral OA recruited from general population in 14 Swedish counties. Controls not checked by X-ray (postal survey)
Vingard [35]	CC	503	50-70	Hip	Radiographic THR	Postmenopausal females recruited from 5 counties in western Sweden and in the referral areas of 5 hospitals. All cases had undergone total hip replacement as result of primary hip OA
PREVALENCE STUDIES: Low quality						
Dennison [38]	CC	826	72	Hip	Radiographic Symptomatic THR	Postmenopausal Females (age: 45+) recruited from general population in two health districts in England. Cases drawn from waiting list for THR.
Schneider [39]	Nested CS	1081 fem.	Cases: 78.1 Controls: 67.8 (50-96)	Hand Hip Knee	Symptomatic	Community dwelling females participating in Rancho Bernardo study
Samanta [40]	CC	690	70 (60-78)	Hand Hip Knee	Symptomatic	Females recruited from an OA Research Clinic at the City Hospital Nottingham. All cases had been referred with symptomatic lower limb radiological OA. Controls recruited from same general practice as cases attended.

* = The study population used by Oliveria et al. was obtained from their previous study on estrogen replacement therapy. In this review the populations are considered different due to differences in mean BMI and mean age of the described study populations, THR = Total Hip Replacement, TKR = Total Knee Replacement, OA = Osteoarthritis, (N)CS = (nested) cross-sectional study, CC = case-control study, WOMAC = Western Ontario and McMaster Universities osteoarthritis index.

RESULTS

Identification and selection of the literature

The systematic search initially resulted in the identification of 1064 references in Medline, which were screened on title and abstracts. This led to a full-text reading of 61 articles of which 25 met our inclusion criteria. Six of the 25 initially included articles were subsequently excluded: three studies did not specify the joint affected by the OA [16-18], one study reported on patello-femoral OA only [19], one study did not specify a cut-off point for OA presence [20] and for one study we were unable to calculate relevant outcomes [21]. Screening the reference lists of the selected studies did not add any new studies. Finally, 19 studies were included in this systematic review. Figure 2.1 shows the flow chart of this selection process.

Methodological quality assessment

The two reviewers each scored 343 items from the 19 studies included and initially agreed on the quality score of 252 items (= 73%, kappa: 0.55). Disagreements of 75 items were solved in one consensus meeting and 16 items were presented to the assigned co-author for final judgment. The average rating was 62.5%, (range 20.0% to 73.3%). Table 2.1 gives a description of the characteristics of the included incidence studies and prevalence studies. The size of the study populations included in this review ranged from 120 to 16049 (median=678). Four of six studies on incidence included met the criteria for high quality [22-25], as well as 10 of 13 prevalence studies [26-35]. The quality scores of the included studies are presented in Table 2.2.

Heterogeneity

All, but one [24], included studies are observational and heterogeneous with regard to the determinants- and outcome measures and study population, making pooling impossible. Even within the studied determinants heterogeneity on these points was too large to justify pooling. Therefore we refrained from pooling and performed a best evidence synthesis.

Results of the studies included

In the description of the results a subdivision is used in type of OA: radiological OA (rOA), indicating radiological changes only and clinical OA (cOA), where both radiological

Table 2.2: Quality of the included studies. (Shaded = High-quality study; not shaded = Low-quality study)

Reference	Adjusted for age	Adjusted for BMI	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	q	Obtainable SCORE	N +	QUALITY (% +)
Incidence studies																						
Zhang [23]	+	+	+	-	+	-	+	-	+	-	+	+	+	+	+	+	?	+	+	17	12	**70.6**
Cirillo [24]	+	-	+	+	-	-	-	+	+	+	+	+	-	+	+	+	+	+	-	17	12	**70.6**
Hart [22]	-*	-*	+	+	-	+	+	?	+	-	+	+	+	+	+	-	-	+	-	17	11	**64.7**
Oliveria* [25]	-	-	-	NA	NA	+	+	+	+	?	+	?	+	?	+	+	-	+	-	15	9	**60.0**
Oliveria* [37]	-	+	-	NA	NA	-	+	+	+	?	+	?	+	+	-	+	?	+	-	15	8	**53.3**
Lane [36]	+	+	+	-	-	+	+	+	+	-	-	?	+	?	+	-	-	+	+	17	9	**52.9**
Prevalence studies																						
Cooley [26]	+	+	-	NA	NA	-	+	+	+	+	+	?	+	+	+	+	?	+	+	15	11	**73.3**
Carbone [30]	+	+	-	NA	NA	+	+	+	+	?	+	-	+	+	+	+	?	+	+	15	11	**73.3**
Spector [29]	+	+	-	NA	NA	-	+	+	+	-	+	?	+	+	+	+	+	+	+	15	11	**73.3**
Von Muhlen [31]	+	+	-	NA	NA	?	+	+	+	+	+	?	+	+	+	+	?	+	+	15	11	**73.3**
Cicuttini [32]	+	+	-	NA	NA	-	+	-	+	+	+	?	+	+	+	+	+	+	+	15	11	**73.3**
Hannan [33]	+	+	+	?	-	-	+	-	+	-	+	+	+	+	+	+	+	+	+	17	12	**70.6**
Sowers [27]	-	-	-	NA	NA	-	+	+	+	+	+	+	+	-	+	+	-	+	-	15	10	**66.7**
Nevitt [28]	+	+	-	NA	NA	-	+	+	+	?	+	?	+	+	+	+	?	+	+	15	10	**66.7**
Sandmark [34]	+	-	-	NA	NA	+	+	+	-	-	+	-	+	+	-	+	+	+	-	15	9	**60.0**
Vingard [35]	+	-	-	NA	NA	+	-	+	-	+	+	-	+	+	-	+	+	+	-	15	9	**60.0**
Dennison [38]	-	+	-	NA	NA	+	+	+	-	-	+	?	+	+	-	+	-	+	-	15	8	**53.3**
Schneider [39]	+	+	-	NA	NA	?	+	-	+	?	+	?	+	?	+	+	?	+	+	15	8	**53.3**
Samanta [40]	-	-	-	NA	NA	?	?	-	+	-	-	?	+	-	-	-	?	+	-	15	3	**20.0**

* = patient population matched for age and BMI, NA = This item was Not Applicable to this study due to design, ? = unknown (data could not be extracted from the article), Appendices II and III explain the items scored.

changes and symptoms are present in the same joint. cOA includes total replacements of hip (THR),- knee (TKR) or - joint (TJR, hip or knee).

Description of the studies included

Nineteen studies on exogenous hormone use were included [22-40]. Four studies have a prospective cohort design [22,23,36], of which one Randomized Controlled Trial [24]. There are 6 retrospective studies [25,34,35,37,38,40] and 9 cross-sectional studies [26-

Table 2.3: Results included studies on OA incidence. (Shaded = High-quality study; not shaded = Low-quality study)

Reference	Study design	N OA+	N OA-	Adj. Age	Adj. BMI	Case definition (incident OA-case if):	Specification Hormone use (never use = reference)	Outcome (OR (95%CI))
Hand								
Oliveria* [25]	N-CC	134	134	-	-	rOA score ≥ 2 on K&L-scale+ symptoms (cOA)	Estrogen (ORT); ever use	1.14* (0.4-3.1)
Hip								
Cirillo [24]	RCT	T1:-- T2:--	-- --	- ?	- ?	Positive if incident THR (considered viable proxy outcome for severe OA) [61] (cOA)	Trial 1: hysterectomized women randomly assigned to receive 0.625mg/day conjugated equine estrogens vs.placebo Trial 2: non-hysterecomized women randomly assigned to receive estrogens (same as trial 1) plus 2.5mg/day medroxyprogesterone acetate vs. placebo	Trial 1: HR = **0.55 (0.35-0.88)** P = 0.01† Trial 2: HR = 1.08 (0.72-1.61) P = 0.71†
Oliveria* [25]	N-CC	134	134	-	-	rOA score ≥ 2 on K&L-scale+ symptoms (cOA)	Estrogen (ORT); ever use	0.4* (0.1-1.2)
Lane [36]	Cohort	566	4363	+	+	Positive X-ray score according to Croft OA-atlas in 1 or both hips or THR due to OA (cOA)	Estrogen use; current use	1.08* (0.86-1.36)
Knee								
Zhang [23]	Cohort	--	--	+	+	Positive modified K&L-score ≥ 2 (rOA)	Estrogen (or PME), most used conjugated equine estrogens; current use (still receiving estrogens at exam 18), past users (only used estrogen up to exam 18 (1983-1985)) pas use further divided: <6 years, >/= 6 years	Past: 0.8 (0.5-1.4) Current: 0.4 (0.1-3.0)

Table 2.3: Results included studies on OA incidence. (Shaded = High-quality study; not shaded = Low-quality study) (continued)

Reference	Study design	N OA+	N OA-	Adj. Age	Adj. BMI	Case definition (incident OA-case if):	Specification Hormone use (never use = reference)	Outcome (OR (95%CI))
Hart [22]	Cohort	95	620	-	-	Positive if baseline X-ray score was 0 and subsequently developed at least a grade 1 osteophyte or JSN according to [62]	Estrogen (ORT); current use (user at first visit and continued the following 48 months (excluding those who stopped ORT use)), past use (ORT use >=60 months, but not the 12 months prior to baseline)	Osteophytes: Ever: 0.73 (0.32-1.67) Current: 0.41 (0.12-1.42) JSN: Ever: 1.17 (0.59-2.33) Current: 0.88 (0.86-4.11)
Cirillo [24]	RCT	T1:-- T2:--	-- --	- ?	- ?	Positive if incident TKR (considered viable proxy outcome for severe OA) [61] (cOA)	Trial 1: estrogens vs.placebo Trial 2: estrogens plus progestin vs. placebo (see specification above in hip OA)	Trial 1: P = 0.01† HR = 0.80 (0.61-1.05) Trial 2: P = 0.72† HR = 0.95 (0.71-1.27)
Oliveria* [25]	N-CC	134	134	-	-	rOA score ≥ 2 on K&L-scale + symptoms (cOA)	Estrogen (ORT); ever use	1.17* (0.5-2.5)
Any joint (large joint OA: hip or knee)								
Cirillo [24]	RCT	T1:-- T2:--	-- --	- ?	- ?	Positive if incident TJR (considered viable proxy outcome for severe OA) [61] (cOA)	Trial 1: estrogens vs. placebo Trial 2: estrogens plus progestin vs. placebo (see specification above in hip OA)	Trial 1: P = 0.01† HR = **0.73 (0.58-0.93)** Trial 2: P = 0.77† HR = 1.02 (0.81-1.29)
Oliveria* [37]	N-CC	60	60	-	+	rOA according to ACR-criteria + symptoms (cOA)	Estrogen (ORT); ever use, new user (</= 6 months), past use (not last 6 months, before that >/= 6 months), ongoing user (>6 months); long term use: ongoing use and use before 1987 or past use and use before 1987	Ever: 1.5 (0.7-3.4) New: ∞ ‡ Past: 0.7 (0.3-1.9) Ongoing: 1.4 (0.6-3.3) Long term: 1.0 (0.4-2.8)

* = crude OR, † = P value from Cox proportional hazards analyses stratified by age, ‡ = no new users in control group, OA = osteoarthritis, rOA = radiological OA, cOA = clinical OA (symptomatic + radiological OA), ORT / HRT = estrogen -/ hormone replacement therapy, OC: oral contraceptives, PME = post menopausal estrogen, N-CC = nested case-control study, RCT = randomized controlled trial, TKR = total knee replacement, THR = total hip replacement, TJR = total joint replacement (hip or knee), JSN = joint space narrowing, Statistically significant outcomes are shown in Bold

33,39]. 9 studies are nested in larger cohorts: two retrospective studies [25,37] and 7 cross-sectional studies [27-31,33,39].

Hip OA was also studied in the Fallon-study where a non-significant protective effect of ever estrogen use and incident hip cOA was found in 27 case-control pairs. In the RCT of the Women's Health Initiative (WHI) [24] a significant protective effect of unopposed estrogen use for total hip replacement (THR) was found in hysterectomized women. On the other hand, use of opposed estrogens (a combination of estrogen plus progestin), which is used in non-hysterectomized women, showed no such significant effect. Researchers in the Study of Osteoporotic Fractures (SOF-study) [36] found no relation between current estrogen use and incident hip rOA or THR.

In the Chingford study [22] as well as the Framingham- [23], Fallon- [25] and WHI-study [24] no significant associations were seen between estrogen usage and incident knee rOA or total knee replacement (TKR). For current use both Chingford and Framingham found a non-significant protective effect.

In studying 'any joint cOA' a significant protective effect of unopposed estrogen use was seen in the WHI-study for total joint replacement in hysterectomized women [24]. In the same study this effect was not observed in non-hysterectomized women or in the Fallon-study [25].

Incidence studies: hormone replacement therapy

Six studies report on OA incidence, see Table 2.3. An association with incidence of hand cOA was only examined in the Fallon Community Health Plan [25], where no evidence of an association with ever usage of estrogen was seen.

Prevalence studies: Oral contraceptive use and Hormone replacement therapy

Thirteen studies report on OA prevalence, see Table 2.4. None of the studies found a significant association for the use, or duration of use, of (oral) contraceptives with OA; all outcomes (OR's) ranged from 0.57 to 1.60 indicating 'no relation'.

Four studies on prevalence of hand OA were included in this review [26,27,29,31]. In the Rancho Bernardo study [31] as well as in a population of Tasmanian women [26] a significantly increased risk by estrogen use for hand cOA (presence of Herberden's nodes) was seen. No associations were found with rOA or cOA of DIP and CMC joints.

In the Rancho Bernardo study [31] also a significantly increased risk for cOA of the hip was seen. While for hip rOA the SOF-study [28] found a significantly protective association with current estrogen use and current use for ≥10 years. Dennison et al. [38] and Vingard et al. [35] both found no association between ever estrogen or HRT use and hip cOA.

Table 2.4: Results included studies on OA prevalence. (Shaded = High-quality study; not shaded = Low-quality study)

Reference	Study design	N OA+	N OA -	Adj. Age	Adj. BMI	Case definition (incident OA-case if):	Specification Hormone use (never use = reference)	Outcome (OR (95%CI))
Hand								
Cooley [26]	CS	--	--	+	+	rOA according to Altman atlas + symptoms according to ACR-criteria (cOA)	Hormone replacement therapy (HRT) DIP OA; ever -; current use CMC OA; ever -; current use HN: ever -; current use Oral Contraceptives (OC) use: yes / no	DIP: ever: 2.21 (0.88-5.51); current: 2.10 (0.94-4.68) CMC: ever: 1.60 (0.76-3.39); current: 1.41 (0.72-2.79) **HN: ever: 3.02 (1.42-6.44); current: 2.46(1.34-4.49)** OC: DIP: 0.8 (0.27-2.34); CMC: 0.57 (0.22-1.50); HN: 0.85 (0.40-1.80)
Spector [29]	N-CS	--	--	+	+	rOA score ≥ 2 on K&L-scale	Hormone replacement therapy (HRT):ever use (>12 months at least 24 months previously) , current use (>12 months at time of X-ray)	DIP: ever: 0.67 (0.34-1.35); current: 0.48 (0.17-1.42); CMC: ever: 0.65 (0.34-1.23); current: 0.94 (0.44-2.03)
Von Muhlen [31]	N-CS	--	--	+	+	cOA according to ACR-criteria	Estrogens (PME), past and current use of estrogen alone or in combination with progestin; PME ≥ 1 year vs. 0-< 1 year, current vs. non current, ever vs. never.	**PME use ≥ 1 year vs. 0-< 1 year:1.57 (1.05-2.33)**
Sowers [27]	N-CS	16	557	-	-	rOA score ≥ 2 on K&L-scale	Hormone replacement therapy (HRT): current use	Highest joint score: 1.2 (0.65-2.2) (univariate) Joint score ≤ 2: 0.54 (0.07-4.2) (univariate)

Table 2.4: Results included studies on OA prevalence. (Shaded = High-quality study; not shaded = Low-quality study) (continued)

Reference	Study design	N OA+	N OA -	Adj. Age	Adj. BMI	Case definition (incident OA-case if):	Specification Hormone use (never use = reference)	Outcome (OR (95%CI))
Hip								
Von Muhlen [31]	N-CS	--	--	+	+	cOA according to ACR-criteria	Estrogens (PME), past and current use of estrogen alone or in combination with progestin; PME ≥ 1 year vs. 0-< 1 year, current vs. non current, ever vs. never.	**PME use ≥ 1 year vs. 0-< 1 year: 5.03 (1.70-14.84)**
Nevitt [28]	N-CS	214	4152	+	+	rOA score ≥ 2 on Croft scale	Estrogens (ORT); current use, ever use (ever use ≥ 1 year). (women who had used ORT less than one year were excluded from analysis) ; duration past estrogen use (<10yrs, ≥10 yrs)	**Current use: 0.62 (0.49-0.86)** <10yrs: 0.75 (0.47-1.24), **≥10 yrs: 0.57 (0.40-0.82)** Past use: 1.07 (0.85-1.34) <10yrs: 1.19 (0.92-1.52), ≥10 yrs: 0.79 (0.53-1.18)
Vingard [35]	CC	230	273	+	-	THR due to 'primary arthrosis' according to the Swedish National Register (cOA)	Estrogen use; use ≥ 1 year before or after age 50 (ever use) Oral Contraceptive (OC) use: use ≥ 1 year before age 50 (ever use)	Estrogen use: 0.7 (0.5-1.0) OC use: 1.6 (1.0-2.3)
Dennison [38]	CC	413	413	-	+	rOA score ≥ 2 on K&L-scale, women on waiting list for primary THR over 18 month period (cOA)	Hormone replacement therapy (HRT): ever use + duration (short term use: < 5yrs, Long term use: > 5 yrs) + start use (before (or at same time), after onset pain) Oral Contraceptive (OC) use: ever use	Ever use: 1.4 (0.8-2.4); Short term: 1.7 (0.9-3.3), onset: before: 0.5 (0.2-1.2), after: 1.3 (0.7-2.5) Long term: 0.6 (0.2-1.8), onset: before: 0.5 (0.2-1.5), after: 0.2 (0.0-0.8) OC use: 1.6 (0.8-2.9)

Table 2.4: Results included studies on OA prevalence. (Shaded = High-quality study; not shaded = Low-quality study) (continued)

	Reference
Knee	
Carbone [30]	Results after adjustment for covariates: Estrogen use vs. presence or absence of knee symptoms: P ≥ 0.22 Estrogen use vs. presence or absence tibiofemoral ROA: P ≥ 0.90 Estrogen use vs. presence or absence whole knee ROA: P ≥ 0.43Estrogen use (N = 178 knees) (ever use)rOA score ≥ 2 on K&L-scale and WORMS + symptomatic OA on WOMAC-pain scale (cOA)++390276N-CS
Spector [29]	Current use: **Osteophytes: 0.31 (0.11-0.93),** JSN: Gd1+: 0.70(0.41-1.22) Ever use: Osteophytes: 0.80 (0.43-1.49), JSN: Gd 1+: 1.21 (0.81-1.81)Hormone replacement therapy (HRT): current use (>12 months at time of X-ray), ever use (>12 months at least 24 months previously)rOA score ≥ 2 on K&L-scale++----N-CS
Von Muhlen [31]	PME use ≥ 1 year vs. 0-< 1 year: 1.30 (0.93-1.81)Estrogen use (PME), past and current use of estrogen alone or in combination with progestin; PME ≥ 1 year vs. 0-< 1 year, current vs. non current, ever vs. never.cOA according to ACR-criteria++----N-CS
Hannan [33]	ERT use: 0.93 (0.62-1.40) < 2 years use: 1.54 (0,78-3,04), >/=4 years: 0,71 (0,42-1,20)Hormone use: mostly conjugated estrogen, orallyrOA score ≥ 2 on K&L-scale++329286N-CS
Sowers [27]	**Highest joint score: 2.2 (1.17-4.21)** (multivariate) Joint score ≥ 2: 2.56 (0.68-9.5) (univariate)Hormone replacement therapy (HRT): current use (both unopposed estrogen as estrogen + progestin)rOA score ≥ 2 on K&L-scale--55716N-CS
Sandmark [34]	**ERT: RR =1.8 (1.2- 2.6)** OC-use: RR = 0.9 (0.6- 1.4)Estrogen use (ERT) after age 50 (≥1 year) Oral contraceptive use (OC) (ever use)On waitinglist for TKR due to OA (cOA)+284300CC
Cicuttini [32]	Osteophytes (tibiofemoral) by ERT use: 0.84 (0.31-2.29) Osteophytes (whole knee) by ERT use: 0.93 (0.40-2.18)Estrogen use (ERT) (≥1 year) (ever use)rOA score ≥ 2 on K&L-scale+215110325CS
Any joint	
Von Muhlen [31]	**PME use ≥ 1 year vs. 0-< 1 year: 1.49 (1.10-2.02)**Estrogen use (PME), past and current use of estrogen alone or in combination with progestin; PME ≥ 1 year vs. 0-< 1 year, current vs. non current, ever vs. never.cOA according to ACR-criteria++-----N-CS
Schneider [39]	ERT use: 0.74 (0.53-1.05)Estrogen use: current usecOA according to ACR-criteria++924157N-CS
Samanta [40]	HRT: 0.31 (0.07-1.35) OC: 0.81 (0.33-2.00)Hormone replacement therapy (HRT); any useOral Contraceptive (OC) (ever use)rOA hip or knee, without hand cOA / rOA (cOA)--482208CC

DIP: distal interphalangeal joint, CMC: carpometacarpal joint, OA: osteoarthritis, rOA: radiographic OA, cOA: clinical OA (symptomatic+ radiological), HN: Herberden's- / Bouchard's nodes, JSN: joint space narrowing, K&L-scale: Kellgren and Lawrence-scale, OC = oral contraceptives, PME: post menopausal estrogen, WORMS: Whole-Organ MRI Score, WOMAC: Western Ontario McMaster Universities Index, Statistically significant outcomes are shown in Bold

Prevalence of knee OA was studied in seven studies. The Chingford-study [29] found current HRT use to be protective of knee rOA, while Sowers et al. [27] found it to be significantly increasing the risk of knee rOA in the highest joint score, but not for knee rOA defined as Kellgren and Lawrence-score ≥ 2. Sandmark et al. [34] found ever usage of estrogen to be significantly increasing the risk of knee cOA. Others found ever use of estrogen to be not associated with knee rOA [19,29,33], or knee cOA [30, 31].

In studying 'any joint OA' (hand, hip or knee) with estrogen use, one study found a significantly increased risk [31] and calculating with data from Schneider [39] we found 'no relation', whereas both studies describe the Rancho Bernado study population. Samanta et al. [40] also found no association for this same relation in their study. Finally, 'duration of use' was evaluated in four studies. One study found a dose-response effect for duration of estrogen use [31], with a similar dose-response pattern for hand, knee and hip cOA. They found that, among estrogen users, women with OA had used estrogen significantly longer than women without OA. Three other studies found no such significant relations between duration of estrogen use and knee rOA or cOA [28,33,37].

A sensitivity analysis was performed using binary logistic regression analysis (SPSS-11.0.1). Studies were compared on adjustment for age, BMI, bone mineral density (BMD), assessment manner of OA (clinical or radiological), funding source, and menopausal status of the population. No clear differences in outcomes of the determinants were found.

Evidence synthesis

Incidence studies

Limited evidence for a significant protective effect of unopposed estrogen use for incidence of THR and TJR was observed in hysterectomized women. In non-hysterectomized women, using a combination of estrogen plus progestin, moderate evidence of no association with THR or TJR was found.

For knee rOA limited evidence for no association was seen for both hysterectomized and non-hysterectomized women. However, it should be noted that in both the Framingham and Chingford study a non-significant protective effect for knee OA was observed in women using mostly conjugated equine estrogens, which agrees with the findings in the WHI RCT-study.

In studies where type of estrogen was not specified, evidence of no association was seen for hand (limited-), hip (moderate-) and knee (strong evidence). For this evidence in the knee, current or ever use did not make a difference.

Prevalence studies

The evidence for DIP rOA was conflicting for both ever- and current HRT use. For CMC rOA there was strong evidence for no association. For hand cOA and the presence of

Herberden's nodes, the evidence was strong in the direction of a significantly increased risk.

Limited evidence for a significantly increased risk due to HRT use was found for hip cOA. For hip rOA and current use of HRT no relation was seen for short term use (limited evidence), but for long term use the evidence was limited for a significant protective effect. For ever use, strong evidence of no relation was found, irrespective of duration of use.

Conflicting evidence was seen for a relation between ever estrogen use with knee cOA. Ever use of HRT and knee rOA was found to be not related with strong evidence, while for current use conflicting evidence was seen. For the duration of HRT use (long term or short term) in knee rOA limited evidence was found for no relation. And finally for 'any joint OA' with HRT use conflicting evidence was seen.

DISCUSISON

The assumed relationship between exogenous hormone use and OA of the hand, hip or knee was not clearly observed. Most evidence points in the direction of no relation between osteoarthritis of hand, hip and knee and exogenous hormone use, or the evidence remains conflicting. However, only for the outcomes in incidence of total hip replacements there seems to be a trend of a limited protective effect in women using unopposed estrogen.

There have been other reviews on this subject in the past by Wluka et al. [41] in 2000, invited review, including 11 studies, by Hanna et al. [42], a systematic review in 2004, and the American College of Obstetricians and Gynaecologists [43] (ACOG), also 2004, both including 10 studies. Based on our Medline search we included almost twice as many studies in our systematic review (N=19), while excluding some of the studies included in the reviews of Wluka, Hanna and/or the ACOG due to not complying with our inclusion criteria [21,44-46]. Finally, this led to a more comprehensive and up-to-date overview on the subject.

The use of exogenous hormones is intertwined with other menopausal aspects like hysterectomy and menopause related health complaints, making it difficult to study sec the influence of the hormones used and possibly leading to confounding. Data collection in the studies was sometimes questionable due to limited information, possibly contributing to why no hard evidence was found. For example, studies were not always clear on the type, dosage and duration of hormones used and the reason for using HRT is often not specified. HRT-users are more likely to have low BMD and osteoporosis, which may protect these individuals from developing OA [16]. It would be expected

that if female hormones have the alleged impact on OA development, more significant outcomes would be found in literature.

Also, in the case-control studies there are concerns about validity of identification of cases. It is imaginable that women using hormones, and therefore visiting physicians more often than women who do not, are more likely to have their complaints diagnosed as OA, simply because complaints are more often presented to physicians. This could lead to a false-positive correlation between hormone use and OA in retrospective case-control studies. Also, from animal studies it is known that the hormonal influence from removing the ovaries is not equal to a natural menopause [47,48]. Considering this, it may not be completely fair to compare women with ovariectomy and those with natural menopause. Our quality assessment shows that in case-control studies the OA assessment manner was often not identical for cases and controls, leading to possible bias. On the other hand, if considering only the data from study designs where OA assessment was identical for both study groups, the evidence remains conflicting.

The search performed was extended in used keywords, as was the applied methodological quality assessment. Although we put much effort in identifying relevant articles, our search might have some limitations. Some relevant articles may have been missed because they used other keywords, had unclear abstracts, were not written in English, Dutch, German, South African or any of the Scandinavian languages, not specified the OA affected joint or were not indexed in Medline. However, we do not expect to have missed articles by using only this one database, because an identical search performed in EMBASE up to March 2006 did not yield new articles, and all references of the included articles were checked.

In excluding studies on GOA, without specification of outcomes on hand, hip or knee joint, we may have lost relevant data. However, in analysing the excluded studies on HRT-use and GOA, two studies found HRT-use was protective [16,17], another found an increased risk [49], and two others found no relation [18,44]. Also, no association between HRT-use and frequent knee pain was found in the HERS study [50]. Therefore we postulate that the evidence for the assumed association between HRT-use and OA would remain conflicting, even after including these studies.

In the evidence synthesis used in this review all non-significant outcomes were interpreted as evidence of no relationship between exogenous hormones and OA. Still, it is possible that an association is present, but it could not be found using the applied study designs and corresponding sample sizes.

Despite the limitations of a best evidence synthesis compared to a more quantitative synthesis, we argue that the use of this systematic approach is appropriate. With scoring the quality of the included studies and defining levels of evidence, we give the reader insight in the process of reaching conclusions.

Due to the large heterogeneity in study population and determinant- and outcome measures, statistical pooling data was not feasible. For example, effects of hormones on disease may affect symptoms, structure or both and may have different effects on different joints. In this review the focus of OA assessment (e.g. clinical vs. radiological) and studied joints differ between studies. In case of such large differences in outcome measurements it is preferable to refrain from pooling and divide studies into smaller groups in a best evidence synthesis.

Influence of exogenous hormones on OA is also investigated in animal studies. Animal models on ovariectomy, for example, are frequently used since the 1980s, and well accepted in osteoporosis research. Because both bone and cartilage are sex-hormone sensitive, ovariectomy was expected to result in cartilage changes as well, and this became a topic of study in the last decade. These studies on various species [51-57] showed that ovariectomy resulted in increased cartilage degradation as demonstrated histologically by surface erosions, biomechanically by changed intrinsic material properties, or biochemically measuring cartilage degradation marker (CTX-II) in urine. Estrogen replacement in these models reduced the OA changes [51,53]. However, a recent systematic review on animal models for OA, inconclusive evidence was found for a relation between OA with ovariectomy and estrogen treatment [58].

For future research on OA and exogenous hormone use we suggest to at least adjust for age and BMI. We recommend to specify the type, dosage and duration of the HRT-used and to adjust for BMD, since HRT is often used for women with osteoporosis, which could confound outcomes. However, prescription of HRT (combination estrogens with progesterone) is limited nowadays because of increased risk of breast cancer [59]. A design with estrogen substitution alone might have no effect on breast cancer, but this regimen is only used for hysterectomized women [60]. We hoped that gaining insight in the association between OA and exogenous hormone use would contribute to the formulation of a high-risk profile for OA development and a better understanding of OA etiology. Unfortunately much remains unclear. The fact remains that incidence and prevalence rises quickly in women after the age of 50. Possibly the relationship between exogenous hormones and OA of hand, hip and knee is too complex to appear in epidemiological research as such, or other aspects, yet to be determined, play a role in the increased incidence in women after the age of 50 years.

