Determinants on the Cause and Course of Hip Pain in the Elderly in Primary Care

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Determinants on the Cause and Course of Hip Pain in the Elderly in Primary Care

Determinanten van de oorzaak en het beloop van heuppijn bij ouderen
in de huisartspraktijk

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Introduction and aims of the study

The first decade of the 21st century has been labelled by the United Nations and the World Health Organization as the Bone and Joint Decade.[1] Musculoskeletal diseases strike persons at all ages and across all socio-economic groups. They affect earnings and income during younger ages, as well as functioning and quality of life at older ages. During a survey in 1998, almost three-quarter of the Dutch population aged 25 years and over reported some form of musculoskeletal pain during the previous 12 months.[2] In the Netherlands, musculoskeletal diseases are the third most costly diagnosis presenting in primary care and cost the Dutch economy yearly about €2.000 million, equivalent to about €125 per person.[3]

Understanding the factors involved in the cause and course of specific musculoskeletal diseases is important and can provide valuable insights into the optimal way of managing these diseases.

Osteoarthritis

An important musculoskeletal disease is osteoarthritis (OA). OA is a chronic, degenerative disorder of multifactorial aetiology, characterised by loss of articular cartilage, periarticular bone remodelling and soft tissue changes. The process is clinically characterized by pain of the affected joint, (morning) stiffness, and a reduction of function. The prevalence, risk factors, clinical manifestations and prognosis vary according to the localisation; for example, the hip, knee and/or generalised OA. Since OA is a disease whose prevalence increases with age, it will become even more prevalent in the future as the cohort of 'baby boomers' grows older. It is expected that between 2000 and 2020, the number of persons suffering from OA will increase by 38%.[4] Within the total costs for musculoskeletal diseases, OA (with €300 million) accounts for the largest part.

In the present study we chose to focus on the hip, because hip OA is a disease causing much pain and disability and, compared to the knee, very little is known about its aetiology and prognosis. In a recent Dutch study, almost 10% of the population aged 55 years and over, developed radiological signs of hip OA during a mean follow-up period of 6.6 years.[5] In another survey, almost 13% of the study population aged 25 years and over, reported hip pain during the previous 12 months.[2]

Preventing or delaying the onset of OA could involve lifestyle changes that may prevent clinical problems, including musculoskeletal disability. In order to live a longer life happier, we need to delay the onset of hip OA and diminish its vigour.
Therefore, more studies are needed to improve our understanding of the epidemiology of hip OA and to elucidate which factors predispose to the cause and course of this disorder.

Trochanteric pain

Of all patients presenting with hip pain in primary care, 10-20% can be attributed to trochanteric pain.[6] Patients with this syndrome (also known as trochanteric bursitis or greater trochanter pain syndrome), suffer from pain at the lateral side of the upper thigh, often with radiation to the knee.[7] Although this pain syndrome has been attributed to an inflammation of the bursa that covers the part of the greater trochanter, sonographic effusion of the bursa was seldom found. Moreover, effusion around the trochanteric tendons was more often present than in other patients with hip pain.[8]
Up to now, scientific research on its incidence and on the prognosis is relatively scarce. More knowledge of this syndrome in primary care is needed in order to give the patient accurate information about the disease course and to provide the patient with the most optimal treatment.

Aim of this thesis

The main aim of the work in this thesis is to identify variables involved in the cause and course of hip pain in patients presenting in primary care.
In the first part of the thesis our goal is to systematically summarize all available literature reporting on the relationship between the occurrence of hip OA and obesity, occupational activities, sporting activities and hip dysplasia, as well as on the prognosis of hip OA.
In the second part, we will report on the prognosis of two of the main patient groups presenting with hip pain in general practice, namely osteoarthritis of the hip and trochanteric pain.

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2

Influence of obesity on the development of osteoarthritis of the hip:

a systematic review

Abstract

Objective: To evaluate the evidence for the influence of obesity as a risk factor for the occurrence of osteoarthritis (OA) of the hip.

Methods: A bibliographical search of Medline, Embase and the Cochrane library until April 2000 was carried out. Articles describing studies of the relationship between obesity and the occurrence of hip OA were selected. The quality of the studies was assessed with a standardized set of criteria. The outcome of the studies was compared with respect to study characteristics and the quality score for the studies. A best evidence synthesis was used to summarize the results of the individual studies.

Results: Five longitudinal and 7 cross-sectional studies were included in this review. There was no association between outcome and study design or methodological quality. The associations between obesity and hip OA were, however, stronger in studies in which the diagnosis hip OA was based not only on radiological criteria, but on clinical symptoms as well. Overall, moderate evidence was found for a positive association between obesity and the occurrence of hip OA, with an OR of approximately 2.

Conclusion: The evidence for a positive influence of obesity on the development of hip OA is moderate.

Rheumatology 2002; 41(10): 1155-62.

Introduction

Osteoarthritis (OA) of the hip is a major cause of morbidity and disability in the elderly. This problem increases with the current ageing of the population in western societies. In addition to the pain and discomfort it causes, OA has major economic consequences[1]. Studies in Europe have estimated that approximately 7-25% of Caucasian individuals over the age of 55 years suffer from hip OA; these estimates vary due to differences in the definition of OA or the selection of the study population. The prevalence of hip OA appears to be lowest in Asians, followed by African black and Native American populations, and is highest in white Europeans.[2-5] Over the last two decades many epidemiological studies have investigated the determinants of OA. These studies are important to improve our understanding of the mechanisms leading to OA and to determine whether (modifiable) risk factors exist for which preventive interventions can be developed and investigated.

A frequently studied object of interest is weight, or body mass index (BMI) and its relationship with OA. A review published in 1988 showed that people with a higher BMI are more prone to the development of knee OA. However, due to sparse data and inconsistencies in the reported studies, the impact of obesity on hip OA was less clear.[2]

Since several new studies investigating the relationship between hip OA and obesity have been published, we decided to investigate this topic using modern methods for systematically identifying and assessing the available studies. The result may be of considerable practical and theoretical importance for the management of this disease, including preventive measures.

Methods

Identification and selection of the literature

To identify observational studies on this subject, relevant publications were searched using the following databases: Medline (1966 to April 2000), Cochrane library (1993 to April 2000) and EMBASE (1980 to April 2000). The following keywords were used: (hip and (arthritis or arthrosis or osteoarthritis or osteoarthrosis) or coxarthrosis) and (risk factor or causative or determinants or predictor or etiology) and (case-control or retrospective or prospective or

longitudinal or follow up or cohort). (A detailed list can be obtained from the corresponding author.) We optimized the search strategy by looking at the specificity and sensitivity of the different strategies. We tried to be as sensitive as possible within the bounds of feasibility, because of difficulty in finding the right key words and the different types of design. The search was extended by screening the reference lists of all relevant articles identified.

A study was eligible for inclusion if it fulfilled all of the following criteria: 1) one of the aims of the study was to investigate an association between hip OA and obesity, 2) the articles were written in English, Dutch, German, French, Danish, Norwegian or Swedish, 3) the article was a full text article, 4) the patients in the studies had to suffer from radiological and/or clinical hip OA, a (total) hip replacement, or were on the waiting list for one, and 5) the study design was a cohort, a case-control, or a cross-sectional study.

A study was excluded if the studied population had a specific underlying pathology, such as trauma (fractures), infection, rheumatoid arthritis, ankylosing spondylitis, Perthes' disease, tuberculosis, hemochromatosis, sickle cell disease, Cushing's disease, or femoral head necrosis.

Publication bias

Identification of all relevant articles is crucial to the validity of a systematic review.[6] The amount of potential publication bias in our study was analysed by means of a funnel plot, in which the study outcome was plotted against the sample size of the study. In the absence of publication bias, the plot will resemble a symmetrical inverted funnel.[7] Because of the small number of included studies, and the lack of the required data, we could not perform a test for symmetry, so we visually examined the funnel plot for symmetry.

Methodological quality assessment

The methodological quality of observational studies can vary considerably, which may influence the results and conclusions of the studies at issue and consequently also the results and conclusions of a systematic review. Therefore, the quality of each included paper was assessed using the following method.

Two reviewers (AML and SMABZ) independently scored the quality of the selected papers according to a standardised set of criteria (Appendix 1). These criteria

have been used in previous reviews of observational studies in the field of musculoskeletal disorders[8-10] and were modified to cover the topic of our review. The criteria concern both the internal validity, and the informativeness of the study. Only items reflecting the internal validity of the studies were used to assess the methodological quality.

In case of a disagreement both reviewers tried to achieve consensus; if disagreements were not resolved, a third reviewer (BWK) was consulted in order to achieve a final judgement.

Several items are not applicable to certain types of study design (e.g. cohort or case-control study), and therefore do not contribute to the total score of that particular study. This means that the maximum score (100%) for each study was based only on the items applicable to that particular type of study design. Positive scores were summed up to give an overall internal validity score.

Best evidence synthesis

Because the observational studies were considered to be heterogeneous with regard to the population studied, methodological quality and determinants and outcome measures for hip OA[11], we followed standard practice and refrained from statistically pooling the data and performed a "best evidence" synthesis.[8,12-14] First the studies were classified according to the type of study design. A prospective cohort study was judged as the preferred design, followed by a case-control study, and than by a cross-sectional study. After that, the studies were ranked according to their methodological quality score. The following ranking of the levels of evidence was formulated.[8,10,12]

1. Strong evidence is provided by generally consistent findings in multiple high quality cohort studies.
2. Moderate evidence is provided by general consistent findings
   - in one high quality cohort study and two or more high quality case-control studies.
   - in three or more high quality case-control studies.
3. Limited evidence is provided by (general consistent) findings
   - in a single cohort study
   - in one or two case-control studies
   - in multiple cross-sectional studies.

4. Conflicting evidence is provided by conflicting findings (i.e. <75% of the studies reported consistent findings).
5. No evidence is provided when no studies could be found.

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

Data extraction

Two researchers (AML and SMABZ) collected the characteristics of the included studies independently of each other. They collected items on the definition of the study population, how the presence or absence of hip OA was assessed, the assessment of obesity, if the study corrected for potential confounding factors and which results were reported.

When a study reported several outcomes because of a division of the study population into subgroups, the separate outcomes were combined (where possible) using Mantel Haenszel statistics, methods described by Clayton and Hills[15] or the method described by Tan and colleagues[16] as appropriate.

Results

Identification and selection of the literature

A total of 2921 references were initially identified; of these, only 9 articles met our selection criteria.[4,17-24] The most frequent reason for failing to meet our inclusion criteria were that there was not an appropriate study design (case reports, no data on the control group) or no specific information about the relationship between obesity and hip OA. After screening the reference lists of the selected studies, another four studies were included.[25-28] All of them were indexed in Medline but used other descriptions of the study design.

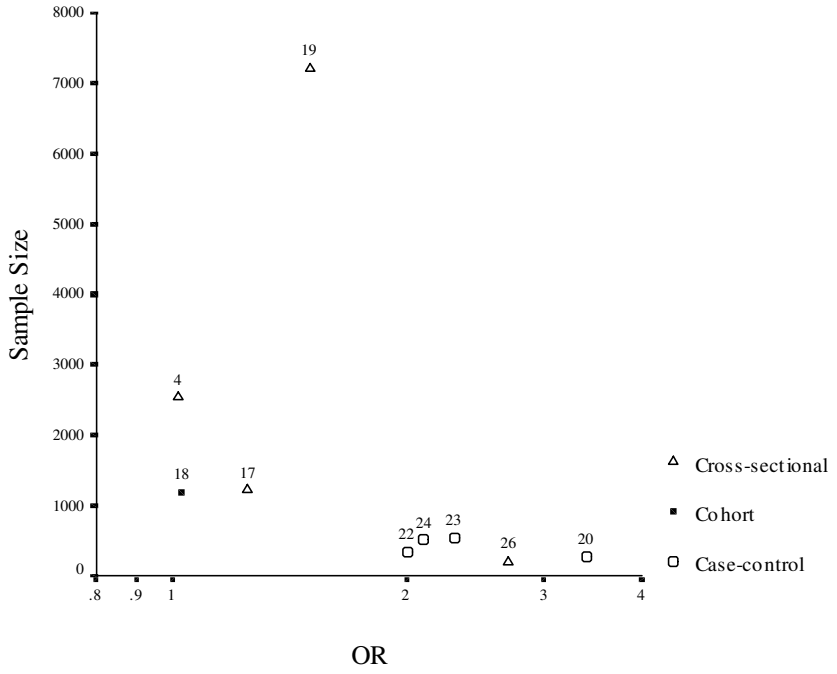
For one study, there were two publications reporting different aspects of the study.[21,23] Both publications were used to extract data regarding the methods used and the results reported. Thus, finally, 12 studies were included in this review.

Publication bias

To investigate the amount of publication bias for our study, a funnel plot was made (Fig. 1). The plot shows the relationship between the distribution of the point

estimates of the association between obesity and hip OA, and the sample size (n). Although the plot shows a more or less equal distribution, there is a lack of small studies showing an inverse association.

Figure 1: Funnel plot showing the distribution of the OR according to the sample size. Of the 12 included studies, only nine provided sufficient data to be included in this plot. The numbers in the graph represent the reference numbers



Description of the studies included

Table 1 gives a detailed description of the characteristics of the included studies. Only five studies had a longitudinal design; viz. one prospective cohort study[18] and four retrospective case-control studies[20-22,24], whereas the remaining seven studies reported only cross-sectional associations between obesity and the presence of OA only.[4,17,19,25-28] In two of the 12 studies, the studied population was hospital based.[22,26] The other 10 studies were population based.

Table 1: Details of the studies included in this review

Cohort studies

Author	Definition population	Assessment hip OA	Adjusted for	Results
Gelber[18]	Male medical students (USA) age 20-29 yr. (n=1180) Follow-up 36 (31-47) yr.	Clinical (self reported at follow-up questionnaire)	age-physical activity-joint injury	BMI < 23 OR 1 (index) BMI 23-25 OR 1.10 [0.4-2.8] BMI >25 OR 1.03 [0.4-2.6]

Case-control studies

Vingard[23] Olsen[21]	All men from Stockholm with a THR between 1984-1988 age 40-70 (n=239)	Random men from Stockholm aged 40-70 yr. (n=302)	*THR	age-smoking occupation-sports	BMI ≤ 25 OR 1 (index) BMI>25 OR 2.3 [1.2-4.4]
Oliveria[20]	Fallon community health plan females (USA) aged 20-89 yr. with hip OA (n=134)	Random selection of women from the Fallon Community (n=134)	*Clinical(ACR/ pain, stiff, swelling) Xray (osteophytes, hypertrophy)	age-gender HRT-smoking	BMI ≤ 24 OR 1 (index) BMI 24–28 OR 3.4 [0.4-25.6] BMI > 28 OR 1.4 [0.1-17.5]
Vingard[24]	All women from South Sweden with THR between 1992-1994 (n=230)	Women from the same area without known hip disorders (n=273)	*THR in that period	age-children-sports-HRT-occupation-smoking	BMI ≤ 20 OR 1 (index) BMI 20-25 OR 1.2 [0.5-2.8] BMI >25 OR 2.1 [0.9-4.6]
Roach[22]	Males in Chicago with a THR or signs of hip OA on X-ray (n= 99)	Same population without signs of hip OA on IV-urograph (n=233)	*Clinical (pain) Xray/IV-urograph (JSW) or THR	various confounders	BMI ≤ 27.7 OR 1 BMI > 27.7 OR 2.0 (1.0-4.0)

Cross-sectional studies

Cooper[17]	Patients on waiting list for THR at 2 clinics in England aged > 45 yr. (n=611)	Patients with the same GP, and no THR (n=611)	Waiting list for THR	age-gender Heberden's nodes-hip-trauma	BMI 25-28 OR 1.3 [0.95-1.7] Bilateral OR 1.3 [0.9-1.8] BMI ≥28 OR 1.6 [1.2-2.2] Bilateral OR 1.7 [1.2-2.4]
Heliovaara[19]	Finnish open population (n=7217) Age ≥30 yr.		History of hip OA or physical findings	age-gender-trauma-stress at work	BMI 25-30 OR 1.5 [1.1-1.9] Bilateral OR 1.4 [1.0-2.0] BMI 30-35 OR 2.0 [1.5-2.7] Bilateral OR 2.3 [1.5-3.5]
Van Saase[27]	Open population of Zoetermeer (the Netherlands) 45-64 yr. (n=2168)		X-ray (Kellgren and Lawrence)	age-gender	"Association is absent"
Hartz[25]	Open population of the USA 40-69 yr. (HANES I) (n=4225)		X-ray (K&L)	age-gender-race	"Relative weight was weakly associated with hip OA"
Tepper[4]	Open population of USA ≥ 55 yr. (NHANES-1) (n=2358)		X-ray (K&L)	gender-race age education	BMI ≤ 27 OR 1 (index) BMI>27 OR 1.02 [0.6-1.7] Bilateral OR 2.0 [0.97-4.2]
Kraus[26]	Patients referred by physicians with hip OA to one clinic in USA (n=100)	Patients at the same hospital (surg-ery/general med.(n=100)	*Clinical (patients) X-ray?	age-gender-race	<20% above ideal weight OR 1 ≥ 20% above ideal weight OR 2.7 [1.4-5.4]
Saville[28]	Patients with prim. hip OA at a dept. for special surgery (USA) aged 15-78 years (n=121)	- US normals height/weight - Pat. from same dept. and no hip OA (n=141)	*Clinical (patients) X-ray (JSN, subchondral sclerosis)		"Body weight distribution among patients with hip OA was similar to that of normal men and women in the US"

* Assessment of hip OA was only carried out for cases. ACR= American College of Rheumatology, THR= total hip replacemen JSN=joint space narrowing, JSW= joint space width, IV-urography= intravenous urography, HRT= hormone replacement therapy, BMI= bodymass index, K&L=Kellgren and Lawrence

Three studies included only males[18,21,22], and two others included only females.[20,24] The ages of the studied populations diverge, but most studies investigated subjects aged 40 years and older. All studies were carried out in the USA[4,18,20,22,25,26,28] or in Northern Europe.[17,19,21,24,27] Most of the studies determined obesity with the BMI. One study used the ideal body weight[26], and another study used relative weight[25]; both measurements were derived from a normal distribution of height and weight in the population[29]. One study used weight only.[28]

The assessment of hip OA varied in several studies. Two studies relied on clinical information only[18,19] while three other studies used an X-ray score only[4,25,27] and another three studies used a combination of these two[20,22,28] as an outcome measure. Three studies used a (total) hip replacement (THR), or waiting for a THR in a specific period as an outcome.[17,21,24] One study did not clearly describe how the assessment of hip OA was done; i.e. only clinically or also using an X-ray.[26]

Results of the studies included

Nine of the 12 studies showed exact data of the outcomes; the other three described the outcome in global terms only.[25,27,28]

Seven studies showed a positive association between obesity and hip OA (OR ≥ 1.25)[17,19,20,22-24,26], of which five were statistically significant[17,19,22,23,26], indicating that subjects with a higher BMI (approximately >25) have an increased risk for developing hip OA. Four of these 7 studies had a case-control design and the other three a cross-sectional design.

Three studies showed a weak positive relation (RR/OR 1-1.25)[4,18,25]; one of these studies had a prospective cohort design. There were no studies reporting a negative association.

There were four studies reporting outcomes on the association between moderate obesity (BMI >25) and hip OA, but also between more severe obesity (BMI >27) and hip OA.[19, 21, 22, 26] Three of these studies showed a clear dose-response relationship.[19, 21, 26]

Three studies also investigated the relationship of the BMI and the presence of a bilateral disease.[4,17,19] The outcomes show a comparable strength of the relationship as found in unilateral hip OA.

In contrast with the nine studies which used clinical information (e.g. physical complaints, need for a THR) for the diagnosis of hip OA, the three studies using

only an X-ray as evidence for hip OA[4,25,27] reported no, or only a very weak positive association with hip OA.

Methodological quality assessment

The two reviewers scored 404 items and agreed on 378 items (94%, kappa 0.87). The 26 disagreements were resolved in a single consensus meeting. Table 2 shows the studies in order of their methodological quality score, subdivided in the different types of study design.

The scores range from 15% to 77% of the maximum obtainable score for each study design. The mean quality score was 57%. The participation rates of the

Table 2: Results of the quality-score of the studies.

Criteria no.	1	2	3	4	5 *	6	7	8	9	10	11	12 *	13	14	15	16 *	17 *	18	19	Score	Obtainable	Total score
Cohort studies																						
Gelber [18]	1	-	1	-	1	1	-	1	1	0	0	0	1	1	1	0	1	0	1	9	12	75%
Case-control studies																						
Olsen [21]/ Vingard [23]	1	1	1	1	1	0	1	1	0	1	1	1	0	-	-	-	1	1	1	10	13	77%
Oliveria [20]	1	1	1	1	0	0	1	1	0	0	1	1	0	-	-	-	1	1	1	9	13	69%
Vingard [24]	1	1	1	1	1	0	1	0	0	1	1	1	0	-	-	-	1	1	1	9	13	69%
Roach [22]	0	1	0	0	1	0	1	0	0	1	1	1	0	-	-	-	1	1	1	6	13	46%
Cross-sectional studies																						
Cooper [17]	1	1	1	0	1	0	1	0	1	1	1	1	0	-	-	-	1	1	1	9	13	69%
Heliovaara [19]	0	-	1	-	1	0	-	0	1	1	1	0	0	-	-	-	1	1	1	6	10	60%
van Saase [27]	0	-	0	-	0	1	-	0	1	1	1	1	0	-	-	-	1	1	1	6	10	60%
Hartz [25]	0	-	0	-	1	0	-	0	1	1	1	1	0	-	-	-	1	1	1	5	10	50%
Tepper [4]	0	-	0	-	1	0	-	0	1	1	1	1	0	-	-	-	0	1	1	5	10	50%
Kraus [26]	1	1	1	1	1	0	1	0	0	0	0	0	0	-	-	-	1	0	1	6	13	46%
Saville [28]	1	0	0	0	0	0	1	0	0	0	0	0	0	-	-	-	1	0	0	2	13	15%

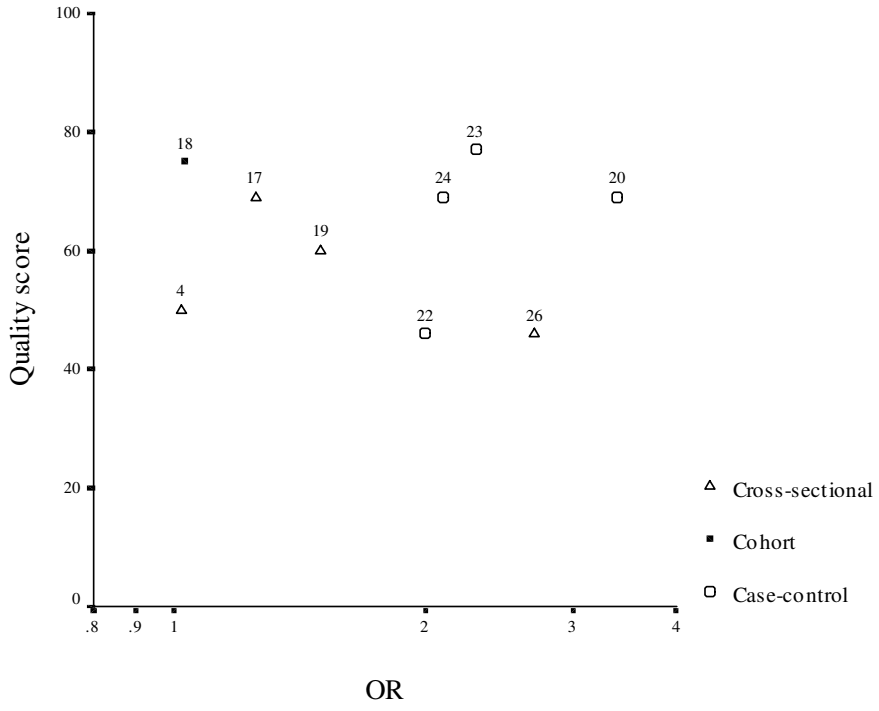
Each item was scored as "1" when it met the specified criteria listed in the appendix A. (see chapter "appendices") When it did not meet the criteria, or when it was not described at all, a "0" was assigned. Positive scores were summed up to an overall internal validity score.
- = not applicable *)= Informativity item. Not included in the analysis.

studied populations (Appendix 1, items 3, 4) scored very low; these criteria were fulfilled by three of the four case-control studies and the cohort study, but by only one out of the 7 cross-sectional studies.

In contrast with the assessment of obesity, where there was almost always an identical or comparable assessment within the different groups of the population (Appendix 1, item 7), the assessment of hip OA (item 9) diverges substantially. In studies with a cohort as study base, (longitudinal and cross-sectional data) there was always an identical assessment of hip OA.

No correlation was found between the quality score and the study outcome (Figure 2) (Pearsons correlation -0.04 p-value 0.9).

Figure 2: Quality score of nine of the 12 studies in relation to the odds ratio. The numbers in the graph represent the reference numbers



Three of the 12 studies could not be plotted due to a lack of precise data on the OR/RR. Of these, van Saase and colleagues[27] achieved a quality score of 67% and reported no association between obesity and hip OA. Hartz et al.[25] scored 56% and reported a weak association, whereas Saville and Dickson[28] achieved a score of 17% and showed no association between obesity and hip OA.

Best evidence synthesis

There were five longitudinal studies, and four of them reached the level of high quality. The high quality cohort study reported an OR of 1.03 (95% CI 0.41-2.60), whereas the three high quality case-control studies reported an association of 2.3 (95% CI 1.2-4.4), 3.4 (95% CI 0.4-25.6) and 2.1 (95% CI 0.9-4.6). This means that there is moderate evidence for a positive association between obesity and hip OA with an OR of approximately 2.

In the subgroup of studies reporting on the association between bilateral hip OA and obesity, only three cross-sectional studies were found, of which two reached the level of high quality.[17,19] This means that with the best evidence synthesis we can conclude that there is only limited evidence for a positive association between obesity and the occurrence of bilateral hip OA. The strength of the association is comparable to the strength found for unilateral hip OA.

For the subgroup of articles assessing hip OA on clinical information (e.g. physical complaints, need for a THR), six[17-21,24] of the nine articles reached the level of high quality. One had a cohort design[18], three a case-control[20,21,24] and two a cross-sectional design.[17,19] The reported OR's were 1.03, 2.3, 3.4 and 2.1. This means that there is moderate evidence for a positive relation between clinically assessed hip OA and obesity.

All three studies assessing hip OA with radiological parameters, had a cross-sectional design.[4,25,31] The reported outcomes were "absence of an association", "a weak association" and an OR of 1.02. One of them reached the level of high quality[31], so there is limited evidence for no association in the subgroup of radiological assessed hip OA.

Discussion

In this systematic review, we summarized the available evidence in the literature on the influence of obesity on the development of OA of the hip. Based on the evidence, we may conclude that there is moderate evidence for a positive association between hip OA and obesity. For the subcategory bilateral hip OA only limited evidence was found. The strength found in this subgroup was comparable to the strength found in the overall conclusion.

For a subcategory of articles in which hip OA was assessed clinically, moderate evidence was found for a positive association, in contrast to radiological assessed hip OA, for which limited evidence for no association was found. This review may, however, suffer from several restrictions.

