Hand osteoarthritis
Epidemiology and clinical consequences

Saeideh Dahaghin

Acknowledgments

The work presented in this thesis was conducted at the Department of General practice and Department of Rheumatology of the Erasmus Medical Centre-University Medical centre Rotterdam, The Netherlands.
The studies described in this thesis were performed in the Rotterdam study.
The Rotterdam study is supported by the Erasmus MC-University Medical Centre, Rotterdam,
The Netherlands Organisation for Scientific Research (NWO),
The Netherlands Organisation for Health Research and Development (ZonMW),
The research institute for disease in the elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry of Health, Welfare And Sports, the European Commission (DG XII), and the Municipality of Rotterdam.
The Contribution of the general practitioners, pharmacists of the Ommoord district for the Rotterdam study are gratefully acknowledged.

The financial contribution of Reumafonds and Stichting Anna fond for printing of this thesis are gratefully acknowledged.

Layout: Legatron Electronic Publishing, Rotterdam
Printers: PrintPartners Ipskamp, Enschede

Cover Design: Mehdi Afshar-Payam
ISBN-10: 909020041X
ISBN-13: 9789090200415

Hand Osteoarthritis
Epidemiology and clinical consequences

Hand artrose
Epidemiologie en klinische consequenties

Thesis
to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus
Prof. dr. S.W.J. Lamberts
and in accordance with the decision of the Doctorate Board

The public defense shall be held on
Thursday 10 November 2005 at 13.30 o'clock

by

Saeideh Dahaghin

born in Tehran, Iran

Promotion commission

Promotors:	Prof. dr. B.W. Koes
	Prof. dr. J.M.W. Hazes
Other members:	Prof. dr. S.E.R. Hovius
	Prof. dr. P.E. Slagboom
	Prof. dr. W.A.B. Stalman
Co promotor:	Dr. S.M.A. Bierma-Zeinstra

To Mehdi and Amir

To my parents

Contents

1

Introduction

Introduction

The term osteoarthritis describes a common, age-related, heterogeneous group of disorders characterised pathologically by focal areas of loss of articular cartilage in synovial joints, associated with varying degrees of osteophyte formation, subchondral bone change, and synovitis. Joint damage is caused by a mixture of systemic factors that predispose to the disease, and local mechanical factors that dictate its distribution and severity.[1] Osteoarthritis can arise in any synovial joint in the body, but most often in the hands, feet, spine, knees, and hip joints. A single joint can be involved, but more commonly several joints are affected. As arthritis and rheumatic diseases receive far less attention in the scientific literature than is warranted by their enormous and growing disease burden,[2] the principal aim of this study is to contribute to the understanding of osteoarthritis, and especially a frequently occurring form of osteoarthritis, hand osteoarthritis and its clinical consequences for the patients.

The three major themes of hand osteoarthritis were investigated in this thesis:

Epidemiology and clinical burden of hand osteoarthritis

The hand joints are one of the most frequently involved joints in osteoarthritis; in the hand joints, osteoarthritis occurs earlier in life compared with other joints.[3] From a clinical point of view it is valuable to know what the clinical consequences of osteoarthritis are in the hand joints. In **Chapter 2** we investigate the prevalence and pattern of hand osteoarthritis in the open population. Further, radiographic findings in the hand joints are evaluated in relation to the presence of hand pain and hand disability.

In **Chapter 3** we investigate the main patient-related outcomes, namely hand pain and hand disability. More specifically we address the contribution of different determinants, including radiographic hand osteoarthritis, to explain the variability of hand pain and hand disability in the open population.

Chapter 4 summarizes the existing evidence for the association between radiographic osteoarthritis in the hand, with hand pain or hand function impairment.

Hand osteoarthritis as predictor of future hip/knee osteoarthritis, or as indicator to identify homochromatosis

Osteoarthritis tends to occur in more than one joint in the body due to systemic predisposition of this disease.[4-6] In addition, some studies showed that the clinical burden of radiographic osteoarthritis in the hip or knee (weight-bearing joints) is higher compared to that of the hand joints.[7,8] Based on these suggestions, in **Chapter**

5 we evaluate whether osteoarthritis in the weight-bearing joints later in life can be predicted by the presence of osteoarthritis in the hand joints.

Studies have shown that one of the common inherited disorders associated with hand osteoarthritis, is type I hemochromatosis.[9,10] It is considered to be one of the differential diagnoses in the presence of osteoarthritis in atypical joints of the hand. In **Chapter 6** we examine whether the presence of C282Y and H63D, mutations of the hemochromatosis gene, can be identified by the presence of osteoarthritis in the metacarpophalangeal joints.

Etiology of osteoarthritis

Osteoarthritis appears to be a mechanically driven but chemically mediated process in which there is attempted (or aberrant) repair.[11] An opportunity for the development of new prevention and intervention strategies might arise when we increase our understanding of the role of these chemical factors. Especially obesity, but also diabetes and hypertension, are suggested to be associated with osteoarthritis through chemical effects in the body. However, whether the presence of these metabolic factors together have an additional effect on osteoarthritis has not yet been evaluated.

In **Chapter 7** we try to elucidate how obesity, separately or combined with other metabolic factors, influences hand osteoarthritis.

Finally, **Chapter 8** presents a discussion of our findings, makes some recommendations for future research, and discusses clinical implications of the work in this thesis.

References

1. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. *Lancet* 2005;365:965-73.
2. Glazier R, Fry J, Badley E. Arthritis and rheumatism are neglected health priorities: a bibliometric study. *J Rheumatol* 2001;28:706-11.
3. van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. *Ann Rheum Dis* 1989;48:271-80.
4. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in women: a twin study. *Bmj* 1996;312:940-3.
5. Bijkerk C, Houwing-Duistermaat JJ, Valkenburg HA, Meulenbelt I, Hofman A, Breedveld FC, Pols HA, van Duijn CM, Slagboom PE. Heritabilities of radiologic osteoarthritis in peripheral joints and of disc degeneration of the spine. *Arthritis Rheum* 1999;42:1729-35.
6. Kellgren JH, Lawrence JS, Bier F. Genetic Factors in Generalized Osteo-Arthrosis. *Ann Rheum Dis* 1963;22:237-55.

7. Carman WJ. Factors associated with pain and osteoarthritis in the Tecumseh Community Health Study. *Semin Arthritis Rheum* 1989;18:10-3.
8. Lawrence JS, Bremner JM, Bier F. Osteo-arthrosis. Prevalence in the population and relationship between symptoms and x-ray changes. *Ann Rheum Dis* 1966;25:1-24.
9. Faraawi R, Harth M, Kertesz A, Bell D. Arthritis in hemochromatosis. *J Rheumatol* 1993;20:448-52.
10. Axford JS. Rheumatic manifestations of haemochromatosis. *Baillieres Clin Rheumatol* 1991;5:351-65.
11. Sowers M. Epidemiology of risk factors for osteoarthritis: systemic factors. *Curr Opin Rheumatol* 2001;13:447-51.

2

Prevalence and pattern of radiological hand osteoarthritis and association with pain and disability
(The Rotterdam study)

S. Dahaghin, S.M.A. Bierma-Zeinstra, A.Z. Ginai, H.A.P. Pols, J.M.W. Hazes, B.W. Koes

Ann Rheum Dis 2005;64:682-7

Abstract

Objective: To investigate the prevalence and pattern of radiographic osteoarthritis (ROA) of the hand joints and their association with self-reported hand pain and disability.

Methods: Baseline data on a population based study (age ≥ 55) were used (n= 3906). Presence of Kellgren-Lawrence ≥ 2 in a hand joint was defined as ROA. A group of hand joints (DIPs, PIPs, MCPs, CMC1/TS) was defined positive if one or more joint showed ROA. Presence of hand pain during the previous month was defined as hand pain. Health assessment questionnaire was used to measure hand disability.

Results: 67% of the females and 54.8% of the males showed ROA in at least one of the joints of the hand. 47.3% of the participants showed ROA of the DIPs, 35.8% of the CMC1/TS, 18.2% of the PIPs and 8.2% of the MCPs of the right/left hand. 56% of the DIPs involvement by ROA, 88% of the PIPs, 86% of the MCPs, and 65% of the CMC1/TS co-occurred with ROA of the other joint groups (right hand). Hand pain showed an odds ratio of 1.9 (1.5 – 2.4) with the ROA of the hand (right). Hand disability showed an odds ratio of 1.5 (1.1 – 2.1) with ROA of the hand (right/left).

Conclusions: Hand ROA is a frequently occurring disease in the elderly, especially in females. ROA co-occurs more frequently in different joint groups of the hand than it occurs solely. We showed a modest to weak association of ROA of the hand with hand pain and disability varying with the site of involvement.

Key words: Osteoarthritis, Hand, Pattern, Pain, Disability

Introduction

Osteoarthritis is the most common form of arthritis among the elderly and one of the leading musculoskeletal causes of disability in western countries.[1,2] The hand is a frequently involved site in the patient suffering from osteoarthritis. Estimated prevalence of osteoarthritis in the hand varies depending on the definition. Although point prevalence of radiographic osteoarthritis (ROA) are reported to be as high as 28.9% to 76% in population-based studies, the prevalence of symptomatic hand osteoarthritis is much lower with a point prevalence of 4% to 6.2%.[3-5] The pattern of hand joints involvement found among affected individuals remains contentious. In addition, despite advances in our understanding of the disease, a discrepancy remains between structural markers of pathology and the clinical syndrome of osteoarthritis typified by joint pain and disability.[6-8] Zhang et al. reported that symptomatic hand osteoarthritis limits several daily functional activities in the Framingham study.[9] Jones *et al.* reported a modest association between the presence of ROA and the presence of pain and disability in a population with diagnosis of hand osteoarthritis.[10]

However, whether the association between ROA and hand pain and disability differentiates for different hand joint group has not been evaluated well. The purpose of this study is to enlarge the evidence concerning the prevalence and pattern of ROA in the hand joints, and to investigate the association between ROA of different joints in the hand and self-reported hand pain and disability in an open population.

Methods

Study population: For this study cross-sectional baseline data of the Rotterdam Study, a population-based cohort was used. The Medical Ethics Committee of the Erasmus Medical Centre approved the study, and written informed consent was obtained from all participants. The baseline measurements were conducted between 1990 and 1993. The complete study design has been described previously.[11] All inhabitants of a suburb of Rotterdam aged 55 years and older were invited to participate. In total, 7983 participants (response rate of 78%) were examined. At baseline, trained interviewers performed an extensive home interview on demographic characteristics, medical history, risks factor for chronic diseases and medication use. X-rays were taken at the research centre at baseline. For feasibility reasons only hand radiographs of 3906 participants including all participants who were available for follow-up 6 years later (n= 3585) were scored for ROA.

Measurements

Radiographic scoring: Two trained assessors (SD, UC) who were blind for clinical and demographic data scored standard anteroposterior radiographs of both hands in 2002. Radiographs were scored for six individual radiographic features of osteoarthritis in the five distal interphalangeal joint (DIPs), four proximal interphalangeal joint (PIPs), five metacarpophalangeal joint (MCPs), first carpometacarpal joint (CMC1) and trapezioscaphoid joint (TS). Osteophytes were differentiated into three grades (small, moderate, large) while joint space narrowing, sclerosis, cysts, lateral deformity and cortical collapse were scored as either present or absent. Lateral deformity was defined as malalignment of at least 15 degrees (Modified Kallman score).[12] Each joint was graded for overall ROA using a modified Kellgren-Lawrence (K-L) grade scaled 0-4 used previously (Appendix 1).[13] ROA for each joint was defined as a K-L grade ≥ 2. DIPs, PIPs, MCPs and CMC1/TS groups were defined positive if at least one joint of the group showed K-L ≥ 2. Hand ROA was defined as the presence of K-L≥ 2 in two out of three groups of hand joints (DIPs, PIPs and CMC1/TS) of each hand. The same definition was used for the cut-off point K-L ≥ 3 or K-L = 4.

To investigate the reliability of the scoring, the two assessors both scored a random subset of 205 radiographs independently. Interobserver reliability of K-L 2 or more as a dichotomous variable expressed by kappa statistics was as follows: DIPs; 0.60, PIPs; 0.61 MCPs; 0.63 and CMC1/TS (base of the thumb); 0.74.

Hand pain: The following questions were asked during the home interview: Did you have pain on the right (left) hand during the last month?

They also asked: How long did you have pain? The answer ranged from less than one month to more than 5 years.

Hand disability: Stanford Health Assessment Questionnaire (HAQ) was used to assess disability. Eight questions on the HAQ concerning hand function were used to assess hand disability (Appendix 2). Each question scored from no difficulty (0) to unable to do (3). Of the components with more than one question related to the hand function the highest score was considered (as in the original HAQ).[14,15] Dependence on equipment or physical assistance was ignored and it represents residual disability after compensatory efforts. The scores are averaged into an overall hand disability score on a scale from zero (no hand disability) to three (hand severely disabled). A mean score ≥ 0.5 was used which means a moderate to severe hand disability.

Data Analysis

Point prevalence of ROA was calculated for each joint, the joint groups and the hand. A rectangle diagram (Venn diagram with 4 variables) was used to show the distribution of ROA of the four hand joint groups.

Univariate and multivariate logistic regression analysis was used to evaluate the strength of the association of ROA in the different hand joint group in each hand and also to examine associations between ROA and hand pain and disability. The associations are presented as odds ratios (OR) with confidence interval (95%CI) and were adjusted for age and gender. All analyses were performed at the level of the person. Association between ROA and hand pain was evaluated for each hand separately, while the association with hand disability was evaluated for the presence of ROA in either right or left hand as well as for ROA of the dominant hand. The association with hand pain and disability were also examined with number of joints with ROA (continuous variable) and also more severe forms of ROA (K-L ≥ 3 or K-L = 4).

The SPSS (version 10) program was used for all analyses. The Span program was used to generate rectangle diagrams.[16]

Results

A total of 3906 participants, 58.3% female, with a mean age of 66.6 years were evaluated (Table 1).

Prevalence and pattern of ROA

In total, 61.7% of our study population showed a K-L≥ 2 in at least one of the joints of the hand (67% of the females and 54.8% of the males). DIPs showed the highest frequency (47.3%), followed by CMC1/TS (35.8%), PIPs (18.2%) and MCPs (8.2%) of the right/left hand.

ROA in the separate DIP joints (right hand) occurred from 6.8 - 17% and 9.7 – 28.6% for the males and females, respectively. The ranges were 3 – 5.6% and 4.4 – 7.6% in the PIPs, 0.2 - 2.2% and 0.4 – 4.9% in the MCPs, 11.4% - 12% and 18.8% - 21.2% in the CMC1/TS for males and females, respectively (Figure 1).

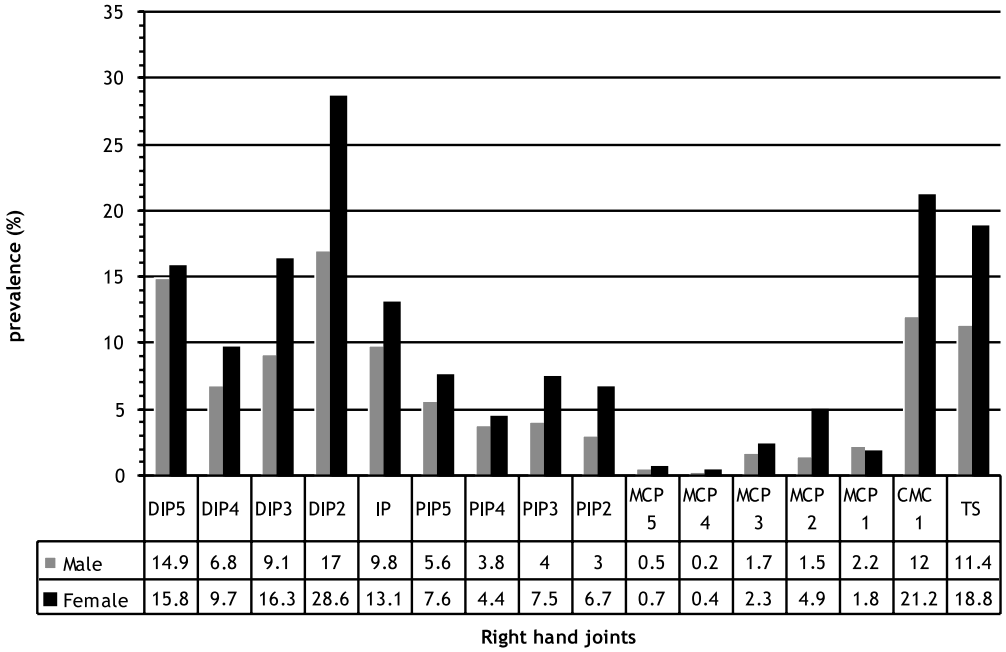
Except for DIP2 (Right=23.5%, Left=16.8%), CMC1 (Right=17.2%, Left=21.3%) and TS (Right=15.6%, Left=17.6%) the other hand joints showed almost the same frequency in the right and left hand.

Table 1 **Baseline characteristics of the study population**

Characteristics	N=3906		
Female %	58.3		
Age (years) Mean ± SD	66.6 ± 7.3		
+ Hand disability %	5.8		
++ Overall disability index %	20.2		
	Right/Left	Right	Left
* ROA of DIPs	47.3	38.6	34.8
* ROA of PIPs %	18.2	13.4	11.6
* ROA of MCPs %	8.2	6.1	4.4
* ROA of CMC1/TS %	35.8	25.8	30.2
$^{\Delta}$ Hand ROA %	28.3	21.5	20.6
Hand pain %	16.8	14.2	13.5

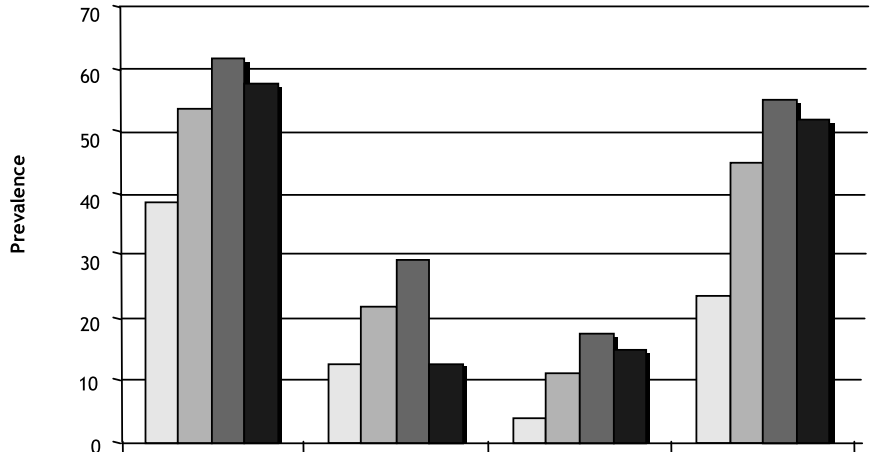
\+ Hand disability: mean score of 0.5 or more of various components composed of 8 questions related to hand function on the Stanford Health Assessment Questionnaire (HAQ)
++ Total disability index: mean score of 0.5 or more of HAQ index (range 0-3)
* ROA: presence of K-L ≥ 2 in at least one joint of the group
$^{\Delta}$ Hand ROA: Presence of K-L ≥ 2 in two out of three groups (DIPs, PIPs, CMC1/TS)

Figure 1 **Point prevalence of ROA (K- L ≥ 2) in the hand joints of males and females (N= 3906)**



Hand ROA was present in 21.5% of the right hand and 20.6 of the left hand. The prevalence of ROA increased by age up to 84 years, but decreased in the group aged 85 years and older (Figure 2).

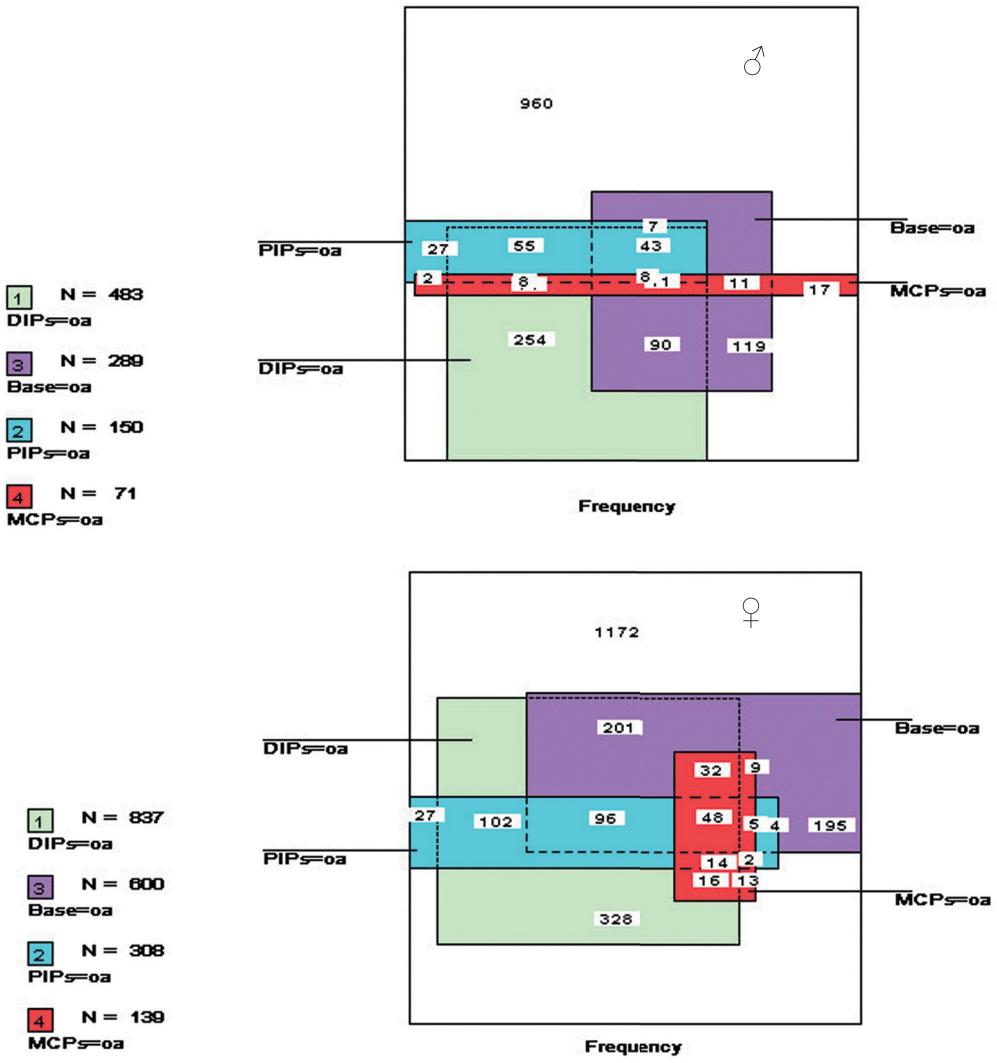
Figure 2 **Age specific point prevalence (%) of osteoarthritis in hand joint groups (right/left)**



	DIPs	PIPs	MCPs	CMC1/TS
55 - 64	38.8	12.5	3.7	23.5
65 - 74	53.8	22	11	45.2
75 - 84	61.9	29.5	17.4	55.1
>=85 years	57.7	12.5	14.8	51.9

Using a rectangle diagram showed that in females ROA in one joint group more often co-occurred with ROA of the other joint groups than in males. 61% versus 47% ROA of the DIPs, 91% versus 82% ROA of the PIPs, 91% versus 77% ROA of the MCPs and 68% versus 59% ROA of the CMC1/TS of the female versus male co-occurred with other joint groups in the right hand (Figure 3). Evaluating the strength of the relations, the PIPs and the MCPs showed the highest OR with ROA of the other joint groups of the right hand OR;9.1 CI (6.8 – 12.4) and OR; 5.4 CI (3.6 – 8.0) respectively. CMC1/TS showed the lowest association with other joint groups of the right hand OR;3.1 CI(2.6 – 3.6)(Table 2). The left hand showed similar results.

Figure 3 **Rectangle diagram of the ROA in the hand joint groups (N = 3906)**



* Presence of K-L ≥ 2 in at least one joint of the group (DIP, PIP, MCP, base=CMC1/TS) of the male and female of the right hand

Table 2 **Pattern of radiographic osteoarthritis (OR, 95%CI) of the hand joint groups of the right hand (N= 3906)**

	Right hand			
	PIPs	MCPs	Base of the thumb	Any other joint group
DIPS	9.1 (7.1 – 11.7)	3.9 (2.9 – 5.5)	2.9 (2.5 – 3.4)	4.4 (3.7 – 5.0)
PIPS		4.7 (3.5 – 6.4)	2.8 (2.3 – 3.5)	9.1 (6.8 – 12.4)
MCPs			3.8 (2.9 – 5.2)	5.4 (3.6 – 8.0)
CMC1/TS				3.1 (2.6 – 3.6)

Adjusted for age and gender

ROA and hand pain

Prevalence of hand pain (right) was 14.2%, of which 97% of the participants suffered from hand pain longer than one month. Table 3 gives the association between hand pain and ROA in the joint groups of the right hand, the strongest with the CMC1/TS. Right hand pain showed an association (OR;1.9, CI 1.5 – 2.4) with ROA of the related hand. Using cut-off point K-L≥ 3 showed nearly the same association (OR;1.8 CI 1.3 – 2.5), but the cut-off point K-L= 4 showed stronger associations with pain of the right hand (OR;3.6 CI 2.2 – 5.8). An increased in the number of joints with ROA showed higher association with pain (OR;1.1, CI 1.1 – 1.2)(right hand). Additionally, a general form (ROA of all four joint groups of the right hand) showed stronger association with hand pain (OR;2.7 CI 1.4 – 5.2). Association of hand pain and ROA in the left hand showed similar results but are not presented.

Table 3 **Association of hand pain with radiographic osteoarthritis in the hand joint groups (right hand)**

Joint group	Univariate	Multivariate
* DIPs	1.5 (1.2 - 1.8)	1.1 (0.9 - 1.4)
* PIPs	1.8 (1.4 - 2.3)	1.4 (1.1 - 1.9)
* MCPs	1.6 (1.1 - 2.3)	1.2 (0.8 - 1.7)
* CMC1/TS	2.0 (1.6 - 2.4)	1.7 (1.4 - 2.2)

* Presence of K-L ≥ 2 in at least one joint of the group (right hand)

ROA and hand disability

Prevalence of hand disability was 5.8%. Presence of hand ROA (right /left) showed an association OR=1.5 (CI 1.1 - 2.1) with hand disability. Specification to the presence of ROA in the dominant hand showed nearly the same results. Table 4 shows the association between hand disability and ROA (right/left) differentiated for hand joint groups which were only statistically significant for MCPs (OR; 2.0, CI 1.3 – 3.0) and were not significant for the other groups. The association of ROA of the base of the thumb became significant when the analysis was specified to the presence of ROA of the dominant hand. However MCPs of the dominant hand showed similar OR with base of the thumb with regard to hand disability.