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Chapter 3

No clear association between female-hormonal aspects and osteoarthritis of the hand, hip and knee: a systematic review

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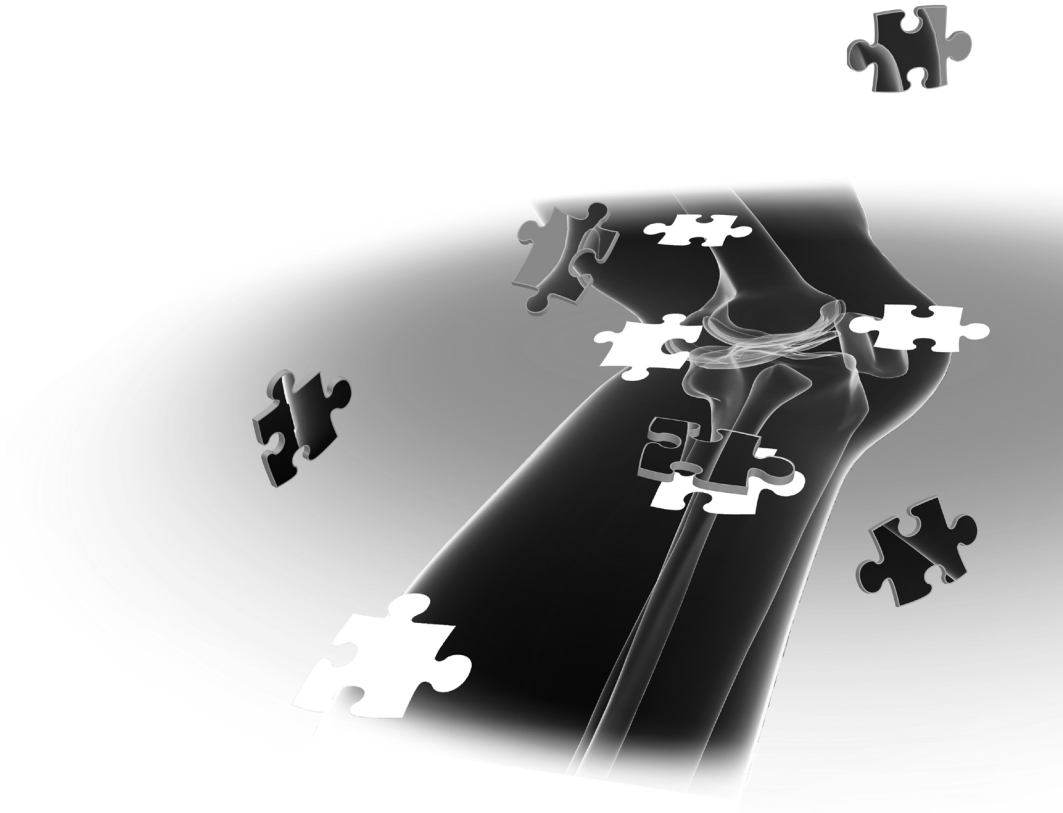

ABSTRACT

Objectives

Incidence of osteoarthritis (OA) rises steeply in women above age 50; the climacteric period for women. The simultaneous occurrence of these events suggests an association between OA and changes in female-hormonal aspects. This systematic review studies the assumed association between OA and aspects concerning the fertile period (duration, endogenous hormones, age at menarche/menopause) and the menopause (menopausal status, years since menopause (YSM), surgical menopause).

Methods

Medline and EMBASE were searched for articles assessing associations between hand/hip/knee OA and female-hormonal aspects. Methodological quality was assessed systematically and results were summarized in a best-evidence synthesis.

Results

16 studies were included. For most hormonal aspects no association was found. Conflicting evidence was found for an association of age at menarche with Herberdens' nodes (HN) and hand rOA, YSM with knee rOA and ovariectomy with hip OA. An increased risk was seen for low estradiol serum levels in the early follicular phase with incident knee rOA, age at menarche being ≤11 years old with total hip replacement, being postmenopausal and YSM with the presence of HN. A protective effect was seen for age at menopause being ≥52 years with total knee replacement. Evidence level was limited for all.

Conclusions

The assumed relationship between the female-hormonal aspects and OA was not clearly observed in this review. The relationship is perhaps too complex, or other aspects, yet to be determined, play a role in the increased incidence of OA in women aged over 50 years.

INTRODUCTION

Prevalence of osteoarthritis (OA) is higher in women than in men and incidence rises with ageing. Incidence of this common progressive joint disease rises faster in women than in men after the age of 50 years [1]; around the same age of the climacteric transition in women. In studying the association between exogenous hormone use and OA in a previous systematic review [2], we found no convincing evidence of an association. We did, however, find a limited protective trend for incidence of total hip replacement for hysterectomized women using unopposed oestrogen, but, given the prevalence of this determinant, this does not explain the rise in incidence.

Menopausal women have lower oestrogen levels than normally menstruating women [3]. Considering this, and the sex-specific incidence and prevalence difference, oestrogen may play a role in OA regulation. Determinants influencing endogenous serum oestrogen levels longterm, defined by the fertile period or menopause, may be associated with OA development. The aim of this systematic review is to gain insight in the current stage of knowledge on the association between OA and female-hormonal aspects.

METHODS

The methods used in this systematic review are similar to those previously described in our review on OA and HRT use [2]. Here the methods are repeated shortly. Study identification

The articles were identified by systematically searching the databases of Medline and EMBASE up to October 2008. Inclusion criteria and keywords (osteoarthritis, oestrogen, menopause, ovariectomy and equivalents of these words) are shown in Appendix I. The search was extended by screening the reference lists of all included studies and relevant reviews.

Methodological quality

The methodological quality of the included studies was based on previously used lists [4,5] (Appendix II, with specifications in Appendix III), but modified to cover our topic and concerns both the internal validity and informativeness of the article. All articles were scored independently by two reviewers and consensus was aimed for in case of disagreement.

Evidence synthesis

Evidence from homogeneous studies was pooled. In case of heterogeneity, we refrained from statistical pooling and performed a 'best-evidence synthesis' [5, 6].

A study was considered to be of high quality if the methodological score was ≥60%.

The best evidence synthesis was performed using the following levels of evidence [5, 7]:

- *Strong evidence*: Consistent findings (>75%) in multiple high-quality studies
- *Moderate evidence:* Consistent findings (>75%) in: one high-quality study and some other low-quality studies or multiple low-quality studies
- *Limited evidence:* Only one high-quality study
- *Conflicting evidence:* Inconsistent findings in several studies of equal quality
- *Insufficient evidence:* No high-quality study and at most one low-quality study available
- *No evidence:* Provided when no studies could be found

In the evidence synthesis a subdivision is used for the type of OA: 1) radiological OA (rOA), indicating radiological changes only and 2) clinical OA (cOA), indicating complaints of pain and stiffness in the described joint or presence of palpable Herberden's nodes (HN), with or without radiological changes present in the same joint. cOA includes total replacements of hip (THR),- knee (TKR) or - joint (TJR, hip or knee).

Data extraction

Two researchers independently collected characteristics of the included studies. Extracted outcomes are relative risks (RR) or odds ratios (OR) and were dichotomized into significant outcomes (association present) and non-significant outcomes (no association present)[6].

RESULTS

Study identification and methodological quality

The systematic search resulted in the identification of 464 references which were screened on title and abstract, leading to the inclusion of 16 studies. The two reviewers each scored 266 items from 16 studies and initially agreed on the quality score of 194 items (= 73%, κappa: 0.54). Table 3.1 gives a description of the characteristics of the included studies. The quality scores of the included studies are presented in Table 3.2.

Heterogeneity

All included studies were heterogeneous with regard to the determinants, outcome measures and study population, causing clinical heterogeneity and making statistical pooling illogical. Even within the studied determinants heterogeneity on these points was too large to justify pooling. Therefore we performed a best evidence synthesis for all studied determinants.

Results

The hormonal aspects reviewed are related to the fertile period and menopause and about 50% of the studies report on multiple aspects (Table 3.3). The hormonal aspects included are: endogenous hormones [8, 9], age at menarche and/or menopause [10-14], duration of fertile period [11, 12], menopausal status [8, 12, 15-18], years since menopause [12, 19, 20] and surgical menopause [12, 16, 21-23].

Endogenous hormones

Sowers et al. studied estradiol serum levels in OA and reported on their studies in 1996 [8] and 2006 [9]. In 2006 they used a combination of two separate cohorts (SWAN and MBHS) collectively known as the Southeast Michigan Arthritis Cohort study and found that women who had baseline endogenous-early-follicular–phase-estradiol concentrations in the lowest tertile had greater odds of developing knee rOA.

The study population of Sowers et al. in 1996 was also included in the 2006 study, therefore only the 2006 study is considered for evidence synthesis. Considering this, limited evidence is seen for significant increased risk between lower blood estradiol levels and incident knee rOA. No relation was seen for this with prevalence of knee rOA.

Age at menarche and/or menopause

Four studies report on the relation between OA and the age at menarche [10, 11, 13, 14] and four on age at menopause [10-12, 14]. Two studies found a negative association: Kalichman [13] found an association with hand rOA and Liu [14] with THR. Both found younger age at menarche increasing the risk of OA. The other studies did not find such associations [10-12].

The Zoetermeer study [12] reported a higher menopausal age (≥51 years) to increase the risk of having HN, while for TKR due to OA The Million women study [14] found age at menopause ≥52 years old to be protective. For age at menarche with hand rOA the evidence is conflicting. For THR limited evidence was seen for a significantly increased

Table 3.1: Characteristics included studies (studies are ranked in descending order of quality)

Reference	Design	N	Mean age(yr)	Joint	OA *	Definition cases (=OA+) / population	Hormonal aspect
INCIDENCE STUDIES							
High quality							
Sowers [9]†	Cohort	736	42 (26-54)	Knee	x-ray	Women from the South East Michigan Arthritis Cohort (combination of two separate cohorts (the Study of Women's Health Across the Nation (SWAN) and the Michigan Bone Health study (MBHS)))	Endogenous hormones
Low quality							
Oliveria [15]¥	N-CC	268	(20-89)	Hand Hip Knee	x-ray sympt.	Continuous female members of Fallon Community Health Plan. None of the participants had OA at baseline	MP status
Oliveria [16]	N-CC	120	60	Hand Hip Knee	x-ray sympt.	Pre- and Postmenopausal females. Continuous female members of Fallon Community Health Plan. None of the participants had OA at baseline	MP status
PREVALENCE STUDIES							
High quality							
Cooley [11]	CS	348	Cases: 79 Contr: 51 (40-85)	Hand	x-ray sympt.	All Tasmanian females with hand OA and a history of at least one living relative with hand OA were invited to take part. with their families (both affected and unaffected) Cases recruited from records of rheumatology practice.	Age MP Dur.fertile
Sowers [9]	Cohort	842	42 (26-54)	Knee	x-ray	Women from the South East Michigan Arthritis Cohort (combination of two separate cohorts (the Study of Women's Health Across the Nation (SWAN) and the Michigan Bone Health study (MBHS)))	Endogenous Hormones
Kalichman [13]	CS	745	48 (18-84)	Hand	x-ray	Women recruited for Chucasha Skeletal Aging Study (ChuSAS), all not using medication for OA	Age at menarche
Sowers [8]	N-CS	573	37 (24-45)	Hand Knee	x-ray	Pre- and Perimenopausal females participating in Michigan Bone Health study (MBHS) in 1992 (recruited from general population). X-rays of dominant hand and knees were examined	MP status Endogenous hormones
Liu [14]	N-CS	1.3 millon	56 (50-64)	Hip Knee	THR TKR	Women participating in Million Women Study. Case if OPCS-4 code present in NHS health records. Controls not checked for OA	Age Men/MP MP status

Table 3.1: Characteristics included studies (studies are ranked in descending order of quality) (continued)

Reference	Design	N	Mean age(yr)	Joint	OA *	Definition cases (=OA+) / population	Hormonal aspect
Spector [21]	CS	326	45-65	Hand Knee	x-ray sympt.	Females recruited from general population in the suburbs of East London. All cases were hysterectomized at Whipps Cross Hospital; Controls had in tact uteri	Surgical MP
Nevitt [22]	N-CS	4366	72	Hip	x-ray sympt.	All females participating in Study of Osteoporotic Fractures study	Surgical MP
Schouten [12]	N-CS	645	45-55	Hand	x-ray sympt.	Pre- and postmenopausal females participating in Zoetermeer study (recruited from general population)	Age MP, Surgical MP, MP status, YSM, Dur. fertile
Low quality							
Cvijetic [19]	CS	325	58.6	Knee	x-ray	Females from general population participating in twin study; only one twin included	YSM
Cicuttini [17]	N-CS	306	63.6 (45+)	Hand Hip Knee	x-ray	Postmenopausal females selected from population records from ten municipal offices in Zagreb. Radiographs taken as part of larger Epidemiological Study of Physical. Social and Psychological Health of Elderly People.	MP status
Dennison [23]	CC	826	72	Hip	x-ray sympt. THR	Postmenopausal Females (age: 45+) recruited from general population in two health districts in England. Cases drawn from waiting list for THR.	Surgical MP
Iwamoto [20]	CC	674	67 (46-90)	Knee	x-ray sympt.	Postmenopausal females visiting hospital in Shozuoka. Japan. Cases were visiting hospital because of knee pain.	YSM
Tepper [10]	CS	2358 (incl. ♂)	55-74	Hip	x-ray	Females participating in NHANES-I study; recruited from general population	Age men / MP
Samanta [18]	CC	690	70 (60-78)	Hand Hip Knee	x-ray sympt.	Females recruited from an OA Research Clinic at the City Hospital Nottingham. All cases had been referred with symptomatic lower limb radiological OA. Controls recruited from same general practice as cases attended.	MP status

* = assessment manner OA either radiographic (x-ray) or symptomatic (sympt.)† = incidence (N=736) + prevalence study (N=842) ‡ = The study population used by Oliveria et al. [16] was obtained from their previous study on oestrogen replacement therapy [15]. In this review the populations are considered different due to differences in mean BMI and mean age of the described study populations, THR = Total Hip Replacement, TKR = Total Knee Replacement, OA = Osteoarthritis, (N)CS = (nested) cross-sectional study, CC = case-control study, Dur. Fertile = duration fertile period in a woman's life (age menopause-/-age menarche), MP = menopause, Age Men. = Age menarche, YSM = years since menopause

Table 3.2: Quality of the included studies

Reference	Adjusted for age	Adjusted for BMI	a	b	c	d	e	f	g	h	i†	j	k	l†	m	n	o	p	q	Obtainable SCORE	N +	QUALITY (% +)
Incidence studies																						
High quality																						
Sowers [9]	+	+	+	+	?	-	-	+	+	?	1a.+	+	+	1a.+	+	+	+	+	+	17	13	**76.5**
Low quality																						
Oliveria [15]¥	-	-	-	NA	NA	+	+	+	+	?	2a.-	?	+	2a.?	+	+	-	+	-	15	8	**53.3**
Oliveria [16]	-	+	-	NA	NA	-	+	+	+	?	2c.+ 2a.-	?	+	2c.- 2a.-	-	+	?	+	-	17	7	**41.2**
Prevalence studies																						
High quality																						
Cooley [11]	+	+	-	NA	NA	-	+	+	+	+	2d.+ 1b.+ 1c.+	?	+	2d.+ 1b.+ 1c.+	+	+	?	+	+	19	15	**79.0**
Sowers [9]	+	+	+	+	?	-	-	+	+	?	1a.+	+	+	1a.+	+	+	+	+	+	17	13	**76.5**
Kalichman [13]	-	-	-	NA	NA	+	+	+	+	+	+	?	+	?	+	+	?	+	+	15	11	**73.3**
Sowers [8]	-	-	-	NA	NA	-	+	+	+	+	1a.+ 2a.?	+	+	1a.+ 2a.+	+	+	-	+	-	17	12	**70.6**
Liu [14]	+	+	+	-	-	-	+	+	+	-	2a.+ 1b.+	+	+	2a.? 1b.?	+	+	+	+	+	19	13	**68.4**
Spector [21]	+	+	-	NA	NA	-	-	-	+	-	2d.+	+	+	2d.+	+	+	+	+	+	15	10	**66.7**
Nevitt [22]¥	+	+	-	NA	NA	-	+	+	+	?	1a.+	?	+	1a.+	+	+	?	+	+	15	10	**66.7**
Schouten [12]	+	+	-	NA	NA	-	+	-	-	?	2c.+ 2d.+ 2b.+1b.+ 1c.+	?	+	2c.? 2d.? 2b.+1b.+ 1c.+	+	+	?	+	+	23	14	**60.9**

Table 3.2: Quality of the included studies (continued)

Reference	Adjusted for age	Adjusted for BMI	a	b	c	d	e	f	g	h	i†	j	k	l†	m	n	o	p	q	Obtainable SCORE	N +	QUALITY (% +)
Low quality																						
Cvijetic [19]	-	-	-	NA	NA	-	+	+	+	-	2b.+	-	?	2b.+	+	+	-	+	-	15	8	**53.3**
Cicuttini [17]	+	+	-	NA	NA	-	+	-	+	+	2d.- 2a.-	?	+	2d.? 2a.?	+	+	+	+	+	17	9	**52.9**
Dennison [23]	-	+	-	NA	NA	+	+	+	-	-	2d.+	?	+	2d.?	-	+	-	+	-	15	7	**46.7**
Iwamoto [20]	+	+	-	NA	NA	-	?	+	+	?	2b.+	?	+	2b.+	-	+	?	-	+	15	7	**46.7**
Tepper [10]	+	-	-	NA	NA	?	+	-	-	?	4.+ 1b.+	?	+	4.? 1b.?	+	+	?	+	-	15	6	**40.0**
Samanta [18]	-	-	-	NA	NA	?	?	-	+	-	2d.+ 1b.+	?	+	2d.? 1b.+	-	-	?	+	-	17	6	**35.3**

* Scoring this item was Not Applicable (NA) to this study, Items scored (explained in Appendices II and III) a) Prospective design was used, b) Withdrawals ≤ 20%, c) Information on completers versus withdrawals (selective loss to follow-up), d) Selection before disease was present or at uniform point, e) Nonbiased selection of participants and with exclusion criteria applied equally to all, f) Description of relevant inclusion and exclusion criteria source population, g) Sufficient description of baseline characteristics source population, h) Participation rate ≥ 80% for source population, i) Definitions of determinants are valid, j) Exposure assessment was blinded, k) Exposure was measured identical in entire studied population, l) Minimal exposure time determinant over 6 months, m) OA was assessed identically in studied population with and without the determinant, n) Presence of OA was assessed according to valid definitions with standardized classification, o) Presence of OA assessed independent of determinants, p) Data presentation of most important outcomes, q) Adjusted for most important confounders

† Point i and l: 1a = endogenous hormones, 1b = age at menopause / menarche, 1c = duration of fertile period, 2a = menopausal status, 2b = years since menopause, 2c = type of menopause, 2d = surgical menopause (bilateral ovariectomy), ‡= patient population matched for age and BMI , ¥ = self-calculated outcomes (outcomes not adjusted for confounders)

Table 3.3: Results female-hormonal aspects

Reference	Study design	N OA+	N OA -	Adj. age	Adj. bmi	Case definition	Specification female-hormonal aspect	Outcome menopausal aspect (OR (95%CI))
Incidence studies								
Hand, hip, knee								
Sowers [9] HQ	Cohort	736	--	-	-	rOA: score ≥ 2 on K&L-scale	Endogenous hormones	Knee OA: Log estradiol (pg/ml); C statistic = 0.74 ≤ **33rd percentile (<47 pg/ml) = 1.88 (1.07-3.51);** 33rd-66th percentile (47-77 pg/ml) = Referent; ≥ 66th percentile (>78 pg/ml) =1.04 (0.52-2.09)
Oliveria [15]*	N-CC	134	134	-	-	rOA (ACR-criteria) + symptoms	Menopausal status†	Hand cOA: 1.54 (0.2-9.7), Hip cOA: 0.48 (0.04-5.63), Knee cOA: 1.09 (0.7-1.7)
Oliveria [16]	N-CC	60	60	-	+	rOA (ACR-criteria) + symptoms	Menopausal status†	Large joint (hip or knee) cOA: 2.5 (0.5-12.9)
Prevalence studies								
Hand								
Sowers [8] HQ	N-CS	--	--	-	-	rOA: score ≥ 2 on K&L-scale	Endogenous hormones Menopausal status‡	Estradiol serum level (pg/ml): highest joint score = 1.0 (1.00-1.00); Joint score of ≥ 2 = 1.0 (0.99-1.00) Menopausal status: Highest joint score = 0.56 (0.06-4.73) (all univariate outcomes)

Table 3.3: Results female-hormonal aspects (continued)

Reference	Study design	N OA+	N OA -	Adj. age	Adj. bmi	Case definition	Specification female-hormonal aspect	Outcome menopausal aspect (OR (95%CI))
Schouten [12] HQ	N-CS	176	469	+	+	cOA (HN) or rOA: score ≥ 2 on K&L-scale	Age at menopause§	Age at MP + rOA**: ≤**45 yrs: 1.40 (0.66-2.96), 46-50 yrs: 0.87 (0.46-1.65), ≥51 yrs: 1.58 (0.71-3.52) cOA: ≤45 yrs: 1.74 (0.45-6.71), 46-50 yrs: 1.25 (0.37-4.17), **≥51 yrs: 4.76 (1.40-16.19)**
							Duration fertile (yrs)	Duration fertile + rOA: ≤30 yrs: 1.28 (0.57-2.84), 31-35 yrs: 0.82(0.39-1.75), ≥36 yrs: 1.37 (0.70-2.65) Duration fertile + cOA: ≤30 yrs: 1.20 (0.25-5.79),
							Menopausal status: (Natural MP‡)	31-35yrs: 1.63 (0.46-5.70), ≥36 yrs: 2.78 (0.93-8.32) MP + rOA0: 1.33 (0.80-2.20)¶, 45-49 yr + rOA: 0.84 (0.33-2.13), 50-54 yr + rOA: 1.59 (0.89-2.85) **MP + cOA: 2.43 (1.00-5.90)¶**, 45-49 yr + cOA: 1.88 (0.39-9.02), 50-54 yr + cOA: 2.73 (0.96-7.74)
							YSM**	YSM + rOA: 1-2 years 1.11 (0.49-2.48); 2-4 years: 1.10 (0.56-2.16); ≥ 4 years: 1.21 (0.62-2.36)
							Ovariectomy (bilateral)	YSM + cOA: 1-2 years: 2.68 (0.83-8.65); 2-4 years: 2.15 (0.73-6.33); ≥ 4 years: 1.20 (0.35-4.04) Ovariectomy: rOA: 0.84 (0.44-1.59), cOA: 1.02 (0.28-3.71) MP 45-49 yr + rOA: 0.51 (0.19-1.37) MP 45-49 yr + cOA: 1.48 (0.31-7.00) MP 50-54 yr + rOA: 1.19 (0.51-2.71) MP 50-54 yr + cOA: 0.49 (0.06-4.36)
Kalichman [13] HQ	CS	--	--	-	-	rOA: score ≥ 2 on K&L-scale	Age at menarche (yrs)	Only difference given: **β =-0.066, P = 0.012**
Cvijetic [19]	N-CS	--	--	-	-	rOA score ≥ 2 on K&L-scale	YSM **	Only difference given: DIP: β = -0.05, PIP: β = -0.05, CMC: β = -0.18

Table 3.3: Results female-hormonal aspects (continued)

Reference	Study design	N OA+	N OA -	Adj. age	Adj. bmi	Case definition	Specification female-hormonal aspect	Outcome menopausal aspect (OR (95%CI))
Spector [21] HQ	CS	19	24	+	+	rOA score ≥ 2 on K&L-scale or cOA (symptoms)	Ovariectomy (bilateral)	DIP: 0.82 (0.36-1.86), PIP: 0.36 (0.11-1.21), CMC: 1.79 (0.69-4.66) (rOA or cOA not specified)
Cooley [11] HQ	CS	--	--	+	+	rOA according to Altman atlas or cOA (HN) scored on hand picture (not x-ray)	Age at menarche (yrs) Age at MP (yrs) Duration fertile (yrs)	Age at menarche + rOA: DIP: 0.96 (0.82-1.13), CMC: 1.03 (0.88-1.21), cOA: 0.93 (0.81-1.08) Age at menopause + rOA: DIP: 1.02 (0.93-1.11), CMC: 1.02 (0.96-1.09), cOA: 1.03-(0.97-1.09) Duration fertile period + rOA: DIP: 1.01 (0.92-1.10), CMC: 1.00 (0.94-1.07), cOA: 1.02 (0.97-1.08)
Hip								
Liu [14] HQ	N-CS	12124	--	+	+	Positive if THR due to OA, controls not x-ray checked for OA	Age at menarche (yrs)†† Age at MP ‡‡ Menopausal status ‡	Age at men.:**≤11: 1.15 (1.08-1.22),** 13:1.00 (0.94-1.06), 14:1.02(0.96-1.08),15+:1.01(0.95-1.07), P=0.02 Age at MP: 49-51: 1.01 (0.93-1.09), 52+: 0.98 (0.91-1.06) P =0.5 Menopausal status: 0.97 (0.77-1.24)
Nevitt [22]	N-CS	214	4152	+	+	rOA score ≥ 2 on Croft scale. Grade 0-1 are reference	Surgical MP (Ovariectomy)	**rOA: 0.66 (0.48-0.90)** §§
Dennison [23]	CC	413	413	-	+	cOA: rOA on K&L-scale + on waiting list for primary THR (>18 months)	Ovariectomy (combination both uni- and bilateral removal of ovaries)	**cOA: 1.9 (1.0-3.7) (P<0.05)**
Cvijetic [19]	N-CS	--	--	-	-	rOA score ≥ 2 on K&L-scale	YSM **	Only difference given: β = -0.13

Table 3.3: Results female-hormonal aspects (continued)

Reference	Study design	N OA+	N OA -	Adj. age	Adj. bmi	Case definition	Specification female-hormonal aspect	Outcome menopausal aspect (OR (95%CI))
Tepper [10]	CS	36	--	+	-	rOA score ≥ 2 on K&L-scale	Age at menarche¶¶ Age at menopause ***	Age at men.: 13-14 yrs: rOA: 1.03 (0.47-2.21), ≥15 yrs: rOA: 0.86 (0.34 (0.34-2.16) Age at MP: 45-49 yrs: rOA: 0.84 (0.36-1.95), ≥50 yrs: rOA: 0.71 (0.31-1.58))
Knee								
Sowers [9][HQ]	Cohort	842	--	+	+	rOA: score ≥ 2 on K&L-scale	Endogenous hormones	Log estradiol (pg/ml); C statistic = 0.74; 33rd percentile (<47 pg/ml) = 1.20 (0.75-1.91); 33rd-66th percentile (47-77 pg/ml) = Referent ; ≥ 66th percentile (>78 pg/ml) = 1.06 (0.66-1.71)
Sowers [8] [HQ]	N-CS	--	--	-	-	rOA: score ≥ 2 on K&L-scale	Endogenous hormones Menopausal status‡	Estradiol serum level (pg/ml): highest joint score = 1.0 (0.99-1.01)(univariate); **Joint score of ≥2 = 1,01 (1.004-1,02)** (multivariate) MP status: **Highest joint score = 0,79 (1,01-3,49)**†††; Joint score of ≥ 2 = 2,96 (NC)
Liu [14] [HQ]	N-CS	9977	--	+	+	Positive if THR due to OA, controls not x-ray checked for OA	Age at menarche (yrs)†† Age at MP ‡‡ Menopausal status ‡	Age men.:≤11:1.09(1.03-1.16), 13: 0.97 (0.91-1.03), 14: 0.96 (0.90-1.03), 15+:1.03 (0.96-1.11), P=<0.0001; Age at MP: 49-51: 0.98 (0.89-1.07), **52+: 0.92 (0.84-1.00)** P =0.06 Menopausal status: 0,76 (0,52-1,10)
Spector [21] [HQ]	CS	2	41	+	+	rOA score ≥ 2 on K&L-scale or cOA (symptoms) Ovariectomy (bilateral)	Ovariectomy (bilateral)	1.09 (0.22-5.48) (ROA or cOA not specified)
Cicuttini [17]	CS	110	215	+	+	rOA score ≥ 2 on Burnet atlas	Menopausal status†	Tibiofemoral rOA: 1.02 (0.05-11.20) Combined tibiofemoral rOA + patello-femoral rOA: 0.46 (0.07-2.83)

Table 3.3: Results female-hormonal aspects (continued)

Reference	Study design	N OA+	N OA -	Adj. age	Adj. bmi	Case definition	Specification female-hormonal aspect	Outcome menopausal aspect (OR (95%CI))
Cvijetic [19]	N-CS	--	--	-	-	rOA score ≥ 2 on K&L-scale	YSM **	Only difference given: β = -0.05
Iwamoto [20]	CC	305				rOA score ≥ 2 on K&L-scale	YSM **	Only correlation given: **YSM vs. K&L-grade: 0.145 (P<0.05)**
Any joint (large joint OA: hip or knee)								
Samanta [18]	CC	208	482	-	-	rOA hip or knee with hand rOA, without hand cOA	Menopausal status†	rOA: 1.36 (0.20-9.16) ¶

* all outcomes from Oliveria are calculated by the authors of this review and unadjusted for possible confounders, † Menopausal status: MP=menopause, post-MP = ref., ‡ Natural MP: menopause defined as last menstrual period at least one year earlier, ref = pre-MP, § ref = pre-MP women aged 45-50 years, ¶ = unadjusted outcome, **: years since natural menopause, reference = premenopausal women, ††= ref. category = 12yrs, ‡‡ ref. category ≤ 48 (all women with natural MP and never used HRT), §§ = calculated by the authors of this review and unadjusted for possible confounders, ¶¶= ref. category <13yrs, *** = ref. category < 45 yrs, ††† = 95% CI combined with given OR seems incorrect, but given by authors

[HQ]= High quality study, if not mentioned: low quality study, CC = case-control study, K&L = Kellgren and Lawerence scale, DIP = distal interphalangeal joint, CMC = Carpometacarpal joint, Duration fertile = as the number of years between age at menopause and age at menarche, PIP = Proximal Interphalangeal joint**,** THR = total hip replacement, Nodes (HN) = Herberdens' nodes, (N)CS = (nested) cross-sectional study, OA = Osteoarthritis, cOA = clinical OA, Surgical MP = bilateral ovariectomy at the age at which menstruation stopped, rOA = radiological OA, YSM = years since menopause, Statistically significant outcomes are shown in Bold

risk of age at menarche being ≤11 years. For cut-off points with older ages the evidence was limited for no relation with the same trend for hip rOA. For TKR and age at menarche evidence of no relation was seen.

Conflicting evidence was seen for age at menopause being ≥51 years with hand cOA (HN), for other ages and for age at menopause with CMC and DIP rOA the evidence was strong in the direction of no relation. Limited evidence for no relation for THR with age at menopause and the same trend with hip rOA. For TKR limited evidence was seen for a borderline significant protective effect of age at menopause being ≥52 years, but not with younger ages; there the evidence was in the direction of no relation.

Duration Fertile period

The duration of the fertile period with hand OA was studied by two groups [11, 12], one of which found a non significant increased risk for a duration of ≥36 years [12]. Further no associations were found for this determinant.

Only evidence for an association with hand rOA and presence of HN was found, this was strong in the direction of no relation.

Menopausal status

Seven studies reported on the association of menopausal status of women with OA [8, 12, 15-18]. For one study [15] the association between cOA and the menopausal status was calculated by us. In the Zoetermeer study [12] an increased risk was found between natural menopause and hand cOA (HN), but not with hand rOA.

In prevalence studies strong evidence was found for no relation between menopausal status and hand rOA. Limited evidence was seen for a borderline significant increased risk with hand cOA. In incidence studies the same trend of no relation with hand cOA was seen.

For knee OA limited evidence was seen for a significantly protective effect of being postmenopausal for the highest knee score, but this effect disappeared in a multivariate model, leaving evidence of no relation. Moderate evidence was seen for no relation between knee rOA score ≥2 and menopausal status and limited evidence for no relation with THR and TKR.

Years since menopause

In studying the YSM, no relationship with hand rOA or hip rOA [12, 19] was found. One study found YSM to be (weakly) correlated with the K&L-grade of the knee [20].