Identification and selection of the literature

Although we put much effort into identifying the relevant articles, our literature search might have some limitations. Some relevant articles may have been missed because they used other keywords or had unclear abstracts and not all published articles are indexed in databases. Besides that, we excluded articles written in languages other than English, Dutch, German, French, Danish, Norwegian or Swedish.

The presumed absence of publication bias found in our results (Fig. 1) can be explained by a selection of studies that were published for their 'exciting' positive results that satisfy current dogma. When assessing the funnel plot, we have to keep in mind that three of the 11 studies could not be included in the analysis due to insufficient data to deduce a point estimate.[25,27,28] We believe, however, that these data are unlikely to greatly influence our results.

Unfortunately, only one prospective study studying the association between obesity and hip OA could be found. This type of study design is known to be the most valid type of observational studies. Having more data from this type of design would have allowed to provide a more valid and precise conclusion.

The decision to include cross-sectional studies is based on the results of several studies reporting a similarity between current BMI and historical BMI in patients with hip OA.[24,32,33] Our data support these findings. We acknowledge, however, that the strength of the evidence of cross-sectional studies is much lower than the evidence provided by prospective cohort studies and, to a lesser extent, case-control studies.

Quality assessment and best evidence synthesis

The quality assessment was challenging because no tested and validated criteria lists have been published for observational studies in the field of OA. Also, limited data were found to perform a best evidence synthesis with observational studies.

Therefore we presented them in a reproducible manner, and the criteria we used were relatively strict.

A very notable item in the quality assessment was the difference in the assessment of hip OA between the patients and controls in the case-control designed studies (either longitudinal or cross-sectional). Most studies took as cases all patients with hip OA, and as controls a sample of the underlying population, but without screening them for hip OA. This means that some controls might have had hip OA, so these studies would be biased towards a null result.

There have been opinions suggesting that controls do not need to be evaluated for the occurrence of the disease, but rather must represent the base population, which will include such cases.[34] Considering the fact that there are still contradictory opinions on this subject, we prefer to follow the classical point of view; namely that controls must be free of the disease in study.

The most interesting finding in our study is the difference found between clinically assessed hip OA. Whereas the former group of studies shows that obese people suffer more from hip OA, the latter shows that there is no difference in the presence of hip OA. This may suggest that obese patients suffer more from the same radiological degree of hip OA than non-obese patients do. Thus, obese patients may have more hip complaints at an equal radiological stage, due to the weight on the hip joint, and therefore qualify earlier for THR than non-obese patients. Unfortunately, there are only few studies reporting on weight loss in relation to knee OA, and none in relation to hip OA, to support this explanation.[35,36]

In view of the moderate evidence for an association, knowledge of the origin of the relationship between hip OA and obesity is important. Future research, especially well-designed prospective follow-up cohort studies with adequate follow-up time, will not only strengthen the conclusion of this review but might also throw light on the cause of this relationship.

Conclusion

This systematic review shows that in the literature, there is moderate evidence for a positive influence of obesity on the development of hip OA.

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3

Influence of work on the development of osteoarthritis of the hip: a systematic review

Abstract

Objective: To evaluate the evidence for the influence of physical workload on the occurrence of osteoarthritis (OA) of the hip.

Methods: We carried out a database search of Medline, Embase and Cochrane library to identify observational studies, and articles on the relationship between workload and hip OA were identified. Methodological quality of the selected studies was assessed using a standardised set of criteria. The outcome of the individual studies was compared with its study characteristics and methodological quality score. Finally, a best evidence synthesis was used to summarize the results from the individual studies.

Results: Two retrospective cohort studies and 14 case-control studies were included in this review. There was a slight negative, but not significant association between the study outcome and the methodological quality score. Overall, moderate evidence was found for a positive association, with an OR of approximately 3, between previous heavy physical workload and the occurrence of hip OA. In addition, for the subcategories, i.e. ≥10 years farming or lifting heavy weights (≥25 kg), moderate evidence was found for a positive relationship with hip OA. Possible selection of the populations studied may be partly responsible for the association we identified.

Conclusion: The evidence for the influence of previous heavy physical workload on the occurrence of hip OA is moderate.

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Introduction

Osteoarthritis (OA) of the hip is a major cause of morbidity and disability in the elderly, and the problem will increase with the current aging of the population in Western societies. In addition to the personal and social discomfort, the economic consequences are enormous. Roughly, the costs of OA have risen over recent decades accounting for up to 1-2.5% of the gross national product for countries such as the USA, Canada, the UK, France and Australia.[1]

Over the last few decades, many epidemiological studies have investigated potential determinants of OA. These studies are important for our understanding of the causes of OA and will lead to the further improvement of preventive measures. One of the recognised determinants of interest for hip OA is the amount of physical workload, where forces or loads act upon the hip joint. Besides several narrative reviews[2-4], Meatzel and colleagues performed a systematic review on this topic in 1997, in which a consistently positive but weak association between work related exposure and hip OA was reported.[5] However, several new articles have now become available, investigating the influence of workload on the development of hip OA. More data on this subject, gives us the opportunity to update the literature and carry out a subgroup analysis for the type of workload or a the way the hip OA was measured.

We therefore performed a systematic review, using modern methods for systematically identifying and assessing the available studies to provide update knowledge of the proposed association of physical workload and the occurrence of OA of the hip.

Methods

Identification and selection of the literature

To identify the observational studies on this subject, relevant publications were searched using the following databases: Medline (1966 to April 2000), Cochrane library (1993 to April 2000) and EMBASE (1980 to April 2000). The following keywords were used: (hip and (arthritis or arthrosis or osteoarthritis or osteoarthrosis) or coxarthrosis) and (risk factor or causative or determinants or predictor or etiology) and (case-control or retrospective or prospective or longitudinal or follow up or cohort). (A detailed list can be obtained from the

corresponding author.) The search was extended by screening the reference lists of all relevant articles identified.

A study was eligible for inclusion if it fulfilled all the following criteria: 1) one of the aims of the study was to investigate an association between hip OA and the amount of workload, 2) the articles were written in English, Dutch, German, French, Danish, Norwegian or Swedish, 3) the article was a full text article, 4) the patients in the studies had to have a radiological and/or clinical hip OA, a (total) hip replacement, or were on the waiting list for one, and 5) the study design was a cohort or a case-control study.

A study was excluded if the studied population had a specific underlying pathology, such as trauma (fractures), infection, rheumatoid arthritis, ankylosing spondylitis, Perthes' disease, tuberculosis, hemochromatosis, sickle cell disease, Cushing's disease, or femoral head necrosis.

Methodological quality assessment

Variation of the methodological quality of observational studies may influence the results and conclusions of our investigation. Therefore, the quality of each included study was assessed using the following procedure. Two reviewers (AML and SMABZ) independently scored the quality of the selected papers according to a standardised set of criteria (Appendix 1). These criteria have been used in previous reviews of observational studies in the field of musculoskeletal disorders[7,6] and were modified to cover the topic of our review. The criteria concern both the internal validity, and the informativeness of the study. Only items reflecting the internal validity of the studies were used to assess the methodological quality. In case of a disagreement, both reviewers tried to achieve consensus; if disagreements were not resolved, a third reviewer (BWK) was consulted in order to achieve a final judgement.

Several items are not applicable to a certain type of study design (e.g. cohort study or case-control study), and therefore do not contribute to the total score of that particular study. This means that the maximum score of each study (=100%) was based only on the items applicable to that particular type of study design. Positive scores were summed up to an overall internal validity score.

Best evidence synthesis

Because observational studies are heterogeneous with regard to the study population, methodological quality and determinants and outcome measures for hip OA, we refrained from statistically pooling the data[8], and performed a "best evidence" synthesis.[9,10] The studies were divided into subgroups according to the type of study design. A cohort study was judged as the most valid design, followed by a case-control study. After that, the studies were ranked according to their methodological quality score.[11]

1. Strong evidence is provided by generally consistent findings in multiple high quality cohort studies.
2. Moderate evidence is provided by general consistent findings
   - in one high quality cohort study and two or more high quality case-control studies.
   - in three or more high quality case-control studies.
3. Limited evidence is provided by (general consistent) findings
   - a single cohort study
   - in ≤ 2 case-control studies
4. Conflicting evidence was provided by conflicting findings (i.e. <75% of the studies reported consistent findings).
5. No evidence was provided when no studies could be found.

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

Data extraction

Two researchers (AML and SMABZ) collected the characteristics of the included studies independently of each other. They collected items on the definition of the studied population, how the presence or absence of hip OA was assessed, the assessment of the amount of workload, if the study corrected for potential confounding factors, and which results were reported.

When a study reported several outcomes because of a division of the study population into subgroups, the outcomes were combined (where applicable and possible) using Mantel Haenszel statistics, methods described by Clayton and Hills[12] or the method described by Tan and colleagues.[13] Because of dissimilarity according to the outcome, where possible, we computed the odds ratios. We abstracted outcomes on heavy workload in general, and made subgroups for farming and heavy lifting, where possible.

Publication bias

For the validity of a systematic review, identification of all relevant articles is crucial.[14] The amount of potential publication bias in our study was analysed by means of a funnel plot, in which the study outcome (OR) was plotted against the sample size of the study. In the absence of publication bias, the plot will resemble a symmetrical inverted funnel[15]; we visually examined the funnel plot for symmetry.

Results

Identification and selection of the literature

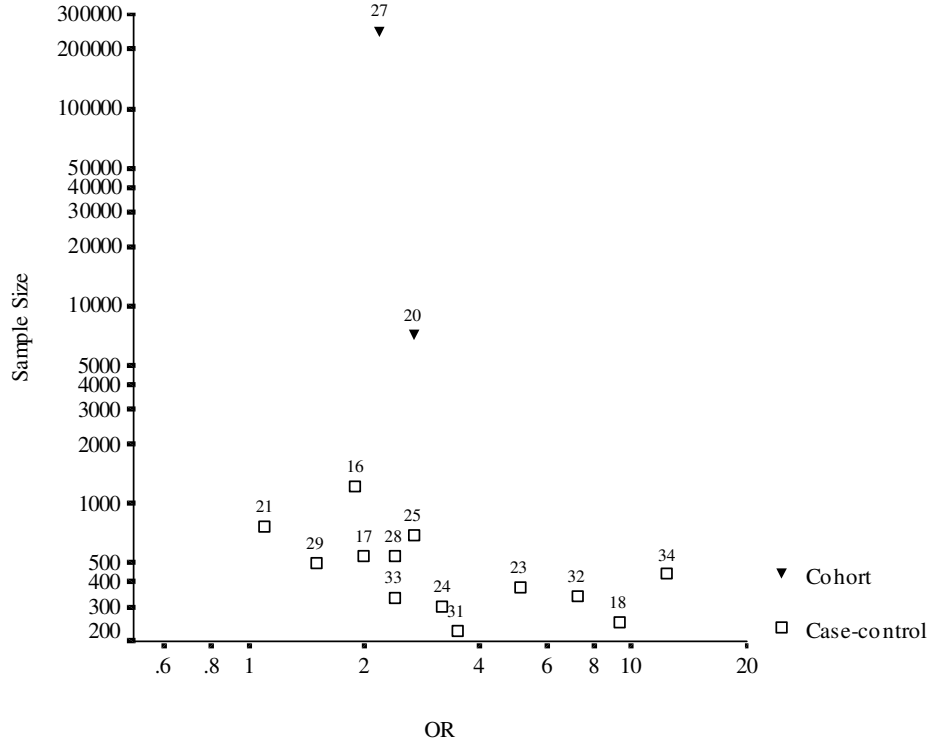
2921 references were initially identified; of these, 16 articles met our selection criteria[16-31]. After screening the reference lists of the selected studies, another three studies were included.[32-34] For three studies, there was more than one publication, reference numbers 22 and 28, 19 and 30 and 26 and 27, reporting different aspects of the study. All publications were used to extract data regarding the methods used and the results. Thus, finally 16 studies were included in this review.

Publication bias

To investigate the amount of publication bias for our study, a funnel plot was made (Fig. 1). The plot shows the relationship between the distribution of the point estimates of the association between obesity and hip OA, and the sample size (n). One study[30] could not be plotted due to a lack of data to deduct an OR.

The plot shows a more or less equal distribution.

Figure 1: Funnel plot. The numbers in the graph represent the reference numbers.



Description of the studies included

Table 1 gives a description of the characteristics of the included studies.

All studies collected their data in a retrospective manner. Two studies had a cohort design[20, 17] and 14 studies were of a case-control design.[16-19, 21, 23-25, 27-29, 31-33]

Eight studies included only males[17, 18, 23, 24, 28, 32-34], whereas two included only females.[29, 30] Fourteen studies were carried out in Northern Europe; most of them in Scandinavia[20, 21, 24, 25, 27-29, 32, 34], but also in England.[16-19, 23] The two others where carried out in the US[33] and in Japan.[31]

The assessment of physical workload was in 13 studies carried out by means of an interview or a questionnaire[16-18, 20, 23-25, 28, 29, 31-34], whereas two studies used the inclusion criteria (e.g. workers at a shipyard or physical education teachers).[19, 21] One study used registered information.[27] The assessment of the amount of physical workload was in nine of the 16 studies done by using the subjects' job title, e.g. agricultural workers, bricklayers, dockers etc.[18, 19, 21, 23-25, 27, 32, 34]. The seven other studies collected information on specific occupational activities, such as kneeling, squatting, heavy lifting etc. Besides workload in general, seven

studies reported on farming separately.[17, 18, 24, 25, 27, 32, 34] Most of them used a cut-off point of ≥10 years of farming and compared that with no, < 1 year or <10 years of farming. Six studies reported on heavy lifting activities separately[16, 17, 28, 29, 31, 32], where heavy weight was mostly described as ≥25 kg.

The assessment of hip OA was most of the times based on clinical information (e.g. on waiting list for a (total) hip replacement (THR), after a THR, physician diagnosed hip OA), but three studies characterised hip OA by radiographic materials only (e.g. X-ray, IV-urograph).[17, 18, 21]

Results of the studies included

All studies showed a positive association between heavy vs. light physical workload (defined in various ways) and hip OA. The OR diverged between 1.1[21] and 13.8[34]. Twelve studies reported a statistical significant outcome[16-18, 20, 24, 25, 27, 28, 31-34], where the OR diverged between 1.9[16] and 13.8.[34]

Looking at subgroups, the seven studies reporting on farming vs. light physical workload or no farming, the outcomes diverge between an OR of 2 and 13.8, of which six were statistically significant.[18, 24, 25, 27, 32, 34] The six studies on lifting heavy weights, reported OR's between 1.5 and 3.5, when compared to no or a low exposure to lifting heavy weights. Five of these were statistically significant.[16, 17, 28, 29, 31, 32] Twelve studies analyzed if the relationship changed with an increased exposure to the heaviness of the physical workload.[16-18, 20, 24, 25, 28, 29, 31-34] Ten of these showed a clear dose-response relationship between hip OA and the amount of workload.[16-18, 20, 24, 25, 28, 29, 31, 33, 34] No relationship could be found between the outcome of the individual studies, and the way they assessed hip OA (on clinical evaluations, or with X-ray only) or the gender studied (i.e. males or females).

Methodological quality assessment

The two reviewers scored 663 items and agreed on 630 items (95%, kappa 0.90). The 33 disagreements were resolved in a single consensus meeting. Table 2 shows the studies in order of their methodological quality score, subdivided in the different types of study design (i.e. cohort and case-control studies).

The scores range from 77% to 23%, and the average rating was 54%.

Table 1: Details of the studies included

Cohort studies

Author	Definition population	Assessment of hip OA	Adjusted for	Results
Heliovaara[20]	Finnish open population Retrospective follow-up Age ≥30 (n=7217)	Physician diagnosed (questionnaire) or findings at examination	age, gender, trauma	Heavy workload OR 2.7 (1.7-4.4)
Vingard[26, 27]	Swedish open population Retrospective follow-up 11-13 yr. Age 45-75 (n=250217)	Clinical (Registered ICD-diagnose for hip OA)	age, gender, county	Heavy vs. light workload Male: RR 2.2 (1.6-2.8) Female: RR 1.6 (0.9-3.1) Farming (≥10 yr.) Male OR 3.8 (2.9-3.9) Female OR 1.5 (0.9-2.9)

Case-control studies

Author	Definition cases/ population	Definition controls	Assessment of hip OA	Adjusted for	Results
Yoshimura [31]	Patients waiting for a THR in Japan age ≥45 (n=114)	Random selection of the source population (n=114)	Waiting list for THR	age, gender, knee pain	Lifting <10 kg OR 1 Lifting ≥ 25 kg OR 3.5 (1.3-9.7)
Coggon[16]	Residents of 2 districts in England waiting for a THR Age 45-91 (n=611)	Random selection of the source population without hip problems age 45-91 (n=611)	On waiting list for THR	age, gender, BMI, trauma, Heberden's nodes	No lifting OR 1 Lifting ≥ 25 kg ≥10 yr. OR 1.9 (1.2-3.0)
Vingard[29]	Women in a region of Sweden with a THR Age 50-70 (n=230)	Random selection of women in the same area without hip problems (n=273)	After THR	age, gender, BMI, sports smoking children, HRT	Low exposure to lifting OR 1 Heavy lifting OR 1.5 (0.9-2.5)
Croft[17]	Males with signs of hip OA on an IV-urograph, or a THR in a district in England Age 60-75 (n=245)	Males with an IV-urograph without signs of hip OA (n=294)	X-ray (JSW ≤1,5 mm) or a THR	age, gender, hospital	Lifting ≥25 kg ≥20yr. vs. <1 yr. OR 2.5 (1.0-7.3) Farming ≥10 yr. vs. <1 yr. OR 2.0 (0.9-4.4)
Croft[18]	Random selection of male farmers at five general practices in England Age 60-76 (n=167)	Random selection of man who spent there entire careers in office work (n=83)	Complaints and X-ray (JSW ≤ 1,5 mm) or THR	age, gender, height, weight Heberden's nodes	Office work OR 1 Farming ≥10 yr. OR 9.3 (1.9-44.5)
Jacobsson [32]	Males with signs of hip OA on an IV-urograph or waiting for a THR in South Sweden (n=106)	Males with an IV-urograph without signs of hip OA (n=236)	X-ray/IV-urograph (JSW < 3 mm) or waiting list	gender	Heavy work OR 7.2 (3.0-17.1) Farming OR 2.0 (1.3-3.2) Heavy lifting OR 2.4 (1.3-4.3)
Olsen, Vingard[22, 28]	Males in the area of Stockholm who received a THR age 50-70 (n=239)	Random selection of males in the same area (n=302)	*After THR	age, gender, BMI, smoking, sport	Heavy work OR 2.4 (1.5-4.0) Heavy lifting (>40 kg < 30 yr. of age) OR 2.4 (1.5-3.7)
Thelin[24]	Male patients of 2 hospitals in Sweden who received a THR age 55-70 (n=98)	Random selection of males from the same area Age 55-70 (n= 201)	*After THR	gender, residence	Farming > 10 years vs. other jobs OR 3.2 (1.8-5.5)
Thelin[25]	Population of province in Sweden with signs of hip OA on radiological examination Age >70 (n=216)	Random selection of civilians of the same area (n=479)	*X-ray (JSW < 3 mm)	age, gender residence	Farming vs. no farming OR 2.7 (1.9-3.8)

Author	Definition cases/ population	Definition controls	Assessment of hip OA	Adjusted for	Results
Roach[33]	Males in Chicago with a THR or signs of hip OA on X-ray (n= 99)	Same population without signs of hip OA on IV-urograph (n=233)	*Clinical (pain) THR/ X-ray/IV-urograph (JSW)	various confounders	Heavy vs. light workload ≥ 15 yr. OR 2.4 (1.3-4.3)
Eastmond, White[19, 30]	Female physical education teachers of five colleges in England Age 48-54 (n=577)	Women from general population (n=?)	*Clinical (pain, stiffness) X-ray (Only for teachers)	age, gender	age 48-54 chi^2=2.52 age 55-60 chi^2=0.43
Vingard[34]	Swedish males from the Stockholm region with a disability pension due to hip OA (n=140)	Random selection of males from the same area without disability pensions for hip OA (n=298)	Disability pensions due to hip OA	age, gender, residence	Heavy workload >20 yr. OR 12.4 (6.7-23.0) Farm > 10 yr. OR 13.8 (4.0-48.1)
Lindberg[21]	Heavy labour workers of shipyard at Malmö (n=332)	-White collar workers at same shipyard and male teachers (n=352) -random sample of citizens of Malmö (n=438)	*X-ray (JSW < 4 mm at age < 70, JSW < 3 mm at age > 70)	age, gender	compared to controls 1 OR 1.1 (0.5-2.5) compared to controls 2 OR 2.1 (0.8-5.5)
Partridge[23]	Civilian male dockers Age 25-64 (n=206)	Male civil servants at government dep. Age 25-64 (n=171)	Clinical (pain, physical examination)	gender	Civil servants OR 1 OR 5.1 (0.6-42.8)

*Assessment of hip OA was only carried out for cases
THR= total hip replacement HRT= hormone replacement therapy JSW= joint space width

A weak negative correlation between the quality score and the study outcome could be found (Spearman's correlation coefficient = -0.148), implying that the higher the quality score, the smaller the association between physical workload and hip OA (Figure 2). However, these findings were not statistically significant. Besides that, we have to keep in mind, that one study could not be plotted due to a lack of data to deduct a point estimate.[30]

Best evidence synthesis

The two cohort studies did not meet the criteria of high quality.[20,27] However, nine of the 14 case-control studies[16-18, 24, 25, 28, 29, 31, 32] could be labelled as 'high quality'. The outcomes of these studies diverge between an OR of 1.5 and 9.3 for high vs. light physical workload. This implies that there is moderate evidence for a positive association between previous physical workload and hip OA with an OR of approximately 3.

Table 2: Results of the quality score of the studies

Item	1	2	3	4	5 *	6	7	8	9	10	11	12 *	13	14	15	16 *	17 *	18	19	Score	Obtainable	Total score
Cohort																						
Heliovaara[20]	0	-	1	-	1	0	-	0	1	1	1	0	0	0	0	0	1	1	1	6	12	50%
Vingard[26, 27]	0	-	1	-	0	0	-	0	1	0	0	0	0	1	0	0	1	1	1	5	12	42%
Case-control																						
Yoshimura[31]	1	1	1	1	1	0	1	0	1	1	1	1	0	-	-	-	1	1	1	10	13	77%
Coggon[16]	1	1	1	0	1	0	1	0	1	1	1	1	0	-	-	-	1	1	1	9	13	69%
Vingard[29]	0	1	1	1	1	0	1	0	1	1	1	1	0	-	-	-	1	1	1	9	13	69%
Croft[17]	0	1	0	0	1	1	1	0	1	1	1	1	0	-	-	-	1	1	1	8	13	62%
Croft[18]	1	1	0	0	1	0	1	0	1	1	1	1	0	-	-	-	1	1	1	8	13	62%
Jacobsson[32]	1	1	1	1	1	0	1	0	1	1	1	1	0	-	-	-	1	0	0	8	13	62%
Olsen, Vingard[22, 28]	1	1	1	0	1	0	1	0	0	1	1	1	0	-	-	-	1	1	1	8	13	62%
Thelin[24]	1	1	1	1	0	0	1	0	0	1	1	1	0	-	-	-	1	1	0	8	13	62%
Thelin[25]	0	1	1	1	0	0	1	0	0	1	1	1	0	-	-	-	1	1	1	8	13	62%
Roach[33]	0	1	0	0	1	0	1	0	0	1	1	1	0	-	-	-	1	1	1	6	13	46%
Eastmond, White[19, 20]	1	0	0	0	0	0	0	0	0	1	1	1	0	-	-	-	1	1	1	5	13	38%
Vingard[34]	0	1	0	0	0	1	0	0	1	0	0	0	0	-	-	-	1	1	1	5	13	38%
Lindberg[21]	1	1	1	1	0	0	0	0	0	0	0	0	0	-	-	-	1	0	1	5	13	38%
Partridge[23]	0	0	1	1	0	0	0	0	1	0	0	0	0	-	-	-	1	0	0	3	13	23%

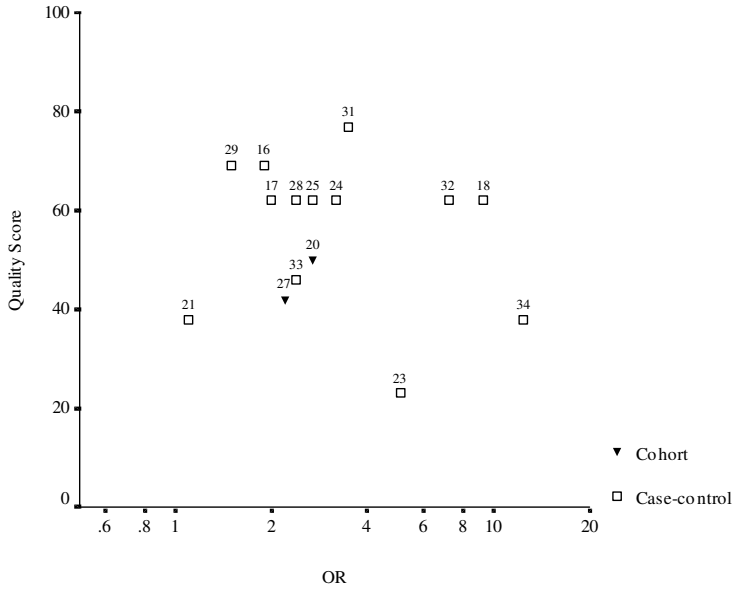
Each item was scored as "1" when it met the specified criteria listed in Appendix A. (see chapter “appendices”)
When it did not meet the criteria a "0" was assigned. Positive scores were summed up to an overall score.
*= informativity item. Not included in the analysis - = not applicable

For the farming subgroup, the single cohort study did not reach the level of high quality study.[27] Five of the seven case-control studies had a high quality score[17, 18, 24, 25, 32], and the outcomes of these studies diverge between an OR of 2 and 9.3. So, also for this subcategory, there is moderate evidence for a positive relationship between a history of (more than ten years) farming, and the occurrence of hip OA, when compared with light workload or no farming.

The six case-control studies reporting on the association between lifting heavy vs. low weights and hip OA, all had a high quality score.[16, 17, 28, 29, 31, 32] The outcomes

diverge between an OR 1.5 and 3.5. This also implies that there is moderate evidence for a relationship between a history of frequent lifting heavy weights (≥25 kg), and the occurrence of hip OA.

Figure 2: Quality score as a function of the OR.
The numbers in the graph represent the reference numbers.



Discussion

In this systematic review, we summarized the available evidence in the literature on the influence of physical workload on the development of OA of the hip. Based on the evidence, we may conclude that there is moderate evidence for a positive association between hip OA and previous workload in general, as well as for the subcategories farming and lifting heavy weights.

Although 12 of the included 16 studies showed a significant positive association between previous heavy workload and hip OA, the evidence could not reach the level of strong evidence. The main reason is that there are no high quality cohort studies. The two cohort studies included in this review, as well as the case-control studies, all had a retrospective design. With this type of design, we have to be cautious with recall bias occurring in the way physical workload was defined; on job title only or with a questionnaire asking for specific activities. Although a specific questionnaire will provide more precise information, the amount of recall bias will be more extensive. In addition to restrictions of the included studies, this review may have other limitations, as follows.

