OSTEOARTHROSIS IN THE GENERAL POPULATION

A follow-up study of osteoarthrosis of the hip

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ARTROSE IN DE BEVOLKING

Een vervolgonderzoek naar artrose van de heup

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR AAN DE ERASMUS UNIVERSITEIT ROTTERDAM OP GEZAG VAN DE RECTOR MAGNIFICUS PROF. DR. A.H.G. RINNOOY KAN EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN. DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP WOENSDAG 17 MEI 1989 DES NAMIDDAGS TE 13.45 UUR

door

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geboren te Hazerswoude

PROMOTOR	: Prof. Dr. H.A. Valkenburg
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Our knowledge of osteoarthrosis is incomplete, perhaps beause it is one of those dull commonplace disorders that are hard to study with enthusiasm, but new knowledge of osteoarthrosis must be gained if the later years of our lengthening lives are not to be plagued by increasing pain and disability.

J.H. Kellgren
Osteoarthrosis in Patients and Populations
British Medical Journal 1961;2:1-3

Voor mijn ouders, Marisol, Claudia and Viviana

Cover: The Beggars. Hieronymus Bosch (1450-1516)

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CHAPTER I

INTRODUCTION

1.1 Osteoarthrosis

Joints, like other organ systems, loose their functional reserve during the process of ageing, in spite of a degree of self-repair. If no functional reserve is left joint failure or osteoarthrosis[1]* appears [1]. It is remarkable that little is known about the cause(s) of osteoarthrosis (OA) while it is a health problem of considerable magnitude bringing about much pain and disability. Epidemiologic research on the etiology and pathogenesis of this chronic slowly progressive disorder is a complicated task and is often accompanied by failings as may be evident from quotations by two scientists who spent a good deal of their scientific carreer on the epidemiology of rheumatic diseases. Kellgren [2] wrote about "*a dull and commonplace disorder that is hard to study with enthusiasm*" and Acheson [3] in his famous 1981 Heberden Oration sighed "*it is to be hoped that some young investigators will engage in careful analytical hypothesis testing, using the epidemiological approach, and meet with more success than I*". More optimistic sounds came from the Workshop on Etiopathogenesis of Osteoarthritis [4]: "*the conference succeeded in meeting our primary objective for it, namely, to identify and develop new research initiatives*" and "*there is an impressive list of epidemiologic research projects to be pursued*". This list contains the following recommendations: Develop new taxonomic systems of OA designed specifically for epidemiologic studies; analyse existing data sets; perform longitudinal (cohort) clinical-epidemiologic studies; intensively study populations with little or no detectable evidence of OA; use diseases that are comorbid with OA to suggest etiologic hypothesis and consider the concept of etiology separately from factors that promote the disease. Future will decide whether the optimism of the workshop is justified, however, most of the proposals represent no more than general lines of thought and need further development.

1* Osteoarthrosis has been described under 54 different names, osteoarthritis is mostly used in the American medical literature while osteoarthrosis is more common in Europe. In this investigation we will use osteoarthritis as well as osteoarthrosis and abbreviate it as OA.

1.2 Structure of the Investigation

Describing the prevalence and the radiological and clinial abnormalities as they occur in the Zoetermeer population survey and fixing the position of the EPOZ data regarding OA amidst other population surveys on rheumatic diseases was the first aim of this study. This will be, together with the study of determinants that play an initiating, promoting or protecting role, the major subject of this thesis. This very large random population survey containing data about several chronic diseases was held between 1975 and 1978 in Zoetermeer. The first part of this investigation is the result of an analysis of the existing data and contains publications on radiological OA of hands, feet, spine, pelvis, knees and shoulders and the relationship with several anthropometric variables and life style habits. All radiographs were initially read by Prof.Dr. H.A. Valkenburg and were coded for osteoarthrosis, rheumatoid arthritis and chondrocalcinosis. Dr. H. Haanen who was the second reader of most of the radiographs presented a thorough description of the design and construction of the EPOZ study in his thesis on epidemiological aspects of low back pain [5].

Dr. L.K.J. van Romunde started an analysis of the pattern of OA by means of homogeneity analysis. The conclusions from this method were that a coherent pattern existed of degenerative joint disease. Disc degeneration of the cervical and lumbar spine from the age of 45 and OA of some small joints of hand and feet from the age of 55 can be considered 'normal aging' in this pattern. OA of the hips and to a lesser extent OA of the knees seemed to be exceptional within this pattern. Evidence of a divergent pattern of the hips was also mentioned by R.M. Acheson [3]. He considered the diviating relation between osteoarthrosis and body mass to be an argument for an the exceptional place of the hip in the pattern of OA. This special place that OA of the hip seems to occupy was reason for a special investigation, the result of which constitute the second part of this thesis.

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PART I. OSTEOARTHROSIS IN THE GENERAL POPULATION: THE ZOETERMEER SURVEY 1975-1978

CHAPTER 2

EPIDEMIOLOGY OF OSTEOARTHRITIS: ZOETERMEER SURVEY, COMPARISON OF RADIOLOGICAL OSTEOARTHRITIS IN A DUTCH POPULATION WITH THAT IN 10 OTHER POPULATIONS.

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2.1 Introduction

Osteoarthritis (OA) causes morbidity that will be of increasing importance in populations yielding greater proportions of elderly people. Epidemiology can establish important leads to find causes of chronic diseases like osteoarthritis [1]. One of the major tools used by epidemiologists to accomplish this is by comparing populations. With regard to osteoarthritis, epidemiological studies have shown that radiological OA (ROA) is an ubiquitous disorder. Although in some persons already present around age 25, osteoarthritis mainly affects older age groups [2,3]. Several investigations compared the prevalences of osteoarthritis of different races, different populations and geographic areas. Although a number of carefully conducted large population surveys is available, only a limited number of these were adequately compared [4-7]. In this manuscript we describe the prevalence of radiological OA of 18 joints and groups of joints in a random population sample of 6585 inhabitants of Zoetermeer in the Netherlands. The results are compared with results from 10 similar population surveys.

2.2 Populations and methods

Zoetermeer population

To study the prevalence and determinants of rheumatic and cardiovascular diseases, a population survey was conducted between 1975 and 1978 in two districts of Zoetermeer, a suburban metropolitan area near The Hague in The Netherlands [8]. Respondents were inhabitants of the original agricultural village and the recently built parts, which were principally inhabited by white collar workers. All inhabitants of the old village centre and one part of the new area were invited to participate in this survey. Of 4134 eligible men and 4523 eligible women of 19 years and older, 6585 (76.1%) participated in the study (3109 men and 3476 women). The completion rate was greatest in persons between 20

and 64 years of age (78.2%) compared to a response rate of 61% in those over 65. Information was gathered on previous medical history, rheumatic complaints, profession, daily activities, drug-use, schooling history and life style habits by means of a questionnaire. In a special equipped centre, joints were investigated, blood pressure, weight and height were measured and radiographs were taken of all 6585 participants. Blood was obtained for rheumatoid factor, total serum cholesterol and uric acid.

Radiographs

Radiographs were obtained of hands, forefeet and lateral cervical spine. Several additional radiographs were taken of all respondents of 45 years and older; lumbar spine in ante- and dorsiflexion, and pelvis and knees in antero-posterior and standing position. During the last year of the survey radiographs of both shoulders were taken of all respondents of 45 years and older. Examination of radiographs was performed by two investigators independently, based on the grading system for ROA according to the Standard Atlas of Radiographs of Arthritis [9]. This atlas contains radiographic examples of osteo-arthritis of several joints in several stages of the disease. A five point scale has been used for staging (0=absent, 1=dubious, 2=mild, 3=moderate, 4=severe). Small joints of hands and feet were graded as groups (figures 2-1 and 2-2) according to the most affected joint of the whole group. Right and left side were not separated, except for hips, knees, shoulders and sacro-iliac joints. When a one point difference in grading occurred between both investigators, the higher score was accepted, but where there was more disagreement on the grading or when one observer scored grade 1 and the other grade 2 the films were reassessed at a joint reading session until a final score had been agreed upon. Inter-observer and intra-observer agreement was discussed elsewhere [10].

Criteria for comparison populations

Population surveys suited for comparison were cross-sectional and contained random or stratified population samples. Not all surveys could be used: radiographs had to be available of nearly all respondents without regard to complaints; an acceptable sample size of mostly above 500 participants was necessary; sex and age specific information about ROA had to be available and ROA had to be presented for individual joints or groups of joints. Furthermore information about the origin of the population, the sample size, the sampling technique and the range of age and the joints of which radiographs were taken had to be available. The basic data of 10 populations with a total of 22,629 participants are presented in table 2-1. Two large surveys, the Alaskan Eskimo [11] and the Jamaica survey [12] were not included because no age and sex specific prevalence rates were presented for individual joints.

Japanese population data from Kamitonda [19] were included in spite of a 45% lack of radiological information because no other acceptable population survey data were available about Asian people. The Sofia data are the only ones from Eastern Europe but they were presented while the survey was not fully completed and it is uncertain whether this was reason for bias. The Standard Atlas of Radiographs was used in all surveys except the Tecumseh study [15]. Most radiographs were interpreted by investigators originally trained by JS Lawrence or JH Kellgren.

Results

Sex and age specific prevalence rates of ROA of 22 joints and joint groups of the Zoetermeer population are presented as graphs (figures 2-1 and 2-2). Age specific rates for both mild and severe osteoarthritis, which we obtained in this survey are given in full in appendix I, chapter 2. Kellgren's grade 0 and 1 were considered as absence and grade 2, 3 and 4 as presence of ROA. Shoulders were included in the graphs although radiographs were taken in

Table 2-1. Data from eleven population survey's regarding radiological osteoarthritis.

Population [Reference]	*Age*	*Radiographs*	*Sample size*	*Method*
Leigh [3,13] 1954 England	55-64	h,f,c,l,p(35+)	1343	stratified sample 200/decade
Wensleydale [3,13] 1958 England	15+	h,f,c,l(35+), p(35+)	891	village (urban and rural)
Blackfeet indians [14] 1961 USA	30+	h,f,c,p(45+)	1101	tribe
Pima indians [14] 1965 USA	30+	h,f,c,p(45+)	969	tribe
Tecumseh [15] 1962 USA	35+	h,c	4415	age and social class strata
Sofia [16] 1964 Bulgaria	15+	h,f,c,l,p	4318	age-stratified random sample
Tswana [6] 1970 South Africa	30+	h,f,p(55+), l(55+)	801	village
HANES I [17,18] 1971-1974 USA	25+	k,p	6913	representative sample
Iwata Kamitonda [19] 1972 Japan	30+	h,f,p	1335	village
Tsikundamalema [7] 1984 South Africa	18+	h,f	543	village

Abbreviations:h=hands, f=forefeet, c=cervical spine, l-lumbar spine, k=knee p=pelvis, s=shoulders, (45+)=from the age of 45.

only one third of the total population sample and only few persons were present in higher age categories, the standard errors of the prevalence of these joints will therefore be larger.

The process of ageing is strongly related to an increase of ROA. This holds for small joints as well as for large weight bearing joints and for both men and

Figure 2-1. Age-specific prevalence rates of osteoarthritis of hands and feet for inhabitants of Zoetermeer. DIP: distal interphalangeal joints, CMC-I: first carpometacarpal joint, MCP: metacarpophalangeal joints, PIP: proximal interphalangeal joints, CMC-lat: II-V carpometacarpal joints. MTP-I: first metatarsal phalangeal joint, MTP-lat: II-V metatarsal phalangeal joints, TMT: tarsometatarsal joints.

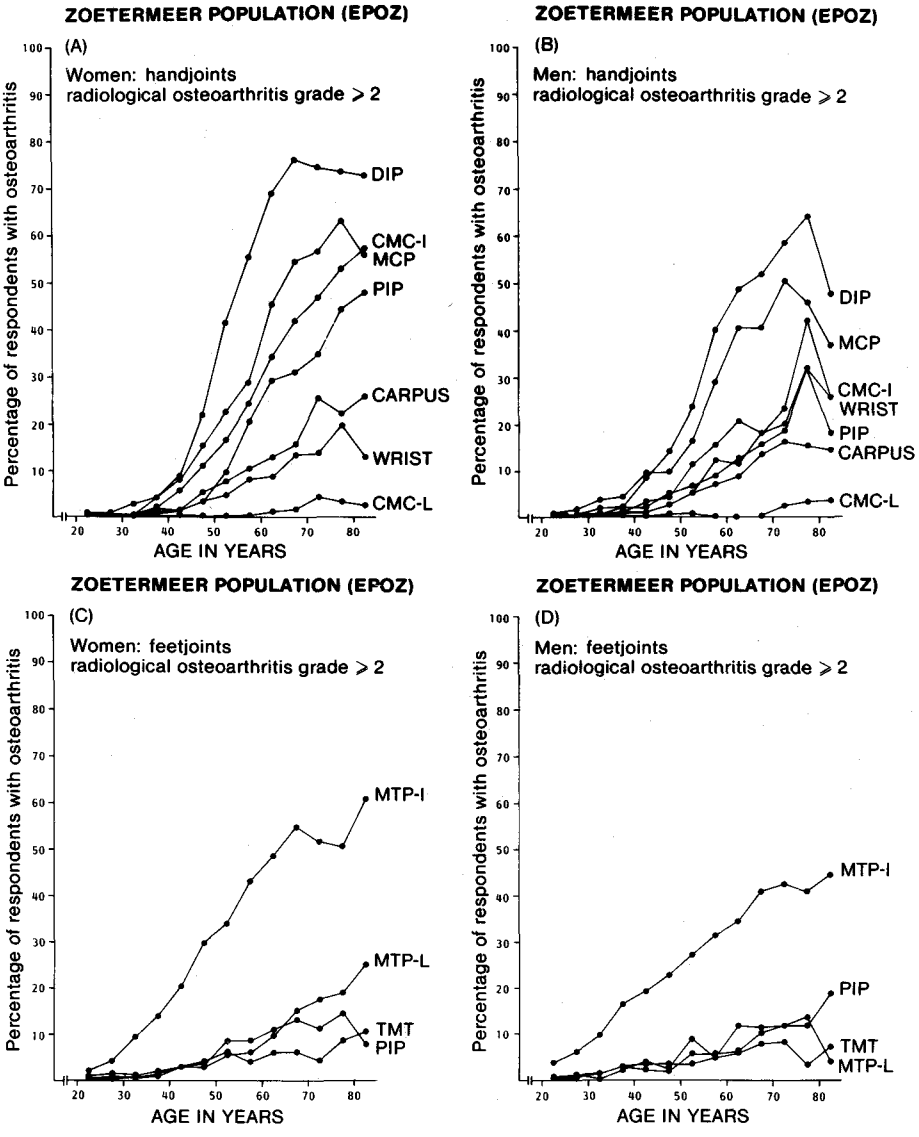


Figure 2-2. Age-specific prevalence rates of osteoarthritis of large joints and disc degeneration for inhabitants of Zoetermeer. L: left, R: right, Shoul: Shoulder, Cerv sp-dd: cervical spine disc degeneration, Cerv sp-oa: cervical spine osteoarthritis, Lumb sp-dd: lumbar spine disc degeneration.

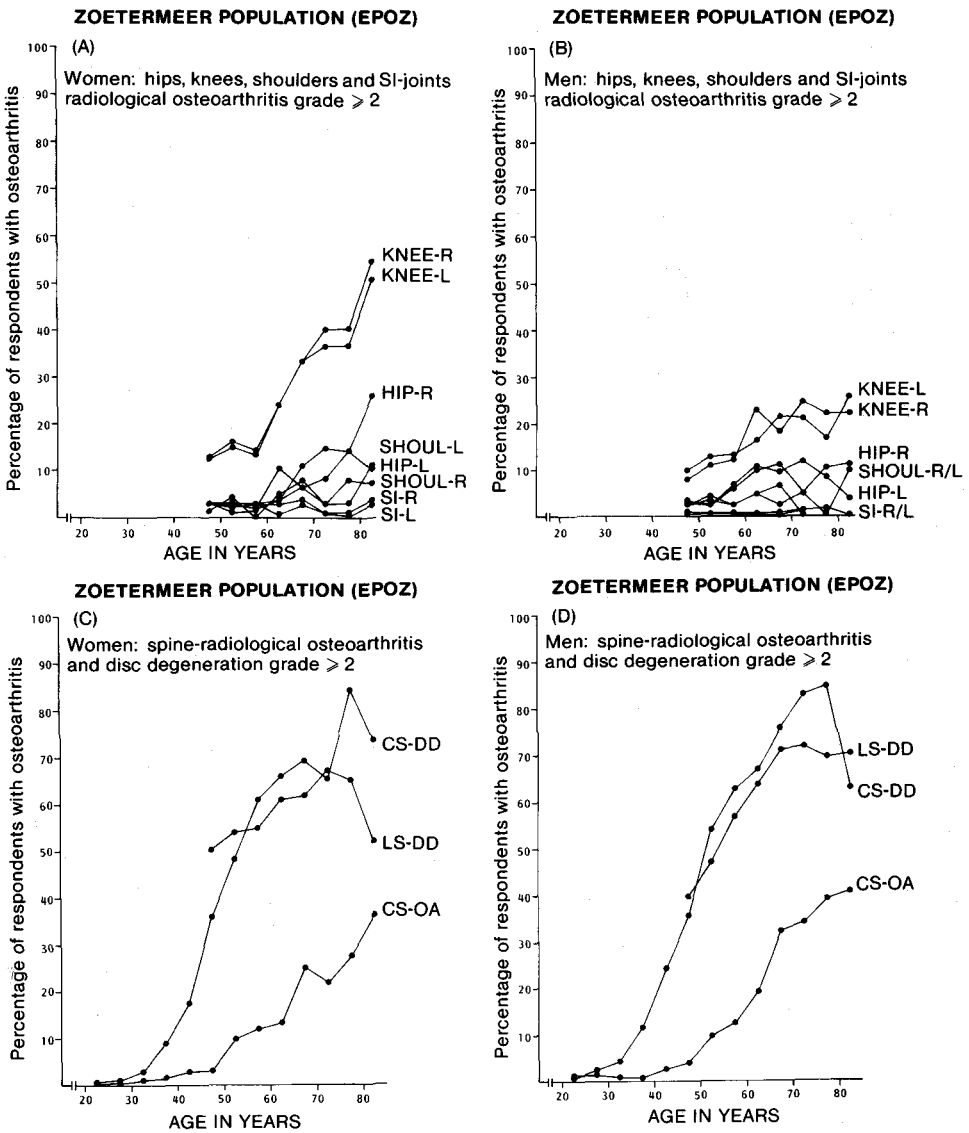


Figure 2-3. Age-specific prevalence rates of cervical spine disc degeneration and osteoarthritis of the knees in different populations. LW: Leigh and Wensleydale, ZM: Zoetermeer, TC: Tecumseh, KA: Kamitonda, HA: HANES, SO: Sofia.

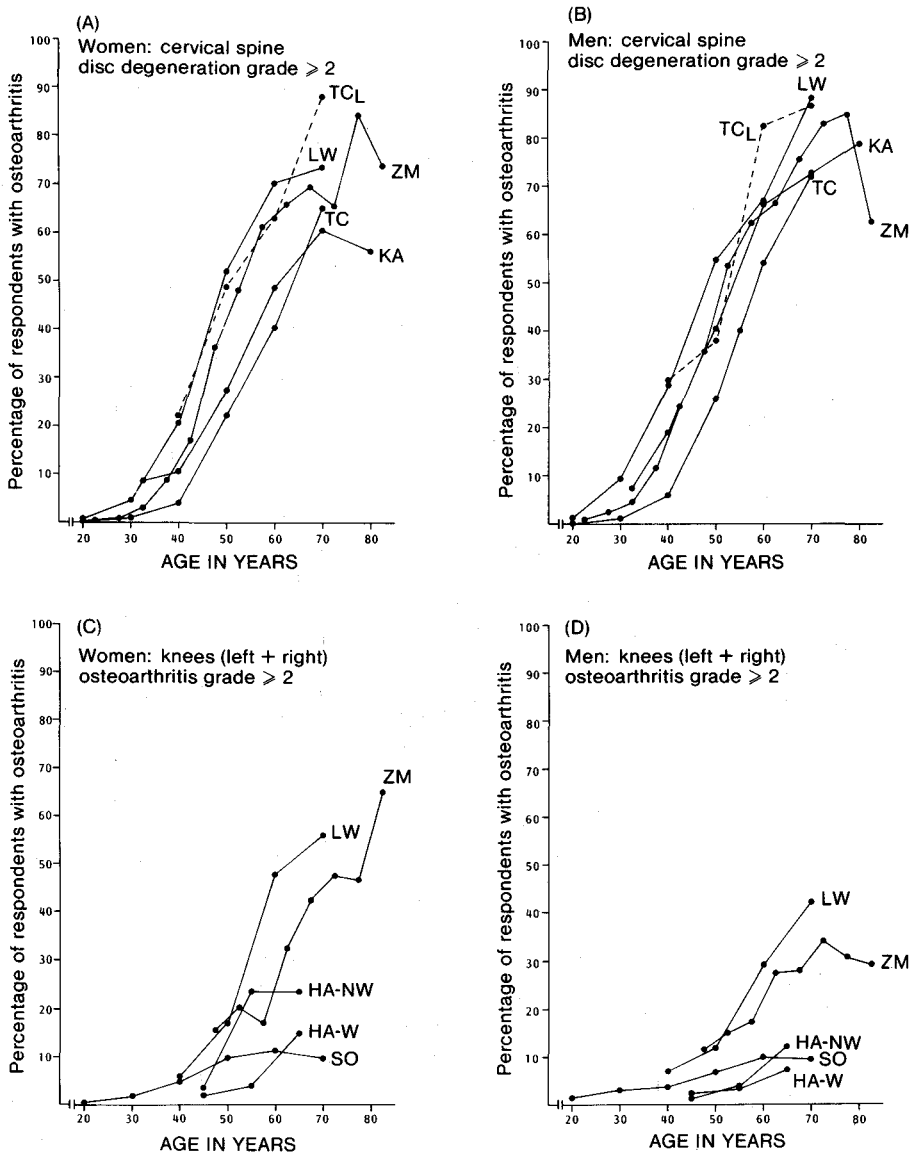
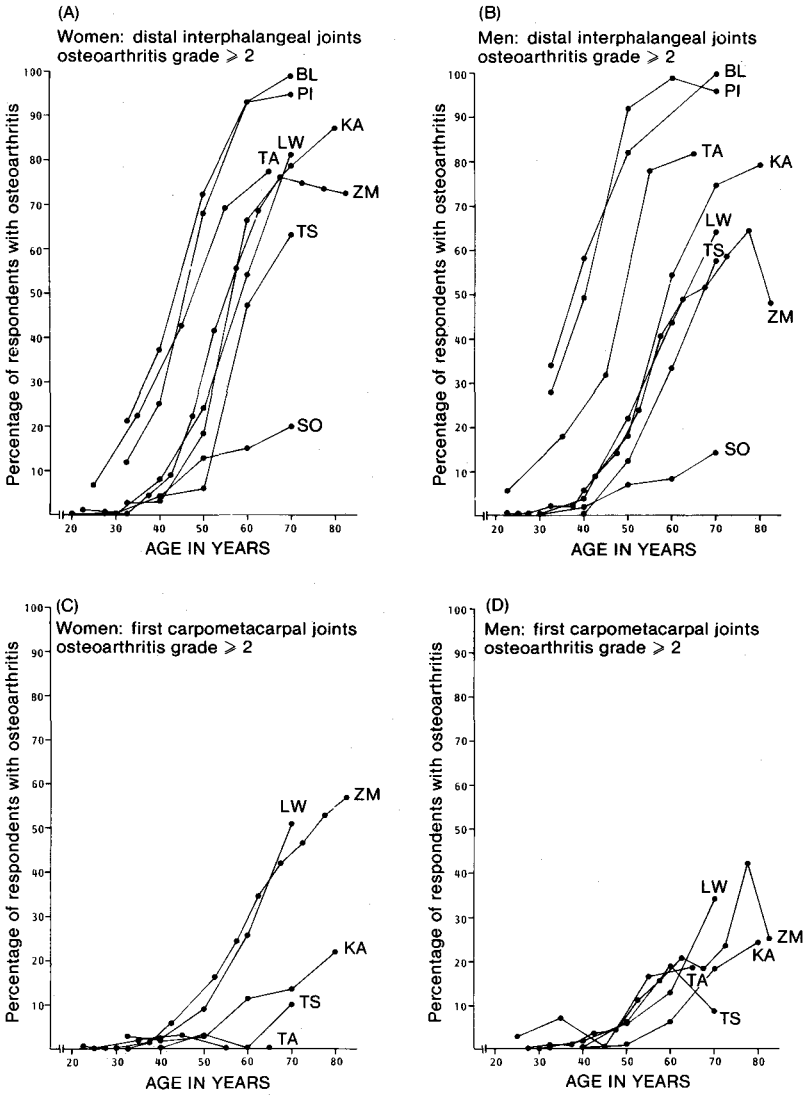


Figure 2-4. Age-specific prevalence rates of distal interphalangeal joints and carpometacarpal joints in different populations. BL: Blackfeet Indians, PI: Pima Indians, KA: Kamitonda, LW: Leigh and Wensleydale, ZM: Zoetermeer, TS: Tswana, TA: Tsikudamalema, SO: Sofia.



women. Small joints of the hands, tarsometatarsal and lateral metatarsophalangeal joints of the feet and both knees were more often involved in women of all ages. The hips were more often involved in middle-aged men and the lumbar and cervical spine were more often involved in all men. There was no significant sex difference except for knees, hips in those age 65 and over and distal interphalangeal joints of the hands.

Considerable differences were found for the age of onset and the rate of increase of ROA with age of different joints. Distal interphalangeal and metacarpophalangeal joints were already affected in 10% and first metatarsophalangeal joints even in 20% of the normal population at the age of 40. Disc degeneration of lumbar and cervical spine was more often present than absent in both men and women above the age of 50.

To compare differences and similarities of prevalences of ROA between the populations studied so far, graphs were used in which the percentages of involved joints are plotted against age. Not all joints about which data were available are presented here, very different joints are given as examples (figures 2-3 and 2-4). Standard errors are not indicated on the graphs because they were not always available and because of the density of the lines. During the assessment of the graphs however, it had to be taken into account that sample sizes (table 2-1) were sometimes small. The highest age category was almost always a loose end with little participants and will certainly not always be an adequate sample of the population.

The graphs demonstrate firstly that there are differences in level between populations and secondly that the slope of most lines is very much the same for individual joints and groups of joints in the various populations. Notable exceptions are Blackfeet and Pima indians who have very high prevalence rates of ROA of the distal interphalangeal (DIP) joints, Bulgarians who show a very low prevalence of ROA of the DIP joints and Tswana and Tsikundamalema women who have a very low carpometacarpal (CMC) joint involvement. We are not certain whether the CMC joints were separated in lateral CMC and first CMC (base of thumb) joints, data from Zoetermeer and Kamitonda concern

CMC-I. Furthermore, it is remarkable that participants from the village of Tsikundamalema have a relative high prevalence of ROA of the DIP joints and a low prevalence of the CMC joints. Other joints showed similar patterns: the same slope for the same joint, with differences in level and occasional exceptions. None of the populations had a low or high prevalence rate for all joints investigated.

Discussion

The Zoetermeer population survey confirms the high prevalence of radiological ROA. The disorder increases progressively with age, mild radiological OA is more frequent in women and severe radiological OA is much more frequent in women. From post-mortem studies it is known that the pathologic process takes place several years before radiological detection of the disorder is possible [21], so the prevalence of radiological OA by age as presented here is an underestimation of the actual frequency of cartilage degeneration.

The prevalence of ROA decreased slightly in very old people for a number of joints. This might be attributed to response bias, it was however reported recently that women with x-ray changes of the knee were at increased risk for subsequent mortality [22]. Obesity [18,20,23], hypertension [24] and diabetes mellitus [25], all associated with both osteoarthritis and a lower average life expectancy, might be responsible for this observation. An excess of ROA of the right hip was found after the age of 75, when looking at the prevalence this might be due to a single high or low figure.