YSM was only studied in prevalence studies and even then evidence for an association with hip, knee or 'any joint' rOA was insufficient. There was moderate evidence for no association between YSM and hand rOA (independent of number of YSM), while the evidence with knee rOA was conflicting. Limited evidence was found for a non-significant increased risk of YSM 1-4 years with hand cOA.

Surgical menopause: ovariectomy

Four studies describe the relation between the surgical menopause (ovariectomy) and OA [12, 21-23]. One study [23] reports an increased prevalence of hip cOA, while another reports a bilateral ovariectomy to be protective for hip rOA [22]. Spector et al. [21] reports that the rate of OA for most joint groups was lower in those women who had both their ovaries removed compared with women who maintained at least one (data not shown).

Ovariectomy was only studied in prevalence studies. For hand OA strong evidence was found for no relation, the same relation was seen for knee rOA but with limited evidence. For hip OA the trend of evidence was conflicting with two low quality studies, one found ovariectomy to be protective for rOA, the other increasing risk for cOA.

No clear differences in outcomes were found when dividing the studies on the basis of 1) optimal adjustment for confounders (age, BMI, bone mineral density, hormone replacement therapy use), 2) rOA or cOA, 3) menopausal status of the population or 4) study size.

DISCUSSION

The assumed relationship between the studied female-hormonal aspects and OA of the hand, hip or knee was not clearly observed in this systematic review. Most evidence points in the direction of no relation between osteoarthritis of hand, hip and knee and the studied determinants, or remains conflicting. To our knowledge, we are the first to systematically review the literature on these associations, providing a comprehensive overview on the subject.

From animal studies it is known that removing the ovaries is not equal, concerning hormonal influence, to a natural menopause [24, 25]. Considering this, it may not be completely fair to compare women with ovariectomy and those with natural menopause.

The studied determinants are all intertwined, making it difficult to study them individually and leading to possible mutual confounding of determinants. Data collection in the individual studies was sometimes questionable due to limited information presentation on the determinants, possibly contributing to why no hard evidence was found.

The association between OA and female-hormonal aspects has been studied from different angles. Sniekers et al. [26] systematically reviewed the association between OA and ovariectomy in animal studies and found inconclusive evidence. We reviewed the association between OA and HRT [2] and also found the association to be unclear, and now again, we found the same evidence in epidemiological studies for female-hormonal aspects. One would expect that if an association is present this would also be found in a large enough epidemiological study.

In the evidence synthesis used in this review all non-significant outcomes were interpreted as evidence of no relationship between the studied determinant and OA. Still, it is possible that a relationship is present, but it could not be found using the applied study designs and the corresponding sample sizes. When pooling is not possible, the risk exists that small studies showing effect, but not significantly, are defined as negative studies. However, of all our relatively small studies (N<500) three studies were classified as low quality and the other two showed OR of ≈1. The next smallest studies (N=573, N=645 respectively) [8, 12] both showed significant results. We therefore think that our results are not biased by small studies.

For future research on OA and female-hormonal aspects we suggest to use a large number of subjects (at least <500), at least adjust for age and BMI, and if possible, collect data on suspected effect modifiers (e.g. oestrogen-related genes). In studying ovariectomy and OA we recommend to specify number of ovaries removed and possible usage of hormone replacement therapy (HRT). We hoped that gaining insight in the association between OA and female-hormonal aspects would contribute to the formulation of a high-risk profile for OA development and a better understanding of OA etiology. Unfortunately much remains unclear. The fact remains that incidence and prevalence rises quickly in women after the age of 50. Possibly the relationship between female-hormonal aspects and OA of hand hip and knee is too complex to appear in epidemiological research as such, or other aspects, yet to be determined, play a role in the increased incidence in women after the age of 50.

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Chapter 4

Cartilage degeneration is not the earliest MRI knee OA feature visualized in association with menopausal aspects

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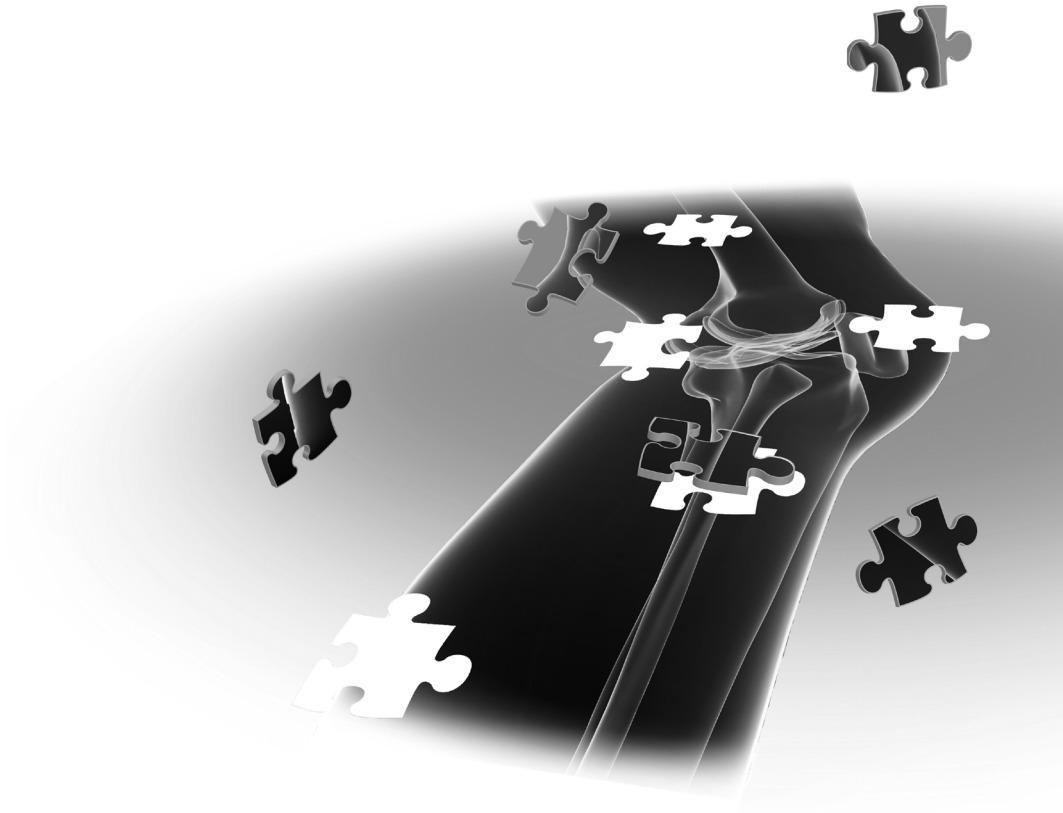
Submitted



ABSTRACT

Purpose

The role of female hormones in osteoarthritis (OA) remains uncertain. However, if there is a relation between OA and menopausal aspects, it may be clearer at an earlier stage of the disease. Therefore, this MRI study examined cross-sectional associations between early degenerative signs of knee tissue and menopausal aspects in middle-aged women.

Methods

Data on the RS.III.1 population cohort study were used. Eligible were female subjects (n=823; 45-60 years) with available knee MRI data and without radiographic OA in both knees (Kellgren & Lawrence (KL) grade <2). Examined menopausal aspects were menopausal status (PostMP), early menarcheal age (<12 years), and years since menopause (YSM). Assessed tissues were meniscus, cartilage and bone (osteophytes and bone marrow lesions, BMLs). Joint effusion was also examined. Because BMI is a strong risk factor for knee OA, adjusted associations with general estimating equations analysis were tested separately for low/normal BMI (kg/m^2 <27) and high BMI.

Results

Included were 466 women with low/normal BMI (mean age 53.5 years, 932 knees, 13.0% KL grade 1) and 357 with high BMI (mean age 53.8 years, 714 knees, 17.8% KL grade 1). Significant associations were found only in high BMI women: PostMP with osteophytes (OR=2.36 (1.18–4.70)), PostMP with BMLs (OR=1.96 (1.00–3.84)), YSM with BMLs (OR=1.11 (1.03–1.19)). No significant association was found with cartilage degeneration.

Conclusions

Several OA features are associated with menopausal aspects. Specifically, early degenerative signs of knee tissue in overweight women, in relation with the menopause, can be first visualized in bone (BMLs and osteophytes), but not in cartilage.

INTRODUCTION

Knee osteoarthritis (OA) is a common chronic joint disease, causing progressive pain, disability and irreversible damage to the joint. The menopausal transitional period is concurrent with an increased incidence of OA in women [1, 2]. Although this simultaneous occurrence suggests a role for female hormones in OA development [3], the underlying mechanism is not yet established. Articular tissues have long been considered unresponsive to estrogens, however, there is increasing evidence that activity of joint tissue is influenced by estrogens through complex pathways [4].

The development of OA can be influenced by a high body mass index (BMI) in various ways. Not only locally by higher biomechanical or differential knee loading [5], but also systemically by secretion of inflammatory mediators and estrogens by adipose tissue [6, 7]. Thus, besides the greater risk due to BMI, changes in hormone levels can have a different effect in overweight women than in their normal weight peers. In support of this, we found indications for a possible interaction between increasing BMI and postmenopausal status for prevalence of knee OA (see Chapter 5). Hormonal levels change in two specific periods during a woman's life: around the time of menarche and in the menopausal transitional period. Also, although current use of hormone replacement therapy (HRT) and years since menopause (YSM) influence the hormonal state, there is no or conflicting evidence about the associations of these factors with OA [8-10].

OA affects all joint tissues, i.e. not only cartilage but also bone and connective tissues, such as the menisci, synovial membrane and ligaments [7, 11, 12]. The sequence of degeneration of these tissues may vary between patients and it is feasible that different subsets of OA have different etiological pathways that finally result in an apparently similar end stage. Little is known about the sequence of pathological changes in the different tissues, but subchondral bone likely plays a key role in the mechanism of OA [12]. When studying prevalent OA cases with radiography it is impossible to precisely distinguish where the degeneration of individual joint tissues started. Magnetic resonance imaging (MRI) can visualize degeneration of individual tissues in an earlier stage than radiography and is purported to be the best imaging technique now available to detect early osteoarthritic changes [13-15]. Using MRI in a population at high risk of knee OA development, such as overweight middle-aged women, may help elucidate in which tissue the damage is first present.

To develop preventive strategies for OA, more data are needed on risk factors for the development of OA in a population where preventive strategies can be applied [16]. Knowledge on which knee tissue is probably affected first may help to develop specific strategies for the primary prevention of OA, define specific intermediate outcomes for such interventions, and identify women at high risk. For this reason, and because established radiographic OA in early menopausal women may be more strongly related

to factors other than female hormones, a study population without radiographic OA (Kellgren & Lawrence score 0/1) will probably provide clearer associations.

Therefore, to gain insight into the associations between female hormonal aspects and early degenerative signs of knee tissues on MRI, and on where the degeneration of joint tissues visually starts, this study investigated the cross-sectional associations of menopausal determinants with the prevalence of early degenerative signs in knee tissues on MRI, in women subdivided according to their BMI (kg/m^2 <27 and ≥27). The investigated hormonal determinants were menopausal status, early age at menarche, and YSM.

METHODS

Setting and study population

We used data from the third cohort of the Rotterdam Study (RS.III.1 cohort). The Rotterdam Study is an open population prospective cohort study (with follow-up every 3-4 years) ongoing since the early 1990s and conducted in Ommoord (Rotterdam, the Netherlands). In 2010 a design update was published [17]. The Rotterdam Study was approved by the Medical Ethics Committee of the Erasmus University Medical Center. All participants were interviewed at home and were invited to attend the research center for medical examinations and radiographs.

The RS.III.1 cohort started in 2006 as an extension of the original Rotterdam Study: 6,057 persons were invited to participate (response rate 65.2%) [17], and includes 3,932 subjects aged ≥45 years. The first follow-up for this cohort will start in 2012.

All women up to age 60 years from the RS.III.1 cohort were invited to participate in a sub-study on knee OA at the research center. This study included MRI of both knees, an additional knee-specific questionnaire, and a physical examination of both knees performed by two trained researchers. Women were excluded from participation if they had contraindications for undergoing MRI (including metal fragments in the eyes, recent operations including metal implants, claustrophobia and possible pregnancies), or were unable to fill out a questionnaire independently due to limited mastery of the Dutch language. Measurements were conducted between August 2007 and July 2009.

Radiological assessment

Weight-bearing anterior-posterior X-rays of the knees were taken at the research center. Knees were radiographed in extended position with the patella as center point using High Resolution G 35x43 cm film (Fujifilm Medical Systems, Stamford, CT, USA), at 70 kV, a focus of 1.8 mm^2, and focus-to-film distance of 120 cm. Radiological OA (rOA) of the

tibiofemoral (TF) joint was assessed using the KL grading scale [18] and was defined as a KL grade ≥2 of one or both joints, or a total joint replacement. A total of 3,071 persons from the RS.III.1 cohort had radiographs of both knees. All available radiographs were scored independently by two trained researchers (kappa=0.62) [19]. Both researchers were blinded to all of the subject's clinical and demographic data.

MRI assessment

All subjects in the OA sub-study underwent multi-sequence MRI scans of both knees using an 8-channel cardiac coil. For this open population the use of a cardiac coil was preferred to a knee coil because people with a high BMI (who generally have larger knees) might be unable to fit their knees into a knee coil. Another advantage of the cardiac coil is that knees can be scanned consecutively, without repositioning the participant.

Scans were performed using a 1.5-T whole body MRI unit (General Electric Healthcare, Milwaukee, Wisconsin, USA). The sequences and parameters used were: a fast-spin echo (FSE) proton density and T2 weighted sequence (transversal plane, TR/TE 4900/11/90, flip angle of 90-180, slice thickness 3.2 mm, field of view, FOV, 15 cm^2), a FSE T2 weighted sequence with fat saturation (transversal plane, TR/TE 6800/80, flip angle 90-180, slice thickness 3.2 mm, FOV 15 cm^2), a spoiled gradient echo sequence (sagittal plane, TR/TE 20.9/2.3, with fat saturation, flip angle 35, slice thickness 3.2 (1.6) mm, FOV 15 cm^2) and a Fiesta C-T1/T2 weighted sequence without fat saturation (sagittal plane, TR/TE 5.7/1.7, flip angle 35, slice thickness 1.6 mm, FOV 15 cm^2). Total scanning time was 27 minutes for two knees. The Fiesta sequence could be reformatted into the coronal and transversal plane, so that a 3D image of the knee could be acquired.

The MRIs were scored independently by one trained researcher and one trained radiologist using the MR Knee Osteoarthritis Scoring System (KOSS) [20], scoring amongst others: cartilage degeneration, meniscus degeneration, osteochondral defects, and features of inflammation such as joint effusion and synovitis.

Outcome measures

In this study degeneration of the following tissues was assessed: cartilage, meniscus and bone (osteophytes and bone marrow edema-like lesions (BMLs)). In addition ´joint effusion and/or Baker's cysts were assessed as a sign of inflammation or irritation in the joint.

Cartilage defects (diffuse and/or focal combined) were scored per compartment (medial or lateral) TF compartment.

Meniscus degeneration was scored for the meniscal body, anterior horn and posterior horn, and combined into one score. The medial and lateral TF compartments were assessed separately. We considered horizontal tears as degenerative lesions [21]. In case

a horizontal tear was present without degenerative signs in the meniscal body, anterior horn or posterior horn, the outcome measure of meniscus degeneration was scored as present in the applicable compartment. The outcome for meniscal degeneration was dichotomized into 0 (KOSS scores 0/1= reference) and 1 (KOSS scores 2/3/4/5). BMLs and, separately, osteophytes were dichotomized into 0 (absence=reference) vs. 1 (any present). Location of BMLs and osteophytes in the medial and/or lateral compartment in the femur and/or tibia was recorded. 'Joint effusion and/or Baker's cyst' was considered present if any effusion (small, moderate or massive) was visible on MRI (absence=reference).

Determinants

The following determinants were tested on their associations with the outcome measures.

- Menopausal status: pre-menopausal women (=reference) vs. post-menopausal (PostMP) women. A woman was considered to be PostMP if she reported not having menstruated in the previous 12 months; women who had stopped menstruating after surgery (e.g. hysterectomy) were excluded from analysis.
- Early age at menarche: ≥12 years (=reference) vs. < 12 years old [22].
- Years since menopause (YSM): number of years since last menstruation, only available for PostMP; women who had stopped menstruating after surgery (e.g. hysterectomy) were excluded from analysis.

Statistical analysis

MRI KOSS data were assessed using a logistic generalized estimating equation (GEE) model from the generalized linear models for repeated measure analysis. GEE takes into account the dependence between repeated measures within the same individual. Here we used 'knee side' as within-subject variable. Analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, USA). All analyses were adjusted for age and BMI and, where applicable, for current HRT use.

RESULTS

Study population

891 women participated in the knee OA sub-study. All women without radiological OA in both knees (KL <2), a total of 823 women (1646 knees), were included in the analysis. Reijman et al. found a high BMI ≥27 to be clearly associated with incident knee rOA [31]. There-

fore, the women were divided according to BMI using the population mean (BMI=27) as cut-off point. This resulted in two groups: a low/normal BMI group of 466 women (BMI<27, mean age 53.5 (SD 3.69), 932 knees, 13.0% KL-grade 1), and a high-BMI group of 357 women (BMI ≥27, mean age 53.8 (SD 3.97) years, 714 knees, 17.8% KL grade 1). All women had two knees available for analysis. Table 4.1 shows the population characteristics.

Table 4.1: Characteristics of the study population (n=823)

	Low/normal BMI (<27)		**High BMI (≥27)**	
	n knees	Mean (SD) % present	n knees	Mean (SD) / % present
Age (years)	932	53.5 (SD = 3.69)	714	53.8 (SD = 3.97)
Body mass index (kg/m^2)	932	23.7 (SD = 2.13)	714	30.9 (SD = 3.62)
KL score 1	932	18.0%	714	24.6%
Post-menopausal status[1]	802	57.6%	572	60.1%
Years since menopause	442	5.8 (SD = 4.39)	334	6.3 (SD = 4.34)
Early age at menarche[2]	918	11.4%	704	21.6%
Current use of HRT[3]	932	4.3%	472	2.2%
Pain or stiffness in knee[4]	932	28.5%	712	34.6%
Clinically relevant knee pain[5]	932	4.3%	710	9.9%

1) premenopausal/peri-menopausal (=reference) vs. post-menopausal. A woman was considered post-menopausal if she reported not having menstruated in the previous 12 months; women who had stopped menstruating after surgery (e.g. hysterectomy) were excluded from analysis, 2) ≥12 years old (=reference) vs. <12 years old [22], 3) current use of hormonal replacement therapy for menopausal complaints, 4) answer positively to the question 'do you have pain or stiffness in your knees?', 5) clinically relevant pain score: WOMAC patient acceptable symptom score (PASS) considered elevated if >30 (range: 0-100) [27]

Associations

Meniscus degeneration

Degenerative signs of the medial meniscus were present in 13.8% of the low/normal BMI women, and in 11.4% of the high BMI women. In the lateral meniscus these percentages were 5.8% and 5.6%, respectively. Table 4.2 shows the results of the GEE analysis for meniscus degeneration. We analyzed the medial and lateral meniscus separately because of differences in biomechanical loading. No significant associations were observed.

Cartilage defects

Cartilage defects in the medial TF compartment were present in 10.3% and 12.1% in low/normal BMI women and high BMI women, respectively (Table 4.3); in the lateral TF compartment these rates were even lower, i.e. 2.2% and 4.6%, respectively. In the lateral compartment early age at menarche could not be calculated due to cells containing zero. Analysis of the determinant as continuous variable was not significant (OR=0.91 (0.72-1.14)). None of the tested associations was significant.

Table 4.2: Associations between meniscus degeneration (MD) and female hormonal aspects

Medial meniscus degeneration						
Risk factor	**n[4]**	**% MD[5]**	**BMI <27: OR (95%CI)**	**n[4]**	**% MD[5]**	**BMI <27: OR (95%CI)**
PostMP[1]	800	12.8	0.80 (0.45 – 1.43)	569	10.7	1.51 (0.45 – 5.07)
Early menarche[2]	916	13.5	1.18 (0.62 – 2.23)	697	11.4	0.60 (0.29 – 1.26)
YSM[3]	442	12.9[6]	0.97 (0.91 – 1.07)	333	11.1[6]	0.91 (0.83 – 1.01)
Lateral meniscus degeneration						
Risk factor	**n[4]**	**% MD[5]**	**BMI <27: OR (95%CI)**	**n[4]**	**% MD[5]**	**BMI <27: OR (95%CI)**
PostMP[1]	800	5.6	0.57 (0.22 – 1.50)	569	5.6	1.13 (0.50 – 2.58)
Early menarche[2]	916	5.9	0.89 (0.35 – 2.28)	696	16.7	0.39 (0.13 - 1.16)
YSM[3]	442	6.6[6]	0.99 (0.89 – 1.09)	333	6.0[6]	0.92 (0.81 – 1.05)

1) PostMP: post-menopausal (cessation of menstruation not due to operation), 2) Age menarche: ≥12 years old (=reference) vs. <12 years old [22], 3) YSM: Years Since Menopause (continuous), 4) n=number of knees in analysis, 5) % MD: percentage presence meniscus degeneration in subjects with risk factor present, 6) prevalence outcome measure in women with natural menopause. All results are adjusted for age and BMI (within the group)

Table 4.3: Associations between diffuse cartilage degeneration (CD) and female hormonal aspects

cartilage degeneration medial compartment tibiofemoral joint						
Risk factor	**n[4]**	**% CD[5]**	**BMI <27: OR (95%CI)**	**n[4]**	**% CD[5]**	**BMI ≥27 : OR (95%CI)**
PostMP[1]	801	9.4	1.16 (0.54 – 2.50)	569	11.6	0.99 (0.47 – 2.09)
Early menarche[2]	916	10.2	1.06 (0.50 – 2.24)	698	11.9	0.70 (0.36 – 1.35)
YSM[3]	442	11.3[6]	1.01 (0.93 – 1.10)	333	12.9[6]	1.01 (0.94 – 1.08)
Diffuse cartilage degeneration lateral compartment tibiofemoral joint						
Risk factor	**n[4]**	**% CD[5]**	**BMI<27: OR (95%CI)**	**n[4]**	**% CD[5]**	**BMI ≥ 27 : OR (95%CI)**
PostMP[1]	801	1.9	0.49 (0.17 – 1.26)	569	6.0	1.64 (0.57 – 4.70)
Early menarche[2]	-	2.2	NAC	698	6.6	1.23 (0.55 – 2.76)
YSM[3]	442	1.4[6]	1.01 (0.87 – 1.16)	333	6.6[6]	0.97 (0.89 – 1.05)

In the definition of cartilage degeneration diffuse and focal damage were combined into one score 1) PostMP: post-menopausal (cessation of menstruation not due to operation), 2) Age menarche: ≥12 years old (=reference) vs. <12 years old [22], 3) YSM: Years Since Menopause (continuous), 4) n=number of knees in analysis, 5) % CD: percentage presence cartilage degeneration in subjects with risk factor present, 6) prevalence outcome measure in women with natural menopause. All results are adjusted for age and BMI (within the group), NAC: Not able to calculate due to cells containing zero.

Bone: BMLs and osteophytes

BMLs were present in 19.0% of the low/normal BMI women and in 18.1% of the high BMI women. In overweight women the presence of BMLs was associated with being PostMP (OR=1.96 (1.00–3.84)) and increasing YSM (OR= 1.11 (1.03-1.19)). Assessment of the medial and lateral TF compartment separately yielded similar results (data not shown).

Osteophytes were present in 26.0% in the low/normal BMI group and in 40.1% in the high BMI group. In the high BMI group, being postmenopausal was significantly associ-

Table 4.4: Associations between bone marrow edema-like lesions (BMLs) / osteophytes (OP) / joint effusion (JE) and female hormonal aspects

Bone Marrow Edema-like Lesions						
Risk factor	**n[4]**	**% BML[5]**	**BMI<27: OR (95%CI)**	**n[4]**	**% BML[5]**	**BMI ≥27 : OR (95%CI)**
PostMP[1]	796	19.2	1.22 (0.73 – 2.04)	**566**	**16.5**	**1.96 (1.00 – 3.84)**
Early menarche[2]	910	19.1	1.09 (0.62 – 1.92)	694	17.8	1.01 (0.58 – 1.78)
YSM[3]	440	21.8[6]	0.96 (0.91 – 1.01)	**331**	**19.3[6]**	**1.11 (1.03 – 1.19)**
Osteophytes						
Risk factor	**n[4]**	**% OP[5]**	**BMI<27: OR (95%CI)**	**n[4]**	**% OP[5]**	**BMI ≥27 : OR (95%CI)**
PostMP[1]	801	25.5	0.88 (0.54 – 1.43)	**566**	**40.1**	**2.23 (1.24 – 3.98)**
Early menarche[2]	916	25.7	0.84 (0.46 – 1.55)	694	39.8	0.99 (0.63 – 1.56)
YSM[3]	442	29.2[6]	0.99 (0.94 – 1.05)	332	47.3[6]	0.99 (0.93 – 1.05)
Joint effusion and/or Baker's Cysts						
Risk factor	**n[4]**	**% JE[5]**	**BMI<27: OR (95%CI)**	**n[4]**	**% JE[5]**	**BMI ≥27 : OR (95%CI)**
PostMP[1]	796	42.2	0.78 (0.50 – 1.22)	566	45.6	0.73 (0.44 – 1.23)
Early menarche[2]	911	42.3	0.79 (0.48 – 1.28)	694	46.1	1.02 (0.67 – 1.56)
YSM[3]	440	40.7[6]	0.99 (0.94 – 1.05)	331	46.8[6]	0.96 (0.90 – 1.02)

1) PostMP: post-menopausal (cessation of menstruation not due to operation), 2) Age menarche: ≥12 years old (=reference) vs. <12 years old [22], 3) YSM: Years Since Menopause (continuous), 4) n=number of knees in analysis, 5) % BML/OP/JE: percentage presence Bone Marrow Edema-like Lesions/Osteophytes/Joint effusion and/or Baker's Cysts in subjects with risk factor present, 6) prevalence outcome measure in women with natural menopause. All results are adjusted for age and BMI (within the group)

ated with presence of osteophytes (OR=2.23 (1.24-3.98)). In women with low/normal BMI no significant association was found (Table 4.4). Because having a KL grade 1 may overrule this association with osteophytes, the model was tested again including the KL grade (KL grade of either 0 or 1). The association between KL grade 1 and osteophytes was OR=1.60 (0.98-2.62). However, the observed association of PostMP with osteophytes in the high BMI women remained intact (OR=2.16 (1.21-3.86)).

Inflammation signs: Joint effusion and/or Baker's cyst

Joint effusion and/or Baker's cyst were present in 42.6% in the low/normal BMI group and in 46.0% in the high BMI group (Table 4.4). None of the tested determinants were significant.

DISCUSSION

We found clear indications that early degenerative signs of knee tissue, in relation with the menopause, can be visualized in bone (BMLs and osteophytes) but not in cartilage.

Significant associations seen only in high BMI women were: being postmenopausal with osteophytes (OR=2.36 (1.18-4.70)), being postmenopausal with BMLs (OR=1.96 (1.00–3.84)), and years since menopause with BMLs (OR=1.11 (1.03–1.19)). No significant association was found with cartilage degeneration. Our conclusions are in line with the hypothesis of Davies-Tuck et al., that changes in the tibial plateau bone may occur before significant pathological changes in cartilage [23]. Recently, a set of 11 propositions was accepted through Delphi consensus for defining structural OA on MRI [24]; they also recommended focusing on early, pre-radiographic cohorts to further develop an OA MRI definition. In the present study, degenerative signs of several joint tissues were assessed in a high-risk group of early menopausal disease-free women, and both BMLs and osteophytes (which are part of the consensus definition) were associated with menopausal factors.

In our relatively young and healthy population, the prevalence of cartilage defects was low. In the total study population degenerative signs were present in 11.1% of the knees in the medial compartment and in only 4.0% in the lateral compartment. Perhaps degenerative processes, such as glycosaminoglycan leakage, are indeed present in cartilage but are not (yet) visible on MRI. It is even possible that related changes in mechanical properties of the cartilage came first, causing the changes now visible in the bone. More advanced and quantitative MRI techniques (such as delayed gadolinium-enhanced MRI of cartilage or $T_{1\rho}$) may elucidate the changes in cartilage before morphological change occurs. Zhao et al. examined the relationship between BMLs and cartilage degeneration of knee OA using a 3-T MR T1rho quantification protocol, allowing to study cartilage on a more biochemical level; they found a local spatial relationship between BMLs and more advanced and accelerated cartilage degeneration in OA knees [25]. Hunter et al. found that BMLs that enlarge over time, compared to those that stay the same, were strongly associated with more cartilage loss [26]. In our population the correlation between cartilage degeneration and BMLs per compartment was significant (2-tailed, $p<0.01$) but relatively low (Pearson's correlation medial compartment: 0.246, lateral compartment: 0.096); this was to be expected given the low prevalence, but subsequently not explaining much variance.

This study has some limitations. First, the cross-sectional study design prevents examining causality; however, in 2012 the first follow-up measurements for this cohort will allow to explore causality and predictive values. In addition, a large part of the BMLs and osteophytes may not develop into OA. Second, because we performed multiple analyses, the borderline significant result of PostMP with BMLs ($p=0.049$) may be merely a chance finding (type I error). However, because the associations between PostMP and osteophytes, and between YSM and BMLs were highly significant ($p=0.006$ and $p=0.004$, respectively), we believe that these observations are valid. To test this we analyzed all women together, increasing the statistical power, adjusting for age, BMI, KL score and

current HRT use and with an interaction term in the model (i.e. PostMP*BMIcategory). We still found significant ORs for PostMP (*BMIcategory) in analyzing osteophytes (n=1367 knees, OR=2.11 (1.50-2.98), and the same for YSM with BMLs (n=1362 knees, OR=1.13 (1.04-1.23)). Although PostMP with BMLs was no longer significant (n=1362, OR=1.46 (0.85-2.52)), the same trend was observed. One explanation (amongst others) for the conflicting evidence on the associations of OA with menopausal or hormonal factors might be the difference in estrogen effect in overweight women, or perhaps in the higher prevalence of the tested MRI features. This complex association between overweight and menopausal aspects warrants further study. Third, we did not consider the patellofemoral joint in the selection of rOA-free women because no X-ray data were available for this joint. It is possible that we included women who did have patello-femoral rOA, but this does not change our findings of early signs for the TF-joint. Fourth, not all tested outcome measures were highly prevalent. Especially in the lateral TF compartment cartilage and meniscal degeneration the prevalences were low. We had a relatively young and healthy study population in whom degenerative signs may be less prevalent. However, another possibility is that the selection of MRI sequences (based on semi-quantitative scoring and assessment of quantitative measures of cartilage and bone) in combination with a limited scan time and the coil used, may have influenced image quality. Therefore, these results should be interpreted with caution. On the other hand, because the prevalence of these features was lower than that of the other tested MRI features, it is still likely that cartilage is not the first feature able to be visualized on MRI. Fifth, for current HRT use the prevalence was also low (and only available for PostMP women). We did, however, adjust for current hormone use in analysis for post-menopause and YSM, since it may be of influence [10], but it did not change the results. Sixth, the prevalences of degenerative features were not all equally distributed over low/normal BMI and high BMI women, therefore we refrained from comparing the two BMI groups and reported data for the two groups separately. Finally, because we did not use contrast MRI we could not assess the presence of synovitis, which was subsequently excluded as an outcome measure for inflammation.