Identification and selection of the literature

Although we put much effort into identifying all relevant articles, our literature search might have some limitations. First, some relevant articles may have been missed because they used other keywords or had unclear abstracts. Second, not all published articles are indexed in databases. Third, we excluded articles written in languages other than English, Dutch, German, French, Danish, Norwegian or Swedish. The presumed absence of publication bias found in our results (Figure 1) might be expected in this field of research. Studies that would have found no (or a negative) relationship have, in our opinion, the same opportunities for publication because there are no obvious conflicts of interest.

Quality assessment and best evidence synthesis

The quality assessment was challenging because there were no previously tested and validated criteria lists published for observational studies in the field of OA. In addition, limited data was found on performing a best evidence synthesis with observational studies (in contrast with RCT's). Thus we presented them in a reproducible manner, and the criteria we used were relatively strict.

Comparison with the results of previous reviews

It is interesting that the results of this review differ from the conclusions drawn in the systematic review of Meatzel et al.[5]. Generally, besides considerably more evidence for the relation between physical workload and the occurrence of hip OA, this review shows that this relation is stronger than suggested in the earlier review. This difference is partly due to the fact that five studies, published before 1994, could be included[20, 23, 27, 30, 34], and partly to the fact that there has been an expansion in this field of research in recent years, what resulted in four more articles.[16, 25, 29, 31]

Explanation for the relationship

Considering the possibility for recall bias in all papers we studied, this could at the most only partly explain the relationship we found between high workload and hip OA. In our opinion, the most reasonable explanation is studied by Radin and colleagues[35]. They described that microfractures appear in the subchondral bone due to repeated high forces across a joint. Because of a less absorbing capacity of

the more compact and rigid bone structure, the overlaying cartilage has to absorb more forces. These forces will in fact cause degeneration of the cartilage tissue. Thus, by this mechanism, exposure to repetitive mechanical stress can lead to the development of hip OA. This explanation is supported by our finding that 10 of the 16 studies, showed a clear dose-response relationship; one of the criteria for a biological gradient.[36]

A frequently postulated explanation for the relationship between high physical workload and hip OA is that people with physical high demanding jobs, may obtain treatment earlier and/or more often than people in less demanding occupations; not necessarily because they have a higher incidence of OA, but possibly because they are more handicapped by it when it occurs. These people will be overrepresented; the exposure of interest may then be associated with the decision to seek treatment. This kind of selection is suggested in an earlier review on the influence of weight on the occurrence of hip OA[37], where a difference was found between the clinically assessed hip OA vs. the radiological OA. In this review however, the outcome of the individual studies is not related to the way they assessed hip OA; clinically[16, 20, 23-25, 27-34] or radiologically.[17, 18, 21] The precise reason for the increased risk remains uncertain. Prospective studies providing information on the causal factors of the association between physical workload and hip OA are needed.

Conclusion

The available evidence found in the literature indicates that there is moderate evidence for a positive association between the amount of physical workload and the occurrence of hip OA. Also for the subgroups farming and lifting heavy weights, the evidence found is moderate. Future studies, especially prospective cohort studies, should further clarify the precise reasons for this relationship.

Acknowledgement

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4

Influence of sporting activities on the development of osteoarthritis of the hip: a systematic review

Abstract

Objective: To evaluate the evidence for the existence of sporting activities as a risk factor for the occurrence of osteoarthritis (OA) of the hip.

Methods: A bibliographical search of Medline, Embase and the Cochrane library until April 2000 was carried out. Articles with the aim to study a relationship between sporting activities and the occurrence of hip OA were selected. The quality of the studies was assessed using a standardised set of criteria. The outcome of the studies was compared with respect to study characteristics, and the quality score. A best evidence synthesis was used to summarise the results of the individual studies.

Results: One cohort study and 21 cross-sectional studies were included in this review. Overall, moderate evidence was found for a positive association between physical sporting activities and the occurrence of hip OA, with an OR of approximately 2. Possible selection of the studied populations may partly be responsible for the association found, or may have diluted the real association.

Conclusion: The evidence for a positive association between certain sporting activities and the development of hip OA is moderate. The highest risks are found in high intensity activities, especially for hip OA with a clinical presentation.

Arthritis Rheumatism 2003; 49(2): 228-36.

Introduction

Osteoarthritis (OA) of the hip is a common cause of disability of the elderly in western societies. It affects 7-25% of the Caucasian people over the age of 55.[1] Besides pain and discomfort, hip OA has substantial economic consequences[2], and with the aging of the population this problem will increase.

Recreational physical activities, including sporting activities, are widely encouraged as a major public health initiative to reduce cardiovascular diseases and osteoporosis.[3,4] Also recent research suggests that regular exercise can be helpful in reducing the discomfort and dysfunction of OA[5-7], but the risks associated with increased sporting activities are yet unclear.

In recent years, more studies have become available investigating sporting activities and its association with hip OA, and even several reviews have been published on sporting activities and hip OA.[8-11] However, none of the published reviews included clearly defined in- and exclusion criteria, a methodological quality assessment of the studies, as well as explicit criteria on which the assessment of the strength of the evidence was based.

We therefore performed a systematic review, using modern methods for systematically identifying and assessing the available studies, in order to provide update knowledge for patients, doctors and policy makers, on the relation between sporting activities and the occurrence of hip OA. A similar evaluation of the evidence for physical workload as a risk factor for hip OA has been reported elsewhere.[12]

Methods

Identification and selection of the literature

To identify observational studies on this subject, relevant publications were searched using the following databases: Medline (1966 to April 2000), Cochrane library (1993 to April 2000) and EMBASE (1980 to April 2000). The following keywords were used: (hip and (arthritis or arthrosis or osteoarthritis or osteoarthrosis) or coxarthrosis) and (risk factor or causative or determinants or predictor or etiology) and (case-control or retrospective or prospective or longitudinal or follow up or cohort). A detailed list can be obtained from the

corresponding author. The search was extended by screening the reference lists of all relevant articles identified.

A study was eligible for inclusion if it fulfilled all of the following criteria: 1) one of the aims of the study was to investigate an association between hip OA and physical sporting activities, 2) the articles were written in English, Dutch, German, French, Danish, Norwegian or Swedish, 3) the article was a full text article, 4) the patients in the studies had to suffer from radiological and/or clinical hip OA, a (total) hip replacement, or were on the waiting list for one, and 5) the study design was a cohort or a case-control study.

A study was excluded if the population studied had a specific underlying pathology, such as trauma (fractures), infection, rheumatoid arthritis, ankylosing spondylitis, Perthes' disease, tuberculosis, hemochromatosis, sickle cell disease, Cushing's disease, or femoral head necrosis.

Publication bias

Identification of all relevant articles is crucial to the validity of a systematic review.[13] The amount of potential publication bias in our study was analysed by means of a funnel plot, in which the study outcome (Odds ratio (OR) on a log scale) was plotted against the sample size of the study. In the absence of publication bias, the plot will resemble a symmetrical inverted funnel.[14] Because of the lack of required data, we could not perform a statistical test, so we visually examined the funnel plot for symmetry.

Methodological quality assessment

The methodological quality of observational studies can vary considerably, which may influence the results and conclusions of the studies at issue and consequently also the results and conclusions of a systematic review. Therefore, the quality of each included paper was assessed using the following method. Two reviewers (AML and SMABZ) independently scored the quality of the selected papers according to a standardised set of criteria (Appendix 1). These criteria have been used in previous reviews of observational studies in the field of musculoskeletal disorders[12,15,16] and were modified to cover the topic of our review. The criteria concern both the internal validity, and the informativeness of the study. Only items

reflecting the internal validity of the studies were used to assess the methodological quality.

In case of a disagreement the reviewers tried to achieve consensus; if disagreements were not resolved, a third reviewer (BWK) was consulted in order to achieve a final judgement.

Several items are not applicable to a certain type of study design (e.g. cohort study or case-control study), and therefore do not contribute to the total score of that particular study. This means that the maximum score of each study (100%) was based only on the items applicable to that particular type of study design. Positive scores were summed up to an overall internal validity score.

Best evidence synthesis

Because the observational studies were considered to be heterogeneous with regard to the population studied, methodological quality and determinants and outcome measures for hip OA[17], we refrained from statistically pooling of the data and performed a best evidence synthesis.[12,18,19] First the studies were classified according to the type of study design. A prospective cohort study was judged as the most valid design, followed by a case-control study. After that, the studies were ranked according to their methodological quality score. The following ranking of the levels of evidence was formulated.[12,20]

1. Strong evidence is provided by generally consistent findings in multiple high quality cohort studies.
2. Moderate evidence is provided by general consistent findings
   - in one high quality cohort study and two or more high quality case-control studies.
   - in three or more high quality case-control studies.
3. Limited evidence is provided by (general consistent) findings
   - in a single cohort study
   - in ≤ 2 case-control studies
4. Conflicting evidence is provided by conflicting findings (i.e. <75% of the studies reported consistent findings).
5. No evidence is provided when no studies could be found.

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

Data extraction

Two researchers (AML and SMABZ) collected the characteristics of the included studies independently of each other. They collected items on the definition of the study population, how the presence or absence of hip OA was assessed, the assessment of sporting activities, if the study corrected for potential confounding factors and which results were reported.

When a study reported several outcomes because of a division of the study population into subgroups, the separate outcomes were combined (where possible) using Mantel Haenszel statistics, methods described by Clayton and Hills[21] or the method described by Tan and colleagues.[22] We abstracted outcomes on sporting activities in general, and made subgroups for (long distance-) running, soccer, athletic activities, and ballet dancing, where possible.

Results

Identification and selection of the literature

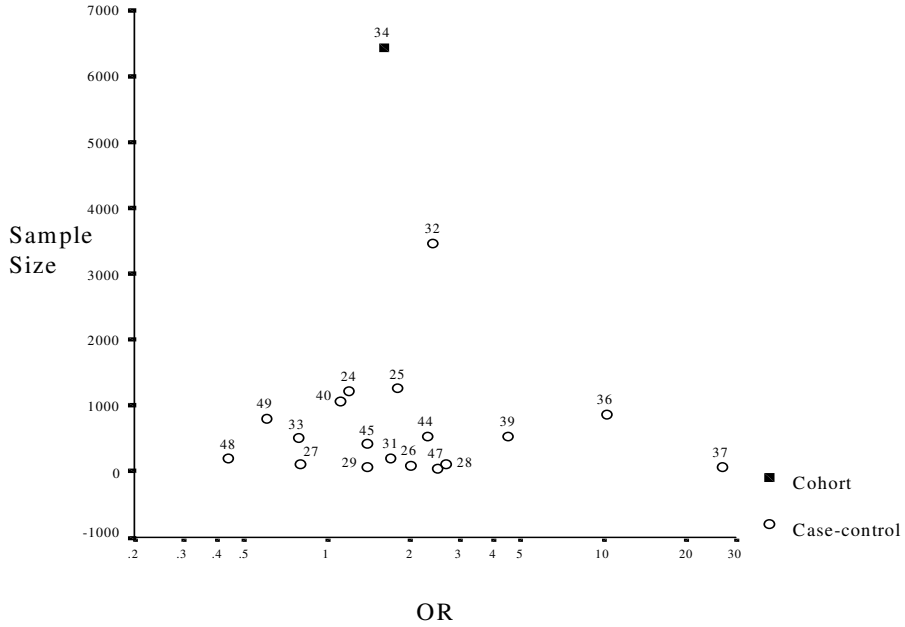
A total of 2921 references were initially identified; of these, 24 articles met our selection criteria.[23-46] After screening the reference lists of the selected studies, another 3 studies were included.[47-49]

For 4 of the studies, there appeared to be more than one publication ([29,30], [37,38], [25,46] and [39,42,43]), reporting different aspects of the study. All publications were used to extract data regarding the methods used and the results. Thus, finally, 22 studies were included in this review.

Publication bias

To investigate the amount of publication bias for our study, a funnel plot was made (Figure 1). The plot shows the relationship between the point estimates of the association between sporting activities and hip OA, and the sample size (n). Nineteen of the 22 included studies, provided sufficient data to be included in the plot. The plot shows a more or less symmetrical shape.

Figure 1: Funnel plot showing the distribution of the OR according to the sample size. Of the 22 included studies, 19 provided sufficient data to be included in this plot. The numbers in the graph represent the reference numbers.



Description of the studies included

Table 1 gives a description of the characteristics of the included studies.

One cohort[34], and 21 case-control studies[23-29,31-33,35-37,39-41,44,45,47-49] were included in this review, of which only one had a prospective design.[26]

Within the case-control studies, 17 of the 21 studies defined the cases by people who participated in sporting activities, and the controls by people who did not.[23,26-29,32,33,35,36,38,40,41,45-49] These studies are sometimes referred to as trohoc studies.[50] The other four case-control studies defined the cases by people with, and the controls without hip OA.[24,31,39,44]

Seven studies included only males[27,29,33,36,39,45,47], whereas five others included only females.[25,34,40,41,44] All studies were carried out in the USA[31,34,35,47,49], or in Europe.[23-29,32,33,36,38-41,44,45,48] Different kinds of sporting activities were studied. Eight studies reported results on a combination of different sporting activities as a group, like basketball, hockey, weight lifting, soccer, bowling, jogging, long distance running, swimming, golf.[24-27,32,34,43,44] Ten studies reported on long distance/cross-country running separately.[27,29,32,35,38-40,43,47,49] Five studies reported on soccer players[24,27,28,36,39], four on athletics[31,32,45,48], and two on ballet.[23,41]

Table 1: Details of the studies included

Cohort study

Author	Definition population	Assessment of hip OA	Assessment of sports	Adjusted for	Results
Lane[34]	All women from population based listings in 4 areas of the USA n=6418 age ≥65	Clinical (pain) X-ray (JSN, osteophytes, cysts, sclerosis, femoral neck deformity)	Times per year in different sports activities	age, gender, BMI	Clinical hip OA: 1vs. 0x week OR 1.1 (0.7-1.7) >4 vs. 0x week OR 1.6 (1.0-2.5) X-ray hip OA OR 1.3 (0.9-2.0)

Case-control studies

Author	Cases/population	Controls	Hip OA	Sports	Adjusted	Results
Marti[37,38]	Swiss national teams in long distance running n=27 age 35 yr.	Healthy untrained volunteers and bobsleigh n=32 age 42 yr.	Clinical (pain function,) X-ray (JSN, sclerosis,)	Trohoc design	age, gender	Hip pain OR 26.7 (1.5-490.4) X-ray hip OA OR 12.4 (0.6-242.5)
Vingard[44]	All female patients with a THR due to prim. hip OA in 5 counties in Sweden n=242 age 50-70 yr.	Random selection of women from same area without hip problems n=298 age 50-70 yr.	After THR	Total hours of different kind of sports activities	gender, age, BMI, workload, hormone	Med. vs. low sports: OR 1.5 (0.9-2.5) High vs. low sports: OR 2.3 (1.5-3.7)
Cooper[24]	Patients on waiting list for THR (prim OA) at 2 clinics in England n=611 age ≥45 yr.	Patients with the same GP n=611 age ≥45 yr.	Waiting for THR	Freq. and duration of sports since leaving high school,	age, gender, Heberden's nodes, hip trauma	All sports OR 1.2 (0.9-1.6) Soccer OR 1.1 (0.7-1.6)
Kujala[32]	Former male Finn athletes competing in int. championship from '20-'65 n=2049	Finnish males who at their 20 were fit (military exam). n=1403	Clinical (physician diagnosed. ICD-codes)	Trohoc design	age, gender, area of residence	All sports OR 2.4 (1.5-4.0) Endurance OR 1.7 (1.0-3.0) Mixed OR 1.9 (1.2-2.9) Power OR 2.2 (1.4-3.3)
Konradsen [29,30]	Danish cross country and long distance runners in nat. championships between '50-'55 n=27 age 50-68 yr.	Males who have had a pelvic radiograph n=27 age 53-65 yr.	X-ray (JSW<3mm, sclerosis, osteophytes)	Trohoc design	age, gender, BMI, workload	X-ray hip OA OR 1.4 (0.4-5.8)
Olsen[39] Vingard[42,43]	All male patients with a THR due to prim. hip OA in Stockholm n=233 age 50-70 yr.	Random selection of man living in the referral areas n=302 age 50-70 yr.	After THR	Total hours of different kind of sports activities	age, gender, BMI, work, smoking	Med. vs. low exposure OR 2.6 (1.5-4.5) High exposure OR 4.5 (2.7-7.6) Soccer OR 2.3 (0.7-7.7) Long run OR 2.1 (0.6-6.8)
Lindberg[36]	Men from 10 soccer clubs in Malmö (Sweden) n=286 age 40-88 yr.	Random selection of male population of Malmö n=572 age 40-88 yr.	Clinical (need for THR) X-ray (JSW)	Trohoc design	age, gender	THR OR 10.2 (1.2-87.3) X-ray OR 2.1 (1.0-4.2) vs. controls (elite OR 3.7 (1.4-10.1) non-elite OR 1.0 (0.2-4.1))
Vingard[45]	All former Swedish male winner athletes n=109 age 50-80 yr.	Random selection of males from the population records n=302 age 50-80	Clinical (reported diagnosis)	Trohoc design	age, gender	Clinical hip OA OR 1.4 (0.3-5.7) Prevalence ratio 3.6 (1.4-9.3)
Kettunen[27]	Former male elite sporters from Finland n=88 age 58 (45-67) yr.	Former male elite shooters n=29 age 61 (50-68)	Clinical (pain, disability) X-ray (JSN, cysts, deformation femur head)	Trohoc design	gender	Hip pain OR 0.8 (0.2-2.4) X-ray hip OA OR 0.5 (0.2-1.6) Long distance running hip pain OR 1.3 (0.9-4.9) X-ray OR 0.4 (0.1-1.9) Soccer hip pain OR 0.7 (0.2-3.0) X-ray OR 0.4 (0.1-1.9)

Author	Cases/population	Controls	Hip OA	Sports	Adjusted	Results
Kraus[31]	Patients referred by physicians with prim. hip OA (USA) (n=100)	Patients at the same hospital at dep. surgery or general medicine (n=100)	Clinical (patients)	athletic activities during high school,	age, gender, race	Participating in athletic activities at high school OR 1.7 (0.8-3.4)
Kujala[33]	Orienteering male cross-country runners in Finland n=269 age 37-61 yr.	Finnish males who at their 20 were fit (military exam). n=229	Clinical (hip pain, physician diagnosed)	Trohoc design	age, gender, area of residence	Clinical hip OA OR 0.8 (0.35-1.73)
Lane[35]	Long distance runners living in the USA n=28 age 66.4	Persons living within 100 miles of the Stanford university n=27 age 66.4	X-ray (JSN, sclerosis, osteophytes)	Trohoc design	age, education, workload	X-ray hip OA similar for runners and non runners
Spector[40]	English female ex elite middle and long distance runners + tennis players n=81 age 40-65 yr	Females from the general population of N-E- London n=977 age 40-65 yr.	Clinical (pain) X-ray (JSN, osteophytes)	Trohoc design	age, gender, height, weight	Hip pain OR 1.12 (0.6-2.0) X-ray hip OA OR 1.6 (0.7-3.5)
Sohn[49]	Cross country runners of 7 USA colleges competing between '30-'60 n=504 age 23-77 yr.	Swimmers of 3 schools who competed between '30-'60 n=287 age 23-77	Clinical (pain, need for a THR)	Trohoc design	age, gender, weight, education, soc. class	THR OR 0.6 (0.1-2.28)
White[46] Eastmond[25]	Female physical education teachers of five colleges in England n=440 age 46-60 yr.	Woman from general population n=887	X-ray (Kellgren and Lawrence)	Trohoc design	age, gender	X-ray hip OA OR 1.8 (0.8-3.9)
Jucker[26]	Sporters from Switzerland n=41 age 35 yr.	Volunteers n=38 age 36	Clinical (function) X-ray (not specified)	Trohoc design	-	Hip pain OR 2.0 (0.5-8.6) X-ray hip OA OR 32.6 (0.1-9492)
Klunder[28]	Former active football players in Vejle (Denmark) n=57 age 40-79 yr.	Patients without lower extremity problems and never active footballers n=57 age 42-80 yr.	X-ray (JSN, sclerosis, cyst)	Trohoc design	age, gender, weight	X-ray hip OA OR 2.7 (1.2-5.9)
Panush[47]	Volunteer current male runners n=17 age 50-74	Male volunteer non runners n=18 age 50-74	Clinical (complaints, physical examination)	Trohoc design	gender	Hip pain OR 2.5 (0.4-15.6)
Van Dijk[41]	Former female members of major Dutch ballet companies n=19 age 50-70 yr.	Female patients of the plastic and orthopaedic surgery without lower extremity problems n=19	X-ray (JSW, osteophytes, sclerosis, cysts, bone destruction)	Trohoc design	age, gender, height, weight	No statistically difference in the two groups.
Puranen[48]	All male athletes from Finland from int. championships in '20-'65 n=74 age (31-81) yr.	Files and X-rays of male patients at univ. hospital. without hip complaints n=115 age 40-75 yr.	X-ray (osteophytes and OA changes)	Trohoc design	gender	X-ray hip OA OR 0.4 (0.1-1.7)
Andersson[23]	Former ballet dancers from 5 places in Sweden n=44 age 44-80 yr.	General population in 2 cities in Sweden n=?	Clinical (history, need for THR) X-ray (JSN)	Trohoc design	-	OA occurred more often in ballet dancers (p<0.001)

THR= total hip replacemen JSN=joint space narrowing, JSN= joint space narrowing, JSW= joint space width, BMI= bodymass index, K&L=Kellgren and Lawrence

Four studies specified the amount of sporting activities and made different levels of the amount of sporting (e.g. lowest quartile vs. highest quartile of total amount of hours sported)[34,37,43,44], whereas all others analysed the odds ratio (OR) with participation in the sporting activity or not.[23,25-28,30-33,35,41,45,47-49]

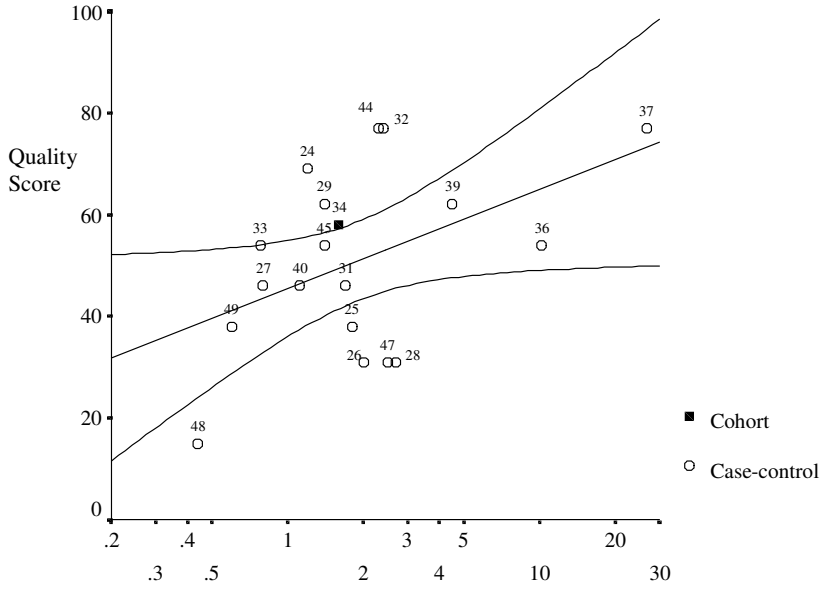
The assessment of hip OA also varies in several studies. Fourteen studies relied on clinical information (e.g. seen at a clinic, need for a THR)[24,26,27,31-33,36,38-40,44,45,47,49], and 11 studies reported data with a radiological assessment of hip OA.[25-29,35,36,38,40,47,48] The other studies based the presence of hip OA on a combination of clinical and radiological parameters.[23,34,41]

Methodological quality assessment

The two reviewers scored 620 items and agreed on 568 items (92%, kappa 0.83). The 52 disagreements were resolved in a single consensus meeting. Table 2 shows the studies in order of their methodological quality score, subdivided in the different types of study design (i.e. cohort and case-control studies). The scores range from 0% to 77% of the maximum obtainable score for each study design. The mean quality score was 47%. Six of the 22 (27%) studies were considered of high quality (≥60%).

A clear correlation was found between the quality score and the study outcome (Figure 2) (Pearson correlation 0.5, p-value 0.05)

Figure 2: Quality score of 19 of the 22 studies in relation to the odds ratio. The numbers in the graph represent the reference numbers. The lines represent the linear regression line and the 95% confidence interval.



This implies that the higher the quality score of the study, the stronger the reported association between sporting activities and hip OA. However, three of the 22 studies could not be plotted due to a lack of precise data on the OR/RR.

Table 2: Results of the quality score of the studies

Item	1	2	3	4	5 *	6	7	8	9	10	11	12 *	13	14	15	16 *	17 *	18	19	Score	Obtainable	Total score
Cohort																						
Lane [34]	1	-	0	-	1	0	-	0	1	1	1	1	0	1	0	0	1	1	1	7	12	58%
Case-control																						
Marti [37,38]	0	0	1	1	0	1	1	1	1	1	1	1	0	-	-	-	1	1	1	10	13	77%
Vingard [44]	1	1	1	1	1	0	1	0	1	1	1	1	0	-	-	-	1	1	1	10	13	77%
Cooper [24]	1	1	1	0	1	0	1	0	1	1	1	1	0	-	-	-	1	1	1	9	13	69%
Kujala [32]	0	1	1	1	1	1	1	1	1	0	0	0	0	-	-	-	1	1	1	9	13	69%
Konradsen [29]	1	0	1	0	1	0	0	1	1	1	1	1	0	-	-	-	1	1	1	8	13	62%
Olsen/Vingard [39,42,43]	1	1	1	0	1	0	1	0	0	1	1	1	0	-	-	-	1	1	1	8	13	62%
Lindberg [36]	0	1	0	0	0	1	0	1	0	1	1	1	0	-	-	-	1	1	1	7	13	54%
Vingard [45]	0	1	1	1	1	0	0	1	1	0	0	0	0	-	-	-	1	1	1	7	13	54%
Kettunen [27]	0	0	1	1	1	1	1	0	1	0	0	0	0	-	-	-	1	1	0	6	13	46%
Kraus [31]	1	1	1	1	1	0	1	0	0	0	0	0	0	-	-	-	1	0	1	6	13	46%
Kujala [33]	0	1	1	1	0	0	0	0	1	0	0	0	0	-	-	-	1	1	1	6	13	46%
Lane [35]	0	1	0	0	0	1	0	1	1	1	1	1	0	-	-	-	1	0	0	6	13	46%
Spector [40]	0	0	0	0	0	1	0	0	1	1	1	1	0	-	-	-	1	1	1	6	13	46%
Sohn [49]	0	1	0	0	0	0	1	1	1	0	0	0	0	-	-	-	0	0	1	5	13	38%
White [25,46]	1	0	0	0	0	0	0	0	0	1	1	1	0	-	-	-	1	1	1	5	13	38%
Jucker [26]	0	0	0	0	0	1	0	1	1	0	0	0	1	-	-	-	1	0	0	4	13	31%
Klunder [28]	0	0	1	0	1	0	0	0	1	0	0	0	0	-	-	-	1	1	1	4	13	31%
Panush [47]	0	0	0	0	1	0	1	0	1	1	1	0	0	-	-	-	1	0	0	4	13	31%
van Dijk [41]	1	0	0	0	1	0	0	0	1	0	0	0	0	-	-	-	1	1	1	4	13	31%
Puranen [48]	0	0	0	0	0	1	0	1	0	0	0	0	0	-	-	-	1	0	0	2	13	15%
Andersson [23]	0	0	0	0	0	0	0	0	0	0	0	0	0	-	-	-	1	0	0	0	13	0%

Each item was scored as "1" when it met the specified criteria listed in Appendix A. (see chapter “appendices”)
When it did not meet the criteria, or it was not described at all a "0" was assigned
Positive validity scores were summed up to an overall internal validity score.
*= informativity item. Not included in the analysis - = not applicable

Of these, Lane and colleagues[35] achieved a quality score of 54% and reported no association between sporting and hip OA. Van Dijk et al.[41] scored 31% and reported no association, but Andersson[23] achieved a score of 0% and reported a significant positive association between sporting and hip OA.