Using cut-off point K-L ≥3 or K-L =4 (right/left) showed nearly the same association with hand disability (OR; 1.6 CI 1.1 – 2.5) and (OR; 1.6 CI 0.9 – 2.9) respectively. An increase for the number of hand joints with ROA showed a borderline significant association with hand disability. This association increased to a significant level when the number of joints with ROA of only the dominant hand was analysed with hand disability (OR; 1.1 CI 1.0 – 1.2). Additionally, a general form (ROA in all four hand joint groups) showed stronger association with hand disability (OR; 2.7 CI 1.3 - 6.0).

Table 4 **Association of hand disability with radiographic osteoarthritis in the hand joint groups**

Joint group	Univariate	Multivariate
* DIPs	1.3 (0.9 - 1.8)	1.2 (0.8 - 1.7)
* PIPs	1.1 (0.8 - 1.7)	0.9 (0.6 - 1.4)
* MCPs	2.0 (1.3 - 3.0)	1.8 (1.2 - 2.9)
* CMC1/TS	1.3 (1.0 - 1.9)	1.2 (0.8 - 1.7)

Presence of K-L ≥ 2 in at least one joint of the group of the right/left hand

Discussion

The results of the current study confirmed that hand ROA is a frequently occurring disease in the elderly, especially in females. ROA co-occurs more frequently in different joint groups of the hand than it occurs solely which is more in female. More than 90% of the ROA of the PIPs and MCPs in females and about 80% in males co-occurred with the other hand joint groups. We confirmed a modest association between ROA and hand pain, the strongest relationship being with the base of the thumb. Hand disability showed a rather weak association with ROA, the strongest relationship with MCPs and base of the thumb.

Considering the fact that the hand joints are small, the features are often difficult to define, interpreting the radiographs of these joints is challenging, therefore the inter-observer reliability is good and similar to the results of other studies.[9,17] The predominance giving to the osteophyte in the original definition of K-L has been discussed previously.[18] In the present study we used the modified definition of K-L, defining the grade 3 of ROA as a diminution of joint space regardless of osteophyte. This will eliminate the predominance giving to the osteophyte and therefore will probably give more valid results. Definition of hand OA (ROA in two out of three groups hand joints) reported by Hirsch *et al.*,[17] which we used, does not include MCPs. To evaluate whether including MCPs in the definition would change the association with hand pain and disability we also tested an alternative definition of hand ROA including MCPs in the definition {ROA in two out of four hand joints groups of each hand}. With this alternative definition the same results were shown.

In our study, above 55% of the participants showed ROA in at least one joint of the hand. This means that cartilage degeneration or subchondral bone reaction is present in at least one joint of the hand in more than half of the open population aged 55 years and over. This high frequency of ROA, increasing with age and more frequent in the females confirmed the previous findings.[4,12,19] Van Saase reported a slight decrease in the prevalence of ROA in very old people, which was repeated in our study in the people aged ≥ 85. However, only 47 participants (1.2%) of our study population reached ≥ 85, which may lead to an unstable estimate in this group. Considering that osteoarthritis is a chronic disease, another possible explanations are the selection of healthy survivors and/or a lower response rate of disabled persons.

Order of involvement of the hand joint groups in our study was also comparable with other findings. DIPs and the base of the thumb were the most frequently involved groups, followed by PIPs. This was also reported by Kellgren et al. and Egger *et al.*[20,21] MCPs had the lowest frequency in our population, which is in accordance with findings of Chaisson et al. but in contrast with the findings of Saase et al. whom reported a higher prevalence of ROA in the MCPs than in the PIPs group.[4] Chaisson et al. also reported this inconsistency.[22]

For the first time, we visualised the pattern of ROA of the hand joint groups occurring solely or co-occurring with other joint groups, by a rectangle diagram. This shows that PIPs and MCPs groups are often concurrently affected with the other joint groups and rarely affected alone. This finding was also confirmed by a logistic regression analysis. Base of the thumb showed the lowest OR with the other joint groups. This finding may support the idea that systemic factors play a more important role than physical factors in ROA of the PIPs and MCPs but a local mechanical factor might play a more effective role in ROA of the base of the thumb.

With regard to the association between a structural marker of OA and its clinical impact, presence of hand ROA shows modest to weak association with clinical symptoms such as hand pain and disability as reported previously.[9,10] Surprisingly, performing the analysis in an open population we found the same association of ROA and hand pain and disability as Jones et al. while they performed analysis in a group of subjects with diagnosis of hand osteoarthritis. In addition, we found a dose response relation with hand pain, increasing with the number of hand joints affected by ROA, increasing with a general form of ROA with all four hand joint group involved, and also increasing with the severe form of ROA (K-L= 4). However, only a general form of ROA in which four joint groups are affected showed significant increase of the association with hand disability. A severe form of ROA did not change the association with hand disability.

We examined the association between hand pain and ROA of the different hand joint groups; showing that ROA in the base of the thumb has the strongest association with hand pain. This supports the hypothesis that ROA of the base of the thumb has a greater impact on pain than the other hand joint groups. ROA of the base of the thumb (right/left side) showed lower association with hand disability compared to the MCPs. However ROA of the base of the thumb in the dominant hand showed a higher and significant association with hand disability similar to the association with the MCPs group in the dominant hand. Our first idea was that the relationship with the MCPs might be due to another inflammatory disease such as rheumatoid arthritis. However, ROA of the MCPs are concurrent more than 80% with ROA of other joint groups of the hand, while this is a rare occurrence in rheumatoid arthritis. Therefore, the result indicates that ROA at the MCPs is more disabling than at other sites, or indicates again that a more general form of hand ROA is more disabling.

This study has a number of potential limitations. First, the study was primarily designed as a study of determinants and prognosis of chronic diseases in elderly and not specifically designed for hand disease. Therefore, we did not have data on the exact location or a severity measure of hand pain. Secondly, there is some selection bias in our study population compared to the total population of the Rotterdam study. We scored radiographs of 3906 participants including all participants available for follow-up 6 years later. Our study population was younger, had less proportion of females and was less disabled in comparison to the total population at baseline. To examine whether the result of our study can be generalised to the total Rotterdam study, we estimated the point prevalence of hand ROA in the total Rotterdam study. Adjusted for the different age groups it resulted in an almost 3% higher estimation. The estimation was almost 2% higher when adjusted for the severity of general disability. Therefore the point prevalence of ROA shown in our study is probably

somewhat underestimated. However, the prevalence of hand pain was the same for both populations. The association with hand pain and disability might also be underestimated in our population.
In conclusion, we present extensive data on the prevalence of ROA of hand joint groups in a large open population of elderly including both genders, which will contribute to the existing knowledge on this issue. This study also adds that PIPs and MCPs groups are often concurrently affected with the other joint groups and rarely affected alone. We have shown that, of the separate hand joint groups, ROA of the CMC1/TS is the main determinant for hand pain, followed by PIPs. Although DIPs is the most affected joint group of the hand, it seems clinically unimportant. ROA of the MCPs and base of the thumb both showed associations with hand disability.

Appendix 1

Definition of the Kellgren-Lawrence radiographic grades

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

Appendix 2

Questions on the Health Assessment Questionnaire (HAQ) used for the hand disability index.

Are you able to?

1. Dress yourself, including handling of closures?
2. Comb your hair or do your own make-up?
3. Turn taps on and off?
4. Cut your meat, and lift a full cup or glass to your mouth?
5. Open a new milk carton?
6. Open car doors?
7. Hold a pen or a pencil?
8. Open jars, which have been previously opened?

References

1. Felson DT. Epidemiology of hip and knee osteoarthritis. *Epidemiol Rev* 1988;10:1-28.
2. March LM, Bachmeier CJ. Economics of osteoarthritis: a global perspective. *Baillieres Clin Rheumatol* 1997;11:817-34.
3. Carmona L, Ballina J, Gabriel R, Laffon A. The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. *Ann Rheum Dis* 2001;60:1040-5.
4. van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. *Ann Rheum Dis* 1989;48:271-80.
5. Niu J, Zhang Y, LaValley M, Chaisson CE, Aliabadi P, Felson DT. Symmetry and clustering of symptomatic hand osteoarthritis in elderly men and women: the Framingham Study. Rheumatology (Oxford) 2003;42:343-8.
6. Peat G, Croft P, Hay E. Clinical assessment of the osteoarthritis patient. *Best Pract Res Clin Rheumatol* 2001;15:527-44.
7. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, Kington RS, Lane NE, Nevitt MC, Zhang Y, Sowers M, McAlindon T, Spector TD, Poole AR, Yanovski SZ, Ateshian G, Sharma L, Buckwalter JA, Brandt KD, Fries JF. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med* 2000;133:635-46.
8. Dieppe P. Management of hip osteoarthritis. *Bmj* 1995;311:853-7.
9. Zhang Y, Niu J, Kelly-Hayes M, Chaisson CE, Aliabadi P, Felson DT. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. *Am J Epidemiol* 2002;156:1021-7.
10. Jones G, Cooley HM, Bellamy N. A cross-sectional study of the association between Heberden's nodes, radiographic osteoarthritis of the hands, grip strength, disability and pain. *Osteoarthritis Cartilage* 2001;9:606-11.
11. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;7:403-22.
12. Kallman DA, Wigley FM, Scott WW, Jr., Hochberg MC, Tobin JD. The longitudinal course of hand osteoarthritis in a male population. *Arthritis Rheum* 1990;33:1323-32.
13. Cooper C, Egger P, Coggon D, Hart DJ, Masud T, Cicuttini F, Doyle DV, Spector TD. Generalized osteoarthritis in women: pattern of joint involvement and approaches to definition for epidemiological studies. *J Rheumatol* 1996;23:1938-42.
14. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: Dimensions and Practical Applications. *Health Qual Life Outcomes* 2003;1:20.
15. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol* 1982;9:789-93.
16. Marshall RJ. Displaying clinical data relationships using scaled rectangle diagrams. *Stat Med* 2001;20:1077-88.
17. Hirsch R, Lethbridge-Cejku M, Hanson R, Scott WW, Jr., Reichle R, Plato CC, Tobin JD, Hochberg MC. Familial aggregation of osteoarthritis: data from the Baltimore Longitudinal Study on Aging. *Arthritis Rheum* 1998;41:1227-32.
18. Hart DJ, Spector TD. Radiographic criteria for epidemiologic studies of osteoarthritis. *J Rheumatol Suppl* 1995;43:46-8.
19. Kalichman L, Cohen Z, Kobyliansky E, Livshits G. Patterns of joint distribution in hand osteoarthritis: Contribution of age, sex, and handedness. *Am J Human Biol* 2004;16:125-34.
20. Kellgren JH, Moore R. Generalized osteoarthritis and Heberden's nodes. *Br Med J* 1952;1:181-7.

21. Egger P, Cooper C, Hart DJ, Doyle DV, Coggon D, Spector TD. Patterns of joint involvement in osteoarthritis of the hand: the Chingford Study. *J Rheumatol* 1995;22:1509-13.
22. Chaisson CE, Zhang Y, McAlindon TE, Hannan MT, Aliabadi P, Naimark A, Levy D, Felson DT. Radiographic hand osteoarthritis: incidence, patterns, and influence of pre-existing disease in a population based sample. *J Rheumatol* 1997;24:1337-43.

3

Prevalence and determinants of one-month hand pain and hand-related disability in the elderly (Rotterdam study)

S. Dahaghin, S.M.A. Bierma-Zeinstra, M. Reijman , H.A.P. Pols, J.M.W. Hazes, B.W. Koes

Ann Rheum Dis 2005;64:99-104

Abstract

Objective: To study the prevalence of hand pain and hand disability in an open population, and the contribution of their potential determinants.
Methods: Baseline data were used from 7983 participants in the Rotterdam study (a population based study in people aged >55 years). A home interview was used to determine the presence of hand pain during the previous month, rheumatoid arthritis, osteoarthritis in any joint, diabetes, stroke, thyroid disease, neck/shoulder pain, gout, history of fracture in the past five years, and arkinson's disease, as well as age, sex, and occupation. Hand disability was defined as the mean score of eight questions related to hand function. Body mass index was measured and hand x rays were taken.
Results: The one month period prevalence of hand pain was 16.9%. The prevalence of hand disability was 13.6%. In univariate analysis for hand pain, rheumatoid arthritis had the highest explained variance (R2) and odds ratio. For hand disability, aging showed the highest explained variance and Parkinson's disease had the highest odds ratio. All determinants together showed an explained variance of 19.8% for hand pain and 25.2% for hand disability. In multivariate analysis, positive radiographic hand osteoarthritis was a poor explanation for hand pain (R2 = 0.5%) or hand disability (R2 = 0).
Conclusions: The contribution of available potential determinants in this study was about 20% for hand pain and 25% for hand disability in an unselected population of elderly people. Thus a greater part of hand pain/hand disability remains unexplained.
Key word: Prevalence, Pain, Hand, Disability, Elderly

Introduction

The life expectancy in western societies has increased over the last decades. However, many people reach old age with increasing chronic pain and disability. In a recent UK survey, the incidence of self-reported pain was 50%, which was generalised to 46.5% of the general UK population.[1] The three most common causes of chronic pain are musculoskeletal disorders, neuropathic disorders and tumours.[2]

Estimated prevalence of distal upper limb pain varies depending on the severity, period of time and duration of symptoms. Hand or wrist pain is reported to occur in 3 to 25.9% of the general population.[3-5]

Disability is reflected in difficulties in performing activities of daily living (ADL), of which hand function is an important aspect. The ability to use the hand effectively depends on anatomical integrity, mobility, muscle strength, sensation, co-ordination, and absence of pain.[6-8] Although chronic pain and disability receive much attention in the literature, less is known about hand pain and hand disability specifically. To achieve effective management of pain and disability in the hand, the potential determinants need to be understood. Rheumatoid arthritis, other chronic arthritis, osteoarthritis, carpal tunnel syndrome, different forms of tendinitis in the hand and wrist, referred pain from neck/shoulder, diabetes, other peripheral neuropathy, fracture in the hand and wrist, fibromyalgia, stroke, thyroid disease, gout, Parkinson's disease, obesity, manual occupation, age and gender are all potential determinants described as being related to hand pain or hand disability.[3,8-21] However, most of these factors have not been investigated in relation to each other. Therefore, this study investigated the prevalence of hand pain/ hand disability in the elderly, and the contribution of several potential determinants to these problems.

Subjects and methods

Study population

The present study was conducted as a part of the Rotterdam Study, a prospective population-based cohort study of determinants and prognosis of chronic diseases in the elderly. The Medical Ethics Committee of the Erasmus Medical Centre approved the study, and written informed consent was obtained from all participants. The baseline measurements were conducted between April 1990 and July 1993. The complete study design was described previously.[22]The focus is on cardiovascular, neurogeriatric, ophthalmologic and locomotor diseases. All inhabitants of Ommoord (a suburb of Rotterdam) who were aged 55 years and over were invited to participate.

In total, 7983 participants (response rate of 78%) were examined. At baseline, trained interviewers performed an extensive home interview on demographic characteristics, medical history, risks factor for chronic diseases and medication use. To investigate the occurrence of hand pain/hand disability and the contribution of potential determinants we used the data from the home interview with the baseline population. We also used assessment of height and weight to calculate BMI, and hand X-rays, which were performed at the centre at baseline. To study the influence of radiographic hand osteoarthritis, available data from a sub-sample (3906 individuals aged 55 years and over) were used.

Measurements

Hand pain: Trained interviewers asked participants the following questions about hand pain during the home interview: Did you have pain at the right (left) hand during the last month?

They also asked; How long did you have pain? The question was answered by; less than one month, 1 - 3 months, 3 - 6 months, 6 months - 1 year, 1 - 5 years and more than 5 years.

Hand disability: The Rotterdam study investigated various aspects of disability; during the home interview, disability was assessed using the Stanford Health Assessment Questionnaire (HAQ). The HAQ assesses disability by eight components, composed of 24 questions. To assess hand disability, eight questions concerning hand function were used from the HAQ questionnaire (Appendix 1). Each question scored from 0 to 3, representing normal (no difficulty) = 0, some difficulty = 1, much difficulty = 2, unable to do = 3. Dependence on equipment or physical assistance was ignored and it represents residual disability after compensatory efforts. Of the components with more than one question related to the hand function (grip, eating) the highest score was considered (as in the original disability index).[23-25] The scores were averaged into an overall hand disability score on a scale from zero (no hand disability) to three (completely hand disabled). A mean score of 0.50 or greater was defined as the presence of hand disability, which means moderate to complete hand disability. This cut off point was also used for the overall disability index.

Determinants: Self-reported determinants were used to assess the contribution to the presence of hand pain and/or hand disability. Rheumatoid arthritis, osteoarthritis in any joint, diabetes, stroke, thyroid disease, neck/shoulder pain during the last month, gout, history of fracture in the past 5 years (hand/wrist), Parkinson's disease, age, gender and current or last occupation were collected by interview at baseline.

In addition, hand pain was considered as a determinant for hand disability. Age was analysed as categorised variable in 2 groups; 55 to 69 years, and 70 years or more, as well as a continuous variable. Occupation was classified according to the Central Office of Statistics Netherlands (C.B.S.) code 1984.[26] A comparison was made between participants with a history of manual occupation versus participants with all other occupation.

The cut-off point of 30 (kg/m^2) or higher was used as a measure of obesity of body mass index (BMI).

We used baseline data concerning the presence of joint complaints in the other joints during the previous month to evaluate co-existence of other joint complaints with the hand pain.

Two trained assessors (SD, UC) scored 3906 of the baseline hand radiographs (antro-posterior view) in 2002. This selection was chosen for another study aim and included all participants available for follow-up 6 years later. The readers were blinded for other data such as clinical or demographical variables. Radiographs were scored for six individual radiographic features of osteoarthritis in the distal interphalangeal joint (DIP), first interphalangeal joint (IP), proximal interphalangeal joint (PIP), first carpometacarpal joint (CMC1), and trapezioscaphoid joint (TS). Osteophyts were differentiated into three grades (small, moderate, large) while joint space narrowing, sclerosis, cysts, lateral deformity, and cortical collapse were scored as either present or absent. Lateral deformity was defined as malalignment of at least 15 degrees (Modified Kallman score).[27] Definite radiographic osteoarthritis for each joint was defined as a Kellgren-Lawrence (K-L) grade 2 or more (Appendix 2). Three groups of hand joints were defined and a group was considered positive if at least one joint of the group showed K-L $\geq$ 2. Hand osteoarthritis was defined as the presence of K-L $\geq$ 2 in two out of three groups of hand joints (DIP/IP, PIP, and CMC1/TS) on the left and/or right side, a definition of radiographic hand osteoarthritis, which has been used in other studies.[28,29]

To measure interobserver reliability of the scoring, the two assessors (SD, UC) both scored (independently from each other) a random subset of 205 radiographs.

Statistical analysis

Kappa statistic was used for measure of agreement between two assessors for radiographic osteoarthritis, K-L $\geq$ 2 (binary measurement).

Prevalence data were calculated for men and women separately. Univariate logistic regression analysis was used initially to examine associations between hand pain/hand disability and available potential determinants. Associations were expressed in odds ratios (OR) with 95% confidence interval (CI) and in explained variance (R^2).

In a multivariate logistic regression model, the total contributions of the available determinants with significant univariate relationships (p-value < 0.2) to the hand pain at the right/left side or hand disability were analysed.

In a subgroup of 3906 subjects for whom we had data on radiographic hand osteoarthritis, we studied the additional contribution of radiographic hand osteoarthritis (right/left) concerning hand pain/hand disability using multivariate logistic regression analysis.

In addition, logistic regression for repeated measurement (Generalised Estimating Equations; GEE) was used, to take into account the contribution of side-specific determinants such as shoulder pain, history of fracture (hand/wrist) and radiographic hand osteoarthritis of the right or left side with regard to hand pain on the same side (SAS PROC GENMOD).[30]

The SPSS (version 10) and SAS (version 6.12) programs were used for all analyses.

Results

Table 1 shows the baseline characteristics of the study population. Mean age was 70.6 year with 61.1% females. The subgroup (n=3906) was younger with a mean age of 66.6 years and 58.3% was female.

Interobserver reliability between the two assessors for scoring radiographs (K-L ≥ 2 dichotomous variables) expressed by Kappa statistics was 0.68 for the left hand and 0.77 for the right hand.

Table 1 **Baseline characteristics of the total study population and the subgroup**

Characteristics	N=7983	N=3906
Female	61.1%	58.3%
Age (years) Mean ± SD	70.6 ± 9.8	66.6 ± 7.3
Body mass index (kg/m^2) Mean ± SD	26.3 ± 3.7	26.3 ± 3.6
Disability Index*	34.1%	20.2%
Hand disability	13.6%	5.8%
Hand pain (left/ right)	16.9%	16.8%
Any other joint complaints +	46.4%	46.3%

* A score of 0.5 or greater measured by Health Assessment Questionnaire (HAQ)
\+ Neck, shoulder, elbow, low back, hip, knee, foot pain (right and/or left)

Hand pain

One-month period prevalence of hand pain left/right was 16.9% (9.7% in males and 21.6% in females). 97.2% of the participants suffered from hand pain longer than one month which 42.9% was longer than 5 years. A much higher percentage of people with hand pain in comparison to people without hand pain (71.6% versus 41.3%) reported complaints at the other joints. Univariate analysis showed that prevalence of hand pain was not significantly changed in the people aged 70 years and older compared with the younger age group (55-69 years) (OR=1.02, 95% CI: 0.90 - 1.15). In additional analysis, age as continuous variable or as narrower age groups yielded no significant relationship. Hand pain occurred more frequently in females (OR=2.6; 95% CI: 2.2 - 3.0).

Rheumatoid arthritis showed the highest relationship (OR=12.4) and the highest explained variance (R^2) in the univariate analysis for hand pain, followed by pain in the neck/shoulder region, osteoarthritis in any joints, and female gender. Thyroid disease, obesity (BMI≥30), history of fracture, diabetes and manual occupation each had an R^2 of less than 1%. In addition, gout, Parkinson's disease, stroke and age did not explain any variance in the univariate model (R^2=0). All determinants showing a relationship with a p-value < 0.2 in the univariate analysis together showed an R^2 of 19.8% for the hand pain. Associations of available determinants for hand pain in the univariate and multivariate analysis (OR, 95% CI, R^2) are presented in table 2.

Table 2 **Logistic univariate and multivariate analysis of the contribution of available determinants for hand pain (n=7983)**

Determinants	Frequency %	R^2 in the univariate analysis	Odds ratio (95% CI)	
			univariate analysis	multivariate model †
Rheumatoid Arthritis	3.6	0.082	12.4 (9.5 - 16.2)	9.5 (6.9 - 13.1)
Pain in neck/shoulder	22.0	0.076	3.5 (3.1 - 4.0)	2.5 (2.1 - 2.8)
Osteoarthritis in any joints	24.2	0.068	3.2 (2.8 - 3.6)	2.7 (2.3 - 3.2)
Gender: Female	61.1	0.043	2.6 (2.2 -3.0)	2.0 (1.7 - 2.4)
Thyroid disease*	16.9	0.009	1.7 (1.5 - 2.1)	1.4 (1.1 - 1.8)
BMI ≥ 30 kg/m^2	14.5	0.004	1.4 (1.2 - 1.7)	1.1 (0.9 - 1.3)
History of fracture (hand/wrist)	13.8	0.002	1.4 (1.1 - 1.7)	1.3 (0.9 - 1.8)
Diabetes	6.7	0.001	1.3 (1.0 - 1.6)	1.1 (0.8 - 1.5)
Manual occupation	28.3	0.001	1.1 (1.0 - 1.3)	0.9 (0.7 - 1.0)
Gout	0.8	0.000	1.6 (0.9 - 2.9)	1.4 (0.6 - 2.9)
Stroke	4.6	0.000	1.0 (0.7 - 1.3)	---
Age (years) 55-69				
≥70	48.2	0.000	1.0 (0.9 - 1.2)	---
Parkinson's disease	1.0	0.000	1.1 (0.6 - 2.1)	---

Total explained variance of hand pain with all determinants in the multivariate logistic regression model was 19.8%

* Thyroid disease consists of hypothyroidism, hyperthyroidism or other thyroid disease

† Determinants with p-value > 0.2 omitted from the multivariate logistic regression model

Hand disability

Prevalence of hand disability was 13.6 % (7.2% in males and 17.8% in females). This prevalence was increased in people aged 70 years and older compared to those in the relatively younger age group (OR=6.4, 95% CI: 5.4 - 7.6). Hand disability was more frequent in females (OR=2.8, 95% CI: 2.4 - 3.3). Hand pain showed an odds ratio of 2.6, 95% CI: 2.3 - 3.1 with hand disability. It also showed a comparable odds ratio of 2.3; 95% CI: 2.0 - 2.6 with the overall disability index.

Ageing had the highest explained variance (R^2) in the univariate analysis with hand disability while Parkinson's disease showed the highest odds ratio (OR = 18.4). Furthermore, stroke and rheumatoid arthritis showed a high OR but, because of the relatively low prevalence, these variables showed a lower explained variance than ageing. Thyroid disease, diabetes, history of fracture, osteoarthritis in any joint and obesity (BMI≥30) each showed less than 2% explained variance. Gout did not explain any variance in the univariate model (R^2=0). All determinants showing a relationship with a p-value < 0.2 in the univariate analysis together showed an R^2 of 25.2% for the hand disability. Associations of available determinants for hand disability in the univariate and multivariate analysis (OR, 95% CI, R^2) are presented in table 3.