To summarize, in studying a high-risk group for OA development in healthy middle-aged OA-free women, the most important finding was an indication that early degenerative signs of knee tissue, in relationship with menopausal aspects, can be first visualized on MRI in the bone (BMLs and osteophytes), but not in cartilage. In addition, the complex relation between overweight and the influence of female hormonal factors on OA needs further study in order to elucidate the underlying mechanisms.

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Chapter 5

Risk factors and symptoms of radiological knee osteoarthritis and their interactions with BMI

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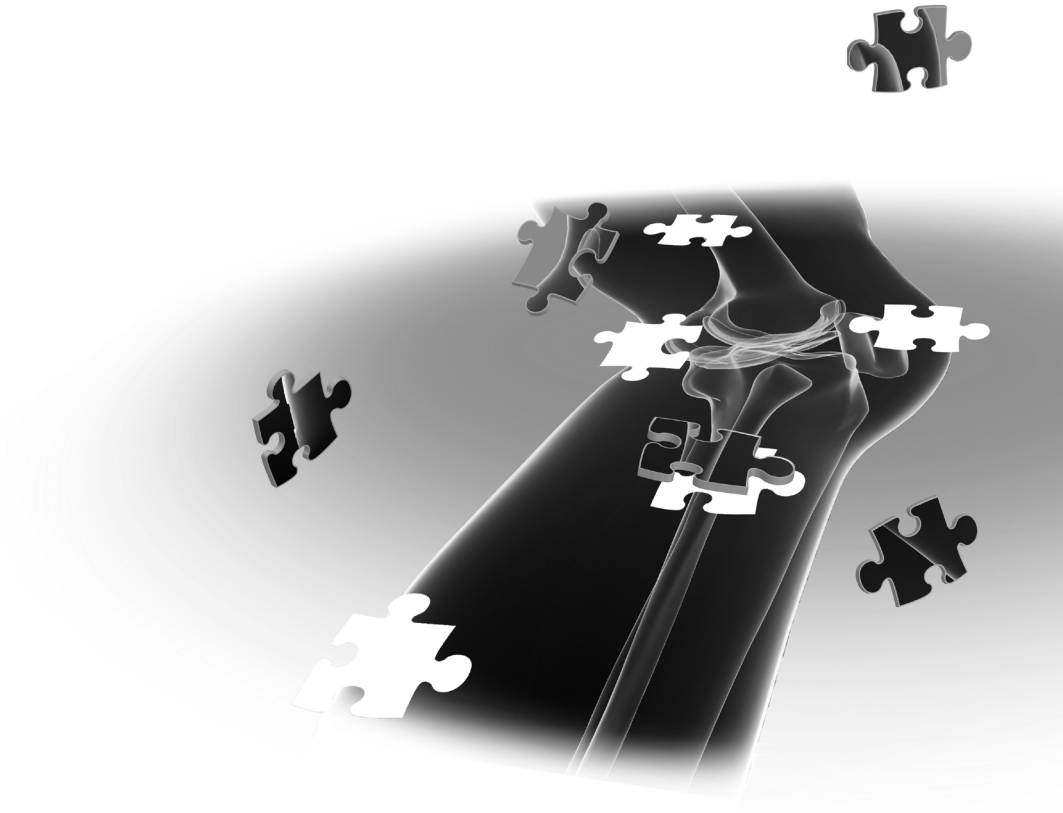
Submitted



ABSTRACT

Objectives

BMI is one of the most important risk factor for (symptomatic) knee osteoarthritis (OA). This might be because it interacts with other risk factors. Knowledge on such interactions is currently limited. Therefore, we investigate whether associations of known risk factors and knee symptoms with radiological (r)OA differ between women with a high BMI (≥27) and women with a low/normal BMI (<27) in a general population.

Methods

Baseline data of a population-based cohort study was used: 649 women with low/normal BMI and 741 high BMI women were included (aged 45-60 years). Univariate logistic regression analysis was used to test the association of potential risk factors and symptoms with knee rOA (Kellgren & Lawrence score≥2) in high and low/normal BMI. Risk factors and symptoms showing differences between the groups in univariate analysis were tested for interaction with BMI. All analyses were adjusted for age.

Results

Significant risk factors and symptoms in the low/normal BMI group were: post-menopause and age at menarche <12 years. In the high BMI group these were: varus alignment, Heberden's nodes, limited extension, WOMAC-PASS >30, and morning stiffness <30 minutes.

A significant interaction was found between BMI and knee morning stiffness <30 minutes (OR=3.19, p<0.05). Being post-menopausal and tenderness on palpation showed a trend for an interaction.

Conclusions

Risk factors for, and symptoms of knee rOA differ in magnitude between those with low/normal and high BMI in this open study population. A significant interaction was found between BMI and knee morning stiffness.

INTRODUCTION

Osteoarthritis (OA) is a common progressive joint disease causing pain and disability. OA is frequently experienced by middle-aged and older people[1], and most often affects the hip and knee joint. Because both life expectancy and the number of overweight people are increasing[2,3], the prevalence of OA is expected to continue to rise, as will the associated costs and burden for society.

The exact OA etiology remains unclear. Several important risk factors for knee OA are already known, like age and body mass index (BMI=kg/m^2). Being overweight or obese is arguably the most important modifiable OA risk factor[4] which affects both the development and progression of the disease[2,5], [6]. A high BMI (≥27) has been found to be clearly associated with an increased risk of radiological knee OA[5]. Although the exact mechanism is not yet fully elucidated, it has been suggested to be mechanical[7] ('wear and tear') with an additional systemic role for adipose tissue[8,9]. BMI is possibly such an important risk factor partly because it might interact with other risk factors. Local risk factors, such as previous knee trauma[10] and varus alignment[11,12], may be influenced by BMI through higher mechanical loading on the joint. A known systemic factor is, for example, generalized OA[4], suggesting genetic predisposition.

Identification of risk factors which strongly interact with BMI may help identify populations at high risk of OA development. Interaction of risk factors means that the effect of having one risk factor present, like high BMI, results in modification of the effect of other risk factors. The influence of the important risk factor 'BMI' on other OA risk factors has only rarely been studied. Vrezas et al.[13] have studied interactions between BMI and life style factors and physical workload in men with knee OA. Coggon et al.[4] studied interactions between BMI and knee injury, surgery and generalized OA in a population with severe OA requiring surgical treatment. Both studies found interactions between BMI and other risk factors, but in both cases the studied population already had well established knee OA and is therefore not directly generalizable to an open population.

Another important risk factor for knee OA is female gender. Around the age of 50 years the incidence of OA rises in women, but not in men, suggesting a role for female hormones. Compared to men, women are not only more likely to have OA, they also have more severe symptoms[14]. The exact mechanism is not clear, nor is the exact association between female hormonal aspects, such as age at menarche or being post-menopausal, and OA[15].

Apart from structural changes due to OA, also symptoms in OA may be differently influenced by BMI and people might become earlier, or more severe, symptomatic. Being overweight is already reported to be associated with knee pain[16], having a limited range of motion[17], and having morning stiffness, but whether these symptoms also interact with higher BMI is not yet completely elucidated.

Therefore, this study investigates whether the associations of known risk factors or knee symptoms with the prevalence of radiological knee OA differ between women with a high BMI (≥27) and women with a low/normal BMI (<27). For this study we used data of an open study population of women at a menopausal transitional age.

METHODS

Setting and study population

The Rotterdam Study is a population-based prospective cohort study on chronic and disabling diseases in the elderly which started in 1990 in Ommoord, a suburb of Rotterdam (the Netherlands). Follow-up takes place every three to four years[18].

For the present study we used baseline data from the RS.III cohort. This new cohort joined the Rotterdam Study in 2006; of the 6,057 persons living in the study area at that time, 3,932 (response rate 72%) persons joined this new cohort. These participants were men and women aged 45 years and over who lived in the study area and who had not yet been examined in earlier cohorts of the Rotterdam Study [18]. For each participant written informed consent was obtained. The study was approved by the Medical Ethics Committee of the Erasmus University Medical Center.

In this cross-sectional study, eligible subjects were all women aged 45-60 who were invited for an additional sub-study on knee OA. Of these women knee specific data was collected, including MRI scans of both knees, physical examination carried out by two trained researchers and a questionnaire assessing possible knee complaints. Subjects were subdivided according to their BMI (<27 versus ≥27), and were analysed in two separate analyses.

OA assessment

At baseline, weight bearing anterioposterior X-rays of the knees were taken at the research center. Knees were radiographed in extended position with the patella as center point. Radiological OA (rOA), of both hips and knees, was assessed using the original Kellgren and Lawrence (KL) grading scale and considered present if the KL score was ≥2 [19,20]. All available radiographs of the knees and the hips were scored independently by two trained researchers (kappa = 0.62). Both researchers were blinded to all of the subject's clinical and demographic data.

Determinants

Risk factors

We selected known risk factors to test whether these differ for women with low/normal vs. high BMI. Selection of these risk factors was based on the literature and availability in the Rotterdam Study. The following risk factors were selected for testing in all women: 1) hip rOA[21]: case if hip KL score ≥2, 2) Heberden's nodes: absent on both hands (=reference) vs. any present, assessed in the physical examination, 3) knee trauma: case if positive answer to the question 'have you ever had knee trauma with swelling and/or knee trauma with a doctor's consultation?', 4) alignment: case if varus alignment (<181°) in one or both knees, assessed on digital X-rays by using the Medis' QBone® Planner, 5) menopausal status: premenopausal/peri-menopausal (=reference) vs. post-menopausal. A woman was considered post-menopausal if she reported not having menstruated in the previous 12 months, and 6) age at menarche: ≥12 years old (=reference) vs. <12 years old[22].

Symptoms

The following symptoms were selected for analysis: 1) WOMAC patient acceptable symptom score (PASS) for functional impairment: score considered elevated if >30 (range 0-100)[23], 2) morning stiffness: case if present up to 30 min [24], and from the physical examination: 3) limited extension: limited range of knee motion (<0^0 extension: unable to fully extend the knee while lying on the back) vs. normal/hyper mobile (≥0^0), and 4) tenderness on palpation: case if tenderness/pain was reported on palpation of the knee joint space in 90° bent position (medial or lateral, femoral or tibial).

Statistical analysis

Univariate logistic regression analysis was used to test risk factors for, and symptoms of, knee rOA in women with high and low/normal BMI; two separate analyses were performed, one in each group. The symptom analysis was repeated comparing women with KL grade 0 versus KL grade 2 in order to exclude possible influence of OA severity on the results. Adjusting for OA severity directly in the model was not an option because the KL grade was part of the outcome (OA presence).

All outcomes from the univariate logistic regression analysis, for risk factors and symptoms, were adjusted for age and BMI (within the groups). To make sure the results are not only due to the chosen BMI cut-off, we repeated our analysis dividing the eligible subjects according to the BMI groups BMI < 25, BMI 25-30 and BMI > 30.

All risk factors and symptoms that were statistically significant (p≤0.05) in the univariate analysis in one group, but not in the other, were tested for interaction with BMI using

multivariate logistic regression analysis, by including interaction terms in the model (e.g. BMI*trauma). Analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, USA).

From a clinical point of view it is interesting to know the difference in risk of knee rOA between normal-weight and overweight women in those presenting morning stiffness in clinical practice. In case a determinant showed significant interaction we assessed the attributable risks (AR) of the significant determinants. The AR, also called the excess risk, is the 'incidence of a disease in the exposed that would be eliminated if exposure were eliminated'[25].

RESULTS

Study population

A total of 1390 women were eligible for the present study, of which 885 participated in the knee OA sub-study. The eligible women were classified according to their BMI score which resulted in 741 in the low/normal BMI group and 649 in the high BMI group (see Figure 5.1).

The low/normal BMI group had a mean age of 54.4 (SD ±4.1) years and a mean BMI of 23.8 (SD ±2.10). In this group 41 participants (5.5%) had knee rOA. In the high BMI group the mean age was 54.7 (SD ±4.3) years and mean BMI was 31.5 (SD ±4.21). In this group 65 women (10.0%) had knee rOA. Table 5.1 shows the population characteristics of the tested groups.

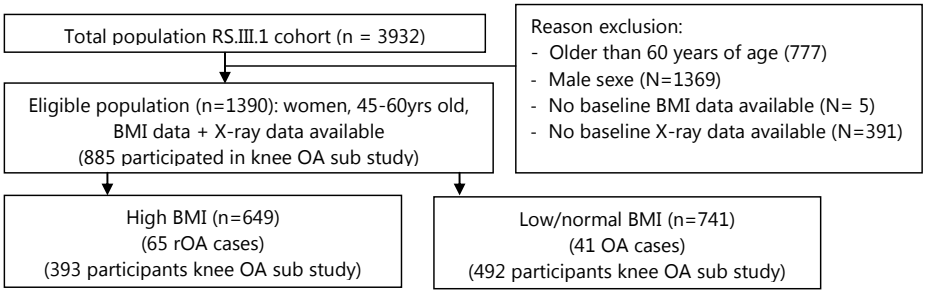


Figure 5.1: Flow chart inclusion study population.

Risk factors

In both groups the risk factors age and BMI (continuous; within the two separate groups) were significant ($p<0.05$, data not shown); however, BMI was only borderline significant in the normal weight group. 'Having varus alignment in one or both knees' and the 'pres-

Table 5.1: Characteristics of the total eligible population and the women studied according to their BMI category.

	All women		Low/normal BMI		High BMI	
	n	Mean (SD) / % present	n	Mean (SD) / % present	n	Mean (SD) / % present
Knee rOA	1390	7.6 %	741	5.5 %	649	10.0 %
Age (years)	1390	54.6 (SD 4.20)	741	54.5 (SD 4.11)	649	54.7 (SD 4.30)
BMI (kg/m^2)	1390	27.4 (SD 5.02) (median:26.6)	741	23.8 (SD 2.10) (median: 24.2)	649	31.5 (SD 4.30) (median: 30.0)
RISK FACTORS						
Hip rOA (KL≥2)	1304	10.6 %	716	12.2 %	588	8.7 %
Past knee trauma	1020	23.4 %	558	22.0 %	462	25.1 %
Varus alignment	1369	67.1 %	731	71.7 %	638	61.9 %
Post-menopausal status	1377	69.9 %	732	69.0 %	645	71.0 %
Age at menarche < 12 years	1363	17.2 %	726	12.5 %	637	22.4 %
Heberden nodes	881	26.8 %	490	26.5 %	391	27.1 %
KNEE SYMPTOMS						
WOMAC-PASS > 30	883	8.2 %	492	4.7 %	391	12.5 %
Morning stiffness < 30 min	1386	13.0 %	741	10.0 %	645	16.4 %
Limited extension	881	17.7 %	490	16.7 %	391	18.9 %
Tenderness on palpation	880	17.3 %	490	12.7 %	390	23.1 %

rOA = radiographic osteoarthritis (KL≥2), KL= Kellgren & Lawrence grade, BMI = body mass index, n = number of women in this group

ence of Heberden nodes' were more important risk factors in the high BMI group (resp. odds ratio (OR) =2.33, p <0.01 and OR=2.19, p=0.04) than in the low/normal BMI group (OR=1.40, p=0.34 and OR=1.65, p=0.25) (Table 5.2). 'Being post-menopausal' and 'first menses at age <12 years' seemed to be more important risk factors in the low/normal BMI group (resp. OR=3.98, p=0.02 and OR=2.56, p=0.02) than in the high BMI group (OR=1.31, p=0.52 and OR=1.73, p=0.07). In both groups, the tested risk factors 'having had knee trauma in the past' and 'having hip rOA' were not statistically significant.

Symptoms

All tested symptoms were statistically significant in the high BMI group compared with none in the low/normal BMI group (Table 5.2). The results of the repetition of the analysis including only the women scoring KL=0 and KL=2 (Table 5.3) were comparable to the first analysis. It is therefore not likely that the results are due to differences in OA severity in the two groups.

Repeating our analysis dividing the eligible subjects according to the BMI groups BMI < 25, BMI 25-30 and BMI > 30, yielded a similar trend for the tested risk factors and

Table 5.2: Associations with prevalent radiological knee osteoarthritis; Risk factors Kellgren & Lawrence (KL) score 0-5, Symptoms KL score 0-4

	Low/Normal Body Mass Index (< 27) n Total population = 741 (of which 41 knee rOA cases)						High Body Mass Index (≥ 27) n Total population = 649 (of which 65 knee rOA cases)					
RISKFACTORS[1]	**n total**[2]	**% pos. in OA+**[3]	**% pos. in OA-**[4]	**P-value**	**OR**[5]	**95% CI**[6]	**n total**[2]	**% pos. in OA+**[3]	**% pos. in OA-**[4]	**P-value**	**OR**[5]	**95% CI**[6]
Hip rOA	716	12.5	12.1	0.95	0.97	0.37 – 2.57	588	12.7	8.3	0.34	1.53	0.64 – 3.66
Knee trauma	558	29.0	21.6	0.34	1.49	0.66 – 3.34	462	33.3	24.1	0.35	1.37	0.71 – 2.62
Varus alignment	730	63.2	57.8	0.34	1.40	0.71 – 2.77	638	64.3	46.6	**<0.01**	**2.33**	**1.29 – 4.22**
Post-menopause[8]	722	90.0	67.8	**0.02**	**4.37**	**1.29 – 14.85**	641	81.0	69.9	0.86	1.09	0.44 – 2.68
Age menarche <12 years	726	26.3	11.8	**0.02**	**2.56**	**1.18 – 5.58**	637	35.5	21.0	0.07	1.73	0.97 – 3.09
Herberdens' nodes	490	40.0	25.8	0.25	1.65	0.71 – 3.83	391	44.4	25.4	**0.04**	**2.19**	**1.05 – 4.57**
KNEE SYMPTOMS[9]												
WOMAC-PASS >30	492	12.0	4.3	0.15	2.66	0.72 – 9.89	391	38.2	9.9	**<0.01**	**4.89**	**2.15 – 11.1**
Morning stiffness <30 min	739	12.8	9.6	0.57	1.34	0.50 – 3.57	636	40.7	13.4	**<0.01**	**3.85**	**2.07 – 7.13**
Limited extension	490	28.0	15.9	0.11	2.13	0.85 – 5.34	391	47.1	16.2	**<0.01**	**3.26**	**1.50 – 7.06**
Tenderness on palpation	490	12.0	12.7	0.75	0.82	0.23 – 2.86	390	41.2	21.3	0.05[7]	2.11	0.99 – 4.53

All ORs are adjusted for age and BMI within the group, [1] Risk factors: outcome including Kellgren & Lawrence (KL)scores 0-5, [2] N total = total N subjects included in analysis per risk factor / symptom [3]Percentage of tested risk factor/symptom present in OA cases, [4] Percentage of tested risk factor/symptom present in OA non-cases, [5] OR = Odds Ratio, [6] 95%CI = 95% Confidence Interval, [7] Borderline significant, [8]reference = pre-menopause and peri-menopausal: these ORs are additionally adjusted for not-natural menopause, [9] Symptoms: outcome including KL-scores 0-4, all significant outcomes are printed **Bold**

Table 5.3 Associations with prevalent radiological knee osteoarthritis, Kellgren & Lawrence scores 0 versus 2

	Low/Normal Body Mass Index (< 27)						High Body Mass Index (≥ 27)					
KNEE SYMPTOMS[1]	**N total**	**% pos. in OA+**[2]	**% pos. in OA-**[3]	**P- value**	**OR**[4]	**95% CI**[5]	**N total**	**% pos. in OA+**[2]	**% pos. in OA-**[3]	**P- value**	**OR**[4]	**95% CI**[5]
WOMAC-PASS >30	405	13.0	3.7	0.06	3.64	0.93 – 14.20	294	37.0	7.5	**<0.01**	**6.70**	**2.60 – 17.29**
Morning stiffness[7]	595	11.4	9.3	0.67	1.27	0.43 – 3.81	483	37.2	11.6	**<0.01**	**4.14**	**2.04 – 8.40**
Limited extension	403	26.1	15.8	0.14	2.11	0.78 – 5.68	296	37.3	16.0	0.05[6]	2.42	1.00 – 5.84
Tenderness on palpation	404	13.0	12.1	0.91	0.93	0.26 – 3.34	295	44.4	18.7	**0.01**	**2.94**	**1.27 – 6.85**

[1] Symptoms: outcome including Kellgren & Lawrence scores 0 versus 2, [2] Percentage present tested risk factor/symptom in OA cases, [3] Percentage present tested risk factor/ symptom in OA non-cases, [4] OR = Odds Ratio, [5] 95%CI = 95% Confidence Interval, [6] Borderline significant, [7] stiffness ;30 minutes; all significant outcomes are printed **Bold**

symptoms. This analysis showed a dose-response effect for trauma, Heberden's nodes, and morning stiffness (all ORs increased with increasing BMI) and for post-menopause and age at menarche (ORs decreased with increasing BMI) (Appendix IV).

Interactions

We tested the risk factors and symptoms that differed between the groups, in statistical significance, on interactions with BMI (Table 5.4). A significant interaction was found between BMI (<27 vs. ≥27) and having morning stiffness < 30 min ($p<0.05$, OR=3.19 (95% CI=1.02–9.99)), indicating that overweight women have more morning stiffness of the knee associated with knee rOA compared to their non-overweight peers.

Further, we found indications for possible interactions between BMI and 'being post-menopausal' (p=0.16), and BMI and 'tenderness on palpation' (p=0.18), indicating that both these increase with higher BMI.

Table 5.4 Test results for interactions with Body Mass Index

Risk factors	P-value	OR[1]	95% CI[2]	Knee symptoms	P-value	OR[1]	95% CI[2]
Varus alignment	0.29	1.62	0.67 – 3.93	Morning stiffness <30 min	**<0.05**	**3.19**	**1.02 – 9.99**
Heberdens' nodes	0.65	1.29	0.43 – 3.82	Limited extension	0.22	1.06	0.96 – 1.18
Post-menopause	0.17	0.42	0.12 – 1.46	WOMAC-PASS >30	0.36	2.04	0.45 – 9.26
Age at menarche <12 years	0.51	7.28	0.28 – 1.88	Tenderness on palpation	0.18	2.66	0.63 – 11.24

Included Kellgren & Lawrence scores = 0-4, BMI <27=reference in these interactions, [1] OR = Odds Ratio, [2] 95%CI = 95% Confidence Interval, [3] men + women, remainder: women only, all significant outcomes are printed **Bold**

Attributable risk

In Figure 5.2 the pre and post tests of the two BMI categories in relation to morning stiffness are shown. In all women with morning stiffness 19.4% had knee rOA (=pre test probability). The post probabilities of knee rOA in overweight women with knee morning stiffness is 26.4%, while in non-overweight women this is only 9.5%. The attributable risk of a BMI≥27 in those with morning stiffness is 16.9 per 100 cases. In women without morning stiffness such a large difference between overweight and normal weight women is not present (AR=1.4 per 100 cases).

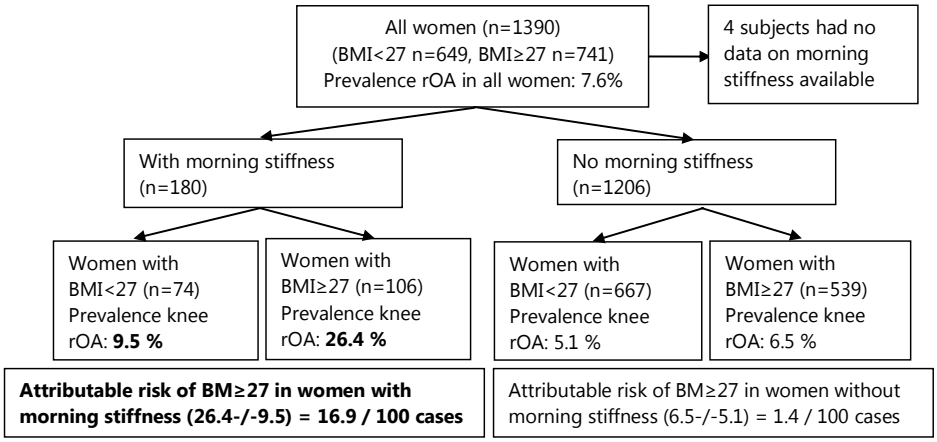


Figure 5.2: Pre test and post test risks of knee rOA in relation to knee morning stiffness.

DISCUSSION

In the present study, risk factors for, and symptoms of knee rOA differ between women with low/normal BMI versus women with high BMI. The most striking finding was the significant interaction between BMI and morning stiffness <30 min ($p<0.05$, OR=3.19). Translated to everyday clinical practice this means that in middle-aged overweight women consulting their physician for knee complaints, it is more likely that knee morning stiffness is related to knee rOA, than in their normal-weight peers.

Another interesting finding is that post-menopausal women with low/normal BMI have a four times higher odds ratio for having knee rOA compared to post-menopausal women (adjusted for having a not natural menopause) with high BMI; number of years since menopause did not seem to make a difference. All tested symptoms of knee rOA in women seem to differ, especially the WOMAC-PASS for functional impairment, morning stiffness of the knee, and tenderness on palpation; all with higher odds ratios in overweight women. Presence of these symptoms in women with a high BMI appear to be more frequently associated with knee rOA. Although, we assessed the diagnostic relation of symptoms with rOA in overweight and non-overweight women, the other way around we found also to be true; overweight women with rOA appeared to have more severe symptoms, or more frequently, than non-overweight women with rOA, data not shown.

Further, we found a difference in significance and magnitude of the OR for the risk factors varus alignment, age at menarche <12 years, and having Heberden's nodes. However, interactions between BMI and these risk factors did not reach significance in their relation to prevalent knee rOA.

Investigating interactions requires substantial statistical power. This might explain why they are not often observed in complex diseases such as OA. For the present study we examined a relatively young and healthy population and were careful not to test too many variables to prevent statistical chance findings (type I error). We did find a significant interaction between BMI and morning stiffness. There may also be indications for possible interactions with being post-menopausal (p=0.16) and tenderness on palpation (p=0.18), but these may be chance findings and require further study. Not finding more interactions in the present study might be due to the small numbers of subjects for analysis and thus limited statistical power.

Others also found indications that being overweight may interact with other risk factors for developing knee OA, for example: alignment[12,26]. Brouwer et al. [12] found an association between increasing varus alignment and development of knee rOA, which seemed particularly applicable in overweight and obese persons. Niu et al.[26] found an intermediate effect of obesity in those with valgus alignment in progression of knee rOA. Further, Englund et al.[27] found an interaction between hand OA and knee trauma with respect to the development of knee OA. Unfortunately, for the present study population data on hand OA were not yet available.

In a previous systematic review we found no evidence for a relation between knee rOA and menopausal status, and knee rOA and age at menarche[15]. Hormonal balance is influenced by fat through estrogen secretion. Changes in estrogen secretion peak in two moments in a woman's life. First in early adolescence, at the age of menarche with the start of cyclical secretion of estrogen, and secondl around the time of menopause [28]. Jarvinen et al.[28] argued that focusing on perimenopause alone, which is often the case, may therefore be too narrow. Girls that start menstruating at a relatively young age are generally heavier than their later starting peers. An earlier age at menarche is associated with premenarcheal BMI and both these factors are associated with greater adult BMI[29].

A systematic review showed that on epidemiological grounds, so far, the evidence of an association between hormonal factors and knee OA, like menopausal status and age at menarche, remains conflicting[15]. In the present study there was an indication that post-menopausal women with low/normal BMI had a 4 times higher odds ratio for prevalent knee rOA compared to overweight post-menopausal women. The studies included in the systematic review all had mean BMIs falling within the 95% CI of the low/normal BMI group in the present study; all had a mean BMI <27, but with overlapping 95%CIs with our high BMI group. However, this does not explain why the summarized evidence for the association between knee rOA (KL ≥ 2) and the post-menopausal status was moderate for no relation in our systematic review. It is possible that in our study the women with high BMI already had knee rOA and were therefore no longer at risk to develop this condition by the onset of menopause.

To ensure that the variables post-menopause and age at menarche were correctly tested as separate variables, we checked the correlation between these variables. There seemed to be no problem in separate testing because the correlation coefficient was very small (r=0.054, p=0.045).

All examined symptoms were more strongly associated with knee rOA in the high BMI group than in the low/normal BMI group. It is possible that women with high BMI have a different phenotype of OA[30,31], leading to more prevalent symptoms and pain. This may be related to the presence of inflammation, which is probably stimulated by the presence of higher fat levels[9]. Treatment in overweight women should therefore, besides loosing weight, perhaps focus more on inflammation.

This study has some limitations which need to be addressed. First, because the data were cross-sectional we were unable to assess if the occurrence of rOA in the overweight women was before or after the onset of menopause. This will be studied in the future, because the data used here were baseline data of an ongoing prospective cohort. Second, we did not include men in our study because the symptom data was only available for women. We did test the risk factors hip rOA, past knee trauma, varus alignment and female gender in the two separate BMI groups including men and women. However, this gave similar results and made the results less readable, therefore we decided to report on women only. Third, data on knee trauma were assessed by asking if the participant had ever had knee trauma with swelling and/or knee trauma with a doctor's consultation; because this information was not checked in the medical records, due to inavailability of data, we do not know the extent of the actual injury. This may lead to an underestimation of the actual estimate, since people may report having had trauma while the knee joint was not actually damaged. Fourth, in the 1990s, obesity was defined by the WHO as a BMI >30[32]. Here, we used 27.0 as the cut-off for BMI because this has been shown to be clearly associated with incident knee rOA. We consider that using this cut-off is appropriate since 1) the "method used to establish BMI cut-off points has been largely arbitrary"[32], 2) it is close to that defined by the WHO (which also suggested an overweight cut-off point of 27.5[32]) and our population mean, and 3) analysis according to BMI groups BM<25, BMI 25-30, and BMI>30 showed similar results. Finally, we used rOA as the outcome in our analysis and not clinical OA, which may have been more applicable for daily practice, since not all people with rOA have pain in the affected joint.

In conclusion, risk factors for, and symptoms of knee rOA differ between women with low/normal BMI versus high BMI in our open study population. We found a significant interaction between BMI and morning stiffness and some indications for interactions with post-menopausal status and tenderness on palpation. Our findings indicate that future research should further elucidate the interactions between BMI and knee OA. Collaborative initiatives to combine large cohort data may be needed to obtain sufficient statistical power to adequately examine the interactions under study.