One of the main concerns of the internal validity of observational studies is that of confounding.[51] In case of confounding, the observed effect may occur due to a combination of several determinants that are prevalent in the study population. In hip OA two potential confounders are age and gender, and there should have been a correction for at least these determinants in the individual studies. Six of the 22 studies did not meet this criterion[23,26,27,35,47,48], all the others did by means of matching, restriction or adjustment in the analysis.

Strength of relationship

Nineteen of the 22 studies showed exact data on the outcomes; the other three described the outcome in global terms.[23,35,41].

Fourteen studies showed a positive association between sporting activities and hip OA (OR $\geq$ 1.25)[23,25,26,28,29,31,32,34,36,38,39,44,45,47] of which five were statistically significant[28,32,36,43,44], indicating that subjects with certain sporting activities have an increased risk for developing hip OA as compared to non sporters. Five of these studies reached the level of high quality.[29,32,34,38,44]

Four studies reported a negative relationship[27,33,48,49], but none of these were statistically significant or reached the level of high quality. Four studies reported no association (0.8< OR <1.25).[24,35,40,41] One reached the level of high quality.[24] In order to investigate the existence of a dose response relationship, we selected the studies reporting on different levels of sporting activities. We also compared the results of normal sporting activities vs. high intensity (elite) sporting activities. All of the four studies analysing different levels of sporting activities did report a clear dose response relationship (table 1).[34,36,43,44] A higher level or frequency of sporting activities raised the OR with a factor 1.5 to 3.7. There were seven studies reporting activities on elite athletes.[27,29,32,38,40,45,48] The controls in six of these studies were nonathletes. In one study they were elite shooters.[27] The OR's in these studies seem to be comparable to the OR's found in studies reporting on normal sporting activities (table 1 and 3).

Looking at a division between a clinical vs. a radiological assessment of hip OA, four out of six studies[26,27,34,36,38,40] reporting on both outcomes, reported a stronger association in the clinical, as compared to the radiological assessed hip OA.[27,34,36,38] The other five studies reported on radiological hip OA only, and the OR's were comparable to the OR's found in studies with a clinical assessment of hip OA (table 1 and 3).

Table 3: Best evidence synthesis

	X-ray	Clinical	Quality score	Best evidence synthesis
Combination of sports				
Vingard [44]		2.3 (1.5-3.7)	77	>3 high quality case-control studies + consistent findings for a positive association = MODERATE EVIDENCE
Cooper [24]		1.2 (0.9-1.6)	69	
Kujala [32]		2.4 (1.5-4.0)	69	
Lane [34]	1.3 (0.9-2.0)	1.6 (1.0-2.5)	58	
Kettunen [27]	0.5 (0.2-1.6)	0.8 (0.2-2.4)	46	
Eastmond [25]	1.8 (0.8-3.9)		38	
Jucker [26]	32.6 (0,1-9492)	2.0 (0.5-8.6)	31	
Running				
Marti [38]	12.4 (0.6-242.5)	26.7 (1.5-490.4)	77	>3 high quality case-control studies + consistent findings for a positive association = MODERATE EVIDENCE
Kujala [32]		1.7 (1.0-3.0)	69	
Olsen [39]		2.1 (0.6-6.8)	62	
Kujala [33]		0.8 (0.4-1.7)	46	
Lane [35]	No difference		46	
Kettunen [27]	0.4 (0.1-1.9)	1.3 (0.9-4.9)	46	
Spector [40]	1.6 (0.7-3.5)	1.1 (0.6-2.0)	46	
Sohn [49]		0.6 (0.1-2.3)	38	
Panush [47]	1.1 (0.0-56)	2.5 (0.4-15.6)	31	
Soccer				
Cooper [24]		1.1 (0.7-1.6)	69	2 high quality case-control studies + conflicting findings = CONFLICTING EVIDENCE
Olsen [39]		2.3 (0.7-7.7)	62	
Lindberg [36]	2.1 (1.0-4.2)	10.2 (1.2-87.3)	54	
Kettunen [27]	0.4 (0.1-1.9)	0.7 (0.2-3.0)	46	
Klunder [28]	2.7 (1.2-5.9)		31	
Athletics				
Kujala [32]		1.9 (1.2-2.9)	69	One high quality case-control study = LIMITED EVIDENCE
Vingard [45]		1.4 (0.3-5.7	54	
Kraus [31]		1.7 (0.8-3.4)	46	
Puranen [48]	0.4 (0.1-1.7)		15	
Ballet				
Van Dijk [41]	No significant difference (X-ray)		31	Conflicting findings in the 2 case-control studies = CONFLICTING EVIDENCE
Andersson [23]	Significant more in dancers (Clinical)		0	

Best evidence synthesis

Based on the best evidence synthesis (Table 3), we may conclude that there is moderate evidence for a positive relationship between physical sporting activities in general and hip OA, with an OR of approximately 2. With the best evidence synthesis on the different subgroups, the evidence found on the relationship between running and the occurrence of hip OA, is also moderate, with an OR of approximately 2. On the subgroup of athletics and hip OA the evidence found is limited for a positive relationship, and for the subgroups of soccer playing and ballet dancing the evidence is conflicting.

Discussion

In this systematic review, we summarized the available evidence in the literature on the influence of physical sporting activities on the development of OA of the hip. Based on the evidence, we may conclude that there is moderate evidence for a positive association between hip OA and sporting activities. Notable was that most of the studies had a trohoc design, where the cases were people who performed some kind of sporting activities, and the controls were people who did not.[23,25-29,32,33,35,36,38,40,41,45,47-49] In this type of design, bias can occur firstly because this design is retrospective, and secondly because sporters differed from non sporters on other prognostic factors possibly related to hip OA. Not only the life expectancy of sporters compared to the non sporters is higher[52], also the BMI, the pain threshold[40], the amount of trauma to the lower extremities, and the occupational and leisure activities of sporters may differ from non sporters. These confounders may cause an underestimate or an overestimate of the real OR, but in only some of these studies, there was a correction for the BMI[29,40,41,49] or workload.[29,35] These shortcomings of the included studies, as well as the heterogeneity in the studies population and outcomemeasures, limit the level of certainty of our conclusion. Besides limitations of the included studies, this review may suffer from several restrictions as well.

Although we have put much effort into identifying the relevant articles, our literature search might suffer from some limitations. Some relevant articles may have been missed because they used other keywords or had unclear abstracts and not all published articles are indexed in databases. Besides that, we excluded

articles written in languages other than English, Dutch, German, French, Danish, Norwegian or Swedish.

The presumed absence of publication bias found in our results (Figure 1) might be expected in this field of research. Studies that would have found no (or a negative) relationship have, in our opinion, the same opportunities for publication because there are no obvious conflicts of interest. When assessing the funnel plot, we have to keep in mind that three of the 22 studies could not be included in the analysis due to insufficient data to deduce a point estimate. We believe, however, that these data are unlikely to greatly influence our results. Unfortunately, only one cohort study studying the association between sporting activities and hip OA could be found. This type of study design is known to be the most valid type of observational studies. Having more data from this type of design would have allowed us to provide a more valid and precise conclusion.

The quality assessment was challenging because there were no previously tested and validated criteria lists published for observational studies in the field of OA. Due to a lack of information about the induction time of the sporting activities on the development of hip OA, a part of the advantage of a longitudinal study versus a case-control study disposes.

Also, limited data were found to perform a best evidence synthesis with observational studies. Therefore we presented them in a reproducible manner, and the criteria we used were relatively strict.

Although we are aware of the possibility for bias in most of the articles, the best evidence synthesis results in moderate evidence for a positive relation between sporting activities and the occurrence of hip OA. In this review we found a stronger association in the clinically assessed hip OA, as compared with the radiological assessed hip OA. Similar results were found in another review.[12] One explanation for this finding could be that people participating in regular sporting activities do suffer more from the same radiological degree of degeneration from the hip joint than do nonparticipants, because sporting activities place great demands on the body. Another explanation could be that the hip complaint reflect hip symptoms due to nonarticular problems (e.g. tendinitis, bursitis, muscle strain etc.), because in 5 of the 6 studies clinical hip OA was defined as ‘hip pain’.

Should we now all stop participating in sporting activities?

If the only thing we should prevent was hip OA, the answer to this question should probabilly be yes. But besides the scientifically marginal literature this review is based upon, we do not know if physical sporting activities accelerate the development of hip OA, or if sporters do suffer more from the same degree of hip OA than non sporters.

Conclusion

The best evidence synthesis in this systematic review shows that there is moderate evidence for a positive relation between certain physical sporting activities and the occurrence of hip OA . The quality of studies reporting on this relationship, however, is disappointingly low. Future studies, especially prospective cohort studies, are clearly needed to gain better evidence.

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5

Influence of hip dysplasia on the development of osteoarthritis of the hip: a systematic review

Abstract

Objectives: It has been proposed that some patients with primary hip osteoarthritis (OA), the disease occurs as a consequence of acetabular dysplasia or hip dysplasia. To investigate the association between acetabular dysplasia and hip OA, we performed a systematic review.

Methods: To identify all observational studies for this systematic review, a database search of Medline, Embase and Cochrane library was carried out, and articles that aim to study the relationship between HD and hip OA were identified. The methodological quality of the selected studies was assessed using a standardised set of criteria, and a best evidence synthesis was used to summarise the results from the individual studies.

Results: Five cohort studies and four case-control studies were included in this review. One cohort study had the correct design to be able to address to the question and reached the level of high quality study. This study reported a positive association between HD and hip OA. Overall, limited evidence was found for a positive association between HD and hip OA. However, most studies included persons at a higher age group. In younger age groups the relation between HD and OA or hip complaints may be much higher.

Conclusion: The evidence for the influence of HD on the occurrence of hip OA, at age 50-60 or older, is limited.

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Introduction

Osteoarthritis of the hip (hip OA) is an increasing problem in western societies, and is a major cause of morbidity and disability, especially among the elderly. In addition to the pain and discomfort it causes, OA has major economic consequences.[1]

The reported prevalence figures of hip OA varies widely due to differences in the definition of OA or the selection of the study population. Studies in Europe have estimated that approximately 7-25% of Caucasian individuals over the age of 55 years suffer from hip OA. The prevalence of hip OA appears to be lowest in Asians, followed by African black and Native American populations, and is highest in white Europeans.[2-5]

It has been proposed that in a part of patients with primary hip OA, the disease occurs as a consequence of acetabular dysplasia or hip dysplasia (HD), which persist into adult life. Some radiological observations in patients with hip OA, and follow-up studies of subjects with HD support this theory.[6-8] However, not all studies have reported a positive association.[9]

To investigate if HD pre-dates hip OA, we performed a systematic review, using modern methods for systematically identifying and assessing the available studies.

Methods

Identification and selection of the literature

Relevant publications were searched using the Cochrane library (1993- April 2000), Medline (1966- April 2000) and Embase (1980-April 2000) databases. The following keywords were used: (hip and (arthritis or arthrosis or osteoarthritis or osteoarthrosis) or coxarthrosis) and (risk factor or causative or determinants or predictor or aetiology) and (case-control or retrospective or prospective or longitudinal or follow up or cohort). A detailed list can be obtained from the corresponding author

We extended the search by screening the reference lists of all relevant articles identified.

A study was eligible for inclusion if it fulfilled all of the following criteria: 1) one of the aims of the study was to investigate an association between HD and hip OA, 2) the articles were written in English, Dutch, German, French, Danish, Norwegian

or Swedish, 3) the article was a full text article, 4) the patients in the studies had to have a radiological and/or clinical hip OA, a (total) hip replacement, or were on the waiting list for one, and 5) the study design was a cohort or a case-control study.
A study was excluded if the studied population had a specific underlying pathology, such as trauma (fractures), infection, rheumatoid arthritis, ankylosing spondylitis, Perthes' disease, tuberculosis, hemochromatosis, sickle cell disease, Cushing's disease, or femoral head necrosis.

Methodological quality assessment

The variation of the methodological quality of observational studies may influence the results and conclusions of a systematic review. Therefore, the quality of each included study was assessed using the following procedure.
Two reviewers independently scored the quality of the selected papers according to a standardised set of criteria (Appendix 1). These criteria have been used in previous reviews of observational studies in the field of musculoskeletal disorders and were modified to cover the topic of our review.[10-13] The criteria concern both the internal validity, and the informativeness of the study. Only items reflecting the internal validity of the studies were used to assess the methodological quality.
In case of a disagreement, both reviewers tried to achieve consensus; if disagreements were not resolved, a third reviewer was consulted in order to achieve a final judgement.
Several items are not applicable to a certain type of study design (e.g. cohort study or case-control study), and therefore do not contribute to the total score of that particular study. This means that the maximum score of each study (=100%) was based only on the items applicable to that particular type of study design. Positive scores were summed up to an overall internal validity score.

Best evidence synthesis

Because observational studies are heterogeneous with regard to the study population, methodological quality and determinants and outcome measures for hip OA, we refrained from statistically pooling the data,[14] and performed a "best evidence synthesis".[10,11,14-17]
The studies were stratified according to the type of study design. In order to clarify the question whether AD pre-dates hip OA, the only studies which can really

address this question are prospective cohort studies: i.e. they follow patients without hip OA with the presence or absence of HD measured, forward in time, and identify who develops hip OA subsequently. Therefore these studies were judged as the most valid design. Studies with cross-sectional data on hip OA and HD were not considered in the best evidence synthesis. Furthermore, the studies were ranked according to their methodological quality score:[10,11,18]

1. Strong evidence is provided by generally consistent findings in multiple high quality cohort studies.
2. Moderate evidence is provided by general consistent findings
   - in one high quality cohort study and two or more high quality case-control studies.
   - in three or more high quality case-control studies.
3. Limited evidence is provided by (general consistent) findings
   - a single cohort study
   - in ≤ 2 case-control studies
4. Conflicting evidence was provided by conflicting findings (i.e. <75% of the studies reported consistent findings).
5. No evidence was provided when no studies could be found.

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

Data extraction

Two researchers (AML and SMABZ) independently collected the characteristics of the included studies. They collected items concerning the definition of the studied population, how the presence or absence of hip OA was assessed, the assessment of HD, if the study corrected for potential confounding factors, and which results were reported.

Results

Identification and selection of the literature

2921 references were identified. After an initial shifting on the title and the abstract of the references, the full text papers were screened whether they met our selection criteria. Of these, 12 articles met the criteria.[6,9,19-28]

After screening the reference lists of the selected studies, one other study was included. [8]

For three studies, there was more than one publication, reporting different aspects of the studies.[20,21], [6,22], [9,19,28] All publications were used to extract data regarding the methods used and the results.

Finally, 9 studies were included in this review.

Description of the studies included

Table 1 gives a description of the characteristics of the included studies.

Five studies had a cohort design.[6,20,23,25,28] After screening the reference lists of the selected studies, one other study was included.[8]

For three studies, there was more than one publication, reporting different aspects of the studies.[20,21], [6,22], [9,19,28] and four studies had a case-control design.[8,24,26,27]

Three of the five cohort studies collected the data in a prospective manner,[6,20,25] and only one study followed up patients without hip OA, forward in time.[6]

One study included only males,[23] and one other only females.[6] Six studies included patients with the age of 60 – 65 years or older,[6,23-25,27,28] the other three included a population with younger individuals as well.[8,20,26] Data on congenital HD are lacking.

Three studies reported data on Asian,[20] or on Asian and Caucasian populations.[23,28] All others reported on Caucasian people.

Only one study was community based,[6] all others were hospital based. Of these hospital-based studies, two actually selected the patients not on the presence or absence of hip OA, but on having had an intra-venous urography (IVU).[23,28]

In all studies, the assessment of HD was done by measuring the center-edge (CE)angle (is the angle between 1) a vertical line drawn from the center of the femoral head at right angles to the line joining the 2 femoral head centers, and 2) a line from the center of the femoral head to the lateral edge of the acetabular roof).

Seven of the nine studies also measured the acetabular depth (AD; the perpendicular distance from the deepest point of the acetabular roof to the line joining the the lateral margin of the acetabular roof and the upper corner of the symphisis pubis on the same side), index or ratio.[6,8,20,23,25,27,28]

Table 1: Details of the studies included in this review

Author	Cases/ population	Definition controls	Definition hip OA	Definition dysplasia	Results
Cohort					
Lane[6,22]	White female in four regions of the USA with (K&L 2-4) and without (K&L 0) hip OA (n=58/118, ≥65 yr.) Nested case control with 8.3 (7.4-10.4) yr. prospective follow-up		X-ray (K&L)	CE-angle <30° AD <9mm.	Female with vs. without hip OA had a smaller CE-angle OR 3.3 (1.1-10.1) a smaller AD OR 0.6 (0.1-3.3) dysplasia OR 2.8 (1.0-7.9)
Murphy[25]	Patients after THR because of hip OA, with (K&L 3-4) and without (K&L 0-2) controlateral hip OA (n=74/43, ≥65 yr.) Nested case control prospective follow-up		X-ray (K&L)	CE-angle AD index (depth/width)	CE-angle and acetabular index were significantly smaller in the OA patients (p<0.0001)
Hasegawa [20,21]	Japanese patients with pre or early hip OA (n=64, 13-62 yr.) Prosp. follow-up 12.8(10-25) yr.		X-ray (JSN, sclerosis)	CE-angle AD-ratio	Patients with a fast progression from pre to early hip OA had a significant smaller CE-angle, and a smaller AD-ratio (p<0.001)
Yoshimura [28] Croft[19] Smith[9]	British patients after IV urography (n=1498, 60-75 yr.) and Japanese people after pelvic X-ray (n=198, 60-79yr.) Cross sectional		X-ray (MJS)	CE-angle AD	Correlation between MJS and CE-angle: British male r = -0.37 female r= -0.25 Jappanese male r= -0.39 female r= -0.26 Correlation between MJS and AD: British male r = -0.15 female r= -0.11 Jappanese male r=-0.09 female r=-0.07
Lau[23]	Male Chinese and British* patients after IV urography (n=999, 60-75 yr.) Cross-sectional		X-ray (MJS≤1.5)	CE-angle <25° AD <9mm.	People with a MJS ≤1.5 vs. >4 mm had a smaller AD (OR 0.4 (0.05-2.9)) and a smaller CE-angle (OR 0.5 (0.03-8.7))
Case-control					
Laforgia[24]	Patients in Italy on waiting list for osteotomy or THR (n=60, age 77 yr.) Cross-sectional	Trauma patients with an X-ray without hip OA (n=49, age 77)	Waiting list	CE-angle	CE-angle is significantly smaller in superolat. OA, and sign. higher in concentral/ medial OA as compared to controls
Murray[8]	British patients with hip OA (n=50) Cross-sectional	Patients without hip OA (n=200)	Clinical (patients) X-ray (JSN, cysts, osteophytes)	CE-angle <25° AD <9mm.	Patients with HD showed an earlier age of onset of hip OA (50,8 yr. versus 57,7 yr. in control)
Terjesen[26]	Patients in Norway at orthopaedics with hip complaints, with CE≥20° (n=50, 48-81 yr.) Cross-sectional	Patients of the same department without a hip disease, with CE≥20° (n=30, 52-84 yr.)	Clinical (pain, disability) X-ray	CE-angle <25°	No significant difference in CE-angle between patients with vs. without hip OA
Wedge[27]	Patients in Canada with prim. hip OA (n=30, 65 yr.) Retrospective	Random selection of post injury X-rays n=54 52 yr.	Clinical (patients) X-ray	CE-angle <25° AD <14mm. on AP X-ray	Patients with hip OA had a significant smaller CE-angle and AD

K&L= Kllgren and Lawrence AD= acetabular depth IV= intra venous JSN= joint space narrowing MJS= mean joint space

The cut-off point for the definition of HD according to the CE-angle was ≤25° in three studies[6,8,23,27] and ≤30° in one study.[6] One study used a CE-angle ≤20° as an exclusion criterion for the studied patients.[26]

Two of the five cohort studies defined the presence of hip OA by a radiographic scoring system, described by Kellgren and Lawrence.[6,25] In the three other cohort studies, the assessment of hip OA was based on the measurements of the joint space width. The four case-control studies based their case series on hospital patients with hip OA, so their definition of hip OA was a combination of clinical signs or complaints and radiographic abnormalities.[8,24,26,27]

Results of the studies included

The included studies presented their results in various ways; one reported a correlation coefficient,[28] and two reported an odds ratio (OR).[6,23] The six other studies described the outcomes in global terms only.[8,20,24-27]

In order to provide a global overview of the reported outcomes, we assessed whether the relationship between HD and the occurrence of hip OA was 'positive' (the presence of HD is a risk factor for hip OA), 'negative' (HD protects for hip OA) or 'no' (there is no (significant) relation). A more detailed description of the outcomes is given in table 1.

Six studies reported a positive association,[6,8,20,24,25,27] ; five of them reported the outcomes in global terms, and the only prospective follow-up study reported that patients with dysplasia had a 2.8 higher risk in developing hip OA.[6] Two studies reported a negative association[23,28]; one reported a correlation coefficient of approximately –0.38 implying that a smaller CE-angle is correlated to a broader MJS.[28] The other study reported that people with dysplasia had a 0.5 to 0.4 smaller risk of having a hip OA.[23] Both studies reported partially on the same population. Only one study reported no relationship.[26]

Methodological quality assessment

The two reviewers scored 514 items and agreed on 467 items (95%, kappa 0.80). The 47 disagreements were resolved in a single consensus meeting. Table 2 shows the studies in order of their methodological quality score, subdivided in the different types of study design (i.e. cohort and case-control studies). The scores range from 75% to 23%, and the average rating was 45%.

Table 2: Quality scores of the of the studies included in this review

Criteria no.	1	2	3	4	5 *	6	7	8	9	10	11	12 *	13	14	15	16 *	17 *	18	19	Score	Oobtainable	Total score
Cohort																						
Lane [6,22]	1	-	0	-	1	0	-	1	1	1	1	1	1	1	0	0	1	1	1	9	12	75%
Murphy [25]	1	-	1	-	1	0	-	1	1	1	1	1	1	0	0	0	1	0	0	7	12	58%
Hasegawa [20,21]	1	-	0	-	0	0	-	0	1	0	0	0	1	1	1	1	1	1	0	6	12	50%
Yoshimura[28], Croft[19] Smith[9]	0	-	1	-	0	0	-	0	1	1	1	1	0	0	0	0	1	1	1	6	12	50%
Lau [23]	0	-	1	-	0	0	-	0	1	1	1	1	0	0	0	0	1	0	1	5	12	42%
Case-control																						
Laforgia [24]	1	0	0	0	1	0	1	0	1	1	1	1	0	-	-	-	1	0	0	5	13	38%
Murray [8]	1	0	0	0	0	0	1	0	1	0	0	0	0	-	-	-	1	1	1	5	13	38%
Terjesen [26]	1	0	0	0	0	0	1	0	1	0	0	0	0	-	-	-	1	0	1	4	13	31%
Wedge [27]	1	0	0	0	0	0	1	1	0	0	0	0	0	-	-	-	1	0	0	3	13	23%

- = Not applicable. * = Informativity item. Not included in the analysis.

Best evidence synthesis

Only one of the three prospective cohort studies had the design that really could address to the research question, and this study reached the level of high quality. The other two prospective cohort studies did not reach the level of high quality.

The high quality prospective cohort study reported a positive association between HD and the occurrence of hip OA with prospective data, implying that a patient with HD, has a higher chance of getting hip OA. This means that there is limited evidence for a positive association between HD and the development of hip OA.

Discussion

In this systematic review, we summarised the available evidence in the literature on the influence of HD on the development of hip OA. Based on the evidence, we may conclude that there is limited evidence for a positive association between HD and hip OA. However, most studies included persons at a higher age group (e.g. 50-60 years or older). In younger age groups the relation between HD and OA or

hip complaints seem to be much higher.[29] In these kind of populations however, it is difficult to study the relationship, because the power of a prospective cohort study to estimate an effect in this rare disease would need for implausibly large samples.

Five out of nine studies had cross-sectional data. One of the most important biases in these studies is that the measurements of HD can be modified by the OA-process. For example, osteophyte formation might make it difficult to correctly locate the lateral acetabular margin, resulting in less reliable measurements of the CE-angle and AD. Moreover, medial migration of the femoral head may increase the CE-angle.

In fact, the data we found support the theory that changes in the hip joint geometry as a result of OA may be responsible for the (weak) negative association. All three prospective studies, including the only study with a hip OA free population at the beginning of the study, reported a positive relationship between HD and the occurrence of hip OA, and the single retrospective study reported no association.

Two of the five cohort studies included people after having had an IVU. Although these populations are hospital based, the requirement for an IVU implies no marked differences in acetabular dimensions, and therefore biases due to selection for treatment of hip OA, are avoided. But, the leg position during X-ray is not standardised for an IVU, and patients with sustained hip OA tend to lie with the leg in external rotation. This rotation of the hip may influence the measurements of the CE-angle. Although these differences are estimated to be small,[30] they may produce less reliable results. Both studies performed with data from IVU reported a negative association, whereas five of the seven other studies reported a positive, and none reported a negative association. Also the difference in the X-ray techniques used (e.g. for trauma, IVU and before hip replacement) might make it more difficult to compare the data.

Besides restrictions of the included studies, this review may suffer from several restrictions as well.

Identification and selection of the literature

Although we have put much effort into identifying all relevant articles, our literature search might have some limitations, not only because some relevant articles may have been missed because they used other keywords or had unclear abstracts,

but also not all published articles are indexed in databases. Besides that, we excluded articles written in languages other than English, Dutch, German, French, Danish, Norwegian or Swedish.

To investigate the amount of potential publication bias for our study, we planned to make a funnel plot,[10] but only three of the nine studies provided enough data to allow us making this funnel plot. Unfortunately this implies that we are unable to visualise the possibility of publication bias in this review.

Quality assessment and best evidence synthesis

The quality assessment was challenging because there were no previously tested and validated criteria lists published for observational studies in the field of OA. In addition, limited data was found on performing a best evidence synthesis with observational studies (in contrast with RCT's).[31] We therefore presented our methods in a reproducible manner, in order to give the reader insight in the pathway how our level of evidence is reached.