All data were obtained from cross-sectional population surveys and were therefore less suited for evaluation of the process of joint involvement by age. Conclusions about joint involvement and age can therefore only be drawn from these data if birth cohort effects are negligible. This might be a source of bias e.g. for populations where selective mortality occurred during periods of starvation or war. However, since no follow-up surveys are available, we ignored possible birth cohort effects, and compared the results of the Zoetermeer

survey with 10 other population surveys. Figures 2-3 and 2-4 demonstrate identical slopes (parallelism) together with differences in level for the majority of the joints. This means that when the process of osteoarthritis first occurs in a certain joint or group of joints, the rate of increase of degeneration of that joint or group of joints per unit of time is the same in all populations from that point on. A higher level means that the radiologic appearance of osteoarthritis occurs at younger ages. Differences in level showed a tendency to increase while differences of slope remain minimal when several joints were added up as demonstrated for all the joints of the hand [4]. Differences between populations can be explained in several ways. Firstly, different investigators may be more or less inclined to give a higher or lower score and interobserver variation is likely to occur with procedures like the interpretation of radiographs. Furthermore, the freedom of interpretation of the standardizing atlas is rather large. Interobserver variation as the sole cause for differences in level is less probable. Lawrence and Sebo [5] read radiographs from 17 surveys with a total of 7919 participants, they found important differences between populations, although it was not stated whether these were differences in level or differences of slope. Secondly, it is very well possible that differences between populations are not artificial. Evidence from genetic as well as environmental studies is present that differences are, at least in part, true differences. An increased or decreased presence of risk factors or protective factors, might be responsible for these differences in level. Osteoporosis for instance seems to protect against osteoarthritis [26]. Factors that influence (subchondral) bone density, like vitamin D and alcohol consumption and anthropometric status, differ between races and populations [27-29]. Furthermore differences in level might in part be explained by a different distribution of these risk factors. Obesity is a strong risk factor for osteoarthritis for a number of joints [18,23]. Between populations with a high and a low percentage of obese persons, a level difference is likely. If this obesity-osteoarthritis relation is not linear, a difference of slope would exist.

Another explanation for differences in level is the distinction, as proposed by

the American Rheumatism Association [30], between idiopathic and secondary types of osteoarthritis. This distinction was not reported separately in any of the populations. Therefore it is even more surprising that, without the information of the distribution of idiopathic and secondary osteoarthritis, the graphs show such strong parallelism. This might imply that secondary osteoarthritis has more or less the same frequency in different populations or that the frequency of secondary osteoarthritis is low and does not influence the slope. Lack of information about risk factors and about the frequency of secondary osteoarthritis limits causal inferences based on these comparison data. Surveys in areas were the frequency of osteoarthritis is determined by the occurrence of special joint diseases like Mseleni Joint Disease [31] and Kashin-Beck disease [32,33] were not included in this study.

Osteoarthritis is a slowly developing process which makes it very difficult to approach the problem by means of intervention studies. We had hoped that comparison data of very different populations would give solutions for the many problems that surround the causes and development of this disease or group of diseases. The only data that could be compared from a reasonable number of surveys were the radiologic data. Data on body mass index, pain, limitation of movement, bone mass etc. are not available from most of the populations. Further epidemiological efforts regarding osteoarthritis, specially when prevention is one of the ultimate goals, should be directed on differentiating osteoarthritis, secondary types like crystal arthropathy, osteoarthritis developing in the course of endocrine disorders and psoriasis should be separated from the so called idiopathic osteoarthritis. For a number of population surveys it is probably sufficient to re-evaluate the existing data and re-read the radiographs.

We conclude that osteoarthritis is a worldwide disease and that no population investigated so far has been spared. Differences exist between populations, between races and between men and women within and between populations. These differences are differences in level and whether these are real or due to interobserver variation or due to differences in the distribution of risk factors or genetic differences has yet to be established. Joints with a low prevalence of

osteoarthritis in one population are relatively spared in all populations while frequently affected joints show signs of degeneration in all populations. It is therefore most likely that the etiology of the majority of osteoarthritis is the same in all populations.

Cartilage changes are the result of longstanding metabolic and mechanical processes. The relative importance of each of these processes can, unfortunately, not be compared because they are only scarcely available and if available they lack methodological standardization. Similarities of slopes argue in favour of the possibility of extrapolating results from one population survey to others as well. Conclusions drawn about this Dutch population can be applied to other populations.

Summary of the chapter

The prevalence of mild and severe radiological osteoarthritis was investigated in a random sample of 6585 inhabitants of a Dutch village. Radiographs were graded 0-4 according to the criteria described by Kellgren and Lawrence. The prevalence of radiological osteoarthritis increased strongly with age and were highest for cervical spine (peak: men 84.8%, women 84.3%), lumbar spine (peak: men 71.9%, women 67.3%) and distal interphalangeal joints of the hands (peak: men 64.4%, women 76%). Prevalence did not exceed 10% in sacroiliac joints, lateral carpometacarpal joints and tarsometatarsal joints. Severe radiological osteoarthritis (grade 3 or grade 4) was uncommon under age 45; in elderly persons the prevalence of severe radiological OA did not exceeded 20% except for the cervical spine and lumbar spine, distal interphalangeal joints of the hands and, in women only, metacarpophalangeal joints, first carpometacarpal joints, first metatarsophalangeal joints and knees. Overall, differences between men and women were small except for hips and knees; however, severe radiological osteoarthritis was found in a higher proportion in most of the joints in women. Our data were compared with data from similar population surveys. The slope between joint involvement and age was strikingly

constant for most of the joints. Differences between populations were mainly differences in level. These differences of prevalence of radiological osteoarthritis may be attributed to interobserver differences - that is, different criteria used to establish radiological osteoarthritis, in addition to genetic or environmental factors, or both.

Acknowledgements

The authors wish to thank Dr HCM Haanen who was the second reader of most of the radiographs and Dr K Shichikawa who supplied the data from the Kamitonda study.

Appendix

Age-specific prevalence of radiological osteoarthritis
for men and women separately in the zoetermeer survey.

List of abbreviations used in table 2-1 and table 2-2.

CS-DD :Cervical Spine Disc Degeneration
CS-FJ :Cervical Spine Facet joints
LS-DD :Lumbar Spine Disc Degeneration
DIP :Distal Inter-Phalangeal joints
PIP :Proximal Inter-Phalangeal joints
MCP :Meta-Carpo-Phalangeal joints
CMC-I :First Carpo-Meta-Carpal joints
CMC-L :Lateral Carpo-Meta-Carpal joints
TMT :Tarso-Meta-Tarsal joints
MTP-I :First Meta-Tarso-Phalangeal joints
MTP-L :Lateral Meta-Tarso-Phalangeal joints
SI :Sacro-Iliac joints

*Table 2-1. Prevalence (%) of mild and severe osteoarthritis in **men**, Zoetermeer (EPOZ study), The Netherlands*

	Grade	Age group (years)											
		20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80+
		n=292	n=338	n=324	n=383	n=395	n=353	n=309	n=216	n=174	n=115	n=82	n=59	n=27
CS-DD	2+	0.7	2.4	4.3	11.5	24.3	35.4	53.7	62.5	66.6	75.6	82.9	84.8	63.0
	3+	-	0.3	0.6	2.4	5.2	15.6	29.1	34.7	39.0	59.1	64.4	56.0	55.6
CS-FJ	2+	1.1	1.5	0.6	0.8	2.9	3.9	9.7	12.5	19.0	32.2	34.1	39.0	40.7
	3+	-	-	-	-	-	0.3	1.9	2.8	5.2	8.7	7.3	3.4	11.1
LS-DD	2+						39.4	47.0	56.8	63.8	71.1	71.9	69.5	70.4
	3+						13.8	18.1	23.8	31.6	38.6	34.1	33.9	44.4
DIP hands	2+	0.3	0.3	2.2	2.3	8.6	14.1	24.0	40.5	48.9	51.7	58.8	64.4	48.1
	3+	-	-	-	-	1.0	1.1	3.5	4.5	10.7	9.5	9.4	27.1	14.8
PIP hands	2+	0 3	0.3	0.3	1.0	1.0	3.0	5.4	12.3	11.8	18.1	20.0	32.2	18.5
	3+	-	-	-	-	-	-	0.6	0.5	0.6	2.6	3.5	5.1	-
MCP hands	2+	0.7	1.8	3.7	4.4	9.7	9.7	16.7	29.1	40.5	40.5	50.6	45.8	37.0
	3+	-	-	0.3	-	0.3	0.6	1.0	2.3	2.3	9.5	16.5	13.6	18.5
CMC-I hands	2+	-	-	0.9	1.0	3.5	4.4	11.5	15.5	20.8	18.1	23.5	42.4	25.9
	3+	-	-	-	-	-	-	1.0	3.6	3.9	6.9	1.2	11.9	11.1
CMC-L hands	2+	-	0.3	-	-	-	0.3	0.3	-	-	-	2.4	3.4	3.7
	3+	-	-	-	-	-	-	-	-	-	-	1.2	-	-
CARPUS hands	2+	0.3	0.3	-	1.6	1.0	3.3	5.8	7.3	9.0	13.8	16.5	15.3	14.8
	3+	-	0.3	-	-	-	-	0.6	1.4	2.2	3.4	4.7	5.1	3.7
WRIST hands	2+	-	0.6	0.3	2.3	2.0	5.0	6.7	9.1	12.4	20.7	18.8	32.2	25.9
	3+	-	-	-	0.5	-	0.6	1.0	0.5	6.2	8.6	5.9	8.5	11.1
TMT feet	2+	-	0.9	1.2	2.8	3.3	3.3	3.8	5.0	5.6	7.8	8.2	3.4	7.4
	3+	-	-	-	0.5	0.3	0.3	0.3	-	-	0.9	-	1.7	-
MTP-I feet	2+	3.8	5.9	9.8	16.5	19.2	22.9	27.2	31.4	34.3	40.6	42.4	40.7	44.4
	3+	-	0.3	1.2	1.6	3.3	2.5	4.5	9.5	10.1	10.4	16.5	11.9	18.5
MTP-L feet	2+	-	0.3	1.2	2.9	2.3	1.9	5.8	5.5	6.2	10.4	11.8	13.6	3.7
	3+	-	-	-	-	-	-	-	-	-	0.9	-	-	-
PIP feet	2+	0.3	1.2	-	2.3	3.8	2.5	9.0	5.0	11.8	11.2	11.8	11.9	18.5
	3+	-	-	-	-	-	0.3	0.3	-	-	0.9	-	-	-
Hip right	2+						2.8	2.2	5.9	10.1	11.2	4.7	10.2	11.1
	3+						0.6	-	1.4	1.7	0.9	2.4	3.4	-
Hip left	2+						3.3	2.2	6.4	10.7	9.5	11.8	8.5	3.7
	3+						0.3	-	2.3	1.7	1.7	2.4	-	3.7
Knee right	2+						7.7	11.2	11.8	23.0	18.1	24.7	22.0	22.2
	3+						0.3	2.2	1.4	5.6	6.9	7.1	8.5	7.4
Knee left	2+						9.7	12.8	12.7	16.3	21.6	21.2	16.9	25.9
	3+						1.1	2.6	1.8	3.4	3.4	4.7	5.1	3.7
SI right	2+						0.6	0.3	0.9	-	-	1.2	1.7	-
	3+						-	-	-	-	-	-	-	-
SI left	2+						0.3	0.6	0.5	0.6	0.9	1.2	1.7	-
	3+						-	-	-	-	-	-	-	-
Shoulder right	2+						2.5	4.4	2.4	4.7	6.8	-	-	10.0
	3+						0.8	-	-	-	-	-	-	-
Shoulder left	2+						2.5	3.5	2.4	4.7	2.3	4.8	-	10.0
	3+						-	-	-	1.6	-	4.8	-	-

*Table 2-2. Prevalence (%) of mild and severe osteoarthritis in **women**, Zoetermeer (EPOZ study), The Netherlands*

	Grade	Age group (years)											
		20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80+
		n=297	n=389	n=375	n=405	n=428	n=375	n=290	n=226	n=182	n=180	n=119	n=108	n=77
CS-DD	2+	0.3	0.8	2.9	8.9	17.1	36.0	48.3	60.6	66.0	69.4	65.4	84.3	74.0
	3+	-	-	0.5	2.5	5.1	12.3	21.7	29.2	40.7	47.7	42.0	56.5	36.4
CS-FJ	2+	-	0.5	0.8	1.5	2.6	2.8	9.4	11.8	13.2	25.0	21.9	27.8	36.4
	3+	-	-	-	-	-	-	0.7	0.4	2.2	4.4	3.4	2.8	6.5
LS-DD	2+						50.4	54.1	54.7	61.1	61.9	67.3	65.1	51.9
	3+						19.6	18.1	25.8	22.5	29.5	35.4	36.7	24.7
DIP hands	2+	1.0	0.5	0.3	4.2	8.9	22.0	41.6	55.5	68.9	76.0	74.7	73.5	72.7
	3+	-	-	-	0.2	0.2	0.8	4.7	8.3	15.1	19.7	26.3	23.1	36.4
PIP hands	2+	-	-	0.3	1.0	1.4	3.6	9.7	20.5	29.6	31.1	35.2	44.4	48.1
	3+	-	-	-	-	-	-	-	0.9	1.6	3.3	4.1	6.8	2.6
MCP hands	2+	0.7	1.0	2.9	4.2	8.2	15.5	22.5	29.2	45.6	54.6	56.6	63.2	55.8
	3+	-	-	-	-	-	0.8	1.7	3.9	6.4	15.8	15.6	18.8	24.7
CMC-I hands	2+	0.3	-	-	1.5	5.8	10.9	16.4	24.5	34.5	42.1	46.7	53.0	57.1
	3+	-	-	-	-	0.2	1.3	4.0	6.1	6.5	13.1	15.6	19.7	36.4
CMC-L hands	2+	0.7	0.5	-	-	0.2	0.3	0.3	0.4	1.1	1.6	4.9	3.4	2.6
	3+	-	-	-	-	-	-	-	-	-	0.5	0.8	0.9	1.3
CARPUS hands	2+	0.3	0.3	0.5	0.5	1.6	5.4	8.1	10.5	12.9	15.8	25.4	22.2	26.0
	3+	-	-	-	0.2	0.2	1.6	0.3	1.7	3.8	4.4	6.6	8.5	14.3
WRIST hands	2+	-	-	0.3	2.2	1.4	3.6	4.7	8.3	8.6	13.7	13.9	19.7	13.0
	3+	-	-	-	-	0.2	0.3	0.7	1.7	-	2.7	4.1	6.8	3.9
TMT feet	2+	0.7	1.3	0.8	1.7	2.6	3.9	6.3	3.9	5.9	6.0	4.1	8.5	10.4
	3+	-	-	-	-	-	0.5	0.3	0.4	1.1	1.6	-	0.9	5.2
MTP-I feet	2+	2.0	4.1	9.3	13.8	20.1	29.8	33.9	43.2	48.4	55.2	51.6	50.4	61.0
	3+	-	0.5	-	1.0	0.9	7.0	7.0	10.9	12.9	12.6	24.6	18.8	23.4
MTP-L feet	2+	-	0.5	0.5	0.7	2.8	2.8	5.4	5.7	9.7	14.8	17.2	18.8	24.7
	3+	-	-	-	-	0.2	-	0.3	0.4	-	1.6	2.5	4.3	1.3
PIP feet	2+	-	-	1.1	1.2	2.6	3.4	8.4	8.3	10.8	13.1	10.7	14.5	7.8
	3+	-	-	-	-	0.2	-	0.3	-	-	0.5	-	-	1.3
Hip right	2+						2.6	2.0	2.6	3.8	10.9	14.8	14.5	26.0
	3+						0.5	-	1.3	1.6	4.4	4.9	4.3	10.4
Hip left	2+						2.8	2.7	1.7	3.8	6.6	8.2	14.5	10.4
	3+						0.3	-	0.4	1.1	1.6	4.2	4.3	2.6
Knee right	2+						12.7	16.1	14.0	24.2	33.3	40.2	40.2	54.6
	3+						1.6	2.7	0.4	4.8	9.8	16.4	14.5	29.9
Knee left	2+						12.4	15.1	13.1	24.7	33.3	36.6	36.9	50.6
	3+						1.8	2.0	1.3	6.5	10.4	13.9	19.7	24.7
SI right	2+						2.6	3.0	2.6	0.5	2.7	0.8	0.9	3.9
	3+						-	-	-	-	-	-	-	-
SI left	2+						2.8	3.4	2.6	2.7	3.8	0.8	-	2.6
	3+						-	-	-	-	-	-	-	-
Shoulder right	2+						2.9	0.9	1.3	10.9	6.2	2.6	8.1	7.4
	3+						-	-	-	3.1	1.5	2.6	2.7	3.7
Shoulder left	2+						1.4	4.3	-	4.7	7.7	2.6	2.7	11.1
	3+						-	-	-	-	-	-	-	7.4

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CHAPTER 3

OSTEOARTHRITIS AND OBESITY IN THE GENERAL POPULATION

A relationship calling for an explanation

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Introduction

In 1945, Fletcher [1] suggested obesity is important in the etiology of osteoarthritis (OA). Since then the relationship between OA and obesity has been a matter of considerable debate in the rheumatologic and orthopedic literature. Kellgren [2] in 1961 called "*the mechanical effect of excess body weight upon joints of the lower limbs self-evident.*" This mechanical effect could explain the excess OA of the knees in obese persons; the absence of excess hip OA, however, remained unexplained. Furthermore, the excess of OA of nonweight bearing joints - the distal inter-phalangeal (DIP) joints of the hands - described some years earlier, did not support this mechanical theory [3].

Views about the relationship between OA and obesity were challenged in experimental as well as in clinical studies. Silberberg, et al. [4] demonstrated the importance of genetic and dietary influences on the development of OA of the knee joint in mice. Goldin et al. [5] did not find a higher prevalence of OA in a group of 25 males with severe obesity and Saville and Dickson [6] demonstrated that body weight and height did not differ between a group of 121 men and women with OA of the hips and the general population. Recently Hartz, et al. [7] gave new attention to the problem by presenting data from the HANES population survey. Relative weight was strongly associated with OA of the knees but only a minor influence was found on OA of the hips in this survey of 4225 persons.

The debate has considerable practical and theoretical importance. If OA is a result of "wear-and-tear" aggravated by obesity, it should be found mainly in weight bearing joints. If, on the other hand, OA is mainly the consequence of genetic influences or of an underlying metabolic abnormality associated with obesity, the association should be an overall one, and it is not immediately obvious that a modicum of prevention might be possible. To try to differentiate between these 2 possibilities, we analyzed radiological and anthropometric data collected on 1071 males and 1097 females, all aged 45 - 64 during a population survey of a single Dutch town.

Materials and methods

Between 1975 - 1978 a population survey was undertaken in the Dutch town of Zoetermeer, a suburb of The Hague, to determine the prevalence of several chronic diseases and their determinants. Of a total of 13,462 invited inhabitants aged 5 years and over, 10,532 participated. The overall response rate was 78%; in persons aged 45 - 64, it varied between 84% for the younger and 74% for older persons. Further details of the survey are described elsewhere [8,9].

Respondents were investigated in a specially equipped survey centre. Radiographs were taken of hands, forefeet and the lateral cervical spine in anteflexion, of all respondents from age of 19 onwards; in those older than 45 films were also obtained from knees, pelvis and the lateral lumbar spine in ante and retroflexion. All radiographs were examined by two observers, independent of each other and unaware of physical findings. The first observer was H.A. Valkenburg, professor of epidemiology and originally trained by J.S Lawrence MD, FRCP, the second reader was H.C.M Haanen, rheumatologist.

Radiological abnormalities were graded from 0 - 4, grade 2 being a definitely abnormal finding and grade 3 and 4 being severe and very severe OA or disc degeneration with loss of joint space and joint destruction. The atlas of Kellgren [10] was used as a reference.

A total of 20 joints or groups of joints were evaluated (tables 3-1 and 3-3). Separate codings for the right and left side were only made for hips, knees and sacro-iliac joints; the other joints were considered as groups. The worst grading in one of the joints belonging to a group gave the grading of the group. When a one point difference in grading occurred between both investigators, the higher score was accepted. Where there was more disagreement or if the score of one of the readers differed between grade 1 (doubtful) and grade 2 (abnormal), the radiograph was reinspected by both investigators in a common session. The problem of inter-observer agreement with regard to reading radiographs of joints is discussed elsewhere [8,11,12].

We limited the present analysis to persons aged 45 - 64. This group represents

a more or less homogeneous age group with an uniformly high response rate. Complete sets of radiographs were available from most of these respondents. The proportion of OA, although high, was not too high to make a comparison between respondents with normal and abnormal joints. Furthermore, by restricting the analysis to this relative young age group, exposure from other risk factors might be of limited importance compared to elderly people.

The line between a normal joint and an abnormal joint may be drawn between grade 1 and grade 2 or between grade 2 and grade 3 dependent on whether osteophytes, sclerosis or cysts occurring as sole radiologic abnormalities are regarded to be OA. In the first analysis the OA scores were recoded into presence of OA (values 2 - 4) and absence of OA (values 0 and 1). In the second analysis grade 3 and 4 were recoded into presence and the lesser grades into absence of OA. As a measure of obesity, we used the Quetelet's index, which is weight in kgs divided by squared height in meters; this index is regarded as the best weight-for-height index for epidemiologic purposes [13]. The distribution of this index was subdivided according to its quintiles (1st - 5th 20% of the distribution). Among males the interquintile ranges were 16.8 - 22.8, 22.9 - 24.2, 24.3 - 25.6, 25.7 - 27 and 27.1 - 38.4. Among females the ranges were 15.6 - 22.9, 23.0 - 24.4, 24.5 - 25.9, 26 - 27.9 and 28 - 40. The Quetelet's index ranges were largest in the highest and lowest quintile.

For each quintile the frequency of presence of OA was counted for each of the joints. To compare the frequency of OA by quintile of Quetelet's index, we needed to take age differences into account. Due to our age limitation the distribution of weight for height was quite uniform, although there was a slight tendency for the more obese persons (those in the upper quintile) to be also the older ones, and vice versa. Since OA is strongly associated with age, the association of age with Quetelet's index could explain some of the excess of OA in the upper quintiles of the Quetelet's index distribution. To undo this age effect, we standardized for age by the direct method. The age standard used was the overall age distribution of males and females separately, in five-year age categories. The difference between the standardized figures and the original crude ones was not large, however. For

Table 3-1. Prevalence of OA and disc degeneration, grade 2 or more by quintiles of Quetelet's index, among 1071 men, aged 45-64 standardized for age. Between brackets: Mantel-Haenzsel odds ratio of quintiles computed with lowest quintile as reference, standardized for age. Joints listed according to frequency of OA.

	Frequency OA grade ≥ 2	*Quintile of Quetelet's Index*					*p of Trend*
		I	*II*	*III*	*IV*	*V*	
CSP-DD	51.9	49.5	42.9	55.5	54.3	58.2	
		(1.0)	(0.8)	(1.3)	(1.2)	(1.6)*	≤ 0.001↑
LSP-DD	49.6	45.1	42.8	55.3	59.9	57.9	
		(1.0)	(0.9)	(1.5)*	(1.2)	(1.7)*	≤ 0.01↑
DIP-H	28.9	24.4	26.0	32.6	24.2	36.0	
		(1.0)	(1.1)	(1.5)	(0.9)	(2.1)*	≤ 0.001↑
MTP-I-F	28.5	22.5	27.7	28.7	33.0	31.2	
		(1.0)	(1.5)	(1.5)	(1.8)*	(1.7)*	≤ 0.001↑
MCP-H	20.1	14.6	17.4	25.9	19.7	23.2	
		(1.0)	(1.2)	(1.8)*	(1.3)	(1.8)*	≤ 0.001↑
Right Knee	12.5	7.3	11.2	16.0	8.8	18.8	
		(1.0)	(1.7)	(2.5)*	(1.3)	(3.7)*	≤ 0.009↑
Left Knee	12.7	10.1	8.9	14.4	12.1	18.0	
		(1.0)	(0.9)	(1.6)	(1.3)	(1.8)	≤ 0.022↑
CMC-I	11.8	9.4	10.4	14.4	12.5	12.4	
		(1.0)	(1.1)	(1.9)*	(1.3)	(1.3)	≤ 0.15
CSP-FJ	10.0	9.5	8.9	9.8	10.9	11.1	
		(1.0)	(0.8)	(1.0)	(1.1)	(1.4)	≤ 0.001↑
WRIST	7.9	6.1	5.0	8.8	10.5	9.4	
		(1.0)	(0.8)	(1.7)	(1.6)	(1.8)	≤ 0.29
PIP-H	7.2	2.7	7.5	10.8	4.6	10.5	
		(1.0)	(2.7)	(4.7)*	(1.5)	(5.4)*	≤ 0.001↑
PIP-F	6.7	6.7	7.4	4.6	7.3	8.0	
		(1.0)	(1.4)	(0.9)	(1.0)	(1.1)	≤ 0.001↑
CARP-H	6.0	5.7	6.2	5.1	4.4	8.1	
		(1.0)	(1.1)	(0.7)	(0.8)	(1.5)	≤ 0.06
Left Hip	5.1	3.8	2.7	7.8	3.2	7.7	
		(1.0)	(0.8)	(1.9)	(0.8)	(2.2)	≤ 0.35
Right Hip	4.7	2.6	4.0	5.5	2.6	8.2	
		(1.0)	(1.4)	(2.4)	(1.1)	(3.2)	≤ 0.002↑
TMT-F	4.3	4.4	4.4	4.4	3.3	5.8	
		(1.0)	(1.0)	(1.1)	(0.7)	(1.4)	≤ 0.33
MTPL-F	4.3	5.2	3.7	4.6	3.8	4.1	
		(1.0)	(0.9)	(0.9)	(0.8)	(1.2)	≤ 0.33
R-SI	0.5	0.5	0.0	1.4	0.6	0.0	
L-SI	0.5	0.0	0.0	1.0	1.7	0.0	
CMC-L	0.2	0.5	0.0	0.5	0.0	0.0	

* = *Odds Ratio significantly positive at 95% confidence interval*
↑ = *significant increase of frequency with increase of BMI*
↓ = *significant decrease of frequency with increase of BMI*

Table 3-2. Prevalence of OA and disc degeneration, grade 3 and 4 by quintiles of Quetelet's index, among 1071 men, aged 45-64 standardized for age. Between brackets: Mantel-Haenzsel odds ratio of quintiles computed with lowest quintile as reference, standardized for age. Joint listed according to frequency of OA.