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Chapter 6

Development of radiological knee osteoarthritis in people with knee complaints

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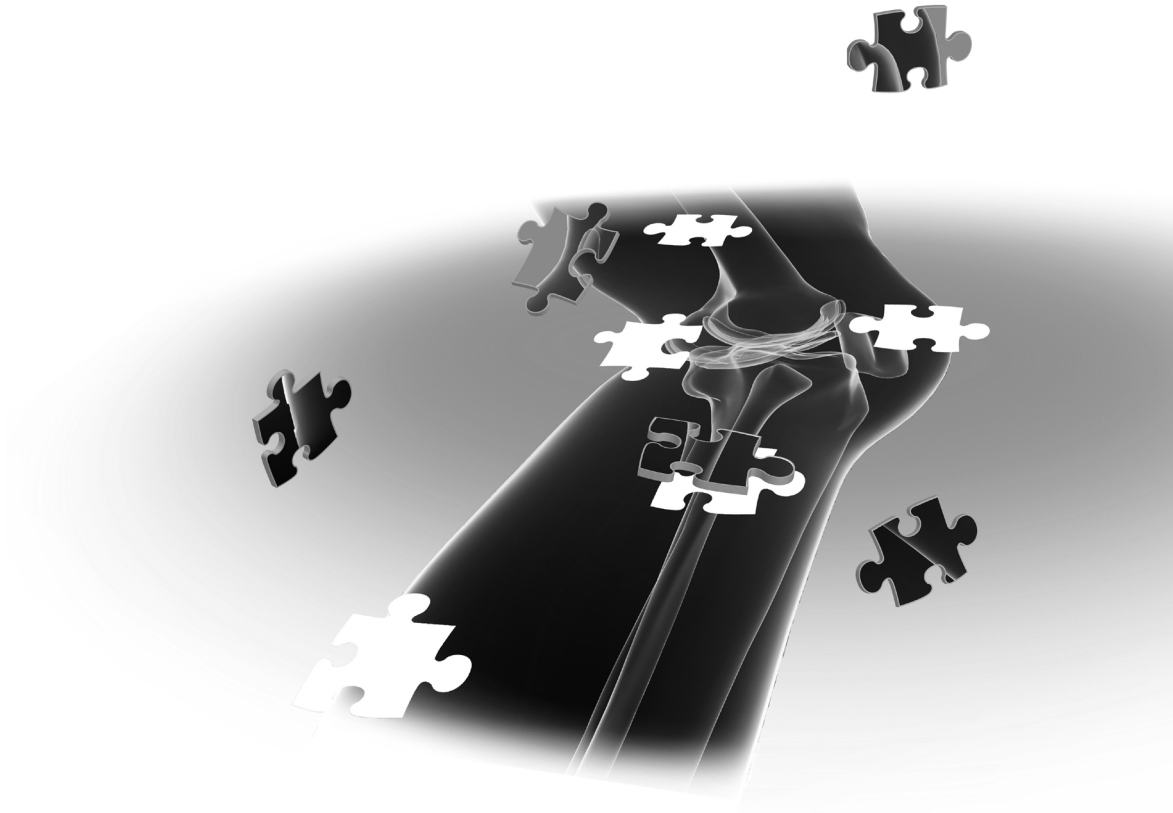

ABSTRACT

Purpose

It is currently impossible to identify which patients with knee complaints presenting to the general practitioner will, or will not, develop knee osteoarthritis (OA) pathology in a later stage. This study examines the determinants for developing OA pathology on X-ray in persons with knee complaints but no radiological OA at baseline in the painful knee.

Methods

Data of the prospective Rotterdam cohort study (including subjects aged ≥55 years) were used. Analysis was performed on 623 subjects with knee complaints at baseline and their data at 6-year follow-up (T1; n=607) and at 11-year follow-up (T2; n=457). At baseline, none had radiological OA (rOA=Kellgren and Lawrence (KL) grade ≥2) in the painful joint. At follow-up, predictors for rOA were determined using multivariate ordinal logistic regression analysis.

Results

At T1 8.5% of the group had developed knee rOA; by T2 this had increased to 23%. Determinants remaining significant in the multivariate analysis were: female gender (OR=1.95, 95% CI=1.15-3.36), other joint complaints (OR=2.22, 95% CI=1.12-4.35), and KL grade 1 at baseline in the painful knee joint (OR=7.14, 95% CI=4.55-11.1). All outcomes are adjusted for all included determinants.

Conclusion

The best predictors of knee rOA development are a combination of female gender, other joint complaints, and KL grade 1 in the painful joint. KL grade 1 in combination with knee pain should be considered as an early OA in patient management.

INTRODUCTION

Many people consult their general practitioner (GP) with knee complaints[1]. In elderly patients this pain is often due to osteoarthritis (OA)[2], but not all these people have radiological signs of OA in the painful joint. This discrepancy between presence of pain and OA pathology on X-ray is well reported[3-5]. In daily GP practice the absence of radiological established OA may lead to different patient management.

A consensus guideline (mainly for clinical diagnosis of knee OA) was published in 2010 by The EULAR OA Task Force[6]. It stated that the diagnosis should be based on three key symptoms: persistent knee pain, morning stiffness and functional impairment, and three typical clinical signs: crepitus, restricted movement and bony enlargement. However, several of these symptoms are features of advanced disease and may not be applicable in early diagnosis of OA in a primary care setting. Also, the fact that radiological OA (rOA) is not often established in early disease leaves the GP with even less certainty about the diagnosis.

In general practice much information related to OA is available. Known risk factors like age, comorbidities (such as hypertension[7] and diabetes[8]), data on other joint diseases or complaints, and OA in other joints[9] are registered in the GP's database. Other risk factors can be measured or determined, e.g. body mass index (BMI), history of heavy workload[6, 10-11], familial OA, presence of morning stiffness in the painful knee[12], and lower limb disability score[13] through the Health Assessment Questionnaire (HAQ) questionnaire. After referral, radiographic data are available on e.g. knee alignment (for which evidence of an association with knee OA incidence is not yet established[14]), and the presence or absence of rOA[15].

Although many risk factors are known, a high-risk profile for early identification of knee OA is still lacking. People presenting with knee complaints might be in an early stage of OA development. Early recognition of knee OA will help the diagnostic process and the establishment of early intervention studies.

The EULAR Taskforce also proposed a 'future research agenda'[6]. One of the agenda items was the 'development of diagnostic criteria for early symptomatic knee OA (e.g. by prospective investigation of people with knee pain who fulfil the criteria of knee OA several years later)'. The present study aims to identify the best prognostic determinants for developing rOA (Kellgren & Lawrence grade (KL) $\geq$2) at follow-up, in elderly people with knee complaints at baseline but no rOA (KL<2) in the painful joint at baseline.

METHODS

Setting and study population

The Rotterdam Study is a population-based prospective cohort study on chronic and disabling diseases in the elderly which started in 1990. Follow-up takes place every 2-3 years. Participants were aged 55 years and older, living in Ommoord (Rotterdam, the Netherlands). There were 7,983 participants, i.e. 78% of 10,215 invitees[16]. Written informed consent was obtained for each participant. The Rotterdam Study was approved by the Medical Ethics Committee of the Erasmus University Medical Center.

All participants were interviewed at home and were invited to the research center for medical examinations and radiographs. A total of 6,450 participants underwent baseline measurements.

For the present study, eligible subjects were those with knee X-rays and data on knee complaints (pain or stiffness) available at baseline, and on at least one of the two follow-up moments. Subjects were only included if they reported knee complaints (previous month and/or past 5 years) at baseline, but had no rOA in both knees at baseline (KL<2).

OA assessment

Weight-bearing anterior-posterior X-rays of the knees were taken at the research center. Knees were radiographed in extended weight-bearing position with the patella as center point. rOA of the tibiofemoral joint was assessed using the KL grading scale[17]. All radiographs were scored independently by three trained researchers. Inter reader variability was moderate (0.55 (95% CI 0.50-0.59)) for the KL grades 0 vs. 1; for a KL grade ≥2 this was good (0.68 (95% CI 0.61-0.75)). In total 5,652 knee X-rays were scored at baseline, 3,288 X-rays at first follow-up, and 2,503 radiographs at second follow-up. All researchers were blinded to all of the subjects' clinical and demographic data. Knee rOA is defined as a KL grade ≥2 of one or both joints, or a total joint replacement (TJR). Hand OA is defined as presence of a KL grade ≥2 in 2 out of 3 hand joint groups (DIPs, PIPs, CMC1/TS) of each or both hands. Incidence of knee OA is defined as a KL <2 at baseline and KL ≥2 at follow-up/incident TJR at follow-up.

Pain assessment

Data were collected via a standardized interview at home, in which participants were asked if they had suffered knee pain in the previous month (yes/no) and/or in the past 5 years (yes/no). Pain in the knees was defined as having pain in the left or right joint, or

both, either during the previous month or during the past 5 years. Pain was assessed in this way at baseline and at follow-up.

Determinants

Potentially relevant baseline variables were selected based on the literature and availability in the clinical setting of the GP and in the Rotterdam study:

- General information: Age, gender, BMI[18] (kg/m2), and heavy workload[10] (having worked outdoors for 4 h/day or more during at least 25 years).
- Joint complaints: General joint complaints in the previous month (yes/no; positive score if pain reported in one or more of the following places: arm, neck, shoulder, elbow, low back, hip, knee or foot; collected via standardized interview), and the duration of these general joint complaints (<1 year vs. ≥1 year), the HAQlower limb disability score[13] (functional impairment score: no trouble (score 0) vs. any trouble (score 1,2 or 3)) and morning stiffness (<30 min)[12].
- Comorbidities: Hypertension[7] (SBP ≥ 160 mmHg, DBP ≥100 mmHg, or use of antihypertensive medication), diabetes[8] (prevalent case if: using antidiabetic medication and/or abnormal nonfasting or postload glucose level (11.1 mmol/L or over) and/or an abnormal oral glucose tolerance test), joint disease other than OA (Bechterev, gout or rheumatoid arthritis: all reported for the previous month or the past 5 years) and familial rheumatoid arthritis.
- OA variables: rOA in hip or hand[9] (prevalent cases at baseline KL ≥2).
- Imaging data: alignment in the painful joint, and a KL grade of 1 at baseline in the painful joint.

Statistical analysis

Ordinal logistic regression analysis was used to investigate associations between the potentially relevant determinants and the development of knee rOA. All the before mentioned determinants are included in the model. The outcome was measured at two follow-up moments and was categorized as: 1) no rOA incidence on first (T1) or second follow-up (T2), 2) late rOA development: incident rOA at second follow-up, and 3) fast rOA development: incident rOA at first follow-up moment. For subjects with missing X-ray data at T1 who had no rOA at T2 we imputed that they also had no rOA at T1.

Analysis was performed using R 2.11.1 and OpenBugs 3.0.3 using the BRugs package. The model was run taking 20,000 samples (the first 10,000 were discarded) from each of three independent Markov chains. Convergence was checked both visually and using the Gelman-Rubin Statistic [19]. Standard non-informative priors were used.

RESULTS

Study population

Subjects were only included if, at baseline, they reported knee pain in the previous month or the past 5 years, but had no knee rOA in the painful joint. This resulted in 944 eligible subjects. The mean time from baseline to T1 was 6.5 (range 5.5-8.8) years, and mean time from baseline to T2 was 11.1 (range 9.4-13.2) years.

Of these 944 subjects, 321 did not return for X-ray follow-up at T1 or T2 and are therefore not available for analysis. This leaves 623 subjects for the analysis; follow-up X-ray data at T1 were available for 607 subjects, and at T2 for 457 subjects, see flowchart in Figure 6.1 (see the reasons for non-participation at each stage Appendix V).

Because a large number of patients had missing information for variables 'hand rOA' or 'deviant knee alignment in painful knee' these variables were excluded from analysis.

Baseline GP consultation data for joint complaints were available for 159 subjects included in the analysis. Of these, 58.5% had visited their GP both in the previous month and in the past 5 years; 10% had consulted their GP in the previous month, and 26.5% had done so in the past 5 years but not in the previous month. Only 5% had never visited their GP for joint complaints. These percentages for GP consultation related to joint complaints are comparable to those in the total eligible population (n=944).

Table 6.1 shows the gender distribution of the subjects included in the ordinal regression analysis. Age ranged from 55-85 (mean 64.5) years and mean BMI was 26.2 kg/m^2

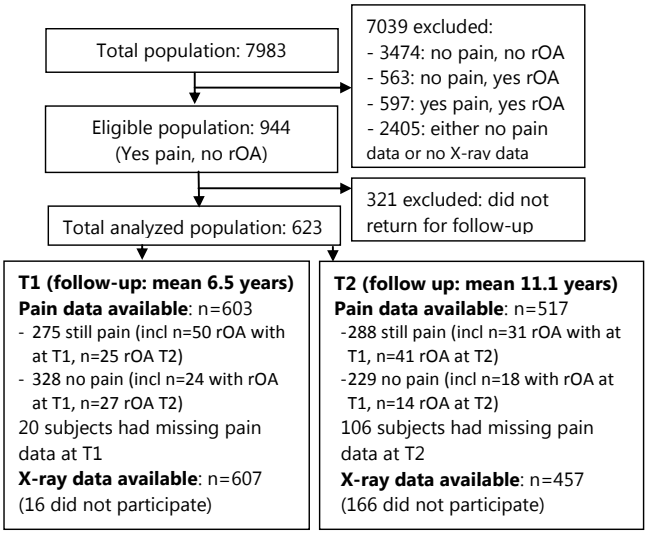

Figure 6.1: Flow chart inclusion of study population.

Table 6.1: Distribution of women/men and complaint status at follow-up according to osteoarthritis development status.

Osteoarthritis (OA) development status	Total	Women	Men
No OA development	344	217	127
Slow OA development (T2)	74	58	16
Fast OA development (T1)	53	36	17
No OA or slow OA development [a]	136	81	55
Fast or slow OA development [b]	16	11	5
Total in analysis	**623**	**403**	**220**
Lost to follow-up	321	216	105
Total eligible population	944	619	325

[a] Subjects without knee radiological OA at T1 and missing X-ray data at T2, [b] Subjects with incident knee radiological OA at T2 but with missing X-ray data at T1

Table 6.2: Results of the ordinal logistic regression analysis; showing all in the analysis included determinants.

GENERAL INFOMATION	Mean (sd) / n (%)	OR	95% CI
Age in years	64.5 (6.5) [a]	1.22	0.97 - 1.52
BMI	26.2 (3.5) [a]	1.18	0.94 - 1.47
Female gender	**623 (64.7)**	**1.95**	**1.15 - 3.36**
Heavy workload [b]	623 (14.9)	1.61	0,83 - 3,11
JOINT COMPLAINTS			
HAQ lower limb disability [c]	623 (10.0)	0.81	0.38 - 1.,69
General joint complaints last month	**623 (80.7)**	**2.22**	**1.12 - 4.35**
Duration general joint complaints [d]	503 (60.5)	0.64	0.37 - 1.08
Morning stiffness <30 min in legs	620 (10.3)	0.93	0.44 - 1.82
COMORBIDITIES			
Hypertension	617 (28.5)	0.82	0.50 - 1.35
Diabetes	622 (8.8)	0.57	0.24 - 1.30
Other rheumatic diseases	623 (4.8)	1.54	0.67 - 3.57
Family rheumatoid arthritis	623 (18.1)	0.97	0.56 - 1.64
OSTEOARTHRITIS (OA) VARIABLES			
Hip rOA	617 (9.0)	0.83	0.39 - 2.08
Family OA	588 (27.1)	1.08	0.68 - 1.72
IMAGING DATA			
KL-grade 1 in painful joint	**623 (30.3)**	**7.14**	**4.55 - 11.1**

[a] Mean (SD) rest =n (%), [b] Worked outdoors for 25 years 4 h/day, [c] No disability vs. any disability, [d] <1 year vs. ≥1 year, BMI = body mass index kg/m^2, HAQ = Health Assessment Questionnaire, (r)OA = (radiological) osteoarthritis, KL (grade) = Kellgren & Lawrence (grade), significant outcomes are printed **bold**

(SD 3.46). At baseline, 211 subjects reported having bilateral knee complaints during the previous month, while 224 reported knee pain in the past 5 years but not in the previous month.

Determinants of knee rOA development

Table 6.2 presents results of the ordinal logistic regression analysis. All determinants were tested in one multivariate model, adjusting all outcomes for all included determinants. Three determinants were significantly associated: female gender, having other joint complaints, and a KL grade of 1 at baseline in the painful joint.

Risk of rOA development

In total, 23% of the subjects developed knee rOA at some point during follow-up. Of the 623 subjects who had no rOA at T1, 136 were lost to follow-up by T2. In the total population the risk to develop rOA (for an average person) at some point during follow-up was 16% (Table 3). Comparison of various subgroups shows that the risk of rOA development in the total eligible population differs between subgroups (Table 6.3). For example, in the group with KL grade 0, 13.5% developed knee rOA during follow-up (fast or slow)

Table 6.3: Odds of radiological osteoarthritis OA (rOA) development according to KL grade, gender and presence (or absence) of other joint complaints for an average subject with knee pain in the total eligible population.

		Risk of rOA development			
Baseline variable	**n**	**rOA by T1** (% (95%CI))	**rOA by T2** (% (95%CI))	**rOA at T1 or T2** (% (95%CI))	**No rOA T1 and T2** (% (95%CI))
Risk total eligible population	944	6.1 % (4.3-8.2)	9.9 % (7.3-13.0)	16.0 % (12.5-20.1)-	84.0 % (79.9-87.5)
KL grade 0	585	5.1 % (3.5-7.0)	8.4 % (6.1-11.3)	13.5 % (10.2-17.4)	86.5 % (82.6-89.8)
KL grade 1	**359**	**27.1 % (20.9-33.8)**	**25.1 % (19.5-31.0)**	**52.2 % (44.3-60.0)**	**47.8 % (40.0-55.7))**
Male gender	325	4.1 % (2..3-6.4)	7.0 % (4.3-10.4)	11.1 % 6.9-16.3)	88.9 % (83.7-93.1)
Female gender	**619**	**7.6 % (5.3-10.5)**	**11.9 % (8.6-15.6)**	**19.5 % (14.9-24.6)**	**80.5 % (75.4-85.1)**
No general joint complaints	176	4.4 % (2.3-7.4)	7.5 % (4.3-11.7)	11.9 % (6.8-18.5)	88.1 % (81.5-93.2)
General joint complaints [a]	**768**	**7.1 % (5.0-9.6)**	**11.2 % (8.2-14.7)**	**18.3 % (14.2-22.9)**	**81.7 % (77.1-85.8)**

[a] Combined score of other joint complaints in pain in arm, neck, shoulder, elbow, low back, hip, knee and foot. Significant risk factors are printed **bold**

compared with 52.2% in the group with KL grade 1. For male vs. female gender the risks were 11.1% and 19.5%, respectively, and for no general joint complaints vs. having general joint complaints the risks were 11.9% and 18.3%, respectively.

DISCUSSION

In the present study the three determinants found to be the best predictors for developing knee rOA were a knee KL grade 1 at baseline in the painful knee, female gender, and having general joint complaints during the previous month.

Female gender may have its relation with OA in the path of estrogen deficiency and general joint complaints may possibly be an indication for generalized OA. We found having a KL grade 1 to be the strongest predictor and we therefore focus on this in this discussion. Analysis of the data in two separate models (either fast or slow rOA development) gave similar results, though with less statistical power.

In this study population, those who reported knee complaints but had no established knee rOA (KL grades 0 or 1) had higher odds for knee rOA development compared to their complaint-free peers. Of course, the reported knee complaints may have had differential diagnosis, such as wide spread pain, soft tissue pain (tendinitis/bursitis) or referred pain from hip pathology. The population attributable risk for rOA development sometime during follow-up (mean 11.1 years) in those with knee complaints and KL grade 0 was 11.5% and in those with knee complaints and KL grade 1 was 56.8%; in subjects without complaints these values were 8% and 41.2%, respectively.

Due to lack of physical examination data we were unable to test the key clinical signs as suggested by the EULAR taskforce[6]. However, the key symptoms 'morning stiffness' and 'functional impairment' proved to be non-significant. These symptoms may be more relevant in people with a more advanced disease and may not be sensitive for early disease or predictive for rOA development.

Persons consulting the GP for knee complaints may be in an early stage of OA disease, which is not yet visible on X-ray. In the Dutch guidelines for GPs (and in the UK guidelines), the use of X-ray as a diagnostic tool for knee OA in patients with knee complaints in primary care is considered inappropriate[20-22]. This is because the absence of visible radiological abnormalities does not exclude knee OA; nevertheless, in practice X-ray is regularly used for diagnostic purposes. According to Bedson et al., the presence of OA changes on X-ray clearly influences the treatment and referral decisions of the GP; they found that this was the case for GPs that would not have chosen to X-ray the patient in the first place, as well as for those who would have done so[20].

Hart and Spector[15] suggested that, in using the KL scoring system in epidemiological studies, KL grade 1 should not be grouped with KL grade 0, but that KL grade 1 should

be considered as a 'pre-diseased group' with KL grade 0 as control group in comparison. Our study supports this finding and that a KL grade 1 predicts future development of radiological disease of the tibiofemoral joint in people with knee complaints. Thorstensson et al. also tested the hypothesis that idiopathic chronic knee pain is an early sign of knee OA and concluded that this was the case[23]. In the present study we did not investigate chronic knee pain but only duration of general joint complaints (e.g. knee pain or stiffness). We found a significant association with the presence of general joint complaints in the previous month, but not with the duration of these complaints (< 1 year vs. ≥ 1 year).

Peat et al. investigated whether a 'false-positive' clinical diagnosis of knee OA was equivalent to an early diagnosis of pre-radiographic disease over 3 years; their analysis suggests that this is not so[24]. However, their follow-up period may have been too short to reveal similar results to ours, since our study (as well as that of Hart et al.[15] and Thorstensson et al.[23]) had a longer follow-up period: i.e. 11 years, 10 years and 12 years, respectively.

Currently, the usefulness of radiographs is not aimed at confirmation of osteoarthritic disease but rather to rule out other diseases[25]. MRI potentially has additional value since it can visualize tissue damage at an earlier stage. The clinical value of the present study lies in highlighting the potential additional value of X-rays in the diagnostic process in people who consult their GP for a knee complaint that has no clear cause. Radiologists do not generally report the actual KL grade to the GP, but simply whether (or not) a patient has an established rOA. In case of no established rOA a radiologist may report 'minimal degeneration complying with normal ageing' or 'mild degenerative signs', which might comply with a KL grade of 1. The chance that someone with KL grade 1 will develop knee rOA in the future is significantly greater than a person with KL grade 0.

Some limitations of the present study need to be addressed. First, because a relatively large number of patients had missing information for the variables 'hand rOA' and 'deviant knee alignment in painful knee', these determinants were disregarded for analysis. Analysis including these two variables, considering only the complete cases for these variables, produced a model with observations for only 215 subjects. Because neither of these two variables was significant in that analysis, excluding them was appropriate. Second, it is possible that subjects with knee complaints at baseline, but no tibiofemoral OA, had complaints related to a prevalent patellofemoral OA. Mazzuca et al. reported a 41% presence of patellofemoral rOA in subjects with a tibiofemoral KL grade 0-1[26]. Unfortunately, because only AP radiographs were available for the present study, we were unable to review the presence of patellofemoral OA and only considered radiographic tibiofemoral OA as knee rOA. Third, because no data on physical examination were available for this cohort, we were unable to test the applicability of the clinical signs (as

suggested by the EULAR Taskforce[6]) for early OA diagnosis in primary care. Perhaps restricted movement or crepitus in the knee, or even joint line tenderness, may better predict future rOA development and should therefore be examined whenever possible. We plan to do this using the third cohort of the Rotterdam study, in whom baseline data include crepitus, restricted movement and bony enlargement; follow-up measurements of this cohort will start in 2012. Fourth, we included people who reported having knee complaints in the previous month and/or in the past 5 years. Since pain is episodic and activity-related[6, 27] (especially in the early stages of disease), we included those with knee complaints in the past 5 years because complaints of, e.g. 1.5 months ago, would otherwise be missed. This led to the inclusion of 224 subjects who had not had knee complaints in the previous month, of which 48 developed OA during follow-up. Inclusion of these people might have led to an underestimation of the estimates. Therefore, we believe that including people without knee complaints in the previous month, but with knee complaints in the past 5 years, was appropriate. Fifth, selecting subjects on the basis of availability of X-ray data at baseline and follow-up introduced a type of selection bias called the 'healthy-worker-effect', since subjects in better health are more likely to revisit the research center for follow-up measurements. On the other hand is the long follow-up period a strength of the study. Currently, it is not possible to prevent degeneration into established OA due to the lack of disease-modifying interventions. Conservative treatments available for OA symptom relief are weight reduction in case of overweight/obesity, exercise, suitable footwear, pain medication, referral to a physiotherapist, and insoles or braces. The GP generally starts by giving advice, followed by pain medication if a lifestyle change is insufficient. Generally, guided exercise therapy, and insoles and braces are not the first choice, although exercise therapy should be according to the guidelines of NICE [28], OARSI[29] and EULAR[6]. The effect of these therapies on symptoms in people with knee complaints but without established OA is not yet clear.

To summarize, in this open population: being a woman, having general joint complaints besides knee complaints, and having KL grade 1 in the painful knee are the most important variables predicting the development of knee rOA. Early recognition of those at high risk of developing rOA will help GPs in the diagnosic process.

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Chapter 7

Predicting determinants for incident knee pain in middle-aged women: a longitudinal osteoarthritis study

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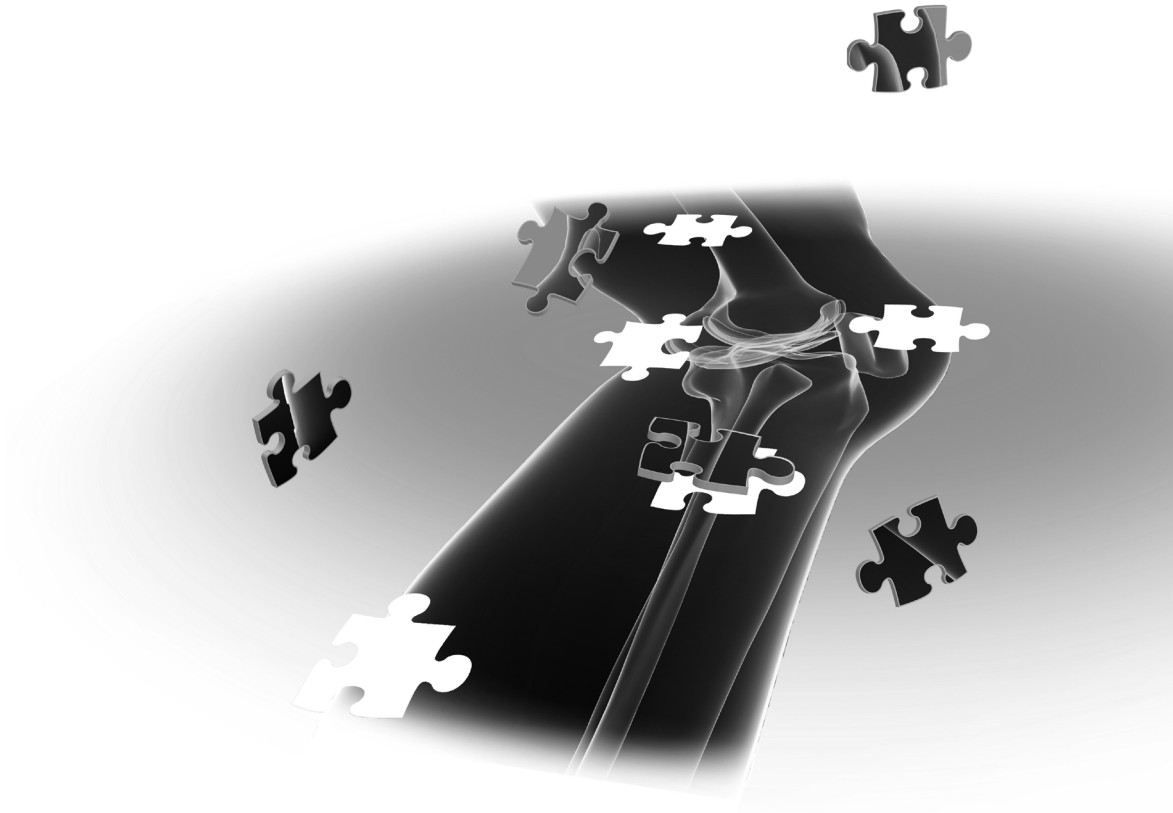

ABSTRACT

Background

Early recognition of knee osteoarthritis (OA) remains a problem since specific high-risk profiles are lacking. Predicting who will develop knee pain at a later stage is one step in the process of identifying persons at high risk of OA development. This study aims to identify prognostic determinants for new knee pain in women of middle age.

Methods

Data of 673 women (aged 45-60 years) from the Rotterdam Study who had at least one pain-free knee at baseline were used. Assessed at baseline were degenerative signs of knee tissues (MRI), physical examination/history taking, and OA risk factors. Pain after two years was assessed using questionnaires. Analyses were performed using GEE.

Results

The best predicting determinants for incident knee pain after two years in all women were: past knee trauma and pain in the other knee at baseline. In women with no pain in either knees at baseline, the best predictors were: tenderness on palpation of the tibiofemoral joint space, past knee trauma and lateral meniscus degeneration, whereas in women with pain in one knee at baseline these were: past knee trauma, being post-menopausal, crepitus on active movement and BMI.

Conclusion

Contralateral knee pain and past knee trauma are the best predictors for incident knee pain reported after two years. The predicting factors differed between women with pain in one knee and those without knee pain.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis in middle-aged and elderly people [1-3]. It most often affects the hip and knee joint, but the knee joint is affected twice as often as the hip. OA is a progressive disease affecting all joint tissues and causing irreversible joint damage.

Early recognition, or diagnostic criteria, of knee OA, are a problem in clinical practice since there are no specific high-risk profiles for OA development. A complicating factor in early identification of knee OA is the well-known discrepancy between radiographic OA and symptoms [4,5]. Identification of high-risk groups for, and early signs of, OA development might enable more effective recruitment of populations for studies on disease prevention or early stage treatment. So far, most intervention studies were performed in populations already showing clinical signs of OA with manifest radiological degenerative changes in the joint, indicating irreversible joint damage. Magnetic resonance imaging (MRI) is suggested to be the best imaging technique for detecting early osteoarthritic changes since it visualizes degeneration of individual tissues in an earlier stage than radiography [6-8]. Studies on disease prevention, disease modification, or early stage treatment might be even more successful in a pre-clinical stage [9],

Identification of those at high risk to develop OA in the near future would enable early intervention studies. Pain is the most important clinical symptom of OA and in middle-aged people knee pain is most often attributed to (early) OA [10]. Predicting who will develop knee pain in the near future can therefore be considered one step in the process of identifying persons at high risk of OA.

After age 50 years the incidence of knee OA increases more rapidly in women than in men, making middle-aged women without knee complaints a suitable population for prospective studies on specific high-risk groups for knee OA development. Early degenerative signs on MRI, physical examination data and general risk factors, e.g. age, body mass index (BMI) and malalignment of the knee, may be associated with knee pain development and contribute to a high-risk profile of OA susceptible persons. Therefore, this study aims to identify prognostic determinants for incident knee pain after two years in women without knee pain at baseline.

METHODS

Study population

We used baseline and intermediate follow-up data from the third cohort of the Rotterdam Study (RS.III.1 cohort), an open population-based prospective cohort study on

the determinants and prognosis of chronic diseases in elderly. This third cohort started in 2006 and includes 3,932 subjects (response rate 65.2%) aged ≥45 years [11]. The Rotterdam Study was approved by the Medical Ethics Committee of the Erasmus University Medical Center.

We invited all women aged up to 60 years from the RS.III.1 cohort to participate in a sub-study on knee OA. Extensive baseline measurements (conducted between August 2006 and June 2009) included X-ray and MRI of the knees, a knee-specific questionnaire, an extensive home interview, and physical examination of the knees performed by two trained researchers. Two years post baseline, a knee-specific questionnaire was again sent to all participants to evaluate the current state of potential knee complaints.