In the best evidence synthesis, we defined that only prospective cohort studies are able to address the research question. In fact only those with a disease free population at the beginning of the study are able to do that, but because populations with an early hip OA that were studied prospectively in time can support the evidence, we included them as well. We are however cautious with this kind of information because of the bias that can be introduced. (Acetabular deformity can pre-date hip OA)

Despite the above mentioned biases and limitations, the evidence for an association between HD and the development of hip OA is limited. A hypothetical mechanism to explain the association is the increased joint stress due to decreased joint surface area (smaller CE-angle), or joint incongruity (smaller acetabular depth).[32,33]

In view of the limited evidence on the positive relationship between mild forms of HD and the occurrence of hip OA in the elderly, and the lack of information in the younger individuals, more well designed prospective population based studies are needed in order to provide more precise and valid information on this relation.

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6

Prognostic factors of progress of hip osteoarthritis: a systematic review

Abstract

Objective: To systematically summarise the available articles on the prognostic factors of osteoarthritis (OA) of the hip

Methods: The identification of the articles was done by means of a systematic database search of Medline, Embase and the Cochrane library. Articles with the aim to study the prognostic factors of hip OA were selected and their methodological quality was assessed using a standardized set of criteria. Data of the individual studies were combined where possible and a best evidence synthesis was conducted.

Results and conclusions: Twelve studies were included in this review. Ten studies had a cohort design, of which five collected their data prospectively. Two studies had a case-control design. The methodological quality scores ranged from 25% to 100% of the maximum obtainable score for each type of study design. The mean quality score was 58%. Based on the evidence, we may conclude that there is strong evidence that people with a supero- (lateral) type of migration of the femur head or an atrophic bone response show a more rapid progression of hip OA as compared with a medial migration c.q. hypertrophic bone response. Also strong evidence is found that there is no relationship with obesity and the progression rate of hip OA.

Limited evidence is found that, when there is a more severe joint space narrowing at first consultation, there will be an earlier need for a (total hip replacement) THR, as well as for no relation between hip dysplasia and the progression of hip OA.

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Introduction

Osteoarthritis (OA) of the hip affects 7-25% of Caucasian people over the age of 55.[1] In addition to the related pain and discomfort, hip OA has substantial economic consequences[2], and with the current aging of the population in western societies this problem will increase. Unlike most other sites affected, hip OA can, besides remaining stable or progress, also show regression.[3] Up to now, two reviews have been published on the prognosis of hip OA[3,4], but due to sparse data[5-7], no firm conclusions could be drawn, other than a brief summary of the information available. Since then several new studies investigating the prognosis of hip OA have been published.[8-13] They describe prognostic factors, which potentially can predict the course of the disease. These prognostic factors are, unlike risk factors, not necessarily causally related to the outcome, rather than just describe the presence of an association. Some of these factors are modifiable, like obesity, and therefore will be appropriate for clinical intervention, but most of them are not modifiable (e.g. gender, age, type of bone response). Information on these factors can be of importance though; not only to give prognostic information to the patients and doctors, but also for health care provision.

In order to gain insight in the different factors predicting the course of hip OA, we systematically reviewed the available studies on this topic, using modern methods of systematically identifying and assessing and summarizing the available evidence.

Methods

Identification and selection of the literature

To identify the observational studies on this subject, relevant publications were searched using the following databases: Medline (1966- April 2000), Cochrane library (1993- April 2000) and Embase (1980-April 2000). The following keywords were used: (hip and (arthritis or arthrosis or osteoarthritis or osteoarthrosis) or coxarthrosis) and (prognosis or progression or progressive or disease course or predictive or precipitating or predictor) and (case-control or retrospective or prospective or longitudinal or follow up or cohort). (A detailed list can be obtained from the corresponding author.) The search was extended by screening the reference lists of all relevant articles identified.

A study was eligible for inclusion if it fulfilled all of the following criteria: 1) one of the aims of the study was to investigate factors associated with the progression of hip OA, 2) the articles were written in English, Dutch, German, French, Danish, Norwegian or Swedish, 3) the article was a full text article, 4) the patients in the studies had to have a radiological and/or clinical hip OA, a (total) hip replacement, or were on the waiting list for one, and 5) the study design was a cohort or a case-control study.
A study was excluded if the studied population had a specific underlying pathology, such as trauma (fractures), infection, rheumatoid arthritis, ankylosing spondylitis, Perthes' disease, tuberculosis, hemochromatosis, sickle cell disease, Cushing's disease, or femoral head necrosis.

Methodological quality assessment

The variation of the methodological quality of observational studies may influence the results and conclusions of a systematic review. Therefore, the quality of each included study was assessed using the following procedure. Two reviewers (AML and SMABZ) independently scored the quality of the selected papers according to a standardized set of criteria (Appendix 3). These criteria have been used in previous reviews of observational studies in the field of musculoskeletal disorders[14-16] and were modified to cover the topic of our review. The criteria concern both the internal validity, and the informativeness of the study. Only items reflecting the internal validity of the studies were used to assess the methodological quality.
In case of a disagreement, both reviewers tried to achieve consensus; if disagreements were not resolved, a third reviewer (BWK) was consulted in order to achieve a final judgement.

Best evidence synthesis

Because observational studies in this systematic review were considered to be heterogeneous with regard to the study population, methodological quality and determinants and outcome measures for hip OA, we on forehand refrained from statistically pooling the data[17], and performed a "best evidence" synthesis.[18-20] First the studies were classified according to the type of study design. A cohort study was judged as the most valid design, followed by a case-control study. After

that, the studies were ranked according to their methodological quality score. The following ranking of the levels of evidence was formulated[18 14,16];

1. Strong evidence is provided by generally consistent findings in multiple high quality cohort studies.
2. Moderate evidence is provided by general consistent findings
   - in one high quality cohort study and two or more high quality case-control studies.
   - in three or more high quality case-control studies.
3. Limited evidence is provided by (general consistent) findings
   - in a single cohort study
   - in ≤ 2 case-control studies
4. Conflicting evidence was provided by conflicting findings (i.e. <75% of the studies reported consistent findings).
5. No evidence was provided when no studies could be found.

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

Results

Identification and selection of the literature

Twelve of the initially 2921 identified references, met our selection criteria.[6-12,21-25] For two studies, there was more than one publication[22,23] and[11,12,21], reporting different aspects of the study. All publications were used to extract data regarding the methods used and the results reported. Also two studies reported of the same source population, but had a totally different design[8,9], so these will be discussed separately. After screening the reference lists, another three studies could be included.[26-28] Thus, finally 12 articles were included.

Description of the studies included

Tables 1 and 2 give detailed description of the characteristics of the included studies.

We included 10 cohort studies[6,7,9-11,22,24-27], of which five collected their data prospectively[6,7,9,11,22], and two case-control studies.[8,28] All studies were hospital-

based. None of the studies reported on regression of hip OA, there were only reports on the progression of hip OA.

Table 1: Details of the studies included.

Author	Study design	Definition population	Assessment progression	Results
Cohort studies				
Conrozier[9]	Prospective follow-up 1 yr.	Patients referred to a rheumatology dept. in Sweden or France with primary hip OA (ACR-criteria)(n=48) Mean age 56.4 (±14.1) yr.	X-ray (JSN, YMN)	r (JSW (at entry) - YMN)=0.66 (p<0.001) no correlation between BMI and YMN
Dougados[11]	Prospective follow-up 3 yr.	Patients from a multicentre base in France with primary hip OA (ACR-criteria and K&L-grade) (n=508) Mean age 63 (50-75) yr.	Clinical (need for THR)	Parameters predictive for the requirement for a THR: Age ≥ 70 RR 1.65 (1.06-2.56) Female RR 1.71 (1.11-2.62) Superolateral migration RR 1.96 (1.27-3.02) JSW < 2 mm RR 1.85 (1.18-2.90)
Conrozier[10]	Retrospective follow-up 64 (18-300) months	All patients who received a THR at 2 hospitals in France between '92-'93 because of primary hip OA (superior JSN and evidence for OA at operation) (n=61) Mean age 62 (30-80) yr.	X-ray (YMN)	Correlation to YMN: Atrophic bone response More superolateral migration (NS) No correlation to YMN: gender, age, weight, height, hip dysplasia, JSW at entry
Ledingham[7]	Pros- and retrospective follow-up 24 (3-72) months	Patients attended to rheumatology/ orthopaedic clinic with symptomatic hip OA (K&L ≥ 2) (n=136 prospective, 30 retrospective) Mean age 65 (29-86) yr.	Clinical (need for THR) X-ray (JSN, osteophytes, cysts, sclerosis and attrition)	Rapid progression on X-ray: female OR 2.53 (0.91-7.41) atrophic bone response OR 8.31 (3.18-21.98) superior migration OR 9.0 (1.24-183.52) THR needed: atrophic bone response OR 3.13 (1.28-7.69)
Tron[24]	Retrospective follow-up 5.2 (±3.6) yr.	Patients at a clinic in France with symptomatic hip OA (K&L) (n=39) Mean age 55.5 (30-87) yr.	X-ray (YMN)	r (YMN - BMI)= 0.26 (p=0.06) r (YMN-CE-angle)= -0.28 (p<0.05) Superolateral deteriorated more than other locations (NS) YMN older age > YMN younger age (p=0.008) YMN atrophic bone response >YMN hypertrophic bone response (NS) YMN was not related to gender
Danielsson[6]	Prospective follow-up 8-12 yr.	All patients who attended to the only orthopaedic clinic in Malmö with hip complaints and X-ray changes (n=168) Mean age 69.4 (± 0.91) yr.	Clinical (need for THR) X-ray (JSN, osteophytes, cysts and sclerosis)	X-ray progression was greater in a lateral localization than in the medial or mixed type Need for THR not age related
Hasegawa [22]	Prospective follow-up 13 (10-26) yr.	Patients of 6 hospitals in Japan, with subluxation or dysplasia from the hip (n=64) Average age 29.5 (13-62) yr.	X-ray (JSN)	Joint incongruence (p≤0.05), and a broken Shenton's line (p≤0.01) were predictors for a development from pre/early- hip OA to advanced hip OA Age and BMI are not related.

Author	Study design	Definition cases	Definition controls	Assessment progression	Results
Vinciguerra [25]	Retrospective follow-up 58 (1-358) months	Outpatients of a rheumatology clinic in France with hip OA (ACR) (n=149) Mean age 58 (±14) yr.		Clinical (need for a THR)	Factors predictive for a THR: Age at diagnosis > 54 yr. RR 3.15 (1.81-4.48) More severe JSN RR 2.97 (1.66-5.32) BMI > 27 RR 2.26 (1.23-3.99)
Auquier[26]	Retrospective follow-up 10 (6-23) yr.	Patients who went to a health resort in France and were treated for hip OA (n=273) Mean age 51.8 (±8.6) yr.		Clinical (functional status: pain, walking distance, walking stick)	Primary OA in women showed more worsening than other forms (0.05 < p < 0.02))
Macys[27]	Retrospective follow-up	Patients who received a THR at a clinic in the US, because of prim hip OA (n=183)		Clinical (need for a THR)	At least 50% of the males had symptoms for > 5 years prior to surgery, which was longer than most females
Case-control studies					
Conrozier[8]	Retrospective follow-up study 64 (18-300 months	Patients from a cohort study [9] with a rapidly progressive hip OA (YMN> 1mm) (n=11) Mean age 71.2 (±10.6)	Patients from the same cohort with a slowly progressive hip OA (YMN<0.2 mm) (n=24) Mean age 60.5 (±11.8) yr.	X-ray (YMN)	CRP, JSW and the age were all independently related to the rapidly progressive group as compared to the slowly progressive group (p=0.01, p=0.006 and p=0.02)
Perry[28]	Retrospective follow-up study 5 yr.	Patients from rheumatology clinic in England with hip OA (K&L ≥2) with recovery of JSW after 5 yr. (n=14) Age 58,6 (43-71)	Patients from the same clinic with hip OA (K&L ≥2) and progressive deterioration of the JSW after 5 yr. (n=9) Age 56,3 (43-69)	X-ray (JSW)	The average weight for each group was comparable

JSW= joint space width, JSN= joint space narrowing, K&L-grade= Kellgren and Lawrence grade, YMN= yearly mean narrowing of the joint space, THR= total hip replacement surgery, BMI= body mass index, VAS= visual analogue scale, COMP= cartilage oligomeric matrix protein, BSP= bone sialoprotein.

The assessment of the course of hip OA can be divided in two main categories; progression on clinical parameters (e.g. the need for a total hip replacement (THR)), or progression measured by radiological parameters, like the joint space narrowing (JSN) or the yearly mean narrowing (YMN) of the joint space. Six studies reported on a clinical assessment of the hip OA progression.[6,7,11,25-27] Seven studies assessed the deterioration with radiological parameters.[6-10,22,24,28]

A variety of factors, which may influence the progression of hip OA, have been studied. The seven most frequently studied factors are: age at first consultation,

gender, the site of the JSN (type of migration), joint space width (JSW) at first radiograph, type of bone response (e.g. hypertrophic, atrophic), BMI or weight and hip dysplasia. Other factors like the presence of osteophytes, cysts or Heberden's nodes, or the Kellgren and Lawrence classification, pain or functional status at entry were studied only in one or two publications, and therefore will not be discussed in this review.

Table 2: Results of the methodological quality score of the studies.

Item	1	2	3	4	5 *	6	7	8	9	10	11	12 *	13	14	15	16 *	17 *	18	19	Score	Otainable	Total score
Cohort																						
Conrozier [9]	1	-	1	-	1	1	-	1	1	1	1	1	1	1	1	1	1	1	1	12	12	100%
Dougados [11]	1	-	1	-	1	1	-	1	1	1	1	1	1	1	1	1	1	1	1	12	12	100%
Conrozier [10]	1	-	1	-	1	0	-	0	1	1	1	1	0	1	0	0	1	1	1	8	12	67%
Ledingham [7]	1	-	1	-	1	0	-	0	1	1	1	1	1	1	0	0	1	0	1	8	12	67%
Tron [24]	1	-	1	-	1	1	-	0	1	1	1	1	0	1	0	0	1	0	0	7	12	58%
Danielsson [6]	1	-	0	-	0	0	-	1	0	1	1	0	1	1	0	0	0	0	0	6	12	50%
Hasegawa [22]	1	-	0	-	0	0	-	0	1	0	0	0	1	1	1	1	1	1	0	6	12	50%
Vinciguerra [25]	1	-	0	-	1	0	-	0	1	1	1	1	0	0	0	0	1	1	0	5	12	42%
Auquier [26]	1	-	0	-	1	0	-	0	1	0	0	0	0	1	0	0	1	0	0	3	12	25%
Macys [27]	1	-	0	-	1	0	-	0	1	0	0	0	0	0	0	0	1	0	1	3	12	25%
Case-control																						
Conrozier [8]	1	1	1	1	1	0	1	0	1	1	1	1	0	-	-	-	1	1	1	10	13	77%
Perry [28]	1	1	0	0	0	0	1	0	1	0	0	0	1	-	-	-	1	0	0	5	13	38%

Each item was scored as "1" when it did meet the criteria listed in Appendix A. (see chapter appendices" When it did not meet the criteria a "0" was assigned. Positive validity scores were summed up to an overall internal validity score.
na = not applicable. *= informativity item. Not included in the analysis.

Results of the studies included, their methodologic quality assessment and best evidence synthesis

The included studies presented their results in various ways. Six studies described the outcome in global terms only.[6,8,22,26-28] The others presented the measures of

association with an OR of RR[7,11,25] or a correlation coefficient[9,10,24] (Table 1). Because of this poor data presentation, we present the outcomes in terms of a 'positive' (the factor studied, increases the progression of hip OA), a 'negative' (the factor decreases the progression of hip OA) or 'no' (the factor has no influence on the progression of hip OA) association (Table 3).

Table 3: Results of the best evidence synthesis.

Factor	Studies *	Association †	Best evidence synthesis
Higher age at T_0	2 HQ cohort studies [10,11] 1 HQ case control study [8] 4 LQ studies [6,22,24,25]	No, positive Positive No, no, positive, positive	Conflicting evidence
Female	3 HQ cohort studies [7,10,11] 3 LQ studies [22,24,27]	No, positive, positive No, no, positive	Conflicting evidence
Migration	3 HQ cohort studies [7,10,11] 2 LQ studies [6,24]	Superolateral, superolateral, superior Lateral, superolateral	Strong evidence for a faster progression in a supero-lateral migration of the femur head
JSW at Baseline			
Need for THR	1 HQ cohort study [11] 1 LQ study [25]	negative negative	Limited evidence for a negative relationship (smaller JSW increases the risk for a THR)
Progression of YMN	2 HQ cohort studies [9,10] 1 HQ case-control study [8]	No, positive Negative	Conflicting evidence
Atrophic response	2 HQ cohort studies [7,10] 1 LQ study [24]	Positive, positive Positive	Strong evidence for faster progression when there is an atrophic bone response
BMI/ weight	2 HQ cohort studies [9,10] 4 LQ studies [22,24,25,28]	No, no No, positive, positive, no	Strong evidence for no relationship between BMI/weight and progression
Dysplasia	1 HQ cohort study [10] 2 LQ studies [22,24]	No Positive, positive	Limited evidence for no relationship between dysplasia and progression

Underlined outcomes are studies with a clinical assessment of the progression of hip OA.
T_0= Measured at baseline *=HQ: High quality/ LQ: Low quality study (measured with methodological quality score)
†= Positive association: the presence/higher level of the factor will result in a faster deterioration of hip OA.
No association: the rate op progression is not influenced by the factor.
Negative: the presence/higher level of the factor will result in a slower deterioration of hip OA.

The two reviewers scored 594 items and agreed on 562 items (95%, kappa 0.89). The 32 disagreements were resolved in a single consensus meeting. Table 2 shows the studies in order of the study design (i.e. cohort/ case-control study) and their methodological quality score. The scores ranged from 25% to 100% of the

maximum obtainable score for each study design. The mean methodological quality score was 58%.

Age at first consultation

Seven studies reported outcomes on the relationship between the age of the patient at consultation, and the progression of the hip OA.[6,8,10,11,22,24,25] Of these, two high quality cohort studies reported no[10], respectively a positive[11] association. The one high quality case-control study[8] reported a positive association. This means that there is conflicting evidence for an association between the age of first consultation and the progression rate of hip OA.

Gender

Six studies reported on the gender in relation with the progression of the hip OA.[7,10,11,22,24,27] Two of the three high quality cohort studies[7,11] in this group, reported that females had a higher progression of hip OA than men. The other high quality cohort study reported that there was no association.[10] There were no high quality case-control studies; therefore, we may conclude that there is conflicting evidence for an association between gender and the progression of hip OA.

Type of migration

Five studies reported on the association between the site of the JSN (type of migration) (e.g. superior, lateral, medial) and the progression of hip OA.[6,7,10,11,24] Two of the three high quality cohort studies reported a more rapid progression of hip OA when there was a superolateral migration of the femur head.[10,11] The other high quality cohort study reported a higher rate in a superior migration.[7] This means that we can conclude that there is strong evidence for a more rapid progression of hip OA when there is a supero- (lateral) migration of the femoral head, as compared to a medial migration.

Joint space width at the first X-ray

Because of the different ways of correlation (when there is a small JSW, the part left to decrease (the YMN) will be small), we subdivided these studies in type of outcome; need for a THR and YMN.

There were two studies reporting on the relationship of the JSW at first X-ray and the need for a THR.[11,25] There was one high quality cohort study[11], so we can

conclude that there is only limited evidence for a negative relationship (the smaller the JSW at entry, the higher the need for a THR).

JSW and YMN

We found three studies reporting on the association between the YMN (measured in mm) and the first measured JSW.[8,9,10] Because[8] and[9] reported of the same baseline population, these conclusions will not be summed up in the best evidence synthesis, but only the data of one study[9] will be included in the conclusion. Both studies[9,10] had a high quality score, but showed conflicting results, so we can conclude that there is conflicting evidence for an association between the JSW at entry and the YMN.

Atrophic bone response

Three cohort studies investigating this relationship[7,10,24] showed a positive association, of which two reached the level of high quality.[7,10] Therefore we may conclude that there is strong evidence for a positive relationship, implying a faster progression of hip OA when there is atrophic bone response, as compared to a hypertrophic bone response.

BMI / Weight

Six studies investigated the relationship between weight or the BMI and the progression of hip OA[9,10,22,28], of which two high quality cohort studies both reported no association.[9,10] There were no case-control studies of high quality. This means that we found strong evidence for no association between the BMI and the progression rate of hip OA.

Hip dysplasia

Three studies reported on the relationship between hip OA and the CE-angle[10,22,24], and of these, only one reached the level of high quality[10], thus we can conclude that there is limited evidence for an absence of a relation between hip dysplasia and the progression of hip OA.

Discussion

In this systematic review, we summarized the available evidence in the literature on the influence of several factors on the course of hip OA. A problem by drawing conclusions in this systematic review is the way the included studies presented their results. A result described in this review as "no" association can mean

various outcomes; a not significant "positive", "negative" or "no" association. Because some articles only described their data globally, rather than by giving exact numbers, we were not able to distinguish between these different meanings of the results.

Another problem arises with the selection of the populations studied; all of these populations were hospital based, so they are not representative of community-based hip OA. Of all factors studied, the only factor that can be influenced is obesity. In this review, obesity appears to have no relationship with the progression of hip OA. We have to be cautious though, to not advise the obese patient with beginning hip OA to lose weight. This information is based only on studies where the BMI is measured at the beginning of the study. None of the studies assessed the BMI during follow-up.

In a recent review the evidence found for a relationship between obesity and hip OA was moderate.[29] One of the explanations for this relationship was that obese people suffer earlier from the same degree of hip OA. This very well might state our findings that obese persons suffer earlier, but show just as much progression of hip OA compared to non-obese persons. On the other hand, the findings in this review on obesity are based on six studies, and only one of them used clinical parameters as an outcome. All the others used radiological parameters.

Besides the limitations related to the included studies, there are some restrictions of this review itself. Although we put much effort into identifying all relevant articles, our literature search might have some limitations. Besides some relevant articles that may have been missed because they used other keywords, had unclear abstracts or were not indexed in databases, we also excluded articles written in languages other than English, Dutch, German, French, Danish, Norwegian or Swedish.

In our analysis we did not include the paper of Seifert and colleagues[5], although it has been cited frequently, because the publication was an abstract and we refrained from including publications other that full text articles. However, we did score the methodological quality of this paper, and mainly due to the short descriptions they would have only scored 25% of the obtainable 100%.

The quality assessment was challenging because there were no previously tested and validated criteria lists published for observational studies in the field of OA. In

addition, limited data was found on performing a best evidence synthesis with observational studies (in contrast with RCT's).

In spite of the presented limitations, we argue that the use of this systematic approach with scoring the quality of the studies included and defining levels of evidence is appropriate. One important aspect of this relatively new approach of observational studies is to give the reader insight into the process of reaching conclusions. Readers are now able to repeat the analysis and it provides insight in how the results might be influenced if slight changes are made in the assessment of the findings or the methodological quality of the studies.

For example, if only the studies in which the progression of hip OA was assessed by clinical findings[6,7,11,25,27], the results in the best evidence synthesis would have changed slightly, except for the analysis on the subgroup of gender; the conclusion would than change from "conflicting evidence" to "strong evidence" for a faster progression in women.

This illustration also suggests that when more articles will become available in time, the conclusions will become more solid. Now one additional single publication can have an enormous impact on the results.

Future research, especially prospective cohort studies, with an adequate follow-up time, is needed to strengthen the conclusions.

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7

Prognosis of trochanteric pain in primary care

Abstract

Background*:* Trochanteric pain is the second most important diagnosis of hip problems presenting in primary care. The incidence and prognosis though is largely unknown.

Aim*:* To determine the one and five-year prognosis of trochanteric pain and the predictive variables for consistent complaints.

Design of the study*:* Retrospective cohort study.

Setting*:* One hundred and sixty-four patients (mean age = 55 years, 80% female) with incidental trochanteric pain in the years 1996 or 2000 were asked in 2001 for past and present symptoms of trochanteric pain. Therapeutic interventions, demographic factors and co-morbidity were also investigated.

Methods*:* The databases of 39 general practitioners were screened in order to identify all incident cases with a suspicion of trochanteric pain in the years 1996 or 2000. These cases were sent a questionnaire.

Results*:* The incidence of trochanteric pain in primary care is 1.8 patients per 1000 per year. After 1 year 36% still suffered from trochanteric pain, and after 5 years this was 29%.

Patients with osteoarthritis in the lower limbs had a 4.8-fold risk of persistent symptoms after one year, as compared to patients without osteoarthritis. Patients who had received a corticosteroid injection had a 2.7-fold chance of recovery after 5 years, as compared to patients who had not received an injection.

Conclusion*:* Trochanteric pain shows to be a chronic disease in a substantial part of the cases. The disorder is associated with much impairment in daily activities.

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Introduction

Trochanteric pain, also known as trochanteric bursitis or pseudotrochanteric bursitis is a frequently occurring problem. The pain experienced by 10-20% of all patients with hip problems presenting in primary care can be attributed to trochanteric pain.[1]

In 1979, Little described trochanteric pain as pain at the lateral side of the upper thigh, often with radiation to the knee.[2] Although it has been attributed to trochanteric bursitis and/or tendinitis, one study reported that sonographic effusion of the bursa was seldom found. Effusion around the trochanteric tendons, however, was more often present than in other patients with hip pain.[3]

Trochanteric pain has been described as a solitary syndrome, as a result of trauma but also as a co-morbid condition in patients with low-back pain or osteoarthritis (OA) of the hip.[4-6], [7-10] Some authors have even described trochanteric pain as one of the first symptoms in developing hip OA.[9,11]

In order to gain more insight in trochanteric pain, we performed a retrospective cohort study in general practice, focussing on the one and the five-year prognosis.

In this article we want to address the following questions:

- What is the incidence of trochanteric pain in general practice?
- What is the impact of trochanteric pain on daily activities?
- What therapy is given?
- What is the prognosis of trochanteric pain after 1 and 5 years?
- What variables might predict the prognosis?

Methods

Identification and selection of the cases

General practitioners (GPs) using electronic medical databases were approached in the year 2001 for participation in the study. Patients aged 18 years and older who presented to their GP in the 1996 or 2000 with pain at the region of the greater trochanter were identified. The identification of these patients was done in the electronic medical databases using the keywords troch* or pain* and hip*. The medical records of these patients were read and they were identified as possible incident cases if they had consulted their GP for the first time in two years with these symptoms. Only patients who confirmed by questionnaire that they had

suffered from pain at the lateral side of the upper leg were considered incident cases with trochanteric pain. Patients with trochanteric pain in 1996 were asked for the present condition of their symptoms. These data were used for the prognosis after five years. The data from patients with trochanteric pain in 2000 were used for the "one year" follow-up, subdivided in four groups: those presenting in January / March 2000 were asked for the 16 months follow-up, those from April / June for the 13 months follow up, from July / September for the 10 months, and finally those from October / December 2000 for the seven months follow-up.

Questionnaire

The questionnaire covered patient characteristics, (demographic data, daily activities and co morbidity) and various characteristics of the trochanteric pain, (past and present symptoms, localisation, pain severity (VAS, 0-100) and kind of therapy).