Table 3 **Logistic univariate and multivariate analysis of the contribution of available determinants for hand disability (n=7983)**

Determinants	Frequency %	R^2 in the univariate analysis	Odds ratio (95% CI)	
			univariate analysis	multivariate model †
Age (years) 55-69				
≥70	48.2	0.143	6.4 (5.4 - 7.6)	4.5 (3.6 - 5.6)
Rheumatoid Arthritis	3.6	0.045	6.3 (4.9 - 8.1)	3.3 (2.3 - 4.7)
Stroke	4.6	0.043	5.2 (4.1- 6.5)	4.8 (3.4 - 6.8)
Gender Female	61.1	0.044	2.8 (2.4 - 3.3)	2.2 (1.7 - 2.8)
Hand pain	16.8	0.035	2.6 (2.3 - 3.1)	2.4 (1.9 - 3.0)
Parkinson's disease	1.0	0.033	18.4 (10.9 - 30.8)	23.8 (11.4 - 49.5)
Pain in neck/shoulder	22.0	0.026	2.2 (1.9 - 2.5)	1.8 (1.4 - 2.2)
Manual occupation	28.3	0.025	2.0 (1.8 - 2.3)	1.5 (1.2 - 1.8)
Thyroid disease *	16.9	0.015	2.0 (1.7 - 2.3)	1.2 (0.9 - 1.6)
Diabetes	6.7	0.014	2.4 (2.0 - 3.0)	1.6 (1.1 - 2.2)
History of fracture (hand/wrist)	13.8	0.008	1.8 (1.5 - 2.1)	0.9 (0.6 - 1.3)
Osteoarthritis in any joint	24.2	0.009	1.6 (1.4 - 1.9)	1.1 (0.9 - 1.4)
BMI ≥ 30 kg/m^2	14.5	0.001	1.3 (1.0 - 1.5)	0.8 (0.6 - 1.1)
Gout	0.8	0.000	0.9 (0.4 - 2.0)	---

Total explained variance of hand disability with all determinants in the multivariate logistic regression model was 25.2%

* Thyroid disease consists of hypothyroidism, hyperthyroidism or other thyroid disease

† Determinants with p-value > 0.2 omitted from the multivariate model

Subgroup analysis

For 3906 participants data were available for investigation of radiographic hand osteoarthritis. Radiographic hand osteoarthritis showed an odds ratio of 1.4, 95% CI: 1.1 - 1.7 with hand pain and an odds ratio of 1.4, 95% CI: 0.9 - 2.0 with hand disability in_the multivariate model. All aforementioned determinants and radiographic hand osteoarthritis in relation to hand pain/hand disability showed that positive radiographic hand osteoarthritis was a poor explanation for hand pain (R^2=0.005) or hand disability (R^2=0.000) in this population. Associations of available determinants for hand pain/ hand disability (OR, 95% CI, R^2) of the subgroup are presented in appendix 3.

Additional analysis using the GEE technique yielded similar results compared to the ordinary logistic regression model.

Discussion

About 16.9% of this elderly population had pain in the left or right hand during the previous month and 13.6% had moderate to complete hand disability. Contribution of available potential determinants in this study was about 20% for hand pain and about 25.2% for hand disability in an open population of the elderly. Therefore, a greater part of hand pain/hand disability remains unexplained.

People with hand pain showed a higher prevalence of joint complaints at the other sites in comparison to the people without hand pain. The tendency to report concurrent complaints at different joints might support the concept that systemic factors play more important roles than local factors. Contrary to our expectation, age was not a determinant for hand pain. The same results were reported for pain in the hip joints in the Rotterdam study.[31] Helme *et al.* reported that pain increases with age only up until the seventh decade. They attributed this to a lower response rate in older people, a select sample of survivors, misattribution of the pain symptom to the ageing process itself, or possible age-related changes in the function of pain pathways.[32] Therefore, age-related pain differences should probably be studied in participants with a broader age range.

As expected, rheumatoid arthritis and osteoarthritis in any joint were major determinants for hand pain in our study. However, the contribution of rheumatoid arthritis and osteoarthritis in any joints may be overestimated. Firstly, because the diagnosis was probably based on a consultation for the dependent variable of interest (hand pain). Secondly our measurement was based on self-reports and participants may have misattributed another form of hand pain to rheumatoid arthritis. Compared to other studies a relatively high percentage of our population reported to have

rheumatoid arthritis (3.6% vs 0.7 to 2%).[33,34] However, as Picavet et al. confirmed in an earlier study, prevalence of all self-reported disease is high.[35]

We used R^2, the fraction of variance explained by a certain determinant, to evaluate the contribution of potential determinants to the occurrence of hand pain/ hand disability in the population. For example, Parkinson's disease showed an OR of 18.4 with hand disability, indicating a high risk for individuals with Parkinson's disease. However it is a rare disease (prevalence: 1%) and therefore the fraction of variance explained by this determinant is low (0.033). A determinant with a higher prevalence, for instance "ageing", shows a higher fraction of explained variance (0.143), although the relationship of ageing with hand disability is weaker in individuals (OR=6.4). Nevertheless, we presented both values (OR and R^2).

It complicated to take into account the contribution of side-specific determinants such as; shoulder pain, history of fracture (hand/wrist) and radiographic hand osteoarthritis of the right /left side with regard to hand pain at the same side. For this purpose, logistic regression for repeated measurement (the GEE) was used. This technique calculates the relationships of each hand as the unit of analysis, but accounts for the correlation between fellow hands. However, the ORs computed by the GEE technique (in the total population and in the subgroup) were almost the same as when using ordinary logistic regression. Because the GEE technique does not compute explained variance (R^2), the tables present only the results of ordinary logistic regression analysis.

Hand pain showed a nearly the same relationship with hand disability and overall disability index which might be explained by the fact that hand pain is strongly co existing with pain in the other joints and/or it might also be the results of the strong relationship between hand disability and the overall disability index (r=0.83).

We assume that our hand disability index has sufficient validity, because the questions on the HAQ related to hand function were used for construction of the hand disability index. Furthermore, the construction of hand disability index was performed in exactly the same way as it used for the overall disability index. Many validation studies of the HAQ have demonstrated good validity, reproducibility and sensitivity.[25,36,37] Limaye *et al.* reported that the Log Sollerman D-score, which is a performance-based test assessing unilateral and bilateral hand grips function in activities of daily living, accurately reflects patient function as measured by the HAQ.[38]

Finally, this study has a number of potential limitations. First, the Rotterdam study was primarily designed as a study of determinants and prognosis of chronic diseases in the elderly, and not specifically for hand disease. Therefore, we do not have information on all determinants of interest, such as carpal tunnel syndrome and

other specific wrist/ hand diseases or psychosocial factors. Second, there is some selection in the subgroup used for the analysis of radiographic hand osteoarthritis. Data on radiographic hand osteoarthritis were only available for the 3906 participants who were accessible for follow-up 6 years later. The total population available at baseline (n=7983) was older, much more disabled and had a more females than the subgroup with data on radiographic hand osteoarthritis (n=3906). Prevalence of hand pain was the same, but the prevalence of hand disability was much lower in the subgroup. Although the total explained variance in the total population and in the subgroup were comparable, but the OR of the determinants differed slightly for the hand pain but more pronounced for the hand disability. This is probably because of a marked difference in prevalence of hand disability in the total population compared to the subgroup. Also the prevalence of some determinants differed from the total population. Therefore, the additional explained variance of radiographic hand osteoarthritis may be underestimated. Third, our participants were above 55 years, therefore most of them were retired and their latest job was included in the analysis. An active working population probably will show a higher association of manual occupation with hand pain or disability.

Despite these limitations, to our knowledge this is the first study, which gives some insight into hand pain/hand disability and their potential determinants studied in relation to each other in an elderly population. This study shows that about 20% of hand pain and about 25.2% of hand disability can be explained by potential determinants available in our population. It also shows that determining the presence of radiographic osteoarthritis contributes very little to the total explained variance of hand pain/hand disability. Considering the fact that only 20% of hand pain and 25.2% of hand disability were explained by all available potential determinants together, a greater part of explained variance of hand pain or hand disability remains unexplained. Further investigations should aim to identify other main determinants (local and systemic) of hand pain and disability in the elderly. Psychological factors should also be considered as an explanation for hand pain/hand disability in future studies.

Appendix 1

Questions on the Health Assessment Questionnaire (HAQ) used for the hand disability index.

Are you able to?

1. Dress yourself, including handling of closures?
2. Comb your hair or do your own make-up?
3. Turn taps on and off?
4. Cut your meat, and lift a full cup or glass to your mouth?
5. Open a new milk carton?
6. Open car doors?
7. Hold a pen or a pencil?
8. Open jars, which have been previously opened?

Appendix 2

Definition of the Kellgren-Lawrence radiographic grades

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

Appendix 3

Table 4 **Logistic univariate and multivariate analysis of the contribution of available determinants for hand pain in the subgroup (n=3906)**

Determinants	Frequency %	R^2 in the univariate analysis	Odds ratio (95% CI)	
			univariate analysis	multivariate model
Rheumatoid Arthritis	2.8	0.044	8.8 (5.7 - 13.9)	7.4 (4.5 - 12.1)
Pain in neck/shoulder	21.9	0.048	2.8 (2.3 - 3.4)	2.0 (1.6 -2.5)
Osteoarthritis in any joints	24.7	0.077	3.5 (2.9 - 4.2)	3.0 (2.4- 3.7)
Gender Female	58.3	0.052	2.8 (2.3 - 3.5)	2.3 (1.8- 2.9)
Thyroid disease*	11.5	0.005	1.6 (1.2 - 2.2)	1.1 (0.8- 1.6)
BMI ≥ 30 kg/m^2	13.8	0.001	1.2 (0.9 - 1.5)	0.8 (0.6 - 1.1)
History of fracture (hand/wrist)	9.3	0.000	1.2 (0.8 - 1.6)	1.0 (0.6 - 1.4)
Diabetes	4.7	0.002	1.5 (1.0 - 2.2)	1.3 (0.8 - 2.0)
Manual occupation	29.4	0.000	1.1 (0.9 - 1.3)	0.8 (0.7 - 1.1)
Gout	0.8	0.000	1.6 (0.6 - 3.9)	1.3 (0.4 - 3.6)
Stroke	2.6	0.000	1.0 (0.6 - 1.8)	---
Age (years) 55-69				
≥70	30.8	0.000	1.0 (0.8 -1.2)	---
Parkinson's disease	0.4	0.000	0.5 (0.1 - 3.6)	---
Radiological hand OA	28.3	0.016	1.8(1.4 - 2.1)	1.4 (1.1- 1.7)

Total explained variance of hand pain with all determinants in the multivariate logistic regression model was 17.9%

* Thyroid disease consists of hypothyroidism, hyperthyroidism or other thyroid disease

Table 5 **Logistic univariate and multivariate analysis of the contribution of available determinants for hand disability in the subgroup (n=3906)**

Determinants	Frequency %	R^2 in the univariate analysis	Odds ratio (95% CI)	
			univariate analysis	multivariate model
Age (years) 55-69				
≥70	30.8	0.033	2.7 (2.0 - 3.7)	2.2 (1.5- 3.3)
Rheumatoid Arthritis	2.8	0.032	6.5 (3.8 - 11.1)	2.5 (1.3- 4.8)
Stroke	2.6	0.016	4.4 (2.4 - 8.0)	2.3 (1.0 - 5.6)
Gender Female	58.3	0.046	3.7 (2.5 - 5.5)	2.3 (1.4- 3.7)
Hand pain	16.8	0.082	5.2 (3.7 - 7.1)	3.8 (2.6 - 5.7)
Parkinson's disease	0.4	0.031	40.3 (12.0 - 135.1)	59.4 (15.1 - 234.6)
Pain in neck/shoulder	21.9	0.039	3.0 (2.2 - 4.2)	1.8 (1.2- 2.6)
Manual occupation	29.4	0.017	2.1 (1.5 - 2.9)	1.7 (1.2- 2.5)
Thyroid disease *	11.5	0.003	1.6 (1.0 - 2.5)	1.0 (0.6 - 1.8)
Diabetes	4.7	0.004	1.9 (1.1 - 3.4)	1.5 (0.7 - 3.1)
History of fracture (hand/ wrist)	9.3	0.001	1.4 (0.8 - 2.4)	1.1 (0.6 - 2.0)
Osteoarthritis in any joint	24.7	0.034	2.8 (2.0 - 3.8)	1.5 (1.0- 2.2)
BMI ≥ 30 kg/m^2	13.8	0.000	1.0 (0.6 - 1.6)	0.7 (0.4 - 1.6)
Gout	0.8	0.000	0.8 (0.1 - 5.9)	---
Radiological hand OA	28.3	0.019	2.1 (1.5 - 2.9)	1.4 (0.9 - 2.0)

Total explained variance of hand disability with all determinants in the multivariate logistic regression model was 21.2%
* Thyroid disease consists of hypothyroidism, hyperthyroidism or other thyroid disease

References

1. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. *Lancet* 1999;354:1248-52.
2. Wilder-Smith OH, Mohrle JJ, Dolin PJ, Martin NC. The management of chronic pain in Switzerland: a comparative survey of Swiss medical specialists treating chronic pain. *Eur J Pain* 2001;5:285-98.
3. Palmer KT. Regional musculoskeletal conditions: pain in the forearm, wrist and hand. *Best Pract Res Clin Rheumatol* 2003;17:113-35.
4. Palmer KT, Syddall H, Cooper C, Coggon D. Smoking and musculoskeletal disorders: findings from a British national survey. *Ann Rheum Dis* 2003;62:33-6.
5. Urwin M, Symmons D, Allison T, Brammah T, Busby H, Roxby M, Simmons A, Williams G. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. *Ann Rheum Dis* 1998;57:649-55.
6. Eberhardt KB, Fex E. Functional impairment and disability in early rheumatoid arthritis--development over 5 years. *J Rheumatol* 1995;22:1037-42.
7. Dellhag B, Bjelle A. A five-year followup of hand function and activities of daily living in rheumatoid arthritis patients. *Arthritis Care Res* 1999;12:33-41.
8. Dellhag B, Hosseini N, Bremell T, Ingvarsson PE. Disturbed grip function in women with rheumatoid arthritis. *J Rheumatol* 2001;28:2624-33.

9. Zyluk A, Zyluk B. [Shoulder-hand syndrome in patients after stroke] Zespol bark-reka u chorych po udarze mozgu. *Neurol Neurochir Pol* 1999;33:131-42.
10. Allander E. Epidemiology of the rheumatic diseases. *Curr Opin Rheumatol* 1994;6:122-31.
11. Qiao Q, Keinanen-Kiukaanniemi S, Rajala U, Uusimaki A, Kivela SL. Rheumatic pains of previously undiagnosed diabetic subjects. *Scand J Rheumatol* 1995;24:234-7.
12. Carmeli E, Patish H, Coleman R. The aging hand. *J Gerontol A Biol Sci Med Sci* 2003;58:146-52.
13. Viegas SF. Atypical causes of hand pain. *Am Fam Physician* 1987;35:167-72.
14. Moore JR, Weiland AJ. Gouty tenosynovitis in the hand. *J Hand Surg* [Am] 1985;10:291-5.
15. Acheson RM. Heberden Oration 1981: epidemiology and the arthritides. *Ann Rheum Dis* 1982;41:325-34.
16. Fredriksson K, Alfredsson L, Koster M, Thorbjornsson CB, Toomingas A, Torgen M, Kilbom A. Risk factors for neck and upper limb disorders: results from 24 years of follow up. *Occup Environ Med* 1999;56:59-66.
17. Karpitskaya Y, Novak CB, Mackinnon SE. Prevalence of smoking, obesity, diabetes mellitus, and thyroid disease in patients with carpal tunnel syndrome. *Ann Plast Surg* 2002;48:269-73.
18. Dillon C, Petersen M, Tanaka S. Self-reported hand and wrist arthritis and occupation: data from the U.S. National Health Interview Survey-Occupational Health Supplement. *Am J Ind Med* 2002;42:318-27.
19. Kalb RL. Evaluation and treatment of wrist and hand pain. *Hosp Pract* (Off Ed) 1998;33:129-32, 35.
20. Makabe H, Sakamoto K. Judgment of disability stages in Parkinson disease patients due to pathological tremor of index finger. *Electromyogr Clin Neurophysiol* 2000;40:397-409.
21. Harris TB. Invited commentary: body composition in studies of aging: new opportunities to better understand health risks associated with weight. *Am J Epidemiol* 2002;156:122-4; discussion 25-6.
22. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;7:403-22.
23. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol* 1982;9:789-93.
24. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: Dimensions and Practical Applications. *Health Qual Life Outcomes* 2003;1:20.
25. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. *Clin Rheumatol* 1984;3:305-9.
26. Beroepenclassificatie. list voor benamingen per beroepencode / Central bureau voor de statistiek, ISBN 90-6786-040-9. 1984.
27. Kallman DA, Wigley FM, Scott WW, Jr., Hochberg MC, Tobin JD. New radiographic grading scales for osteoarthritis of the hand. Reliability for determining prevalence and progression. *Arthritis Rheum* 1989;32:1584-91.
28. Hirsch R, Lethbridge-Cejku M, Hanson R, Scott WW, Jr., Reichle R, Plato CC, Tobin JD, Hochberg MC. Familial aggregation of osteoarthritis: data from the Baltimore Longitudinal Study on Aging. *Arthritis Rheum* 1998;41:1227-32.
29. Hirsch R, Lethbridge-Cejku M, Scott WW, Jr., Reichle R, Plato CC, Tobin J, Hochberg MC. Association of hand and knee osteoarthritis: evidence for a polyarticular disease subset. *Ann Rheum Dis* 1996;55:25-9.
30. Diggle PJ LK, Zeger SL. Analysis of longitudinal data. Oxford: Clarendon press 1994.
31. Odding E, Valkenburg HA, Algra D, Vandenouweland FA, Grobbee DE, Hofman A. Associations of radiological osteoarthritis of the hip and knee with locomotor disability in the Rotterdam Study. *Ann Rheum Dis* 1998;57:203-8.
32. Helme RD, Gibson SJ. The epidemiology of pain in elderly people. *Clin Geriatr Med* 2001;17:417-31, v.

33. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, Heyse SP, Hirsch R, Hochberg MC, Hunder GG, Liang MH, Pillemer SR, Steen VD, Wolfe F. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998;41:778-99.
34. Rasch EK, Hirsch R, Paulose-Ram R, Hochberg MC. Prevalence of rheumatoid arthritis in persons 60 years of age and older in the United States: effect of different methods of case classification. *Arthritis Rheum* 2003;48:917-26.
35. Picavet HS, Hazes JM. Prevalence of self reported musculoskeletal diseases is high. *Ann Rheum Dis* 2003;62:644-50.
36. Liang MH, Larson MG, Cullen KE, Schwartz JA. Comparative measurement efficiency and sensitivity of five health status instruments for arthritis research. *Arthritis Rheum* 1985;28:542-7.
37. van der Heijde DM, van Riel PL, van de Putte LB. Sensitivity of a Dutch Health Assessment Questionnaire in a trial comparing hydroxychloroquine vs. sulphasalazine. *Scand J Rheumatol* 1990;19:407-12.
38. Limaye V, Frankham A, Disney A, Pile K. Evaluation of hand function in patients undergoing long term haemodialysis. *Ann Rheum Dis* 2001;60:278-80.

4

The clinical burden of radiographic hand osteoarthritis: a systematic appraisal

S. Dahaghin, S.M.A. Bierma-Zeinstra, J.M.W. Hazes, B.W. Koes

Submitted

Abstract

Objective: To summarise current knowledge on the association between radiographic signs of osteoarthritis (ROA) in the hand and clinical symptoms.
Methods: A bibliographical search of Medline (published data before 30 June 2004) was carried out. Articles describing studies on the association between radiographic hand ROA and hand pain or hand function impairment were selected. The initial search resulted in 1180 potentially relevant articles of which 10 papers met the inclusion criteria. After screening the reference lists of these articles, an additional 2 articles were included. We also included two articles (from our group), which were submitted for publication and met our inclusion criteria.
Results: The sample size of the studies included in this appraisal ranged from 32 - 3906 subjects. Most of the studies included participants aged 45 years old and over, and more females were included (52-100%). Review of these articles revealed that there is a positive association between hand ROA and hand pain in general, but the reported strength of the association ranges from weak to strong (OR ranges from 1.9 to 6.5). Results on hand function impairment and ROA were inconsistent, ranging from no association to moderately associated. A severe form of ROA showed a stronger association with hand pain but, again, data on hand function impairment were inconsistent. An increasing number of joints with ROA showed a stronger association with both hand pain and hand function impairment.
Conclusion: This review revealed a great heterogeneity in terms of measurement of hand pain, hand function impairment and also hand ROA, suggesting that a uniform definition for each of these measurements might reduce the difficulty in comparing the results. Data on the association between a severe form of hand ROA or a general form of hand ROA with pain and dysfunction are limited and should be studied more thoroughly.

Introduction

Osteoarthritis is a leading musculoskeletal cause of disability in most western countries and the most common form of arthritis among the elderly.[1] The magnitude of this problem is increasing with the current ageing of the population in many countries. The hand is a frequently involved site in the patient suffering from osteoarthritis. Although the point prevalence of radiographic hand osteoarthritis (ROA) is reported to be as high as 28.9% to 76% in population-based studies, the prevalence of symptomatic hand osteoarthritis is much lower with a point prevalence of 4% to 6.2%.[2-4] Because only those with clinical symptoms of osteoarthritis seek medical care, it is important to know: 1) How many persons with radiographic signs of osteoarthritis suffer from clinical consequences of the disease such as hand pain or hand function impairment. In other words, what is the strength of the association between ROA and clinical symptoms? 2) Do persons with a severe form of ROA report more severe hand pain or hand function impairment? 3) As the hand consists of many joints, does an increasing number of hand joints with ROA influence the frequency or severity of hand pain or hand function impairment? 4) Does the location of the joints with ROA affect the association between radiographic signs and clinical symptoms? 5) In addition, most clinicians want to know to what extend hand ROA, among other possible determinants, contributes to an explanation of hand pain or hand function impairment in their patients. To address these questions, this study reviews and summarizes the existing knowledge on the clinical burden of radiographic hand osteoarthritis.

Methods

The literature was searched to identify relevant papers reporting on the association between radiographic hand osteoarthritis and association with pain and functional impairment.

To identify the studies a search was carried out in the Medline/Pubmed database (1966-June 2004). The search strategy is shown in the Appendix. The search was subsequently extended to screening the reference lists of all identified relevant articles.

A study was included in this review if it fulfilled all of the following criteria: 1) The article presented original data, 2) Radiographic hand osteoarthritis was measured, 3) At least one of the clinical symptoms including hand pain, hand functional impairment (such as grip strength, range of motion, hand disability measured by questionnaire

or observer, morning stiffness, etc.) was measured, 4) At least one association was reported between radiographic hand osteoarthritis and clinical symptoms, 5) The articles were written in English, Dutch, German, French, Danish, Norwegian, Swedish or the Persian language.

Statistical Analysis: To enhance compatibility of the results of the studies, and if the information provided in the studies allowed, we calculated odds ratios and 95% confidence intervals for the association between pain and radiographic findings. This was not possible for any of the studies evaluating hand function impairment. The calculation was performed based on the most commonly used radiographic scoring system (Kellgeren–Lawrence) used in ten studies with cut-off points of K-L= 2-4 versus K-L= 0-1 and its relationship with hand pain. The remaining results were compared in the way that they were originally reported.

Results

Identification and selection of the literature

The initial searches resulted in 1180 potentially relevant articles. Two reviewers (SMBZ, SD) independently evaluated the abstracts of the studies, which resulted in a selection of 45 articles according to the predefined inclusion criteria for full text review. One reviewer (SD) performed a full text review of the 45 articles resulting in the inclusion of 10 articles. After screening the reference lists of these ten articles, an additional two articles were included. We also included two articles (from our group) which met our inclusion criteria for this review; both studies were submitted for publication at the time of inclusion.

Finally, 14 studies met our selection criteria and were included.[5-18] Table 1 lists the characteristics of the studies. The sample size ranged from 32 - 3906 subjects. Most of the studied participants were females (52-100%). Except for two studies (Acheron et al., Lawrence *et al.*)[6,13] which both included younger subjects, the studies concerned participants aged 45 years and older. Hart *et al.*[8,9] and Dahaghin *et al.*[17,18] each used the same study population in two different studies, each reporting on different aspects. Similarly, Poiraudeau *et al.*[7] used a sub-sample of the study population of Spacek *et al.*[15] and reported on the association between hand ROA and hand function.

Table 1 **Characteristics of the included studies (N = 14)**

Author	Year	Setting	Size (n)	Female %	Age (in years)
Acheson *et al.*[13]	1973	* Open population (Six areas of the city of New Haven represent different socio-economic strata)	437	62	21 and over
Bagge *et al.*[14]	1991	Open population	160	62	Two groups (79 and 85 years old)
Baron *et al.*[12]	1987	Open population (independent elderly population)	32	81	76.8 (Mean)
Carman *et al.*[5]	1989	Open population	1491	54	50-74 (Range)
Dahaghin *et al.*[17] Dahaghin *et al.*[18]	2005 2005	Open population Open population	3906	58	55 and over
Hart *et al.*[9] Hart *et al.*[8]	1994 1991	Open population (Age-sex register of a general practice, Chingford) A sub-population of the Chingford study	1003 541	100	45-65 (Range) 54 (Mean)
Jones *et al.*[10]	2001	Rheumatology practice (all subjects who had a diagnosis of OA and a family history of OA)	524	66	Male: 53.2 (Mean) Female: 57 (Mean)
Labi *et al.*[16]	1982	Geriatric institution	67	64	81.9 (Mean)
Lawrence *et al.*[6]	1966	Open population (Leigh and Wensleydale)	2292	52	15-65+ (Range)
Pattrick *et al.*[11]	1989	Rheumatology practice and medical clinics in 3 groups (nodal generalised OA (NGOA), patient with erosive change on x-rays (EOA) and matched control group)	NGOA; 57 EOA; 10 Control; 52	92 90 92	69 (Mean) 70 71
Spacek *et al.*[15] Poiraudeau *et al.*[7]	2004 2001	Rehabilitation and Rheumatology This is a sub-population of the Spacek et al. population	160 90	92 90	62.1± 7.4 63.2 ± 8.9 (Mean ± SD)

* Acheson et al. used a sub-population for this study; the population was divided into those aged< 50 and > 50 years

Type of studies

The types of studies included in this appraisal were cross-sectional studies, cohort studies and one case-control study. Notifying that the association between ROA and hand pain or hand function impairment in the cohort studies and the case-control study was based on cross-sectional data and therefore we did not mention the type of each study specifically.

Measurements

Tables 2 and 3 present the measurements and the results as originally reported in the studies. In addition, the data of two studies[5,6] on hand pain enabled us to calculate odds ratio, which are also reported in Table 2. No study on hand function impairment had sufficient data to calculate odds ratios.

Hand ROA was assessed by different measurements. Ten studies[5,6,8,9,12-14,16-18] defined radiographic hand ROA by the Kellgren-Lawrence grading score. Jones *et al.*[10] and Pattrick *et al.*[11] used the modified Altman grading score, and Spacek *et al.*[15] and Poiraudeau *et al.*[7] used the Kallman grading score.

Hand pain was also measured in various ways. In some studies[6,8-10] the exact location of the pain in different hand joint groups was measured, whereas in other studies hand pain was reported only in general.[5,12,14,16-18] Lawrence *et al.*[6] in addition to reporting pain of specific hand joints, also reported on a group of individuals (with hand pain in general) who had difficulty in localizing pain in the specific joints of the fingers. Although Baron *et al.*[12] measured pain in specific hand joints, their results were based on the sum of the score for all hand joints together. Pain severity,[10] pain during performing manoeuvres[8,16] and clinical OA index[12] were also investigated.