Excluded from participation were women with contra-indications for MRI, those with insufficient mastery of the Dutch language, and those included in the Rotterdam Study after June 2009.

Imaging data

X-ray assessment

Weight-bearing anterior-posterior X-rays of the knees of all women from the RS.III.1 cohort were made. Radiographic (r)OA of the tibiofemoral (TF) joint was assessed using the Kellgren and Lawrence (KL) grading scale. Knee OA was defined as having a KL grade ≥2 in one or both knee joints, or a total knee replacement [12]. All RS.III baseline radiographs were scored independently by two trained researchers (kappa=0.62) [13], who were blinded to all clinical and demographic data.

MRI assessment

The MRI protocol as was performed in this cohort was described extensively in Chapter 4. In short: we performed a multi-sequence MRI protocol in the sagittal view, on a 1.5-T MRI scanner, using an 8-channel cardiac coil. The protocol consisted of a fast spin echo (FSE) proton density and T2 weighted sequence, a sagittal FSE T2 weighted sequence with fat suppression, a spoiled gradient echo sequence with fat suppression and a fast imaging employing steady state acquisition (FIESTA) sequence. This FIESTA sequence could be reformatted into the coronal and axial planes to enable 3D visualization of the knee. Total scanning time for two knees was 27 minutes.

MRI scans were assessed using the MR Knee Osteoarthritis Scoring System (KOSS) [14]. The scans were scored independently by one trained researcher and one radiologist. The interobserver reliability for TF-joint cartilage defects, cysts (both also for patellofemoral (PF-)joint), osteophytes, bone marrow edema-like lesions (BMLs), meniscal degeneration and joint effusion was moderate to good (range 0.40-0.72); however, for osteophytes and BMLs of the PF-joint the interobserver reliability was low (0.24 and 0.33, respectively).

Knee pain assessment

Knee pain was defined as present if a woman answered positive on either or both of the following questions: 'Do you have pain in or around your knee at this moment?' and/or 'Have you had pain in or around your knee in the past 12 months?'. For both questions answering possibilities were: 1) no, 2) yes, only in the right knee, 3) yes, only in the left knee, 4) yes, in both knees. These same questions were asked both at baseline and in the intermediate questionnaire two years after baseline.

Incident knee pain was defined as reporting knee pain in the intermediate questionnaire, but not at baseline. This was assessed separately per knee side. Therefore, a woman could have incident knee pain at follow-up in one knee, whereas she had knee pain at baseline in the other knee.

Tested potential predictors

General risk factors

The determinants analyzed in this group were: age, BMI, postmenopausal status, self-reported knee trauma in the past, and pain in the other knee at baseline (compared with pain at follow-up).

Age (years) at time of interview and body mass index (BMI = kg/m^2) were assessed at the research center. Postmenopausal status was defined as absence of menstruation for 12 months or more; women whose menses had stopped after an operation (i.e. hysterectomy) were excluded. Past knee trauma was considered present when answering positively the question: 'Have you ever had knee trauma with swelling or for which you consulted a physician?'. Knee alignment was measured as the medial angle formed by the femur and tibia [15,16] and assessed on digital X-rays.

Degenerative features on MRI

The determinants analyzed in this group were: cartilage defects, meniscus degeneration, presence of osteophytes, BMLs and joint effusion. Presence of degenerative signs on the meniscus was dichotomized into a KOSS score 0/1 vs. 2/3/4/5, with the 0/1 group (absent/minimal) as reference. All other MRI outcomes were dichotomized into score 0 (absent = reference) vs. 1 (any present).

Cartilage defects (diffuse and/or focal combined) were scored per compartment (medial or lateral TF compartment or patella). Meniscus degeneration was scored for the meniscal body, anterior horn and posterior horn, and combined into one score. The medial and lateral TF compartments were assessed separately. We considered horizontal tears as degenerative lesions [17]. In case a horizontal tear was present without degenerative signs in the meniscal body, anterior horn or posterior horn, the outcome measure of

meniscus degeneration was scored as present in the applicable compartment. Location of BMLs and osteophytes in the medial and/or lateral compartment in the femur and/or tibia was recorded. Joint effusion was considered present if any effusion (small, moderate or massive) was visible on MRI. No effusion present was considered the reference.

Physical examination data

In this group the determinants were: tenderness on palpation of the TF-joint space and patella, crepitus on active movement, and Heberden's nodes:

The patella (including the lateral/medial borders, quadriceps tendon and/or patellar ligament) and the TF-joint space were assessed for tenderness on palpation (possible answers: yes/no). Crepitus of the knees on active movement (on flexion and/or extension) was assessed by asking the participant to stand on one knee, actively bend that knee, then straighten up again. Meanwhile the researcher placed one hand on the patella to feel possible vibrations whilst listening for a possible grinding noise. Heberden nodes were assessed by palpation of the distal interphalangeal joints and scored as present or absent.

Statistical analysis

MRI KOSS data were assessed using a binary logistic generalized estimating equation (GEE) model from the generalized linear models for repeated measure analysis. The dependent variable was 'new pain at follow-up' (outcome: yes/no). The dependence between repeated measures within the same individual, here the knee side, is taken into account by GEE. Analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, USA).

We performed multivariate GEE analysis per group of determinants mentioned above (general risk factors, MRI features and physical examination data), so each determinant is adjusted for all other determinants in the applicable group. We performed two subgroup analyses: 1) in women without knee pain in both knees at baseline, and 2) in women who had knee pain in one knee at baseline. To acquire a more general view of the best pain predicting factors in our population, we finally analyzed all determinants with $p<0.1$ in the three separate determinant group analyses, in one overall model for the total population and per subgroup. Determinants were considered statistically significant if $p<0.05$ in the final overall analysis. Finally, we assessed the attributable risks (AR) of the significant determinants. The AR, also called the excess risk, is the 'incidence of a disease in the exposed (subject) that would be eliminated if exposure were eliminated' [18]. All analyses were also adjusted for knee pain at baseline in the other knee, the KL score in the applicable TF joint, age, and BMI. In the analysis, only cases with complete data for all included determinants were assessed.

RESULTS

Study population

Of 1116 invited women from the RS.III.1 cohort, 891 women (79.8%) were willing to participate in this sub-study. Of these women 754 reported no pain in at least one knee at baseline and were subsequently eligible for the present study.

At baseline, 208 eligible women reported knee pain in one knee and 465 women reported not having any knee pain. Finally, 673 women (1346 knees) were included in the analysis (Fig. 7.1). Mean age of the included subjects was 53.9 (SD 3.77) years and BMI 27.0 (SD 4.58). The 137 women excluded because of bilateral knee pain at baseline were comparable in age and BMI to those who were included.

In the group of women with unilateral knee pain at baseline, 16.6% had incident knee pain in the pain-free knee at baseline. In the women who were pain free at baseline the incidence was 23.1%. The total risk of reporting any knee pain at the moment of questioning and/or in the past 12 months at follow-up, in the women with one painful knee at baseline was 65.1%. Table 7.1 shows the baseline characteristics for all analysed groups.

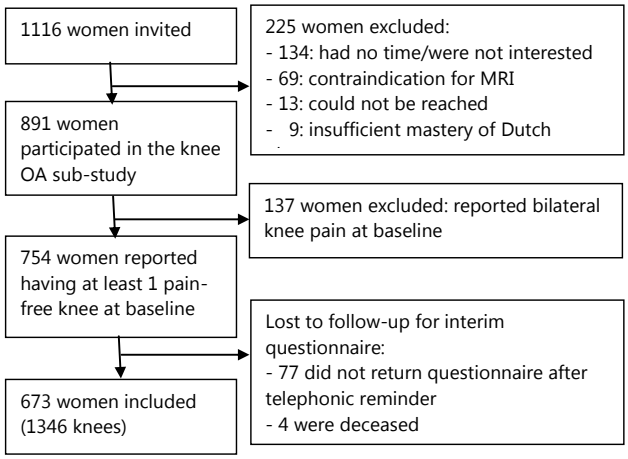

Figure 7.1: Flow chart showing inclusion of the study participants.

Results GEE analysis per determinant group

Table 7.2 shows all determinants with a p-value <0.1 in the analysis. In the total group of all women the following determinants had a p-value<0.1: past knee trauma, pain in the other knee, tenderness on palpation of the TF-joint space and BMI. In the subgroup

Table 7.1: Characteristics of all women without knee pain in at least one knee at baseline, and the subgroups divided according to baseline knee pain status.

	All included women		Women without pain in both knees		Women with pain in one knee	
	n knees	Mean (SD) / % present	n knees	Mean (SD) / % present	n knees	Mean (SD) / % present
New pain at follow-up, in pain-free knee at baseline	1346	21.1%	930	23.1%	416	16.6%
GENERAL RISK FACTORS						
Age (years)	1346	53.9 (SD 3.77)	930	53.8 (SD 3.77)	416	54.0 (SD 3.78)
BMI (kg/m^2)	1342	27.0 (SD 4.58)	926	26.7 (SD 4.31)	416	27.8 (SD 5.07)
Past knee trauma	1032	24.0%	710	19.4%	322	34.2%
Post-menopausal woman	1336	67.1%	922	65.1%	414	71.5%
Pain in other knee at baseline	1346	15.5%	930	0.0%	416	50.0%
X-RAY DATA						
Knee alignment (degrees)	1326	181.2 (SD 2.85)	916	181.2 (SD 2.80)	410	181.1 (SD 2.95)
KL score 0	1344	81.2%	929	84.3%	415	74.2%
1	1344	15.1%	929	13.8%	415	18.1%
2	1344	3.3%	929	1.6%	415	7.0 %
3	1344	0.2%	919	0.2%	415	0.2%
4 / 5[1]	1344	0.2%	929	0.1%[2]	415	0.5%
MRI FEATURES – TIBIOFEMORAL						
Meniscus degeneration medial	1338	12.6%	924	10.4%	414	17.4%
Meniscus degeneration lateral	1337	6.4%	923	4.6%	414	10.6%
Cartilage defects medial	1337	13.4%	924	11.0%	413	18.6%
Cartilage defects lateral	1337	4.3%	924	3.0%	413	7.3%
Osteophytes	1336	34.1%	923	30.1%	413	42.9%
Joint effusion (0 vs.any)	1330	39.1%	920	37.7%	410	42.2%
BMLs	1335	20.2%	924	17.7%	411	25.8%
MRI FEATURES – PATELLOFEMORAL						
Cartilage defects	1331	21.4%	920	18.8%	411	27.3%
Osteophytes	1332	32.3%	919	28.7%	413	40.2%
BMLs	1324	20.4%	924	17.5%	412	27.2%
PHYSICAL EXAMINATION DATA						
Crepitus on active movement	1318	43.2%	909	40.6%	409	49.1%
Tender on palpation TFjs[3]	1342	9.0%	929	5.0%	413	18.2%
Tender on palpation patella	1346	4.8%	930	2.5 %	416	10.3%
Heberden nodes	1340	27.6%	924	26.2%	416	30.8%

BMLs = Bone marrow edema-like lesions, KL= Kellgren & Lawrence grade, 1) 3x KL=5 in total population, 2) in the analysis, subjects with KL=5 in other joint at baseline were excluded 3) TFjs=Tibiofemoral joint space

Table 7.2: analysis GEE per risk factor group (MRI, general risk factors and physical examination).

	All women		Women without pain in both knees		Women with pain in one knee[1]	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
ANALYSIS GENERAL RISK FACTORS		n=1010		N=693		N=317
Knee trauma in the past	1.59	(1.07 – 2.36)	1.83	(1.08 – 3.09)	1.75	(1.06 – 2.89)
Postmenopausal status	-	-	-	-	1.99	(0.98 – 4.07)
Pain in other knee	2.68	(1.82 – 3.95)	-	-	-	-
BMI (kg/m^2)	-	-	-	-	1.06	(1.02 – 1.11)
ANALYSIS MRI FEATURES		N=1311		N=906		N=405
Degeneration lateral meniscus	-	-	2.09	(1.05 – 4.19)	-	-
Joint effusion	-	-	-	-	0.59	(0.34 – 1.03)
Pain in other knee at baseline	2.00	(1.40 – 2.83)	-	-	-	-
BMI (kg/m^2)	1.04	(1.00 – 1.07)	-	-	1.08	(1.03 – 1.12)
ANALYSIS PHYSICAL EXAMINATION DATA		n=1302		N=897		N=405
Crepitus on active movement	-	-	-	-	1.82	(1.07 – 3.10)
Tenderness on palpation TFjs	1.67	(0.97 – 2.85)	4.27	(2.08 – 8.81)	-	-
Pain in other knee	2.01	(1.41 – 2.87)	-	-	-	-
Age (years)	-	-	-	-	-	-
BMI (kg/m^2)	1.04	(1.00 – 1.07)	-	-	1.08	(1.03 – 1.14)
FINAL MULTIVARIATE ANALYSIS		n=1023		N=701		N=309
Degeneration lateral meniscus	-	-	**2.16**	**(1.00 – 4.65)**	-	-
Joint effusion	**-**	**-**	**-**	**-**	**0.50**	**(0.27 – 0.92)**
Knee trauma in the past	**1.58**	**(1.06 – 2.36)**	**1.71**	**(1.00 – 2.92)**	**1.98**	**(1.18 – 3.33)**
Postmenopausal status	-	-	-	-	**2.33**	**(1.12 – 4.84)**
Crepitus on active movement	-	-	-	-	**2.14**	**(1.19 – 3.84)**
Tenderness on palpation TFjs	1.19	(0.67 – 2.12)	**3.22**	**(1.39 – 7.48)**	-	-
Pain in other knee	**2.71**	**(1.83 – 4.00)**	-	-	-	-
Age (years)	0.97	(0.92 – 1.02)	0.95	(0.89 – 1.02)	0.96	(0.88 – 1.04)
BMI (kg/m^2)	1.02	(0.98 – 1.06)	1.00	(0.95 – 1.06)	**1.06**	**(1.00 – 1.11)**
KL-grade	1.08	(0.78 – 1.49)	1.12	(0.67 – 1.88)	1.06	(0.68 – 1.64)

[1]All reported risks are for incident knee pain, thus for the knee without knee pain at baseline. OR = odds ratio, 95% CI = 95% confidence interval of OR, N= number of knees in the analysis, BMLs = bone marrow edema-like lesions, TFjs = tibiofemoral joint space, KL-grade = Kellgren and Lawrence grade (knees with a total knee replacement (KL=5, n=3) were excluded from analysis). All significant outcomes ($p<0.05$) are printed **Bold.** Only results from determinants with $p\leq0.1$ in the multivariate GEE analysis per risk factor group are shown in this table. In the final multivariate analysis all determinants of the three risk factor groups with $p<0.1$ are analyzed together in one overall model (at the bottom of the table).

with no pain in both knees at baseline these were: past knee trauma, lateral meniscus degeneration and tenderness on palpation. In the subgroup with unilateral knee pain at baseline the predicting factors for new pain in the other knee were: joint effusion, past knee trauma, being postmenopausal, crepitus on active movement, and BMI.

Results of the overall multivariate analysis

Table 7.2 also shows the results of the overall multivariate analysis, combining all determinants with p<0.1 in the analysis per determinant group. Determinants remaining significant (p<0.05) in this overall analysis in all women were: past knee trauma and knee pain in the other knee at baseline. In the subgroup of women pain free at baseline these were: tenderness on palpation of the TF-joint space, past knee trauma and lateral meniscus degeneration. In the subgroup of women with unilateral knee pain all tested determinants remained significant.

Attributable risk

Table 7.3 shows the attributable risks (AR) per 100. The risk factors that are easily assessable in everyday practice (thus not MRI) were combined into 1 AR.

Table 7.3: prevalences and risk calculations of risk factors

Risk factor	No. of knees with risk factor(s) present	Percent incident knee pain exposed (I_e)	No. of knees without risk factor(s) present	Percent incident knee pain unexposed (I_o)	AR per 100 cases
ALL WOMEN ($I_{T=}$ 21.1 %, N=1346 KNEES)					
Knee trauma	248	28.2%	784	17.9%	10.3
Pain in the other knee at baseline	208	33.2%	1138	18.9%	14.3
Knee trauma and pain in the other knee combined	55	50.9%	678	15.8%	35.1
WOMEN WITHOUT KNEE PAIN ($I_{T=}$ 23.1 %, N=930 KNEES)					
Tenderness on palpation TFjs	46	56.5%	883	21.3%	35.2
Knee trauma	138	30.4%	572	18.7%	11.7
Lateral meniscus degeneration	42	35.7%	881	22.5%	13.2
Trauma and tenderness on palpation combined	12	41.7%	553	17.7%	24.0
WOMEN WITH KNEE PAIN IN ONE KNEE (I_T = 16.6 %, N=416 KNEES)					
Knee trauma	110	25.5%	212	15.6%	9.9
Postmenopausal status	296	18.9%	118	10.2%	8.7
Crepitus on active movement	201	21.4%	208	12.0%	9.4
Trauma, being postmenopausal, crepitus combined	40	35.0%	31	3.2 %	31.8

I_t: % incident knee pain in total population with current exposure status = prior probability of incident knee pain, I_e= post test probability, I_o= pre test probability, AR = attributable risk (I_o - I_e) is the incidence of a disease (here new knee pain) in the exposed group that would be eliminated if exposure were eliminated, also called excess risk.

DISCUSSION

This study explored prognostic determinants for incident knee pain reported after two years in women without knee pain at baseline. In the total group of women without pain in at least one knee at baseline, the best predicting risk factors were past knee trauma and knee pain in the other knee at baseline. In subgroup analyses of women divided according to their baseline knee pain status, in pain-free women tenderness on palpation of the TF-joint space, past knee trauma, and degeneration of the lateral meniscus were the best predictors. In women with unilateral knee pain at baseline these were: past knee trauma, postmenopausal status, crepitus on active movement, joint effusion and BMI.

Pain and disability are clinically the most relevant factors in knee OA. Pain is related to activity in the early stages, becomes more constant as the disease progresses, whereas the pain level fluctuates over time [19,20]. Knee trauma and BMI are known risk factors for OA development [19] and a degenerative meniscal lesion might suggest early knee OA in a population of middle-aged or older patients [21]; we also found these factors to be associated with incident knee pain. Stratified analysis for BMI (BMI <27.0 or BMI ≥27.0) gave similar results (data not shown). We chose this cut-off since a high BMI of ≥27 has been found to be clearly associated with an increased risk of knee rOA incidence [22]. In all three groups the incidence of new knee pain was higher in those with higher BMI. Even though BMI was a significant predictor in each studied group, in the final analysis it remained significant only in the group with unilateral knee pain at baseline. In this latter group the incidence of knee pain (11.7%) in those with normal/low BMI (<27) was much lower compared to those with high BMI (21.4%). In the other two groups the prevalence of new knee pain was 18.1% and 25.0% in all women, respectively, and 20.6% and 27.0% in those totally pain free at baseline, respectively.

In this relatively healthy population, most MRI features were not predictive of incident knee pain after two years. Cicuttini et al. found that TF-osteophytes on X-ray were associated with knee pain reported in the past year [23]. We scored osteophytes on MRI, what made it possible to include even smaller osteophytes. In an additional analysis of all women included in this study, disregarding baseline knee pain status, analyzing the MRI features with the outcome 'new pain in past 12 months' showed osteophytes to be significantly associated with incident knee pain (OR=1.36, $p<0.05$). An important difference between the present study and that of Cicuttini et al. was the definition used for the of presence of pain. They considered pain present if the subject reported having had pain in the past year for 15 consecutive days or more, thus analyzing severe complaints. In contrast, we only asked 'Have you had pain in the past 12 months', without specifying the duration or severity. Nevertheless, the outcome was similar.

Pain in the other knee was strongly associated with incident knee pain two years later. It is likely that those already experiencing pain have a lower pain threshold and are more sensitive for pain in other areas due to central sensitization [24]. In support of this, Kosek and Ordeberg found that, compared to controls, patients with painful hip OA had lower pain thresholds for pressure stimulation in both the OA affected side and the unaffected contralateral hip, and that after hip replacement surgery pain thresholds normalized [25]. In our group with unilateral knee pain at baseline, being postmenopausal was associated with incident knee pain in the other knee. The relationship between sex hormones and pain perception is not yet fully understood. During the menopausal transitional period, joint aches and stiffness are common and increase in prevalence; however, these complaints are not necessarily related to OA [26]. Pain perception in premenopausal women fluctuates, with an increase in perceived pain in the low estradiol/progesterone phase of the menstrual cycle [27]. Low estrogen levels, such as found in postmenopausal women, are associated with lower levels of catechol-O-methyltransferase (COMT) which, in turn, are also associated with feeling 'downhearted' through its role in dopamine regulation [28]. In women with hip OA the low activity-allele of COMT (158Met) was reported to be associated with increased hip pain [29]. In knee OA this association is not yet established, but deserves further study.

In 2010 the Eular Taskforce published ten key recommendations for the diagnosis of knee OA, and crepitus of the knee was one of the three clinical signs on examination [30]. In our overall analysis, crepitus on active movement was significantly predictive of incident knee pain in women with knee pain in the other knee at baseline. This finding indicates that crepitus may be associated with very early stages of OA, as well as with more advanced disease.

This study has some limitations. First, we were unable to study causality for radiological OA development because our follow-up data comprised questionnaire data and not X-ray or MRI data. Therefore, it is unknown whether the incident pain is concurrent with structural changes of the joint itself. Also, we do not know the duration of the pain and whether it fluctuates in intensity. Follow-up measurements will start in 2012, enabling to study the associations with radiological OA. Second, in testing associations there is always risk of chance findings (type I error); therefore, results need to be repeated in other populations to confirm their validity. Third, we found that joint effusion (on MRI analysis) was protective in women with knee pain in one knee at baseline. Selecting women without baseline knee pain may have caused selection bias, i.e. although effusion was present pain was absent, indicating that these women may already have less chance of knee pain in that particular knee. In the overall analysis, joint effusion remained significant. Fourth, because 'past knee trauma' was self-reported it is unknown whether actual damage to any joint tissues had occurred. Therefore we did not perform subgroup analysis for subjects with and without past knee trauma. Fifth, the experience

and development of pain is multifactorial, and many types of pain exist. Psychological factors are associated with pain experience [31] as are genetic variances like COMT [29], neither of which were analysed in the present study. However, these factors may contribute to pain development and may be important in pain prediction and development of a high-risk profile for early identification of OA.

To summarize, we found that 'pain in the other knee' and 'past knee trauma' were the best predictors for incident knee pain reported after two years. In addition, different predicting factors were found in women with pain in the other knee and in those without pain, at baseline.

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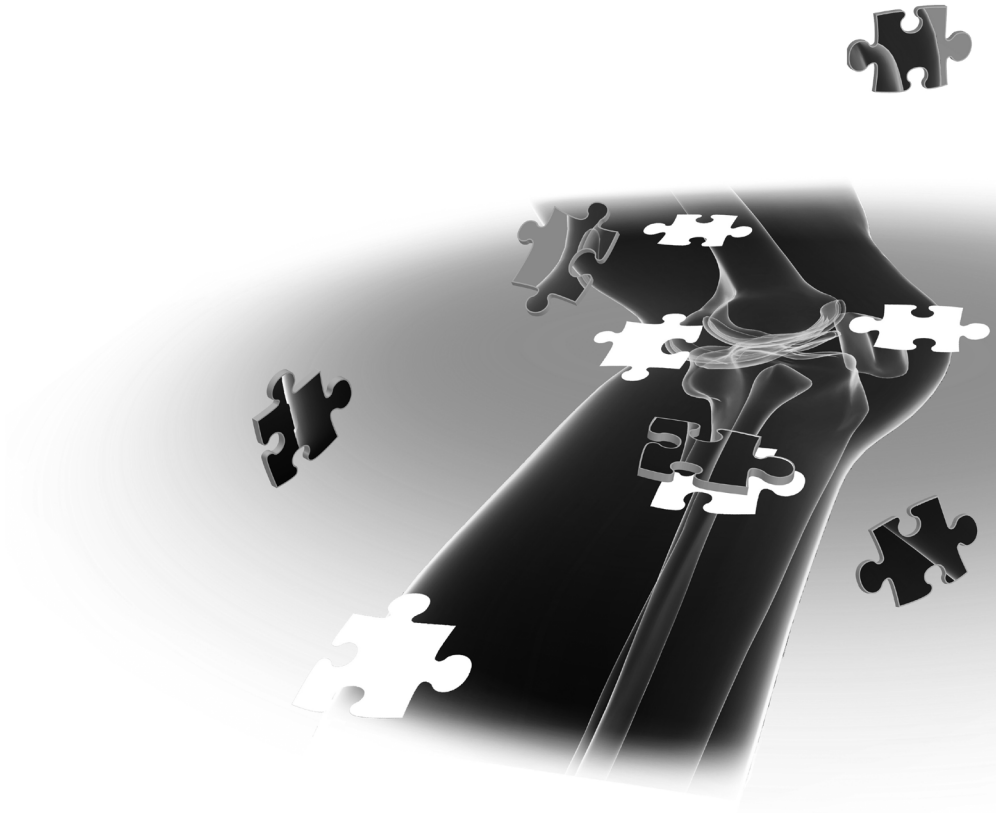
Chapter 8

General discussion



In this thesis we aimed to gain insight into the impact of female gender on OA and its relation with overweight, in order to improve the possibility to identify people at high risk of OA development.

The previous chapters described in detail the findings of each study, as well as the limitations of these studies. This chapter summarizes the main findings from this thesis, discusses the results in relation to current scientific knowledge, and presents implications for daily practice and for future research.

FEMALE HORMONAL ASPECTS AND OSTEOARTHRITIS

Although the simultaneous occurrence of the menopause and OA in women suggests a role for female hormones, the underlying mechanisms for this have not yet been elucidated. Reviewing the associations between OA and exogenous hormone use (**Chapter 2**), and OA and other female hormonal aspects (**Chapter 3**), showed that the assumed associations are not as clear as expected.

In these two systematic reviews, we included a total of 25 studies reporting on the incidence and prevalence of associations between OA and female hormonal aspects. We found limited evidence for a protective effect of 1) unopposed estrogen use for incident total joint replacement (hip or knee), 2) ever breastfeeding for carpometacarpal rOA, and 3) a protective trend for incident rOA of the knee. We also found limited evidence for an increased risk of parity for carpometacarpal and distal interphalangeal rOA, and of low estradiol serum levels in the early follicular phase of the menstrual cycle for incident knee rOA. Most evidence we found was conflicting, or was evidence for 'no association'. It is possible that the relationships with OA are too complex, or other aspects (not yet determined) play a role in the increased incidence of OA in women aged 50 years and over.

Osteoarthritis and other rheumatic diseases have been associated with an increase in the prevalence of cardiovascular diseases (CVDs) in both men and women [1]. As for OA, the prevalence of CVD increases in women with climacteric onset, whereas before that time women have a reduced risk compared to men. Another similarity is that associations between CVD and female hormonal aspects are not yet fully elucidated. Young premenopausal women are less likely to have CVD than their postmenopausal peers. Although this is thought to be due to the diminishing levels of estrogen as a result of the menopause, postmenopausal women do not benefit from hormone replacement therapy (HRT) [2]. Conflicting relations have been observed when studying associations between HRT and CVD. Two large observational studies found lower rates of CVD and cardiac death in postmenopausal women who used HRT compared to those who did not use HRT [3, 4], whereas two randomized placebo-controlled prevention trials could

not confirm a cardio-protective effect of HRT [5, 6]. An explanation for this discrepancy between the results from a clinical trial and observational studies is still lacking.

One important difference is that in the observational studies HRT is mostly prescribed for menopausal complaints, while in the clinical trials women with severe menopausal complaints are excluded or are outnumbered [7]. Van der Schouw et al. hypothesised that, since HRT is mainly prescribed for menopausal complaints, the presence of climacteric complaints are a marker for susceptibility to the beneficial effects of HRT [8]. Subsequently, from the same research group, Gast et al. observed that the risk profile for women with transitional vasomotor complaints (e.g. night sweats and hot flushes) is less favorable than that for women who do not experience these complaints [7]. Also, women who use HRT may differ from women who do not, since women with menopausal complaints may visit their physician more often and might subsequently be more likely to receive HRT [7].

This difference between HRT users and non-users may also be applicable in OA studies, and might partly explain why conflicting findings emerge. In our systematic review on OA and HRT we observed a similar discrepancy, though not as distinct as in the previous example. The results from observational studies were conflicting or no association was found, and we could include only one randomized controlled trial which studied hip and knee replacement [9]. Nine years prior to our systematic reviews, Wluka et al. also reviewed the association between HRT and OA; they concluded that in postmenopausal women, radiological disease progression was reduced and incident disease may be prevented by HRT use, but that hard evidence from trials was lacking [10]. New findings during the nine years since our reviews, show that evidence on the association of HRT and OA remains conflicting. Studying the influence of menopausal vasomotor symptoms may shed new light on the associations between OA and female hormones.

Early degenerative signs and the menopause

In our systematic reviews we did not include any studies assessing OA using MRI, simply because we did not find any relevant studies using MRI that complied with our inclusion criteria. MRI can visualize degeneration of individual tissues in an earlier stage than radiography, and is suggested to be the best imaging technique currently available for detecting early osteoarthritic changes [11-13].

We studied the cross-sectional associations between menopausal aspects and early degenerative signs of knee tissues on MRI in our OA sub-cohort of the Rotterdam Study (**Chapter 4**). Our aim was to establish where degeneration of joint tissues can first be visualized in relation to menopausal aspects. We found indications that in middle-aged women (mainly in those with overweight) early signs of degeneration of knee tissue can first be visualized in the bone (bone marrow edema-like lesions, and osteophytes), but

not in cartilage. This is in agreement with Sniekers et al. [14] who reported that estrogen-receptor knockout mice show an increase in the number and/or size of osteophytes and thinning of the lateral subchondral plate, whilst this was not the case in wild type mice; no differences in cartilage damage was observed between both types of mice [14].

Although cartilage degeneration was long considered the main feature in OA pathology, it is now known that OA affects all joint tissues. However, it is not known which tissue is in fact affected first. Even though MRI is more sensitive than radiography in the visualization of cartilage degeneration, good visualization remains a challenge considering that cartilage is only 1.3-2.5 mm thick in healthy humans [15-17], and even less in OA patients [18]. As discussed in **Chapter 4**, it is possible that alterations in cartilage are actually present, but we are not (yet) able to visualize them on MRI. Studying cartilage on a biochemical level, using advanced quantitative MRI techniques (like dGEMRIC, $T_{1\rho}$ or T2 relaxation time quantification) might provide more information on the degenerative process. Zhao et al. found a local spatial correlation between the presence of bone marrow lesions and advanced cartilage degeneration using $T_{1\rho}$ [19]. In addition, in studying cartilage using fluorescent microscopic representative images, Rolauff et al. found distinct spatial and angular patterns between neighboring chondrocytes in animal and human cadavers [20]; these alterations in cartilage were not macroscopically visible at that point. Even though these advanced techniques are not generally used in daily practice and might not be practical for use in a high-risk profile, they can provide new knowledge on the mechanisms of OA.