The present quality of life was assessed with the Euroqol (0=worst possible quality of life – 1=best possible quality of life).[12] The present functional disability due to the trochanteric pain was assessed with the WOMAC (Western Ontario and McMaster) osteoarthritis index).[13] This index is used to assess disability due to arthritis of the hip or knee. It has three discrete domains: pain (five questions, possible subscale score 0-20), stiffness (two questions, 0-8) and physical functioning (17 questions, 0-68) and has a minimum score of 0 (best score) and a maximum score of 96 (worst score).

Data-analysis

We investigated the percentage of patients who still had symptoms of trochanteric pain in 2001 (observed values). In a sensitivity analysis we assessed whether these figures would change due to potential selective non-response (expected values). In the first analysis we assumed that all non-responders did have trochanteric pain at baseline and were free of trochanteric pain at the time of investigation (best case scenario). In the second analysis we assumed them to still suffer from trochanteric pain at the end of the follow-up (worst case scenario).

Left and right censoring

There were only two measurements in time for each patient: time of diagnosis and the follow-up investigation. This implies that the data on a specified time are only based on that particular subgroup of patients. For example patients with a follow-up of 13 months do not have data on the 7, 10, 16 or 60 months. So if someone has recovered at 13 months, he could already have been recovered at 7 or 10 months. Also, when he has not recovered at that time, he could have been recovered at 16 or 60 months. This is called left and right censoring. In order to correct for this kind of censoring we analysed our data with the SAS program proc life reg. (version 6.12).

Predictive variables

Variables that might have predicted improvement were evaluated using the binary logistic regression mode in SPSS. Variables with a P-value of 0.20 or less in the univariate analysis were considered in the backward stepwise multivariate model. Variables with a P-value of 0.10 or less in the multivariate model were left in the model.

Results

Incidence

Forty-one GPs in the south-west region of the Netherlands were approached, and 39 were willing to participate. A total number of 95297 persons were registered at these GPs. Three hundred and forty-five patients with a suspicion of trochanteric pain were identified and sent a questionnaire, of whom 187 (54%) replied. Of these responders, 164 (87,7%) met our criteria of trochanteric pain (cases). The remaining 23 patients reported pain symptoms in the low back, groin, buttock or knees and not in the region of the greater trochanter. Figure 1 shows the flow chart of the patients and responders.

There were no statistically significant differences between sex and age between the non-responder, responders and cases. Also, no statistically significant differences were found for co-morbidity between the responders and the cases, see table 1.

Figure 1: Flow chart of patients and responders

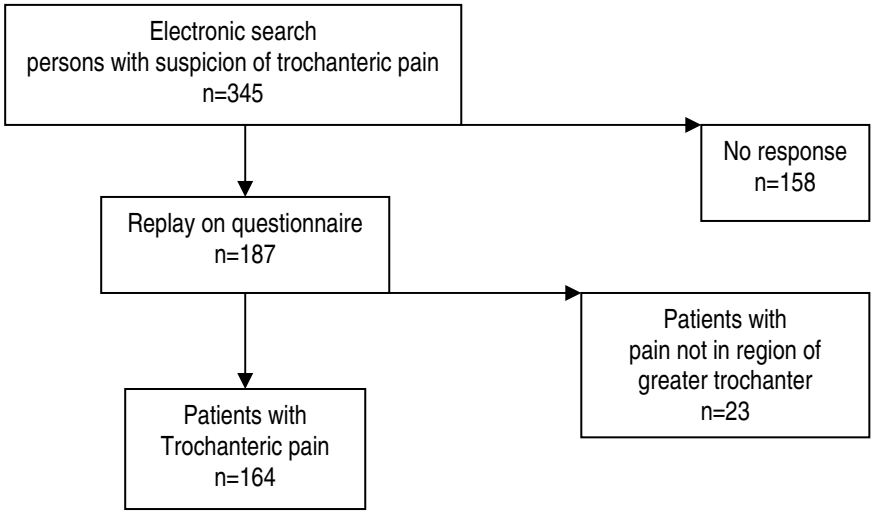


Table 1: Characteristics of all identified patients

	Identified patients	Non-responders	Responders	Cases
N (number of patients)	345	158	187	164
Age, mean (sd)	55.3 (15.4)	54.4 (17.4)	56.0 (13.5)	55.4 (13.5)
Female gender, %	75%	69%	79.9%	79.9%
Arthritis on lower limbs or low back pain, %			48%	58%

Patient characteristics and impact of trochanteric pain

Of the 164 cases 79.9% were female and the mean age at diagnosis was 55.4 years (range 21 - 87 years). For more patient characteristics, see table 2.

Of those working, about 34% were (very) much troubled during work related activities and about a quarter of them have had a history of sick leave due to the trochanteric pain. About 40% of the patients were disturbed during sleeping. Fifty-four percent of the sporting people were (greatly) impaired during their sporting activities. The mean VAS score for hip pain in patients still suffering from trochanteric pain at follow-up is 46,0 and their mean WOMAC score is 36.5. The WOMAC scores for those recovered are 11.2.

The mean Euroqol score for those with prolonged symptoms is 0.97 and for those recovered 0.99. The state of health assessed with the VAS was 68.5 for those with symptoms at follow-up, and 78.6 for those recovered. See table 3.

Table 2: Characteristics of the patients (n=164) with trochanteric pain

	Baseline	Follow-up
Age in years, mean (sd)	55.4 (13.5)	
Female gender, %	79.9	79.9
Localisation: right, %	40	40
bilateral, %	23	23
Body Mass Index		
overweight (BMI 25-30), %		35
obese (BMI >30), %		15
Hip osteoarthritis, %		24
Knee osteoarthritis, %		16
Low-back pain, %		14

Table 3: Pain scores and quality of life scores at follow-up (n=164)

	With GTPS symptoms at follow-up (n=116)	Without GTPS symptoms at follow-up (n=48)	P-value)
Pain (VAS 0-100)	46.0	4.4	(<0.0001)
WOMAC pain (0-20)	8.6	2.3	(<0.0001)
WOMAC function (0-68)	25.0	7.6	(<0.0001)
WOMAC stiffness (0-8)	3.1	1.3	(<0.0001)
WOMAC total (0-96)	36.5	11.2	(<0.0001)
Euroqol	0.970	0.992	(0.024)
State of health (VAS 0-100)	68.5	78.6	(0.008)

Therapy

Of all patients, half of them (55%) were treated by their GP or specialist with medication (paracetamol, NSAID's), and 52% of these patients mentioned (temporarily) improvement. Thirty-seven percent of the cases were injected in the region of the greater trochanter with corticosteroids (66% with improvement).

A third (35%) of the patients were only treated by their GP. Of these, 53% received paracetamol or NSAID's (48% with improvement) and 34% were injected (60%

with improvement). Half (52%) of the patients received physiotherapy (two-third mentioned improvement). A third (36%) of the cases went to the hospital where therapy consisted of administration of paracetamol or NSAID's (36%), or a local corticosteroid injection (34%). Three out of the five patients who received an operative treatment reported a reduction of the pain.

Prognosis

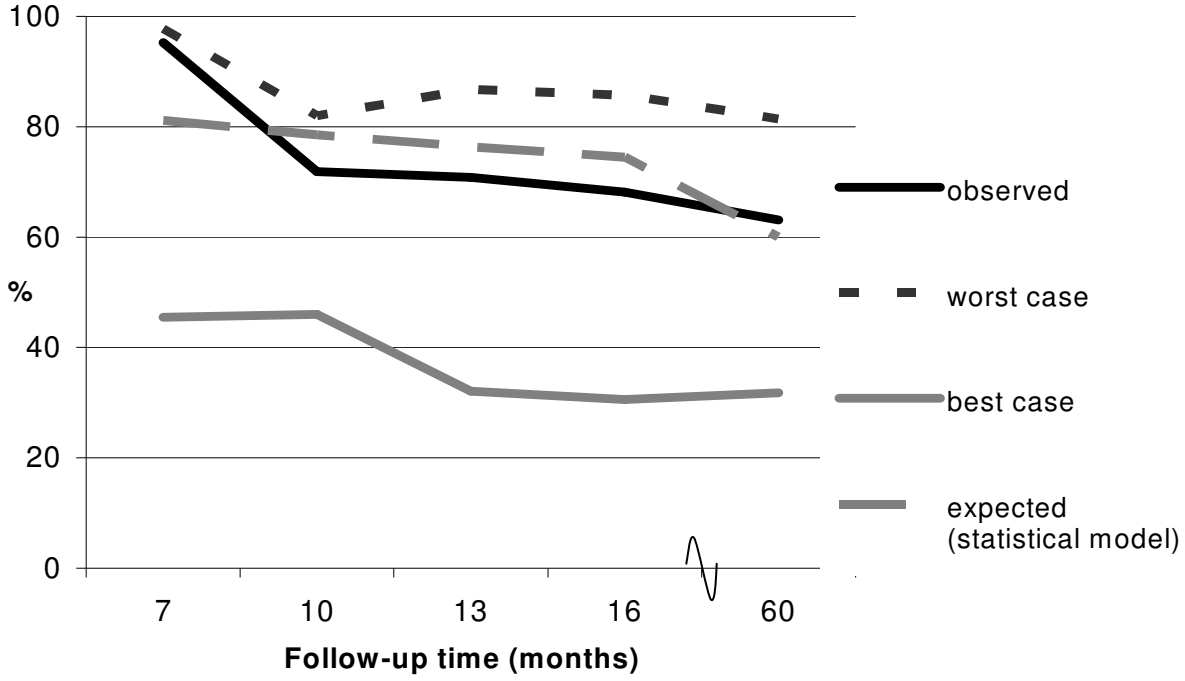
At one year of follow-up, 76% of the responders still suffered from trochanteric pain and at 5 years 63% still did.

In the best case scenario (all non-responders were cured at the time of investigation), at 1 year follow-up, 36% still had trochanteric pain and at 5 years, 29% did.

In the worst case scenario (all non-responders were not cured at the time of investigation), these percentages changed to 84% and 83% respectively.

In the best-fitted analysis (proc life reg. SAS), 78% of the responders had symptoms at one year and 60% at 5 years. All these observed and expected values are shown in Figure 2.

Figure 2: Percentage of patients with symptoms at follow-up time.



Predictive variables

For the prognosis at 1 year, there were 2 variables that predicted sustained symptoms of trochanteric pain; duration of symptoms before the patient visited the GP (more vs. less than 1 week) (odds ratio (OR) 4.9, 90% confidence interval (CI) (1.8-13.2)) and the presence of OA in the lower limb(s) at follow-up (OR 4.8 (CI 1.2-18.5)). In this model, age and gender were considered confounders (Table 4).

Table 4: Possible determinants for prolonged complaints of trochanteric pain (univariate and multivariate analysis)

	1 Year follow-up		5 year follow-up	
Variables	**Univariate OR (P-value)**	**Multivariate OR (CI)**	**Univariate OR (P-value)**	**Multivariate OR (CI)**
Age (continuous)	1.02 (0.30)	1.01 (0.97 – 1.04)	1.00 (0.95)	1.00 (0.96 – 1.04)
Gender (male/female)	1.75 (0.41)	1.39 (0.41 – 4.77)	1.23 (0.74)	0.78 (0.25 – 2.38)
Bilateral symptoms (-/+)	1.03 (0.96)		2.32 (0.19)	2.35 (0.66 – 8.35)
BMI normal (<25)	0.55 (0.21)		**	
overweight (25-30)	2.32 (0.13)	2.38 (0.81 – 6.98)	**	
obese (>30)	0.83 (0.77)		**	
Level of education				
Low (prim. school)	2.98 (0.07)		1.73 (0.31)	
Normal (sec. school)	0.32 (0.03)		0.96 (0.94)	
High (high school)	1.33 (0.68)		0.42 (0.19)	0.38 (0.11 – 1.33)
Duration of symptoms*	5.53 (0.003)	4.88 (1.81 – 13.16)	4.50 (0.10)	5.29 (1.05 – 26.57)
Analgetics (-/+)	1.68 (0.27)		0.63 (0.37)	
Corticosteroid injection (-/+)	1.24 (0.66)		0.45 (0.15)	0.37 (0.13 – 1.00)
Arthritis lower extremities (-/+)	4.26 (0.03)	4.77 (1.23 – 18.50)	**	
Low-back symptoms (-/+)	4.19 (0.18)	2.70 (0.42 – 17.52)	**	

*) before visit to the GP (less than 1 week/ 1 week or more)
**) retrospective data. Not considered continues over time period of 5 years
CI= 90% confidence interval

Patients developing OA did not receive corticosteroid injections more or less often as compared to patients not developing osteoarthritis (chi-square 1.43 P-value 0.71). Also no statistical significant differences were found in specific symptoms at first presentation like pain located only at the greater trochanter or occurrence of the pain by applying pressure (chi-square 1.43 reps. 0.18, and P-value 0.71 and

0.33). In this model, age, gender, BMI, use of analgesics or consultancy of physiotherapy all showed no significant relationship with the prognosis of trochanteric pain.
For the long term prognosis at 5 years, there were 2 variables that predicted sustained symptoms of trochanteric pain; duration of symptoms before the patient visited the GP (more vs. less than 1 week) (OR 5.3 (CI 1.1- 26.6)), and having had a corticosteroid injection (OR 0.4 (CI 0.1–1.0)). Also in this model age and gender were considered confounders.

Discussion

Summary of main findings

The incidence of trochanteric pain in primary care is 1.8/1000/year. After one year, 76% of the responders still suffer from trochanteric pain and after 5 years approximately 63% does. Due to possible selection bias, these figures will probably be lower in reality, but not lower than 36% and 29% respectively.
Predictors associated with improvement within one year are duration of symptoms at the first visit to the GP and the absence of osteoarthritis in the lower limbs. For the improvement within five years, again the duration of symptoms before the first visit to the GP, as well as having had a corticosteroid injection are predictive.

The strengths and limitations of this study

This study is vulnerable for different biases. The first is selection bias. This may be a result of the high number of non responders (46%) and it is probable that patients with sustained symptoms were more likely to return the questionnaire. We were able to correct for this kind of bias in the calculation of the prognosis of trochanteric pain (best/worse case scenario). Likewise it could be that patients without symptoms at the time of the investigation did not return the questionnaire. Therefore, we expect that the real percentage with sustained symptoms is lower than observed, and will approximate those from the best case scenario.
For the calculation of the incidence of trochanteric pain however, the data are likely to be influenced by this selection bias. That is why we choose not extrapolate the 12% inaccurately selected patients with pain located elsewhere, to

the non-responders group, but to calculate the incidence directly from the patients with trochanteric pain as reported by the GP.

The impact of trochanteric pain seems to be substantial; about 30-40% of the patients were impaired in their daily activities. However, these data are also prone to selection bias, because it is likely that patients with sustained symptoms returned the questionnaire more often. Moreover, these data are also prone to a second type of bias introduced; the so called recall bias (historical information reported by the participants is known to be inaccurate).

The third type of bias in this study is the bias by indication. An important finding of this study is that patients who received a corticosteroid injection in the region of the greater trochanter, showed a better prognosis of their hip problems after five years. There might have been bias by indication; perhaps only patients with a lot of pain received this injection. Due to the retrospective character of this study, we were not able to correct for this potential confounder. However, assuming that the more severe cases have a worse prognosis, but also receive an injection earlier, this study gives an indication that corticosteroid injections are more effective than other treatments in trochanteric pain.

To look for other potentially biases by indication, we analysed whether there were variables that might influence the choice of the GP to give an injection. The only two variables found were pain elicited when the patient lay on the affected side and the development of low-back pain at the time of follow-up. However, these variables do not significantly influence the model.

Finally, our study results suggest that patients with osteoarthritis had a higher risk on persistent symptoms after one year, as compared to patients without osteoarthritis. This finding can be biased because the greater trochanter is one of the sites to which hip or knee OA may be referred to.

As we only had information from the questionnaire, we did not have objective information of the condition of the patients. Besides that, the data on OA were collected at the end of the follow-up period, and not at the beginning of the symptoms of trochanteric pain. Therefore, confusion between cause and consequence is possible. Nonetheless we think that data on OA would not have changed much and are quite stable in time period of one year. Therefore, we used them in the model for the one-year follow-up, but not for the five-year follow-up.

Comparison with existing literature

Prognosis

This is the first study on the long-term prognosis of trochanteric pain. There are only a few case series available of patients receiving one type of intervention, but the longest follow-up time reported was 2 years. In that study a recovery rate of about 90% was reported.[5] Another study reported on a follow-up after surgery of maximal 60 months.[14] These highly selected patients however, are not comparable with our population in primary care.

Therapy

In our study-population, 37% received corticosteroid injection(s), and about 66% reported an improvement. This is comparable with the outcome of a case-series, in which about 61% of the patients improved half a year after local injection of corticosteroid and lidocaine.[15]

The improvement found in our study however, differ from earlier case-series in which all patients reported improvement after local corticosteroid injection(s). [5,16] This discrepancy can be due to pre-selection of the patients (outpatient clinic) or the previously mentioned selection bias (patients with sustained symptoms returned the questionnaire more often).

Implications for future research or clinical practice

These data show that trochanteric pain is a prolonged chronic disease in a substantial part of the cases. The disorder is associated with great impairment in daily activities.

A trial, which compares oral medication (analgesics) with corticosteroid injection, is needed in order to investigate common and promising interventions in primary care for patients with trochanteric pain.

Acknowledgement

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8

Prognosis of hip pain in general practice: A prospective follow-up study

Abstract

Objective To determine in patients with hip pain, disease progression after 3 and 6 years of follow-up and the incidence of total hip replacement (THR).

Design Prospective cohort follow-up study.

Setting General practices in the area of Rotterdam (the Netherlands).

Participants 224 men and women aged 50 years and older initially presenting with incident hip pain who were subsequently referred for an X-ray.

Main outcome measures Disease progression was defined as a THR or a high score on the Western Ontario and McMaster Universities osteoarthritis index (WOMAC).

Results After 3 years disease progressed in 29 (15%) patients (23 (12%) with a THR), and after 6 years in 45 (28%) (36 (22%) with a THR). The prognostic variables for a THR after 3 and 6 years related to history taking are age ≥60 years, morning stiffness, and pain in the groin/medial thigh; related to physical examination: decreased extension/adduction, painful internal rotation, and a body mass index (BMI) ≥30 (negative predictive); and for radiological findings a Kellgren-Lawrence grade of ≥2. After adjusting this model for overoptimism, the area under the curve was 0.93.

Conclusion In this study-population about 12% of those presenting with hip pain and subsequently referred for an X-ray of the hip will undergo a THR within three years, and about 22% after six years.

Using the variables obtained from history taking, physical examination and radiological findings enable to better identify persons at high risk for progression of hip OA. This can be helpful to inform patients more precisely about the course of hip pain, and to guide clinical trials regarding subgroup or case definition.

Submitted

Introduction

Osteoarthritis (OA) of the hip is a growing problem in western societies; it affects 7-25% of Caucasians aged ≥55 years and this number will increase with the further aging of the population.[1,2]

Although the pathogenesis and riskfactors for the development of OA of the hip have been reviewed[3-5] few studies have reported on (radiological) variables predicting the prognosis of hip OA.[6]

For many patients the general practitioner (GP) is the first physician consulted in the OA process. The GP will diagnose OA of the hip based on history taking, physical examination and possibly on radiographic information, but is unable to give evidence based information about the further course of OA.

Therefore, we conducted a prospective longitudinal study in patients presenting to their GP with pain in the hip region. This study started in 1996, and some reports related to baseline measurements have already been published.[7,8] The 3 and 6 year follow-up data from this study have now become available. The current study addresses the following questions:

- What percentage of the patients received a total hip replacement (THR) or showed signs of severe hip symptoms 3 and 6 years after the initial visit to their GP?
- Which variables are predictive for progression of hip complaints?

To make these data clinically accessible we developed a clinical prediction rule with the aim to predict the risk of having a THR within 3 years.

Subjects and methods

During 1996, we included consecutive patients aged 50 years and older who presented at their GP with hip pain persisting for 1 month to 2 years and for whom the GP requested an X-ray at one of the two participating hospitals in Rotterdam (the Netherlands). Excluded were subjects with a hip arthroplasty on the painful side, or a suspicion of fracture or tumour, or when participation was not possible due to co-morbidity.

After informed consent was given, all subjects underwent a standardised history taking and physical examination of the low back, hips and knees by one of the authors (SMABZ). Radiographs were taken from both hips separately (in frog leg

position) and from the pelvic region (AP pelvic). Additionally, a sonographic examination of the hip area was performed. Laboratory tests included the erythrocyte sedimentation rate. All examinations were carried out on the same day. Details on patient selection and baseline examination have been described previously. [8,9] In 1999, the 3-year follow-up examination took place. All patients were visited at home and a questionnaire was administered. The 6-year follow-up investigation took place in 2002; a questionnaire was sent to the home address, or in case the person reported to be unable to fill in the questionnaire the researchers visited them at home to help them to complete the questionnaire.

Disease course

We defined disease progression using two clinical outcome parameters. First, whether the patient had received a THR during the follow-up period. Secondly, the patient's health status was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[10] A total WOMAC score up to 32.0 was recoded as mild complaints, over a score of 32.1 and 64.0 was recoded as moderate, and a score over 64.0 was recoded as severe complaints.[11,12] Persons who had a THR were included in the patient group with the maximum WOMAC score.

Analysis

Developing the model

The aim of the analysis was to present a combination of potentially relevant baseline variables that most accurately predict the progression of hip pain within 3 or 6 years. We performed a logistic regression analysis (SPSS version 11.0.1). Variables were entered in the model because they were assumed to have a relation with the risk to have a THR based on earlier studies, plausibility of biological associations, or empirical data derived from general practice. Variables that were univariate significantly associated (P-value ≤0.20) with having had a THR or a WOMAC score >64.0 were entered as candidate variables into a backward stepwise regression model and sequentially removed from the model if their contribution to this model was not significant at a level of P=0.10. With a Wald test, we assessed the statistical significance of the improvement in the model after deleting the different variables.

The prognostic factors associated with the disease course were clustered according to the stepwise approach that follows the decision-making process in clinical practice. Disease history is always available to the GP and was therefore used in the first step. In the second step, variables measured by physical examination were added.
In the third step, information available from X-ray and sonography were added. These steps together resulted in the final model.

Adjusting the model

In a prognostic model, each variable has its own strength of contribution to the total prediction, expressed in the regression coefficients. Models are known to be overoptimistic in predicting when applied in other or future patient groups. To adjust the estimated regression coefficients for overoptimism, we used the shrinkage factor of van Houwelingen and le Cessie.[13,14] The intercept of the model was adjusted such that the number of predicted THR corresponded with the number of observed THR.
To make the total model more useful for daily practice we devised a score chart to obtain a total score for an individual patient, based on the model for predicting a THR at 3 years follow-up; with this score, for each individual the risk for a THR within 3 years can be obtained. The regression coefficients were divided by the smallest regression coefficient, multiplied by 10 and rounded for easy presentation.

Evaluating the model

The predictive accuracy of the models was estimated by their reliability and discrimination. The model's reliability was evaluated by comparing the model's predicted probability of a THR, with the observed probability, and tested using the Hosmer and Lemeshow goodness-of-fit test.[15] The model's ability to discriminate between patients with and without a THR was estimated by the area under the curve (AUC) of a receiver operating characteristic (ROC) curve.

Validating the model

Bootstrapping techniques were used to validate the final prediction model, i.e. to adjust the model performance for overoptimism. The bootstrap samples consisted

of 193 patients, randomly drawn with replacement from the original dataset, and was replicated 100 times. The regression model was fit in these samples to obtain an impression of the optimism in the model. The model's performance obtained after bootstrapping can be considered as the performance that can be expected in other or future patient groups.

Results

Patient characteristics

In a period of 12 months, 244 consecutive patients complied with the inclusion criteria; 227 patients gave informed consent and were examined. Additional exclusion of 3 patients based on severe co-morbidity resulted in a study population of 224 cases. The total study population had a mean age at baseline of 65.6 (SD 9.6) years and 73% was female (Table 1).

Table 1: Patient characteristics

	Baseline	3 years Follow-up	6 years Follow-up
N (%)	224	193 (86)	163 (73)
Follow-up time years (SD)	-	2.7 (0.3)	5.8 (0.3)
Age years: mean (SD)	65.6 (9.6)	68.6 (9.7)	71.6 (9.3)
Gender % female	73.1	72.0	71.8
BMI mean (SD)	27.5 (5.0)	27.0 (4.3)	26.8 (4.2)
THR N (%)	-	23 (11.9)	36 (22.1)
WOMAC score mean (SD)*	-	35.33 (29.8)	45.24 (35.0)
WOMAC >64 N(%)**	-	6 (3.1)	9 (5.5)
THR or WOMAC >64 N (%)	-	29 (15.0)	45 (27.6)
Pain severity (VAS 0-10) mean (SD)*	6.12 (2.08)	5.21 (3.4)	4.64 (3.8)
Pain ≥7 N(%)**	95 (42.4)	62 (32.1)	51 (31.3)

*) people after a THR were recoded as highest score **) including patients after aTHR

The median duration of follow-up was 2.7 (min. 2.2, max. 3.3, SD 0.25) years for the short-term follow-up, and 5.8 (min. 5.3, max. 6.6, SD 0.30) years for the long-term follow-up. After follow-up there was no selective drop-out by age or gender. After 3 years of follow-up the study population consisted of 193 persons (86%);

10 patients were deceased, 6 had moved to an unknown address, 1 had developed severe co-morbidity and was unable to respond, 4 no longer wanted to participate, and 10 were lost to follow-up due to unknown reasons. After 6 years of follow-up, the study population consisted of 163 (73%) patients; an additional 7 patients had died, 4 no longer wanted to participate, 1 suffered from dementia, 5 were too busy, and 13 patients were lost to follow-up due to unknown reasons.

Progression of hip pain

During the 3 year follow-up period 23 (12%) patients had received a THR; after 6 years this number had increased to 36 (22%).

The mean WOMAC score after 3 and 6 years was 35.3 (SD 29.8) and 45.2 (SD 35.0), respectively. After 3 years, 29 patients (13%) had a WOMAC score of ≥64.0 compared with 45 patients (20%) after 6 years. These high WOMAC scores include those patients with a THR. At baseline, 95 patients (42%) had a VAS pain score of ≤7, compared with 62 patients (32%) at 3 years and 51 patients (31%) at 6 years Patients with a THR after follow-up were included in the group with the highest score (Table 1).

Predictive variables for progression

The univariate predictors for a THR within 3 and 6 years are shown in Table 2, and the multivariate predictors are shown in Table 3.

History

The key clinical variables obtained from history to predict a THR within 3 or 6 years are age ≥60 years, morning stiffness, and pain in the groin and/or medial thigh. The same variables are also predictive for a high WOMAC score.

Physical examination

The only variable obtained from physical examination (additional to the selected history variables) that positively predicts a THR within 3 or 6 years, is a decreased active extension of the hip joint. This variable is also predictive for a high WOMAC score after 3 years.

A painful passive internal rotation of the joint is a positive predictive variable for a THR within 3 years, but not for the 6 years outcome. A decreased passive adduction is an additional positive predictive variable for a THR within 6 years, but not within 3 years.