Hand function impairment was also measured with different tools, including grip strength,[10,16] range of motion,[12,13,16] subjective hand disability measured by questionnaires (Health Assessment Questionnaire (HAQ), Cochin hand function and Australian/Canadian osteoarthritis hand Index (AUSCAN))[7,10,13,15,17,18] and objective hand disability measured by time to perform different hand functions, Jebson's test, and the Smith hand function test.[11,12,16]

Settings and study populations

Ten studies[5,6,8,9,12-14,16-18] evaluated the association between ROA and hand pain or hand functional impairment in the open population, including persons with and without the diagnosis of osteoarthritis. In the study of Lawrence *et al.*,[6] an additional sample of persons aged 65 years and over was examined to increase the numbers available in this age group, which tend to be low in a true random sample. Although the study of Labi *et al.*[16] recruited subjects from a geriatric institution, and study of Hart *et al.*[8,9]

recruited women from an age-sex register of large general practices, both studies were considered as an open population setting. Four other studies[7,10,11,15] recruited their population from rheumatology practice, medical or rehabilitation centres consisting of patients with an osteoarthritis diagnosis. However, Pattrick *et al*.[11] also included a control group consisting of people without a diagnosis of osteoarthritis.

Association between radiographic ROA and hand pain

Of the 14 studies, 10 investigated the association between ROA and hand pain (Table 2).[5,6,8-10,12,14,16-18] Because the measurement of hand pain varies among the studies, we categorised the results of the studies into the absence or presence of general pain in hand, pain in different hand joint groups, pain severity, pain during performing manoeuvres, and a clinical osteoarthritis index.

Absence or presence of pain in the hand: Five studies[5,6,14,17,18] reported on the association between hand pain in general and ROA. All studies showed that hand ROA is associated with hand pain in general; however, due to the use of different statistical methods, the strength of the association could not be compared for all the reviewed studies. Comparing only three studies,[5,6,17] using odds ratios on the association of hand ROA and hand pain in general, showed a broad range of the association varying from moderate to strong (OR ranges from 1.9 to 6.5). One study[17] explored the association between ROA and hand pain in terms of ROA in different hand joint groups, hand ROA in general, a more severe form of hand ROA and the increasing number of joints with ROA (Table 2).

Pain in specific hand joints: Four studies[6,8-10] reported on the association between pain localised in a specific hand joint and its association with ROA in the respective joint. Based on the data of Lawrence *et al.*,[6] we calculated odds ratios and confidence intervals for different hand joint groups, which revealed a strong association between hand pain in the specific hand joints with ROA of that joint. However, these odds ratios are not adjusted for age (crude odds ratio). Due to the heterogeneity of the statistical method used, we could not compare these latter results with 3 other studies in this category (Table 2).

Table 2 **Association between Radiological osteoarthritis and hand pain**

Author	Radiographic Osteoarthritis	Hand function impairment	Results	Calculated odds ratio (95%CI)
Absence or presence of pain in hand				
Bagge *et al.*[14]	K-L ≥ 2 in DIP, PIP, IP, MCP, CMC1, Inter-carpal and Radio-carpal joints	Ever pain	Both age groups pooled (79 and 85 years old) Joint complaint in 8% of K-L =1 12% of K-L =2 29% of K-L =3-4 A significant correlation between joint complaint and OA (test of linear trend, p<0.05)	NA
Carman *et al.*[5]	32 joints of hand-wrist graded with K-L score Hand OA: A Maximum score >1	Joint pain during the last month	Joint pain in *Men;* 23% of K-L = 0-1 35% of K-L = 2-4 *Women;* 36% of K-L = 0-1 53% of K-L = 2-4 *Total;* 30% of K-L = 0-1 46% 0of K-L = 2-4 The association of pain with maximum OA grade showed a significant linear trend (p< 0.0001) Mantel Haenzel relative risk of Hand pain with HOA (adjusted for sex); 1.9 (1.5 - 2.4)	*Males:* 1.8 (1.3 – 2.6) *Females:* 2 (1.5 – 2.7) *Total:* 2 (1.6 – 2.5)
Dahaghin *et al.*[17]	K-L ≥ 2 in at least one of the joints of DIP, PIP, MCP, CMC1/TS groups Hand OA; 2 groups out of three groups (DIP, PIP, CMC1/TS) showed K-L≥ 2. -The same definition with cut-off point K-L≥ 3 or K-L=4 -Number of joints with K-L ≥ 2	Hand pain during the last month	OR (95% CI) adjusted for age and gender DIP OA; 1.5 (1.2 - 1.8) PIP OA; 1.8 (1.4 - 2.3) MCP OA; 1.6 (1.1 - 2.3) CMC1/TS OA; 2.0 (1.6 - 2.4) Hand OA K-L≥ 2, OR; 1.9 (1.5 – 2.4) K-L≥ 3, OR; 1.8 (1.3 – 2.5) K-L=4, OR; 3.6 (2.2 – 5.8) Number of joints with OA (continuous variable) OR; 1.1 (1.1 – 1.2) OA of all four joint groups OR; 2.7 (1.4 – 5.2)	NA
Dahaghin *et al.*(2005)[18]	Same as above	Same as above	Radiographic hand OA adds a small part to the explained variance of hand pain (R^2 = 0.005)	

Author	Radiographic Osteoarthritis	Hand function impairment	Results	Calculated odds ratio (95%CI)
Lawrence *et al.*[6]	K-L ≥ 2 in the hand	Rheumatic pain in the hand in the past week	Prevalence of hand pain in general hand OA *Males:* 2.6% of K-L = 0-1 6.8% of K-L = 2 18.3% of K-L = 3-4 *Females:* 4.3% of K-L = 0-1 21.1% of K-L = 2 27.3% of K-L = 3-4	*Males:* 4.7 (2.4-9.1) *Females:* 7.2 (4.4 – 11.6) *Total* 6.5 (4.4 – 9.6)
Pain in specific hand joints				
Hart *et al.* (1994)[9]	Each joint: K-L ≥ 2 IP and CMC1 groups were defined and the highest scores for the joint group were taken	Questionnaire about joint symptoms, including details of pain, stiffness, and swelling in a joint lasting more than a month.	Symptoms in IP joints (grade 0/1 in clinical examination) 10.9% of K-L = 0-1 27.6% of K-L = 2 43.8% of K-L = 3-4 Pain in base of the thumb (grade 0 on clinical examination) 7.9% of K-L = 0-1 22.2% of K-L = 2 47.4% of K-L = 3-4	NA
Hart *et al.* (1991)[8]	Same as above	Same as above	Symptoms in 41% of the patient with DIP OA 32% with PIP OA 37% with CMC OA	NA
Lawrence *et al.*[6]	K-L ≥ 2 in DIP, PIP, MCP, CMC1, Wrist (CMC+ Inter-carpal joints)	Rheumatic pain in the hand joint groups in the past week	Pain in *Males:* DIP: 1.4% of K-L = 0-1 8.1% of K-L = 2 9.4% of K-L = 3-4 PIP: 4.3% of K-L = 0-1 22.7% of K-L = 2 50% of K-L = 3-4 MCP: 3.4% of K-L = 0-1 9% of K-L = 2 22.2% of K-L = 3-4 CMC: 2.2% of K-L = 0-1 3.8% of K-L = 2 33.3% of K-L = 3-4 Wrist: 4.3% of K-L = 0-1 9.1% of K-L = 2 42.9% of K-L = 3-4 *Females:* DIP: 1.3% of K-L = 0-1 6.2% of K-L = 2 25% of K-L = 3-4 PIP: 6.8% of K-L = 0-1 14.1% of K-L = 2 41.2% of K-L = 3-4 MCP: 6% of K-L = 0-1 13.9% of K-L = 2 13.3% of K-L = 3-4 CMC: 3.4% of K-L = 0-1 20.2% of K-L = 2 34.4% of K-L = 3-4 Wrist: 6.5% of K-L = 0-1 4.2% of K-L = 2 0% of K-L = 3-4	*Males:* DIP: 6.6 (2.9-15.1) PIP: 8.9 (4.6 – 17.5) MCP: 3.7 (1.8 – 8.0) CMC: 5.8 (2.4 – 13.9) Wrist: 4.6 (2.2- 9.9) *Females:* DIP: 10 (4.6 – 21.9) PIP: 4.2 (2.4 – 7.3) MCP: 2.5 (1.3 – 4.9) CMC: 9.2 (5.1- 16.5) Wrist: 0.6 (0.08 –4.3)
*Jones *et al.*[10]	Modified Altman score DIP score (0-48) score CMC1 score (0-12)	AUSCAN LK 3.0 (Australian/ Canadian osteoarthritis hand Index) Pain score (0-20) presence in last 48 hours	DIP: pain/any OA kappa=0.16 Severity cut-off point of OA, kappa= 0.23 CMC1 OA: pain/ any OA kappa=0.21 pain/severity cut-off point of OA, kappa=0.25	NA

Author	Radiographic Osteoarthritis	Hand function impairment	Results	Calculated odds ratio (95%CI)
Pain severity (AUSCAN)				
*Jones *et al.*[10]	Same as above	Same as above	Hand pain with DIP Multivariate β = 0.17 (p = 0.003) Hand pain/CMC1 Multivariate β = 0.14 (p = 0.024)	NA
Pain during performing manoeuvres				
Hart *et al.* (1991)[8]	Each joint: K-L ≥ 2 IP and CMC1 groups were defined and the highest scores for the joint group were taken	Pain on movement was examined	Sensitivity of pain on movement DIP OA = 1% PIP OA = 5% CMC1 OA = 36% Specificity of pain on movement DIP OA = 99% PIP OA = 99% CMC OA = 91%	NA
Labi *et al.*[16]	K-L ≥ 2 in DIP, PIP, MCP, CMC1 -Number of joints with OA -Average degree of severity of hand OA	Presence or absence of pain while performing various manoeuvres	Functional problems (pain during extension, flexion, or any wrist motion) in relation with OA in CMC1 were infrequent (no estimates were available).	NA
Clinical OA index				
Baron *et al.*[12]	Each joint: K-L score Total OA score: Sum of the score for all joints Or Number of joints with K-L ≥ 2	Tenderness or pain on motion, osteophytes and crepitus ranged (0-3: none to severe) for each hand joints were assessed. Adduction deformity was measured in CMC. COAI; a clinical OA index by summing the score of all joints for both hands	Clinical OA index (COAI) and OA r = 0.53 p = 0.001	NA

Abbreviations: DIP (distal interphalangeal joints) PIP (proximal interphalangeal joints), IP (interphalangeal joints), MCP (metacarpophalangeal joints) CMC (carpometacarpal joints), TS (trapezioschaphoid joint), K-L (Kellgren-Lawrence score 0-4), r (correlation), p (p value), OR (odds ratio), CI (confidence interval), β (regression coefficient), R^2 (explained variance), NA (not applicable), * Clinical population

Pain severity: Only Jones *et al.*[10] evaluated the severity of pain. They reported a β value of the linear model of the association between hand pain and DIP or CMC1 ROA separately. Adjusted for other factors, they reported a β value of 0.17 for the association between DIP ROA and hand pain. This means that one unit increase in the DIP ROA score (range 0-48) leads to a 0.17 unit increase in pain (range 0-20). They also evaluated the association between CMC1 ROA and severity of pain, showing that one unit increase in the radiographic CMC1 score (range 0-12), leads to a 0.14 unit increase in pain (range 0-20) (Table 2).

Pain during performing manoeuvres: Two studies[8,16] evaluated the presence of pain while performing various manoeuvres, or pain on movement, and their association with ROA. Hart *et al.*[8] found low sensitivity and high specificity of pain on movement in different hand joint groups with respect to the presence of ROA. Labi *et al.*[16] found no association between pain during performing manoeuvres and ROA in the CMC1 joint (Table 2).

Clinical OA index: Baron *et al.*[12] defined a clinical osteoarthritis index, in which pain was one of the criteria, and reported a significant correlation of r=0.53 with ROA (Table 2).

Association between radiographic ROA and hand function impairment

Of the 14 studies, 9[7,10-13,15-18] investigated the association of ROA with different aspects of hand function (Table 2). Because hand function was measured by various methods, we categorised the results of the studies into measurements of grip strength, range of motion, subjective disability (measured by questionnaire), and objective disability (measured by observer).

Grip strength: Two studies[10,16] evaluated the association between grip strength and hand ROA. In the study of Jones et al. grip strength reduces when a higher radiographic score was present. They showed a 0.09 unit reduction of mean grip strength (mean; males 17.4, females 10.6) with increasing one unit ROA score in DIP joints (0 – 48). They also reported a 0.05 unit reduction of mean grip strength (mean; males 17.4, females 10.6) with increasing one unit ROA score in CMC joints (0 – 12). Labi *et al.*[16] reported on the explained variance of grip strength by hand ROA, which was not consistent using different definitions of hand OA. Details are given in Table 3.

Table 3 **Association between Radiological osteoarthritis and hand function impairment**

Author	Radiographic Osteoarthritis	Hand function impairment	Results
Grip Strength			
*Jones *et al.*[10]	Modified Altman score DIP score (0-48) CMC1 score (0-12	Grip measurement: using a bulb dynamometer	Mean grip strength/DIP OA Multivariate β = - 0.09 (p = 0.052) Mean grip strength/CMC1 OA Multivariate β = - 0.05 (p = 0.015)
Labi *et al.*[16]	K-L ≥2 in DIP, PIP, MCP, CMC1 Number of joints with OA Or Average degree of severity of hand OA	Grip strength measured by milimeter of mercury	Both genders showed considerably less mean grip strength in subjects with hand ROA in dominant hand than subjects without ROA. This was not the case in non-dominant hand. Reduction in grip strength was significantly present in both definition of ROA (severity and number of finger joints with ROA). R^2 in regression analysis (p <0.001) Right hand ROA: Severity R^2 = 5.0% Number of joints with ROA R^2 = 0.3% Left hand ROA: Severity R^2 = 0.0% Number of joints with ROA R^2 = 3.9%
Range of motion			
Acheson *et al.*13	Each joint: K-L score Index I =Total score of all the joints divided by the number of joints with K-L ≥1	Range of motion using a goniometer of the left MCP joints	Male < 50 years with limited ROM showed more severe form of ROA but males ≥ 50 years showed more mild form of ROA. Both age group of females < 50 and ≥ 50 years with limited ROM showed more severe form of ROA. The associations were higher for females (no estimates were available)
Baron *et al.*[12]	Each joint: K-L score Total ROA score: -Sum of the score for all joints -Number of joints with K-L ≥ 2	Range of motion (ROM) for each joint Total ROM = the score of all joints of both hands	ROM and ROA, r = 0.44 p = 0.008
Labi *et al.*[16]	K-L ≥2 in DIP, PIP, MCP, CMC1 -Number of joints with ROA or -Average degree of severity of hand ROA	Abnormality in ROM Limitation in wrist extension to less than 30°	A negligible number with ROA in the fingers or wrist or hand ROA in general had incomplete ROM (no estimates were available).

Author	Radiographic Osteoarthritis	Hand function impairment	Results
Subjective disability (measured by Questionnaire)			
Acheson *et al.*[13]	Each joint: K-L score (0-4) Index I =Total score of all the joints divided by the number of joints with K-L ≥1 questionnaire regarding disability	People with morning stiffness and/or pain in the joints during three months before the interview were asked to answer the questionnaire regarding disability	Male < 50 years with disability showed more severe form of ROA but males ≥ 50 years showed more mild form of ROA. Both age groups of females < 50 and ≥ 50 years with disability showed more severe form of ROA. The associations were higher for females (no estimates were available).
Dahaghin *et al.*[17]	K-L ≥ 2 in one of the joint of the groups: DIP, PIP, MCP, CMC1/TS Hand ROA: Hand ROA: 2 out of three groups (DIP, PIP, CMC1/TS) with K-L≥ 2 or K-L≥ 3 or K-L=4 (right/left hand)	Hand disability: 8 questions of Health assessment questionnaire (HAQ) regarding hand function were used. Hand disability: A mean score ≥ 0.5	DIP ROA, OR=1.3 CI (0.9 - 1.8) PIP ROA, OR=1.1CI (0.8 - 1.7) MCP ROA, OR=2.0 CI (1.3 - 3.0) CMC1/TS, ROA OR=1.3 CI (1.0 - 1.9) Hand ROA, K-L ≥ 2, OR; 1.5 CI (1.1 - 2.1) K-L ≥ 3, OR; 1.6 CI (1.1 – 2.5) K-L =4, OR; 1.6 CI (0.9 – 2.9) Number of joints with ROA (continuous variable) of dominant hand OR; 1.1 CI (1.0 – 1.2) ROA of all four joint groups OR; 2.7 CI (1.3 - 6.0)
Dahaghin *et al.* (2005)[18]	Same as above	Same as above	Radiographic hand ROA did not add to the explained variance of hand disability (R^2 = 0.000)
*Jones *et al.*[10]	Modified Altman score DIP score (0-48) score CMC1 score (0-12)	AUSCAN LK 3.0 (Australian/Canadian osteoarthritis hand index) measured hand function (0 -36)	Dysfunction/any DIP ROA kappa=0.30, severity cut-off point of ROA kappa= 0.35, Dysfunction/any CMC1 ROA kappa=0.36, severity cut-off point of ROA kappa =0.44 Function with DIP ROA Multivariate β=0.08 (p=0.057) Function/CMC1 ROA Multivariate β=0.08 (p=0.015)
*Spacek *et al.*[15]	Kallman score for IP, Base of the thumb Total score (range 0-220)	Cochin hand function (CHFS, range 0-90)	CHFS was not correlated with radiographic score. r=0.20 with total ROA score r=0.07 with thumb ROA score r=0.18 with IP ROA score
*Poiraudeau *et al.*[7]	Same as above	Same as above	Cochin scale and Kallman score at baseline r=0.14

Author	Radiographic Osteoarthritis	Hand function impairment	Results
Objective disability (measured by observer)			
Baron *et al.*[12]	Each joint: K-L score Total ROA score: Sum of the score for all joints Or Number of joints with K-L ≥ 2	An overall hand function index (HFI) was obtained from Smith hand function test (time to achieve three types of activity)	HFI did not correlate with ROA.
Labi *et al.*[16]	K-L ≥2 in DIP, PIP, MCP, CMC1 Number of joints with ROA Or Average degree of severity of hand ROA	Performance of Jebson's test: measuring the mean time spent on 7 manoeuvres	No reduction in Jebson test attributed to hand ROA.
*Pattrick *et al.*[11]	**NGOA:** polyarticular IP OA affecting more than 3 rays of each hand with Heberden's node, unrelated to the trauma at least 10 year history of disease **EOA:** above characteristics + subchondral erosive change **Control group:** without any symptom of OA Radiographic scoring for IP, MCP, CMC, TS, radiocarpal using modified Altman score. A summed score for both hands: by adding the score of individual joints.	Each hand function was timed and assessed for presence or absence of pain; difficulty, inability to complete, and use of trick movement. A total time of completion was calculated by adding together all the timed functions (light pinch, heavy pinch and dexterity)	**Control group:** total ROA score correlated with time to complete Light pinch r = 0.29 (p<0.02) Heavy pinch r = 0.27 (p<0.03) Right thumb base ROA with time to perform dexterity r=0.35 (p<0.006) **NGOA group:** total radiographic score correlated with time to perform dexterity r = 0.28 p<0.02 but no other associations were apparent. **EOA and NGOA groups:** The mean ROA score did not differ significantly in those with hand disability compared to those without disability.

Abbreviations: DIP (distal interphalangeal joints) PIP (proximal interphalangeal joints), IP (interphalangeal joints), MCP (metacarpophalangeal joints) CMC (carpometacarpal joints), TS (trapezioschaphoid joint), K-L (Kellgren – Lawrence score 0-4), r (correlation), p (p value), OR (odds ratio), CI (confidence interval), B (regression coefficient), R^2 (explained variance), * Clinical population

Range of motion: Three studies[12,13,16] measured the association between range of motion and hand ROA, of which one[12] showed a moderate correlation between range of motion and ROA in the hand. The two other studies represent their results as figures,[13] or in the text[16] (Table 3).

Subjective disability (measured by questionnaire): Six studies[7,10,13,15,17,18] evaluated disability using different questionnaires including HAQ, Cochin hand function and AUSCAN. Two studies[10,17] explored the association between hand ROA and hand disability in terms of ROA in different hand joint groups, hand ROA in general, a more severe form of hand ROA and the increasing number of joints with ROA (Table 3). In the study of Jones et al. the severity of hand function was also taken into account. Adjusted for other factors including pain, they reported that DIP ROA showed a β value of 0.08 with hand dysfunction, which means that one unit increase in ROA score (range 0-48) leads to 0.08 unit more hand dysfunction (range 0 –36). Further, CMC ROA showed a β value of 0.08 with hand dysfunction, meaning that one unit increase in ROA score (range 0-12) leads to 0.08 unit more hand dysfunction (range 0 –36). Acheson et al. evaluated the presence of hand disability in patients with a history of pain during the last three months. However, because they presented their data on figures, we were unable to derive the exact statistical estimates. The details on these 6 studies are presented in Table 3.

Objective disability (measured by observer): Three studies[11,12,16] evaluated objective disability by measuring the time the persons needs to perform various hand functions. Pattrick *et al.* [11] investigated time to perform different hand function in three groups, including two groups with ROA and one group without ROA. They showed only poor correlation between time to complete hand function with ROA in both groups (with/ without diagnosis of osteoarthritis).

Discussion

A review of 14 articles shows that there is evidence for a positive association between hand ROA and hand pain, but the strength of association varies between studies. There is inconsistent evidence for an association between ROA and hand function impairment, ranging from no association to a moderate association.

Data on severity of ROA or a general form of ROA in the hand and its association with pain were limited. The data suggest that a more severe form of ROA, or an increasing number of hand joints with ROA, is associated with an increase in frequency

or severity of pain in the hand. However, the association between a more severe form of hand ROA and hand function impairment was inconsistent in two studies (no change in one study[17] versus deterioration of hand function in another study[10]). In both these studies, an increasing number of hand joints with ROA were accompanied with a stronger association with hand function impairment.

Further, the association between ROA in hand joints with respect to their location and hand pain did not show consistent results in the studies. Only one study[17] investigated the association of ROA in different hand joints with hand function impairment, and showed a higher association of ROA in MCP groups with hand disability.

The explained variance of hand pain due to hand ROA was evaluated in only one study,[18] which showed that hand ROA added only a small part to the explained variance of hand pain. The explained variance of hand function impairment due to ROA was investigated in only two studies,[16,18] which reported inconsistent results.

We encountered several problems when comparing the results of the reviewed studies. One of the main problems was the diversity of measurement of hand pain or hand function impairment. This heterogeneity was demonstrated when we categorised the results of the studies based on measurement of hand pain or hand function impairment. As an example, R^2 was presented to explain the variance of hand function impairment due to ROA in two studies,[16,18] but because two different measurements were used for hand function (grip strength and hand disability), it was difficult to draw a conclusion. Based on the results of two studies[6,17] one could hypothesize that if the association between pain in the individual hand joint was examined in relation to the ROA in that specific hand joint, it would probably show a stronger association compared to the association between hand pain in general and ROA of an individual hand joint. However, we should bear in mind that the stronger odds ratios were not adjusted for age, and that differences between the study populations might be a reason for the stronger association.

Another feature in the definition of hand pain concerns the duration of hand pain. In the different studies this varied from the presence of any hand pain to hand pain during last 48 hours, past week, past month or past three months, which is likely to influence the association of the hand pain with radiographic findings. However, due to difference in statistical methods, population setting, age difference and definition of ROA of the reviewed studies, it was hard to draw a conclusion in order to investigate this hypothesis.

Another problem encountered when comparing the results was the presence of non-transparent or poor statistics. For example, Acheson *et al.*[13] reported their results as graphs, whereas Labi *et al.*[16] reported significant associations in the text without

giving the exact statistics, or the magnitude of the association and its confidence interval. Jones *et al.*[10] used two different statistical method (kappa measurement and linear regression models, β) to investigate the association of interest. The authors showed a statistically significant moderate association between the ROA score and hand pain or hand function impairment using a linear regression model, but presented a low kappa value when evaluating the same association. The disadvantage of kappa is that if the frequency of disease is very low or high, the calculated kappa will decrease drastically. This might be the reason for a low kappa value in their study.

To better compare the results, when sufficient data was available, we calculated the odds ratio.[5,6] These odds ratios were calculated for male and females separately, but could not be adjusted for age and other possible confounders (crude odds ratio). However, only three studies[5,10,17] presented their data adjusted for other factors.

Further, as is often the case in systematic appraisals, we encountered differences in study population (percentage of males), setting (open population, or patient setting), and age distribution, making it more difficult to compare the results of the reviewed studies. Especially the difference between an open population and a patient population should be emphasized; in a patient population the degree of severity of hand pain will be assessed against ROA, while in an open population the presence or absence of the clinical symptoms are often examined against radiographic findings.

Despite the effort put into identifying all relevant articles, some relevant articles may have been missed because they used different key words, had an unclear abstract, or were not indexed in Pubmed (Medline). Although our search strategy might not be optimal, we believe that we included the most appropriate studies that evaluated the clinical aspects of hand ROA and assume that the data presented here give a clear insight into the currently available studies on this topic.

In summary, this review revealed a great heterogeneity in terms of measurement of hand pain, hand function impairment and also radiographic hand OA, suggesting that a uniform definition for each of these measurements might reduce the difficulty in comparing the results. Further studies on the association between ROA and clinical symptoms (particularly the severity of ROA, and number of hand joints with ROA) using consistent definitions and relevant statistical methods, are recommended.