Frequency OA grade ≥ 3		*Quintile of Quetelet's Index*					*p of Trend*
		I	*II*	*III*	*IV*	*V*	
CSP-DD	26.6	24.3 (1.0)	15.4 (0.8)*	20.6 (1.3)	22.4 (1.4)	26.7 (1.5)	≤ 0.001↑
LSP-DD	20.3	24.9 (1.0)	18.5 (0.9)	24.8 (1.1)	22.9 (0.9)	19.4 (1.1)	≤ 0.06
MTP-I-F	5.9	4.9 (1.0)	7.8 (1.7)	7.1 (1.7)	3.0 (0.8)	6.1 (1.3)	≤ 0.05↑
DIP-H	3.8	3.4 (1.0)	3.4 (1.3)	4.5 (1.9)	1.0 (0.8)	6.6 (2.7)	≤ 0.01↑
Left Knee	2.2	2.2 (1.0)	0.9 (0.6)	1.2 (1.4)	3.0 (2.0)	4.3 (4.4)	≤ 0.003↑
CSP-FJ	1.8	1.5 (1.0)	1.0 (0.6)	1.5 (1.7)	2.5 (1.1)	2.3 (2.1)	≤ 0.13
Right Knee	1.7	1.6 (1.0)	1.4 (1.4)	1.8 (3.7)	2.4 (3.6)	3.0 (5.0)*	≤ 0.001↑
CMC-I	1.7	2 (1.0)	0.5 (0.7)	2.5 (1.5)	1.0 (0.6)	0.9 (0.4)	≤ 0.05↓
MCP-H	1.2	1.5 (1.0)	1.0 (0.7)	0.5 (0.3)	1.5 (1.5)	1.4 (0.9)	≤ 0.05↑

* = *Odds Ratio significantly positive at 95% confidence interval*
↑ = *Significant increase of frequency with increase of BMI*
↓ = *Significant decrease of frequency with increase of BMI*

most joints, it amounted to adding a few percentages of OA to the lower quintile of the Quetelet's index distribution and subtracting some from the highest quintile. Nevertheless, we present only the age adjusted values. As measure of association between Quetelet's index and the presence of OA we used the odds ratio. With the Mantel-Haenszel procedure [14] a combined odds

ratio was calculated for 5-year age strata for each quintile of Quetelet's index with respect to the lowest quintile. To verify whether a gradient of the prevalence of OA existed over the 5 Quetelet's index quintiles, we used the Mantel extension of the Mantel-Haenszel test [15]. We preferred stratified analysis because, in general, results are the same compared to multiple logistic regression analysis. Stratified analysis, limited to the key variables, provides more insights into the data than multiple logistic regression analysis [16].

Results

Tables 3-1 and 3-2 give the age standardized prevalence of radiological OA in 1071 men according to quintiles of Quetelet's index for all OA and for severe OA only. Statistical significance of the gradient of increase of the prevalence is also noted in the table (p of trend). Tables 3-3 and 3-4 present the same data for women. The frequency of OA grade 2 or more is higher in women, except for OA of hips, wrists and facet joints and disc degeneration of the cervical spine. In general, differences between men and women were small, except for sacroiliac joints which were 7 times more frequently involved in women. The lowest overall frequency of OA was found present in the first and second quintile, severe OA was lowest in the second quintile. In both sexes the same joints or joint groups showed a significant positive association of OA with obesity, except for metacarpophalangeal (MCP) joints of the hands, facet joints of the cervical spine and the right hip which were significantly more affected in obese males. A significant negative association between Quetelet's index and OA was found among women and not among men in most of the joints that were abnormal in less than 10%.

Severe OA in relation to Quetelet's index is presented in Tables 3-2 and 3-4, only joints and groups of joints with a prevalence of some importance were included. Disc degeneration of the cervical spine, OA of knees and DIP joints of the hands were more frequent in obese women. First metatarsophalangeal joints of the feet and MCP joints of the hands were positively associated in men

Table 3-3. Prevalence of OA and disc degeneration, grade 2 or more by quintiles of Quetelet's index, among 1097 women, aged 45-64 standardized for age. Between brackets: Mantel-Haenzsel odds ratio of quintiles computed with lowest quintile as reference, standardized for age. Joints listed according to frequency of OA.

Frequency OA grade ≥ 2		*Quintile of Quetelet's Index*					*p of Trend*
		I	*II*	*III*	*IV*	*V*	
LSP-DD	56.0	53.7	56.0	55.2	55.9	57.0	
		(1.0)	(1.1)	(1.1)	(1.2)	(1.3)	≤ 0.001↑
CSP-DD	49.5	47.6	44.4	45.7	52.4	57.3	
		(1.0)	(0.7)	(0.8)	(1.2)	(1.4)	≤ 0.001↑
DIP-H	43.1	38.3	38.0	43.2	47.6	49.6	
		(1.0)	(1.0)	(1.5)	(1.6)*	(1.8)*	≤ 0.002↑
MTP-I-F	37.6	30.8	35.2	38.3	38.2	45.4	
		(1.0)	(1.3)	(1.5)*	(1.7)*	(2.0)*	≤ 0.001↑
MCP-H	26.1	22.5	22.9	22.7	32.7	28.8	
		(1.0)	(1.0)	(1.1)	(1.3)	(1.3)	≤ 0.39
CMC-I	19.6	18.3	19.3	17.6	21.6	19.4	
		(1.0)	(1.0)	(0.9)	(1.2)	(1.0)	≤ 0.30
Right Knee	16.2	9.6	10.3	14.4	24.4	20.3	
		(1.0)	(0.9)	(1.5)	(2.3)*	(1.9)*	≤ 0.001↑
Left Knee	15.6	11.8	10.8	13.0	21.8	18.7	
		(1.0)	(0.9)	(1.3)	(2.3)*	(1.8)	≤ 0.001↑
PIP-H	13.5	7.2	16.7	17.1	13.2	13.1	
		(1.0)	(1.7)	(2.3)*	(1.8)	(2.0)	≤ 0.001↑
CARP-H	8.7	9.2	9.9	9.7	6.8	7.8	
		(1.0)	(0.9)	(1.1)	(0.8)	(0.8)	≤ 0.003↓
CSP-FJ	8.4	7.1	4.6	13.0	9.2	8.4	
		(1.0)	(0.7)	(1.8)	(1.2)	(1.1)	≤ 0.34
PIP-F	7.2	8.9	9.3	2.1	7.4	8.2	
		(1.0)	(0.9)	(0.4)	(0.8)	(0.9)	≤ 0.007↓
WRIST	5.9	3.1	4.5	7.3	7.6	6.2	
		(1.0)	(1.2)	(2.5)	(2.5)	(1.9)	≤ 0.12
MTPL-F	5.4	4.5	5.6	7.3	6.2	3.8	
		(1.0)	(1.0)	(1.3)	(1.1)	(0.8)	≤ 0.33
TMT-F	5.0	5.0	6.2	4.7	4.3	4.4	
		(1.0)	(1.0)	(0.8)	(0.7)	(0.7)	≤ 0.001↓
L-SI	3.7	2.5	4.2	3.2	2.1	2.8	
		(1.0)	(1.3)	(1.0)	(0.6)	(0.9)	≤ 0.001↓
Right Hip	2.7	4.0	2.4	4.1	1.7	1.3	
		(1.0)	(0.6)	(1.2)	(0.5)	(0.4)	≤ 0.001↓
Left Hip	2.7	3.0	2.1	2.1	4.8	1.4	
		(1.0)	(0.7)	(1.1)	(1.9)	(0.7)	≤ 0.38
R-SI	2.5	3.4	3.2	3.6	0.9	1.0	
		(1.0)	(0.8)	(0.8)	(0.4)	(0.5)	≤ 0.001↓
CMC-L	0.5	0.0	0.4	0.0	0.4	1.2	

* = *Odds Ratio significantly positive at 95% confidence interval*
↑ = *significant increase of frequency with increase of BMI*
↓ = *significant decrease of frequency with increase of BMI*

Table 3-4. Prevalence of OA grade 3 and 4, by quintiles of Quetelet's index, among 1097 women, aged 45-64 standardized for age. Between brackets: Mantel-Haenzsel odds ratio of quintiles computed with lowest quintile as reference, standardized for age. Joint listed according to frequency of OA.

Frequency OA grade ≥ 3		*Quintile of Quetelet's Index*					*p of Trend*
		I	*II*	*III*	*IV*	*V*	
CSP-DD	22.2	23.3 (1.0)	15.5 (0.6)*	21.0 (0.9)	22.6 (0.9)	28.8 (1.2)	≤ 0.001↑
LSP-DD	21.6	24.8 (1.0)	19.2 (0.7)	23 (0.8)	22.2 (0.8)	19.2 (0.7)	≤ 0.001↓
MTP-I	8.5	7.8 (1.0)	8.8 (1.0)	7.0 (0.9)	8.6 (1.0)	10 (1.2)	≤ 0.06
DIP-H	5.9	4.4 (1.0)	2.8 (0.5)	7.5 (2.2)	8.2 (1.2)	6.7 (1.2)	≤ 0.001↑
CMC-I	3.9	3.9 (1.0)	5.6 (1.2)	2.5 (0.7)	3.7 (0.9)	3.9 (0.8)	≤ 0.003↓
MCP-H	2.6	2.4 (1.0)	3.3 (1.3)	2.0 (0.9)	2.7 (0.4)	2.0 (0.9)	≤ 0.001↓
Left Knee	2.5	1.9 (1.0)	0.9 (0.5)	2.0 (1.2)	2.8 (1.8)	4.8 (1.9)	≤ 0.001↑
Right knee	2.1	1.5 (1.0)	1.4 (0.9)	2.5 (1.9)	2.3 (1.6)	2.9 (1.4)	≤ 0.003↑
CSP-FJ	0.7	0.5 (1.0)	0.5 (0.8)	1.0 (1.8)	0.5 (0.7)	1.0 (1.3)	≤ 0.24

* = *Odds Ratio significantly positive at 95% confidence interval*
↑ = *Significant increase of frequency with increase of BMI*
↓ = *Significant decrease of frequency with increase of BMI*

also. Neither mild nor severe OA of first carpometacarpal joints of the hands was associated with Quetelet's index. The associations between OA grade 2 or more and Quetelet's index were stronger compared to grade 3 and 4.

Ratios of mild and severe OA and mild and severe disc degeneration showed a large variation. In men this ratio was low for cervical spine disc degeneration

(1.95) and high for OA of the synovial joints like the MCP joints of the hands (16.7). In women this pattern was almost the same. In general, from the joints that were frequently mildly affected, a higher percentage was also more often severely affected.

Discussion

Our results indicate that most of the more frequently affected joints in both men and women show an association between OA and obesity. Joints with a negative association between OA and Quetelet's index gave inconsistent results; moreover, when looking at the prevalence, these negative "significances" might easily be due to a single high or low figure.

The pattern of joint involvement and its relation with body mass index (BMI) does not correspond to what one would expect if mechanical wear-and-tear as a cause of OA were to be aggravated by obesity. The weight bearing joints provide clear examples: it is surprising that hips seem to be protected and knees more often damaged in obese persons.

The pattern of OA and obesity also does not fully correspond to what one would expect if a general (metabolic) cause existed for OA. If a metabolically induced deterioration of cartilage would take place, prevalence differences of OA between joints might be smaller then we found them. Nevertheless, the magnitude of the population studied, the objective appraisal of the radiographs and the clearcut patterns which emerge make it unlikely that our findings are merely a consequence of the hazard of data collection.

Our findings strengthen separate findings from other major population surveys. In 1958 Kellgren and Lawrence [3] concluded that in the 1949-50 survey in Leigh, England, there was an overall association between OA and obesity in the weight bearing joints. The positive association between obesity and OA of the hips was found also in the Leigh survey, but in men only. In their figures this association is, however, not strong, and they note themselves the paradoxical presence of the association in the DIP joints. In discussing the

1960 New Haven survey of joint diseases, Acheson and Collart [17] conclude that overweight almost certainly increases the probability of developing OA in certain weight bearing joints, but that this cannot explain its association with disease in the finger joints. Later, Acheson [18] emphasized the discrepancy in the findings regarding individual joints, most notably, why some weight bearing joints do and others do not show an association with obesity. Hartz, et al. [7] confirmed a strong positive association between relative weight and OA of the knees, especially in women. They also found a weak association for the hip, although this association was confined to Caucasian women and non-Caucasian men.

This pattern of joint involvement and its association with relative weight remains an enigma. The pattern of the association of obesity and OA does not fit 2 major hypotheses mentioned earlier. It is possible that the association in our data does not reflect a true causal relationship between obesity and OA. Therefore, alternative explanations need to be considered. Confounding by an unknown factor associated with both obesity and OA might explain our results. Because Quetelet's index changes with age, adjustment was made for age but this did not cause a major change of the association. The frequency of OA differs between men and women, the association between obesity and OA was, however, remarkably consistent in separate analysis. Several endocrine diseases are associated with both obesity and OA [19]. Dietary factors are a major determinant of obesity in animal experiments; use of saturated and unsaturated fats may respectively promote or suppress the development of OA of the knee in several strains of mice [6,20]. Genetic factors were of major importance in these experiments [21]. Since no such investigations were done in man, however, it is speculation to contribute a major role of dietary factors to the development of OA in man.

The possibility that obesity is the consequence of OA because of immobility is highly unlikely: painful weight bearing joints may cause inactivity and thereby an increase in weight, yet OA of small joints of the hand and facet joints of the cervical spine cannot be regarded as a cause of obesity.

A quite different possibility is that our conjectures are still too broad. Maybe, we should not try to explain all of OA by a single general mechanism. The amount of force on articular cartilage from muscle contraction is much larger than the amount of force from weight bearing [22]. A convincing specific mechanism of lesions by intra-articular pressure of the DIP joints by pinching has been shown by Landsmeer [23]. Furthermore, also extra-articular changes, digital extensor tendon thickening, precede the development of Heberden's nodes and Bouchard's nodes [24]. The development of Heberden's nodes is also strongly influenced by genetic factors [25]. Radin, et al. [26] proposed also a mechanistic approach based on repetitive impulsive loading. Subchondral bone is more stiff in obese than in non-obese persons [27] and the stiffer the subchondral bone, the less it is capable of absorbing energy from repetitive impulse loading. A possible explanation for this difference in stiffness is a decreased bone loss with age and thereby a relatively less decreased stiffness of subchondral bone in obese persons compared to non-obese persons. Higher levels of circulating estrogens, generated by the peripheral aromatization of androstenedione by fatty tissue, probably form the metabolic background for this observation [28].

Whatever the final explanation for the etiology of OA, we believe that it will have to take into account the strange pattern of the association between OA and obesity. Our data do not support the hypothesis that prevention of OA by weight reduction is possible in general. However, OA is not a single disease; it is a heterogeneous condition and site specific associations are strong. Odds ratio approaches 5 for knee OA and there is a dose response relationship in both mild and severe involvement. Therefore, especially knee OA might benefit from weight reduction. Intervention studies might reveal whether the induction or the progression of the disease is prevented.

Summary of the chapter

The association between obesity and osteoarthritis (OA), was studied by

analysis of data from an epidemiologic survey of a population of 1071 men and 1097 women in The Netherlands. A total of 20 joints and groups of joints were investigated. OA was clearly associated with obesity in the most frequently affected joints, weight bearing as well as nonweight bearing. This association was less strong for severely affected joints than for mildly affected joints. This pattern was neither compatible with a generalized (metabolic) abnormality nor with weight induced mechanical "wear-and-tear". OA is a heterogeneous condition and some site specific associations with obesity are strong, thus there is scope for prevention by weight reduction for some sites.

Abbreviations used in the tables.

OA :Osteoarthritis
LSP-DD :Lumbar Spine Disc Degeneration
CSP-DD :Cervical Spine Disc Degeneration
DIP-H :Distal Interphalangeal Joint of the Hands
MTP-I-F :First Metatarsophalangeal Joint of the Feet
MCP-H :Metacarpophalangeal Joints of the Hands
CMC-I :First Carpometacarpal Joints of the Hands
PIP-H :Proximal Interphalangeal Joints of the Hands
CARP-H :Carpal Joints of the Hands
CSP-FJ :Facet Joints of the Cervical Spine
PIP-F :Proximal Interphalangeal Joints of the Feet
MTPL-F :Lateral Metatarsophalangeal Joints of the feet
TMT-F :Tarsometatarsal Joints of the Feet
L-SI :Left Sacro-iliac Joints
R-SI :Right Sacro-iliac Joints
CMC-L :Lateral Carpometacarpal joints

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PART II. THE FOLLOW-UP PART OF THE INVESTIGATION: 1985-1986

CHAPTER 4

OSTEOARTHROSIS OF THE HIP

Literature review

Introduction

Osteoarthrosis (OA) of the hip is not one distinct clinical entity, the gradual or fast destruction of a joint may have different causes and a varying radiological and clinical presentation. Often no etiological factors can be found, however, two broad pathways are generally accepted [1]: abnormal stresses being transmitted through a normal joint and normal stresses being transmitted through an abnormal joint. The present investigation is mainly concerned with the prevalence, determinants and clinical findings of OA of the hip. Reviews on the etiology and pathogenesis of OA in general are widely available [2-7]. It is not always possible to distinguish between epidemiological and 'other' investigations. A variety of patients is described; case reports, case-series, large groups of persons visiting orthopaedic outpatient clinics and population surveys with or without selection. Investigations conducted for etiologic or descriptive purposes were included, investigations for evaluation of therapeutical measures are beyond the scope of this review. Table 4-1 summarizes some of the major investigations.

History

OA is a disorder as old as mankind itself. OA was diagnosed in Neanderthal, Cro-Magnon and Paleolithic skeletons [8]. It is the most common skeletal abnormality in archaeologic material, for instance, OA of the hip (joint space narrowing, sclerosis and osteophytes) was found in Merneptah [9], one of the royal pharaohs. The mummy of this Pharaoh also showed signs of severe atherosclerosis of the aorta. Skeletons from all ages were investigated for the presence of OA, e.g. the prevalence of OA of the hip was 3.8% from skeletons from the 17th and 18th century, collected during the renovation of the Hoogland Church at Leiden, The Netherlands [10].

Diagnostic criteria and prevalence

Prevalence is defined as the presence of a disease (or event) at a certain point in time (point prevalence) or all cases of a disease (or events) prevailing at a given time period (period prevalence) [11]. The prevalence of OA of the hip (and any other disease) is not only dependent on that point in time or period of time, but also on the criteria used to define the disorder. In 1986 the Subcommittee on Classification Criteria of Osteoarthritis of the American Rheumatism Association [12] adopted the classification system of Lesquesne [13] and Gofton [14] which separates idiopathic and secondary OA of the hip.

Idiopathic OA is subdivided in a lateral (or superior or eccentric), a medial and an axial (or diffuse or complete) subset of joint space narrowing. Secondary OA of the hip is diagnosed in those cases with known traumatic events, associated diseases (e.g gout) or local anatomical abnormalities (e.g. congenital disorders of the hip). However, prevalence studies conducted so far did not use this classification system. Most of the epidemiologic surveys used the Standard Atlas of Radiographs of Arthritis [15] as a reference. The investigations measuring the prevalence of OA of the hip [16-20] were cross-sectional and radiographs were often made for unrelated purposes. Low prevalence figures were described by Hoaglund [19] in Chinese men and women over the age of 55 years: men 1.2% and women 0.8%. From a South African Negro population [20] low prevalence figures were recorded too.
Two out of 61 men and 1 out of 138 women were found to have OA of the hip. Danielsson [16] recorded an average prevalence of primary coxarthrosis in Sweden in age groups below 55 of less than 1%, in age groups around 85 the frequency was almost 10%. The mean prevalence above 55 years of age was 3.4%, 31% being bilateral. Later he repeated a survey on X-rays of 4027 double contrast colon roentgenograms [18] and found the same prevalence figures as in the earlier study. Furthermore joint space narrowing was measured; lateral, medial and complete narrowing occurred in the same frequency, medial and complete narrowing were somewhat more frequent in men and both types

Table 4-1. Studies of prevalence, incidence and determinants of OA of the hip.

First Author	*Population*	*Design**	*Study Factor*
Kellgren (27) 1958	173 men 206 women	N-D, cross-sectional random population sample	weight cholesterol
Pearson (64) 1962	203 men 197 woman	F, case serie	presenting symptoms development of radiological progression
Murray (65) 1965	115 men 135 women	B, case-control (200 cases and 50 controls)	radiology secundary OA
Danielsson (16) 1966	1965 men 1938 women	N-D, cross-sectional stratified sample of radiologic colon investigations	prevalence, secundary osteoarthrosis
Gofton (66) 1967	14 men and women	N-D, case serie	disparity of leg length in patients with unilateral hip OA
Saville (31) 1968	50 men 71 women	N-D, case serie orthopedic patients	age, weight, height, secundary osteoarthrosis
Detmar (67) 1968	145 men 210 women	N-D, case serie	frequency of primary and secundary hip OA
Lawrence (68) 1969	547 men 632 women	N-D, cross-sectional random population sample	differences between nodal and non-nodal OA
Hoaglund (19) 1973	248 men 252 women	N-D, cross-sectional sample of hospital patients	prevalence, anthropometric attributes
Solomon (20) 1975	61 men 138 women	N-D, cross-sectional random population sample	prevalence
Yazici** (69) 1975	73 men 242 women	N-D, case control	Heberden's nodes, hip OA and knee OA
	29 men 47 women	B, case serie	Heberden' nodes, hip OA and knee OA
Goldin (28) 1976	25 men	B, case serie	OA in grossly overweighted men

Table 4-1. (continued) Studies of prevalence, incidence and determinants of osteoarthritis of the hip.

First Author	*Population*	*Design**	*Study Factor*
Solomon (70) 1976	131 men 196 women	B, case serie	radiology, life style habits, secundary OA
Marks (71) 1979	44 men 56 women	N-D, cross-sectional	relation between OA of the hip and OA of other joints
Jörring** (17) 1980	6321 men and women	N-D, cross-sectional sample of persons with radiologic colon investigations	prevalence
	108 men and women	F, cohort from cross-sectional study	occupation, sighns, symptoms, radiology, sport
Solomon (49) 1982	128 men 258 women	N-D, case serie	somatotype, bone density, disk degeneration and polyarticular OA
Stewart (72) 1983	37 men 49 women	F, case serie	radiological progression
Danielsson (18) 1984	1975 men 2070 women	N-D, cross-sectional stratified sample of radiologic colon investigations	prevalence, joint space narrowing
Hoaglund (73) 1985	126 men 273 women	N-D, case serie	differences between races (Japan - USA)

* *N-D: Non-Directional, F: Foreward, B: Backward*
** *both investigations described in one article*

gave fewer symptoms than loss of cartilage in the superior joint 'space'. Jörring [17] also studied X-rays of colon examinations, mild OA was found equally common in both sexes, severe OA was twice as common in women above 60 years of age compared to men. Fifty percent was laterally and 24% medially narrowed, the medial type hardly ever produced symptoms. The overall prevalence in this Danish population was 4.7%, 5.6% in women and 3.7% in men. Fifty percent was asymptomatic and 43.8% was bilateral.

Incidence studies

Incidence is the number of new cases within a given period [21,22]. Radiological OA of the hip is asymptomatic in a high percentage of the affected persons. To determine the incidence of such a disorder radiographs of the pelvis have to be made of all members of a population, regardless of signs or symptoms, with regular intervals, with a long enough time in between. Because hip OA is a chronic disease, the incidence is low in spite of the rather high frequency at higher ages. So far no investigations were conducted that could be regarded as incidence studies.

Several authors tried to estimate the incidence from prevalence data [16,18]. Jörring [17] performed a follow-up study on the group of 299 persons who had X-rays of their colon several years earlier. He probably could have computed the incidence of progression of OA of the hip, however, he did not measure the follow-up time. Furthermore, 179 persons died during the time of follow-up, mortality that might be related to the problem that was reason for the X-ray examination. Calculation of the incidence is possibly biased through such selective mortality.

Determinants

- **Age**: In Chapter 2 the increase of radiological OA with age was described and several populations were compared. The graphs give the impression that a high proportion of OA is the consequence of ageing, sometimes described as "wear-and-tear", or a complicated combination of physical and chemical changes of cartilage. A recent study performed at the Jan van Breemen Institute in Amsterdam [23,24] demonstrated differences between hip and knee cartilage and differences between upper and lower layers of cartilage. The composition of cartilage changes with age [25] and this will certainly have an effect on the shock absorbing capacity. Studying cartilage is impossible in population epidemiology (cartilage is a black box for the epidemiologist), the biochemical

properties and changes will therefore not be further discussed.

- **Body Mass Index (Quetelet's Index)**: The association between body mass index and OA is confusing; not only are epidemiological investigations, case-series and experimental work often conflicting, there are also discrepancies between joints. The whole idea of this relationship was based on intuition, more than on surveys and experiments. Or, as stated by Kellgren in 1961 [26]: "*the mechanical effect of excess body weight upon joints of the lower limbs is self evident*". This "mechanical self-evidence" was adopted by Brandt [4] too. If this mechanical effect is of any importance it must act through an increased weight bearing. Persons with activities that increase the load upon a joint, which possibly leads to more damage, could be expected to have an excess of OA of the hip and knee. Associations between OA and obesity (or leanness) may be positive or negative. OA of the distal interphalangeal joints and knees is positively associated in almost all population surveys with a high body mass index. OA of the hip does not occur more often in obese people as was demonstrated in many investigations [27-32]. Data from Saville [31] indicate that both men and women with OA of the hip are similar to the general population with respect to weight and height, body mass index was not calculated. Goldin [28] did not find evidence that overweight males (mean body weight 201 kg, mean age 44.7 years) are more prone to develop OA of their hips and knees, unfortunately his group was not only rather young but also rather small. In the cross-sectional data from the EPOZ survey [32] this association was also absent, for all different types of OA as well as for different radiologic types of joint space narrowing. Convincing data regarding a positive association between OA of the knee and obesity were recently published by Felson, et al. [33] from the Framingham Heart Study Cohort. Age adjusted relative risk for women in the most overweight quintile compared to the lower quintiles was 2.07 (95% CI, 1.67-2.55) and for men 1.51 (95% CI, 1.14-1.98) during a 36 year follow-up period. One of the conclusions from studies on the association between body mass index, weight, height and OA of the hip and knee must be that, until now, not even a weak association could be demonstrated for obesity and OA of the

hip and a definitely positive association exists between obesity and OA of the knee. Therefore, pathogenetic mechanisms of OA (load bearing, metabolic pathways) will probably be different for these joints.

- **Sport, occupation and load bearing:** Load bearing, increased use of joints or repetitive impulsive loading [34] as a cause of OA has been investigated for several joints. Just like body mass index and OA, data are conflicting in this field too. Hunter, et al. [35] demonstrated a slight increase of OA of the elbows and shoulders in a group of 286 pneumatic drillers, however, Burke, et al. [36] were not able to confirm these findings. In farmers [37] the prevalence of OA of the hip is higher compared to the average population. Jörring [17] was not able to demonstrate heavy work to be a cause of OA. During a prospective follow-up study by Glyn [38], 100 patients who had suffered an attack of poliomyelitis at least 10 years previously, were evaluated for the development of OA in the hip and knee. The prevalence of radiological OA of the hip and knee joint of the weaker limbs was considerably lower than the prevalence in the stronger limbs (3.1% versus 10.2% for hips and 5.1% versus 12.3% for knees). This prevalence was different from an age-matched control group (7.6% for hips and 17.1% for knees). It was concluded that patients with poliomyelitis developed less OA because their activities were restricted. Most studies argue, in the discussion more than in the results, in favour of the hypothesis that load bearing damages joints. Lindberg [39,40] compared hips and knees from 332 laborers of a shipyard with hips and knees from white collar workers and hips and knees from a random population sample. Differences between the three groups were not found present for the hips, circumstantial evidence suggested an association between heavy work and the development of OA of the knee. Lawrence [3] reviewed a number of investigations about the prevalence of OA and different occupational groups, and concluded that the increased use of joints causes an increase in the prevalence of OA (hips were not included). Murray [41] investigated sports activities and made X-ray films of the pelvis of adolescents, a higher percentage of minimal epiphysiolysis (tilt deformity) was reported in the group of boys who were engaged in active sports regimens.

The validity of the final conclusion that "*athletic activity in adolescence is likely to be an important cause of subsequent degenerative hip disease*" goes way beyond the data. If load bearing or repetitive impulsive loading is important in the development of OA, the disorder should certainly be present in a high percentage of hips and knees of long distance runners. Puranen [42] found OA of the hips in only 4% of a group of 74 Finnish marathon runners compared to 8.7% in his control group. Lane [43] did not find differences in the frequencies of OA of knees and hips between a control group and 41 long distance runners aged 50-72 years. Two groups, with and without sporting antecedents, showed a slight difference in rheumatic complaints in a retrospective study by Boyer, et al. [44], and, finally, in an investigation by Panush, et al. [45] the prevalence of degenerative joint disease in a group of high-mileage (28 miles/wk for 12 years) runners was not different from a control group.