OVERWEIGHT

In the menopausal transitional period the production of female hormones by the ovaries diminishes dramatically, resulting in the end of the fertile period. This transition usually occurs over a period of several years and is a normal part of natural aging. As stated above, the prevalence of OA and CVD increases with climacteric onset, whereas before that time women have reduced risk compared to men in both diseases. Similar to OA, CVD is associated with obesity [21] and it is suggested that a pathological alteration of fat mass (such as in overweight and obese persons) could be the link between CVD and rheumatic diseases [1].

Around the time of menopause the distribution of body fat changes and women get more body fat overall, but specifically, more abdominal and visceral fat [22, 23]. Intra-abdominal fat tissue is functionally and metabolically different from subcutaneous tissue [24, 25].

High body weight and high body fat levels can influence the development of OA in various ways, not only locally by higher biomechanical or differential loading of the

knees [26], but also systemically by secretion of inflammatory mediators and estrogens by adipose tissue [27, 28]. Being overweight, and thus having a lot of adipose tissue, has been proposed to cause a state of permanent low-grade, sub-clinical inflammation of this adipose tissue [25]. Especially visceral fat seems to play an important role in this process.

It is not yet fully elucidated what role sex hormones have in the change in body fat distribution in perimenopausal women [29]. When estrogen levels become sufficiently low, it is generally assumed that accumulation of visceral fat occurs [30]. It is also suggested that estrogens limit fat storage in visceral adipocytes in premenopausal women [24], due to regulation of lipolysis and lipogenesis. It is possible that changes in body fat distribution combined with changes in hormonal levels play a role in the increased OA incidence in menopausal women.

Interactions between BMI and other OA risk factors

Being overweight is the most important modifiable risk factor for OA, especially in those who also have other risk factors [31]. Moreover, risk factors can interact with each other, making it even more challenging to identify OA at an early stage and to develop preventive strategies. Before our study, very few studies had investigated interactions between BMI and other risk factors and, those that did, mostly included populations with established knee OA.

However, identifying persons at high risk requires a study population that is actually 'at risk' for OA development. Therefore, in **Chapter 5** we studied interactions between the known risk factor 'body mass index' (BMI=kg/m^2) and other known risk factors. Reijman et al. found a high BMI ≥27 to be clearly associated with incident knee rOA [32]. Therefore, in a general population we investigated the associations of known risk factors and knee symptoms with rOA to see whether they differ between women with a high BMI (≥27) and with a low/normal BMI (<27).

In this open study population we found that risk factors for, and symptoms of knee rOA differ in magnitude between those with low/normal BMI and with high BMI, irrespective of OA severity. Although exploring interactions is difficult because a high level of statistical power is needed to reveal significant results, we found a significant interaction between BMI and knee morning stiffness lasting <30 minutes (OR=3.19, $p<0.05$). Also, being post-menopausal and tenderness on palpation of the knee joint space showed a trend for interaction.

SYMPTOMS

Pain perception, similar to OA, is a multifactorial phenomenon. There are different types of pain which can generally be distinguished according to the pathogenesis [33]. Normal tissue sends out physiological nociceptive pain signals as a warning when it is actually damaged or at high risk of becoming damaged. This is absolutely necessary for survival because it triggers acute pain-avoiding behavior. Pathophysiological pain is triggered by inflammation or injury to the joint. In OA pain is considered to be mainly pathophysiological nociceptive [33], although other mechanisms have also been reported [34].

Sensitivity to pain is highly variable among humans [35] and the development of chronic pain is partly dependent on genetic variance. Therefore, people who develop chronic pain might have an unfavorable genetic make up [36]. Catechol-0-methyltransferase (COMT) is an enzyme that degrades neurotransmitters like dopamine [37]. Dopamine plays a role in the general feeling of well-being and in experiencing pleasure and happiness. The secretion of COMT is influenced by estrogen levels; low estrogen levels, such as found in post-menopausal women, cause lower levels of COMT [38]. Wise et al. found that psychological factors fluctuate with experiencing pain in knee OA patients [39], and in animal studies the inhibition of COMT secretion was shown to increase pain sensitivity [40, 41]. Low levels of COMT are also associated with anxiety phenotypes in women [38].

Van Meurs et al. examined whether individuals with the Val158Met variant of COMT (a well-known functional polymorphism) experienced more hip pain in relation with hip OA [36]. They found that women carrying the 158Met allele of COMT, compared to carriers of the ValVal genotype, were almost 3-fold more likely to experience hip pain, while women with the 158Val allele were 4.9-fold more likely to experience hip pain. These associations were not observed in men, but may also have been due to statistical power problems. For the pain due to knee OA an association with this polymorphism of COMT is not yet established [36].

The relationship between sex hormones and pain perception is not yet fully understood. During the menopausal transitional period, joint aches and stiffness are common and increase in prevalence, but these complaints are not necessarily related to OA [42]. Pain perception in premenopausal women fluctuates, with an increase in perceived pain in the low-estradiol/progesterone phase of the menstrual cycle [43]. This is in line with the decline of COMT levels with the diminishing of estrogen levels in postmenopausal women, making these women more susceptible to experience pain. However, not all postmenopausal women with knee rOA experience knee pain.

Early degenerative signs and symptoms

In **Chapter 4** we found that bone marrow lesions (BMLs) were associated with being postmenopausal in overweight women. Changes in the size of BMLs were associated with changes in knee pain in those with and without established knee rOA [44, 45], and another study reported that BMLs were associated with the risk of knee joint replacement in persons with knee rOA [46]. The relation between BMLs and the presence of pain was systematically reviewed in 2011, and the overall evidence was moderate to strong [47]**.** In our study, in disease-free women BMLs were significantly associated with being postmenopausal and increasing years since menopause. These findings were adjusted for current hormone use, of which the prevalence was low. Estrogen use has been found to be protective for BMLs [48].

The histology of BMLs is heterogeneous, and the presence of BMLs in other joint diseases (such as rheumatoid arthritis) may have a different pathological basis [44]. On MRI, BMLs are defined by the Knee Osteoarthritis Scoring System (KOSS) [49] and the Whole-Organ Magnetic Resonance Imaging Score (WORMS) [50] as ill-defined areas of increased signal intensity to the subchondral bone. In vivo BMLs are found to represent multiple histological abnormalities, including bone marrow fibrosis, bone marrow necrosis, bone marrow edema and trabecular abnormalities [51], which are not specifically characteristic for OA. The size of MRI-detected BMLs in the knees is not static [52] and in persons in an early stage of OA, fluctuation in knee pain may be due to changes in BMLs [44]. It is possible that in advanced disease, pathology of other structures contribute to knee pain.

Predicting radiographic disease and knee pain

Not everyone with knee rOA has knee complaints and vice versa. In the RS.I.1 cohort, Odding et al. found that in subjects with rOA in the knees, knee pain was present in 25.4% of the men and 34.2% of the women [53]. In subjects with knee pain, 32.9% of the men had knee rOA as did 44.7% of the women [53]. Also in other population studies, large variations were seen [54, 55]. This discrepancy between pain experience and prevalence of knee rOA is well reported [54, 56, 57].

Currently, it is impossible to identify which patients with knee complaints presenting to their physician will, or will not, develop rOA pathology in the knee at a later stage. Knowledge on which risk factors predict rOA development in the future will help to formulate a 'high-risk profile' which can be used in daily practice. We studied possible predictors for developing OA pathology on X-ray in persons with knee complaints, but with no rOA at baseline in the painful knee. This study (presented in **Chapter 6**) revealed that the best predictors of knee rOA development are female gender, having

joint complaints in joints other than the knee, and having a Kellgren & Lawrence grade 1 in the painful joint.

It would be even better to prevent people from becoming symptomatic, in other words to prevent the development of (OA-related) knee pain. Pain is the most important clinical symptom of OA and in middle-aged people knee pain is most often attributed to (early) OA [58]. Predicting who will develop knee pain in a later stage can therefore be considered an important step in the process of identifying persons at high risk of OA. In **Chapter 7** we took another step back in the process of early identification of OA. We earlier found that women with knee pain are at higher risk of developing rOA in the future. Therefore, we studied predicting factors for knee pain development after two years in women without knee pain at baseline. When we analyzed all women together (irrespective of the pain status of the other knee at baseline), we found that having knee pain in the other knee, and having had knee trauma in the past, were the best predictors of OA. In a subgroup analysis of women without knee pain in either knee at baseline, the best predictors of knee pain were 1) tenderness on palpation of the tibiofemoral joint space, 2) knee trauma in the past, and 3) lateral meniscus degeneration. In women with pain in one knee at baseline, the best predictors for new pain in the other knee were 1) knee trauma in the past, 2) crepitus on active movement, 3) being postmenopausal, and 4) high BMI.

BMI was a significant predictor in all studied groups. However, in the final analysis which included all predictors with a p-value <0.1 in the separate determinant groups (see **Chapter 7**), BMI remained significant only in the group with unilateral knee pain at baseline. In this latter group the incidence of knee pain in those with normal/low BMI (<27) was half that compared to those with high BMI. In the other groups this difference was somewhat smaller. This may indicate that in women with unilateral knee pain, losing weight is even more important for prevention of new knee pain than in women who do not have knee pain. In obese persons, symptom relief in knee OA was found to be more closely associated with decreasing body fat and increasing physical activity, than decreasing body weight [59]. Therefore, the advice to start exercising and adopt a healthy diet might be most valuable for the group of women who already have knee pain in one knee.

It should be noted that, at the moment we assessed knee pain, this pain had been present for only a short period of time; also, the severity of this pain was not evaluated. The incident knee pain that we found does not necessarily become chronic or disabling. A prospective study to establish which persons with knee pain develop chronic knee pain may provide new insight into the etiology of (chronic) pain development. This is currently being investigated in the CHECK cohort in the Netherlands, which includes subjects with knee or hip OA and related symptoms due to suspected early OA [60].

However, a problem is that once knee pain is established, we do not know whether it is already too late to reverse or stop the process.

STUDY LIMITATIONS AND FUTURE CHANCES

Set-up of the study

The original plan for this study was to collect and report on both the baseline data and the follow-up data of 400 overweight women without rOA but with knee complaints. We wanted to study the incidence of knee OA, with the aim to compose a high-risk profile to be used in daily clinical practice for early identification of OA, or to identify women at high risk of developing OA. The overall aim of the original research proposal was formulated as 'to identify determinants and early predictive signs of clinically manifest osteoarthritis of the knee in a high-risk group of overweight middle-aged women', with focus on early identification with MRI imaging, studied by one PhD student, and on early identification with DEXA scans, markers and clinical signs by another student. This thesis is the result of the latter focus.

By embedding this study in the RS.III.1 cohort of the larger Rotterdam Study, longer follow-up was guaranteed together with the possibility of more valuable data collection in the future. Unfortunately, this created logistic limitations which made it impossible to perform both the baseline and the follow-up analyses within the time span allotted for this research project. Therefore, we decided to invite all women within the RS.III.1 cohort, irrespective of rOA status and knee pain status, thereby making it an open-population prospective cohort with as many women in the baseline measurement as possible. This was made possible by an additional grant from the MUsculoskeletal Science Center (MUSC) of the Erasmus University Medical Center, of which our department of General Practice is a member. In total 891 women were included, of which 397 had a BMI ≥27 kg/m^2 at the moment of baseline measurements. All these women underwent an MRI of the knees, filled-in a knee-specific questionnaire, and had a physical examination of both knees. This is a large and valuable cohort, but with one important limitation for this thesis: it was impossible to study the incidence of rOA or causality in OA development because only baseline data collected at the research center were available.

In the future, when follow-up data become available, these aspects will be studied by new PhD students. Fortunately, we were able to distribute and process an intermediate questionnaire which will allow to study predictors for pain development. In 2012 the first follow-up will start at the research center. When these analyses are completed the answers to our original study questions will become available. Also, when follow-up is

completed, data from the DEXA scans, and serum and urine samples, will also be analyzed. All this will certainly shed light on the sequence of pathological findings.

Why is it so difficult to study the role of female hormones in OA?

In reviewing the associations between OA and female hormonal aspects and HRT, as described in **Chapters 2** and **3**, it was not possible to pool the results due to heterogeneity of the included studies. Heterogeneity between the hormones used and the outcome measurements was too large to justify pooling. Therefore, we chose to perform a best-evidence synthesis. Also, because female hormonal aspects are intertwined and (in most studies) not all known relevant factors are reported, it impossible to adjust for them in the analysis.

Another problem when studying the relation between OA and estrogen is the fact that estrogen levels in premenopausal women change almost daily. In addition, one has to take into account the circulating levels of estradiol, and the contribution of estrone as a reservoir for the production of estradiol in premenopausal and postmenopausal women [61]. If one combines all these complicating factors with the production of estrogen by body fat, the role of changing body fat distribution, the influence of genes, and the associations of estrogen with separate risk factors and early signs (such as BMLs [62]), it becomes very clear that the entire pathway is highly complex and much remains to be discovered.

SUGGESTIONS FOR FUTURE RESEARCH

This study is one of the first steps in the process of developing a high-risk profile for persons at high risk of developing OA; in other words, just one piece of a complex puzzle. It is clear that many more steps need to be taken before we can actually identify people in the earliest stages of the disease and start trials for potential disease-modifying or disease-preventing intervention studies. Prevention entails intervening in people's lives, at a stage in which they have no complaints, for a (suspected) disease that they may or may not develop in the (distant) future. For these reasons, it may be difficult to motivate people to implement structural lifestyle changes. However, in a preventive trial, currently conducted at our General Practice department (the PROOF study), it was shown that in overweight women who suffered of knee OA and hand OA, adherence of chondroprotective treatment was quite satisfactory [63], showing that prevention interventions may be feasible.

Most important is that we focus on the most bothersome clinical outcomes of OA, namely pain and functional impairment. Pathology on X-ray is not a problem in itself

[64], as Liang stated: 'X-rays don't weep' [65]. On the other hand, in order to be able to compose a high-risk profile for early OA detection, we need to understand why one person does and the other does not experience pain. For this, we need knowledge on the full spectrum of OA and its causal pathways.

In this thesis all studies are based on observational epidemiological human data. Studies on genes related to OA (genome-wide associations), as well as animal studies and biomarkers, fall largely outside the scope of this thesis, but are equally important in OA research. Female hormones and their relation with OA are also of interest in these areas of science. Perhaps combining studies of all relevant scientific fields will provide further insight, not only on early development and identification of structural features of OA, but also on the complex relationships between estrogens, body fat and pain experience.

A subject not yet discussed in this thesis, but which might shed new light on this process, is the role of the androgen testosterone. Testosterone is associated with several of the items addressed in this general discussion. An increase in testosterone levels is related to an increase in abdominal and visceral fat in postmenopausal women, and also to COMT levels. The role of testosterone is of interest in OA research and warrants in-depth investigation in the future.

In our research on OA we collected many more data than were actually used for the studies in this thesis. Data on biomarkers in blood and urine, such as C-reactive protein and C-telopeptide fragments type II, vitamin D levels, and bone mineral density data from DEXA scans, have not yet been analyzed and are a valuable source of information awaiting analysis.

In the future, we hope to be able to identify people at high risk of OA development, and expect that a preventive or disease-modifying agent will be available. Then, the next challenge will be to persuade people who have no pain, but who might develop rOA in the next 20-40 years, to take the drug or apply the intervention [65]. This is not a simple task, but will certainly need to be addressed.

IMPLICATIONS FOR CLINICAL PRACTICE

Besides suggestions for future research the findings reported in this thesis also have implications for the everyday practice of a general practitioner (GP).

We found that the associations between OA and female hormonal aspects or hormone use are not as clear as expected. The simultaneous occurrence of menopause and increased OA incidence could not be explained by the evidence of associations reported in the literature. The results from the systematic reviews will be implemented in the 2011 update of the climacteric guideline from the Dutch College of General Practitioners (NHG).

In studying an early-menopausal cohort of disease-free women we found that postmenopausal women were at higher risk of having bone marrow (edema-like) lesions than premenopausal women, but we only observed this relation in overweight women. We still need to establish whether these bone marrow lesions are an early sign of future rOA.

For routine GP practice it is helpful to know that, in middle-aged overweight women consulting for knee complaints, it is more likely that knee morning stiffness is related to knee rOA than in their normal-weight peers. We found indications that this may also be the case for overweight women with knee complaints who are postmenopausal women (compared to their premenopausal peers) or have tenderness on palpation of the tibiofemoral joint space (compared to their overweight non-tender peers).

In general practice, X-ray is not recommended as a tool for diagnosis of OA because the absence of abnormalities on X-ray does not exclude OA. However, imaging may provide additional information and is often applied in clinical practice. Our study on risk factors predicting rOA showed that it is important when a patient with knee complaints has a KL grade 1 on X-ray; these women more often develop an established rOA. Another study found that the GP applies different types of patient management, irrespective of their initial choice to make an X-ray or not [66]. Usually, radiologists do not report back the actual KL grade, but may report 'minimal degeneration complying with normal aging' or 'mild degenerative signs', which might comply with a KL grade 1. Therefore, in patient management, minimal degenerative signs on X-ray in combination with knee pain should be considered as early OA. The other determinants best predicting rOA development in patients with knee pain (aged ≥55 years) were female gender and having joint complaints in other joints besides the knee.

Finally, in our study population we found that 'pain in the other knee' and 'past knee trauma' were the best predictors for incident knee pain reported after two years, and we observed different predicting factors in women with knee pain in the other knee and those without. In clinical practice it is probably better to proactively address knee pain rather than a policy of 'watchful waiting'. Especially in women with unilateral knee pain it is important to advise them to lose weight (if applicable), to increase their physical activity, and to wear suitable footwear [67, 68]. This is not only for treatment of the painful knee, but also because this might prevent new pain in the other knee.

It is hoped that the work presented in this thesis has contributed some knowledge to improve the detection and treatment of persons with osteoarthritis.

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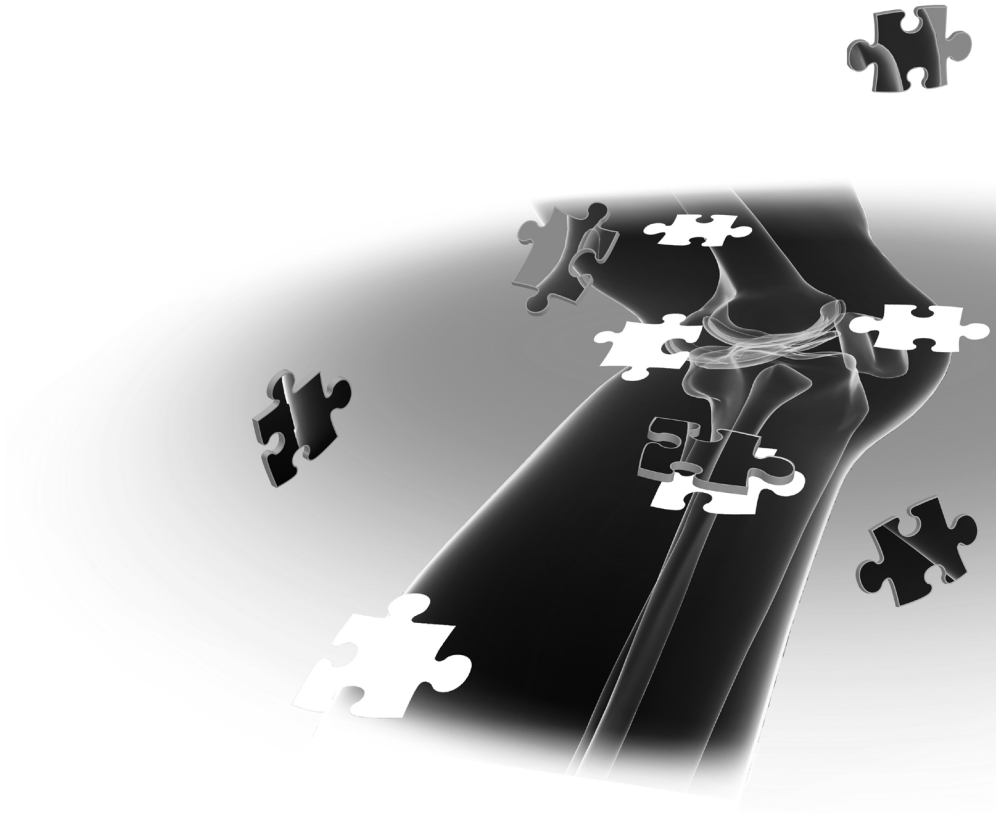
Summary



Osteoarthritis (OA) is the most common form of arthritis, and a major cause of pain and disability in middle-aged and elderly persons. As life expectancy increases, so does the prevalence of OA and the related burden for society. Current treatments of OA are mainly symptom driven, since no cure is currently available.

Chapter 1 shows that, although treatment may be more effective in a pre-clinical stage of the disease, we are not yet able to predict who will develop clinical disease or identify those at high risk of developing OA. The discrepancy between experiencing pain and the absence of radiological findings, makes this situation even more complicated. However, female gender and being overweight are well-established risk factors for OA development.

In this thesis we aimed to gain insight into: 1) the impact of female gender on OA and its symptoms, 2) the relationship between female hormonal aspects and overweight in OA, and to contribute to the knowledge needed to identify people at high risk of knee OA development in an earlier stage of the disease.

For nearly all the studies presented in this thesis, data were used from either the first cohort (RS.I) or the third cohort (RS.III) of the Rotterdam Study. This is a large prospective population-based cohort study conducted in Rotterdam, the Netherlands. All middle-aged and older people living in Ommoord (a suburb of Rotterdam) who were willing to participate were included. All women from the third cohort, who were aged 45-60 years at baseline, were invited to participate in an additional sub-study on knee OA.

Although the simultaneous occurrence of menopause and OA incidence suggests a role for female hormones, the exact underlying mechanism for this has not yet been elucidated. Therefore, we systematically reviewed the associations between OA and exogenous hormone use (**Chapter 2**), and between OA and other female hormonal aspects (**Chapter 3**). Medline was searched up to March 2008 for our review on exogenous hormone use, and up to October 2008 for our review on other female hormonal aspects. Articles evaluating associations between OA of hand, hip or knee, as well as female hormone-related aspects, were included. The methodological quality of the studies in the reviews was assessed systematically. The results are summarized in a best-evidence synthesis.

In **Chapter 2** we found limited evidence for a protective effect of unopposed estrogen use for incidence of hip replacement/joint replacement, and a protective trend for incident radiological (r)OA of the knee. In prevalence studies, there was conflicting evidence for use of hormone replacement therapy with rOA of the distal interphalangeal joints and 'any joint OA', and estrogen use with clinical knee OA. We found limited evidence for a significantly increased risk with use of hormone replacement therapy for clinical hip OA, and a significant protective effect of long-term use of unopposed estrogen for hip rOA. For all other studied relations no associations were found with OA.

In reviewing the associations between OA and female hormonal aspects (**Chapter 3**) we found no associations with OA for most of the studied aspects. There was conflicting evidence for an association of 1) age at menarche with Herberden's nodes and hand rOA, 2) years since menopause with knee rOA and 3) ovariectomy with hip OA. An increased risk was seen for 1) low estradiol serum levels in the early follicular phase with incident knee rOA, 2) early age at menarche (<12 years) with total hip replacement, 3 & 4) being post-menopausal and years since menopause with the presence of Herberden's nodes. A protective effect was seen for age at menopause being ≥52 years with total knee replacement. The evidence level was limited for all findings. We found that evidence for the associations between OA and female hormonal aspects was not as clear as expected. Evidence ranged from protective to increasing risk, but most often the evidence was conflicting or evidence of 'no association' was found. It is possible that the relationships with OA are too complex, or perhaps other aspects (not yet determined) play a role in the increased incidence in women aged >50 years.

None of the studies included in our systematic reviews used Magnetic Resonance Imaging (MRI) for OA assessment. MRI has the advantage over X-ray of being able to visualize degenerative signs in an earlier stage of the disease; not only in bone and cartilage, but also in soft joint tissues. In our OA sub-study, all knees of the participants were scanned using MRI. The aim of **Chapter 4** was to gain insight into where in the joint the degeneration starts, by using MRI in relation to the menopause. We used baseline data of the RS.III cohort. Eligible female subjects for this study (n=823, aged 45-60 years) had available knee MRI data and were without rOA in both knees, i.e. Kellgren & Lawrence (KL) grade <2. Examined menopausal aspects were postmenopausal status, early menarcheal age (<12 years), and years since menopause. The assessed tissues were menisci, cartilage and bone (osteophytes, and bone marrow lesions); joint effusion was also examined. Because body mass index (BMI) is a strong risk factor for knee OA, using general estimating equations, associations were tested separately for low/normal BMI (kg/m^2 <27) and high BMI. We studied associations between degenerative signs of knee tissues with female hormonal aspects in a population at high risk of OA development, i.e. in early menopausal disease-free women. Even though cartilage degeneration is a main feature of OA, we found no associations with any of the female hormonal aspects. However, bone marrow lesions were associated with being postmenopausal and the number of years since menopause. Also, a significant association between early menarcheal age and degeneration of the lateral meniscus was observed in overweight women, but not in non-overweight women. Although we have no clear explanation for this finding, we suspect that this association is based on persistence of overweight into adulthood, since both age at menarche and adult obesity are associated with childhood obesity.

In order to develop preventive strategies for knee OA, knowledge on interactions between the important risk factor BMI and other risk factors is needed. Knowledge on such

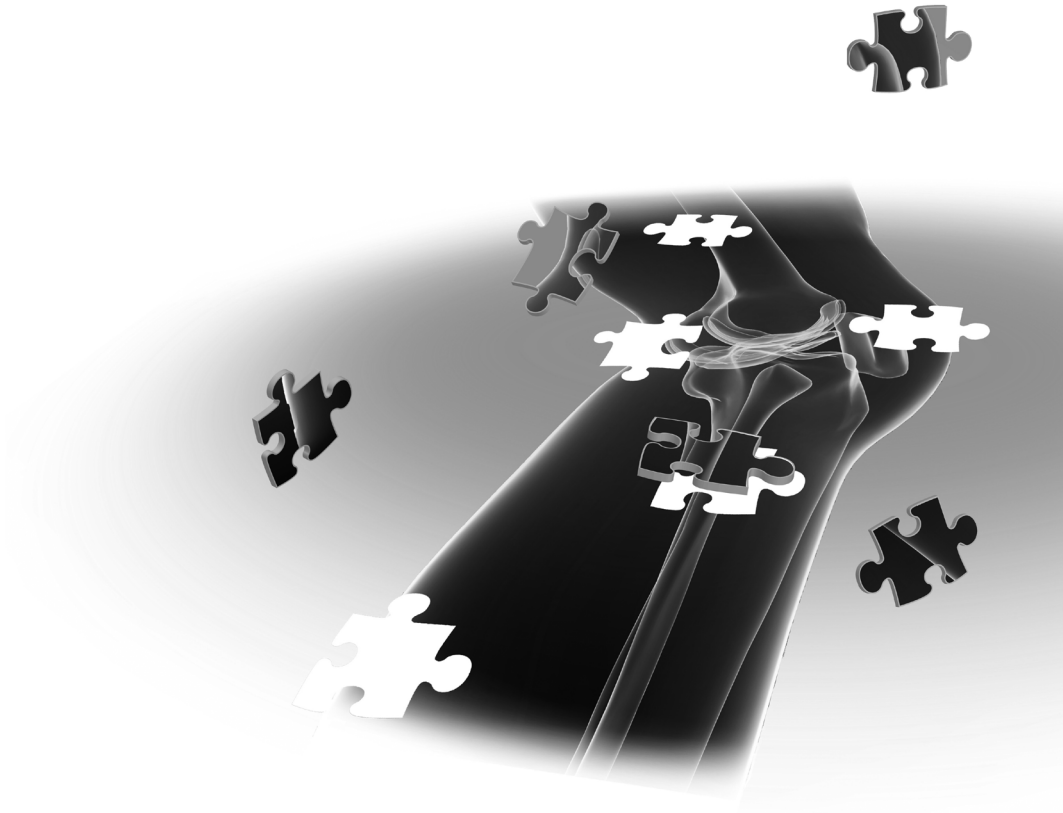
interactions is currently limited. Therefore, in a general population and using univariate logistic regression analysis, we investigated whether associations of known risk factors and knee symptoms with rOA differ between women with a high BMI (≥27) and with a low/normal BMI (<27) (**Chapter 5**). Again, baseline data from the RS.III cohort were used and we included 649 women with low/normal BMI and 741 women with high BMI (all aged 45-60 years). Risk factors and symptoms showing differences between the groups in univariate analysis were tested for interaction with BMI. All analyses were adjusted for age. We found that in this population risk factors for, and symptoms of knee rOA differ in magnitude between those with low/normal and high BMI. Significant risk factors and symptoms in the low/normal BMI group were being postmenopausal and having an early menarche (<12 years). In the high BMI group these were varus alignment, Heberden's nodes, limited extension, a WOMAC-Patient Acceptable Symptom Score >30, and morning stiffness lasting <30 minutes. A significant interaction was found between BMI and knee morning stiffness lasting <30 minutes (OR=3.19, $p<0.05$). Being postmenopausal and tenderness on palpation showed a trend for an interaction.

To identify high-risk groups for OA development, knowledge on predicting risk factors is needed. Pain is the most important clinical symptom of OA, and in middle-aged and elderly people knee pain is most often attributed to (early) OA. In **Chapter 6** we studied which factors best predict the development of knee rOA in those with knee pain. This time we used data from the RS.I cohort (including subjects aged ≥55 years). Analysis was performed on 623 subjects with knee complaints at baseline and their data at 6-year follow-up (607 subjects) and at 11-year follow-up (457 subjects). At baseline, none had rOA in the painful joint. At follow-up, predictors for rOA were determined using multivariate ordinal logistic regression analysis. Female gender, having other joint complaints and having a KL grade of 1 in the painful joint were the best predictors.

Knee pain is often an early sign of OA development, and predicting who will develop knee pain in a later stage can therefore be considered one step in the process of identifying persons at high risk of OA development. Therefore, in **Chapter 7** we studied which determinants best predict incident knee pain after two years in women without knee pain at baseline. Data from 673 women aged 45-60 years of the RS.III cohort were used if they had at least one pain-free knee at baseline. Degenerative signs of knee tissues (MRI), physical examination/history taking data, and OA risk factors were assessed at baseline at the research center; the presence of pain two years after baseline was assessed using questionnaires. Analyses were performed using general estimating equations. We found that past knee trauma in the knee with new pain, and having knee pain in the other knee at baseline, were the best predictors for development of incident knee pain. We also found that risk factors differ between women who already have knee pain in one knee and those who do not.

Finally, in **Chapter 8** the main findings emerging from this thesis are summarized and discussed in relation to current scientific knowledge. In addition, limitations of our studies and implications for daily practice are addressed, and recommendations are made for future research.

Samenvatting



Artrose is de meest voorkomende gewrichtsaandoening en een belangrijke oorzaak van pijn en functiebeperking bij mensen van middelbare en oudere leeftijd. Met de vergrijzing van de bevolking zullen ook de prevalentie van artrose en de last voor de samenleving toenemen. De huidige behandelingen voor artrose zijn voornamelijk gebaseerd op symptoombestrijding, omdat genezing nog niet mogelijk is. Zoals in **Hoofdstuk 1** staat beschreven is het denkbaar dat behandeling in een vroeger stadium van de ziekte effectiever is. Helaas kunnen we nog niet voorspellen wie in de toekomst artrosegerelateerde klachten zal ontwikkelen, of mensen herkennen met een hoog risico op het krijgen van artrose. De bekende discrepantie tussen pijn en radiologische bevindingen maakt dit nog moeilijker. Vrouwelijk geslacht en overgewicht zijn bekende risicofactoren voor het krijgen van artrose.