Appendix

The following search keys were used for systematic appraisal

1. OA	17. Impact
2. Osteoarthritis	18. Complain*
3. Osteoarthrosis	19. Burden
4. #2 OR #3 OR #1	20. Pain
5. Hand	21. Disability
6. Finger	22. Community
7. Wrist	23. Grip
8. CMC	24. Pinch
9. DIP	25. Function
10. PIP	26. Clinical
11. IP	27. Symptom
12. MCP	28. Morning stiffness
13. TS	29. Morning
14. Thumb	30. Stiffness
15. #14 OR #13 OR #12 # OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5	31. #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
16. #15 AND #4	32. #31 AND #16

: number
All keys were searched in the Abstract and in the article title

References

1. March LM, Bachmeier CJ. Economics of osteoarthritis: a global perspective. *Baillieres Clin Rheumatol* 1997;11:817-34.
2. van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. *Ann Rheum Dis* 1989;48:271-80.
3. Carmona L, Ballina J, Gabriel R, Laffon A. The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. *Ann Rheum Dis* 2001;60:1040-5.
4. Niu J, Zhang Y, LaValley M, Chaisson CE, Aliabadi P, Felson DT. Symmetry and clustering of symptomatic hand osteoarthritis in elderly men and women: the Framingham Study. *Rheumatology* (Oxford) 2003;42:343-8.
5. Carman WJ. Factors associated with pain and osteoarthritis in the Tecumseh Community Health Study. *Semin Arthritis Rheum* 1989;18:10-3.
6. Lawrence JS, Bremner JM, Bier F. Osteo-arthrosis. Prevalence in the population and relationship between symptoms and x-ray changes. *Ann Rheum Dis* 1966;25:1-24.
7. Poiraudeau S, Chevalier X, Conrozier T, Flippo RM, Liote F, Noel E, Lefevre-Colau MM, Fermanian J, Revel M, Rhumato R. Reliability, validity, and sensitivity to change of the Cochin hand functional disability scale in hand osteoarthritis. *Osteoarthritis Cartilage* 2001;9:570-7.

8. Hart DJ, Spector TD, Brown P, Wilson P, Doyle DV, Silman AJ. Clinical signs of early osteoarthritis: reproducibility and relation to x ray changes in 541 women in the general population. *Ann Rheum Dis* 1991;50:467-70.
9. Hart D, Spector T, Egger P, Coggon D, Cooper C. Defining osteoarthritis of the hand for epidemiological studies: the Chingford Study. *Ann Rheum Dis* 1994;53:220-3.
10. Jones G, Cooley HM, Bellamy N. A cross-sectional study of the association between Heberden's nodes, radiographic osteoarthritis of the hands, grip strength, disability and pain. *Osteoarthritis Cartilage* 2001;9:606-11.
11. Pattrick M, Aldridge S, Hamilton E, Manhire A, Doherty M. A controlled study of hand function in nodal and erosive osteoarthritis. *Ann Rheum Dis* 1989;48:978-82.
12. Baron M, Dutil E, Berkson L, Lander P, Becker R. Hand function in the elderly: relation to osteoarthritis. *J Rheumatol* 1987;14:815-9.
13. Acheson RM, Ginsburg GN. New Haven survey of joint diseases. XVI. Impairment, disability, and arthritis. *Br J Prev Soc Med* 1973;27:168-76.
14. Bagge E, Bjelle A, Eden S, Svanborg A. Osteoarthritis in the elderly: clinical and radiological findings in 79 and 85 year olds. *Ann Rheum Dis* 1991;50:535-9.
15. Spacek E, Poiraudeau S, Fayad F, Lefevre-Colau MM, Beaudreuil J, Rannou F, Fermanian J, Revel M. Disability induced by hand osteoarthritis: are patients with more symptoms at digits 2-5 interphalangeal joints different from those with more symptoms at the base of the thumb? *Osteoarthritis Cartilage* 2004;12:366-73.
16. Labi ML, Gresham GE, Rathey UK. Hand function in osteoarthritis. *Arch Phys Med Rehabil* 1982;63:438-40.
17. Dahaghin S, Bierma-Zeinstra SM, Ginai AZ, Pols HA, Hazes JM, Koes BW. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). *Ann Rheum Dis* 2005;64:682-7.
18. Dahaghin S, Bierma-Zeinstra SM, Reijman M, Pols HA, Hazes JM, Koes BW. Prevalence and determinants of one month hand pain and hand related disability in the elderly (Rotterdam study). *Ann Rheum Dis* 2005;64:99-104.

5

Does hand osteoarthritis predict future hip or knee osteoarthritis?

S. Dahaghin, S.M.A. Bierma-Zeinstra, M. Reijman , H.A.P. Pols, J.M.W. Hazes, B.W. Koes

Arthritis & Rheumatism (in press)

Abstract

Objectives: To evaluate the risk of future hip/knee osteoarthritis (OA) in subjects with hand OA at baseline and to evaluate whether the concurrent presence of hand OA, other risk factors or an OA biomarker (type II Collagen C-telopeptide degradation product) [CTX-II] increase the risk further.

Method: Hand (baseline), hip and knee (baseline and 6.6 years later) radiographs of a randomly selected subset of a population ≥55 years (Rotterdam study) were scored for OA (Kellgren-Lawrence (K-L)). A total of 1,235 subjects without OA of hip/knee (K-L= 0-1) at baseline were included. CTX-II was measured at baseline. Using logistic regression, the independent risk of hand OA for future hip/knee OA was assessed, also stratified for age, gender, BMI, family history of OA and heavy workload.

Results: Overall 12.1% of participants (19.7% of those with hand OA versus 10.0% of those without) developed hip/knee OA (OR 2.1;CI 1.3, 3.1). Hand OA showed an increased risk of future hip OA (OR 3.0;CI 1.6, 5.4), increasing further in the group with a family history of OA. Hand OA showed an OR of 1.6 (CI 1.0, 2.8) for future knee OA, increasing further in overweight people. Concurrent hand OA and high CTX-II increased the risk further for hip/knee OA at follow-up (OR 4.2;CI 2.3, 7.8).

Conclusion: Hand OA showed an increased risk of future hip/knee OA, which is higher for hip OA than for knee OA. Concurrent presence of hand OA and other risk factors or high CTX-II increased the risk further for future hip/knee OA.

Introduction

Osteoarthritis (OA) is the most common form of arthritis among the elderly, and a leading musculoskletal cause of disability in Western countries.[1,2] Due partly to the length of working careers, the substantial prevalence of OA in middle-aged people causes much working time to be lost to illness.[3] Expressed in terms of pain, disability and cost, the clinical and societal impact of OA of the weight-bearing joints (i.e. the hips and knees) is greater than that of hand OA.[1]

It has been suggested that generalized OA may be a distinct disease in which systemic (genetic) predisposition is more important than local (mechanical) factors.[1,4] A post-mortem bone study recently confirmed the hypothesis that OA is caused primarily by a systemic predisposition to a certain type of bone response to mechanical stresses.[5] Hand, hip and knee OA are thus based partly on a systemic predisposition. Though clinically less relevant, the presence of hand OA may therefore predict the more disabling hip or knee OA later in life.

Although other cross-sectional studies have addressed the association of hand OA with hip or knee OA,[6-10] we know of only one study that has examined the link between hand OA earlier in life and knee OA later on.[11] Similarly, no study has evaluated this question for the occurrence of hip OA. By identifying subjects with a tendency for OA and modifying their risk factors, it may be possible to avoid or prevent osteoarthritis-related pain and disability in the weight-bearing joints. OA biomarkers, irrespective of the joints in which they originate, may also have a predictive value. Christgau et al. developed a specific immunoassay for measuring the urinary concentration of collagen type II C-telopeptide degradation product (CTX-II); they reported that patients with OA or rheumatoid arthritis had a higher level of CTX-II than the control group.[12] CTX-II is also reported to be associated with both the prevalence and progression of OA at the knee and hip.[13]

The combination of several risk factors and biomarkers may identify groups at risk for developing OA in the weight-bearing joints. With the overall aim of identifying high-risk groups, this study had the following objectives: 1) to assess the risk of future hip/knee OA in subjects who have hand OA at baseline; 2) to compare the risk of future hip/knee OA according to presence of radiographic OA in different hand joint groups; and 3) to evaluate whether the risk of future hip/knee OA would be further increased by the concurrent presence of hand OA, other risk factors or an OA biomarker.

Subjects and methods

Study population: The present study was conducted as a part of the *Rotterdam Study*, a prospective population-based cohort study of determinants and prognosis of chronic diseases in the elderly (55 years and older). In total, 7983 participants (response rate of 78%) were examined. The complete study design has been described previously.[14]. The baseline measurements were conducted between April 1990 and July 1993. Radiographs of hands, hips and knees were made of all participants at baseline, and hip and knee radiographs were made again at follow-up a mean of 6.6 years later; hand radiographs were not made at this follow-up period. Radiographs of hip and hand were scored for all participants available at follow-up. For practical reasons only radiographs of a randomly selected subgroup of the population available for follow-up were scored for knee OA. Included in this study were 1235 participants with scored radiographs of hip, knee and hand without prevalent OA at hip/knee at baseline, which means that they had a Kellgren-Lawrence (K – L) score of 0 or 1.

Measurements

Hand radiographs

Standard anteroposterior radiographs of both hands were taken for each subject at baseline. In 2002, two assessors were trained by a radiologist to score hand radiographs using a training set of radiographs. Each assessor scored a half of the radiographs of the participants who were available for follow-up, blind for other data such as clinical or demographic variables. The exact method of scoring radiographs was described previously.[15] Definite radiographic OA for each joint was defined as a K-L= 2-4. Four groups of joints were scored: distal interphalangeal joints including interphalangeal joint of the thumb (DIP), the proximal interphalangeal joints (PIP), metacarpophalangeal joints (MCP), and base of the thumb including first carpometacarpal joint and trapezioscaphoid joint (CMC1/TS). A group was considered positive if at least one joint of the group in either hand on the left and/or right side showed a K-L of 2-4.

Hand OA was defined as the presence of a K-L=2 - 4 in two out of three groups (DIP/IP, PIP, and CMC1/TS) of either hand on the left and/or right side. This definition was also used in a previous study.[6]

To measure reliability of the scoring of the hand radiographs the two assessors, both independently of each other, read a random subset of 205 radiographs. Inter-

observer reliability of a K-L= 2-4 (dichotomous variable) expressed by kappa statistics was as follows: DIPs; 0.60, PIPs; 0.61 MCPs; 0.63 and CMC1/TS (base of the thumb); 0.74.

Hip and knee radiographs

Weight-bearing anteroposterior radiographs of the hip and knee were obtained at 70 kV, a focus of 1.8 mm^2, and a focus to film distance of 120 cm, applying a Fuji High Resolution G 35 × 43 cm film. Radiographs of the pelvis were obtained with both feet in 10^0 internal rotations and the X-ray beam centered on the umbilicus, and of the knee with the patellae in central position. A trained reader (MR) scored the hip radiographs of baseline and follow-up, unaware of the clinical status of the participants. All radiographs were grouped by participants and read by pairs chronologically ordered, the order being known to the reader (chronologically ordered reading procedure); this is the recommended procedure in longitudinal studies.[16] The radiographs of the knee were scored for OA by two observers who followed the same procedure independently.[17] The readers of hip and knee radiographs were blinded the finding on hand radiographs. Although hand radiographs were in the same folder with hip and knee radiographs, the hip and knee radiographs were scored for other purposes and the design of the present study was unknown to the readers at the time of scoring. OA of the hip and knee was defined according to the K-L score (atlas-based) in five grades (0 -4).[13] Incidence of hip/knee OA was defined as the presence of a K-L= 2-4 of one or both hips or knees at follow-up in the participants without OA of the hip/knee at baseline (K-L = 0-1). Hip replacement was also considered as a positive OA of the hip. Knee replacement was not present at follow-up.

To measure the reliability of the scoring system for hip OA, two assessors (SMABZ, MR) both read independently of each other a random subset of 148 radiographs. The inter-observer reliability (K-L= 2-4; dichotomous variable) was good (Kappa = 0.68). Of the knee radiographs, after each set of 150 radiographs the scores of the two readers were evaluated. Whenever the K-L score differed, the two readers met to read the radiographs together, and a consensus score was determined.

Assessment of other known OA risk factors

Each subject's age, body mass index (BMI), pain in the hip and knee, family history of OA, and heavy mechanical workload were assessed, since they are known risk factors for OA. Age was analyzed as a categorized variable in two groups; the upper tertile of the age group (70 years and older) was compared with the two lower tertiles (55-62 and 63-69 years). The exact cut-off point for the upper tertile is 68.5 years, which we rounded up to 69 years. Height and weight (for calculating body mass index, BMI) was

measured at the research center and subjects with a BMI higher than 27.4 were defined as overweight (highest tertile of the BMI of the total population of the Rotterdam study).[18] Self-reported presence of pain during the previous month in the left and/or right hip or knee was used for the definition of hip/knee pain. Self-reported presence of OA in one or more family members (parents, children or siblings) was considered as a positive family history. The current or last occupation was asked for, including the number of years worked in this occupation. The jobs were coded according to a job title scheme used at Statistics Netherlands (CBS, Statistics Netherlands, 1985).[19] Heavy mechanical workload was defined as: participants worked in a heavy physically demanding work (indoors/outdoors) and were exposed to such work longer than 8 years (above median of the exposure time).

Measurement of CTX-II

To more specifically identify groups at high risk of OA in the future, we also used a new OA biomarker, the collagen type II C-telopeptide degradation marker (CTX-II). Overnight fasting urine samples were obtained from all subjects at baseline and kept frozen at -20° C. Monoclonal antibody F46, specific for CTX-II C-telopeptide fragments, was used in a competitive enzyme-linked immunosorbent assay (ELISA) format developed for measurement of urine samples.[12] The concentration CTX-II (ng/l) was standardized to the total urine creatinine (mmol/l), and the unit for corrected CTX-II concentration was ng/mmol. The CTX-II concentration in this study population ranged from 31 to 680 ng/mmol (Figure 1). CTX-II was measured for a randomly selected subgroup and therefore these data were only available for 899 participants of our study group. However, the median of the CTX-II concentration in the original measurement[13] was used as a cut-off point in this study. We used the dichotomized variable where CTX-II >177 ng/mmol was compared with the lower concentration.

Statistical analysis

Using univariate and multivariate logistic regression analysis, we performed the following analyses. First, we determined the risk of incident hip OA, knee OA, and hip/knee OA at follow-up in subjects who had radiographic evidence of hand OA at baseline. In multivariate analysis we adjusted for the follow-up period and for those factors (age, gender and BMI) that already showed in our data to be an independent risk factor for either hip or knee OA in the future. We also checked whether the risk of hand OA for future hip/knee OA was independent from possible early signs of hip/knee OA present at baseline (hip/knee pain, and doubtful OA (K-L=1) of the hip/knee) as well as the presence of a high level of an OA biomarker (CTX-II).

Second, we determined the risk of future hip, knee and hip/knee OA in subjects with radiographic evidence of OA in the different hand joint groups at baseline. Adjustment for age, gender, BMI and follow-up period were performed.

Third, we determined the risk of future hip, knee and hip/knee OA in subjects with radiographic evidence of hand OA at baseline stratified according to the presence of other possible risk factors such as age, gender, BMI, heavy workload, presence of family history of OA as well as a high level of CTX-II with additional adjustment for age, gender, BMI and follow-up period, if not already defined in the strata.

Fourth, we determined whether the risk of the concurrent presence of two risk factors (hand OA and OA biomarker) would increase further the risk of future hip or knee OA with additional adjustment as mentioned above. The risk of the combination of hand OA and high CTX-ll was also compared in the subgroups with/without a third risk factor (overweight) adjusted for age, gender and follow-up period.

Risks were expressed as Odds ratios (OR) with 95% confidence interval (CI) and a P-value less than 0.05 considered as significant level. The SPSS (version 10) program was used for all analyses.

To evaluate whether the odds ratios of hand OA for future hip/knee OA were significantly different in different subgroups, we used a standard normal approximation for z, which was calculated as follow:

$$z = \beta 1 - \beta 2 / \sqrt{(SE1^2 + SE2^2)}$$

where β is the log odds of group 1 or 2 and SE is the standard error of this point estimate in the logistic regression analysis. A two-sided test with significance level 0.05 was used, meaning that the difference is significant if $z < -1.96$ or if $z > 1.96$.

Results

A total of 1235 of elderly participants (57.5% females, mean age of 65.8 years) who had no OA of the hip/knee at baseline were evaluated. Table 1 shows the baseline characteristics of the study population. After a mean of 6.6 years of follow-up (SD, 0.4) 12.1% of our population (19.7% of the participants with hand OA versus 10.0% of the participants without hand OA) developed OA of the hip/knee. Hip OA occurred in 5.4% (10.3% of the participants with hand OA vs. 3.7% of the participants without hand OA) and knee OA occurred in 7.3% (10.9% of the participants with hand OA vs. 6.4% of the participants without hand OA).

Hand OA showed an OR of 2.2 (CI 1.5 - 3.3) with incident hip/knee OA at follow-up in the univariate model. Performing this analysis separately for hip or knee OA, hand OA showed a higher risk of future hip OA (OR 3.0; CI 1.7 - 5.4) than for future

knee OA (OR 1.8; CI 1.1 - 3.0) in the univariate model. Additional adjustment for age, gender, BMI and follow-up period yielded almost the same estimate. Furthermore, we did check whether hand OA was still an independent risk factor for future hip/knee OA when age and BMI were entered in the model as continuous variable, which proved to be the case. Restricting the analysis to people with no hip OA at baseline (K-L=0) resulted in an even higher risk of hand OA for future hip OA (OR= 6.5, CI 1.1 – 36.8). Analysis restricted to those with no knee OA at baseline (K-L=0) showed the same magnitude of the association for knee OA (OR= 1.6, CI 0.8 – 3.0) as in those with K-L= 0-1. Restriction of analysis to those with K-L score 0 for hip or knee at baseline still showed a significant risk of hand OA for future hip/knee OA (OR 2.5; CI 1.1 – 5.8). Adjusted for possible early signs of hip/knee OA (K-L=1) at baseline as well as for the presence of hip/knee pain at baseline, hand OA still showed an increased risk of future hip/knee OA (OR 1.9; CI 1.2 – 3.1). Adjusted for the presence of an OA biomarker (CTX-II) hand OA still showed an increased risk of future hip/knee OA (OR 1.7; CI 1.1 – 2.8).

Table 1 **Baseline characteristics of the study population**

Characteristics	Hip OA Follow- up N=58	Knee OA Follow-up N=78	Hip or knee OA Follow-up N=130	Study population N=1235
Female %	63.8	74.4	70	57.5
Age (years) Mean ± SD	67 ± 6.4	66 ± 6.5	66.3± 6.5	65.8 ± 6.6
Body mass index Mean ± SD (kg/m^2)	26 ± 3.2	27.5 ± 3.7	26.7± 3.6	25.9 ± 3.3
Family history of OA %	24.1	12.8	16.2	19.1
Heavy workload %	12.1	10.4	11.6	14.0
High level CTX-II %	60.5	65.2	63.0	42.7
Hand OA at baseline %	47.1	34.7	38.1	23.5
% OA in the hand joint groups				
DIP joints	48.1	55.6	51.3	43
PIP joints	30.2	18.1	21.7	14.6
MCP joints	11.3	19.4	15.8	6.2
Base of the thumb	53.8	48.6	49.6	32.7

DIP=distal interphalangeal joints including interphalangeal joint of the thumb; PIP= proximal interphalangeal joints; MCP= metacarpophalangeal joints; Base of the thumb= first carpometacarpal joint and trapezioscaphoid joint (CMC1/TS); CTX-II = type II collagen C-telopeptide degradation product (>177 ng/mmole)

Further, excluding all participants who underwent a total hip replacement (THR) resulted in about the same OR of hand OA for future hip OA.

Analyses performed on the different hand joint groups adjusted for age, gender, BMI and follow-up period, showed that OA in each hand joint group was a risk of

future hip or knee OA. Presence of OA in the PIPs (OR 2.4; CI 1.3 – 4.6) and base of the thumb (OR 2.4; CI 1.3 – 4.3) showed a higher risk than other joint groups for future hip OA. Presence of OA at the MCPs and OA of the base of the thumb had the highest risk for the incidence of knee OA (OR 4.6; CI 2.3 – 9.2, OR 1.9; CI 1.2 – 3.2, respectively). In the analysis including all hand joint groups together in one model the same order of association was shown; however the risk of OA in some hand joints for future hip or knee OA disappeared (data are not presented).

Figures 2 - 4 present the risk of hand OA for future hip OA, knee OA and hip/knee OA stratified for gender, age, BMI, family history of OA and history of heavy workload, as well as the presence of high CTX-II. The differences in the stratified analysis reached (borderline) significant level only in the following strata: a higher risk of hand OA for future hip OA emerged in those with a family history of OA compared to those without family history (Z=1.70); overweight subjects showed a higher risk of hand OA for occurrence of future knee OA compared to non-overweight subjects (Z=2.83); and the risk of hand OA for future hip/knee OA was also higher in overweight compared with non-overweight subjects (Z=1.93).

Furthermore, a high baseline level of CTX-II showed an OR of 1.8 (CI 0.9 – 3.6) with future hip OA, an OR of 2.7 (CI 1.5 – 4.9) with future knee OA, and an OR of 2.4 (CI 1.5 – 3.8) with future hip/knee OA independent of hand OA (adjusted for age, gender, BMI and follow-up period). The odds ratio for development of hip/knee OA increased to 4.2 (CI 2.3 – 7.8) in the participants with the presence of both hand OA and high CTX-II compared to those who had no hand OA and low CTX-II at baseline, which was almost the same for the hip and knee OA separately (Table 2). Further, we stratified the concurrent presence of hand OA and high CTX-II in the subgroups of overweight versus non-overweight people. In the overweight group the presence of hand OA and high CTX-II showed a higher risk of future hip/knee OA compared to those without hand OA and low CTX-II (OR 11.1; CI 3.2 – 38.8), while in the non-overweight group, the presence of hand OA and high CTX-II showed a lower risk of future hip/knee OA compared to those without hand OA and low CTX-II (OR 2.9; CI 1.4 – 6.1). The difference between the two strata (overweight versus non-overweight) was borderline significant, Z=1.82. The number of incident cases in the group of future hip and future knee OA separately was not large enough to perform a stratification for overweight as a third risk factor.

Figure 1 **The distribution of CTX-II concentration in the study population**

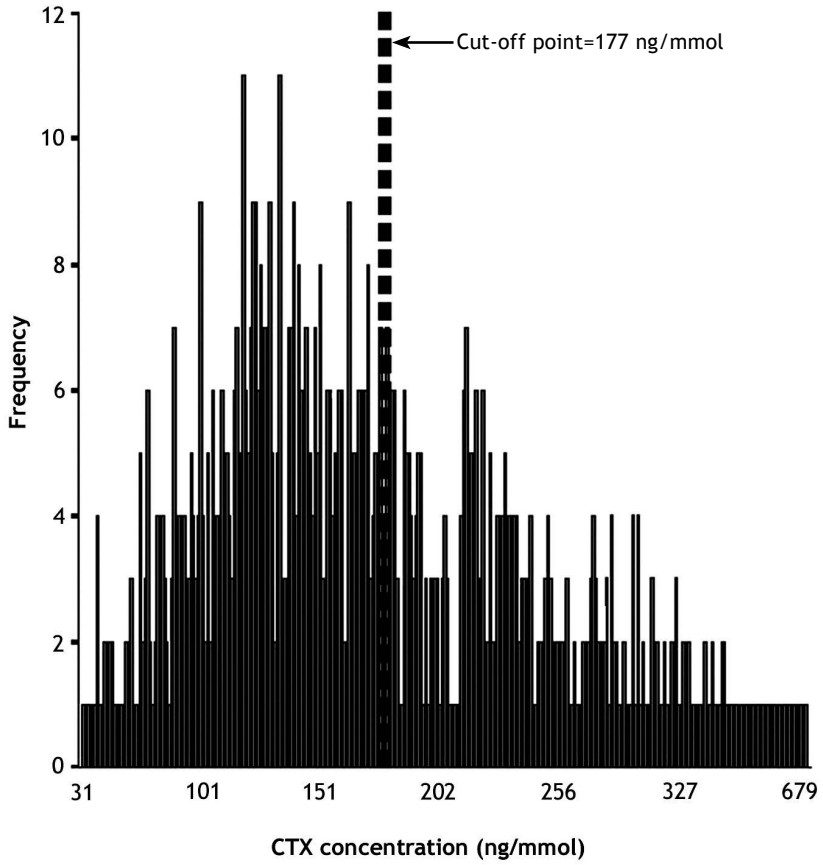
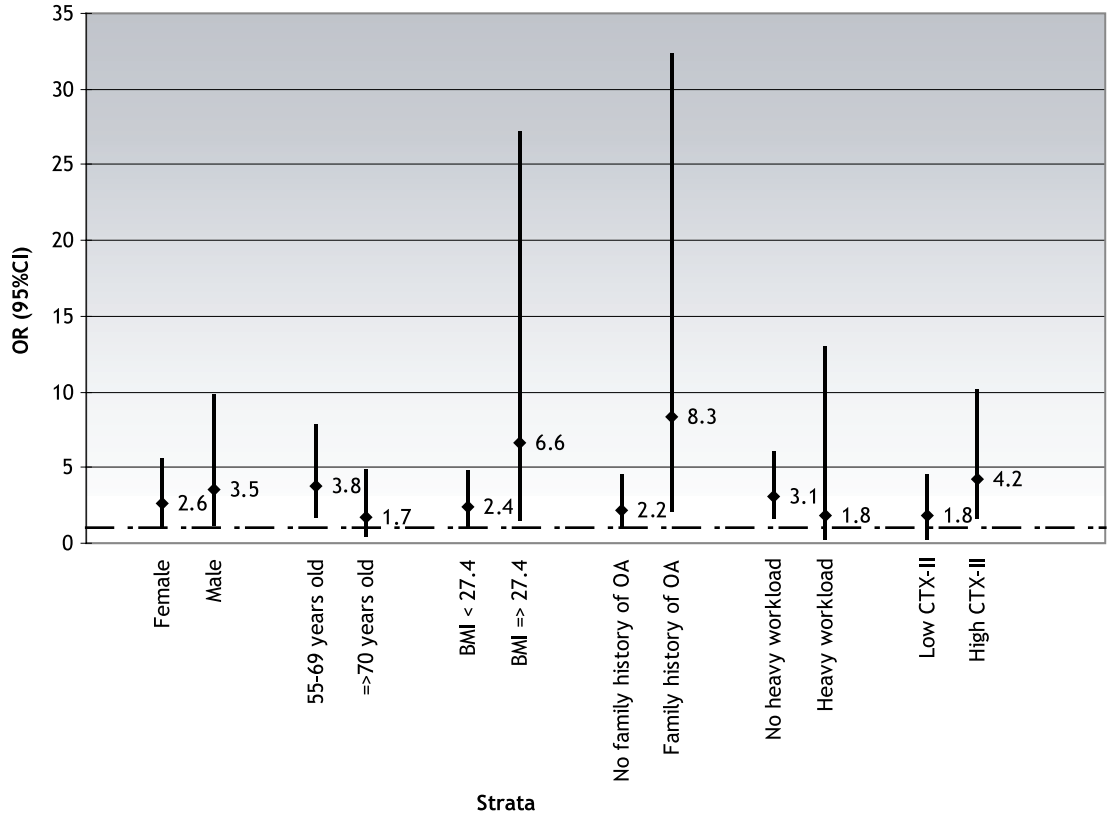
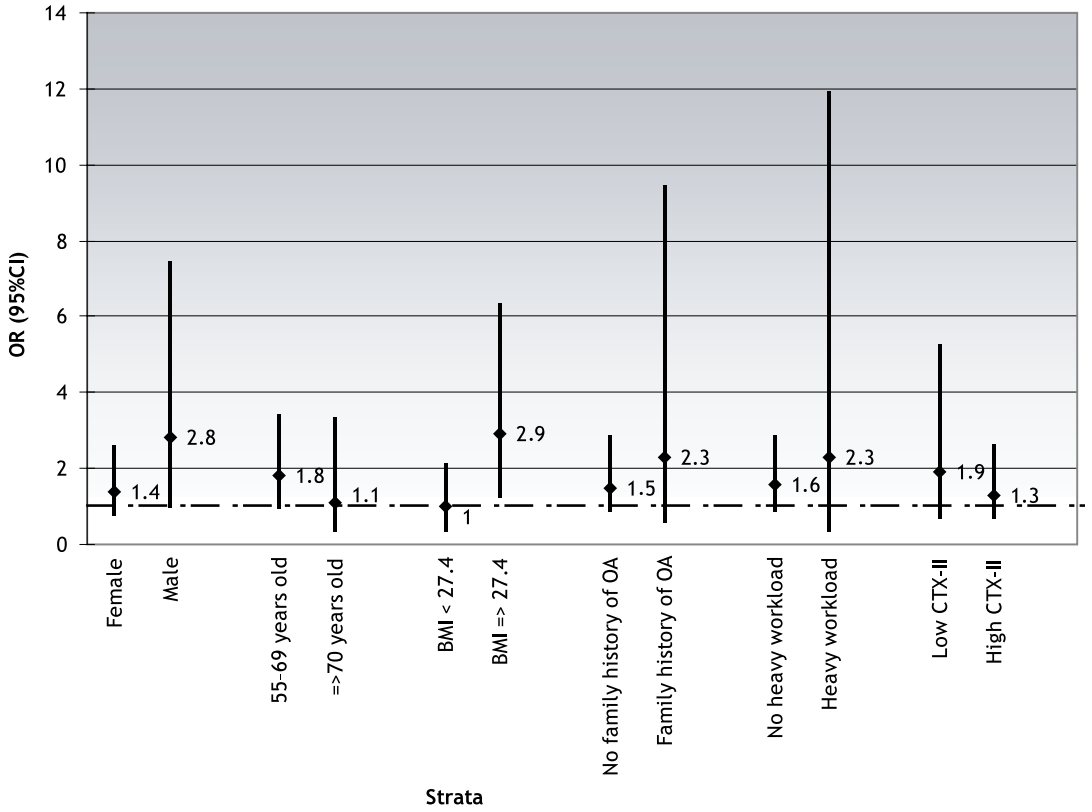