Because most investigations were cross-sectional or retrospective it cannot be determined whether self selection of subjects is of any importance. Furthermore potential confounding variables were not included in the description and analysis of most studies. The question of the influence of occupation, sport and other kinds of physical stress as a major cause of OA remains undecided, although some evidence points in the direction of such a causal relationship.

- **hypertension:** A positive association between hypertension and OA of the hip was demonstrated in four cross-sectional studies [3,46-48]. Whether this association has etiological relevance or whether hypertension is just an epiphenomenon of the real cause is uncertain. Speculations about the pathogenesis (e.g. vascular damage) are not supported by supplementary data.
- **osteoporosis:** Solomon, et al. [49] found OA of the hip and femoral neck fracture to be mutually exclusive. They ascribed this to good muscle and bone density in patients with OA. Several other investigators have found anthropometric differences and a higher bone density in patients with OA compared to patient with osteoporosis [50-53]. The complicated interplay of forces between muscle, body fat and hormones [54] still needs further investigation and the precise mechanism and significance for the pathogenesis

of OA of the hip still has to be elucidated.

- **heredity:** Only one study investigated heredity of primary OA of the hip [55]. A higher prevalence of OA of the hip in siblings of patients operated on for primary OA of the hip was reported compared to a control group (8% versus 3.8%). OA of the hip due to congenital abnormalities (e.g. Perthes disease or acetabular dysplasia) has stronger genetic influences [56].
- **NSAID's:** Experimental data suggest that anti-inflammatory drugs have potential harmful effects on articular cartilage [57]. So far no studies have been designed to separate the possible inhibitory effects on chondrocyte anabolic activity by NSAID's and the natural course of the disease.

Signs and symptoms

In 1771 an adequate description of OA of the hip was provided by the authors of the Encyclopaedia Britannica [58]: "*The sciatica is a violent and obstinate pain in the hip, chiefly in the joint where the head of the thigh bone is received into the acetabulum of the coxendix. The pain will sometimes extend itself to the lower part of the loins, to the thigh, leg and even to the extremity of the foot; yet, outwardly, there is no swelling, no inflammation, nor change of colour in the skin*". Symptoms of OA of the hip may vary from minor restricted mobility to severe pain and complete immobility. The most frequent symptoms are nocturnal pain, stiffness following periods of rest, loss of function and pain that worsens on joint use. During investigation restricted mobility, swelling, local tenderness and crepitus can be found. Pain from the hip may be referred to the groin, the knee, the lower back or the buttock [7]. The prevalence of nocturnal pain was 1.3% in men and 2.6% in women from the New Haven population survey [59]. The prevalence of pain on clinical exam was 2.1% for women and 1.6% for men 40 years and over from the HANES survey [30] and the Leigh and Wensleydale study [60] reported that 6.3% of women and 9.5% of men (without rheumatoid arthritis and age 55 and over) ever suffered from pain in their hips. Furthermore, a high prevalence of anxiety

(55%), irritability (53%), sleep disturbances (36%) and depression (45%) was found in a clinical group of patients with primary OA of the hip and knee [61]. There is great discordance between radiological and clinical findings [60,62] and between pain and pathological findings [63]. Unfortunately, data from most population surveys and from most case-series cannot be compared.

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CHAPTER 5

EPIDEMIOLOGY OF OSTEOARTHROSIS OF THE HIP. Determinants of Different Patterns of Migration of the Femoral Head.

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"Splitters have always contributed more to an understanding of medicine than lumpers." Verna Wright (1983)

Introduction

OA of the hip may result from a variety of mechanical stresses acting on the joint sometimes combined with an intrinsic deformity of the joint. Epidemiologic studies have suggested a causal relation between body mass index [1-5] as well as hard labour [6] and OA of the knee. Considerably less is known about obesity and OA of the hip; both increased and absent risks have been reported. A weak association with obesity was present in the HANES data [3], however, in white women and non-white men only; in the population sample in Leigh [1] obese men were slightly more often affected; in the EPOZ study [4] and in two case series [7,8] no such association was found. Furthermore, epidemiologic investigations have identified increased levels of serum cholesterol [1,9], hypertension [10-12] and hard labor [13] as predictors of the development of OA of the hip, although some reports have indicated an unaltered risk [14].

Narrowing of the joint space is one of the earliest radiological signs in OA of the hip [15-17]. Narrowing of the joint space occurs at different sites of the hip and the site of narrowing might be the expression of a different pathogenetic mechanism of OA of the hip. We therefore studied the association between possible risk factors (age, body mass index, blood pressure, profession and serum cholesterol) and subgroups of OA with radiologically different narrowing of the joint space to obtain indications about the etiology and a useful classification of OA of the hip. The results suggest that radiological differences are in fact the expression of dissimilar diseases with a different etiology.

Methods

Population and methods of sampling

The EPOZ study (EPOZ is a Dutch acronym that stands for Epidemiologic Preventive Investigation Zoetermeer) was established between 1975 and 1978 to assess the prevalence of several chronic diseases and their determinants in 10,532 inhabitants of a single community in the Netherlands. Details of this population survey have been described elsewhere [4,18-20]. In brief, the investigation was carried out in Zoetermeer, a suburban community which is situated 10 kilometers east of The Hague in The Netherlands. Inhabitants of the original agricultural and of one of the recently built parts were invited to participate in the survey. The response for 1,877 men and 2,214 women of 45 years and over was 1350 (72.1%) and 1588 (71.7%) respectively. Elderly, living in situations for non-independent living were included in the survey, their radiographs were made at their homes with portable equipment. The completion rate was most adequate in persons between 45 and 65 years of age (77.1%). From those aged 65 and over the response rate was 61%. Data on cardio-vascular risk factors, medical history, occupation and life style habits were gathered by questionnaires which were verified by a physician. A detailed joint examination was performed, height (in cm) and weight (in kg) were recorded and blood pressure was measured in duplicate with a random zero sphygmomanometer. Radiographs of the pelvis were made in weight-bearing position in every participant aged 45 years and over. For the determination of total serum cholesterol blood was taken by venipuncture from non-fasting subjects.

Interpretation of the radiographs

Initially, the Atlas of Standard Radiographs [21] was used as a reference in this and almost every other epidemiological population survey so far. Joints

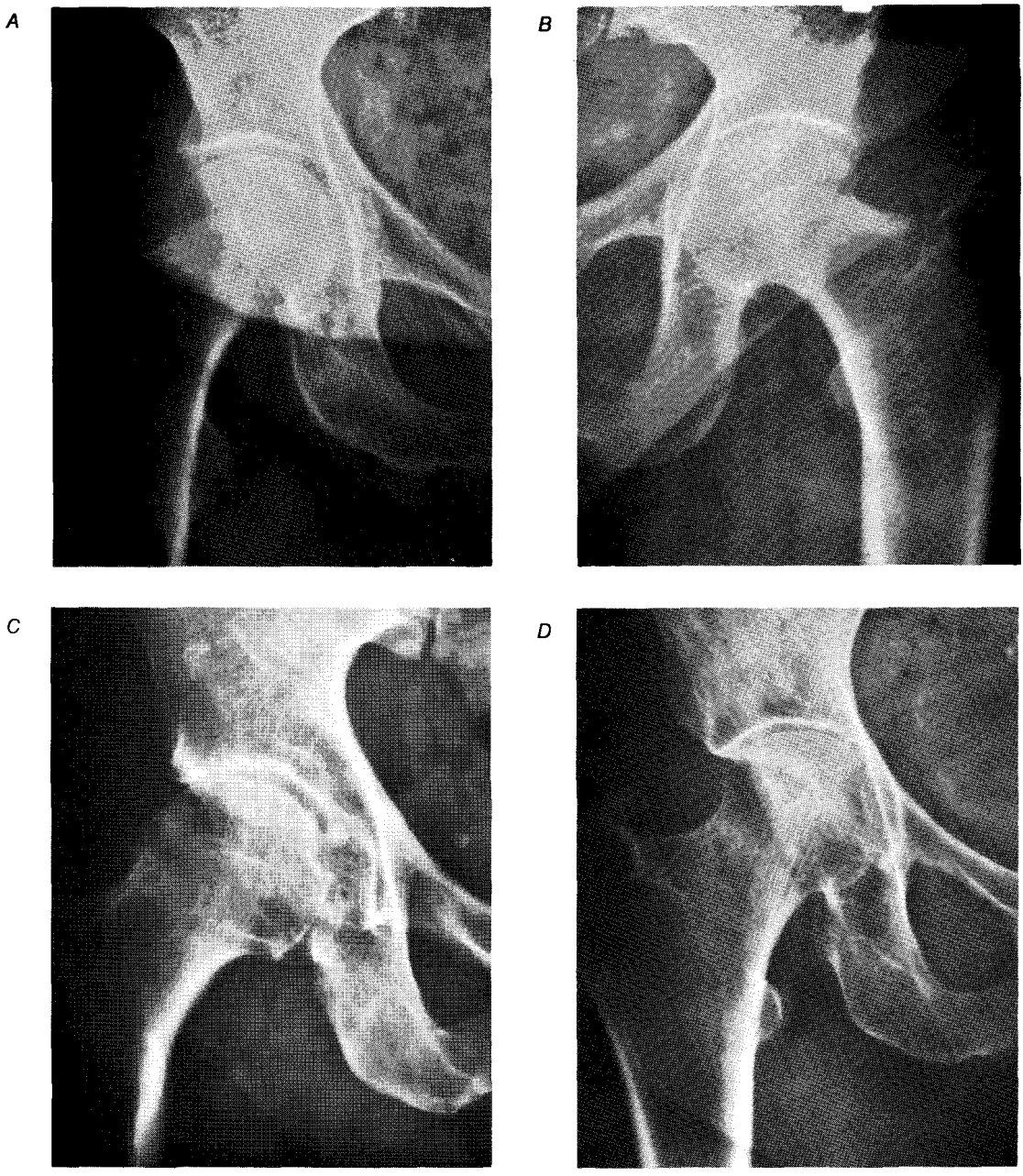

Figure 5-1. Normal joint space (A), Medial joint space narrowing (B), Lateral joint space narrowing (C) and axial joint space narrowing (D). (photographs by T. Rijsdijk)

Table 5-1. Prevalence (%) of Osteoarthrosis and Joint Space Narrowing in Three Categories of Physical Activity in Men (Based on Occupation).

	N*	Joint Space Narrowing			
		Medial	Lateral	Axial	All
I. Little Physical Activity					
Tourism, communication	11	0	0	0	0
Management, administrative	335	5 (1.5)	18 (5.4)	5 (1.5)	28 (8.4)
Teaching, social work	40	0	2 (5)	1 (2.5)	3 (7.5)
Art, science	22	0	1 (4.5)	0	1 (4.5)
totals	408	5 (1.2)	21 (5.1)	6 (1.5)	32 (7.8)
II. Moderate Physical Activity					
Light industry	129	2 (1.6)	11 (8.5)	2 (1.6)	15 (11.6)
Trade, transport, traffic	123	2 (1.6)	9 (7.3)	2 (1.6)	13 (10.6)
Hotel and catering	18	1 (5.6)	1 (5.6)	1 (5.6)	3 (16.7)
Household, nursing	23	0	0	1 (4.3)	1 (4.3)
Police, firebrigade, army	83	2 (2.4)	8 (9.6)	0	10 (12)
totals	376	7 (1.9)	29 (7.7)	6 (1.6)	42 (11.2)
III. Hard Physical Activity					
Heavy industry	267	10 (3.7)	15 (5.6)	5 (1.9)	30 (11.2)
Loading and unloading, Transshipment	106	8 (7.5)	7 (6.6)	2 (1.9)	17 (16)
Agriculture, farming, forestry	155	6 (3.9)	4 (2.6)	2 (1.3)	12 (7.7)
totals	528	24 (4.5)	26 (4.9)	9 (1.7)	59 (11.2)

** 38 men did not report an occupation*

were read for radiological abnormalities matching with OA graded on a scale of 0-4 [4,20]. Radiographs of the pelvis were read a second time with special attention to the location of the joint space narrowing of the femoral head as described by Resnick [15]. Three different migration patterns were distinguished; lateral (or superior) migration, medial migration and axial migration (figure 1A-D). In lateral migration the narrowing takes place in the region of the roof of the acetabulum, the weight bearing surface. This distance can easily be measured and a distance of less than three millimeters was considered to be the consequence of loss of cartilage [22]. There is not always a clearly demarcated joint space in the medial part of the hip, however, other signs of loss of cartilage can be seen as described by Hermodsson [23]. An abnormally short or absent distance between the surface of the femoral head and the tear figure ("floor distance") was considered medial joint space narrowing, this is most obvious in one-sided cartilage loss. Complete narrowing of joint space was coded for when both proximal and medial joint space were narrowed and the femoral head was migrated in an axial direction. In most cases of complete narrowing there was a concomitant protrusion of the acetabulum.

Exclusion criteria

Since we were interested in determinants of idiopathic OA of the hip we excluded persons with secondary OA according to guidelines proposed by the Subcommittee on Classification Criteria of Osteoarthritis of the American Rheumatism Association [24]. Three respondents with congenital hip disease, six with rheumatoid arthritis, three with gouty arthritis and twenty-one with endocrine disorders including diabetes mellitus were not used in the analysis. These 33 respondents were included in the prevalence figures. Furthermore, all 34 respondents with total joint replacement were excluded because of lack of information on the radiology of the joint before operation.

Statistical Analysis

Radiographic patterns of joint space narrowing were divided into normal or abnormal. Age, blood pressure, relative weight, occupation and serum cholesterol were considered risk factors. Quetelet's index (weight/height^2) was used as a measure of relative weight. Systolic and diastolic blood pressure, Quetelet's index and serum cholesterol were divided in quartiles, occupation (in those pensioned past occupation) was divided in three categories; light, moderate and haerd labour (table 5-1). The 'light' category contained persons employed in management, administration and teaching; the 'moderate' category contained persons employed in light industry, hotel and catering industry and commerce and trading; and in the 'hard' category persons were included employed in heavy industry, farming and agriculture. The majority of women ran the household and did not report any other occupation. A small group was occupied or had worked outdoor, and almost all of these women reported their work to be accompanied by moderate physical activity. Therefore, no contrast between various categories of physical activity was obtained in women.

Because of substantial differences between men and women, for both prevalence figures and anthropometric measurements, relative risks were calculated for men and women separately. We calculated relative risks as the rate in a specific category divided by the rate in the lowest category. Adjustment for ten-year age classes was made, according to the method of Mantel and Haenszel [25], and 95 percent confidence limits were estimated according to Miettinen's test based method [26]. Logistic regression was used to control simultaneously for the variables considered a priori to be potential confounders of the results; variables included in the model were age, Quetelet's index, serum cholesterol, systolic and diastolic blood pressure and occupation. The results of the Mantel-Haenszel procedure to adjust for each of the potentially confounding variables individually, were in accordance with the results that we computed by using the logistic regression model.

Results

The highest prevalence was found for medial joint space narrowing of the hips in women and lateral joint space narrowing in men (table 5-2). Differences between men and women relate to the overall prevalence as well as to different types of narrowing of the joint space. Below the age of 60, men were more often affected than women, however, in women the increase with age of medial and axial joint space narrowing was steeper, and as a result the total prevalence in women is higher. The prevalence of lateral joint space narrowing did not increase with age. Average height of men and women with axial joint space narrowing was 3 to 4 cm less, average weight was the same for women with axial narrowing, however, 6 kg less for men with axial joint space narrowing compared to the average weight of all respondents. Average Quetelet's index was higher in women with lateral and women with axial joint space narrowing (table 5-3). However, unadjusted relative risks were not

Table 5-2. Prevalence of Joint Space Narrowing of the Hip, According to Age and Sex (EPOZ Population survey)

MEN					
Age	*N*	*Medial*	*Lateral*	*Axial*	*Total*
45-54	598	9 (1.5)	33 (5.5)	5 (0.8)	47 (7.9)
55-64	437	6 (1.4)	24 (5.5)	3 (0.7)	33 (7.6)
65-74	223	12 (5.4)	13 (5.8)	4 (1.8)	29 (13.0)
75+	96	8 (8.3)	6 (6.3)	9 (9.4)	23 (24)
WOMEN					
Age	*N*	*Medial*	*Lateral*	*Axial*	*Total*
45-54	597	13 (2.2)	12 (2.0)	8 (1.3)	33 (5.5)
55-64	441	13 (2.9)	9 (2.0)	11 (2.4)	33 (7.5)
65-74	284	30 (10.6)	8 (2.8)	17 (6.0)	55 (19.4)
75+	212	29 (13.7)	4 (1.9)	15 (7.1)	48 (22.6)

Table 5-3. Distribution of Characteristics of Men and Women with Medial, Lateral or Axial Joint Space Narrowing of the Hip (EPOZ Population).

WOMEN	*All Women*	*JOINT SPACE NARROWING*			
		MEDIAL	*LATERAL*	*COMPLETE*	*TOTAL*
	N=1588	*N=85*	*N=31*	*N=51*	*N=169*
Age (mean ±SD yr)	61 (11)	70 (11)*	62 (11)	68 (11)*	68 (11)*
Diastolic BP (mean ±SD mmHg)	87 (15)	88 (12)	91 (17)	88 (15)	88 (14)
Systolic BP (mean ±SD mmHg)	141 (23)	148 (17)*	141 (24)	146 (26)	146 (22)+
Quetelet's index (mean ±SD)	261 (37)	261 (36)	273 (42)+	270 (42)+	266 (39)+
Height (mean ±SD cm)	161 (7)	159 (7)+	162 (7)	158 (8)*	159 (8)*
Weight (mean ±SD kg)	68 (10)	66 (9)	71 (11)+	68 (10)	68 (10)
Serum Cholesterol (mean ±SD mg/100 ml)	243 (44)	244 (49)	240 (32)	239 (38)	242 (48)

MEN	*All Men*	*JOINT SPACE NARROWING*			
		MEDIAL	*LATERAL*	*COMPLETE*	*TOTAL*
	N=1350	*N=35*	*N=76*	*N=21*	*N=132*
Age (mean ±SD yr)	58 (10)	66 (11)*	59 (10)	68 (11)*	62 (11)*
Diastolic BP (mean ±SD mmHg)	87 (12)	90 (13)	86 (12)	84 (13)	87 (12)
Systolic BP (mean ±SD mmHg)	138 (19)	150 (22)*	137 (19)	139 (26)	140 (22)+
Quetelet's index (mean ±SD)	251 (28)	250 (31)	253 (24)	244 (33)	250 (27)
Height (mean ±SD cm)	175 (7)	174 (7)	174 (8)	171 (9)+	173 (7)+
Weight (mean ±SD kg)	77 (10)	75 (11)	77 (10)	71 (11)+	75 (10)
Serum Cholesterol (mean ±SD mg/100 ml)	236 (41)	236 (46)	241 (47)	229 (44)	237 (46)

P values were calculated by Student's t-test.
** P < 0.001*
+ P < 0.05

Table 5-4. Relative Risk of All Types of Joint Space Narrowing, According to Sex, Diastolic Blood Pressure, Quetelet's index and Occupation.

MEN		*No. of persons with JSN*	*Unadjusted*	*Adjusted for Age**	*Adjusted for Multiple Variables***
Quetelet's Index	<234+	32/321	1.00	1.00	1.00
	234-250	27/344	0.77	0.74	0.78 (0.45-1.35)
	251-268	33/306	1.09	1.04	1.04 (0.61-1.79)
	>268	40/349	1.17	1.07	1.03 (0.61-1.75)
Diastolic BP	<77+	27/278	1.00	1.00	1.00
	78-85	30/322	0.94	1.14	1.38 (0.76-2.50)
	86-93	32/331	0.99	1.17	1.57 (0.83-2.95)
	>94	43/392	1.15	1.36	1.96 (1.01-3.78)
Occupation	light+	32/408	1.00	1.00	1.00
	moderate	41/376	1.39	1.37	1.33 (0.82-2.18)
	hard	59/528	1.42	1.39	1.42 (0.89-2.29)
WOMEN					
Quetelet's Index	<234+	38/364	1.00	1.00	1.00
	235-256	33/393	0.78	0.77	0.85 (0.51-1.42)
	257-279	45/382	1.14	0.95	1.04 (0.64-1.70)
	>280	49/414	1.15	0.82	0.77 (0.47-1.26)
Diastolic BP	<77+	25/308	1.00	1.00	1.00
	78-85	44/372	1.52	1.66	2.00 (1.14-3.52)
	86-93	44/402	1.39	1.62	1.89 (1.01-3.41)
	>94	52/477	1.38	1.54	1.84 (0.99-3.42)

+ *Reference category.* * *By the Mantel-Haenszel method.*
** *By Multiple Logistic Regression with adjustment for age, systolic and diastolic blood pressure, serum total cholesterol and occupation.*

elevated (table 5-4). After adjusment for age, total serum cholesterol and occupation, an elevated risk was found among respondents with high blood pressure. Different associations were found for different types of joint space narrowing. Among respondents with a high Quetelet's index a decreased risk was found for medial joint space narrowing (adjusted relative risk 0.61, confidence limits 0.24 - 1.19 in men and 0.46, confidence limits 0.24 -0.88 in women). Systolic blood pressure was significantly higher in men (13mmHg) and in women (7 mmHg) with medial joint space narrowing (table 5-3).

Table 5-5. Relative Risk of Different Types of Joint Space Narrowing (JSN), According to Diastolic Blood Pressure, Quetelet's index and Occupation in Men.

Joint Space Narrowing	*Narrowing*	*No. of persons with JSN*	*Unadjusted*	*Adjusted for Age*[*]	*Adjusted for Multiple Variables*[**]
MEDIAL					
Quetelet's Index	<234[+]	9/321	1.00	1.00	1.00
	234-250	8/344	0.93	0.95	0.73 (0.26-2.00)
	251-268	7/306	0.91	0.91	0.57 (0.20-1.61)
	>268	11/349	1.27	1.11	0.61 (0.24-1.19)
Diastolic BP	<77[+]	4/278	1.00	1.00	1.00
	78-85	8/322	1.97	2.53	2.21 (0.60-8.14)
	86-93	9/331	2.17	2.95	2.59 (0.67-10.06)
	>94	14/392	2.87	4.10	3.47 (1.03-11.67)
Occupation	light[+]	5/408	1.00	1.00	1.00
	moderate	6/376	1.29	1.17	1.15 (0.34-3.88)
	hard	24/528	4.43	3.44	3.60 (1.31-9.92)
LATERAL					
Quetelet's Index	<234[+]	17/321	1.00	1.00	1.00
	234-250	16/344	0.98	0.98	0.96 (0.47-1.96)
	251-268	20/306	1.41	1.41	1.39 (0.69-2.68)
	>268	23/349	1.42	1.41	1.47 (0.74-2.93)
Diastolic BP	<77[+]	18/278	1.00	1.00	1.00
	78-85	17/322	0.92	0.92	1.00 (0.48-2.08)
	86-93	18/331	0.95	0.96	1.09 (0.50-2.37)
	>94	23/392	1.02	1.04	1.36 (0.60-3.09)
Occupation	light[+]	21/408	1.00	1.00	1.00
	moderate	19/376	1.52	1.51	1.48 (0.83-2.67)
	hard	26/528	1.11	1.08	1.03 (0.56-1.91)
AXIAL					
Quetelet's Index	<234[+]	6/321	1.00	1.00	1.00
	234-250	3/344	0.52	0.53	0.39 (0.09-1.72)
	251-268	6/306	1.18	1.18	1.04 (0.31-3.47)
	>268	6/349	1.03	0.85	0.66 (0.19-2.36)
Diastolic BP	<77[+]	5/278	1.00	1.00	1.00
	78-85	5/322	0.97	1.33	1.87 (0.46-7.56)
	86-93	5/331	0.95	1.40	2.22 (0.50-9.82)
	>94	6/392	0.96	1.49	2.43 (0.51-11.67)
Occupation	light[+]	6/408	1.00	1.00	1.00
	moderate	6/376	1.08	0.89	0.87 (0.27-2.83)
	hard	9/528	1.34	0.81	0.77 (0.25-2.37)

[+] *Reference category.* [*] *By the Mantel-Haenszel method.* [**] *By Multiple Logistic Regression with adjustment for age, systolic and diastolic blood pressure, serum total cholesterol and occupation.*

Table 5-6. Relative Risk of Different Types of Joint Space Narrowing, According to Diastolic Blood Pressure and Quetelet's index in Women.

Joint Space Narrowing		*No. of persons with JSN*	*Unadjusted*	*Adjusted for Age**	*Adjusted for Multiple Variables***
MEDIAL					
Quetelet's Index	<234+	23/364	1.00	1.00	1.00
	235-256	12/393	0.47	0.38	0.46 (0.22-0.96)
	257-279	28/382	1.17	0.91	0.96 (0.52-1.76)
	>280	22/414	0.83	0.59	0.46 (0.24-0.88)
Diastolic BP	<77+	10/308	1.00	1.00	1.00
	78-85	26/372	2.24	2.58	2.69 (1.20-6.06)
	86-93	21/402	1.64	2.15	2.03 (0.85-4.84)
	>94	28/477	1.86	2.24	2.14 (0.88-5.18)
LATERAL					
Quetelet's Index	<234+	7/364	1.00	1.00	1.00
	235-256	8/393	1.05	1.09	1.22 (0.72-3.50)
	257-279	7/382	0.95	0.94	1.09 (0.36-3.32)
	>280	11/414	1.39	1.51	1.44 (0.50-4.14)
Diastolic BP	<77+	7/308	1.00	1.00	1.00
	78-85	6/372	0.70	0.70	0.92 (0.29-2.91)
	86-93	9/402	0.98	1.01	1.38 (0.43-4.43)
	>94	11/477	1.02	0.94	1.75 (0.50-6.14)
AXIAL					
Quetelet's Index	<234+	10/364	1.00	1.00	1.00
	235-256	14/393	1.31	1.27	1.53 (0.66-3.59)
	257-279	11/382	1.05	0.94	1.03 (0.42-2.56)
	>280	16/414	1.42	0.92	1.06 (0.45-2.51)
Diastolic BP	<77+	8/308	1.00	1.00	1.00
	78-85	12/372	1.25	1.34	1.89 (0.72-4.97)
	86-93	17/402	1.65	1.84	2.72 (1.03-7.21)
	>94	14/477	1.13	1.29	1.84 (0.63-5.36)

*+ Reference category. * By the Mantel-Haenszel method.*
*** By Multiple Logistic Regression with adjustment for age, systolic and diastolic blood pressure, serum total cholesterol and occupation.*

Whereas the age-adjusted relative risk of joint space narrowing of the hip was not increased among respondents with a high Quetelet's index, relative risk

was increased among respondents in the higher quartiles of diastolic blood pressure (above 78 mmHg) compared to the lowest quartile (table 5-4). In men a gradual increase was present in each quartile of diastolic blood pressure, in women the relative risk was about 2 in each quartile compared to the lowest quartile. Respondents with medial and axial joint space narrowing accounted for the age-adjusted increase in risk of all types of joint space narrowing taken together, according to diastolic blood pressure (table 5-5 and 5-6). Systolic blood pressure was associated with medial and axial joint space narrowing in the same way as diastolic blood pressure both men and women (not presented in the tables). Occupation, considered to be an indicator of physical activity, could only be studied in men. An occupation demanding hard physical activity was not associated with all types of joint space narrowing taken together (relative risk 1.42, 95 percent confidence limits 0.89-2.29), however a strong positive association was found with medial joint space narrowing (relative risk 3.67, 95 percent confidence limits 1.31-9.92). The different levels of serum cholesterol did not influence the prevalence of degenerative hip disease. Participants with total hip replacement did not differ from the general population with respect to Quetelet's index, weight, height, blood pressure and total serum cholesterol.

Discussion

Our results indicate that idiopathic OA of the hip consists of a group of diseases and that the type of migration of the femoral head is the expression of different pathogenetic mechanisms. So far, for assessment of radiological OA of the hip in epidemiologic research, the Atlas of Standard Radiographs of Arthritis [21] was used. The severity of radiological OA in this atlas is expressed on a five point scale, however, without attention to different radiological patterns. In 1986 the ARA Subcommittee on Classification Criteria of Osteoarthritis proposed a classification for subsets of OA [24] in which OA is divided in two categories: idiopathic OA and secundary OA, associated with other diseases

or trauma. Idiopathic OA is further divided according to the location of the joint space narrowing, which was already proposed in several earlier publications [15-17,27].