Table 2: Univariate analysis of the prediction of THR at 3 and 6 years of follow-up

		3 years		6 years	
Variable (dichotomous)	**% present at baseline (n=193)**	**OR**	**P-value**	**OR**	**P-value**
History					
Female gender	72	1.2	0.78	1.2	0.70
Age ≥60 years	69	11.7	0.02	6.3	<0.01
Pain duration ≥ 3 months	65	2.1	0.16	1.8	0.16
Pain intensity (VAS score) ≥7	42	1.0	0.94	0.9	0.67
Nocturnal pain	15	0.9	0.83	1.6	0.35
Morning stiffness	39	5.5	<0.01	2.7	0.01
Side of complaints (right)	52	1.5	0.36	1.8	0.11
Bilateral complaints	13	0.6	0.52	0.6	0.37
Pain aggravation					
By sitting	30	0.6	0.36	0.6	0.26
By only moving the hip joint	32	1.8	0.22	1.9	0.08
By lying on the side	60	0.9	0.71	0.8	0.54
By walking	67	2.6	0.10	2.4	0.06
After load	51	1.9	0.16	2.2	0.04
On initial step after rest	76	1.6	0.44	1.1	0.80
Worst pain distribution					
Groin	21	4.4	<0.01	4.4	<0.01
Trochanter	32	0.6	0.28	0.7	0.35
Medial thigh	3	1.9	0.58	7.1	0.04
Anterior thigh	10	2.2	0.21	1.7	0.37
Lateral thigh	7	<0.01	0.71	<0.01	0.68
Buttock	28	0.4	0.1	0.3	0.02
Physical examination					
BMI ≥30	31	0.4	0.06	0.6	0.23
Heberden/ Bouchard noduli	27	1.9	0.17	1.7	0.18
Trendelenburg sign positive	37	1.2	0.69	1.0	0.92
Pain at straight leg raising	11	0.3	0.31	0.2	0.12
Trochanteric tenderness by palpation	59	0.9	0.83	0.9	0.69
Groin tenderness by palpation	24	4.4	<0.01	2.9	0.01
Inguinal ligament tenderness by palpation	29	2.6	0.04	2.0	0.07
Superior iliac posterior spines tenderness by palpation	36	0.8	0.57	0.8	0.47
Sacroiliac joint tenderness by palpation	36	1.4	0.45	1.5	0.26
Ischial nerve tenderness by palpation	16	0.2	0.15	0.4	0.20

		3 years		6 years	
Variable (dichotomous)	**% present at baseline (n=193)**	**OR**	**P-value**	**OR**	**P-value**
Decreased active hip motion with					
Flexion	50	3.3	0.02	2.8	0.01
Extension	39	5.3	<0.01	4.0	<0.01
Abduction	67	3.6	0.04	3.6	0.01
Adduction	32	6.2	<0.01	5.4	<0.01
Internal rotation	45	3.3	0.01	3.1	<0.01
External rotation	18	2.3	0.09	3.1	0.01
Painful passive hip motion in					
Flexion	64	1.7	0.28	1.9	0.12
Extension	40	1.4	0.44	1.4	0.36
Abduction	69	1.7	0.33	2.1	0.11
Adduction	55	2.6	0.06	3.6	<0.01
Internal rotation	62	4.8	0.01	1.8	0.15
External rotation	41	1.4	0.48	1.4	0.40
Laboratory tests					
ESR >20 mm/h	11	1.3	0.71	1.5	0.49
Ultrasound/ Radiology					
Joint effusion	36	0.9	0.78	1.3	0.49
Fluid around tendon	4	<0.01	0.79	<0.01	0.68
Fluid around trochanteric bursa	1	0.02	0.79	0.01	0.76
Kellgren and Lawrence score ≥2	34	13.0	<0.01	17.8	<0.01
Osteophyte formation present	45	3.3	0.01	3.1	<0.01
Joint space <2.5 mm	27	6.6	<0.01	7.1	<0.01

A negative predictive variable for a THR after 3 or 6 years, and for a high WOMAC score after 3 years is a body mass index (BMI) ≥30. However, the BMI is not predictive for a high WOMAC score after 6 years.

These models differ significantly from the variables of history taking only (P-value <0.001 and 0.001, respectively)

Radiology

For both the 3 and 6 years prognosis for a THR, a Kellgren and Lawrence (K-L) score of ≥2 is a positive predictive variable in addition to those variables found in history taking and physical examination. It is also a positive predictor for a high WOMAC score after both 3 and 6 years.

This model also differs significantly from the variables of history taking and physical examination together (P-value 0.02 and <0.001, respectively).

Table 3: Multivariate analysis of the prediction of THR at 3 and 6 years of follow-up

	History	History & Physical examination	History, Physical examination & Radiology	OR after shrinkage
3 YEARS OR (95% confidence interval)				
History				
Age ≥60 years	12.5 (2.2 - 70.6)	14.3 (2.4 – 85.8)	9.9 (1.0 – 96.0)	7.6
Morning stiffness	5.2 (2.2 - 12.4)	4.8 (1.8 – 12.3)	5.3 (1.5 – 18.2)	4.3
Worst pain distribution				
Groin	4.3 (1.9 – 10.0)	2.5 (0.9 – 6.7)	1.6 (0.4 – 5.9)	1.5
Medial thigh				
Physical examination				
BMI ≥30		0.1 (0.03 – 0.5)	0,1 (0.02 – 0.6)	0.1
Decreased active hip motion with				
Extension		3.8 (1.4 – 9.9)	2.9 (0.8 – 10.1)	2.5
Adduction				
Painful passive internal rotation		3.5 (1.1 – 11.2)	3.0 (0.7 - 13.2)	2.7
Ultrasound/ Radiology				
Kellgren and Lawrence score ≥2			7.0 (1.9 – 25.8)	5.6
6 YEARS OR (95% confidence interval)				
History				
Age ≥60 years	7.9 (2.1 – 29.6)	5.2 (1.4 – 19.8)	3.5 (0.9 – 14.3)	
Morning stiffness	2.4 (1.1 – 5.4)	1.9 (0.8 – 4.5)	1.6 (0.6 – 4.3)	
Worst pain distribution				
Groin		3.5 (1.4 – 9.2)	2.8 (1.0 – 8.1)	
Medial thigh		17.8 (1.2 – 260.6)	14.1 (0.4 – 457.2)	
Physical examination				
BMI ≥30		0.4 (0.1 – 1.0)	0.3 (0.1 – 1.0)	
Decreased active hip motion with				
Extension		3.0 (1.2 – 7.6)	2.2 (0.8 – 6.4)	
Adduction		2.4 (0.9 – 6.0)	2.1 (0.8 – 5.8)	
Painful passive internal rotation				
Ultrasound/ Radiology				
Kellgren and Lawrence score ≥2			8.6 (3.0 – 24.6)	

Prognostic modelling

Adjusting the model

The calculated shrinkage factor was 0.88. Multiplying the regression coefficient with this factor, and e raised to the power of this shrunken regression coefficient, resulted in the adjusted ORs shown in Table 3. The exact formula to calculate the individual risk to have a THR within 3 years is:

P= 1/(1+EXP(-(-6.33 + (2.03 * age 60 or above) + (1.47 * morning stiffness) + (0.41 * pain in the groin) + (-2.01 * BMI >30) + (0.93 * decreased extension) + (0.98 * painful internal rotation) + (0.716 * K-L ≥2)))).

The clinical prediction rule is presented in the score chart (Figure 1). The risk scores of the individual prognostic factors add up to a total score that corresponds to the probability to have a THR within 3 years.

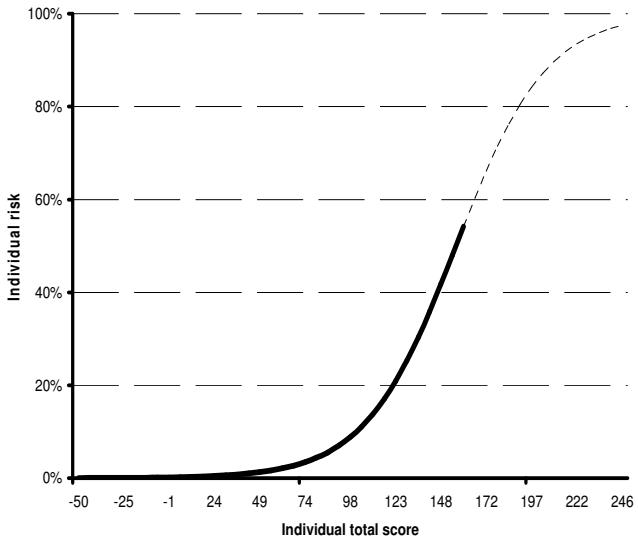
Figure 1: Score chart to obtain the individual risk for a patient for the need of a THR within 3 years

SCORE CHART

To predict the risk of a total hip replacement within 3 years.

If a variable is reviewed positively, the given number needs to be filled in. Subsequently the scores are added to calculate the total individual score. With this total score, the individual risk (%) to undergo a hip replacement within 3 years can be read from the graph.

Age ≥60	50 → …
Morning stiffness	36 → …
Pain in groin	10 → …
BMI ≥30	-50 → …
Decreased extension	23 → …
Painful internal rotation	24 → …
Kellgren-Lawrence ≥2	18 → …
	----------+
TOTAL INDIVIDUAL SCORE	= …



Evaluating the model

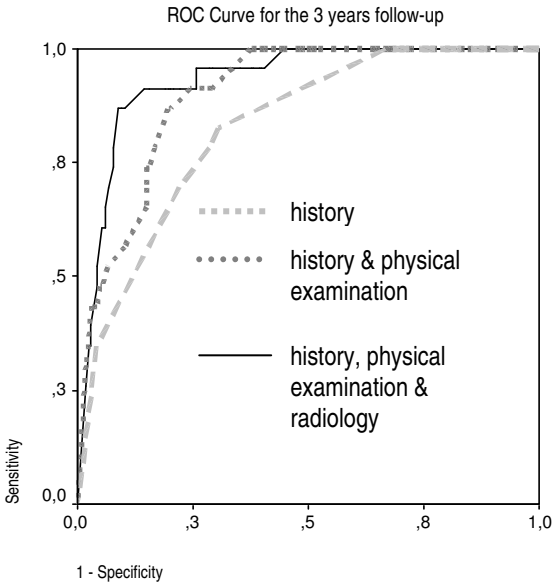
The Hosmer-Lemeshow goodness-of-fit statistic was nonsignificant (P=0.45 for the 3-year follow-up, and 0.20 for the 6-year follow-up) suggesting adequate reliability of the model.

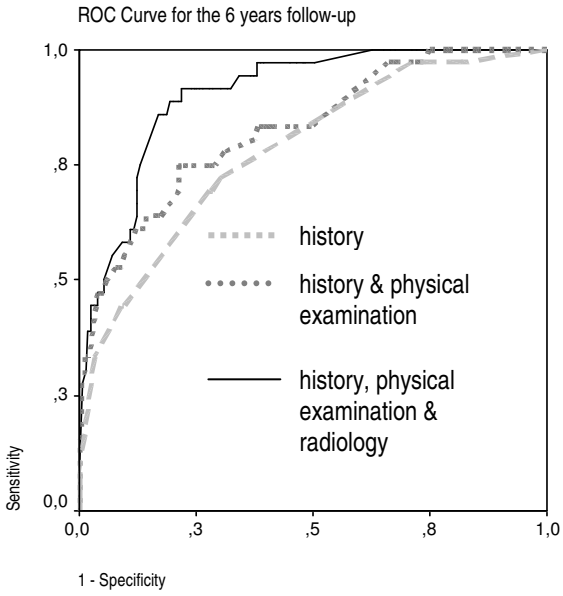
The AUC was 0.93 (95% confidence interval (CI) 0.89 – 0.98) for the 3-year follow-up and 0.91 (CI 0.86 – 0.95) for the 6-year follow-up, indicating good discriminative ability (Figure 2).

Validation of the model

Bootstrapping did not change the AUC significantly (0.94 for the 3-year follow-up and 0.91 for the 6-year follow-up).

Figure 2: ROC for the 3 and 6 years prognosis





3 years follow-up		AUC	(95% CI)
History		0.83	(0.75 – 0.91)
History & physical examination		0.90	(0.85 – 0.95)
History & physical examination & radiology		0.93	(0.89 – 0.98)
Bootstrapping (mean)		0.93	
Adjusted model	History	0.82	(0.73 – 0.90)
	History & Physical Examination	0.90	(0.85 – 0.95)
	History & Physical Examination & Radiology	0.93	(0.89 – 0.98)
6 years follow-up			
History		0.78	(0.70 – 0.87)
History & physical examination		0.83	(0.75 – 0.90)
History & physical examination & radiology		0.91	(0.86 – 0.95)
Bootstrapping (mean)		0.91	

AUC= area under the curve CI= confidence interval

Discussion

Statement of the main findings

Approximately 12 - 22% of the patients initially presenting with hip pain at primary care will receive a THR after 3 and 6 years, respectively and an additional 3 - 5% will have much pain or disability due to their hip condition.

Positive predictive variables for receiving a THR within 3 to 6 years are age ≥60 years, morning stiffness, pain in the groin/medial thigh, restriction of active extension, a painful internal rotation of the hip joint, as well as a K-L score of ≥2. A negative predictive variable for receiving a THR within 3 years is a BMI ≥30. The discriminative ability of these variables combined is around 90%.

Strengths and weaknesses of the study

This is one of the first studies on hip pain in a primary care based population. We chose to include only those patients from whom the GP requested an X-ray, in order to increase the validity of a diagnosis of suspected hip OA. Although our dataset is relatively small (23 and 36 THR after 3 and 6 years of follow-up, respectively), our model appeared to be stable within the 4 outcome categories (THR and WOMAC after 3 and 6 years). Moreover, in our validation process the mean AUC in the bootstrap populations was comparable to the AUC in the original population.

Another problem encountered was the loss to follow-up; 14% after 3 years and 27% after 6 years. However, although there was no selective drop-out for age and gender, there was some drop-out related to the prognostic variables; people without morning stiffness and those with a painful internal rotation are more likely to drop out (P 0.005 and 0.04, respectively). Therefore, the number of THR or severe complaints may have been underestimated.

Due to the nature of this study, we decided to define progression of hip OA as having had a THR (or not) during the follow-up period. Because surgery is also related to other factors (e.g. severe co-morbidity, patients' willingness, age, BMI etc.) we might have introduced some bias, but we also verified the results in patients with a high WOMAC score. Moreover, operation selection was not an issue in our population.

Our choice to group the patients who received a THR together with patients with the highest WOMAC score might be questioned. Therefore, in retrospect it would have been better to have had a WOMAC score of these patients just before they received their operation.

The performance of the predictive model on this dataset will be better than the performance in another (comparable) dataset. This so-called “optimism” can be estimated with the technique called bootstrapping. Bootstrapping replicates the process of sample generation from an underlying population by drawing samples with replacement from the original data set, of the same size as the original data set. In our bootstrap analysis, the prognostic rule seems to be robust. However, if time and costs were of no interest, the most accurate way to validate a prediction rule is to use a new comparable population.

In our final model, 3 of the 7 variables are not significant at the 0.05 level. To see if the model would perform better without these variables, we analysed the 7 variables in a backward stepwise procedure. The variables pain in the groin and a decreased extension would be removed from the model, while the Hosmer and Lemeshow would increase to a significance of 0.982 (better), and the AUC would stay about the same (0.917). Nonetheless, we decided to retain these variables in the model, because this modelling process more accurately reflects the stepwise decision making in practice. Also, in prognostic modelling, adding variables would per definition not introduce bias, but would add prognostic potential.

Relationship to other studies

Several articles have recently been published on factors related to the progression of hip pain/hip OA. [4,16-22]

Whereas we found a positive association between age and progression of hip pain, in our earlier review conflicting evidence was found [4]. The difference might be attributed to selection for surgery: if a patient is relatively young, physicians tend to postpone surgery to avoid the risk of re-surgery after 10-20 years.

For the relationship between obesity and progression, the review found strong evidence for the lack of such an association [4], Flugsrud et al. reported a positive association[17], and in our present study a negative association was found. We are aware, however, that this relationship is easily biased.

Other studies reported a positive association between radiographic evidence of OA and progression;[16,21,22] our study is consistent with these findings.
Three studies[16 19,22]reported a positive association between baseline hip pain and progression of hip OA, whereas we found no such association. The data of two of those studies are population-based.[19,22] Which could explain the difference with our study: all our patients had hip pain complaints, which was the reason to consult their GP. However, a third study with outcome measurements comparable to ours, also found a positive relationship between pain and progression of hip complaints;[16] the reason for this discrepancy is not yet clear.

Explanation of the results found

Not surprisingly, age, morning stiffness, pain in the groin/medial thigh, restriction of the active extension and adduction, a painful internal rotation of the hip joint, as well as radiographic evidence for hip OA were identified as positive predictors for receiving a THR after 3 or 6 years. A BMI ≥30 may be a less obvious finding. However, a BMI ≥30 is a relative contraindication for a THR because physicians tend to instruct the patient to lose weight in order to reduce the pain and the peri-operative risks related to obesity. This advice may reduce the number of patients with OA who would have been operated. If so, the patients who were not operated due to a high BMI, would have a high WOMAC score. Therefore we also tried to analyse whether the BMI would also be a negative predictor for a high WOMAC score. However, because only 6 patients had a high WOMAC score (excluding patients who had a THR) there was insufficient power to perform a logistic regression analysis to see if BMI was associated with a high WOMAC score.

Implications of our findings

In this study about 12% of the population presenting to the GP with hip pain and were subsequently referred for an X-ray of the hip region, will undergo a THR within 3 years, and about 22% after 6 years. The baseline variables most predictive are age ≥60 years, morning stiffness, and pain in the groin and/or medial thigh, decreased extension of the hip joint, a painful internal rotation of the joint (3 years), a painful adduction (6 years), and arthritic changes on the X-ray. A negative predictive variable is a BMI ≥30.

We are now better able to identify persons who are at high risk for progression of hip OA. This can be helpful not only to inform patients more precisely about the course of their hip pain, but also for future clinical trials.

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9

General discussion

In the first part of this thesis, systematic reviews are presented focusing on the risk factors and prognostic factors of osteoarthritis (OA) of the hip. The second part presents studies investigating the prognosis of patients presenting with hip pain in primary care. In this final chapter, we summarize the results found, place them in a broader perspective, and present recommendations for future research.

Hip pain

Two Dutch studies in the open population aged 55 years and older, revealed that about 15-17% of the women and about 7-8% of the men reported hip pain at the moment of the survey.[1,2] Hip complaints in the elderly are generally attributed to hip OA. However, several other conditions can lead to hip pain, including trochanteric pain syndrome (also called trochanteric bursitis), meralgia paresthetica, muscular disorders, tumours, fractures, osteoporosis, and referred pain.[3]

Two of the main causes of hip pain presenting in primary care are investigated in this thesis; osteoarthritis and trochanteric pain syndrome.

Osteoarthritis

Depending on the definition, in the Netherlands about 20,000 new cases of hip OA were diagnosed in 2000, and about 257,000 of the persons aged 55 years and over were suffering from hip OA.[4] Hip OA causes a substantial disease burden and has a high impact on the quality of life in the elderly.

Although new disease-modifying drugs for OA are promising,[5] there is currently no curative therapy for osteoarthritis. In order to prevent the development and the end-stage of hip OA, it is desirable to detect hip OA and its determinants as early as possible. Besides, most of us want to *become* old, but not *be* old, implying that we want to delay the onset of morbidity as well as reduce the burden involved.

It is therefore important to differentiate between determinants for occurrence of disease, which are useful for primary prevention in certain risk groups, and determinants for progression of disease, useful for secondary and tertiary prevention in individuals with existing complaints and early signs of hip OA.

Causes

Risk factors for the onset of hip OA include those that are non-modifiable (e.g. age, gender, family history and race), as well as those amenable to modification, if not in practice, then at least in principle (e.g. obesity, occupational exposure, physical activity, joint injury, hip dysplasia). We are most interested in the latter.

Obesity

In 1945, Fletcher et al. suggested (as one of the first), that obesity is important in the aetiology of OA.[6] From then on, the relationship between OA and obesity has been a matter of considerable debate in the rheumatologic and orthopaedic literature. Also in hip OA, the results of available studies are not unambiguous. For many years it was not clear whether being overweight preceded or occurred as a consequence of hip OA, given the amount of immobility and disability the disease can produce. However, a growing number of studies have shown that being overweight antedates the development of the disease.[7-9]

In an effort to unravel the existing literature on this topic, (*Chapter 2*) our review showed that obesity increases the risk of hip OA.[10] Kellgren called "the mechanical effect of excess body weight upon joints of the lower limbs self-evident." This mechanical effect could explain the relationship between increased body weight and hip OA; however, the relationship with hip OA is weaker than its association with the disease in the knee.[11] One of the explanations mentioned is that a substantial part of the adiposity, especially in women, lies below the hip joint, which does not contribute to the loading of the hip.[12] However, the excess of OA in non-weight bearing joints (e.g. the DIP joints of the hand in overweight persons), does not support this theory, suggesting that the issue might be more than simply mechanical. Several studies reported a relationship between hypertension, hypercholesterolaemia, and blood glucose with OA,[13-15] supporting the concept that OA has an important systemic and metabolic component in its aetiology. Moreover, it has been shown that leptin (a protein hormone with important effects in regulating metabolism) may play an important role in the metabolic pathophysiology of the onset of OA[16]. The difference in the strength of the relationship between obesity and hip OA and knee OA might thus be explained by the additional factors that make the joint more vulnerable.[12]

For hip OA it has been estimated that, if obesity is eliminated, the prevalence would decrease by 25%.[17] However, although tempting, it cannot be concluded that weight loss is effective in preventing either the clinical manifestation or the progression of hip OA, especially if a metabolic component is responsible for the relation between obesity and OA. The finding in our review that obese patients with hip OA suffer earlier from the same grade of hip OA than non-obese patients,[10] more or less implies that weight reduction would be beneficial. Weight reduction was also shown to be useful in lowering the risk for incident radiological knee OA,[18] and for the reduction of symptoms in knee OA.[18-22] However, Flugsrud and colleagues recently published data of a large-population based study, concluding that weight change during the fourth and fifth decade of life (age 34-47 years), did not affect the risk for a total hip replacement resulting from primary OA.[23]

Although we have now clarified some of the mysteries surrounding the relationship between obesity and the onset of hip OA, the different pathways of the causal relationship between obesity and OA remain an enigma. Hence, more research is needed to elucidate which metabolic components are responsible for the onset of OA. If these prove to be modifiable, primary prevention in certain risk groups may then become possible.

Occupational factors

With physical activities that are performed day in and day out, 8 hours a day, 40 hours a week, more than 45 weeks a year, over many years, it is likely that some of these activities will have an effect on the musculoskeletal system. A number of studies have shown that repetitive activities of labourers lead to OA: e.g. in finger joints of cotton mill workers[24], in the base of the thumb in physiotherapists[25]; in knees and spines of miners[26]; in elbows, wrists and metacarpophalangeal joints of jackhammer operators[11], and in hip joints of farmers.[27,28] Our review on workload and the occurrence of hip OA (C*hapter 3*), showed that previous heavy physical workload increases the risk of hip OA.[29] The relation between OA and occupation is, however, difficult to investigate because of the long latency before the pathological process brings work incapacity or the need for medical consultation.

Another finding of our review is that lifting heavy objects (≥25 kg) is likely to increase the risk for the occurrence of hip OA. The underlying mechanism is well

illustrated in a study on a patient who, at the time of total hip arthroplasty, was fitted with a prosthetic hip that contained multiple pressure sensors.
Postoperatively this patient was studied in the gait laboratory under a variety of experimental conditions. It was reported that placing a 4.5 kg weight in either hand produced an increase in pressure in the hip.[30]
Our review also showed that farmers may have an increased risk of hip OA, but the studies in our review could not reveal the exact mechanism. It has been postulated that driving tractors and jumping up and down from the tractor cabin plays a role. A recent study by Järvholm and colleagues, however, reported that the higher risk of hip OA in farmers, can not be attributed to driving vehicles with high levels of whole body vibration.[31] Moreover, another study on a large group of farmers reported that farmers operating a large plant production area (>100 hectares) and with few animal contacts, had a significantly lower risk of hip OA than farmers in general. The presence of animal production showed a significant positive relationship with the risk of hip OA (milking >40 cows/day, >5 h. in animal barns).[32]
In summary, with respect to the relationship between occupation and hip OA, specific activities appear to increase the risk for hip OA purely by a mechanical effect. However, it is unclear whether a change in occupation reduces the risk of OA. It is also unclear whether ergonomic modification of the workplace prevents the development of OA, or lessens its burden. Therefore, further research in this area, especially on ergonomic factors associated with the development of OA, is needed.

Sporting activities

Due to the disappointingly low quality of the studies reporting on the relationship between sporting activities and the occurrence of hip OA, we could only conclude that there is limited evidence for such a relation (*Chapter 4*).[33] Nevertheless, repetitive mechanical load on the joints might have some effects on the weight bearing joints. Moreover, a study on marathon runners showed that levels of cartilage oligomeric matrix protein (a marker of cartilage turnover and destruction) were raised at baseline as compared to healthy non-running controls (perhaps reflecting training), and increased during the marathon.[34] The clinical significance of these findings is as yet unclear.

Similar to the review on obesity and hip OA, the review on sporting activities and hip OA reported a stronger relationship in studies reporting on clinically assessed hip OA compared with radiologically assessed hip OA, suggesting that people participating in regular sporting activities suffer more from the same degree of degeneration from the hip joint than do non-participants, perhaps because sporting activities places great demands on the body. However, another explanation could be that the hip complaint reflects hip symptoms due to non-articular problems (e.g. tendinitis, bursitis, muscle strain, etc.) because in the included studies, clinical hip OA was often defined as “hip pain”.

Another factor probably involved in the onset of hip OA in people with regular sporting activities, is the amount of sporting injuries occurring during sporting activities. An injured joint might be more vulnerable to develop OA compared with a non-injured joint.[11,35]

Although the evidence supporting preventive strategies is weak, efforts to decrease the risk for OA in sports participants should be made. These should include careful pre-participation evaluation of individual risk factors, training that improves joint dynamic stability, and modification of rules to decrease direct player contact and high intensity joint torsion. In addition, early diagnosis and effective treatment of joint injuries and ensuring complete rehabilitation after joint injury should decrease the risk for OA among sport participants.

Hip dysplasia

It is well known in the field of orthopaedics that congenital and developmental hip abnormalities occurring during infancy or childhood, predispose to hip OA in early adulthood (20-30 years). Up till now, however, very few studies have been published on this topic, and most of them reported cross-sectional data on elderly persons with mild forms of hip dysplasia only. The problem with these cross-sectional data is that mild forms of hip dysplasia might cause hip OA, but signs of hip OA (joint space narrowing, osteophytes and medial migration of the femoral head) might make it difficult to correctly measure hip dysplasia. Therefore in our review (*Chapter 5*) we could only conclude that there is limited scientific evidence for a relationship between hip dysplasia and the onset of hip OA.[36]

The most obvious mechanism to explain the association between acetabular dysplasia and hip OA is that the presence of a (mild form of a) biomechanical

abnormality, secondary to either joint incongruity (smaller acetabular depth) or decreased joint surface area (smaller CE angle), that may increase joint stresses.
Given the current primary prevention policy in the Netherlands, whereby almost all newborns are examined for congenital hip abnormalities, it would be interesting to study all persons who were diagnosed with hip dysplasia in a given cohort about 10, 20 and 30 years ago to look for evidence of some association between hip dysplasia and subsequent hip OA.