Figure 2 **The risk of hand OA for future hip OA in the different strata**



Broken line indicate OR=1

Figure 3 **The risk of hand OA for future knee OA in different strata**



Broken line indicate OR=1

Figure 4 **The risk of hand OA for future hip/knee OA in deifferent strata**

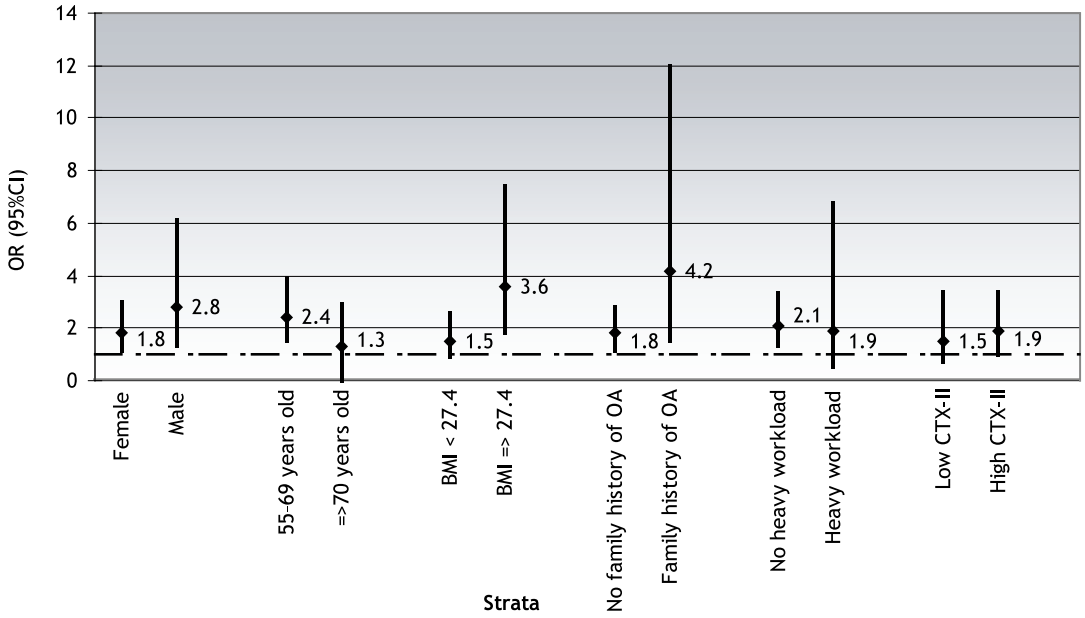


Table 2 **Risk of hand OA and/or CTX-II for future hip OA, future knee OA, and future hip/knee OA**

(Number of subjects)	Non-overweight N (%) OR (95%CI)		Overweight N (%) OR (95%CI)		Total population N (%) OR (95%CI)	
Future hip OA						
No hand OA. Low CTX-II (328)	NA		NA		12 (3.1)	Reference
No hand OA. High CTX-II (234)					9 (3.9)	1.2 (0.5 - 3.1)
Hand OA. Low CTX-II (85)					4 (4.7)	1.5 (0.5 - 5.0)
Hand OA. High CTX-II (113)					15 (13.3)	4.8 (2.0 -11.5)
Future knee OA						
No hand OA. low CTX-II (328)	NA		NA		15 (3.9)	Reference
No hand OA. High CTX-II (234)					28 (12)	3.0 (1.5 – 6.0)
Hand OA. Low CTX-II (85)					6 (7.1)	2.0 (0.7 – 5.2)
Hand OA. High CTX-II (113)					17 (15)	4.0 (1.8 – 8.7)
Future hip/knee OA						
No hand OA. Low CTX-II (328)	23 (8.2)	Reference	4 (3.8)	Reference	27 (7)	Reference
No hand OA. High CTX-II (234)	22 (13.2)	1.5 (0.8 – 2.9)	15 (22.4)	6.5 (2.0 – 21.4)	37 (15.8)	2.3 (1.3 – 3.9)
Hand OA. Low CTX-II (85)	3 (5.1)	0.6 (0.2 – 2.1)	6 (23.1)	8.1 (2.0 – 32.2)	9 (10.6)	1.6 (0.7 – 3.6)
Hand OA. High CTX-II (113)	17 (22.7)	2.9 (1.4 – 6.1)	12 (31.6)	11.1 (3.2 – 38.8)	29 (25.7)	4.2(2.3 – 7.8)

After a mean of 6.6 years follow-up OA of the hip occurred in 5.4%, OA of the knee in 7.3% and OA of the hip/knee in 12.1% of the total population
All odds ratios are adjusted for age, gender and follow-up period (in the last column together with BMI),
NA; not applicable (group not large enough to stratify for weight), CTX-II = type II collagen C-telopeptide degradation product (high >177 ng/mmole; low ≤177ng/mmole)

Discussion

The results of the current study show that hand OA is a risk factor for the occurrence of future hip/knee OA independent of other known risk factors, and is higher for hip OA than for knee OA. Our study demonstrated that hand OA is an even higher risk of future knee OA in overweight persons. However, the risk of hand OA for future hip OA showed to be higher in those subjects with a family history of OA. Additionally, it was shown that the concurrent presence of hand OA and high CTX-II increased the risk of future hip/knee OA further, especially in overweight people.

In a study on the risk factors for incident knee OA, Felson *et al*. found no association between history of hand OA and incident knee OA.[11] However, careful review of their methods revealed possible reasons for not finding an association. For example, hand radiographs were made in 1966-1969, whereas knee radiographs were made in 1983-1985 and if the participants had knee OA at this later time point, they were excluded from the study. Thereafter the participants were followed and knee radiographs were made again in 1992-1993 to measure incident knee OA. It is likely that people with susceptibility to develop knee OA, already developed knee OA within the first 14-19 year period and were therefore excluded from the study at 1983-1985. Moreover, since only a part of participants had available data on a history of hand OA, a small sample size might also have precluded finding a positive association.

In the present study, of the hand joint groups, OA of the PIPs showed the highest risk of future hip OA, and OA of the MCPs showed the highest risk of future knee OA. Our previous study showed that OA of the MCPs and PIPs are concurrent in more than 80% with OA of other joint groups of the hand,[15] indicating a more general form of OA. The present study showed that this susceptibility is not only present in the hand joints, but also develops in the other joints, such as hip or knee (if not yet present), later in life. Moreover, analyzing all hand joints together in one model showed the same order of the association; however, because of a high correlation between OA in the different hand joint groups, the risk of OA in some hand joints for future hip or knee OA for some of the hand joints disappeared.

The risk of hand OA for future hip OA was significantly higher in people with a family history of OA and was higher for future hip OA than for future knee OA. This finding is in accordance with another study, which found familial aggregation between hip and hand OA.[20] The risk of hand OA for future hip OA, knee OA, and also hip/knee OA was higher in overweight people compared to the reference groups. However, the difference was only statistical significant for future knee OA, and not significant for future hip OA. Although we could not find other studies with which to directly compare these findings, obesity is known as a risk factor for knee OA and less consistently for

hip OA, and is explained by the contribution of more local biomechanical factors versus systemic or metabolic factors associated with obesity.[21-23]

When combining three risk factors, we presented our data as adjusted odds ratios as well as crude risks in the different strata. This showed that in the reference groups including persons without hand OA and low CTX-II, the crude risk to develop hip/knee OA was much lower than the crude risk in the total population, resulting in a relatively high odds ratio of the group with both hand OA and high CTX-II compared to this reference group. However, the crude risk in the group with the presence of three risk factors was only tripled compared to the crude risk in the total study population.

The CTX-II level is not seen as a risk factor but rather as a biomarker of OA, or in other words, a disease activity measurement. High CTX-II could be due to an active form of hand OA or a pre-clinical/pre-radiological hip/knee OA, or due to OA of other joints (such as the spinal joints) as a part of generalized OA. In our analysis, high CTX-II showed to be an increased risk of future hip/knee OA independent from hand OA, independent from doubtful hip or knee OA, or from hip or knee pain at baseline (data not shown). Therefore measuring CTX-II at baseline has additional value to predict future hip/knee OA.

Although we could detect some interaction in our study, there were insufficient cases to allow detection of more possible interactions with sufficient statistical significance. This problem became more prominent when we wanted to detect differences in the group with hip or knee OA separately. For the same reason we decided to use the variables such as age and BMI as dichotomous variables instead of making more categories, allowing us to adjust and stratify for these factors with sufficient remaining power.

This study has some limitations. First, we included in the analysis participants who had doubtful OA (K-L=1) of the hip/knee at baseline, which may suggest that the risk of hand OA for future hip/knee OA is due to the progression of a doubtful OA of the hip/knee at baseline. However, adjusted for doubtful OA (K-L=1) or pain of the hip/knee at baseline, the risk estimates due to hand OA for future hip/knee OA did not change. Additionally, as we showed in the results, performing the analysis for the participants with a K-L score 0 at baseline showed a similar or an even higher risk of future hip/knee OA due to hand OA, but because of less power, these associations either had wide confidence intervals (hip OA) or were no longer statistically significant (knee OA). We believe that this analysis, together with the additional adjustment for a K-L score of 1 reported here, provide strong evidence that the predictive values are not due to inclusion of people with a K-L score of 1 at baseline.

A second limitation is that subjects who had undergone a THR were included in the analysis and were defined as incident hip OA; however, THR may also be due to diseases occurring in the follow-up period other than OA. As we showed in the results, excluding participants with THR resulted in the same OR; because this resulted in wider confidence intervals, we decided that in order to maintain enough power in the stratified analysis, we would not exclude these subjects.

A third limitation concerns our finding that the presence of baseline hand OA in the relatively younger age group showed a higher risk of future hip/knee OA compared to the older age group, although the difference was not statistically significant. Because, we performed our analysis in those subjects who had no or doubtful OA in hip and knee at baseline, this may have lead to a selection of older people in the study who are healthy survivors with less susceptibility for OA; this selection may also have caused an underestimation of our findings.

A fourth limitation concerns our finding that the risk of future hip/knee OA in subjects with baseline hand OA was not higher in those with a history of heavy workload. This may be explained by a selection of "healthy survivors" in the study population and also by the fact that we evaluated the history of workload by asking participants about their current or last occupation at baseline and therefore had no information about their workload during the follow-up period. Further, because our study population was 55 years and older at baseline, most of them were retired or would soon retire; therefore workload is not optimally defined in our study.

In conclusion, this study is in line with the findings of previous studies showing that OA is a generalized disease in many patients. However, we have shown that this characteristic of the disease can be used to predict future OA in the weight-bearing joints, which was not shown previously. These findings present an opportunity to identify persons at high risk with the aim to develop preventive strategies to prevent or delay OA in the weight-bearing joints.

References

1. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, Kington RS, Lane NE, Nevitt MC, Zhang Y, Sowers M, McAlindon T, Spector TD, Poole AR, Yanovski SZ, Ateshian G, Sharma L, Buckwalter JA, Brandt KD, Fries JF. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med* 2000;133:635-46.
2. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, Kelly-Hayes M, Wolf PA, Kreger BE, Kannel WB. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. *Am J Public Health* 1994;84:351-8.
3. Kramer JS, Yelin EH, Epstein WV. Social and economic impacts of four musculoskeletal conditions. A study using national community-based data. *Arthritis Rheum* 1983;26:901-7.

4. Felson DT, Lawrence RC, Hochberg MC, McAlindon T, Dieppe PA, Minor MA, Blair SN, Berman BM, Fries JF, Weinberger M, Lorig KR, Jacobs JJ, Goldberg V. Osteoarthritis: new insights. Part 2: treatment approaches. *Ann Intern Med* 2000;133:726-37.
5. Rogers J, Shepstone L, Dieppe P. Is osteoarthritis a systemic disorder of bone? *Arthritis Rheum* 2004;50:452-7.
6. Hirsch R, Lethbridge-Cejku M, Scott WW, Jr., Reichle R, Plato CC, Tobin J, Hochberg MC. Association of hand and knee osteoarthritis: evidence for a polyarticular disease subset. *Ann Rheum Dis* 1996;55:25-9.
7. Hochberg MC, Lane NE, Pressman AR, Genant HK, Scott JC, Nevitt MC. The association of radiographic changes of osteoarthritis of the hand and hip in elderly women. *J Rheumatol* 1995;22:2291-4.
8. Englund M, Paradowski PT, Lohmander LS. Association of radiographic hand osteoarthritis with radiographic knee osteoarthritis after meniscectomy. *Arthritis Rheum* 2004;50:469-75.
9. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in women: a twin study. *Bmj* 1996;312:940-3.
10. Cicuttini FM, Baker J, Hart DJ, Spector TD. Relation between Heberden's nodes and distal interphalangeal joint osteophytes and their role as markers of generalised disease. *Ann Rheum Dis* 1998;57:246-8.
11. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman B, Aliabadi P, Levy D. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. *Arthritis Rheum* 1997;40:728-33.
12. Christgau S, Garnero P, Fledelius C, Moniz C, Ensig M, Gineyts E, Rosenquist C, Qvist P. Collagen type II C-telopeptide fragments as an index of cartilage degradation. *Bone* 2001;29:209-15.
13. Reijman M, Hazes JM, Bierma-Zeinstra SM, Koes BW, Christgau S, Christiansen C, Uitterlinden AG, Pols HA. A new marker for osteoarthritis: cross-sectional and longitudinal approach. *Arthritis Rheum* 2004;50:2471-8.
14. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;7:403-22.
15. Dahaghin S, Bierma-Zeinstra SM, Ginai AZ, Pols HA, Hazes JM, Koes BW. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). *Ann Rheum Dis* 2005;64:682-7.
16. Auleley GR, Giraudeau B, Dougados M, Ravaud P. Radiographic assessment of hip osteoarthritis progression: impact of reading procedures for longitudinal studies. *Ann Rheum Dis* 2000;59:422-7.
17. Odding E, Valkenburg HA, Algra D, Vandenouweland FA, Grobbee DE, Hofman A. Associations of radiological osteoarthritis of the hip and knee with locomotor disability in the Rotterdam Study. *Ann Rheum Dis* 1998;57:203-8.
18. Dahaghin S, Bierma-Zeinstra SM, Reijman M, Pols HA, Hazes JM, Koes BW. Prevalence and determinants of one month hand pain and hand related disability in the elderly (Rotterdam study). *Ann Rheum Dis* 2005;64:99-104.
19. Beroepenclassificatie1984. list voor benamingen per beroepencode / Central bureau voor de statistiek.
20. Riyazi N, Meulenbelt I, Kroon HM, Ronday KH, Hellio le Graverand MP, Rosendaal FR, Breedveld FC, Slagboom PE, Kloppenburg M. Evidence for familial aggregation of hand, hip, and spine but not knee osteoarthritis in siblings with multiple joint involvement: the GARP study. *Ann Rheum Dis* 2005;64:438-43.
21. Davis MA, Ettinger WH, Neuhaus JM. Obesity and osteoarthritis of the knee: evidence from the National Health and Nutrition Examination Survey (NHANES I). *Semin Arthritis Rheum* 1990;20:34-41.
22. Davis MA, Ettinger WH, Neuhaus JM. The role of metabolic factors and blood pressure in the association of obesity with osteoarthritis of the knee. *J Rheumatol* 1988;15:1827-32.
23. Cicuttini FM, Baker JR, Spector TD. The association of obesity with osteoarthritis of the hand and knee in women: a twin study. *J Rheumatol* 1996;23:1221-6.

6

Should patients with osteoarthritis of the metacarpophalangeal joints be screened for hereditary hemochromatosis gene (HFE) mutations?

S. Dahaghin, B.Z. Alizadeh, S.M.A. Bierma-Zeinstra, B.W. Koes, P.E. Slagboom, C.M. van Duijn, OT Njajou, J.M.W. Hazes

Submitted

Abstract

Hemochromatosis is a common differential diagnosis to be considered in patients with metacarpophalangeal (MCP) OA, leading to measurement for possible iron overload. However, persons with no evidence of iron overload may still be carriers of two most common mutations of hemochromatosis gene (C282Y, H63D). The present study investigated whether the chance of identifying these mutations is higher in the presence of MCP OA within a subset of the population-based Rotterdam Study (n=1,547, aged ≥55 years).

H63D homozygosity showed the highest odds ratio with MCP OA (OR 2.2, 0.8-6) of the four hand joint groups tested in the total study population, increasing further in relatively younger age (55-65 years)(OR 11.5, 3.6–36.6). The prior chance to identify H63D homozygosity in the total study population was 2.7%, increasing to 5.4% (posterior chance) when identification was restricted to those with MCP OA. Further analysis in relatively younger age (55-65 years) showed that a prior chance of 2.7% of identifying H63D homozygosity increased to a posterior chance of 20.8% in those with MCP OA. The number of C282Y homozygotes was too low to allow a meaningful statistical analysis. Neither C282Y nor H63D heterozygotes showed a significant association with MCP OA. Compound heterozygotes showed a higher association with MCP OA in those aged 55-65 years compared to non-carriers (OR 2.9, 1.1–7.7).

These results indicate that the chance of identifying H63D homozygotes in persons with MCP OA is higher than identifying this mutation in the total study population especially at a relatively younger age (55-65 years).

Introduction

The hand is a frequently involved site in patients suffering from osteoarthritis (OA). The prevalence of OA increases with age up to more than 70% in those aged 60 years and over.[1,2] Distal interphalangeal joints (DIP) and the base of the thumb are the most frequently involved joints of the hand, followed by the proximal interphalangeal joints (PIP).[3-5] Up to 60% of hand OA is explained by heredity[6-8] and a common inherited disorder associated with progressive degenerative arthritis of the hands is type I hemochromatosis.[9-11] Hemochromatosis-associated OA is of relatively early onset mainly affecting atypical joint sites such as metacarpophalangeal (MCP) and wrist joints.[9-11] In patients with hand OA in whom MCP joints are affected, hereditary hemochromatosis is one of the common differential diagnoses to be considered, leading to measurement of evidence of iron overload in these patients. However, persons with no evidence of iron overload might still be carriers of the hemochromatosis mutation. Early detection of hemochromatosis may prevent irreversible pathology in multiple organs.[12,13] The C282Y and H63D mutations in the HFE gene are the most common mutations involved in hereditary hemochromatosis.[14-17] In an earlier Rotterdam study, an association was found between radiographic OA and H63D homozygotes in those aged 55-65 years.[18] A significant association between hand OA in C282Y heterozygotes has also been reported in those aged 65 years and over.[19]

The present study investigates whether mutations in the HFE gene are associated with OA of the different joint sites of the hand particularly the MCP joints, and whether the chance of identifying C282Y and H63D mutations is higher in the presence of OA at specific hand joint sites.

Methods

Study population

For this study we used cross-sectional data from the Rotterdam Study, a population-based cohort study on the determinants and prognosis of chronic diseases in the elderly. The Medical Ethics Committee of the Erasmus Medical Center approved the study, and written informed consent was obtained from all participants. The baseline measurements were conducted between April 1990 and July 1993. The complete study design has been described previously.[20] All inhabitants of Ommoord (a suburb of Rotterdam) who were aged 55 years and over were invited to participate. In total 7,983 participants (response rate of 78%) were examined. At baseline, trained

interviewers performed an extensive home interview on demographic characteristics, medical history, risks factor for chronic diseases, and medication use. After the home interview, participants also visited the research center, where among other measurements, they underwent radiographic examination. For feasibility reasons, baseline hand radiographs of those participants who were available for follow-up six years later (n=3,585) were scored for OA. The genotypic data were available for 2095 randomly drawn subjects. In total, 1,547 subjects for whom data were available on OA of the hand joints and genotyping were included in this study.

A sub sample (n=166) of the latest population (1,547) had data on iron, ferritin and serum transferrin saturation levels which were used for a complementary analysis. The complete methods of measurement of iron parameters has been described elsewhere.[21]

Radiographic scoring

Standard anteroposterior radiographs of both hands were taken for each subject at baseline. Two study assessors were trained by a radiologist to score hand radiographs using a training set of radiographs. Each assessor scored half of the radiographs of the participants who were available for follow-up, blind for other data such as clinical or demographic variables. The exact method of scoring radiographs was described previously.[5] Definite radiographic OA for each joint was defined as a Kellgren-Lawrence (K-L) = 2-4. Four groups of joints were scored: distal interphalangeal joints including interphalangeal joint of the thumb (DIP), the proximal interphalangeal joints (PIP), metacarpophalangeal joints (MCP), and base of the thumb including first carpometacarpal joint and trapezioscaphoid joint (CMC1/TS). A group was considered positive if at least one joint of the group in either hand on the left and/or right side showed a K-L of 2-4. Hand OA was defined as the presence of a K-L=2 - 4 in two out of three groups (DIP, PIP, and CMC1/TS) of either hand on the left and/or right side. This definition has been used previously.[22]

To measure reliability of the scoring of the hand radiographs the two assessors, both independently of each other, read a random subset of 205 radiographs. Inter observer reliability of a K-L= 2-4 (dichotomous variable) expressed by kappa statistics was as follows: DIP 0.60; PIP 0.61; MCP 0.63; and CMC1/TS (base of the thumb) 0.74.

HFE Genotyping

Blood samples were collected from all subjects by venepuncture and kept frozen until analysis. Genomic DNA was extracted from frozen buffy coat with the salting-out procedure. DNA fragments were amplified by polymerase chain reaction and genotyped by use of oligonucleotides primers as described elsewhere.[14,21.]

Data Analysis

Genotype frequencies were estimated by counting alleles and estimating sample proportion. Chi-squared and Student's t-tests were used to compare proportions and means, respectively. Univariate and multivariate logistic regression analyses were used to examine associations between OA in the hand joints and HFE genotypes. The associations were expressed in odds ratio (OR) with 95% confidence interval (CI); a p-value less than 0.05 was considered significant. All analyses were adjusted for gender. We stratified our analysis by age at a cut-off point of 65 years, because in two previous studies[18,19] the association between HFE mutations and hand OA showed differences between those younger and older than 65 years. Further, we calculated the prior and posterior chance of H63D homozygosity for the total study population and by age category (younger and older than 65 years). The prior chance was defined as the prevalence of C282Y or H63D carriers. The posterior chance was defined as the number of carriers of C282Y or H63D mutations who showed MCP OA divided by the prevalence of MCP OA in the total study population. The prior and posterior chance was also calculated for both age categories separately. The SPSS (version 11) program was used for all analyses.

Results

Table 1 presents the characteristics of the study population. There were no significant differences in baseline characteristics of HFE genotypes compared to non-carriers, except C282Y heterozygotes had a significantly ($p<0.05$) increased body mass index. The prevalence of OA was 48.2% at DIP, 36.6% at the first CMC, 18.8% at PIP, and 7% at MCP joints.

C282Y mutation

No difference was found in the frequency of hand OA between C282Y heterozygotes and non-carriers in the total study population. Further analysis in both age categories and in the separate hand joints also showed no difference in the frequency of OA in C282Y heterozygotes compared to non-carriers (Tables 2, 3). Because only two persons were homozygotes for C282Y, we were unable to calculate any associations for this group.

Further analysis in a sub sample (n=166) with data of iron products showed that about 40% of the subjects with MCP OA were C282Y heterozygotes, of those only 12.5% had the symptom of iron overload (iron saturation level > 45%).