An excess of medial joint space narrowing was found among respondents with an occupation demanding hard physical activity. Radin [28] demonstrated mechanical factors (repetitive impulse loading) to be important in the pathogenesis OA, therefore, it was not surprising to find a higher prevalence of OA of the hip in persons employed in hard labour compared to persons employed in lighter work. However, in contrast with our expectations, hard labour was strongly associated with narrowing of the medial and not with narrowing of the lateral (weight bearing) surface. This finding can be explained from normal hip mechanics. Hard labour may strengthen the abductor muscles. Most of the forces across a joint arise from muscle action and strong abductor muscles create maximal compression medially of the hip joint [29-31]. As far as other physical activity concerns, results are conflicting. Among long distance runners [32-34] and retired football players [35] no increase in the occurrence of idiopathic OA of the hip was found. This "normal" frequency of OA might be explained by self-selection: persons with vulnerable joints do not continue running; or by important differences between using a joint for running and using a joint for doing hard labour. Furthermore, OA was not found more often among laborers working in hard industry in a shipyard in Malmo, however, radiographs were available in only 25% of these men and the same problem of self-selection might have been present [14].

There seems to be no independent role for excessive body weight, although a higher relative weight is responsible for extra load that has to be transmitted through the lateral, weight bearing part of the hip. This is even more surprising knowing that OA of the knee is strongly associated with obesity [4,5], therefore other explanations for our results must be considered. Persons with OA of the hip might have lost weight because they were advised to do so or on their own initiative because of pain or other complaints. It can also be argued that they have gained weight because of decreased mobility. This loss of weight and

Table 5-7. Relative Risk (95 percent Confidence Limits) of Diastolic Blood Pressure and Osteoarthrosis of the Hip in Men, calculated from data presented by J.S. Lawrence [36].

		N	Unadjusted	Adjusted for Age and Weight*
Diastolic BP	< 80	21/212	1.00	1.00
	80-100	43/236	1.99 (1.18-3.34)	1.70 (0.97-3.00)
	>100	22/109	2.30 (1.26-4.18)	2.15 (1.12-4.15)

* *By Multiple Logistic Regression.*

weight increase discussion is an allied problem of the cross-sectional design of this study. Recently Felson, et al. [5] demonstrated that results from a cross-sectional and a follow-up study about the association of OA of the knee and obesity were the same. The association between obesity and OA of the hip was never prospectively studied, however, the absence of an association is very well possible because of the consistent findings from cross-sectional surveys. Secondly, excluding respondents with total hip replacement might have introduced selection bias. Although relative weight from the group with hip operations was the same as from the complete population, obese persons certainly have been advised to lose weight before their operation.

Lawrence [36] demonstrated an increase of the frequency of OA of the hip with age and, surprisingly, with hypertension. Table 5-7 shows the relative risk estimate for diastolic blood pressure and OA of the hip among men, controlling for confounding by obesity and age, calculated from his data presented in 1977. High diastolic blood pressure was accompanied by a higher frequency of OA of the hip in our data also, mainly medial and in men axial joint space narrowing. It is tempting to assume that hypertension induces vascular damage with bleeding or ischaemia of the subchondral bone of the femoral head resulting in necrosis and eventually loss of cartilage [10,36]. Especially the ligamentum teres obliterates in old age and the medial part of the femoral head

might be subjected to a certain degree of ischaemia by vascular damage. However, the circulation within the femoral head does not quantitatively decrease with age in normal persons [37]. Blood supply and bone metabolism even seem to increase in OA of the hip [38]. If a vascular component was causally related to OA we would also expect a positive association between high serum cholesterol and degenerative joint disease, which was absent. Yet another possibility is that the (degenerative) process which makes the arterial wall less compliant at high age is the same process or related to the process of joint degeneration. Matrix components of cartilage (e.g. collagen, proteoglycans) are part of the connective tissue from arterial walls also [39].

From these cross-sectional data it cannot be proven that the association between hypertension and OA is a causal relation and alternative explanations need to be considered here also. Confounding by an unknown factor associated with both hypertension and OA constitutes a possible explanation. Blood pressure rises with age and so does the frequency of OA, therefore age is of considerable importance. However, relative risk did not change after adjustment for age. Dietary factors with an effect on both blood pressure and bones were not measured and could not be included.

We conclude that medial joint space narrowing of the hip is associated with high blood pressure and, in men, with an occupation accompanied by hard physical activity. Quetelet's index is not a risk factor for any type of joint space narrowing of the hip. Some of our findings confirm results of other population data. Further investigations will be necessary, especially to explain the association with high blood pressure. Whether prevention of OA of the hip is possible cannot be concluded from this study, however, if possible treatment of hypertension seems more promising than weight reduction. Furthermore, our findings strongly indicate that different radiologic patterns of OA represent more than a single disease entity.

Summary of the chapter

To measure the prevalence of different patterns of radiologic osteo-arthrosis (OA) of the hip and to determine whether these patterns were associated differently with regard to possible risk factors we studied 2938 persons 45 to 85 years of age from the Epidemiological Preventive Investigation Zoetermeer. Medial joint space narrowing of the hip showed a strong increase with age (from 2.1% to 17.7% in women and from 1.5% to 9.8% in men) and was associated with high blood pressure (men: relative risk 3.47 95% confidence interval 1.03-11.67, women: relative risk 2.14, 95% confidence interval 0.88-5.18). In men, medial joint space narrowing was also strongly associated with a physically hard occupation (relative risk 3.60, 95% confidence interval 1.31-9.92). Relative weight (Quetelet's index) was not associated with any type of joint space narrowing. The prevalence of lateral joint space narrowing was twice as high in men compared to women, there was no increase with age. Axial joint space narrowing was mainly found in women above the age of 65 and in men above the age of 75. Findings from this population survey suggest that different patterns of femoral head migration are associated with a different etiology and that blood pressure and occupation are more important risk factors than body weight.

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CHAPTER 6

A FOLLOW-UP STUDY OF NORMAL AND OSTEOARTHROTIC HIP JOINTS.

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Introduction

The appearently heterogeneous disorder 'osteoarthrosis of the hip' demands many aspects to be taken into consideration for an exploration of its cause and course [1]. Cross-sectional studies demonstrated associations of osteoarthrosis (OA) of the hip with several environmental and host factors. Whether these factors have etiologic importance or occur as epiphenomena or whether they initiate or promote the disease needs to be studied in longitudinal and experimental studies [2]. The cross-sectional EPOZ population survey [3] provided an opportunity for such a longitudinal investigation. From the large number of radiographs and other data about joints we decided to study determinants, the relation between radiological and clinical findings, and pain and disability of the hip joint. The choice was fixed upon this joint for two reasons: firstly, osteoarthrosis of the hip remains a disease that causes much pain and suffering in spite of successful treatment by prosthetic replacement and secondly, very little is known about the etiology and therefore no mode of prevention is possible. An additional reason was the special place of OA of the hip in the homogenity analysis performed to reveal the pattern of radiological OA [4]. This investigation is an explorative observational study, questions regarding the choice of risk factors were discussed in the previous sections.

Population and methods

Population

Persons invited for this investigation participated in the Epidemiologic Preventive Investigation Zoetermeer (EPOZ) between april 1975 and april 1978 in the Dutch town of Zoetermeer, a suburb of The Hague. Details of the EPOZ study were described elsewhere [5,6]. Two groups were invited to participate in the follow-up study. The first group, to study the natural history and determinants associated with progression of osteoarthrosis, contained all

respondents with radiologic osteoarthrosis of the hip at the time of the initial survey: the OA group. Radiographs of the hips were rated from 0-4 based on the method of Kellgren [7], a widely accepted standard for radiological osteoarthrosis. Criteria include one-sided or double-sided joint space narrowing, osteophytes, sclerosis, cysts, malformation of the femoral head or protrusio acetabuli. A candidate group of 78 men and 41 women was available, initially aged 45-65 years. This age range was chosen because no X-rays of the pelvis were available from the younger age categories. Persons of 65 years or more were not invited for two reasons; they had a relatively low response rate of 61% at the time of the first investigation compared to a response rate of 77.2% from the group we selected, and a high mortality was expected in this age group, respondents now being over 75 years of age.

To study the incidence and determinants associated with induction of osteoarthrosis of the hip (new cases) we selected 476 persons (276 men and 200 women) from the same age cohort, initially without joint space narrowing of the hip nor any of the other radiologic criteria mentioned above. The OA group comprised all respondents with OA of the hip during the first EPOZ investigation, including respondents with total hip replacement. The non-OA group comprised a sample of the respondents without OA of the hip. This group was matched for age with the OA group and is therefore not a random population sample.

Methods

Respondents of the EPOZ survey, selected to participate in the follow-up study were invited twice. First a letter was sent in which the forthcoming investigation was announced (appendices I and II), three days later a questionnaire was mailed with a covering letter (appendices III-V) to emphasize the importance of participating in this follow-up investigation. Respondents were requested to return the questionnaire by mail. An appointment for the examination in the EPOZ centre in Zoetermeer was sent together with the

questionnaire and respondents were asked to confirm this appointment on the first page of the questionnaire. Women were also invited for a second investigation on osteoporosis and fractures and received a slightly different questionnaire and a different covering letter [8]. The time between the first letter and the visit to the centre was 5 weeks, this period gave respondents enough time to return the questionnaire and make another appointment if necessary. Persons who did not respond to the first invitations were sent a third letter with the same request and if again there was no response a last attempt was made by telephone. Letters of invitation did not give specific information on the exact aim of the follow-up investigations in order to prevent recall-bias as much as possible and to prevent response bias from respondents with signs and symptoms of their joints. The investigations are summarized in table 6-1.
In the EPOZ investigation centre additional questions were asked on the daily

Table 6-1. Summary of the follow-up investigation.

1. Questionnaire		-causes of secondary osteoarthrosis -work during the last ten years -daily activities -medical history, drug use -signs and symptoms of joint disease -alcohol, coffee and smoking habits -daily intake of vitamin D and calcium
2. Radiographs of hands, knees, pelvis		
3. Joint investigation:	hip	-flexion -outward rotation in flexion -inward rotation in flexion -abduction -adduction -pain, scars
	knee	-flexion -hyperextension -pain, scars, swelling
	hands	-heberden nodules
4. Systolic and diastolic blood pressure		
5. Height, weight, skinfold thickness		

Table 6-2. Non-respons: persons who were not eligible or who did not respond. Men and women, OA and non-OA group.

	MEN		*WOMEN*		
	OA group n=78 (%)	*non-OA group n=276 (%)*	*OA group n=41 (%)*	*non-OA group n=200 (%)*	*Total n=595 (%)*
Deceased	13 (16.7)	34 (12.3)	2 (4.9)	17 (8.5)	66 (11.1)
Moved > 20 km or emigration	4 (5.1)	13 (4.7)	-	5 (2.5)	22 (3.7)
Medical reasons	-	13 (4.7)	3 (7.3)	7 (3.5)	23 (3.9)
No contact	2 (2.6)	8 (2.9)	1 (2.4)	10 (5.7)	21 (3.5)
Refusals	6 (7.7)	14 (5.1)	2 (4.9)	15 (7.5)	37 (6.2)
Miscellaneous	-	3 (1.1)	-	2 (1)	5 (0.8)
Totals	25 (32.1)	85 (30.8)	8 (19.5)	56 (28)	174 (29.2)

intake of calcium and vitamine D. All answers were checked by a physician; joints of the hands, hips and knees were examined before the questionnaire was evaluated and before the radiographs were taken; hand radiographs were made on XUD-films with alpha-2 screens, radiographs of knees and hips were made in anterior-posterior standing position on XD-films with T-16 rare earth screens. Movements of hips and knees were measured according to "The Method of Measuring and Recording of Joint Motion" of the American Academy of Orthopaedic Surgeons [9]. Height and weight were recorded and blood pressure was measured in duplicate using a random zero sphygmomanometer by a trained observer.

Choise of determinants

Fourteen possible risk factors measured during the initial examination between 1975 and 1978 have been investigated (table 6-6). The choice of these deter-

minants was based on the literature. Smoking was included as a risk factor for two reasons: firstly, it was hypothesized that the positive association between high blood pressure and osteoarthrosis of the hip was the result of vascular damage and smoking might cause such injury also and secondly, contrary to this hypothesis, smoking seems to protect against osteoarthrosis of the knee [10]. Cycling was not investigated previously, here hips are used in a non-weight bearing position and this might give some protection compared to walking and running. 'Dorp' and 'Palenstein' were introduced to adjust for the rural and urban background of the respondents.

Analysis

Continuous variables were divided in tertiles with the following cutpoints: height (meters): men 1.71 and 1.77, women 1.59 and 1.64; weight (kilogram): men 71 and 79, women 63 and 70; Quetelet's index (kg/m^2): men 23.7 and 25.8, women 23.8 and 26.4; systolic blood pressure (mmHg): men 127 and 141, women 124 and 141; diastolic blood pressure (mmHg): men 80 and 89, women 82 and 91; total serum cholesterol (mg%)[1]: men 215 and 247, women 222 and 256. Age was divided in 5-year age categories. Participants from the old village (Dorp) and the newly build parts (Palenstein) could be divided based on the different constituencies they belonged to. Calcium intake was not measured directly, however, a crude measurement was produced by combining two questions about dairy produce consumption: respondents using both milk and cheese on a daily basis were supposed to have a high calcium intake, otherwise calcium consumption was considered to be low or moderate. Occupation could be studied in men only and was divided in 3 groups, according to physical activity (chapter 5, pp. 79). In the original questionnaire two questions were asked; what is your present occupation and which of your

[1] Total serum cholesterol was measured in mg%. The conversion for mmol/l is 0.02586, e.g. 215 mg% = 5.6 mmol/l and 256 mg% = 6.6 mmol/l

Table 6-3. Baseline characteristics of categories of invited and deceased subjects.

	Age (SD)	*BMI (SD)*	*Systolic BP (SD)*	*Diastolic BP (SD)*
I. All potential				
responders n=595	56.3 (6.1)	25.2 (2.9)	137.2 (19.4)	87.0 (12.1)
men n=354	57.1 (5.9)	25.1 (2.7)	137.4 (18.4)	86.0 (11.8)
women n=241	55.1 (6.0)	25.4 (3.1)	136.9 (20.7)	88.1 (12.5)
II. With Hip OA				
1. deceased				
men n=13	59.7 (5.4)	25.6 (3.4)	149.0 (22.5)	92.6 (15.8)
women n=2	59.4	25.8	162.5	89.0
2. non-responders				
men n=12	55.1 (5.5)	25.1 (2.7)	139.5 (9.5)	92.0 (11.5)
women n=6	60.1 (6.8)	25.1 (2.5)	136.5 (31.8)	84.1 (16.5)
3. responders				
men n=53	57.5 (6.2)	25.1 (3.0)	134.0 (16.6)	82.6 (11.8)
women n=33	55.5 (6.2)	25.5 (3.8)	138.0 (23.7)	89.1 (13.8)
III. Without Hip OA				
1. deceased				
men n=34	59.7 (4.5)	24.7 (2.8)	135.6 (20.3)	83.6 (13.3)
women n=17	57.2 (5.6)	24.7 (2.8)	148.0 (25.7)	93.7 (15.4)
2. non-responders				
men n=51	57.4 (5.5)	25.3 (2.7)	138.3 (19.4)	85.5 (11.2)
women n=39	55.9 (6.3)	26.1 (3.5)	135.9 (17.4)	86.2 (12.7)
3. responders				
men n=191	56.3 (5.9)	25.0 (2.6)	137.9 (18.5)	87.5 (11.0)
women n=144	54.1 (5.7)	25.3 (2.7)	135.0 (18.7)	87.8 (11.4)

previous occupations did you practice longest. The occupation that had been done for the longest period was used in the analysis, if this question was not answered, the present occupation was used. Other indicators that could give information on the use (or abuse) of joints, like sports activities, were notavailable. Psychological factors in relation to radiologic progression were not investigated. After univariate analysis, a Mantel-Haenszel odds ratio [11] was calculated for the same variables with adjustment for age. All factors were examined individually and variables that seemed important were used during

multivariate analysis. A sensible use of logistic regression with a limited sample size forced selection of variables that showed some significance during univariate and bivariate analysis.

Results

Response

A total of 595 persons (candidate group) were selected for the follow-up investigation (table 6-2). From this group 66 persons died during the follow-up period, 23 were incapable of participating because of various medical reasons (non related to hip problems) and another 22 moved from the Zoetermeer area or emigrated. From the 484 eligible subjects, 421 or 87% participated. Characteristics of respondents, non-respondents and deceased subjects are presented in table 6-3. Not all groups were of equal age, subjects who died were older and their systolic and diastolic blood pressure was higher, except for men without OA of the hip, other characteristics did not differ significantly (table 6-3).

Progression of osteoarthrosis in the OA group

The OA group consisted of 33 women and 53 men, 25 (29%) of whom showed radiological progression during the follow-up period. Double-sided and one-sided progression was present in 8 and 17 cases respectively. Total hip replacement was performed in 7 (4 double-sided) of these 25 respondents. There were not enough respondents with progression for a separate analysis according to the location of the joint space narrowing as proposed earlier (chapter 5). Before the initial investigation 6 (1 double sided) of this 86 respondents had already been operated. Regression of radiological abnormalities was seen in 10 respondents. This regression was restricted to a decrease of sclerosis or decrease of minor joint space narrowing. Severe

Table 6-4. OA group: cases with progression of osteoarthrosis. Risk of developing progression of osteoarthrosis (actuarial method).

Initial age	*N*	*Progression*	*N/1000 person years*	*Cumulative incidence (year)*
45-49	17	6 (35%)	41	0.05
50-54	13	3 (23%)	27	0.03
55-59	31	8 (26%)	30	0.034
60-65	25	8 (32%)	37	0.044
total	86	25 (29%)	33.8	0.04

Table 6-5. Non-OA group: new cases of osteoarthrosis. Risk of developing osteoarthrosis.

Initial age	*N*	*New cases*	*N/1000 Person year*	*Cumulative incidence (year)*
45-49	85	9 (11%)	12.3	0.013
50-54	85	7 (8%)	9.8	0.010
55-59	82	6 (7%)	8.7	0.009
60-65	83	13 (16%)	18.6	0.020
total	335	35 (10.4%)		

osteoarthrosis of the hip showed no improvement.

The frequency of progression of osteoarthrosis of the hip was expressed as the cumulative incidence (CI) [12,13]. This is the proportion of respondents who develop disease progression. Because the number of cases with progression was a relatively high proportion of the total number of respondents with OA of the hip and progression of osteoarthrosis was measured at the end of the follow-up period, a correction was made for the amount of population time. The assumption was made that progression took place exactly in the middle of the follow-up period (4.3 years after the initial EPOZ survey). In formula:

$$\text{Cumulative Incidence} = I / (PT - I * FP/2)$$

Where I is the number of cases with progression of osteoarthrosis, PT is the

Table 6-6. Determinants of Osteoarthrosis of the Hip in Men and Women. OA and non-OA group.

		OA group			non-OA group			Both	
		Cases	Progression		Controls	New Cases			
		n	n	(%)	n	n	(%)	n	(%)
Age	54-59	17	7	(41)	85	9	(11)	16	(16)
	60-64	13	3	(23)	85	7	(8)	10	(10)
	65-69	23	7	(30)	64	6	(9)	13	(15)
	70-75	33	8	(24)	101	13	(13)	21	(16)
Weight	low	26	7	(27)	105	6	(6)	13	(10)
	intermediate	28	4	(14)	115	10	(9)	14	(10)
	high	32	14	(44)	115	19	(17)	33	(22)
Height	small	20	9	(45)	102	6	(6)	15	(12)
	normal	29	6	(21)	108	16	(15)	22	(16)
	tall	37	10	(27)	125	13	(10)	23	(14)
Quetelet's index	low	30	5	(17)	111	8	(7)	13	(9)
	intermediate	25	9	(36)	112	13	(12)	22	(17)
	high	31	11	(35)	112	14	(13)	25	(17)
Serum cholesterol	low	23	8	(35)	108	13	(12)	21	(16)
	intermediate	29	8	(28)	116	9	(8)	17	(12)
	high	34	9	(26)	111	13	(12)	22	(15)
Systolic BP	low	28	6	(21)	110	17	(15)	23	(17)
	intermediate	32	6	(19)	104	9	(9)	15	(11)
	high	26	13	(50)	121	9	(7)	22	(15)
Diastolic BP	low	35	7	(20)	103	15	(15)	22	(16)
	intermediate	21	8	(38)	104	8	(8)	16	(13)
	high	30	10	(33)	128	12	(9)	22	(14)
Sigarets	0	60	19	(32)	216	24	(11)	43	(16)
	1-9	12	3	(25)	29	2	(7)	5	(12)
	>9	14	3	(21)	90	9	(10)	12	(12)
Diuretics	yes	13	3	(23)	43	7	(16)	10	(18)
	no	73	22	(30)	292	28	(10)	50	(19)
Calcium Intake	moderate/low	36	9	(25)	120	11	(9)	20	(13)
	high	50	16	(32)	215	24	(11)	40	(15)
Bicycle	yes	37	8	(22)	153	20	(13)	28	(15)
	no	58	16	(28)	182	15	(8)	31	(13)
Village	yes	64	15	(23)	217	26	(12)	41	(15)
	no	22	10	(45)	109	9	(8)	19	(15)

Table 6-7. Determinants of Osteoarthrosis of the Hip in Women. OA group and non-OA group.

		OA group			non-OA group			Both	
		Cases	Progression		Controls	New Cases			
		n	n	(%)	n	n	(%)	n	(%)
Age	54-59	8	4	(50)	47	5	(11)	9	(16)
	60-64	6	3	(50)	40	4	(10)	7	(15)
	65-69	9	3	(33)	23	2	(9)	5	(16)
	70-75	10	4	(40)	24	5	(21)	9	(26)
Weight	low	13	5	(38)	43	3	(7)	8	(14)
	intermediate	11	3	(27)	51	6	(12)	9	(15)
	high	9	6	(67)	50	7	(14)	13	(22)
Height	small	9	5	(46)	40	2	(5)	7	(14)
	normal	14	3	(21)	50	8	(16)	11	(17)
	tall	10	6	(60)	54	6	(11)	12	(19)
Quetelet's index	low	12	5	(42)	47	5	(11)	10	(17)
	intermediate	10	3	(30)	47	6	(13)	9	(16)
	high	11	6	(55)	50	5	(10)	11	(18)
Serum cholesterol	low	10	4	(40)	48	6	(13)	10	(17)
	intermediate	7	4	(57)	52	4	(8)	8	(14)
	high	16	6	(38)	44	6	(14)	12	(20)
Systolic BP	low	9	2	(22)	50	10	(20)	12	(20)
	intermediate	11	4	(36)	43	3	(7)	7	(12)
	high	13	8	(62)	51	3	(6)	11	(19)
Diastolic BP	low	11	3	(27)	49	6	(12)	9	(15)
	intermediate	8	5	(63)	42	5	(12)	10	(20)
	high	14	6	(43)	53	5	(9)	11	(16)
Sigarets	0	24	10	(42)	106	13	(12)	23	(18)
	1-9	5	2	(40)	18	2	(11)	4	(17)
	>9	4	2	(50)	20	1	(5)	3	(13)
Diuretics	yes	7	2	(29)	28	4	(14)	6	(17)
	no	26	12	(46)	116	12	(10)	24	(17)
Calcium Intake	moderate/low	16	7	(44)	53	3	(6)	10	(14)
	high	17	7	(41)	91	13	(14)	20	(19)
Bicycle	yes	14	5	(36)	82	13	(16)	18	(19)
	no	18	8	(44)	62	3	(5)	11	(12)
Village	yes	22	8	(36)	95	13	(14)	21	(18)
	no	11	6	(55)	45	3	(7)	9	(16)

Table 6-8. Determinants of Osteoarthrosis of the Hip in Men. OA group and non-OA group.

		OA group			non-OA group			Both	
		Cases	Progression		Controls	New Cases			
		n	n	(%)	n	n	(%)	n	(%)
Age	54-59	9	3	(33)	38	4	(9)	7	(15)
	60-64	7	-	-	45	3	(6)	3	(6)
	65-69	14	4	(29)	41	4	(10)	8	(18)
	70-75	23	4	(17)	67	8	(12)	12	(13)
Weight	low	13	2	(15)	62	3	(5)	5	(7)
	intermediate	17	1	(6)	64	4	(6)	5	(6)
	high	23	8	(35)	65	12	(18)	20	(23)
Height	small	11	4	(36)	62	4	(6)	8	(11)
	normal	15	3	(20)	58	8	(14)	11	(15)
	tall	27	4	(15)	71	7	(10)	11	(11)
Quetelet's	low	18	-	-	64	3	(5)	3	(4)
index	intermediate	15	6	(40)	65	7	(11)	13	(16)
	high	20	5	(25)	62	9	(15)	14	(17)
Serum	low	13	4	(31)	60	7	(12)	11	(15)
cholesterol	intermediate	22	4	(19)	64	5	(8)	9	(10)
	high	18	3	(17)	67	7	(10)	10	(12)
Systolic BP	low	19	4	(21)	60	7	(12)	11	(14)
	intermediate	21	2	(10)	61	6	(10)	8	(10)
	high	13	5	(38)	70	6	(9)	11	(13)
Diastolic BP	low	24	4	(17)	54	9	(17)	13	(17)
	intermediate	13	3	(23)	62	3	(5)	6	(8)
	high	16	4	(25)	75	7	(9)	11	(12)
Occupation	light	13	1	(8)	59	4	(7)	5	(7)
	moderate	9	4	(44)	50	5	(10)	9	(15)
	heavy	31	6	(19)	82	10	(12)	16	(14)
Sigarets	0	36	9	(25)	110	11	(10)	20	(14)
	1-9	7	1	(14)	11	-	-	1	(6)
	>9	10	1	(10)	70	8	(11)	9	(11)
Diuretics	yes	6	1	(17)	15	3	(20)	4	(19)
	no	47	10	(21)	176	16	(9)	26	(12)
Calcium	moderate/low	20	2	(10)	67	8	(12)	10	(11)
Intake	high	33	9	(27)	124	11	(9)	20	(13)
Bicycle	yes	23	3	(13)	71	7	(10)	10	(11)
	no	40	8	(20)	120	12	(10)	20	(13)
Village	yes	42	7	(17)	122	13	(11)	20	(12)
	no	11	4	(36)	64	6	(9)	10	(13)

total population time and FP is the mean follow-up period in years. The mean follow-up period for the OA group was 8.6 years (SD 1.3), the ID therefore is 25/(8.6*86 - 25*(8.6/2))=0.0395/year. The percentage of cases with progression was highest in the 55-59 and 70-75 year age categories (table 6-4).

New cases in the non-OA group

The follow-up period for the non-OA group was 8.4 years (SD 1.2), the age distribution is presented in table 6-5. Osteoarthrosis grade 2, 3 or 4 according to the Standard Atlas [7] developed in 35 (10.4%) of 335 respondents with initially normal radiographs of the hips. Total hip replacement was not necessary in any of these participants. Osteoarthrosis was double sided in 12 (34%) respondents. The highest number of new cases was found in the yougest and oldest age groups. The age distribution of this group was not representative for the total population, therefore the incidence was calculated for age strata and not for the whole group. The age distribution of the population allows us to estimate the incidence of the population, however, our age-stratified group is not large enough for such calculations.