In dit proefschrift hadden we als doel inzicht te verkrijgen in 1) de invloed van vrouwelijk geslacht op artrose en bijbehorende symptomen en 2) de relatie tussen vrouwelijk hormoongerelateerde aspecten en overgewicht bij artrose en 3) kenmerken van mensen met een verhoogd risico op knieartrose, of die al in een vroeg stadium van de ziekte verkeren.

Bijna alle studies in dit proefschrift zijn gebaseerd op data van het eerste (RS.I) of derde (RS.III) cohort van de Rotterdam Studie. Dit is een grote prospectieve populatiegebaseerde cohortstudie, uitgevoerd in Rotterdam. In een prospectieve cohortstudie wordt een grote groep mensen gevolgd in de tijd en hier wordt onderzocht of, hoe en wanneer bepaalde ziekten zich ontwikkelen. In dit cohort worden veel gegevens verzameld in het onderzoekscentrum; van röntgenfoto's van vele gewrichten tot afname van bloed en urine en van een groot interview over medische geschiedenis en dagelijks functioneren tot allerlei lichamelijke onderzoeken. Alle mensen van 45 jaar en ouder wonend in de Rotterdamse wijk Ommoord die wilden meedoen zijn geïncludeerd. Alle vrouwen uit het derde cohort, die ten tijde van de baseline metingen tussen de 45 en 60 jaar oud waren, zijn uitgenodigd mee te doen aan een aanvullende substudie over knieartrose.

De leeftijd waarop de overgang optreedt valt samen met de stijging van de incidentie van artrose bij vrouwen. Dit suggereert een rol voor vrouwelijke hormonen, maar het exacte onderliggende mechanisme is nog niet opgehelderd. Wij hebben de literatuur bestudeerd met betrekking tot de relaties tussen artrose en hormoongebruik (**Hoofdstuk 2**) en artrose en andere vrouwelijk hormoongerelateerde aspecten (**Hoofdstuk 3**). We doorzochten de Medline database van medische literatuur voor beide vraagstellingen. Studies naar associaties tussen artrose van hand, heup of knie en vrouwelijk hormoongerelateerde aspecten werden geïncludeerd. De methodologische kwaliteit van de studies werd systematisch beoordeeld.

In **Hoofdstuk 2** vonden we beperkt bewijs voor een beschermend effect van oestrogeensuppletie op het krijgen van een gewrichtsprothese van heup of knie en een be-

schermende trend voor incidentie van radiologische knieartrose. In prevalentiestudies vonden we conflicterend bewijs voor het gebruik van hormoonvervangende therapie (HVT = combinatie therapie van oestrogeen met progesteron) met radiologische artrose van de distale interphalangeale (DIP) gewrichten en met 'artrose in een gewricht' en voor oestrogeengebruik met symptomatische knieartrose. We vonden beperkt bewijs voor een significant verhoogd risico op symptomatische heupartrose bij het gebruik van HVT en een significant beschermend effect van langdurig oestrogeengebruik voor radiologische heupartrose. Voor alle andere bestudeerde relaties werd geen bewijs gevonden.

Bij het bestuderen van de literatuur over mogelijke associaties tussen artrose en vrouwelijk hormoongerelateerde aspecten (**Hoofdstuk 3**) vonden we voor de meeste bestudeerde associaties geen bewijs. Conflicterend bewijs werd gevonden voor een associatie tussen 1) leeftijd waarop de eerste menstruatie plaatsvond (menarche) met Heberden nodes (dit zijn kleine harde knobbeltjes op de gewrichten van de vingers) en met radiologische handartrose, 2) jaren sinds menopauze met radiologische knieartrose en 3) ovariëctomie (verwijdering van de eierstokken) met heupartrose. Een verhoogd risico werd gevonden voor 1) lage estradiolserumwaarden in de vroege folliculaire fase voor de incidentie van knieartrose, 2) vroege menarche (dit is de eerste menstruatie van een meisje jonger dan 12 jaar) voor heupvervanging, 3&4) postmenopauzale status en jaren sinds menopause voor het hebben van Heberden nodes. Een beschermend effect werd gezien voor leeftijd ten tijde van menopauze 52 jaar of jonger voor totale knieprothese. Het bewijsniveau voor alle gevonden associaties was beperkt. Het bewijs voor de associaties tussen artrose en vrouwelijk hormoongerelateerde aspecten was niet zo duidelijk als wij hadden verwacht. Bewijs varieerde van beschermend tot verhoogd risico of we vonden bewijs voor 'geen relatie'. Wellicht is de relatie te ingewikkeld, of andere nader te bepalen aspecten hebben een rol in de verhoogde incidentie van artrose in vrouwen vanaf 50 jaar.

Geen van de publicaties die in onze literatuurstudies zijn geïncludeerd gebruikte beeldvorming met magnetische resonantie (MRI) ter beoordeling van artrose. MRI heeft als voordeel boven röntgen dat het in een vroeger stadium van de ziekte tekenen van degeneratie zichtbaar kan maken, niet alleen van bot en kraakbeen, maar ook van zachte weefsels zoals pezen en meniscus. In onze artrose substudie hebben we de knieën van alle deelneemsters gescand met MRI. Het doel van de in **Hoofdstuk 4** beschreven studie was om met behulp van MRI inzicht te krijgen in waar precies in het gewricht de degeneratie start in relatie tot de menopauze. We maakten daarvoor gebruik van gegevens van het RS.III cohort. Vrouwen tussen de 45 en 60 jaar met beschikbare MRI data en zonder radiografische artrose in beide knieën (Kellgren & Lawrence (KL) graad <2) werden geïncludeerd. De volgende menopauzale aspecten zijn getest: 1) postmenopauzale status (PostMP), 2) vroege menarche (<12 jaar) en 3) jaren sinds menopause. De bekeken

knieweefsels waren de meniscus, kraakbeen en bot (osteophyten en 'bone-marrow-lesions'). Tevens hebben we effusie bekeken. Omdat het gewicht in relatie tot de lengte ('Body Mass Index' (BMI)) één van de belangrijkste risicofactoren is voor knieartrose, hebben we de associaties met 'General Estimating Equations' (GEE) apart geanalyseerd in vrouwen met een normaal/laag BMI (< 27 kg/m^2) en met een hoog BMI (≥ 27 kg/m^2). We onderzochten de relaties tussen degeneratieve tekenen van knieweefsels met vrouwelijk hormoongerelateerde aspecten in een populatie met een hoog risico op artrose, namelijk in vroeg-menopausale vrouwen zonder artrose. Hoewel kraakbeendegeneratie een hoofdaspect is van artrose vonden we hiervoor geen relaties met vrouwelijk hormoongerelateerde aspecten. Bone-marrow-lesions bleken wel geassocieerd met de postmenopausale status en het aantal jaren sinds menopauze. Tevens vonden we een significante relatie tussen vroege menarche en degeneratie van de laterale meniscus, welke we niet konden verklaren. We denken dat deze relatie eigenlijk is gebaseerd op voortdurend overgewicht in de volwassenheid, aangezien zowel leeftijd ten tijde van menarche als overgewicht in de volwassenheid geassocieerd zijn met overgewicht in de kinderjaren.

Om vroege preventieve strategieën voor knieartrose te kunnen ontwikkelen, is kennis nodig over interacties tussen de belangrijke risicofactor BMI en andere risicofactoren. Onze kennis hieromtrent is nu nog beperkt. Daarom onderzochten we in de algemene populatie of relaties tussen bekende risicofactoren met prevalente radiologische knieartrose verschillen tussen vrouwen met een laag/normaal BMI (<27) en vrouwen met een hoog BMI (≥27) (**Hoofdstuk 5**). Tevens bestudeerden we de relaties tussen kniesymptomen en radiologische knieartrose, alle door middel van univariate logistische regressieanalyse. Ook hiervoor gebruikten we gegevens van vrouwen (leeftijd 45-60 jaar) uit het RS.III cohort. We konden 649 vrouwen includeren met een laag/normaal BMI en 741 vrouwen met een hoog BMI. Risicofactoren en symptomen die verschilden in significatie ($p \leq 0.05$) tussen de twee BMI groepen in univariate analyse, werden getoetst op interactie met BMI. In alle analyses zijn is rekening gehouden met de invloed van leeftijd en BMI binnen de groep. We zagen dat risicofactoren voor, en symptomen van, radiologische knieartrose verschilden in belangrijkheid tussen vrouwen met een laag/normaal BMI en vrouwen met een hoog BMI. Significante risicofactoren in de vrouwen met laag/normaal BMI waren: postmenopausale status en vroege leeftijd bij menarche. In de hoog BMI groep waren dit: varusstand van de knie, Heberden nodes, beperkte extensie, WOMAC-patient aanvaardbare symptoom score (PASS) >30 en ochtendstijfheid van de knie < 30 minuten. We vonden een significante interactie tussen BMI en ochtendstijfheid <30 minuten (odds ratio (OR)=3.19, $p<0.05$). Postmenopauzale status en gevoeligheid bij palpatie vertoonden een trend voor interactie.

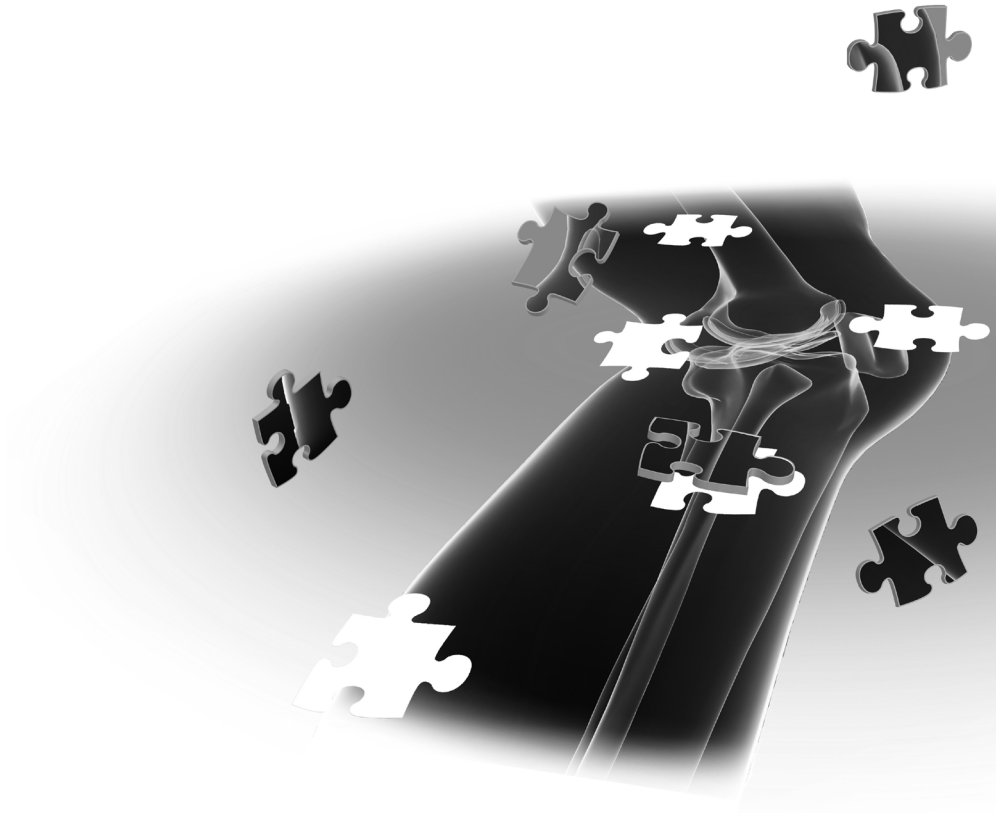
Om hoogrisicogroepen voor de ontwikkeling van artrose te kunnen identificeren is kennis over voorspellende factoren nodig. Pijn is klinisch het meest relevante symptoom

van artrose en bij mensen van middelbare leeftijd en ouderen wordt kniepijn vaak toegeschreven aan (vroege) artrose. In **Hoofdstuk 6** hebben we bestudeerd wat de beste voorspellende factoren zijn voor het ontstaan van radiologische artrose in mensen met kniepijn. Voor deze studie gebruikten we gegevens van het RS.I cohort (deelnemers 55 jaar en ouder). In de analyse werden 623 deelnemers geïncludeerd met knieklachten bij baseline. De deelnemers werden daarna nog twee keer gemeten: na 6 jaar (n=607) en na 11 jaar (n=457). Bij baseline had geen van de geïncludeerde deelnemers radiologische artrose in de pijnlijke knie. We bepaalden de best voorspellende factoren voor het ontstaan van radiologische knieartrose met behulp van mulitvariate ordinale logistische regressie analyse. Vrouwelijk geslacht, het hebben van andere gewrichtsklachten naast de knieklachten en een Kellgren & Lawrence score van 1 in de pijnlijke knie bij baseline waren de beste voorspellers.

Kniepijn is vaak een vroeg teken van artroseontwikkeling. Het voorspellen wie kniepijn zal ontwikkelen kan daarom worden beschouwd als één stap in het proces van identificeren van mensen met een hoog risico op artrose. Om die reden hebben we in **Hoofdstuk 7** bestudeerd welke factoren incidentie van kniepijn na twee jaar het beste voorspellen. Hiervoor gebruikten we de gegevens van vrouwen tussen de 45 en 60 jaar van het RS.III cohort, die in tenminste één knie geen klachten rapporteerden bij baseline. Degeneratieve tekens van knieweefsels op MRI en gegevens van het lichamelijk onderzoek, de medische geschiedenis en risicofactoren voor knieartrose werden verzameld bij baseline op het onderzoekscentrum; aanwezigheid van pijn werd uitgevraagd met vragenlijsten. We vonden dat een knietrauma in het verleden in de knie met 'nieuwe pijn' en pijn in de andere knie bij baseline de beste voorspellers waren voor incidente kniepijn in een knie die pijnvrij was bij baseline. Tevens vonden we dat risicofactoren voor incidente kniepijn verschillen in vrouwen die al unilateraal kniepijn hadden in vergelijking met vrouwen die helemaal geen kniepijn hadden.

Tenslotte worden in **Hoofdstuk 8** de hoofdbevindingen van dit proefschrift samengevat en bediscussieerd in relatie tot de huidige stand van de wetenschap. Tevens worden de beperkingen van de studie, implicaties voor de dagelijkse praktijk en voor toekomstig onderzoek bediscussieerd.

Appendices



APPENDIX I

Keywords used in the Medline search in systematic reviews in Chapter 2 and Chapter 3:

- osteoarthritis
- estrogen OR estrogen* OR female hormone OR oestrogen OR oestrogen* OR menarche OR menopause OR ovariectomy OR hormone status OR hormonal status OR ovari* OR tibolone OR ethynyl oestradiol OR estradiol OR oestradiol OR E2
- HRT OR ERT OR hormone replacement therapy OR hormonal replacement therapy OR estrogen replacement therapy OR HST OR hormon* OR substitution therapy OR ORT OR estrogen replacement therapy
- menopause OR menarche OR postmenopausal OR premenopausal OR perimenopausal OR post-menopausal OR peri-menopausal OR pre-menopausal OR premenopause OR perimenopause OR postmenopause OR pre-menopause OR perimenopause OR post-menopause OR *menopause OR menopau* OR climacteric

Inclusion criteria

A study was included when all the following criteria were fulfilled: (i) the article presents original data on a human study population, (ii) disease of interest is incident or prevalent OA of the hand, hip or knee (tibiofemoral OA), (iii) women with and without OA are compared in the study, (iv) the study reports on any female-hormonal aspect related to OA (e.g. menopause, ovariectomy, (duration-) fertile period), presenting odds ratios, relative risks, p-values or data extended enough for one of these to be calculated, (v) studies on genetics are excluded, (vi) the article was written in English, Dutch, German, African, Norwegian, Danish or Swedish, (vii) the full text article was available. Two independent researchers checked the abstracts on the above-mentioned criteria.

APPENDIX II

List of criteria for the assessment of the methodological quality for cohort, cross-sectional and case control studies measuring prospective determinants. Specification of these criteria is shown in Appendix III. All items are assessed scoring: + / - / ?

Criteria		V/I
Study design		
a)	Prospective design was used	V
b)	Withdrawals ≤ 20%	V
c)	Information on completers versus withdrawals (selective loss to follow-up)	I
Study population		
d)	Selection before disease was present or at uniform point	V
e)	Nonbiased selection of participants and with exclusion criteria applied equally to all	V
f)	Description of relevant inclusion and exclusion criteria source population	I
g)	Sufficient description of baseline characteristics source population	I
h)	Participation rate ≥ 80% for source population	V
Assessment of determinants		
i)	Definitions of determinants are valid	V
j)	Exposure assessment was blinded	V
k)	Exposure was measured identical in entire studied population	V
l)	Minimal exposure time determinant over 6 months	V
Assessment of OA (hand, hip or knee)		
m)	OA was assessed identically in studied population with and without the determinant	V
n)	Presence of OA was assessed according to valid definitions with standardized classification	V/I
o)	Presence of OA assessed independent of determinants	V
Analysis and data presentation		
p)	Data presentation of most important outcomes	I
q)	Adjusted for most important confounders	V

V = criterion on validity / precision
I = criterion on informativeness

APPENDIX III

Specified criteria list for the methodological quality assessment (see APPENDIX II)

Criteria
Study design
a) Positive if a prospective design was used. Also positive in case of a historical cohort when the determinants were measured before the outcome was determined. 'Don't know' if a historical cohort is used, considering determinants at baseline which are not related to the primary research question for which the cohort is created or in case of an ambispective design
b) Positive if the total number of withdrawals was ≤ 20%; not applicable if design was not prospective cohort
c) Positive if at least 3 out of 4 items below were presented for completers and withdrawals: - Age ,BMI, Menopausal status, Selective loss to follow-up In case a retrospective study design was used, a negative score was assigned.
Study population
d) Positive if the study population was selected before any clinical or radiological sign of knee, hip or hand OA was present. Also positive if (sub-)groups were selected at a uniform point in the course of the disease.
e) Positive if participants were drawn from the same source population (primary study base) and exclusion criteria are applied equally to all.
f) Positive if criteria were formulated for at least two out of four: - Age, Menopausal status, OA status , Relevant co morbidity
g) Positive if at least 5 of the following 9 items were reported: - Age (mean and standard deviation) - Body Mass Index (BMI)(mean and standard deviation) - Race - Place of recruitment - Sampling frame of source population (e.g. hospital, primary care, general population etc.) - Sport/leisure time exposure - Smoking habits - Signs of OA in other joints than primary OA site, also positive if multiple sites are looked at for OA - Characteristics of OA on X-ray or other imaging techniques
h) Positive if the participation rate of cases/controls selected and invited to participate at baseline was at least 80%.

APPENDIX III, CONTINUATION

Assessment of determinants

i) Positive if information on relevant determinants is given with the following definitions:
1. Hormones:
1a = exogenous hormone use:
- Information given on duration of exposure through medical records or questionnaires
OR:
- Type of hormones (estrogen, testosterone or oral, transdermal)
1b = endogenous hormone: estradiol levels in blood
2. Type of menopause:
2a = type of menopause: surgical or natural / 2b = bilateral ovariectomy: yes / no
3. Menopausal status / Years since menopause:
3a = menopausal status:
- Postmenopausal: no menstruation for at least one year
- Pre-/Peri-menopausal: all females who menstruated in the last year
3b = years since menopause
4. History of pregnancies:
Any information given on past pregnancies (e.g. number of pregnancies lasting longer than 6 months; yes/no breastfeeding)
5. Age at menarche and/or menopause / duration fertile period:
5a = age at menopause / menarche / 5b = duration of fertile period

j) Positive if the exposure assessment was blinded with respect to disease status.

k) Positive if the exposure was measured in an identical way for the whole studied population.

l) Positive if participants have been exposed to the determinant for at least 6 months/1 year.

Assessment of OA (hand, hip or knee)

m) Positive if the way of assessing OA was identical for the entire studied population.

n) Positive if the classification of the radiological osteoarthritis was standardized using the Kellgren and Lawrence [63] (also Burnett atlas [64]) or Croft classification [65].
Positive if the classification of the clinical osteoarthritis was standardized using the ACR criteria.
Positive if (waiting for) a TKR or THR.

o) Positive if presence of OA was assessed independent of determinants.

Analysis and data presentation

p) Positive if frequency or percentage, mean and standard deviation for a group is given or OR (or β) or RR with CI or P-value of the outcome(s) of the determinant(s) were reported.

q) Positive if there was at least corrected for the confounders age and BMI by means of matching, restriction or adjustment in the analysis.

APPENDIX IV

analysis per BMI category

	BMI <25 (n=493)			BMI 25-30 (n=569)			BMI >30 (n=328)		
	p	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**	**OR**	**95%CI**
Age (mean (sd))	0.13	1.09	0.98-1.22	0.45	1.09	0.87-1.36	0.13	1.07	0.98-1.16
BMI (mean (sd))	0.24	1.18	0.89-1.55	0.04	1.09	1.00-1.18	0.00	1.18	1.10-1.26
Risk factors									
Hip rOA	0.41	1.43	0.61-3.35	0.67	1.15	0.60-2.21	0.92	1.05	0.42-2.65
Knee trauma	0.11	1.37	0.93-2.03	**0.03**	**1.29**	**1.03-1.62**	**0.01**	**2.11**	**1.19-3.74**
Varus alignment	0.79	1.11	0.53-2.32	0.85	0.95	0.58-1.57	**0.001**	**3.42**	**1.62-7.23**
Post-menopause	0.17	**2.59**	0.66-10.21	0.18	**2.10**	0.72-6.14	0.37	**1.63**	0.56-4.71
Age menarche <12 years	**0.05**	**2.95**	**1.02-8.57**	**0.004**	**2.78**	**1.38-5.62**	**0.64**	**1.19**	**0.56-2.5**
Herberdens' nodes	0.43	1.54	0.52-4.57	0.16	1.90	0.77-4.65	0.06	2.46	0.96-6.25
Symptoms									
WOMAC PASS > 30	0.09	4.11	0.81-20.85	**0.002**	**5.05**	**1.83-13.90**	**0.02**	**3.42**	1.20-9.76
Morning stiffness < 30 min	0.13	2.41	0.77-7.53	**0.001**	**3.31**	**1.62-6.77**	**0.00**	**4.27**	2.05-8.91
Limited extension	**0.09**	**2.68**	**0.87-8.25**	**0.002**	**4.27**	**1.71-10.64**	0.17	1.99	0.75-5.27
Tenderness to palpation	0.68	0.65	0.08-5.15	**0.012**	**3.17**	**1.28-7.81**	**0.93**	**0.96**	0.35-2.63

BMI=body mass index, WOMAC-PASS: Western Ontario and McMaster Universities osteoarthritis index – Patient Acceptable Symptom Score (for functional disability), OR = odds ratio, CI= confidence interval

APPENDIX V

Reasons for non-participation at each stage during follow-up

Reason for non-particpation	Elligible; Not in analysis (n=321)	T1 (n=16)	T2 (n=166)
Appointment[1] (KL grade not available)	15	13	38
refusal, not interested	52	3	13
refusal, tired of examinations	4	0	4
refusal physical complaints	12	0	15
refusal, mental complaints (dementia)	2	0	0
refusal, mental complaints (other)	1	0	0
refusal, seen too many doctors	6	0	5
refusal, bad experience	1	0	0
postponement, new appointment	2	0	1
refusal, thinks is too old	12	0	5
deceased	5	0	13
moved places	5	0	3
willing, but lives too far away	1	0	1
not able, physical complaints	12	0	5
not able, dementia	1	0	5
refusal, too busy	3	0	4
inaccessible	18	0	4
examined in nursing home	1	0	7
168 default (unknown)	168	0	43

[1] these people did participate in the large Rotterdam study, yet no KL grades of knees were available for analysis.

DANKWOORD

Jeetje… het dankwoord… Het voelt echt als een afsluiting. Waarschijnlijk is dit het hoofdstuk dat het meeste gelezen zal worden. Ook ik maak me hier regelmatig schuldig aan, hoewel ik in de toekomst algemene inleiding en discussie meer zal gaan lezen. Dit schrijven is naar mijn ervaring het "echte overkoepelende denkwerk" van de onderzoeker ;-)). De afgelopen 5.5 jaar heb ik veel geleerd en met veel plezier gewerkt aan mijn onderzoek. Dat ik zover ben gekomen dat ik nu dit dankwoord kan schrijven, heb ik mede te danken aan vele anderen van wie ik enkele hier apart zal noemen.

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CURRICULUM VITAE

Bianca Monique de Klerk is op 24 maart 1981 geboren in 's-Gravenhage. In 1999 behaalde zij haar VWO diploma aan het Erasmus College te Zoetermeer, waarna zij Bewegingstechnologie studeerde aan de Haagse Hogeschool. Als onderdeel van haar studie liep Bianca stage bij de TU Delft - sectie Mens-Machine Systemen, waar zij een pilot studie deed naar een nieuwe tip waarmee een colonoscoop makkelijker kon worden ingebracht in de darm. Hierna begon zij haar afstudeerproject, ook bij de TU Delft - sectie Mens-Machine Systemen, waarin zij een experiment opzette en uitvoerde naar de aanleerbaarheid van de besturing van de Endo-Periscoop. Dit is een laparoscoop voor Minimaal Invasieve Chirurgie, waarmee de chirurg als het ware om een hoekje kan kijken.

In juni 2004 studeerde zij af van de Haagse Hogeschool, en geïnspireerd door het onderzoek aan de TU Delft, begon zij in september 2004 aan het schakeljaar van de studie Beleid en Management in de Gezondheidszorg (BMG), aan de Erasmus Universiteit in Rotterdam. Tijdens deze studie werkte zij als programma-assistent bij het programma Landelijke Leefstijl campagnes van het Preventie Team bij ZonMw. In juni 2005 studeerde zij af voor de Master Zorgmanagement van BMG middels een stageproject uitgevoerd bij de Inspectie voor de Gezondheidszorg, afdeling Farmacologie en Medische Technologie. Dit onderzoek bestond uit het evalueren van de implementatie van een Europese richtlijn voor patiëntveiligheid van medische technologie.

Op 1 januari 2006 startte zij met haar promotieonderzoek bij de afdeling Huisartsgeneeskunde van het Erasmus MC in Rotterdam. Zij werd begeleid door Prof. dr. Sita Bierma-Zeinstra. In 2009 behaalde zij haar Master of Science in de klinische epidemiologie aan het Nederlands Instituut voor Health Sciences (NIHES). De resultaten van ruim 5.5 jaar onderzoek zijn beschreven in dit proefschrift.

Bianca is in 2007 getrouwd met Evert Boxma en samen hebben zij 2 dochters, Femke (2008) en Sarah (2010). Sinds September 2011 is zij werkzaam als wetenschapsfunctionaris bij het Maasstad Ziekenhuis in Rotterdam.

PHD PORTFOLIO

Name PhD student: Bianca Monique Boxma - de Klerk
Erasmus MC department: General Practice
Phd period: Januari 2006 – Juni 2011
Promotor: Prof. dr. S.M.A. Bierma - Zeinstra

PhD training	Year	Workload
MSc. training in Clinical Epidemiology, NIHES, Rotterdam	2007-2009	70 ECTS
Biomedical English Writing and Communication	2009	40 hours
PRESENTATIONS		
International		
EULAR conference, Barcelona, poster presentation	2007	16 hours
OARSI conference, Montreal, Canada, oral presentation	2009	40 hours
OARSI conference, Brussel, Belgium, poster presentation	2010	16 hours
OARSI conference, San Diego, USA, oral presentation	2011	20 hours
National		
MUSC conference, Rotterdam	2006	16 hours
NHG conference, Rotterdam, poster presentation	2008	16 hours
KNGF conference, Amsterdam, oral presentation	2009	40 hours
PRIMUS conference, Rotterdam, poster presentation	2010	16 hours
CONFERENCES / WORKSHOPS / MINI-COURSES		
CPO mini-course, Methodology patient studies and preparation of grant application, Rotterdam	2006	8 hours
EULAR conference, Amsterdam	2006	8 hours
Spring symposium, Alledaagse ziekten, Rotterdam	2006	8 hours
KARMA days, Amsterdam	2006	16 hours
NWO talent day, Utrecht	2006	8 hours
MUSC retraite, Rotterdam	2006	8 hours
NHG conference, Utrecht	2009	8 hours
TEACHING ACTIVITIES		
Supervising medical student	2011	80 hours

LIST OF PUBLICATIONS

This thesis

de Klerk BM, Schiphof D, Groeneveld FP, Koes BW, van Osch GJ, van Meurs JB, Koes BW, Bierma-Zeinstra SMA, Limited evidence for a protective effect of unopposed oestrogen therapy for osteoarthritis of the hip: a systematic review. Rheumatology 2009;48:104-12

de Klerk BM, Schiphof D, Groeneveld FP, Koes BW, van Osch GJ, van Meurs JB, Koes BW, Bierma-Zeinstra SMA, No clear association between female hormonal aspects and osteoarthritis of the hand, hip and knee: A systematic review. Rheumatology 2009; 48: 1160-65

de Klerk BM, Schiphof D, van Meurs JBJ, Koes BW, Hofman A, Bierma-Zeinstra SMA, Development of radiological knee osteoarthritis in people with knee complaints, submitted

de Klerk BM, Schiphof D, Hofman A, Koes BW, Bierma-Zeinstra SMA, Interactions between overweight and other knee osteoarthritis risk factors and knee osteoarthritis symptoms, submitted

de Klerk BM, Schiphof D, Oei E, Weinans H, Koes BW, Hofman A, Bierma-Zeinstra SMA, Cartilage degeneration is not the earliest MRI knee OA feature that can be visualized in association with menopausal aspects: a cross-sectional study, submitted

de Klerk BM, Schiphof D, Oei E, Weinans H, Koes BW, Hofman A, Bierma-Zeinstra SMA, Predicting determinants for incident knee pain in middle-aged women: a longitudinal osteoarthritis study, submitted

Coauthor

Schiphof D, de Klerk BM, Koes BW, Bierma-Zeinstra S, Good reliability, questionable validity of 25 different classification criteria of knee osteoarthritis: a systematic appraisal, J Clin Epidemiol 2008;61:1205-15.

Runhaar J, Schiphof D, de Klerk BM, Haverkamp D, Waarsing J, Koes B, Bierma-Zeinstra S, Knee joint Bone shape is related to BMI but only marginally to early signs of knee osteoarthritis in healthy middle-aged women, Osteoarthritis Cartilage, 2010;18**:**S208

Schiphof D, de Klerk BM, Kerkhof HJM, Hofman A, Koes BW, Boers M, Bierma-Zeinstra SMA, Impact of different descriptions of the Kellgren and Lawrence classification criteria on the diagnosis of knee osteoarthritis, Ann Rheum Dis 2011;70:1422-7

Schiphof D, van Middelkoop M, de Klerk BM, Hofman A, Koes BW, Bierma-Zeinstra SMA, Associations between clinical findings and MRI osteoarthritis features of the patello-femoral joint, submitted