Table 1 **Characteristics of the total study population**

	Total	C282Y			H63D		
		Non-carriers	Heterozygotes	Homozygotes	Non-carriers	Heterozygotes	Homozygotes
N	1547	1331	175	2	1098	389	43
Female (%)	53.8	53.1	57.1	50.0	53.6	53.6	51.2
Age (years)*	62.3±6.0	65.1±5.9	65.5±6.4	70.5±0.4	65.5±6.0	64.7±5.8	66.8±6.7
Body mass index*	26.4±3.4	26.5±0.2	27.1±0.3 **	24.2±2.4	26.3±0.8	25.8±0.8	26.3±1.0
Pain at hand joints (%)	15.2	23.2	20.7	50.0	23.5	21.0	33.3

* Mean ± SD
** P<0.05 compared to non-carriers

Table 2 **Prevalence of hand OA by the two HFE genotypes**

		Hand OA		
		N	% OA	OR (95% CI)
Total				
C282Y	Non-carriers	1148	29.2	1.0 (reference)
	Heterozygotes	150	28	1.0 (0.7 – 1.4)
	Homozygotes	1	100.0	-
H63D	Non-carriers	938	28.8	1.0 (reference)
	Heterozygotes	335	28.9	1.0 (0.8 - 1.3)
	Homozygotes	36	44.4	2.1 (1.1 - 4.3)
Aged 55-65 years				
C282Y	Non-carriers	607	19.9	1.0 (reference)
	Heterozygotes	50	24.4	1.3 (0.8 - 2.3)
	Homozygotes	-	-	-
H63D	Non-carriers	481	18.9	1.0 (reference)
	Heterozygotes	191	23.4	1.3 (0.9 -2.0)
	Homozygotes	18	33.3	2.7 (0.9 – 7.2)

All analyses adjusted for gender

Table 3 **Prevalence of radiographic OA of the hand joint groups by the two HFE genotypes**

Total			DIP OA		PIP OA		MCP OA		CMC/TS OA	
		N	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
C282Y	Non-carriers	1165	48.4	1.0 (reference)	18.7	1.0 (reference)	6.3	1.0 (reference)	36.2	1.0 (reference)
	Heterozygotes	150	46.7	0.9 (0.7 - 1.4)	16.7	0.8 (0.5 - 1.3)	10.0	1.7 (0.9 - 3.1)	40.7	1.2 (0.9 - 1.8)
	Homozygotes	1	100	-	0	-	0	-	100	-
H63D	Non-carriers	953	47.4	1.0 (reference)	18.7	1.0 (reference)	6.7	1.0 (reference)	36.9	1.0 (reference)
	Heterozygotes	338	48.8	1.1 (0.8 - 1.3)	18.4	1 (0.7 - 1.3)	6.8	1.2 (0.7 - 1.9)	35.6	0.9 (0.7 - 1.2)
	Homozygotes	36	61.1	1.8 (0.9 - 3.6)	22.2	1.3 (0.6 - 2.9)	13.9	2.2 (0.8 - 6)	48.6	1.7 (0.9 - 3.6)
Aged 55-65 years										
C282Y	Non-carriers	612	41.2	1.0 (reference)	14.8	1.0 (reference)	3.1	1.0 (reference)	26.5	1.0 (reference)
	Heterozygotes	78	47.4	1.3 (0.8 - 2.1)	15.4	1.1 (0.6 - 2.0)	5.1	1.7 (0.6 - 5.1)	29.5	1.2 (0.7 - 2.0)
	Homozygotes	0	0	-			-	-		
H63D	Non-carriers	482	41.2	1.0 (reference)	13.5	1.0 (reference)	3.1	1.0 (reference)	26.7	1.0 (reference)
	Heterozygotes	191	41.2	1.0 (0.7 - 1.4)	18.7	1.5 (0.9 - 2.3)	2.1	0.6 (0.2 - 2.1)	27.2	1 (0.7 - 1.5)
	Homozygotes	18	61.1	2.6 (1.0 - 6.6)	22.2	2.0 (0.6 - 6.3)	27.8	11.5 (3.6 - 36.6)	31.6	1.5 (0.5 - 4.2)

All analyses adjusted for gender

H63D mutation

Table 2 presents the association between HFE mutations and hand OA. Persons homozygous for H63D had a significantly higher frequency of hand OA compared to non-carriers (OR 2.1 CI: 1.1-4.3). The analysis stratified for persons younger and older than 65 years showed a higher association between H63D homozygosity and hand OA in the younger (OR 2.7 CI; 0.9–7.2) than in the older age group (OR 1.9 CI: 0.7–5.1).

We also performed this analysis for each hand joint group separately (Table 3). H63D homozygosity showed the highest OR with MCP OA, but did not reach significance level in the total study population. In persons aged 55-65 years, H63D homozygotes showed a significantly higher frequency of MCP OA (OR 11.5 CI: 3.6–36.6) compared to non-carriers. Heterozygotes for the H63D mutation did not have a higher frequency of OA in the hand joints than non-carriers (Tables 2, 3).

Further analysis in a sub sample (n=166) with data of iron products showed that about 50% of the subjects with MCP OA were carrier for H63D mutations (heterozygotes or heterozygotes), of those only 15% had the symptom of iron overload (iron saturation level > 45%).

Chance of identifying H63D homozygotes

Since H63D homozygotes showed significant association with hand OA, we calculated the prior and posterior chance of identifying these subjects in the present study. The prior chance to find H63D homozygosity in the total study population was 2.7%, which is almost the same as for the two age categories separately. When identification of H63D homozygosity was restricted to those with hand OA, the chance increased to 4.1% (posterior chance) in the total study population. More specifically, examining those with MCP OA for H63D mutation resulted in a higher posterior chance (5.4%) of finding H63D homozygosity in the total study population, which increased to 20.8% in persons aged 55-65 years (Table 3).

Compound heterozygotes

In total, 26 persons were compound heterozygotes; these persons had a significant association with MCP OA compared to non-carriers only in the age category 55-65 years (OR 2.9 CI: 1.1–7.7), but they did not have a significant association with OA in the other hand joints. The prior chance to identify compound heterozygotes in those aged 55-65 years was 2.9%, increasing to 8% (posterior chance) when identification was restricted to those with MCP OA.

Discussion

In this population-based setting, the chance of identifying H63D homozygotes in persons with MCP OA is higher than identifying this mutation in the total study population especially at a relatively younger age (55-65 years). Evaluating those persons with MCP OA resulted in a 20% chance of identifying H63D homozygotes compared to a 2.7% chance of identifying H63D homozygotes in all study participants aged 55-65 years.

No association was found between hand OA and C282Y mutations. The number of subjects with C282Y homozygosity was too low to allow a meaningful statistical analysis. C282Y heterozygosity also showed no association with hand OA or OA at a particular joint site. This finding is in contrast to report of an increased prevalence of C282Y heterozygosity in patients with late onset hand OA at any joints compared to controls;[19] however, in the latter study it is unknown whether the reported differences are due to a real difference or due to demographic differences between their OA group and control group.[19]

Previous studies suggested that arthritis is one of the most common clues to a diagnosis of hemochromatosis.[9,11,17,23,24] We speculate in this study that persons with MCP OA but no evidence of iron overload might still be carriers of the hemochromatosis mutations, which our data showed to be true. Therefore, a test to identify hemochromatosis mutation is a better choice in patients with MCP OA than measuring the evidence of iron overload.

In the Rotterdam study population Njajou et al. found earlier that 13% of the males and 8% of the females could be diagnosed with sub-clinical hemochromatosis (defined as a transferrin saturation level above 45%).[21] None of these subjects or their treating physician knew that they were hemochromatotic; they showed that detection of the H63D and C282Y would be effective in detecting individuals at high risk for hemochromatosis. Therefore identifying H63D and C282Y mutations in the population may enable patients and their physicians to be aware of the potential risk of increasing body iron stores as well as the potential risks to their family. There is evidence that the early diagnosis of hemochromatosis due to early-onset OA (as a presenting symptom) may lead to a longer survival in patients.[13,25]

The development of arthropathy in secondary hemochromatosis[26] or cartilage degeneration in immature rabbits overloaded with parenteral iron supports an etiologic role for iron.[24,27] Axford *et al.*[11] suggested that the pathogenesis of hemochromatosis arthropathy has been associated with the presence of iron in joint tissue, a defect in cartilage metabolism and immunological dysfunction. However, in contrast they also suggest that treatment has little effect on clinical, radiological or histological

progression in the same study. Moreover, as we showed, in persons with MCP OA and being carrier of one these mutations only 12 -15% had evidence of iron overload, which again make the relationship between iron overload and development of OA dubious. Therefore, pathogenic mechanisms involved in hemochromatosis arthropathy, including iron overload and the role of HFE mutation, need more study.

In the present study, homozygosity for H63D mutation is associated with hand OA, particularly with OA of the MCP joints in those aged 55-65 years. The current study has revealed a new way of looking at this association. From a clinical point, it is important to identify H63D homozygotes earlier in life; therefore, we calculated the prior and posterior chance of identifying H63D homozygotes, which proved to be much higher in those with MCP OA than in the total population especially in the relatively younger age. One might argue that a clinical symptom, such as joint pain, should be a starting point to detect these mutations. In a previous Rotterdam study, homozygotes for H63D mutation showed a significant association with hand pain compared to non-carriers only in those aged 55-65 years.[18] However, due to lack of data on the exact location of the pain in the hand joints we could not evaluate whether the chance of identifying people with H63D mutation is higher in those with pain of the MCP joints.

In summary, our results show that the chance of identifying H63D mutation in persons with especially OA of the MCP joints is high in those aged 55-65 years. Thus, a genetic test for HFE mutations in patients with OA of the MCP joints may be clinically relevant and may lead to detection of hemochromatosis at an early stage, perhaps preventing irreversible adverse effects of the disease. These findings argue for a cost-effectiveness study on screening for H63D mutation in patients with, or suspected for, MCP OA.

References

1. van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. *Ann Rheum Dis* 1989;48:271-80.
2. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, Heyse SP, Hirsch R, Hochberg MC, Hunder GG, Liang MH, Pillemer SR, Steen VD, Wolfe F. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998;41:778-99.
3. Kellgren JH, Moore R. Generalized osteoarthritis and Heberden's nodes. *Br Med J* 1952;1:181-7.
4. Egger P, Cooper C, Hart DJ, Doyle DV, Coggon D, Spector TD. Patterns of joint involvement in osteoarthritis of the hand: the Chingford Study. *J Rheumatol* 1995;22:1509-13.
5. Dahaghin S, Bierma-Zeinstra SM, Ginai AZ, Pols HA, Hazes JM, Koes BW. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). *Ann Rheum Dis* 2005;64:682-7.

6. Bijkerk C, Houwing-Duistermaat JJ, Valkenburg HA, Meulenbelt I, Hofman A, Breedveld FC, Pols HA, van Duijn CM, Slagboom PE. Heritabilities of radiologic osteoarthritis in peripheral joints and of disc degeneration of the spine. *Arthritis Rheum* 1999;42:1729-35.
7. Spector TD, MacGregor AJ. Risk factors for osteoarthritis: genetics. *Osteoarthritis Cartilage* 2004;12:39-44.
8. Loughlin J. Genome studies and linkage in primary osteoarthritis. *Rheum Dis Clin North Am* 2002;28:95-109.
9. Faraawi R, Harth M, Kertesz A, Bell D. Arthritis in hemochromatosis. *J Rheumatol* 1993;20:448-52.
10. Bulaj ZJ, Ajioka RS, Phillips JD, LaSalle BA, Jorde LB, Griffen LM, Edwards CQ, Kushner JP. Disease-related conditions in relatives of patients with hemochromatosis. *N Engl J Med* 2000;343:1529-35.
11. Axford JS. Rheumatic manifestations of haemochromatosis. *Baillieres Clin Rheumatol* 1991;5:351-65.
12. Niederau C, Fischer R, Purschel A, Stremmel W, Haussinger D, Strohmeyer G. Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology* 1996;110:1107-19.
13. Niederau C, Fischer R, Sonnenberg A, Stremmel W, Trampisch HJ, Strohmeyer G. Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. *N Engl J Med* 1985;313:1256-62.
14. Feder JN, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, Basava A, Dormishian F, Domingo R, Jr., Ellis MC, Fullan A, Hinton LM, Jones NL, Kimmel BE, Kronmal GS, Lauer P, Lee VK, Loeb DB, Mapa FA, McClelland E, Meyer NC, Mintier GA, Moeller N, Moore T, Morikang E, Wolff RK, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* 1996;13:399-408.
15. Hanson EH, Imperatore G, Burke W. HFE gene and hereditary hemochromatosis: a HuGE review. Human Genome Epidemiology. *Am J Epidemiol* 2001;154:193-206.
16. Bacon BR, Powell LW, Adams PC, Kresina TF, Hoofnagle JH. Molecular medicine and hemochromatosis: at the crossroads. *Gastroenterology* 1999;116:193-207.
17. Adams P, Brissot P, Powell LW. EASL International Consensus Conference on Haemochromatosis. *J Hepatol* 2000;33:485-504.
18. Alizadeh BZ, Njajou OT, Hazes JMW, Hofman A, Slagboom PE, H.A.P. P, van Duijn CM. The H63D Mutation in the HFE gene predisposes to joint pain, chondrocalcinosis, and osteoarthritis. *Arthritis & Rheum* 2004;in press.
19. Ross JM, Kowalchuk RM, Shaulinsky J, Ross L, Ryan D, Phatak PD. Association of heterozygous hemochromatosis C282Y gene mutation with hand osteoarthritis. *J Rheumatol* 2003;30:121-5.
20. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;7:403-22.
21. Njajou OT, Houwing-Duistermaat JJ, Osborne RH, Vaessen N, Vergeer J, Heeringa J, Pols HA, Hofman A, van Duijn CM. A population-based study of the effect of the HFE C282Y and H63D mutations on iron metabolism. *Eur J Hum Genet* 2003;11:225-31.
22. Hirsch R, Lethbridge-Cejku M, Scott WW, Jr., Reichle R, Plato CC, Tobin J, Hochberg MC. Association of hand and knee osteoarthritis: evidence for a polyarticular disease subset. *Ann Rheum Dis* 1996;55:25-9.
23. Godard B, ten Kate L, Evers-Kiebooms G, Ayme S. Population genetic screening programmes: principles, techniques, practices, and policies. *Eur J Hum Genet* 2003;11:S49-87.
24. M'Seffar A, Fornasier VL, Fox IH. Arthropathy as the major clinical indicator of occult iron storage disease. *Jama* 1977;238:1825-8.
25. Adams PC, Speechley M, Kertesz AE. Long-term survival analysis in hereditary hemochromatosis. *Gastroenterology* 1991;101:368-72.
26. Abbott DF, Gresham GA. Arthropathy in transfusional siderosis. *Br Med J* 1972;1:418-9.
27. Brighton CT, Bigley EC, Jr., Smolenski BI. Iron-induced arthritis in immature rabbits. *Arthritis Rheum* 1970;13:849-57.

7

Do metabolic factors add to the effect of overweight on hand Osteoarthritis? (Rotterdam study)

S. Dahaghin, S.M.A. Bierma-Zeinstra, B.W. Koes, J.M.W. Hazes, H.A.P. Pols

Submitted

Abstract

Since hand joints are non-weight bearing, the association between overweight and hand OA is critical to understand how overweight may cause OA apart from axial load. Overweight might be associated with occurrence of OA through other metabolic factors. To evaluate the role of overweight in hand OA, we used cross-sectional data of a population-based study (≥55 year, n=3585). We also investigated the role of diabetes, hypertension and total/HDL cholesterol ratio on hand OA, and whether they play an intermediate role in the association of overweight with hand OA. Furthermore, we evaluated the risk of concurrent presence of overweight with other metabolic factors on hand OA.

Independently of other metabolic factors, overweight (BMI >27.4) showed a significant association with hand OA (OR;1.4 CI1.1-1.6). Adjusted for overweight, diabetes was significantly associated with hand OA (OR;2.0 CI 1.0–3.8), only in the younger age group (55-62 years). The association of hypertension with hand OA was weak, which disappeared after adjustment for overweight. The total/HDL cholesterol ratio showed no significant association with hand OA. Concurrent presence of overweight, diabetes and hypertension compared to persons with none of these characteristics resulted to an even higher risk for hand OA (OR;2.3 CI 1.3-3.9); this risk increased further in the younger age group to OR;3.2 CI 1.1-8.8.

No intermediate effect of metabolic factors on the association of overweight with hand OA was found. An additional risk for hand OA however, seems to be present when overweight occurs together with hypertension and diabetes especially at a relatively younger age (55-62 years).

Introduction

Osteoarthritis (OA) is a slowly progressive degenerative disease affecting cartilage and bone, whose aetiology is considered to be multifactorial.[1] It is already the most common form of arthritis and will become even more prevalent as the bulging cohort of baby boomers grows older.[2] To devise possible preventive strategies researchers have focused on identifying potential risk factors. One potentially preventable risk factor for OA is overweight, which may contribute to the development of OA through various mechanisms.[3] Being overweight increases the load across weight-bearing joints and subsequent cartilage breakdown. However, this mechanism fails to explain the association between overweight and OA of the non-weight bearing joints such as the hand. So far however, reports on the association of hand OA with overweight have been inconsistent.[1] An association between overweight with hand OA therefore calls for a consideration of other possible explanations. Adipose tissue may produce atypical hormone or growth factor concentrations that affect cartilage or bone.[4] Leptin secreted primarily by adipocytes has been suggested to be involved in osteophyte formation in OA.[5] It has also been suggested that overweight may be associated with the occurrence of OA through other metabolic factors such as diabetes, hypertension, high triglycerides and total/HDL cholesterol ratio.[1,6,7] Since the hand joints are non-weight bearing, the association between overweight and hand OA is critical for a better understanding of how overweight through metabolic process may cause OA. The objective of this study is therefore to evaluate the association between overweight and OA of the hand joints. In addition, we evaluate the association between other metabolic factors such as diabetes, hypertension or total/HDL cholesterol ratio and hand OA. Further, we investigate whether the simultaneous presence of several metabolic factors together with overweight increases the risk for hand OA, or whether they play an intermediary role in the association of overweight with hand OA.

Subjects and Methods

Study population

For this study we used cross-sectional data from the Rotterdam Study, a population-based cohort study on the determinants and prognosis of chronic diseases in the elderly. The Medical Ethics Committee of the Erasmus Medical Centre approved the study, and written informed consent was obtained from all participants. The baseline measurements were conducted between April 1990 and July 1993. The complete study design has been described previously.[8] All inhabitants of Ommoord (a suburb

of Rotterdam) who were aged 55 years and over were invited to participate. In total 7,983 participants (response rate of 78%) were examined. At baseline, trained interviewers performed an extensive home interview on demographic characteristics, medical history, risks factor for chronic diseases, and medication use. After the home interview, participants also visited the research centre, where among other measurements, they underwent radiographic examination. For feasibility reasons, baseline hand radiographs of those participants who were available for follow-up six years later (n=3585) were scored for OA, and were included in this study.

Measurements

Radiographic scoring: Two trained assessors (SD, UC) scored standard anteroposterior radiographs of both hands. The readers were blind to other data such as clinical or demographic variables. Radiographs were scored for the five distal interphalangeal joints (DIPs), the four proximal interphalangeal joints (PIPs), the five metacarpophalangeal joints (MCPs), the first carpometacarpal joint (CMC1) and the trapezioscaphoid joint (TS). Each joint was scored for OA using a Kellgren-Lawrence score scaled 0-4. OA for each joint was defined as a Kellgren-Lawrence (K-L) score of 2 or more. Four groups (DIPs, PIPs, MCPs and CMC1/TS) were defined, and a group was considered positive if at least one joint in the group showed K-L score of 2 or more. Hand OA was defined as the presence of a K-L score of 2 or more in two out of three groups of hand joints (DIPs, PIPs and CMC1/TS) on the left and/or right side. The complete scoring method has been described elsewhere.[9]

Metabolic risk factors

Height and weight were measured at the research centre; the participants were wearing indoor clothes but no shoes. Body mass index (BMI) was calculated as weight divided by squared height. BMI higher than 27.4 was defined as overweight (highest tertile of the BMI). Blood pressure was measured twice and the average of two consecutive measurements used to calculate the diastolic and systolic pressures. Hypertension was defined as systolic pressure ≥160 mm Hg, diastolic pressure ≥ 100 mm Hg, or the use of antihypertensive medication. Blood samples were taken, and subjects not using antidiabetic medications received a drink of 75 g of glucose. Post-load glucose level was measured two hours later. Diabetes was defined as a random or post-load blood glucose level >11.0 mmol/L and/or the use of antidiabetic drugs (oral or insulin injection). Total serum cholesterol was determined by an automated enzymatic procedure in a non-fasting blood sample. HDL-cholesterol was measured

after precipitation of the non-HDL fraction with phosphotungstate mangnesium.[10] The ratio of total cholesterol to HDL cholesterol was calculated and used as a continuous variable in the analysis.

Statistical Analysis

Univariate and multivariate logistic regression analysis (odds ratios) were used to examine association between radiological OA of the different hand joint groups or hand OA and overweight adjusted for age and gender. We also examined these associations using a categorical variable for different cut-off points for BMI. The same analysis was performed for the association of diabetes, hypertension, and total/HDL cholesterol ratio with radiological hand OA. Interaction with age or gender was tested for all the associations specified above. Finally, when several metabolic factors were present concurrently, crude risks and adjusted odds ratios for hand OA were calculated. The SPSS (version 10) program was used for all analyses.

Results

A total of 3,585 elderly participants (mean age 66.0 years with 58.2% females) were evaluated. Table 1 shows the baseline characteristics of our study population compared to the total population of the Rotterdam study.

Overweight (BMI > 27.4) adjusted for age and gender showed a positive association (OR; 1.4, CI 1.2 – 1.7) with OA of the hand. After additional adjustment for diabetes, hypertension and total/HDL cholesterol ratio, the association of BMI >27.4 with hand OA remained significant. Using a categorical variable for different cut-off points for BMI showed that the risk for hand OA increased in people with a higher BMI (Figure 1).

Differentiation for hand joint groups, adjusted for age and gender showed a similar association of overweight with OA of DIP, PIP and MCP, but no association with OA of the base of the thumb (CMC1/TS). Additional adjustment for concurrent presence of OA in other joint groups resulted in nearly the same estimates (Table 2).

Hypertension showed a weak association with hand OA (OR; 1.2 CI 1.0 – 1.5), adjusted for age and gender. This association disappeared after adjustment for overweight as a continuous variable.

Diabetes showed an association with presence of hand OA (OR;1.3 CI 1.0 – 1.7) adjusted for age and gender. However the association of diabetes with hand OA showed a significant interaction with age and led us to evaluate this relationship in three age groups. This showed that the risk for hand OA is higher in people with diabetes in the younger group (Table 3). People with diabetes in the older age group did not have a

higher risk for hand OA. After additional adjustment for overweight as a continuous variable, the same results were obtained. Total/ HDL cholesterol ratio showed no significant association with hand OA.

Table 1 **Baseline characteristics of the study population**

Characteristics	Study population N=3585	Total Rotterdam study N=7983
Female, %	58.2	61.1
* Age, years	66.0 ± 6.9	70.6 ± 9.8
* Body mass index, kg/m^2	26.3 ± 3.5	26.3 ± 3.7
Diabetes, %	7.4	10.5
Hypertension, %	30.1	36.1
* Total Cholesterol, mmol/l	6.7 ± 1.2	6.6 ± 1.2
* HDL Cholesterol, mmol/l	1.4 ± 0.4	1.4 ± 0.4
* Total/HDL cholesterol ratio	5.3 ± 1.6	5.2 ± 1.6
DIP OA %	47.8	NA
PIP OA %	17.6	NA
MCP OA %	7.8	NA
Base of thumb (CMC1/TS) OA %	35.9	NA
Hand OA %	27.5	NA

OA : presence of K-L ≥ 2 in right or left joint groups (DIP, PIP, MCP, CMC1/TS)
Hand OA: presence of K-L ≥ 2 in two out of three hand joint groups (DIP, PIP, CMC1/TS)
NA : Not Available
* Mean ± SD

Figure 1 **The association of BMI with hand OA**

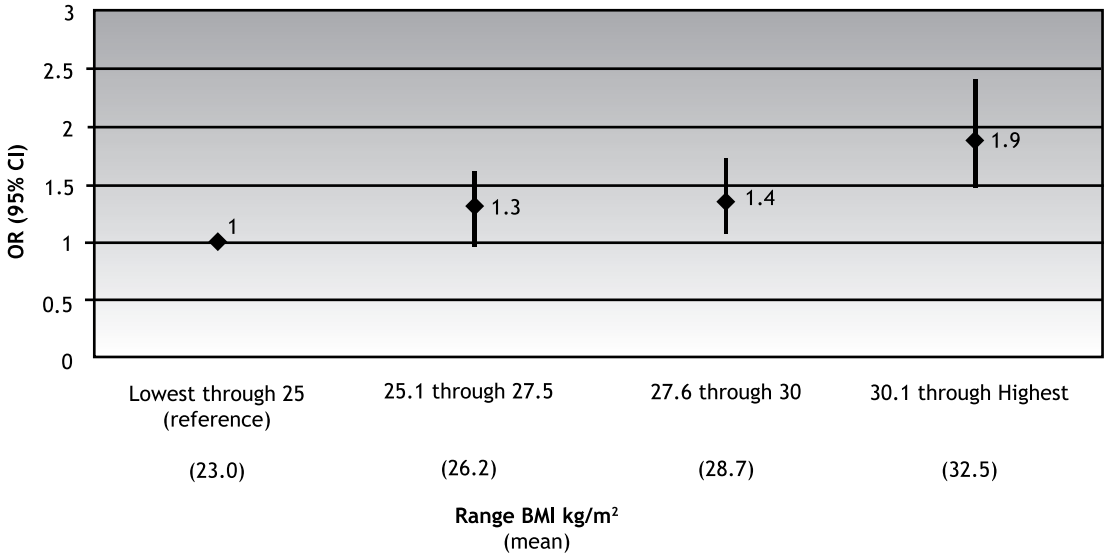


Table 2 **Association of overweight with OA of the different hand joint groups**

BMI > 27.4	Hand joints OA OR (95%CI)			
	DIPs	PIPs	MCPs	Base of thumb
Hand joint groups modelled separately	1.4 (1.2 - 1.6)	1.4 (1.1 - 1.7)	1.5 (1.5 – 2.0)	1.1 (1.0 - 1.3)
Hand joint group modelled together	1.3 (1.1 – 1.5)	1.2 (1.0 – 1.5)	1.3 (1.0 – 1.8)	1.0 (0.8 – 1.2)

All analyses are adjusted for age and gender
Hand joint OA; presence of one or more joint of the group with K-L ≥ 2

Table 3 **Association of Diabetes with hand OA in relationship with age**

	Risk for hand OA %		OR (95%CI)
	No diabetes	Diabetes	
*Total group	27.1	32.6	1.2 (0.9 – 1.6)
Age 55-62	14.2	22.8	2.0 (1.0 – 3.8)
Age 62.1 - 68.7	27	28.9	1.1 (0.7 – 1.8)
Older than 68.8	42.5	41.5	1.0 (0.6 - 1.5)

Age categorized in tertile.
The associations are adjusted for gender and BMI>27.4
* Total group additionally adjusted for age

Concurrent presence of overweight with either diabetes or hypertension led to nearly the same association with hand OA. However, adjusted for age and gender, the simultaneous presence of overweight, diabetes and hypertension (i.e. three metabolic factors together) showed higher association with hand OA than people with none of these conditions (OR; 2.3 CI 1.3 – 3.9) (Table 4). This association increased further in the younger age group (55-62 years old) to OR; 3.2 CI (1.1 – 8.8). Other age groups (62.1 - 68.7 years old and older than 68.8) also showed odds ratios of 1.9 and 1.8 respectively, but likely due to less power in the analysis, it was no longer significant. To further explore the additional effect of diabetes and hypertension, we compared a group of overweight people with diabetes and hypertension to the group with overweight, without diabetes and hypertension (reference group) and an odds ratio of OR; 1.6 CI (0.9 – 2.7) was obtained. Again less power in the analysis resulted to borderline significant association.