Determinants of progression

A summary of crude, unstratfied data (table 6-6, 6-7 and 6-8) shows that progression of osteoarthrosis of the hip occurrs more often in respondents with high weight, intermediate and high Quetelet's index, intermediate and high diastolic blood pressure, high systolic blood pressure, female respondents using diuretics, male respondents with high calcium intake and respondents from the urban district. Progression of osteoarthrosis was found less often in tall male respondents and respondents regularly driving a bicycle. Age-adjusted relative risks (table 6-9) gave the same pattern. A small increase was found among respondents with high calcium intake (crude relative risk 1.3, 95% CI 0.7-2.5). Most associations showed the same positive or negative direction men

Table 6-9. Relative risk estimates (95% confidence interval) of determinants from tabel 6-6.

		Age-Adjusted Relative Risk (95% CI)		
		OA group	*non-OA group*	*Both*
Weight	low	1.0	1.0	1.0
	intermediate	0.3 (0.0-3.2)	1.4 (0.7-2.8)	0.9 (0.0-39)
	high	2.4 (1.0-6.2)	2.6 (1.2-6.0)	2.5 (1.4-4.8)
Height	small	1.0		
	normal	0.3 (0.1-1.3)	2.6 (1.1-6.3)	1.3 (0.7-2.3)
	tall	0.4 (0.1-2.2)	1.7 (0.7-4.1)	1.2 (0.7-2.1)
Quetelet's index	low	1.0	1.0	1.0
	intermediate	1.8 (0.7-4.4)	1.4 (0.7-2.7)	1.5 (0.8-2.7)
	high	2.9 (1.1-7.4)	1.2 (0.7-2.2)	1.7 (0.9-3.1)
Serum cholesterol	low	1.0	1.0	1.0
	intermediate	0.9 (0.1-1.7)	0.6 (0.2-1.9)	0.8 (0.3-1.9)
	high	1.0 (0.3-2.7)	0.9 (0.0-293)	1.0 (0.0-42)
Systolic BP	low	1.0	1.0	1.0
	intermediate	0.5 (0.1-3.5)	0.5 (0.2-1.3)	0.5 (0.2-1.1)
	high	2.7 (1.1-6.8)	0.4 (0.2-1.1)	0.8 (0.4-1.8)
Diastolic BP	low	1.0	1.0	1.0
	intermediate	4.4 (1.4-13.4)	0.7 (0.2-2.4)	1.2 (0.7-2.1)
	high	2.7 (1.0-7.6)	0.8 (0.2-2.6)	1.1 (0.8-1.5)
Occupation*	light	1.0	1.0	1.0
	moderate	0.7 (0.2-3.7)	1.5 (0.7-2.9)	1.0 (0.9-1.2)
	heavy	0.5 (0.8-1.4)	1.4 (0.7-2.7)	0.9 (0.1-6.1)
Sigarets	0	1.0	1.0	1.0
	1-9	0.9 (0.2-3.7)	0.9 (0.0-120)	0.8 (0.1-5.6)
	>9	1.1 (0.8-1.4)	0.9 (0.0-204)	0.8 (0.3-2.0)
Diuretics	no	1.0	1.0	1.0
	yes	1.3 (0.7-2.5)	2.2 (1.0-4.6)	1.6 (0.8-3.0)
Calcium Intake	moderate/low	1.0	1.0	1.0
	high	1.4 (0.7-2.8)	1.1 (0.7-1.9)	1.2 (0.8-1.9)

* *men only*

and women. In men a positive association was found also with moderate and heavy physical activity (estimated from their occupation). This relation was present in the highest age group only (table 6-10), however, numbers were too

Table 6-10. Frequencies of progression and new cases of osteoarthrosis of the hip of men with occupations demanding light, moderate or heavy physical activity.

Age	*55-65*	*66-75*
I. Progression of osteoarthrosis		
Occupation mild	1/7 (14)	0/6 (0)
moderate	1/2 (50)	3/7 (43)
heavy	1/6 (17)	5/24 (21)
II. New cases of osteoarthrosis		
Occupation mild	3/27 (11)	1/31 (3)
moderate	2/22 (9)	3/26 (8)
heavy	1/30 (3)	8/51 (16)

small for multivariate analysis. High blood pressure and body mass index are related phenomena [14,15]. Table 6-11 shows the distribution of systolic bloodpressure within tertiles of Quetelt's index. The relation between osteoarthrosis and obesity and high blood pressure was separately investigated with logistic regression analysis. All other variables were considered confounders. Logistic analysis confirmed the increased risk of progression of osteoarthrosis of the hip among respondents with high blood pressure (table 6-12). Progression was also more common among respondents with a high Quetelet's index, however, the number of participants is small and 95 percent confidence limits are wide.

Determinants of new cases

New cases of osteoarthrosis of the hip were found among respondents with high weight, high Quetelet's index, low blood pressure and use of diuretics during the initial survey (table 6-6). Furthermore, more women with high calcium intake compared to low calcium intake developed osteoarthrosis of the hip (table 6-7). After adjustment for age (table 6-9) an elevated relative risk was found in respondents with high weight (relative risk 2.6, 95% CI 1.2-6.0),

Table 6-11. Progression and New Cases of Osteoarthrosis of the Hip in Relation to Hypertension and Quetelet's Index.*

Tertile of Quetelet's Index	*Tertile of Systolic Blood Pressure*	*OA group Progression n (%)*	*non-OA group New Cases n (%)*
I.	I.	1/8 (12.5)	4/38 (9.5)
	II.	2/11 (18.2)	3/35 (8.6)
	III	2/10 (20)	1/34 (2.9)
	total	5/29 (17.2)	8/111 (7.2)
II.	I.	4/12 (33.3)	6/39 (15.4)
	II.	3/12 (25)	3/36 (8.3)
	III.	2/ 2 (100)	4/37 (10.8)
	total	9/26 (34.6)	13/112 (11.6)
III.	I.	1/ 7 (12.5)	7/29 (24.1)
	II.	1/ 8 (11.1)	3/33 (9.1)
	III.	9/14 (64.3)	4/50 (8)
	total	11/31 (35.5)	14/112 (12.5)

* *Table arranged according to Lawrence [19].*

medium height (relative risk 2.6, 95% CI 1.1-6.3), and use of diuretics (relative risk 2.2, 95% CI 1.0-4.6). Respondents with hypertension were not at risk for the development of osteoarthrosis of the hip (table 6-13); on the contrary, a decreased risk was found. None of the possible confouders influenced this negative association.

Discussion

Our data confirm a strong positive association between high blood pressure and progression of osteoarthrosis of the hip, independent of obesity, age and gender. So far, no prospective studies had been executed to investigate this relation. Several earlier cross-sectional studies demonstrated this association [16], a temporal relationship was not established. The strength of the

Table 6-12. OA group: progression of osteoarthrosis of the hip. Odds ratio's estimated for second and third tertile of quetelet's index and second and third tertile of systolic blood pressure relative to the lowest tertile.

	Systolic blood pressure (2nd quintile)	*Systolic blood pressure (3rd quintile)*	*Quetelet's index (2nd quintile)*	*Quetelet's index (3rd quintile)*
Systolic blood pressure	0.85 (0.24-3.00)	3.67 (1.12-12.00)	-	-
Quetelet's index	-	-	2.54 (0.72- 8.93)	2.64 (0.79- 8.87)
Systolic blood pressure and quetelet's index	0.91 (0.25-3.37)	5.99 (1.50-23.98)	5.30 (1.21-23.30)	2.48 (0.67- 9.12)
CONFOUDERS*				
Sex	0.93 (0.24-3.54)	5.35 (1.67-22.20)	5.41 (1.20-24.33)	2.74 (0.71-10.48)
Age	1.00 (0.25-3.99)	6.13 (1.39-27.00)	5.02 (1.08-23.29)	2.79 (0.71-10.97)
use of diuretics	0.96 (0.24-3.86)	6.27 (1.40-28.10)	5.79 (1.18-28.37)	3.09 (0.76-12.58)
calcium intake	1.00 (0.24-4.09)	7.88 (1.65-37.53)	5.40 (1.08-26.96)	2.77 (0.66-11.55)
smoking	0.90 (0.21-3.92)	7.01 (1.38-35.57)	5.06 (0.93-27.60)	2.91 (0.64-13.16)

* *Logistic regression was used with cumulative inclusion of potential confounders.*

association was not always calculated and adjusment for possible confounding variables was often impossible. Furthermore, it could not be determined from cross-sectional data whether high blood pressure was associated with induction of OA of the hip, progression of OA of the hip or both. The pathogenetic mechanism to explain this finding remains puzzling, specially while the association between high blood pressure differs between progression and new cases. If accelerated arteriosclerosis was the explanation, an association between osteoarthrosis of the hip and high serum cholesterol and smoking was to be expected, however, such positive associations have not been found. Diuretics influence calcium metabolism and are often used to treat hypertension. Use of diuretics was associated with induction of OA of the hip and not with

Table 6-13. Non-OA group: new cases of osteoarthrosis of the hip. Odds ratio's estimated for second and third tertile of quetelet's index and second and third tertile of systolic blood pressure relative to their first tertiles.

	Systolic blood pressure (2nd quintile)	*Systolic blood pressure (3rd quintile)*	*Quetelet's index (2nd quintile)*	*Quetelet's index (3rd quintile)*
Systolic blood pressure only	0.52 (0.22-1.22)	0.44 (0.19-1.03)	-	-
Quetelet's index only	-	-	1.69 (0.67- 4.25)	1.84 (0.74-4.58)
Systolic blood pressure and quetelet's index	0.50 (0.21-1.18)	0.40 (0.17-0.95)	1.75 (0.69-4.43)	2.09 (0.83-5.28)
CONFOUDERS*				
Sex	0.50 (0.21-1.18)	0.40 (0.17-0.95)	1.75 (0.69-4.44)	2.09 (0.83-5.27)
Age	0.50 (0.21-1.19)	0.40 (0.16-0.92)	1.77 (0.70-4.50)	2.02 (0.80-5.13)
use of diuretics	0.51 (0.21-1.22)	0.36 (0.15-0.84)	1.76 (0.69-4.48)	1.83 (0.71-4.72)
calcium intake	0.50 (0.20-1.20)	0.36 (0.15-0.89)	1.77 (0.69-4.50)	1.86 (0.72-4.79)
smoking	0.42 (0.17-1.04)	0.34 (0.14-0.86)	1.74 (0.67-4.52)	1.89 (0.71-5.05)

* Logistic regression was used with cumulative inclusion of potential confounders.

progression as high blood pressure was. Connective tissue (collagen and proteoglycans) constitute 70% of dry weight of arterial walls. These molecules are also the major components of the extracellular matrix of articular cartilage. Changes with age in the arterial wall result in decreased compliance and a higher blood pressure. The same changes may occur in articular cartilage and hypertension and OA possibly develop simultaneously.

Furthermore, many risk factors of disease in themselves are related to ageing, e.g., elevated blood pressure and an elevated body mass index. Theoretical uncertainties exist concerning the ability of current statistical models to unravel these risk factors according to the biological reality. In our data, the strenght of the association between high blood pressure and OA of the hip altered after

adjustment for possible confounding variables, the direction of the association did not change.

Whatever the final explanation, the consistent finding of a higher proportion of persons with osteoarthrosis of the hip among respondents with high blood pressure from population surveys as well as among patients with high blood pressure argues against the possibility that this finding is only a matter of chance.

Recently, for the first time in a prospective cohort study, obesity was demonstrated to be a strong risk factor for osteoarthrosis of the knee [17], an association well known from cross-sectional data. A convincingly positive association between osteoarthrosis of the hip and overweight was not present in cross-sectional studies. Analysis of our data demonstrated a higher risk of progression of radiological osteoarthrosis of the hip among obese respondents after about 8.6 years. Whether obesity is only weakly or not at all causally related to the induction of osteoarthrosis of the hip is uncertain. In our population the risk of obese respondents to develop radiological osteoarthrosis was not increased during a follow-up period of 8.4 years. Obesity does not seem related to new development of OA but to its progression.

An occupation accompanied by heavy physical activity and use of diuretics both increased the risk of development of osteoarthrosis of the hip. Diuretics are a heterogeneous group of drugs; some increase renal tubular calcium reabsorption (thiazide diuretics) and some increase calcium excretion (furosemide, ethacrynic acid) [18]. The altered calcium metabolism might influence subchondral bone density and the development of osteoarthrosis. The importance of different diuretics could not be studied due to the limitied number of respondents with newly developed osteoarthrosis. Occupation, categorized according to the amount of physical activity and considered to increase the loading of cartilage, could only be studied in men. Many problems hamper the interpretation of the slightly elevated risk of development of new cases of osteoarthrosis of the hip. Several respondents retired after the initial survey, persons with the same occupation probably used their joints very differently and

working is only one of many possible activities in which hips are involved.

Finally, three theoretical problems regarding the results need to be addressed. Firstly, due to the limited number of respondents with progression of osteoarthrosis it was not possible to study the relation between risk factors and medial, lateral and axial joint space narrowing separately as we recommended earlier. Secondly, the prospective design of this study reduced the risk of bias, however, our follow-up was incomplete and this may have distorted the results. Respondents did know that degenerative joint disease was studied and selection of persons with symptoms may have occurred. It is uncertain whether this influenced the associations between osteoarthrosis and the risk factors we studied. Thirdly, our investigation is an observational study and not an intervention study. Therefore some caution is needed regarding the interpretation of the value of the associations, specially in relation to possibilities of prevention. Not one single investigation has proven that loss of weight or lowering high blood pressure is beneficial.

In conclusion, both hypertension and obesity are associated with progression of osteoarthrosis of the hip. Although tempting, it cannot be concluded that weight loss is effective to prevent progression of osteoarthrosis. New development of osteoarthrosis was found more often among male respondents with a heavy occupation and use of diuretics. Overweight and hypertension were not associated with new development of osteoarthrosis of the hip. The induction and progression (or promotion) of osteoarthrosis of the hip have different determinants. The importance of these findings needs further study.

Summary of the chapter

To study determinants of incidence and progression of radiological osteoarthrosis of the hip a prospective follow-up study was executed between 1975 and 1986 among 86 persons with OA of the hip and 335 persons with normal hip joints. Progression was found in 25/86 (29%) of the OA group and new cases were detected in 35/335 (10,4%) of the group with initially normal hip

joints. Progression was associated with obesity (age adjusted relative risk 2.9, 95% confidence limits 1.1-7.4) and high blood pressure (age adjusted relative risk 2.7, 95% confidence limts 1.1-6.8). New cases of OA of the hip were mainly found among men with heavy occupation and respondents using diuretics.

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CHAPTER 7

PAIN AND LIMITATION OF MOVEMENT OF THE HIP JOINT

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Introduction

The importance of osteoarthrosis (OA), being a non-lethal disease, is determined by the discomfort induced by the destruction of joints. OA of the hip is feared for its grave pain, the major reason for surgical treatment [1]. The second major problem requiring treatment is limitation of movement. Pain and limitation of movement are associated with radiological OA, the strength of this associa-tion is strongly dependent on the population under investigation. Pain is also related to body mass index, obese persons have more often knee pain as well as hip pain [2]. To determine the value of several signs and symptoms in relation to radiological findings we investigated limitation of movement, self reported pain and pain during investigation in 421 respondents from the EPOZ popula-tion survey.

Materials and methods

The present investigation is based on data about OA collected between 1975 - 1978 and 1985 - 1986 in Zoetermeer. Details of this population survey are described in the previous chapter [3]. In short, a questionnaire was filled in and respondents were asked if hip pain was present at the moment they filled in this questionnaire. Radiographs of the pelvis were made in standing antero-posterior position. A crude estimate of limitation of movement was made and recorded present if respondents showed more than 20% limitation of flexion, rotation or abduction. The follow-up investigation was held between June 1985 and March 1986. We enrolled all respondents with OA of the hip and a selection of respondents with normal radiographs at baseline. Follow-up consisted of 86 persons with OA of the hip and 335 persons with normal hips. Respondents were asked if they suffered from hip pain or pain in the upper leg, lower back, buttocks, knee or groin. Furthermore, several questions were asked about pain during walking, use of a stick for walking and stiffness (appendix 5). Clinical investigation of the hip and knee was performed in all

respondents and it was recorded whether movement of the hip was painful. Joint motion was measured according to the method advised by the American Academy of Orthopedic Surgeons [4], using a goniometer. The following movements were recorded (average ranges between brackets): flexion (0-115 degrees), inward rotation in flexion (0-45 degrees), outward rotation in flexion (0-45 degrees), abduction (0-50) and adduction (0-30).

Results

Limitation of movement during the initial survey (1975-1978) was found more often among respondents with OA compared to respondents with normal radiographs of the pelvis, 28/125 (22%) versus 27/717 (4%) of all hips (table 7-1A). Differences between self reported pain were very small and occurred in 8% (10/125) of the abnormal hips and 6.7% (48/717) of all normal hips (table 7-1B). Progression of OA was found more often among respondents with

Table 7-1A. Limitation of function measured during the initial EPOZ survey and subsequent progression of osteoarthrosis of the hip (left and right).

	limitation of function (1975-78)		*progression (1985-86)*	*N (%)*
ROA +	yes	28	yes	6 (21%)
			no	22 (79%)
	no	97	yes	10 (10%)
			no	87 (90%)
ROA -	yes	27	yes	5 (19%)
			no	22 (81%)
	no	690	yes	47 (7%)
			no	643 (93%)

ROA: radiological osteoarthrosis during the initial survey.

limitation of movement (21% versus 10%) as well as among respondents who developed OA during the follow-up period (19% versus 7%). The prevalence of hip pain, present at the moment of the first EPOZ investigation, did not differ significantly between respondents with and without progression (20% (2/8) versus 14% (14/101)) nor between respondents with newly developed OA (4% versus 7%). So, contrary to pain, limitation of movement preceded both progression and new development of OA.

Similar relations were found regarding pain, limitation of movement and radiological OA during the second part of the investigation. The prevalence of limitation of movement depends on the values considered abnormal. Figure 1 demonstrates the wide range of movements found present in the normal population and an increase of radiological abnormalities with decreasing mobility. It was not possible to use the average range accepted by the American Academy of Orthopedic Surgeons, hardley any of our respondents satisfied the criteria. The line between normal and abnormal was drawn if more

Table 7-1B. Self reported pain during the initial EPOZ survey and subsequent progression of osteoarthrosis of the hip (left and right).

	self reported pain (1975-78)		*progression (1985-86)*	*N (%)*
ROA +	yes	10	yes	2 (20%)
			no	8 (80%)
	no	115	yes	14 (14%)
			no	101 (86%)
ROA -	yes	48	yes	2 (4%)
			no	46 (96%)
	no	669	yes	50 (7%)
			no	619 (93%)

ROA: radiological osteoarthrosis during the initial survey.

Table 7-2. Sensitivity, specificity, predictive values and likelihood ratio's of pain and limitation of movement of the hip.

	Sensitivity	*Specificity*	*Predictive value*		*Likelihood Ratio*	
			test +	*test -*	*test +*	*test -*
pain	11.0	94.1	32.1	80.0	1.86	0.95
flexion						
≤ 95°	27.2	91.5	54.3	83.6	3.02	0.80
pain -	22.2	94.5	49.2	83.6	4.04	0.82
pain +	66.1	89.5	75.0	85.0	6.30	0.38
endorotation						
≤ 15°	83.3	38.4	25.6	90.1	1.35	0.44
pain -	82.6	37.0	23.9	89.9	1.31	0.47
pain +	88.9	34.2	39.0	86.7	1.35	0.32
exorotation						
≤ 20°	48.5	84.9	44.1	86.6	3.21	0.61
pain -	43.3	85.6	41.5	86.5	3.00	0.66
pain +	83.3	65.8	59.5	89.3	2.37	0.25
abduction						
≤ 25°	30.4	93.6	54.4	84.2	4.75	0.75
pain -	25.7	93.8	50.0	84.0	4.15	0.79
pain +	70.6	89.5	75.0	91.9	6.73	0.33
adduction						
≤ 25°	44.1	79.4	35.2	84.9	2.14	0.70
pain -	40.3	79.3	31.9	84.7	1.95	0.75
pain +	76.5	81.6	65.0	88.6	4.16	0.29

than 20% of the respondents had an abnormal radiograph of the hip (figure 1).

For most movements, similarities between men and women were remarkable. Pain and limitation of movement can be considered tests and the radiograph of the pelvis as the golden standard of presence or absence of disease. Sensitivity, specificity, predictive values and likelihood ratio's of these tests (table 7-2) demonstrate a low sensitivity of pain, limited flexion, exorotation, abduction and adduction. These values increase if a combination of pain and limitation of one of these movements is present. The same holds for the other parameters of the tests. The highest prediction of radiological OA results from a combination of pain with limited flexion or limited abduction (predictive value of a positive test 75%). The different directions of limitation of movement were

Table 7-3. Limitation of movement (number of directions) and osteoarthrosis (OA) of the hip (A) and limitation of movement according to pain and osteoarthrosis of the hip (B).

7-3A.

	Limitation of movement (number of directions)					
	0	1	2	3	4	5
OA present	39 (23)	35 (20)	40 (23)	19 (11)	28 (16)	12 (7)
OA absent	250 (38)	241 (37)	94 (14)	48 (7)	20 (3)	6 (1)

7-3B.

	without pain		*with pain*	
Limitation of movement (number of directions)	*0-2*	*3-5*	*0-2*	*3-5*
OA present	111 (64)	44 (25)	3 (2)	15 (9)
OA absent	553 (84)	68 (10)	32 (5)	6 (1)

combined, the result being a higher prevalence of limitation of movement, much higher than the prevalence of pain during investigation, in respondents with radiological OA (table 7-3). Three or more directions of limited movement were found in 34% of respondents with OA compared to 11% in respondents with normal hips. Pain without limitation of movement (no more than 2 directions) occurred in only 2% of all respondents with radiological OA and in 5% of radiologically normal hips. Pain in combination with limitation of movement was present in 15/21 (71%) of respondents with radiological OA.

The frequencies of self reported pain, stiffness and diminished walking distance are summarized in table 7-4. Hip pain and pain located in the upper leg occurred more often in respondents with radiological OA of the hip, specially in respondents with a high Quetelet's index. Knee pain and low back pain occurred more often in the obese, independent of radiological OA of the hip. Climbing stairs (17% versus 9%), using a stick for walking (17% versus 9%)

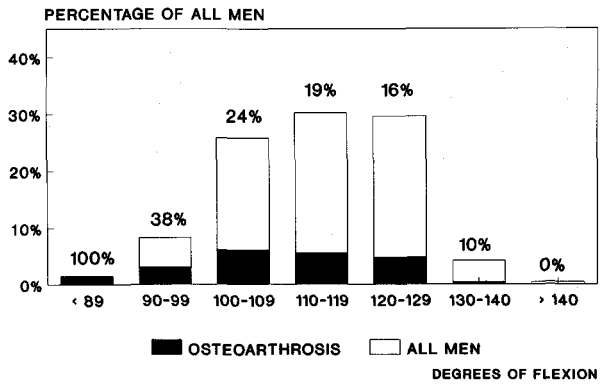
Table 7-4. Symptoms in normal and obese respondents with and without osteoarthrosis of the hip.

Quetelet's index:	*1th and 2nd tertile*		*3rd tertile*	
Radiological OA:	*Present*	*Absent*	*Present*	*Absent*
	N=109	*N=447*	*N=62*	*N=220*
Pain in hip*	19 (17)	47 (11)	15 (24)	25 (11)
Pain in upper leg*	12 (11)	27 (6)	12 (19)	16 (7)
Pain in knee*	19 (17)	77 (17)	17 (27)	59 (27)
Pain in buttock*	9 (8)	26 (6)	7 (11)	14 (6)
Pain in groin*	11 (10)	18 (4)	4 (6)	10 (5)
	N=75	N=205	N=41	N=100
Pain in lower back	17 (23)	52 (25)	14 (34)	36 (36)
Pain climbing stairs	7 (9)	9 (4)	7 (17)	6 (6)
Pain while rising from a chair	11 (15)	14 (7)	9 (22)	7 (7)
Stiffness rising from a chair	14 (19)	30 (15)	16 (39)	12 (12)
Pain during walking	21 (28)	24 (12)	12 (29)	15 (15)
Maximum walking distance: < 500 m	10 (13)	17 (8)	13 (32)	8 (8)
500 m - 5 km	8 (11)	43 (21)	8 (20)	24 (24)
> 5 km	57 (76)	145 (71)	20 (49)	68 (68)
Morning stiffness	24 (32)	63 (31)	16 (39)	35 (35)
Using a stick for walking	7 (9)	6 (3)	7 (17)	3 (3)

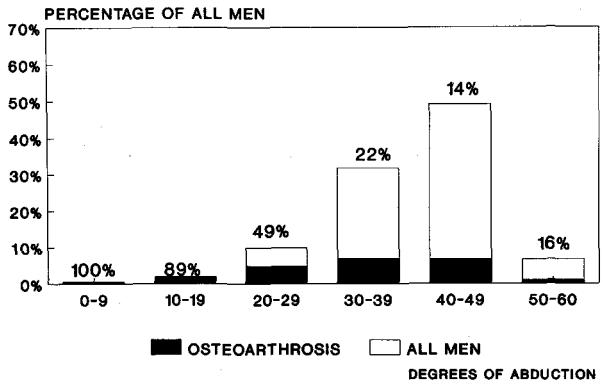
* left and right side added.

and stiffness while rising from a chair (39% versus 19%) were found more often in obese respondents with radiological OA of the hips.

MEN
FLEXION



ABDUCTION



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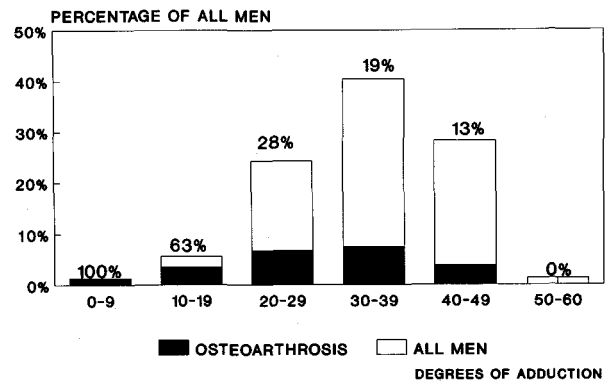


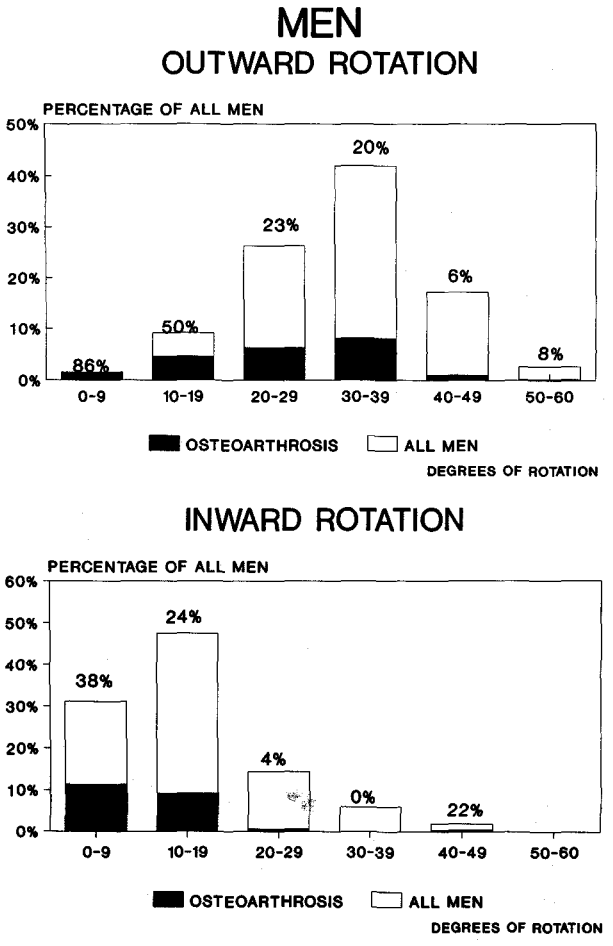
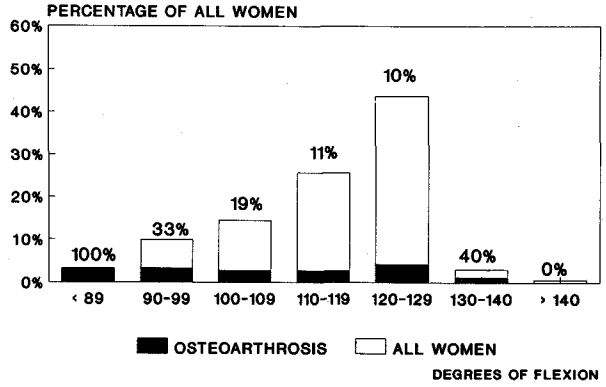
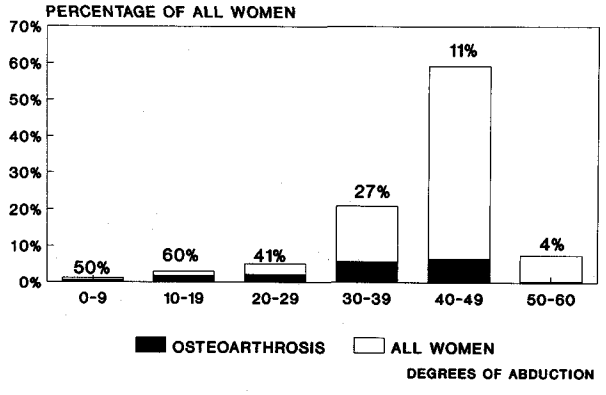


Figure 7-1A. Flexion, abduction, adduction, outward rotation and inward rotation of the hip in men (EPOZ population survey 1985-86).