Course

Predicting the course of hip OA is not only important to give the patient accurate information on the disease course, but also for decisions concearning treatment options. For example for future research in order to define the most appropriate cases, or to enable subgroup analysis to correctly evaluate treatment effects. Secondly, to provide the patient with the most optimal treatment given their prognosis: e.g. although several studies reported the positive effect of glucosamines in pain reduction in OA, patients with more severe disease and higher pain scores do not seem to benefit.[37]
In our systematic review of studies exploring variables predicting a fast progression of hip OA (*Chapter 6*), several variables were reported to have a relationship with the progression of hip OA.[38] However, because all included studies were hospital-based and 5 of the 8 discussed variables were based on radiological information, the information from this review is of limited use in primary care. All the variables obtained from our prospective follow-up study on patients with hip pain presenting at primary care (*Chapter 8*) are signs of severe hip OA. Because surgery will be performed only in patients with signs of severe hip OA, these variables might be related to the study outcome (a total hip replacement), and some circular reasoning therefore is possible. Nonetheless, several intriguing factors will be discussed below.

Obesity

In contrast to the relationship between obesity and the onset of hip OA, our review showed that obesity seems to have no influence on the progression of hip OA.[38] Our follow-up data even reveal that obese persons are less likely to show progression of their hip complaints. This finding might be explained by the fact that

a BMI ≥30 is a relative contraindication for surgery. Physicians tend to instruct these patients to lose weight in order to reduce the pain and to reduce the peri-operative risks involved with obesity. This advice may reduce the number of patients with OA who would have been operated upon. However, due to a lack of power we were not able to verify this explanation on patients with a high WOMAC score (a disability score for OA of the hip/knee). In knee OA, (radiographic) progression might be more dependent on being obese or not.[39] It remains unclear whether a mechanical effect is more likely in knee OA, and a metabolic effect is more important in hip OA. Therefore, intervention studies are needed in which patients with incident complaints of hip OA are randomly put on dietary measures. Outcomes of such studies will give insight into the potential for secondary prevention of patients suffering from hip OA.

Pain

In our follow-up study, pain intensity at baseline was not predictive for progression. However, two recent population-based studies reported that people with radiographic findings of hip OA and hip pain showed a faster progression of radiographic and clinical hip OA as compared to people without hip pain.[40,41] Besides the fact that pain intensity is not totally comparable to the presence or absence of pain, our study is primary-care based rather than population-based (all our patients had pain in the hip) which means that these study populations are not comparable. However, Birrell et al. reported on the prognosis of hip OA in a primary-care based setting, and also reported that the severity of pain is predictive for being put on a waiting list for a total hip replacement.[42]

Thus, if pain predicts progression, the question then arises: *Why* does pain predict OA progression? One of the possibilities is that, as in knee OA, synovial effusion is responsible for the pain and therefore for the deterioration of OA.[43] However, in our follow-up study, we found no evidence to support this theory; in fact, joint effusion at baseline (assessed with ultrasound) is not associated with surgery after 3 or 6 years. A postulated theory in the past about bone marrow oedema and pain in OA has recently been re-discovered.[44,45] Perhaps the clue to pain in OA and its progression lies here; this would be an interesting pathway for further research.

Trochanteric pain

Of all patients presenting in primary care with hip pain, 10-20% can be attributed to trochanteric pain. Although the term 'trochanteric bursitis' is often applied to this condition, the initial pathology usually occurs in the tendons attached to the greater trochanter and the adjacent bursae may then be secondarily involved. In some cases it can be an isolated condition, but it is often associated with other diseases such as low-back pain or sciatica[46,47], OA of the hip[46], avascular necrosis of the femur head[48], or metastatic bone diseases.[49] Therefore we argue that trochanteric pain should be classified as a syndrome occurring in several diseases rather than a separate pathologic entity.

In Chapter 7 we reported an incidence of trochanteric pain of 1.8/1000 persons per year.[50] Another study on trochanteric pain in Dutch primary care, reported an incidence of 5.6/1000 persons per year.[51] Because the data of our research were collected retrospectively, and therefore depended on the registration and definition used by the GP, this might have led to underreporting of the clinical presentation. However, due to the prospective study of the latter survey, overreporting might have occurred due to case finding. Nevertheless, trochanteric pain is a frequently occurring problem. Moreover, a considerable part of the patients enrolled in our study still suffered from pain complaints on the greater trochanter after 1 year and 5 year follow-up. Whether these persisting complaints originate primarily from the soft tissue surrounding the greater trochanter, or from other co-morbid conditions, is not clear. We believe, however, that this co-morbidity is important in the prognosis of trochanteric pain. This finding was also suggested in our study: patients with OA of the lower limbs were almost five times more likely to have sustained complaints after 1 year. However, due to the study design (retrospective questionnaire), we were not able to examine the patients objectively concerning specific co-morbid conditions. Given these considerations, it is important to distinguish any co-morbid condition; firstly, to enable the physician to give the patient optimal information about the prognosis and treatment, secondly, to better define appropriate cases or enable subgroup analysis to correctly evaluate treatment effects in future studies.

The chronicity and burden of the syndrome in patients with trochanteric pain, justifies future research efforts on the pathophysiology, the prognosis, and the treatment options. Therefore, a group of patients presenting to the general practitioner with complaints of trochanteric pain should be enrolled into a prospective study in which a thorough history taking should take place to look for any potential cause, such as co-morbidity, trauma or repetitive strain. A physical examination should also be performed, including at least a low back and hip examination. In addition, a radiological examination should reveal any pathophysiological changes in the region. This cohort of patients should be followed for at least 3 years in order to establish the prognosis and to examine whether these patients more often develop conditions such as osteoarthritis and low-back pain.
After we are able to define relevant subgroups (based on any co-morbid condition and/or the prognosis), intervention studies are needed to find the most effective treatment for patients with trochanteric pain.

In conclusion, the studies in this thesis have provided some evidence-based results to guide physicians, policy makers and future research on the cause and the course of hip pain in general practice.

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10

Summary and conclusions

Arthritic musculoskeletal complaints are one of the main causes of pain and disability in the elderly. Hip pain is after knee complaints, the most frequent diagnosis in this field of disorders. Hip pain in the elderly is commonly attributed to osteoarthritis (OA) of the hip, but another widespread diagnosis is trochanteric pain syndrome. Knowledge about the determinants on the cause and the course of hip pain in general practice is essential for medical doctors, decision makers and researchers. Therefore we looked at the determinants on the cause and course of hip pain in general practice.

In **chapter 2 to 6** presents four studies in which we systematically summarized the available literature addressing the influence of obesity, occupational activities, sporting activities and dysplasia on the occurrence of the hip OA In the final review, we systematically summarized all available papers on prognostic factors of hip OA. A bibliographical search of Medline, Embase and the Cochrane library until April 2000 was carried out and articles with the aim to study a relationship between obesity occupational activities, sporting activities, dysplasia or the progression of hip OA were selected. The quality of the studies was assessed using a standardised set of criteria. The outcome of the studies was compared with respect to study characteristics, and the quality score. A best evidence synthesis was used to summarise the results of the individual studies.

In **chapter 2**, the review on obesity and the occurrence of hip OA showed that the evidence for a positive influence of obesity on the development of hip OA is moderate, with an OR of approximately 2. This conclusion was based on 5 longitudinal and 7 cross-sectional papers. The associations between obesity and hip OA were stronger in studies in which the diagnosis hip OA was based not only on radiological criteria, but on clinical symptoms as well.

Chapter 3 presents the data of the review on the influence of physical workload on the occurrence of hip OA. In this review 2 retrospective cohort studies and 14 case-control studies were included. Almost all papers included in this review were prone to biases. Overall, moderate evidence was found for a positive association, with an OR of approximately 3, between previous heavy physical workload and the occurrence of hip OA. In addition, for the subcategories, i.e. ≥10 years farming or

lifting heavy weights (≥25 kg), moderate evidence was found for a positive relationship with hip OA.

Chapter 4 describes the review on sporting activities and the occurrence of hip OA.

In this review, one cohort study and 21 cross-sectional studies were included, and overall, moderate evidence was found for a positive association between physical sporting activities and the occurrence of hip OA, with an OR of approximately 2. The highest risks are found in high intensity activities, especially for hip OA with a clinical presentation. Possible selection of the studied populations however, may partly be responsible for the association found, or may have diluted the real association.

In **chapter 5** we reviewed the influence of acetabular dysplasia on the development of hip OA. Five cohort studies and four case-control studies were included in this review, but only one cohort study had the correct design to be able to address to the question and reached the level of high quality study. This study reported a positive association between acetabular dysplasia and hip OA. Overall, limited evidence was found for a positive association between acetabular dysplasia and hip OA. However, most studies included persons at a higher age group. In younger age groups the relation between acetabular dysplasia and OA or hip complaints may be much higher.

In **chapter 6**, a systematic review on the prognostic factors of hip OA is presented. Twelve studies were included in this review. Ten studies had a cohort design, of which five collected their data prospectively. Two studies had a case-control design. Based on the evidence, we may conclude that there is strong evidence that people with a supero- (lateral) type of migration of the femur head or an atrophic bone response show a more rapid progression of hip OA as compared with a medial migration or hypertrophic bone response. Also strong evidence is found that there is no relationship with obesity and the progression rate of hip OA. Limited evidence is found that, when there is a more severe joint space narrowing at first consultation, there will be an earlier need for a (total hip replacement) THR, as well as for no relation between hip dysplasia and the progression of hip OA.

In the retrospective study presented in **chapter 7**, we investigated the 1 and 5 years prognosis of patients presenting with trochanteric pain in primary care. Patients with incidental trochanteric pain in the years 1996 or 2000 were

questioned in 2001 for past and present symptoms of trochanteric pain. The conclusions of this study were that the incidence of trochanteric pain in primary care is 1.8 / 1000 patients / year. After one year 36 (best case scenario)-76% (worst case scenario) still suffered from trochanteric pain, and after 5 years this was 29-63% respectively. Patients with osteoarthritis in the lower limbs had a 4.8-fold risk of persistent symptoms after one year, as compared to patients without osteoarthritis. Patients who had received a corticosteroid injection had a 2.7-fold chance of recovery after 5 years, as compared to patients who had not received an injection.

In **chapter 8**, we described a prospective follow-up study on patients with incident complaints of hip pain presenting at the GP and were referred for an X-ray. After 3 years 12% and after 6 years 22% of the patients received a total hip replacement. With variables obtained from history taking (age ≥60, morning stiffness, pain in the groin/medial thigh), physical examination (decreased extension or adduction, painful internal rotation and a body mass index (BMI) ≥30 (negative predictive)) and radiological findings (Kellgren-Lawrence grade of ≥2), we are better able to identify persons who are at high risk for a total hip replacement after 3 and 6 years.

Chapter 9 discusses the main findings of this thesis and put them in a broader perspective.

11

Samenvatting en conclusies

Artrotische klachten van het bewegingsapparaat zijn een belangrijke oorzaak van pijn en beperkingen in de oudere populatie. Na knieklachten zijn heupklachten de meest voorkomende diagnose binnen deze groep aandoeningen. Heupklachten bij ouderen wordt meestal toegeschreven aan artrose van het heupgewricht, maar een andere, veel voorkomende diagnose is het trochantair pijn syndroom.
Kennis over de oorzaken en de prognose van heuppijn in de huisartspraktijk is essentieel voor medici, voor beleidsmakers en voor onderzoekers. De hoofddoelstelling van dit onderzoek is dan ook de oorzaken en de prognose van heuppijn in de oudere populatie in de huisartspraktijk te onderzoeken.

In **hoofdstuk 2 tot en met 6** presenteren we 4 studies waarin we de beschikbare wetenschappelijke literatuur over de invloed van overgewicht, werk, sport en heupdysplasie op het ontstaan van heupartrose op een systematische wijze hebben samengevat. In de laatste review hebben we de literatuur samengevat over de prognose van heupartrose.
We hebben een zoekactie verricht in Medline, Embase en de Cochrane bibliotheek tot april 2000 en artikelen met het doel het onderzoeken van de relatie tussen overgewicht, werk, sport, heupdysplasie of de progressie van heupartrose werden geselecteerd. De kwaliteit van de studies werd gemeten met een gestandaardiseerde set criteria en de uitkomsten van de studies werden met behulp van een best evidence synthese samengevat.

In **hoofdstuk 2** werd een matig bewijs gevonden voor de relatie tussen overgewicht en het ontstaan van heupartrose, met een Odds Ratio (OR) van ongeveer 2. Deze conclusie was gebaseerd op 5 longitudinale en 7 cross-sectionele studies. De relatie tussen overgewicht en heupartrose was sterker in studies die niet een radiologisch gemeten artrose (bijvoorbeeld gewrichtsspleetvernauwing), maar klinische symptomen van de heupartrose (bijvoorbeeld pijn of een heupvervangende operatie) als uitkomstmaat hadden.
In **hoofdstuk 3** presenteren we de data van de review over de invloed van werk op het ontstaan van heupartrose. In deze review werden 2 retrospectieve cohort studies en 14 patiënt-controle studies geïncludeerd. Vrijwel alle studies die we in deze review hebben geïncludeerd zijn gevoelig voor bias. Uiteindelijk werd ook hier een matig bewijs gevonden voor een positieve relatie tussen zwaar lichamelijk

werk en het ontstaan van heupartrose, met een OR van ongeveer 3. Daarnaast werd voor de subgroepen ≥10 jaar werken op een boerenbedrijf, of het tillen van zware objecten (≥25 kg), ook een matig bewijs gevonden op het ontstaan van heupartrose.

Hoofdstuk 4 beschrijft de review over de invloed van sporten op het ontstaan van heupartrose. In deze review werden 1 cohort en 21 cross-sectionele studies geïncludeerd en ook hier weer werd een matig bewijs gevonden voor de invloed van fysieke sportactiviteiten op het ontstaan van heupartrose. De OR is ongeveer 2. De hoogste risico's werden beschreven in de studies over hoog intensiteit sportactiviteiten, voornamelijk in studies waarin een klinische presentatie van heupartrose als uitkomstmaat werd genomen. Selectie van de bestudeerde populaties kan echter een deel van de gevonden relatie verklaren, of kan de sterkte van de relatie hebben verdund.

In **hoofdstuk 5** hebben we de invloed van heupdysplasie op het ontstaan van heupartrose onderzocht. In deze review werden 5 cohort studies en 4 patiënt-controle studies geïncludeerd, maar slechts 1 studie had het juiste design om de onderzoeksvraag te beantwoorden. Deze studie rapporteerde een positieve associatie tussen heupdysplasie en het ontstaan van heupartrose. De gehele review kon maar tot een beperkt bewijs komen voor de veronderstelde relatie. Alle onderzoeken echter, waren voornamelijk gericht op milde vormen van dysplasie op de oudere leeftijd en niet op vormen van dysplasie op kinderleeftijd. In vormen van dysplasie in de jongere leeftijdsgroepen kan de relatie met het ontstaan van heupartrose dus sterker zijn.

In **hoofdstuk 6** wordt een review gepresenteerd over de prognostische factoren van heupartrose. In deze review werden 12 studies geïncludeerd; 10 hadden een cohort design, waarvan 5 de data prospectief hadden verzameld en 2 studies hadden een patiënt-controle design. Uit de review bleek dat er sterk bewijs was voor een snellere progressie van heupartrose bij mensen met een supero/laterale vorm van migratie van de femurkop, of een atrofische botrespons, ten opzichte van mensen met een mediale migratie of een hypertrofische botrespons. Ook bleek dat er sterk bewijs was voor een afwezige relatie tussen overgewicht en progressie van heupartrose. Er was beperkt bewijs voor een snelle progressie bij een ernstige mate van gewrichtsspleetvernauwing bij de eerste consultatie en bij de aanwezigheid van heupdysplasie.

In de retrospectieve studie in **hoofdstuk 7** hebben we de 1 en de 5 jaars prognose van trochantaire pijn onderzocht bij mensen die zich presenteerden met deze klacht bij de huisarts. Patiënten met incidente klachten van trochantaire pijn in 1996 of 2000 werden in 2001 gevraagd naar hun initiële en hun eventuele huidige klachten van trochantaire pijn. De conclusies van het onderzoek waren dat de incidentie van trochantaire pijnklachten in de huisartspraktijk 1.8 patiënten per 1000 per jaar is en dat na 1 jaar nog 36% en na 5 jaar nog 29% last had. Patiënten met artrose aan de onderste extremiteiten hadden 4.8 keer zoveel kans op persisterende klachten na een jaar ten opzichte van mensen zonder artrose. Patiënten die een corticosteroïd injectie hadden gekregen hadden 2.7 keer meer kans op herstel na 5 jaar vergeleken met patiënten die geen corticosteroïd injectie hadden gekregen.

In **hoofdstuk 8** presenteren we de resultaten van een prospectieve follow-up studie van patiënten met incidente klachten van heuppijn, die zich presenteren bij de huisarts en die waren verwezen voor een röntgenfoto van het heupgewricht. Na 3 jaar had 12% en na 6 jaar had 22% een heupvervangende operatie ondergaan. Met variabelen verkregen bij de anamnese (leeftijd ≥60 jaar, ochtendstijfheid, liespijn), lichamelijk onderzoek (verminderde extensie/adductie, pijnlijke endorotatie en een body mass index ≤30) en radiologische bevindingen (Kellgren and Lawrence ≥2) zijn we nu beter in staat om patiënten te identificeren die een grotere kans hebben op een heupvervangende operatie na 3 of na 6 jaar.

In **hoofdstuk 9** bespreken we de belangrijkste bevindingen van dit proefschrift en plaatsen we ze in een breder perspectief.

Appendices

Appendix 1:

List of criteria for the assessment of the methodological quality
for cohort and case-control designed studies measuring risk factors

Item	Criteria	V/I*	CH/CC†
	Study population		
1	Selection before disease was present or at uniform point	V	CH/CC
2	Cases and controls were drawn from the same population	V	CC
3	Participation rate ≥80% for cases/cohort	V	CH/CC
4	Participation rate ≥80% for controls	V	CC
5	Sufficient description of baseline characteristics	I	CH/CC
	Assessment of risk factor		
6	Exposure assessment was blinded	V	CH/CC
7	Exposure was measured identical in studied population	V	CC
8	Exposure was assessed prior to the outcome	V	CH/CC
	Assessment of hip OA		
9	Hip OA was assessed identical in studied population	V	CH/CC
10	Presence of hip OA was assessed reproducibly	V	CH/CC
11	Presence of hip OA was according to valid definitions	V	CH/CC
12	Classification was standardised	I	CH/CC
	Study design		
13	Prospective design was used	V	CH/CC
14	Follow-up time ≥ 3 years	V	CH
15	Withdrawals ≤ 20%	V	CH
16	Information on completers vs. withdrawals	I	CH
	Analysis and data presentation		
17	Frequencies of most important outcomes was given	I	CH/CC
18	Appropriate analysis techniques were used	V	CH/CC
19	Adjusted for at least age and gender	V	CH/CC

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

† CH= applicable to cohort designed studies

CC= applicable to case-control designed studies.

Appendix 2:

Specified criteria list for the methodological quality assessment (see appendix 1).

Study population

1. Positive if the study population was selected before any clinical or radiological sign of hip OA was present
   Positive if (sub-) groups were selected at a uniform point of the disease
2. Positive if the cases and the controls were drawn from the same source population (primary study base)
3. Positive if the participation rate of the cases/population selected and invited to participate at baseline was at least 80%
4. Positive if the controls selected and invited to participate at baseline was at least 80%
5. Positive if at least 7 of the following 12 items were reported at baseline
   - Age (mean and standard deviation)
   - Gender (number and/or percentage)
   - Weight (mean and standard deviation)
   - Body Mass Index (BMI)(mean and standard deviation)
   - Race
   - Job description
   - Sport/leisure time exposure
   - History of trauma
   - Smoking
   - Hormone replacement therapy
   - Signs of OA in other joints (OA objectivated in other joints, Heberden's nodes)
   - Characteristics of OA on X-ray or other imaging techniques

Assessment of risk factors

6. Positive if the exposure assessment was blinded with respect to disease status
7. Positive if exposure was measured in an identical way for the whole studied population
8. Positive if the exposure was assessed prior to the disease outcome

Assessment of hip OA

9. Positive if the way of assessing hip OA was identical for the entire studied population
10. Positive if the measurement instruments used for observing or identifying the presence of hip OA were reproducible
    Positive if (waiting for) a (total) hip replacement (THR) was used as an outcome measure for hip OA
11. Positive if the measurement instruments used for observing or identifying the presence of hip OA were standardised using validated definitions
    Positive if (waiting for) a THR was used as an outcome
12. Positive if the classification of the radiological osteoarthrosis was standardised using the Kellgren and Lawrence or the Croft classification
    Positive if the classification of the clinical osteoarthritis was standardised using the ACR criteria
    Positive if (waiting for) a THR was used

Study design

13. Positive if a prospective design was used
14. Positive if the total follow-up time was ≥ 3 years
15. Positive if the total number of withdrawals was ≤ 20% (in case a retrospective cohort design was used, a negative score was assigned)
16. Positive if demographic/clinical information was presented for completers and withdrawals (in case a retrospective study design was used, a negative score was assigned)

Analysis and data presentation

17. Positive if frequency or percentage (or mean and standard deviation/CI) of the outcome(s) of the risk factor(s) were used
18. Positive if confounding variables were used in the statistical analysis.
    (Validated techniques such as multivariate regression or Mantel-Haenszel must have been used)
    Positive if (sub-) group analysis were made in a heterogeneous population
    Positive if no (sub-) group analysis was made in a homogeneous cohort at baseline Positive if there was at least corrected for the confounders age and gender by means of matching, restriction or adjustment in the analysis.

Appendix 3:

List of criteria for the assessment of the methodological quality
for cohort and case-control designed studies measuring progression.

Item	Criteria	V/I*	CH/CC†
	Study population		
1	Selection before disease was present or at uniform point	V	CH/CC
2	Cases and controls were drawn from the same population	V	CC
3	Participation rate ≥80% for cases/cohort	V	CH/CC
4	Participation rate ≥80% for controls	V	CC
5	Sufficient description of baseline characteristics	I	CH/CC
	Assessment of prognostic factors		
6	Exposure assessment was blinded	V	CH/CC
7	Exposure was measured identical in studied population	V	CC
8	Exposure was assessed prior to the outcome	V	CH/CC
	Assessment of hip OA		
9	Hip OA was assessed identical in studied population	V	CH/CC
10	Presence of hip OA was assessed reproducibly	V	CH/CC
11	Presence of hip OA was according to valid definitions	V	CH/CC
12	Classification was standardized	I	CH/CC
	Study design		
13	Prospective design was used	V	CH/CC
14	Follow-up time ≥ 6 months/1 year	V	CH/CC
15	Withdrawals ≤ 20%	V	CH/CC
16	Information on completers vs. withdrawals	I	CH/CC
	Analysis and data presentation		
17	Frequencies of most important outcomes was given	I	CH/CC
18	Appropriate analysis techniques were used	V	CH/CC
19	Adjusted for at least age and gender	V	CH/CC

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

† CH= applicable to cohort designed studies

CC= applicable to case-control designed studies.

Appendix 4:

Specified criteria list for the methodological quality assessment (see appendix 3).

Study population

1. Positive if the study population was selected before any clinical or radiological sign of hip OA was present
   Positive if (sub-) groups were selected at a uniform point of the disease or exposure
2. Positive if the cases and the controls were drawn from the same source population (primary study base)
3. Positive if the participation rate of the cases/population selected and invited to participate at baseline was at least 80%
4. Positive if the controls selected and invited to participate at baseline was at least 80%
5. Positive if at least 7 of the following 12 items were reported at baseline
   - Age (mean and standard deviation)
   - Gender (number and/or percentage)
   - Weight (mean and standard deviation)
   - Body Mass Index (BMI)(mean and standard deviation)
   - Race
   - Job description
   - Sport/leisure time exposure
   - History of trauma
   - Smoking
   - Hormone replacement therapy
   - Signs of OA in other joints (OA objectivated in other joints, Heberden's nodes)
   - Characteristics of OA on X-ray or other imaging techniques

Assessment of prognostic factors

6. Positive if the exposure assessment was blinded with respect to disease status
7. Positive if the exposure was measured in an identical way for the whole studied population
8. Positive if the exposure was assessed prior to the disease outcome

Assessment of hip OA

9. Positive if the way of assessing hip OA was identical for the entire population
10. Positive if the measurement instruments used for observing or identifying the presence of hip OA were reproducible. Positive if (waiting for) a (total) hip replacement (THR) was used as an outcome measure for hip OA
11. Positive if the measurement instruments used for observing or identifying the presence of hip OA were standardized using validated definitions.
    Positive if (waiting for) a THR was used as an outcome
12. Positive if the classification of the radiological osteoarthritis was standardized using the Kellgren and Lawrence or the Croft classification
    Positive if the classification of the clinical osteoarthritis was standardized using the HAQ or the ACR criteria, the Lequesne or the Womac score.
    Positive if (waiting for) a THR was used

Study design

13. Positive if a prospective design was used
14. Positive if the total follow-up time was ≥ 12 months if radiographic parameters were used as an outcome measure.
    Positive if the total follow-up time was ≥ 6 months if clinical parameters were used as an outcome measure.
15. Positive if the total number of withdrawals was ≤ 20% (in case a retrospective design was used, a negative score was assigned)
16. Positive if demographic/clinical information was presented for completers and withdrawals (in case of a retrospective design, a negative score was assigned)

Analysis and data presentation

17. Positive if frequency or percentage (or mean and standard deviation/CI) of the outcome(s) of the risk factor(s) were used
18. Positive if confounding variables were used in the statistical analysis. (with validated techniques such as multivariate regression or Mantel-Haenszel)
    Positive if (sub-) group analysis were made in a heterogeneous population
    Positive if no (sub-) group analysis was made in a homogeneous cohort at baseline
    Positive if there was at least corrected for the confounders age and gender by means of matching, restriction or adjustment in the analysis

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Over de auteur

Annet Lievense werd geboren in Goes, op 8 maart 1971, samen met haar tweelingbroer Elbert. Met haar twee zussen en drie broers groeide zij op in Nieuwerkerk; een klein dorp in de provincie Zeeland. Na het behalen van haar VWO diploma aan de Professor Zeemanschool in Zierikzee in 1990, begon ze met haar studie geneeskunde aan de Erasmus Universiteit Rotterdam. Tijdens haar studie participeerde zij in diverse (landelijke) commissies met als doel het verbeteren van het medisch onderwijs. Aansluitend aan het behalen van het artsexamen in 1997 werkte zij tot 1999 als arts-assistent chirurgie in het Diaconessenhuis in Voorburg. Van 1999 tot 2000 werkte zij op de heelkunde intensive care van het Dijkzigt ziekenhuis in Rotterdam.

Sinds maart 2000 werkt zij op de afdeling huisartsgeneeskunde van het Erasmus MC als arts in opleiding tot huisarts en onderzoeker (AIOT(H)O); een combinatietraject van de opleiding tot huisarts en de opleiding tot onderzoeker. In juli 2003 behaalde zij haar Master of Science in de klinische epidemiologie aan het Nederlands Institute for Health Sciences (NIHES). Sinds 4 februari 2005 staat zij ingeschreven als huisarts in het huisartsregister.

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