WOMEN
FLEXION



ABDUCTION



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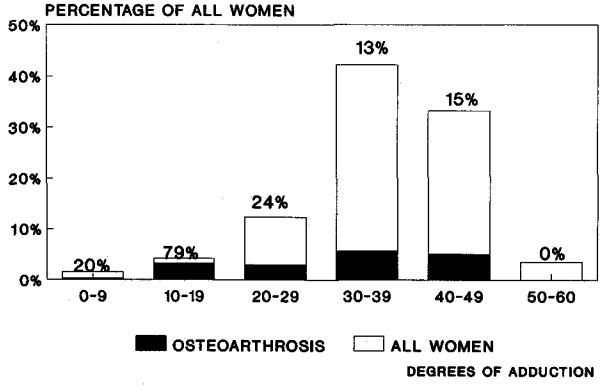

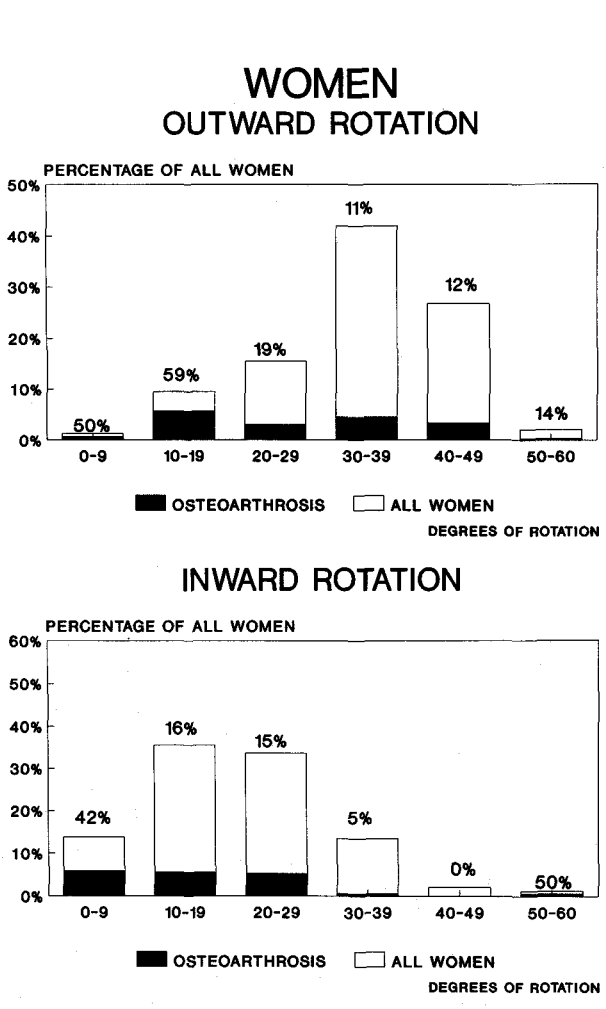

Figure 7-1B. Flexion, abduction, adduction, outward rotation and inward rotation of the hip in women (EPOZ population survey 1985-86).

Discussion

Limitation of movement preceded both progression and new development of OA of the hip, contrary to hip pain that did not precede either progression or new cases of OA. It is possible that limitation of movement is an early symptom of OA, appearing before radiological abnormalities are visible. It is also possible that limitation of movement is a cause of OA. Diminished mobility, rigid joints, could act upon load bearing in an unfavourable manner. The opposite situation, a high joint laxity was found to be associated with OA of the small joints of the hands [5]. Any disturbance of the normal range of movement of joints may even-tually be unfavouable, limitation being the most important determinant for OA of the hip.

It is difficult to decide, if not impossible, which range of movement should be considered normal (or ideal). Receiver operating characteristics (ROC) curves [6] may be of help to find the optimal dividing line between normal and abnormal and be of help to estimate a reasonable prediction of an abnormal radiograph from clinical findings. However, the wide distribution of OA within the range of movement (low sensitivity and low specificity) makes it impossible to construct a ROC curve that is of great help. Radiographs are not neccesary if only minor limitation is present and the patient has no pain. The combination of pain and limitation of movement gives a reasonable prediction of radiological OA, specially while the prevalence of OA is low compared to rheumatologic and orthopedic outpatient clinics where the predictive value of a combination of these findings will be much higher.

Respondents with radiological OA did have more pain, stiffness and mobility problems, specially the ones with a high body mass index. Pain, stiffness and a diminished walking distance have many possible causes, degenerative joint disease of the hip only being one of these. It is remarkable that a high Quetelet's index is associated strongly with joint pain [7], knee pain more than hip pain. Additional mechanical stress resulting from obesity was suggested to be the principal reason for this association. Experimental investigation to find

the biological explanation are lacking and many questions remain. Respondents with radiological OA suffered more often from pain, stiffnes and did more often use a stick for walking.

In conclusion, OA of the hip is a disease that causes much minor and major disability. Our findings suggest that limitation of movement is important to predict the presence of radiological OA of the hip and limitation of movement, preceding radiological abnormalities, is possibly an important cause of OA. Pain, although the most important reason for treatment is only in combination with limitation of flexion or abduction associated with radiological OA.

Summary of the chapter

Limitation of movement and pain are the most troublesome symptoms of OA of the hip. Limitation of movement was associated with progression of OA; 21% of the respondents with radiological OA and limitation of movement showed progression compared to 10% progression of the respondents with radiological OA without limitation of movement. Pain did not more often precede progression. New cases of radiological OA were also found more often among respondent with limitation of movement: 19% versus 7%. During the follow-up we measured limitation of movement in several directions; the frequency of radiological OA was highest in the lowest ranges of movement, there was however, considerable overlap. Limitation of movement was much stronger associated with radiological OA than pain of the hip. All signs and symptoms occurred more often in obese persons, independent of radiological OA.

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CHAPTER 8

EPIDEMIOLOGY AND JOINTS: A JOINT VENTURE FOR THE FUTURE OF JOINTS.

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8.1 Introduction

At the end of this study of the etiology of osteoarthrosis (OA) we conclude with some embarrassment that OA remains an enigma. Fortunately, treatment of OA of the hip is way ahead of our understanding of the pathogenesis of this condition and consequently prevention. Total hip replacement has become a common medical procedure. The absolute number of total hip replacements in the Netherlands increased from 5378 in 1977 to 10.441 in 1985. This increase is still present after adjustment for age [1]. OA of the hip seems to become a nuisance and at present the only prospect is a further increase in the number of total hip replacements. The question arises which medical disciplines are capable of providing us with answers about the etiology of OA and, in particular, whether epidemiological population studies should go on and which problems could be resolved by such studies.

8.2 The theoretical advantage of research directed towards prevention

In order to prevent the development and the end-stage of a disease it is desirable to detect this disease and its determinants as early as possible. OA remains subclinical until far advanced. Epidemiologic population studies, like the EPOZ study [2], can detect osteoarthrosis in an early stage. The importance of this fact becomes clear when related to the paradigm of the compression of morbidity proposed by James F. Fries [3,4]. This paradigm states that the life span of the human species is finite and that the onset of chronic disease is delayed relatively easily. The average period of diminished vigour will therefore finally decrease. Figure 1 and 2 visualize this theory. Figure 1 demonstrates rectangularizing survival curves. The same curves can be drawn for morbidity if adequate preventive measures are possible. Another schematic representation (figure 2) of the natural course of a chronic disease with and without preventive measures illustrates the possible postponement of symptomatic disease.

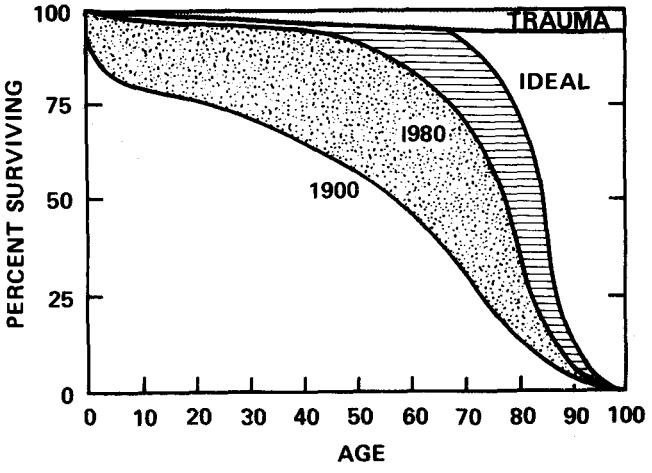

Figure 1. The increasingly rectangular survival curve. Elimination of premature death results in a sharp downslope to the natural life span. (From [3]; reprinted with permission.)

The first part of this paradigm is a matter of debate; mathematical schemes and biological in vitro experiments argue in favour of a finite human life span with an average life expectancy of approximately 85 years [5]. However, observational studies measure an ongoing increase in human life span [6]. Recently Stout and Crawford demonstrated that life expectancy became longer and terminal dependency was postponed among 24.117 elderly people [7]. However, the net result of these two effects was that, contrary to the hypothesis of J.W. Fries, the duration of terminal dependency increased. If life expectation continues to increase and simultaneously the prevention of chronic disease trails behind, we can call this 'the failure of success' with Gruenberg [8].

The second part of the paradigm - the onset of chronic diseases can be delayed relatively easily - is attractive because it is promising. Several examples are available. Lung cancer may be prevented by cessation of cigarette smoking. More than half of the decline in ischemic heart disease mortality can be attributed to changes in lifestyle, particularly to reductions in serum cholesterol and cigarette smoking [9]. However, while risk factors have been studied

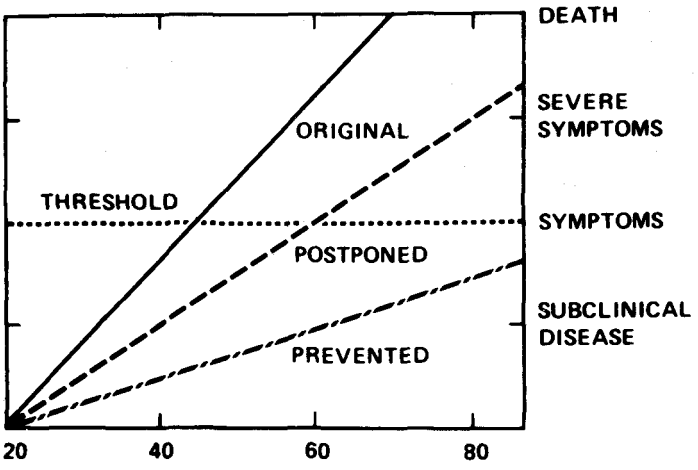

Figure 2. Hypothetical development of a chronic illness. The vertical axis could represent degeneration of articular cartilage. The different slopes represent either different individuals or the same individual operating under different sets of risk factors (From [13]; reprinted with permission.)

thoroughly in lung cancer and ischemic heart disease, the study of risk factors for osteoarthrosis is still in its infancy. In relation to OA it can even be argued that one can better speak of 'risk indicators' than of 'risk factors'.
On the clinical side research has focused on total hip replacement and on drugs to relief pain from OA. The study of human cartilage and the changes that occur in osteoarthritis and 'normal' ageing are a second line of clinical investigation. The importance of this reseach is beyond doubt, the possibilities for prevention, however, are small.

8.3 Future research

From the present investigation it is clear that lifestyle habits and antropometric variables are associated with the development and progression of osteoarthrosis of the hip. However, before we can even think of prevention it is imperative that our results be confirmed by other investigations and it is

necessary to assess whether the same associations are present between the risk indicators we found and osteoarthrosis of other joints. Furthermore, we studied a limited number of possible risk factors (in analogy with cardiovacular risk factors). More relevant determinants might be brought forward by new 'fishing expeditions'.

In 1986 the Workshop on Etiopathogenesis of Osteoarthritis presented a list of recommendations for further research [10]. In addition to this impressive amount of proposals (*chapter* 1, page 12) a number of promising lines of investigation can be brought forward. Hereditary factors are scarcely studied. Diseases occurring in very old age are assumed to be due to causes acting more or less independently of the genotype [11]. However, as OA occurrs in very young persons, poligenetic or even monogenetic causes are possible. Several provocative and intriguing associations have not been thoroughly investigated. As osteoporosis is said to be negatively associated with OA, a low bone mass may protect against progression of cartilage damage. Large scale treatment of post menopausal women with estrogens may then lead to a further increase in the incidence of severe OA in accordance with the principle of 'a low risk for the individual and a large potential risk for the population' [12]. On the other hand, if blood pressure and obesity are true risk factors and not merely risk indicators, a decrease in the incidence of OA is to be expected since many individuals are treated for hypertension and being fat is unpopular. Further investigation of another finding from our study merits consideration. In a number of cases, limitation of movement precedes the development of OA and it predicts the progression of OA. It is uncertain whether limitation of movement is part of the causal pathway or a *mere* consequence of OA. An intervention study to evaluate this possible route of prevention seems justified. Finally there is the puzzling relation with obesity. Cross-sectional data do not argue in favour of an association, nevertheless, this follow-up study found obesity to be an important risk indicator. Furthermore, the strong positive association between obesity and OA of the knee justifies an intervention study here too. The most favourable type of investigation to evaluate whether changes

in lifestyle, weight reduction or lowering blood pressure are beneficial for the prevention of OA are carefully designed prospective epidemiologic intervention studies.

When the hypothesis of Fries is correct and postponement of chronic disease is possible, the scientific responsibility for the society requires to allocate more time and effort to the study of risk factors for disease which prevails at old age. A priority of concern should then be the discovery and control of the causes of osteoarthrosis.

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SAMENVATTING

Dit proefschrift bevat twee afzonderlijke delen. Hoofdstukken 2 en 3 vormen het eerste deel en omvatten de beschrijving en een analyse van de beschikbare EPOZ gegevens over gewrichtsslijtage (artrose) en de determinanten daarvan. Deze gegevens werden verzameld tijdens het Epidemiologisch Preventief Onderzoek Zoetermeer (EPOZ) dat plaats vond tussen april 1975 en april 1978. Het tweede deel is een vervolgonderzoek bij 421 deelnemers uit het eerste onderzoek naar determinanten van zowel het ontstaan als de progressie van artrose van de heup.

Tijdens het EPOZ, een dwarsdoorsnede onderzoek, werden roentgenfoto's gemaakt van de handen, de cervicale wervelzuil en de voorvoeten van 3109 mannen en 3476 vrouwen van 19 jaar en ouder. Bovendien werden de lumbale wervelzuil, het bekken en de knieen gefotografeerd van alle deelnemers van 45 jaar en ouder. Schouderfoto's werden alleen tijdens het laatste onderzoeksjaar vervaardigd. In totaal zijn van 22 gewrichtsgroepen foto's gemaakt; de grote gewrichten werden apart beoordeeld voor links en rechts.

De prevalentie van artrose, onderscheiden in milde en ernstige vormen is het onderwerp van het tweede hoofdstuk. De frequentie van radiologische artrose blijkt zeer hoog. Met name degeneratieve afwijkingen van de tussenwervelschijven van de nek en de lendenwervels, artrose van de distale interfalangeale gewrichten en de metacarpofalangeale gewrichten van de handen en het eerste metatarsale gewricht van de voeten is boven het vijftigste levensjaar vaker regel dan uitzondering. Artrose werd iets vaker gevonden bij vrouwen dan bij mannen, met uitzondering van de knieen en heupen die bij vrouwen, met name op hoge leeftijd, zeer veel vaker bleken te zijn aangedaan. Vergelijking met soortgelijk onderzoek in andere populaties (o.a. eskimo's, japanners, afrikanen en indianen) laat niveauverschillen tussen de populaties zien met een opvallend gelijke hellingshoek tegen de leeftijd. Er is een aantal verklaringen denkbaar voor de verschillen tussen de populaties. Een deel van het verschil is waarschijnlijk reeel. De verschillen kunnen echter ook worden verklaard door

systematische verschillen in de beoordeling van foto's door verschillende onderzoekers (interobservariatie), verschillen in genetische aanleg en verschillen in de frequentie van voorkomen van risicofactoren tussen de populaties.

Een van de mogelijke risicofactoren voor het ontstaan van gewrichtslijtage is overgewicht (hoofdstuk 3). In eerdere onderzoeken werden tegenstrijdige antwoorden gevonden op de vraag of artrose met overgewicht is geassocieerd en zo ja, volgens welk biologisch mechanisme de slijtage van het gewricht tot stand zou kunnen komen. Theoretisch is het mogelijk dat het extra gewicht door mechanische invloeden oorzaak is van een beschadiging van het kraakbeen; ook zijn er aanwijzingen dat vetweefsel via hormonale of metabole veranderingen meer artrose veroorzaakt; voorts kan overgewicht geassocieerd zijn met een andere (onbekende) oorzaak van artrose en tenslotte kan overgewicht door een samenspel van deze mechanismen tot meer artrose leiden. Uit ons onderzoek is gebleken dat artrose van een groot aantal gewrichten sterk met overgewicht was geassocieerd. In de Zoetermeerse populatie bleken vooral de gewrichten waarin zeer vaak artrotische afwijkingen werden gevonden (o.a. de distale gewrichten van de vingers en de knieen) geassocieerd te zijn met een hoog lichaamsgewicht. In tegenstelling tot het kniegewricht was artrose van de heup niet met overgewicht geassocieerd. Deze bevindingen pleiten meer voor een metabole oorzaak dan voor een louter mechanistische.

Het heupgewricht is een kogelgewricht bestaande uit een kom (acetabulum) en een kop waarvan de bovenzijde het gewichtsdragende deel uitmaakt. Op een voorachterwaartse foto van het bekken kan artrose van de heup worden ingedeeld op grond van de lokalisatie van de gewrichtspleetversmalling: lateraal, mediaal en axiaal (hoofdstuk 4). De Amerikaanse Rheumatologen Vereniging (ARA) heeft voorgesteld deze indeling voor klassificatie doeleinden te gebruiken. Tot nu toe was niet duidelijk of de verschillende radiologische lokalisaties berusten op verschillende oorzaken van artrose. Beneden de 55 jaar komt met name het laterale kraakbeenverlies van de heup frequenter voor bij mannen dan bij vrouwen. Versmalling van de mediale gewrichtsruimte komt vaker voor bij vrouwen. Axiaal of circulair kraakbeenverlies wordt het meest gezien op

hoge leeftijd bij zowel mannen als vrouwen.

Geen van de drie vormen van gewrichtspleetver-smalling was geassocieerd met overgewicht (hoofdstuk 5). Mediale versmalling kwam vooral voor in combinatie met hoge bloeddruk en bij mannen was mediale versmalling tevens sterk geassocieerd met zwaar werk. Een plausibele biologische verklaring voor de associatie met hoge bloeddruk is op dit moment niet aanwezig. Een van de mogelijke verklaringen voor deze bevinding zou kunnen zijn dat in de arteriele vaatwand, waar hetzelfde steunweefsel wordt gevonden als in het kraakbeen, veranderingen van het steunweefsel de soepelheid van het vat verminderen. Dezelfde afwijkingen in het kraakbeen zouden gewrichtspleetversmalling kunnen veroorzaken. Het ontbreken van een associatie met overgewicht en de gevonden associatie met zware arbeid kan worden verklaard doordat zware arbeid een ongunstiger mechanische belasting van het heupgewricht veroorzaakt dan gewicht alleen.

Het vervolgonderzoek vond plaats in 1985-86 (hoofdstuk 6). Twee groepen respondenten uit het eerste onderzoek werden uitgenodigd: alle mannen en vrouwen met artrose van de heup (86 respondenten, de OA groep) en een vier maal zo groot aantal met normale heupen (335 respondenten, de niet-OA groep). Alle deelnemers waren 45-65 jaar oud tijdens het eerste onderzoek, de vervolgperiode bedroeg bijna 9 jaar. Het doel van het onderzoek bij de OA groep was na te gaan hoe vaak progressie van artrose van de heup optreedt, wat de kenmerken zijn van personen bij wie progressie optreedt vergeleken met personen bij wie de afwijkingen stabiel bleven. Tevens werd nagegaan hoe vaak klachten voorkomen die kunnen worden toegeschreven aan heupafwijkingen. Alle deelnemers vulden hiertoe een vragenlijst in, de heupen werden onderzocht en er werd een voorachterwaartse staande bekkenfoto gemaakt. Bij de niet-OA groep werd onderzocht bij wie nieuwe artrose is ontstaan tijdens de vervolgperiode; waarin deze mensen eventueel verschilden van de mensen met ongewijzigd normale heupen en in deze groep werd eveneens nagegaan hoe de relatie was tussen klachten, symptomen en radiologische afwijkingen.

Van de OA groep bleken 7 van de 86 mensen een heupoperatie ('kunstheup')

te hebben ondergaan. Nog eens 18 anderen vertoonden toename van de reeds bestaande afwijkingen. De jaarlijkse toename van afwijkingen in de OA groep bedroeg daarmee 4%. Binnen de niet-OA groep ontstond bij 35 van de 335 respondenten artrose van de heup. Het aantal mensen met een nieuw ontstane artrose van de heup bedroeg 1,3% per jaar.

Ook in het vervolgonderzoek bleek er een verband met hoge bloeddruk. Het relatief risico op toename van bestaande afwijkingen was in de groep met een hoge bloeddruk 2,7 (95% betrouwbaarheidsinterval 1,1-6.8). Bovendien bleek dat progressie vaker voorkwam bij mensen met een relatief hoog lichaamsgewicht (relatief risico 2.9, 95% betrouwbaarheidsinterval 1,1-7,4). Het beroep leek geen rol te spelen. De deelnemers met normale heupen die artrose ontwikkelden onderscheidden zich door meer gebruik van diuretica en door een hoger gewicht dan de groep met ongewijzigd normale heupfoto's. In tegenstelling tot de groep met progressie van reeds bestaande afwijkingen hadden de deelnemers uit de niet-OA groep met nieuw ontstane artrose een lagere bloeddruk dan de mensen zonder nieuwe afwijkingen op de heupfoto. Een verklaring voor deze bevindingen is met de voorhanden zijnde onderzoeksgegevens niet goed te geven. Met enige voorzichtigheid kan worden geconcludeerd dat hoge bloeddruk al dan niet oorzakelijk gerelateerd is aan progressie van artrose en dat nieuw ontstane artrose vooral vaker voorkomt bij mensen die diuretica gebruiken en een lage bloeddruk hebben. In tegenstelling tot de bevindingen van het dwarsdoorsnede onderzoek bleek overgewicht zowel met progressie als met nieuw ontstaan van artrose te zijn geassocieerd. Hoofdstuk 7 beschrijft de relatie tussen het voorkomen van klachten en radiologische afwijkingen en bestaat uit twee delen. Het eerste deel is een onderzoek naar de relatie tussen klachten en bewegingsbeperking tijdens het eerste onderzoek en beloop van de radiologische afwijkingen tijdens het vervolgonderzoek. Het tweede deel is een analyse van het voorkomen van bewegingsbeperking en pijn tijdens het vervolgonderzoek.

In tegenstelling tot bewegingsbeperking bleek pijn van het heupgewricht de progressie van artrose niet te voorspellen. Heupen met een beperkte bewege-

lijkheid vertoonden toename van afwijkingen of nieuwe afwijkingen in 11 van de 55 gevallen (20%) terwijl heupen zonder beperking slechts bij 47 van de 797 (6%) een radiologische verslechtering lieten zien. Pijnlijke heupen vertoonden in 8% en niet pijnlijke heupen in 6.7% een toename van afwijkingen.

Tijdens het vervolgonderzoek werd nagegaan wat de waarde van fysisch diagnostische verschijnselen was bij het voorspellen van radiologische afwijkingen. De combinatie van pijn met een beperkte flexie, abductie of adductie leverde de beste voorspelling. Tenslotte bleek er een opvallend sterke relatie tussen de aanwezigheid van klachten en overgewicht. Dikke mensen hadden, onafhankelijk van de radiologische afwijkingen veel vaker pijn, gebruiken vaker een wandelstok en hadden een veel beperkter loopafstand.

Het laatste hoofdstuk bespreekt de noodzaak en mogelijkheden van populatie onderzoek naar oorzaken en preventie van OA. Een toenemend aantal mensen bereikt een hoge tot zeer hoge leeftijd, het aantal eindstadia van chronische ziekten neemt daardoor aanzienlijk toe. Gezien de gunstige resultaten van de preventie van een aantal chronische ziekten is het alleszinds redelijk meer energie te investeren in onderzoek naar mogelijke preventie van artrose.

ERASMUS UNIVERSITEIT ROTTERDAM

APPENDIX I: EERSTE UITNODIGING AAN DE RESPONDENTEN

naam
adres
woonplaats

Rotterdam, 13 mei 1985

Geachte Heer/Mevrouw,

Een aantal jaren geleden heeft u uw medewerking verleend aan het grote bevolkingsonderzoek EPOZ uitgaande van de afdeling Epidemiologie van de Erasmus Universiteit te Rotterdam onder leiding van Prof. Dr. H.A. Valkenburg. Een belangrijk onderdeel was het onderzoek naar reumatische klachten. Dit onderzoek heeft ons veel nieuwe informatie verschaft over gewrichtspijn en slijtageklachten. Nu, na ongeveer tien jaar willen we nagaan hoe het in de afgelopen tijd met uw gewrichten is gegaan. In het byzonder zijn wij geinteresseerd in slijtageverschijnselen van de heupen en knieen. We verwachten door dit vervolgonderzoek verdere aanwijzingen te krijgen over de oorzaak van slijtage verschijnselen van de gewrichten en de oorzaken van pijnlijke gewrichten. Met deze kennis kan dan in de toekomst misschien voorkomen worden dat een sommige mensen deze klachten en afwijkingen op latere leeftijd eveneens krijgen.

U krijgt over enkele dagen een vragenlijst thuisgestuurd. Deze vragenlijst kunt U thuis invullen en in de retourenvelop (postzegel hoeft niet!) aan ons terugzenden. Tevens willen wij u vragen naar het EPOZ centrum in Zoetermeer te komen volgens afspraak. Deze afspraak sturen wij met de vragenlijst mee. Dhr. van Saase, arts met reumatologische ervaring, zal daar de vragenlijst met u doornemen, opnieuw uw gewrichten onderzoeken, er zullen opnieuw enkele foto's worden gemaakt en uw bloeddruk zal worden gemeten. De vragenlijst is nogal uitgebreid, maar niet moeilijk in te vullen. Het onderzoek in het centrum duurt ongeveer een uur.

Wij hopen dat u aan dit voor het reumaonderzoek belangrijke na-onderzoek wilt meedoen.

Bij voorbaat dank, mede namens Prof. Dr. H.A. Valkenburg,

met vriendelijke groeten,

J.L.C.M. van Saase, arts

APPENDIX II: TRANSLATION OF FIRST LETTER OF INVITATION

Dear Sir/Madam,

Some years ago you participated in the large population survey EPOZ, organized by the department of Epidemiology from the Erasmus University in Rotterdam under guidance of Prof Dr H.A. Valkenburg. An important part was the study of rheumatic diseases. This investigation provided us with a lot of new information regarding pain and wear and tear of joints. After a period of ten years we want to investigate the condition of your joints. We are particularly interested in the possible wear and tear of hips and knees. By this follow-up investigation we expect to find more indications about the causes of degenerative joint diseases and the cause of joint pain. This knowledge might be helpful for future generations to prevent the disease.

Within the next few days we will send you a questionnaire. This questionnaire can be returned in the return envelop (stamp not needed). We also would like to ask you to come to our EPOZ centre in Zoetermeer. An appointment will be sent with the questionnaire. Dr van Saase, a physician with rheumatologic experience, will speak with you about the questionnaire, examine your joints, some radiographs will be made and your blood pressure will be measured. The questionnaire is extensive, although not difficult to complete. The investigation in the EPOZ centre will take about one hour.

We hope you want to cooperate in this, for rheumatologic research, important follow-up investigation.

Thanking you, also on behalf of Prof Dr H.A. valkenburg,

Yours sincerely,

J.L.C.M. van Saase, M.D.

ERASMUS UNIVERSITEIT ROTTERDAM

APPENDIX III: BEGELEIDENDE BRIEF BIJ DE ENQUETE

Rotterdam, 22 mei 1985

Geachte Heer/Mevrouw,

Enkele dagen geleden zonden wij u een brief met informatie over een onderzoek naar de oorzaken van gewrichtsslijtage bij ouderen. Voor dit onderzoek zijn wij aangewezen op uw medewerking.
Het eerste deel van het onderzoek bestaat uit de bijgesloten vragenlijst. De lijst is vrij lang, maar de vragen zijn niet moeilijk te beantwoorden. Wij willen u vragen om deze lijst in te vullen en uiterlijk op 1 juni 1985 in de antwoordenvelop terug te zenden aan de Erasmus Universiteit Rotterdam, afdeling Epidemiologie. Een postzegel is niet nodig.

Voor het tweede deel van het onderzoek willen wij u vragen om op

Donderdag 8 juni om 10.00 uur

naar ons centrum te komen. Dr. van Saase, arts, zal dan de vragenlijst met u doornemen. Om te zien hoe het nu met de toestand van uw gewrichten is zouden wij rontgenfoto's willen maken van de handen, de heupen en de knieen. Wij willen tevens uw lengte, uw gewicht en uw bloeddruk meten. Wilt u in verband met de rontgenfoto's voor zover mogelijk, luchtige kleding dragen? Op de vragenlijst kunt u aangeven of het tijdstip voor uw bezoek aan het centrum u schikt.

Al uw gegevens en alle antwoorden die u geeft vallen onder het medisch beroepsgeheim. Wij staan volledig voor geheimhouding in. Als u direkt vragen heeft kunt u maandag en donderdag ochtend telefonisch kontakt opnemen met het EPOZ-centrum, tel. 079-319202.

In de verwachting dat u aan dit belangrijke onderzoek wilt meewerken willen wij u bij voorbaat hartelijk danken.

Met vriendelijke groeten, mede namens Prof. Dr. H.A. Valkenburg,

J.L.C.M. van Saase, arts

APPENDIX IV: TRANSLATION OF COVERING LETTER

Dear Sir/Madam,

A few days ago you received a letter with information about an investigation regarding the causes of degenerative joint disease in the elderly.
For this investigation we need your cooperation. The first part of the investigation is the enclosed questionnaire. The questionnaire is extensive, although the questions are not difficult to answer. We would ask you to return the form before 1st June 1985 in the return envelope addressed to Erasmus University Rotterdam, department of Epidemiology. A stamp is not needed.

For the second part of the investigation we would ask you to visit the EPOZ centre on

Thursday 8th June 1985 at 10 AM

Dr van Saase will speak with you about the questionnaire and to assess the condition of your joint we would like to make radiographs of your hands, pelvis and knees.
Furthermore we would like to measure your height, weight and blood pressure.
If possible, would you please wear airy clothes in connection with the radiographs?
Please indicate on the first page of the questionnaire if the time of the appointment is convenient.

Your answers to this questionnaire will be treated as stricly confidential.
We guarantee that your privacy is maintained. If you have immediate questions, please phone us on monday or thursday in the morning at the EPOZ centre, tel. number 079-319202.

We expect that you will be prepared to cooperate in this investigation and we would like to take this opportunity to thank you for doing so.

Yours sincerely,

J.L.C.M. van Saase, M.D.

also in the name of: Prof. Dr H.A. Valkenburg

Appendix V. English translation of the questionnaire.

EPOZ

(EPIDEMIOLOGICAL PREVENTIVE INVESTIGATION ZOETERMEER)

THIS QUESTIONNAIRE IS BOUND FOR:

name :

street :

zip code :

residence :

date of birth :

1. In case the information mentioned above is incorrect, would you please fill in the correct information below ?

name :

street :

zip code :

residence :

date of birth :

2. Please indicate whether the appointment to visit the EPOZ-centre is convenient Yes [ ] No [ ]

Under what phone number can you be reached in case the appointment has to be changed?

Phone number: ..... - .....

Data in this dossier are subject to medical professional secrecy

---

Explanation of the questionnaire

This questionnaire consists of 16 pages. The majority of the questions can be answered with a cross in the appropriate box. Please use a pencil, so you can make corrections if necessary. If you are unable to answer a question, please put a cross **in front of the number** of the question.

EXAMPLES:

If you are in the possession of a car put a cross **behind** "yes" as is indicated here:

1. Are you in the possession of a car ? Yes [x] No [ ]

If you prefer to eat spinach put a cross **before** spinach as is indicated here:

2. What vegetables do you like best ?
   - [ ] Cabbage
   - [x] Spinach
   - [ ] Courgette

If you are unable to answer the following question put a cross **before** the question as is indicated here:

x 3. Have you had mumps ? Yes [ ] No [ ]

Some of the questions concern the use of medication. Please bring along to the centre all medication you **currently** use

The following questions concern fractures of the bones and accidents

1. Did you fracture any one of your bones in the past ten years (after january 1st 1975) ? Yes [ ] No [ ]

If NO, please continue with question 7.

2. If YES, what did you fracture .....

3. Could you indicate as accurate as possible when this happened ? Please give month and year.

   Month: ..... Year: .....

4. What was the cause of the fracture ? (For example: traffic accident, sporting accident, fall from the last step of the stair).

   .....

5. What was your opinion of the accident ?

   [ ] The accident was so insignificant, that I was actually surprised I had a fracture.

   [ ] The impact of the smash was so strong, that I was not surprised I had a fracture.

6. By whom and where were you treated for this fracture ?

   [ ] General practitioner Name: .....

   [ ] Hospital Name: .....

   Name doctor: .....

7. Did you have any fractures more then 10 years ago (before january 1st 1975) ? Yes [ ] No [ ]

   If YES, how many times did you have a fracture ? .... times.

8. Did you have an accident in the past ten years, for which you had to go to your General Practitioner or the hospital, without having a fracture ? Yes [ ] No [ ]

9. Did you fall in the past year ? Yes [ ] No [ ]

If YES, how many times did you fall ? ..... times.

What was the cause of falling ? (several answers possible)

[ ] stumbling or slipping

[ ] dizziness

[ ] fainting

[ ] sudden weakness in the legs

[ ] other (please describe) .....

10. Do you have difficulties with walking ? Yes [ ] No [ ]

11. Do you use a stick if you walk outdoors ? Yes [ ] No [ ]

12. Did you have to stay in bed for a period of two weeks or more the past 10 years ? Yes [ ] No [ ]

If YES, how long did you have to stay in bed ? ..... weeks.

Please fill in for what reason and when this had been ?

.....

13. Do you spent regular time outdoors in summer ? (more than 8 hours per week) Yes [ ] No [ ]

The following questions concern pain in the back

---

1. Have you had attacks of pain in the back lasting longer than two weeks in the past 10 years ? Yes [ ] No [ ]

If NO, please continue on the next page.

2. If YES, how often did these attacks occur ? .... times.

3. How long did an attack last ? .... weeks.

4. Did you have to stay in bed because of it ? Yes [ ] No [ ]

5. Have you been treated for these attacks ? Yes [ ] No [ ]

If YES, what did the treatment consist of ? .....

6. Do you know what caused the pain ? Yes [ ] No [ ]

If YES, please describe .....

The following questions concern your work and daily activities

1. Do you have work (besides your household) ? Yes [ ] No [ ]

If NO, please continue on the next page.

2. How do you got to your work (more than one answer is possible) and how much time does that take.

   [ ] by foot ..... minutes
   [ ] by public transport ..... minutes
   [ ] by bicycle ..... minutes
   [ ] by autocycle ..... minutes
   [ ] by car or taxi ..... minutes

3. How many years do you work in your current profession ? ... years

4. What is your current profession ?
   Please give the specific name of your profession or function

   .....

5. How many hours per day do you work ?

   [ ] 1-4 hours (half days or less)
   [ ] 5-9 hours (half to full days)
   [ ] full days
   [ ] more than 9 hours (more than full days)

6. How many days per week do you work ?

   [ ] 1 or 2 days ?
   [ ] 3 or 4 days ?
   [ ] 5 days ?
   [ ] 6 or 7 days ?

7. Are you physically active at your work ?

   [ ] No, I sit virtually all the time
   [ ] Not very active, some walking and/or lifting
   [ ] Yes, I am on the move all the time during work

8. Do you perform your own domestic work ?

[ ] Yes, I do all my domestic work on my own

[ ] Yes, and everyone in the house gives a hand

[ ] Yes, and I have help for ... hours per week

[ ] No, my domestic work is done by someone else

If NO, please continue with question 11.

9. For how many persons do you keep house ? (Include yourself) .... persons

10. How many hours per day do you spent on domestic work ? ..... hours

11. How many hours per day do you cycle ?

[ ] None

[ ] Less than half an hour per day

[ ] More than half an hour per day

12. How many hours per day do you walk outdoors ?

[ ] None

[ ] More than half an hour

[ ] More than half an hour, but less than an hour

[ ] More than an hour per day, namely ... hour

13. Do you climb stairs daily? Yes [ ] No [ ]

If YES, how often ?

- indoors usually .... times per day

- outdoors usually .... times per day

14. Do you work in the garden sometimes ? Yes [ ] No [ ]

If YES, how many hours per week .... hours

How many years do you do this work .... year

15. Are you a handyman (do you make repairs or do maintenance work yourself) Yes [ ] No [ ]

16. Do you perform sporting, gymnastic or jogging activities ? Yes [ ] No [ ]

If NO, please continue with question 20.

17. What kind of sporting activities do you perform and for how long ? (i.e. korfball since 1975)

    1. ..... since 19...

    2. ..... since 19...

18. How many hours per week do you spent on sporting activities ?

    .... hours

19. Do you participate in sport competitions ? Yes [ ] No [ ]

The following questions concern your work, hobbies, etc. in the past ten years

---

20. Did you work in the past ten years ? Yes [ ] No [ ]
    (not including your present work)

If NO, please continue with question 26.

21. What kind of work did you do for the longest period in the past ten years ? (not including your present work)

    .....

22. How did you got to your work (more than one answer is possible) and how much time did that take.

    [ ] by foot ..... minutes
    [ ] by public transport ..... minutes
    [ ] by bicycle ..... minutes
    [ ] by autocycle ..... minutes
    [ ] by car or taxi ..... minutes

23. How many hours per day did you work ?

    [ ] 1-4 hours (half days or less)
    [ ] 5-9 hours (half to full days)
    [ ] full days
    [ ] more than 9 hours (more than full days)

24. How many days per week did you work ?

    [ ] 1 or 2 days ?
    [ ] 3 or 4 days ?
    [ ] 5 days ?
    [ ] 6 or 7 days ?

25. Were you physically active at your work ?

[ ] No, I sat virtually all the time

[ ] Not very active, some walking and/or lifting

[ ] Yes, I was on the move all the time during work

26. Did you perform sporting, gymnastic or jogging activities in the past ten years ? (Not including current sporting activities) Yes [ ] No [ ]

If NO, please continue with question 30.

27. What kind of sporting activities did you perform and for how long ? (i.e. korfball from 1976 until 1981)

1. ..... from 19... until 19...

2. ..... from 19... until 19...

28. How many hours per week did you spent on sport activities ?

.... hours

29. Did you participate in sport competitions ? Yes [ ] No [ ]

The following questions concern your activities in the past month

---

30. How much time did you spent on the following activities on an average week-day and on an average weekend-day in the past month ?

A. Very strenuous activity ?
(digging in the garden, vigorous domestic work, vigorous sporting, cycling with adverse wind, etc.)

Week-day (hours per day) .....

Weekend-day (hours per day) .....

B. Moderately strenuous activity ?
(light domestic work, light sporting, walking, cycling calmly)

Week-day (hours per day) .....

Weekend-day (hours per day) .....

Have you had any of the following diseases or conditions

INFECTIOUS DISEASES

1. An infection of a joint — Yes [ ] No [ ]
   If YES, which joint ? .....
2. An infection of a part of the skeleton — Yes [ ] No [ ]
   If YES, which part ? .....
3. Tuberculosis of the lungs — Yes [ ] No [ ]

CARDIOVASCULAR DISEASES

4. High blood pressure — Yes [ ] No [ ]
5. Chest pain — Yes [ ] No [ ]
6. Heart attack — Yes [ ] No [ ]
7. Cerebral haemorrhage — Yes [ ] No [ ]
8. During a walk, do you get pain in the calves that recovers after a few minutes rest ? — Yes [ ] No [ ]

OTHER DISEASES

9. Diabetes Mellitus — Yes [ ] No [ ]
10. Diseases of the thyroid — Yes [ ] No [ ]
11. Infantile paralysis ("polio") — Yes [ ] No [ ]
12. Rachitis — Yes [ ] No [ ]
13. Asthma — Yes [ ] No [ ]
14. Chronic bronchitis — Yes [ ] No [ ]
15. Diseases of the kidneys — Yes [ ] No [ ]

The following questions concern physician treatment now and in the past

OPERATIONS

16. Have you ever been operated ? Yes [ ] No [ ]

17. If YES, please indicate the kind and year of operation.

    1. ..... in 19...

    2. ..... in 19...

    3. ..... in 19...

    4. ..... in 19...

18. Have you been admitted to a hospital for a reason other than operation ? Yes [ ] No [ ]

19. If YES, please indicate what for.

    1. ..... in 19...

    2. ..... in 19...

    3. ..... in 19...

    4. ..... in 19...

MEDICATION AND CURRENT TREATMENT

20. Are you at present being treated by your general practitioner or by a medical specialist ? Yes [ ] No [ ]

21. Do you use medication (powders, pills, potions, capsules, injections,etc) ? Yes [ ] No [ ]

    If YES, please indicate what medication.

    1. ..... since 19...

    2. ..... since 19...

    3. ..... since 19...

    4. ..... since 19...

Please bring along all your current medication to the centre!

The following questions concern rheumatic and skeletal diseases

Have you ever had one of the following diseases ?

1. Acute arthritis as a child — Yes [ ] No [ ]
2. Chronic arthritis as a child — Yes [ ] No [ ]
3. Gout — Yes [ ] No [ ]
4. Crooked back — Yes [ ] No [ ]
   If YES, were you treated for it ? — Yes [ ] No [ ]
5. Different length of the legs — Yes [ ] No [ ]
   If YES, were you treated for it ? — Yes [ ] No [ ]
   Do you wear special shoes or arch support ? — Yes [ ] No [ ]
6. Other rheumatic or skeletal diseases — Yes [ ] No [ ]
   If Yes, please specify.....
7. Do you **currently** have pain in one of the following joints ?
   left hand — Yes [ ] No [ ]
   right hand — Yes [ ] No [ ]
   in the lower part of the back — Yes [ ] No [ ]
   in the upper part of the back — Yes [ ] No [ ]
   left hip — Yes [ ] No [ ]
   right hip — Yes [ ] No [ ]
   left knee — Yes [ ] No [ ]
   right knee — Yes [ ] No [ ]
   other joint (please specify) ..... — Yes [ ] No [ ]
8. Do you have pain in the joints **at night** ? — Yes [ ] No [ ]
   If YES, in which joints ?
   1. .....
   2. .....
   3. .....
   4. .....
9. If YES, is the pain worse than at daytime ? — Yes [ ] No [ ]

10. Do you climb stairs ? Yes [ ] No [ ]

If NO, what is the reason of this .....

If YES, do you have pain:

in the upper part of the back Yes [ ] No [ ]

in the lower part of the back Yes [ ] No [ ]

in the hips Yes [ ] No [ ]

in the knees Yes [ ] No [ ]

11. Do you have pain while rising from a chair:

in the back Yes [ ] No [ ]

in the hips Yes [ ] No [ ]

in the knees Yes [ ] No [ ]

12. Are you stiff while rising from a chair?

in the back Yes [ ] No [ ]

in the hips Yes [ ] No [ ]

in the knees Yes [ ] No [ ]

13. Do you currently have pain in the left buttock Yes [ ] No [ ]

in the right buttock Yes [ ] No [ ]

in the left uuper leg Yes [ ] No [ ]

in the right upper leg Yes [ ] No [ ]

in the left groin Yes [ ] No [ ]

in the right groin Yes [ ] No [ ]

14. What is your maximum walking distance without needing a rest ?

[ ] less than 110 meters (till the end of the street)

[ ] 100 - 500 meters (to the bus stop)

[ ] 500 meters - 1 kilometer (shopping)

[ ] 1 - 5 kilometers

[ ] more than 5 kilometers

15. Do you currently have stiff joints in the morning rising from your bed ? Yes [ ] No [ ]

If YES, how log does this stiffness last ?

[ ] less than 15 minutes

[ ] 15 - 30 minutes

[ ] 30 minutes - 1 hour

[ ] 1 - 2 hours

[ ] more than 2 hours

The following questions concern the smoking of cigarettes and shag

1. Did you ever smoke cigarettes or shag ? Yes [ ] No [ ]

If NO, please continue with question 7.

2. Do you still smoke currently ? Yes [ ] No [ ]

If NO, please continue with question 6.

3. How many cigarettes do you smoke on average per day ? .... cig./day

4. How long have you smoked this number of cigarettes ? ..... years

5. How many cigarettes per day did you smoke 10 years ago ?
   [ ] I smoked more
   [ ] I smoked less
   [ ] I smoked the same number

6. If you stopped smoking, how long ago was that ? .....

The following questions concern the use of alcohol and coffee

7. Have you ever used alcoholic beverages ? Yes [ ] No [ ]

If NO, please continue on the next page.

8. If YES, do you still drink alcoholic beverages occasionally ? Yes [ ] No [ ]

If NO, please continue with question 12.

9. How many glasses of light alcoholic drinks (beer, wine, sherry, etc.)
   do you use on average per day ? ..... glasses
   per week ? ..... glasses
   per months ? ..... glasses

10. How many glasses of strong alcoholic drinks (genever, vieux, etc.)
    do you use on average per day ? ..... glasses
    per week ? ..... glasses
    per months ? ..... glasses

11. Do you drink coffee regularly ? Yes [ ] No [ ]

If NO, please continue with the next section.

12. How many cups of coffee do you usually drink per day ?

..... cups

13. How long do you drink this number of cups of coffee ?

.... years

14. How many cups of coffee did you use before that ?

[ ] less

[ ] same

[ ] more

Finally, we have some general questions

---

1. Do you currently have a pension ? Yes [ ] No [ ]

   If YES, since 19...

2. Are you medically declared unable to work ? Yes [ ] No [ ]

   If YES, since 19...

   What is the reason for this ? .....

3. If you work now, or have a pension, were you ever medically declared unable to work in the past ? Yes [ ] No [ ]

   If YES, from 19... until 19 ..., because of .....

4. Which hand do you use most ? left hand Yes [ ] No [ ]

   right hand Yes [ ] No [ ]

5. Please fill in the name of your general practitioner ?

   .....

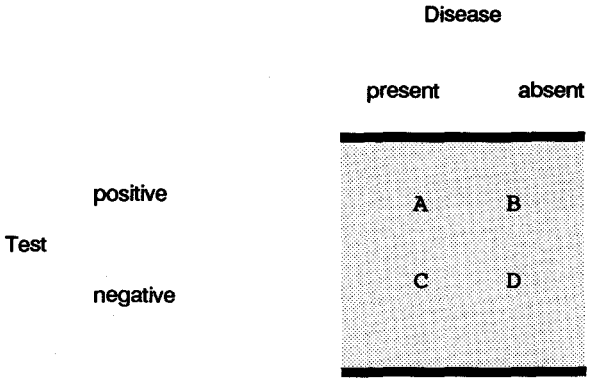
6. Did you find it difficult to complete this questionnaire ? Yes [ ] No [ ]

Below you can indicate what your opinion is about the questionnaire or you can give additional comment.

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE!

Appendix VI

Signs and symptoms found during physical examination can be considered as diagnostic tests. Testing is performed to increase or decrease the probability of the presence of a disease. The accuracy of a test can be described using a 2 x 2 table:



The **sensitivity** of a test is the probability that a diseased person has a positive test: A/A+C.

The **specificity** of a test is the probability that a non-diseased person has a negative test: D/B+D.

Both sensitivity and specificity are independent of the frequency of the disease in the population studied. Tests used to predict the presence or absence of a disease have an accuracy that can be described with the **predictive value**. The predictive value of a positive test is calculated by dividing all diseased persons with a positive test by all persons with a positive test: A/A+B. The predictive value of a negative test is calculated by dividing all persons without the disease and with a negative test by all persons with a negative test: D/D+C. As can be seen from the 2 x 2 table the predictive values of a test are dependent on the frequency of a disease in the population tested as well as on the sensitivity and specificity of that test.
It is also possible to quantify the increase or decrease of the probability that a disease is present before and after a test. It is necessary to know the **pretest odds** (or prior odds) and the **likelihood ratio** of a positive and of a negative test.

The odds in favour of a disease are defined as the change that a disease is present divided by the change that a disease is absent. E.g., if we know that the prevalence of coxarthrosis in a population is 9% than the odds are 0.09/1-0.09 = 0.0989 that a member of that population has coxarthrosis. If this is the only knowledge we have about the change that someone has the disease this might be considered as the **pretest odds** in favour of the disease.

The **likelihood ratio** is a ratio of probabilities. For a positive test it is the number of 'true positive' tests divided by the number of 'false positive' tests or the sensitivity divided by 1 - specificity.

In formula: (A/A+C) / 1 - (D/D+B)

Equivalently, the likelihood ratio of a negative test is the number of 'false negative' tests divided by the number of 'true negative' tests or 1 - sensitivity divided by the specificity.

In formula: 1 - (A/A+C) / (D/D+B)

The **posttest odds** (or posterior odds) depends on the pretest odds and the likelihood ratio: **POSTTEST ODDS = PRETEST ODDS x LIKELIHOOD RATIO.**

Epiloog

Het in dit proefschrift beschreven onderzoek werd uitgevoerd in Zoetermeer. De analyse van de gegevens en het beoordelen van de roentgenfoto's vond plaats op de afdeling epidemiologie van de Erasmus Universiteit te Rotterdam, de teksten kwamen in Zoeterwoude tot stand.

Met medische problemen heb ik leren omgaan dank zij de internisten van het St. Elisabeth Ziekenhuis te Leiderdorp. De Leidse reumatologen leerden mij naar gewrichten kijken en Professor Dr. Arnold Cats stelde mij voor om enkele jaren in Rotterdam aan dit onderzoek te werken.

Epidemiologie was in Leiden in 1985 een weinig ingeburgerd verschijnsel en pas enkele maanden na aankomst in Rotterdam kreeg ik enig idee over de mogelijkheden en de beperkingen van epidemiologisch populatie onderzoek. De grootste bijdrage bij het tot stand komen van dit epidemiologisch besef werd geleverd door de 'kritische massa' van de afdeling, met name tijdens de wekelijkse werkbesprekingen.

De homogeniteits analyse van Dr. Leo K.J. van Romunde vormde de aanleiding voor een onderzoek naar artrose van het heupgewricht. De uitwerking kon tot stand komen door de ervaring en inspiratie van Professor Dr. Hans A. Valkenburg. Helen de Bruijn, Marijke ter Haar en Carlie Valkenburg, waren niet alleen onmisbaar voor het verzamelen van de gegevens, zij dwongen mij tevens te stoppen met roken. Niemand kan in Rotterdam promoveren zonder de secretariele hulp van Cilia Kuynders en Ina Bakker en de computer ondersteuning van Bram van Laar en Leo Muller. Hanny Leezer heeft de adresbestanden bijgewerkt en het eerste administratieve deel van het onderzoek vlekkeloos verzorgd. Leny Janssen-van der Pijl was zo vriendelijk mijn 'engels' bij te werken.

Het moeilijkste deel van dit onderzoek bleek de relatie tussen het 'design' en de vraagstelling. Dank zij Bert van Hemert die als praatpaal en reflexiescherm wilde dienen is het hier en daar toch goed gekomen. Door een gelukkig 'toeval' kunnen we over de praktijk en theorie van medische kennis en medisch

handelen nog een aantal jaren 'filosoferen' aan de Leidse Universiteit.
In Leiden kon ik op de afdeling klinische epidemiologie van professor dr. Jan P. Vandenbroucke aankloppen voor hardware, software, advies en koffie.
Dr. Jan-Karel van der Vijver en Professor Dr. Edo Meinders hebben mij in staat gesteld de internisten opleiding te voltooien.
Indachtig de stelling dat een proefschrift niet het einde maar het begin van een wetenschappelijke carriere dient te zijn ben ik Professor Dr. Jan Vandenbroucke en professor dr. L.A. van Es dankbaar voor de mogelijkheid die zij mij bieden om enkele jaren klinisch epidemiologisch onderzoek te doen op de afdeling nierziekten van het Academisch Ziekenhuis te Leiden.
De laatste alinea is voor de drie thuis, Marisol, Claudia en Viviana, die mij wat weinig hebben gezien door de combinatie van een internisten opleiding en het schrijven van een proefschrift in de avonduren. Het is goed om, anders dan op het werk, ook thuis een 'kritische massa' te hebben.

ABOUT THE AUTHOR

Jan van Saase was born in Hazerswoude, The Netherlands on November 2nd, 1953. After completing secundary education at the Roman Catholic College Leeuwenhorst in Noordwijkerhout and 1 year of military service, medical studies were started in 1974 at the Leiden State University, the Netherlands. From 1976-1977 he studied philosophy at the same university. In 1981 he obtained his medical degree and started specialist training in Internal Medicine at the department of Internal Medicine of the St. Elisabeth Hospital Leiderdorp (Head: Dr W.J. van Amstel). He interrupted his training in this hospital for a period of 9 months to work at the department of Rheumatology (Head: Prof. Dr. A. Cats) of the Academic Hospital of the Leiden State University. In the fall of 1984 he started a training in Epidemiology at the Erasmus University, Rotterdam and commenced the investigation described in this thesis; planning the investigation, and gathering data were completed in December 1986, analysing and writing was done in the evening hours of the following years. In January 1987 he continued his specialist training in Internal Medicine in the Leyenburg Hospital, The Hague (Head: Dr J.C.M. van der Vijver). The last period of his specialist training was spent at the Department of Internal Medicine at the Leiden State University (Head Prof. Dr. A.E. Meinders). From April 1987 he has been guest co-worker of the department of Clinical Epidemiology of the Leiden State University (Head: Prof. Dr. J.P. Vandenbroucke). At present he works at the Intensive Care department of the Leiden University Hospital.