Table 4 **Association of concurrent presence of metabolic factors with hand OA**

	Hand OA		
	Mean of BMI	**Risks of hand OA %**	**OR (95%CI) ***
BMI ≤ 27.4 (reference group) BMI > 27.4	24.4 30.2	24.6 33.2	1.4 (1.2 – 1.7)
BMI ≤ 27.4, No Diabetes (reference group) BMI > 27.4 + Diabetes	24.3 30.8	24.4 38.2	1.6 (1.0 - 2.4)
BMI ≤ 27.4, No hypertension (reference group) BMI >27.4 + hypertension	24.2 30.5	23.2 35.7	1.5 (1.2 – 1.9)
BMI ≤ 27.4, No hypertension, No Diabetes (reference group) BMI > 27.4 + Diabetes+ hypertension	24.2 31.2	22.7 45	2.3 (1.3 - 3.9)

* Adjusted for age and gender
Absolute risk for hand OA in our study population: 27.5%

Discussion

Our cross-sectional study confirms that overweight is associated with hand OA, independently of other metabolic factors. This association is stronger in people with a higher BMI. Differentiation for hand joint groups showed that overweight was associated with OA of the DIP, PIP and MCP but not with OA of the base of the thumb. Although the association between diabetes and hand OA in the total population was weak and not significant, in the younger age group it became stronger and statistically significant independently of overweight. The presence of overweight concurrently with diabetes and hypertension resulted in an even higher risk for hand OA.

This study adds to the scattered positive associations of overweight and hand OA reported in previous studies.[1,11,12] In a large open population cohort, Carman et al. found that overweight at baseline was associated after 23 years follow up with more incident hand OA.[11] Van Saase *et al.* reported that overweight in males had a positive association with OA of the DIP, PIP and MCP and in females with OA of the DIP and PIP.[12] As in our study, they did not show positive association between overweight and OA of the base of the thumb. Studies by Hochberg et al. did not find any association between overweight and hand OA in males or females.[13,14]

We showed, that independently from other metabolic factors, overweight contributes to the presence of hand OA; we also rule out the possible intermediary effect of metabolic factors in explaining the role of overweight on OA. The metabolic influence of overweight on OA may possibly be explained by leptin, which we were unfortunately unable to evaluate due to lack of data. Leptin consists of small

polypeptides encoded by the obese gene; it is produced by adipose tissue and was initially discovered as a central regulator of appetite and energy uptake at the hypothalamus level. Leptin may also be involved in regulating of metabolic activity in the bone and cartilage. Recent study suggests that it might promote osteophyte formation in OA by increasing the production of transforming growth factor β (TGFβ).[5,15] Dumond et al. have also found that leptin levels in synovial fluid of OA patients were significantly correlated with BMI. They also found that leptin has a peripheral function on chrondrocyte metabolism and indicate that leptin may play an important role in the pathophysiology of OA.[16]

Earlier results on association between diabetes and OA were inconsistent. Hart *et al.* showed an association of diabetes with knee radiological OA independent of overweight, while Frey et al. could not show any association between diabetes and clinical OA.[17,18] Possibly, this inconsistency may be explained by a different definition of OA (radiological OA in the first versus clinical OA in second study). We found only an age-dependent association between diabetes and hand OA, and then solely in the younger age group. This might explain why in study of Sturmer et al., the association between diabetes and generalised OA was no longer significant after adjustment for potential confounders including age.[19]

Different mechanisms have been suggested for the association of diabetes with OA. The anabolic effect of Insulin-like growth factor-I (IGF-I) on the chondrocyte is likely to be affected by an altered serum concentration of IGF-binding proteins, which have been reported for Diabetes.[20] Other explanations have also been suggested for the mechanism whereby diabetes might act through OA: elevated glucose levels may lead to IGF-I resistance of the chondrocyte; diabetic micro and macroangiopathy may contribute to OA by influencing synovial tissue and subchondral bone; or increased non-enzymatic glycation of collagen may alter the functional properties of articular cartilage.[19] Although the mechanism that may underline for diabetes and overweight are different, the simultaneous presence of both resulted in only a slight increase in the risk for hand OA.

At least two studies have reported a significant association between hypertension and knee OA independently of the overweight.[17,21] It has been suggested that hypertension may be associated with atherosclerotic disease, leading to defects in the subchondral plate of the weight-bearing joint.[17] This mechanism may not be strongly involved in the non-weight-bearing joints: in our study the association between hypertension and hand OA, which was already weak, disappeared after adjustment for overweight as a continuous variable. Nevertheless, we showed that the simultaneous presence of three metabolic factors (diabetes, hypertension and overweight) led to an increased risk for hand OA. One might speculate that although hypertension alone

exerts no strong influence on hand OA, it might play an additional role when diabetes and overweight have already harmed the joint. In other words, a joint might be injured more vigorously when two other metabolic factors also affected the joint. Still one could suggest that the increased risk in the group with three metabolic factors is due to the higher BMI in this group. However this was not the case, as the mean of the BMI in the group with three metabolic factors was lower than the mean of the BMI in the highest subgroup of obese people (shown on Figure 1), while the latter group showed an even lower odds ratio. In further analysis, obese people with diabetes and hypertension showed a borderline significant higher risk for hand OA compared to obese people without diabetes and hypertension. Therefore the additional effect from diabetes and hypertension seems to be present resulting in a higher risk for hand OA.

Although we used a valid dataset derived from the Rotterdam study, some limitations are present. First, there might be some selection bias in our study population compared to the total Rotterdam population. Hand radiographs were scored of the participants available for follow-up six years later (n=3585). The total population at baseline was older, had a higher proportion of females and a higher frequency of diabetes and hypertension. However there were no differences between BMI in either population. The lower frequency of diabetes and hypertension may be due to a selection of the older healthy survivors, which may have caused the association of metabolic disorder and hand OA to be underestimated in our data. Second, because we evaluated the association of overweight with hand OA in a cross-sectional data, we were unable to show whether overweight is a cause of OA or whether the disability due to OA leads to overweight. However, prospective data presented evidence that overweight is an antecedent to the occurrence of OA rather than a subsequent event.[11,22]

In summary, by showing that the presence of overweight with diabetes and hypertension has an additive influence on hand OA, our data support the previous suggestion that OA has a metabolic component in its etiology.[17]

References

1. Felson DT, Chaisson CE. Understanding the relationship between body weight and osteoarthritis. *Baillieres Clin Rheumatol* 1997;11:671-81.
2. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, Kington RS, Lane NE, Nevitt MC, Zhang Y, Sowers M, McAlindon T, Spector TD, Poole AR, Yanovski SZ, Ateshian G, Sharma L, Buckwalter JA, Brandt KD, Fries JF. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med* 2000;133:635-46.

3. Cicuttini FM, Baker JR, Spector TD. The association of obesity with osteoarthritis of the hand and knee in women: a twin study. *J Rheumatol* 1996;23:1221-6.
4. Sowers M. Epidemiology of risk factors for osteoarthritis: systemic factors. *Curr Opin Rheumatol* 2001;13:447-51.
5. Loeser RF. Systemic and local regulation of articular cartilage metabolism: where does leptin fit in the puzzle? *Arthritis Rheum* 2003;48:3009-12.
6. Davis MA, Neuhaus JM, Ettinger WH, Mueller WH. Body fat distribution and osteoarthritis. *Am J Epidemiol* 1990;132:701-7.
7. Davis MA, Ettinger WH, Neuhaus JM. The role of metabolic factors and blood pressure in the association of obesity with osteoarthritis of the knee. *J Rheumatol* 1988;15:1827-32.
8. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;7:403-22.
9. Dahaghin S, Bierma-Zeinstra SM, Ginai A, Pols H, Hazes J, Koes B. Prevalence and pattern of radiological hand osteoarthritis and association with pain and disability (The Rotterdam study). *Ann Rheum Dis* 2004.
10. Humphries KH, Westendorp IC, Bots ML, Spinelli JJ, Carere RG, Hofman A, Witteman JC. Parity and carotid artery atherosclerosis in elderly women: The Rotterdam Study. *Stroke* 2001;32:2259-64.
11. Carman WJ, Sowers M, Hawthorne VM, Weissfeld LA. Obesity as a risk factor for osteoarthritis of the hand and wrist: a prospective study. *Am J Epidemiol* 1994;139:119-29.
12. van Saase JL, Vandenbroucke JP, van Romunde LK, Valkenburg HA. Osteoarthritis and obesity in the general population. A relationship calling for an explanation. *J Rheumatol* 1988;15:1152-8.
13. Hochberg MC, Lethbridge-Cejku M, Plato CC, Wigley FM, Tobin JD. Factors associated with osteoarthritis of the hand in males: data from the Baltimore Longitudinal Study of Aging. *Am J Epidemiol* 1991;134:1121-7.
14. Hochberg MC, Lethbridge-Cejku M, Scott WW, Jr., Plato CC, Tobin JD. Obesity and osteoarthritis of the hands in women. *Osteoarthritis Cartilage* 1993;1:129-35.
15. Scharstuhl A, Glansbeek HL, van Beuningen HM, Vitters EL, van der Kraan PM, van den Berg WB. Inhibition of endogenous TGF-beta during experimental osteoarthritis prevents osteophyte formation and impairs cartilage repair. *J Immunol* 2002;169:507-14.
16. Dumond H, Presle N, Terlain B, Mainard D, Loeuille D, Netter P, Pottie P. Evidence for a key role of leptin in osteoarthritis. *Arthritis Rheum* 2003;48:3118-29.
17. Hart DJ, Doyle DV, Spector TD. Association between metabolic factors and knee osteoarthritis in women: the Chingford Study. *J Rheumatol* 1995;22:1118-23.
18. Frey MI, Barrett-Connor E, Sledge PA, Schneider DL, Weisman MH. The effect of noninsulin dependent diabetes mellitus on the prevalence of clinical osteoarthritis. A population based study. *J Rheumatol* 1996;23:716-22.
19. Sturmer T, Brenner H, Brenner RE, Gunther KP. Non-insulin dependent diabetes mellitus (NIDDM) and patterns of osteoarthritis. The Ulm osteoarthritis study. *Scand J Rheumatol* 2001;30:169-71.
20. Clauson PG, Brismar K, Hall K, Linnarsson R, Grill V. Insulin-like growth factor-I and insulin-like growth factor binding protein-1 in a representative population of type 2 diabetic patients in Sweden. *Scand J Clin Lab Invest* 1998;58:353-60.
21. Lawrence JS. Hypertension in relation to musculoskeletal disorders. *Ann Rheum Dis* 1975;34:451-56.
22. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham Study. *Ann Intern Med* 1988;109:18-24.

8

General discussion

General discussion

The main objective of this thesis is to evaluate the epidemiology and clinical consequences of hand osteoarthritis (OA). This chapter presents some discussion concerning our findings, the clinical implications, and makes suggestions for future research.

Epidemiology and clinical burden of hand osteoarthritis

In all surveys of osteoarthritis, classification of hand osteoarthritis remains a problem which has yet to be resolved.[1] The estimate of the prevalence or incidence of OA will of course be influenced by the definition of osteoarthritis that has been used in the study concerned. Osteoarthritis can be defined clinically, radiographiclly or as a combination of both radiographic and clinical signs. The definition of hand OA suggested by the American College of Rheumatology (ACR) criteria is mostly based on clinical symptoms, and the presence of Heberden's and/or Bouchard's nodes. According to the ACR criteria, osteoarthritis in hand joints is defined as pain or stiffness on most days of the preceding month in addition to three of the following four criteria: bony swelling of two or more of the 10 selected joints {bilateral distal interphalangeal (DIP) joints 2+3, bilateral proximal interphalangeal (PIP) joints 2+3, and first Carpometacarpal (CMC1) joints}, bony swelling of two or more DIP joints, fewer than three swollen metacarpophalangeal (MCP) joints, and deformity of at least one of the 10 selected joints. Heberden's nodes and Bouchard's nodes are firm swellings over the superolateral and dorsal aspects of the distal and proximal interphalangeal joints, respectively.[2] They are associated with underlying radiographic changes of interphalangeal OA, especially with osteophytes.[2,3] However, the ACR criteria could not be used in the Rotterdam study, because we were dependent on the already existing data collected at baseline in this cohort study. Data on Heberden's nodes were available only for a sub-group of the Rotterdam study, and no data were available for Bouchard's nodes. At baseline, however, all participants received a hand X-rays, which allowed us to define hand OA based on radiographic hand OA.

Furthermore, the presence of pain is necessary to fulfil the ACR criteria. Pain in osteoarthritis can result from structural pathology in the joints, but also can be a consequence of physical activities, psychological and other causes of distress, and of pain thresholds. In addition, in osteoarthritis pain may be related to muscular weakness.[4] Therefore, to obtain a clearer insight into the etiology of OA, a radiographic definition of hand OA is the better choice, because it is not based on pain, which has

different risk factors. For the same reason, as symptoms and structural markers of OA are different phenomena, we did not use a combined definition of OA (i.e. presence of joint pain together with evidence of radiographic disease) to study the etiology of OA. Moreover, the ACR criteria define as the absence or presence of the disease, which does not give the possibility to measure the severity of OA. To study clinical aspects of OA, a clinical definition of the disease (such as the ACR criteria) might be preferable. However, as discussed above, no data were available for this.

In this thesis we evaluated hand OA using a radiographic definition. In **Chapter two** we showed that, over 55% of the studied patient had radiographic OA in at least one joint of the hand. This means that cartilage degeneration or subchondral bone reaction is present in at least one hand joint in more than half of the open population aged 55 years and over. Hand joints are thus one of the most frequent sites of involvement of OA compared with the hip or knee joints.[5] Moreover, OA co-occurs more frequently in different joint groups of the hand simultaneously than it occurs solely, and somewhat more often in female, confirming a systemic predisposition to OA. OA in groups of PIPs and MCPs co-occurred very often with OA in another hand joint group, again indicating a systemic predisposition. However, OA in the thumb base occurs less often simultaneously with OA in the other hand joints. Earlier, Jonsson *et al*. found a relationship between hypermobility and the development of thumb base OA.[6] All these findings may support the hypothesis that systemic factors play a more important role than physical factors in radiographic OA of the PIPs and MCPs, but a local mechanical factor might play a more important role in radiographic OA of the thumb base. However, in this study, it was not possible to control for the role of local mechanical factors on OA of different hand joints but this should definitely be studied in the future.

In addition to studying the epidemiology of hand OA, in **Chapter two** we also investigated the association between radiographic findings of OA with clinical symptoms in an open population (the Rotterdam study). Hand OA was found to have a moderate association with hand pain or hand disability. An increase in the number of hand joints with OA or the presence of OA in all four joint groups resulted in a more frequent occurrence of hand pain or hand disability. However, persons with a more severe form of OA only report more hand pain, but not more hand disability. The association between radiographic OA in the thumb base and hand pain/disability is stronger than in the other hand joints. The group of MCPs also showed a strong association with hand disability. Because radiographic OA of the MCPs co-occur in more than 80% of the cases with radiographic OA of other joint groups of the hand, these results might indicate again that a more general form of hand radiographic OA is more disabling.

Chapter three, addresses patient-related outcomes such as hand pain and hand disability, assessing the contribution of potential determinants to explain hand pain or hand disability in the open population. We found that about 17% of our study population had pain in the left or right hand during the previous month, and 14% had moderate to severe hand disability. We used R^2 (the fraction of variance explained by a certain determinant in the population) to evaluate the contribution of available determinants to the occurrence of hand pain or hand disability. All available determinants together explained only a small part of the variance (about 20% of the variance of hand pain and about 25.2% of the variance of hand disability). Radiographic hand OA was a poor explanation for hand pain and added only 0.5% to the total explained variance, and no additional value to the total explained variance of hand disability. A greater part of hand pain/hand disability remained unexplained. Unfortunately, some of the potential determinants associated with hand pain or hand disability such as local factors (e.g. carpal tunnel syndrome and tendonitis) and systemic factors (e.g. presence of psychological factors and distress) were not available in the Rotterdam study. These factors might be a part of the explained variance of hand pain/hand disability, and should be studied in more details.

Chapter four summarizes the existing knowledge concerning the clinical burden of hand OA, including our two previous studies (Chapter 2 and 3). We found a positive association between radiographic hand OA and hand pain. However, the strength of this relationship was inconsistent, ranging from weak to strong associations. Although the association between radiological OA and hand dysfunction was positive in some of the studies with varying degrees of strength, the absence of an association was also reported in some studies. Due to the large heterogeneity in terms of measurement of hand pain, hand function impairment, hand radiographic OA and also the use of different statistical tests in the reviewed studies, we suggest that the use of a uniform definition for each of these measurements in future studies might reduce the difficulty in comparing the results.

Hand osteoarthritis as predictor of future hip/knee osteoarthritis, or as indicator of homochromatosis

Chapter five showed that persons with hand OA have a higher risk to develop hip or knee OA in the future. In addition, the presence of a collagen biomarker (CTX-II) showed an increased risk for future hip or knee OA. Further, we evaluated whether concurrent presence of two or three risk factors implies a higher risk for future hip or knee OA, which was the case in only some of the analyses. However, evaluation of

certain combinations of risk factors was not always possible. In order to identify high-risk groups more specifically, we needed to combine more than three risk factors. This implies a simultaneous presence of three or more risk factors (interaction of different risk factors on each other) in individuals, which is a great challenge. Smaller sample sizes and subsequently a lower statistical power will be inevitable when evaluating multiple risk factors simultaneously. Although, we used a relatively large sample of 1235 subjects, we could not combine more than two or three risk factors together with enough statistical power. Future studies should include sample sizes large enough to detect potential interaction effects of the simultaneous presence of more risk factors. The magnitude of the association should also be considered (i.e. the magnitude of the association should be clinically relevant).

We confronted the same problem in our study aiming to identify homozygous individuals with H63D mutation of the hemochoromatosis gene (**Chapter six**). We could provide statistical evidence show that the chance of identifying H63D homozygous persons is higher in the presence of MCP OA in the younger age group, but not in the overall population. Vice versa, the risk of hand OA for H63D homozygocity reached a statistical significant level in the total population, but not in the younger age group. This might be due to the limited statistical power in the analysis, as described above.

Etiology of osteoarthritis

A loss of homeostasis in the maintenance of a healthy articular cartilage leads to the pathologic degeneration of articular cartilage in osteoarthritis.[7] **Chapter seven** evaluated the role of obesity and other metabolic factors in hand OA, showing that obesity is associated with hand OA independent from other metabolic factors. Obesity is suggested to be associated with OA of the non weight-bearing joints through its metabolic effect on the cartilage.[8,9] The metabolic influence of overweight on OA may be explained by the leptin. Leptin is produced by adipose tissue and is higher in the synovial fluid of the patient with OA, and likely to regulate the metabolic activity of the bone and cartilage.[10] Animal studies showed that leptin strongly stimulated anabolic functions of chondrocytes and induced the synthesis of IGF-1 and TGFbeta1 in cartilage at both the messenger RNA and the protein levels.[9] In addition, a recent study showed that leptin plays a proinflammatory role in the chondrocytes.[11]

In our study, independent from other metabolic factors, diabetes appeared to be associated with hand OA, but only in the younger age group. We could not find any direct explanation for this finding. Different mechanisms have been suggested for the

association of diabetes with OA, which we discussed in **Chapter seven**. In a recent study, insulin showed positive effects on matrix metabolism in isolated chondrocytes and articular cartilage explants from animals and humans.[12]

Further, in **Chapter seven**, we showed that the presence of overweight concurrently with diabetes and hypertension resulted in an even higher risk for hand OA. We speculate that the joint might be injured more vigorously when two other metabolic factors have some effect on the cartilage. However, this hypothesis has to be evaluated more thoroughly in future studies. To study the influence of obesity in OA, again hand joints might be a better joint to explore because of its simple joint structure and the absence of axial load.

Recommendations for daily practice

Based on the results of this thesis, some implications for daily practice are suggested. Firstly, the presence of OA on hand X-rays is only in some cases an explanation for the presence of hand pain or hand disability. Therefore general practitioners should consider other reasons for hand pain and hand disability, including local and systemic factors.

Secondly, because our study showed that overweight people with hand OA are at higher risk to develop hip or knee OA in the future, these persons should be advised to reduce weight.

Thirdly, in this thesis we showed that the crude chance of finding homozygous persons for H63D mutation of hemochoromatosis in population is only 2.7%, while the chance increases to 20% when persons with OA in the MCP joints were examined. To identify the hemochoromatosis disorder earlier in life and therefore prevent the irreversible pathology of this disease, we suggest that general practitioners may apply for detection of this gene in persons with OA in the MCP joints.

Suggestion for future studies

In each chapter of this thesis we have presented some suggestions for future research. Based on the results of our study, the major issues to be evaluated in the future include:

Early identification of groups at risks for OA: Because OA of the weight-bearing joints is one of the leading musculoskeletal disorders causing disability in the population, future research should focus on earlier identification of persons

susceptible to OA in order to prevent the burden of this disease. We suggested in this thesis that the presence of two or three risk factors simultaneously (e.g. hand OA, CTX-II, obesity, family history of OA) may help to identify those at high risk to develop OA of the weight-bearing joints. To identify high-risk groups more specifically, future studies should focus on models consisting of various concurrent risk factors. However, this is not an easy task. Further studies on this issue will open the possibility to recruit people at risk for inclusion in preventive trials.

Study of the etiology of OA: The mechanism by which obesity may cause OA needs further investigation. Although it has been suggested that obesity may act on OA through leptin, we had insufficient data to study the association between leptin and OA in this population. Data on the role of leptin on osteoarthritis are limited[9-11,13] and should be studied in the future more thoroughly.

Moreover, as obesity showed to be a risk factor for hand OA in our population, and was also a risk factor for OA in other joints in another study,[14] the role of weight reduction to reduce the burden of osteoarthritis in the body should be studied further.

Conclusion

The work presented here shows that hand joints are very frequently affected by osteoarthritis, increasingly with age, and more commonly in females. Distal interphalangeal joints and base of the thumb are the most frequently affected joint groups in the hand.

We have shown that hand pain and hand disability are moderately associated with radiographic OA in the hand joints. Further, OA in the hand joints is an indicator of future hip or knee OA especially, in those with other risk factors such as overweight or family history of OA. Moreover, we suggested that persons with OA in the MCP joint could be screened for the presence of H63D mutation of the hemochoromatosis gene. Finally, this thesis suggested a possibility of an additional effect of hypertension and diabetes in the presence of overweight on hand osteoarthritis.

References

1. McAlindon T, Dieppe P. Osteoarthritis: definitions and criteria. Ann Rheum Dis 1989;48:531-2.
2. Thaper A, Zhang W, Wright G, Doherty M. The relationship between Heberden's nodes and underlying radiographic changes of osteoarthritis. *Ann Rheum Dis* 2005.
3. Stern AG, Moxley G, Sudha Rao TP, Disler D, McDowell C, Park M, Schumacher HR. Utility of digital photographs of the hand for assessing the presence of hand osteoarthritis. *Osteoarthritis Cartilage* 2004;12:360-5.
4. Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. *Radiol Clin North Am* 2004;42:1-9, v.
5. Reijman M, Hazes JMW, Bierma-Zeinstra SMA, Koes BW, Christgau S, Christiansen C, Uitterlinden AG, Pols.H.A.P. A new marker for osteoarthritis: cross-sectional and longitudinal approach. *Arthritis Rheum.* 2004;50:2471-8.
6. Jonsson H, Valtysdottir ST, Kjartansson O, Brekkan A. Hypermobility associated with osteoarthritis of the thumb base: a clinical and radiological subset of hand osteoarthritis. *Ann Rheum Dis* 1996;55:540-3.
7. Poole AR. Can serum biomarker assays measure the progression of cartilage degeneration in osteoarthritis? *Arthritis Rheum* 2002;46:2549-52.
8. Felson DT, Chaisson CE. Understanding the relationship between body weight and osteoarthritis. *Baillieres Clin Rheumatol* 1997;11:671-81.
9. Dumond H, Presle N, Terlain B, Mainard D, Loeuille D, Netter P, Pottie P. Evidence for a key role of leptin in osteoarthritis. *Arthritis Rheum* 2003;48:3118-29.
10. Schaffler A, Ehling A, Neumann E, Herfarth H, Tarner I, Scholmerich J, Muller-Ladner U, Gay S. Adipocytokines in synovial fluid. *Jama* 2003;290:1709-10.
11. Otero M, Gomez Reino JJ, Gualillo O. Synergistic induction of nitric oxide synthase type II: in vitro effect of leptin and interferon-gamma in human chondrocytes and ATDC5 chondrogenic cells. *Arthritis Rheum* 2003;48:404-9.
12. Cai L, Okumu FW, Cleland JL, Beresini M, Hogue D, Lin Z, Filvaroff EH. A slow release formulation of insulin as a treatment for osteoarthritis. *Osteoarthritis Cartilage* 2002;10:692-706.
13. Miller GD, Nicklas BJ, Davis CC, Ambrosius WT, Loeser RF, Messier SP. Is serum leptin related to physical function and is it modifiable through weight loss and exercise in older adults with knee osteoarthritis? *Int J Obes Relat Metab Disord* 2004;28:1383-90.
14. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, Kington RS, Lane NE, Nevitt MC, Zhang Y, Sowers M, McAlindon T, Spector TD, Poole AR, Yanovski SZ, Ateshian G, Sharma L, Buckwalter JA, Brandt KD, Fries JF. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med* 2000;133:635-46.

9

Summary

Summary

Osteoarthritis (OA) is the most frequent cause of rheumatic complaints. OA is a group of distinct overlapping diseases, which may have different aetiologies (causes), but have similar biologic, morphologic (form), and clinical outcomes. OA can arise in any synovial joint in the body, but most often in the hands, feet, spine, knees, and hip joints. Because arthritis and rheumatic diseases receive far less attention in the scientific literature than is warranted by their enormous and growing disease burden, this study aims to contribute to the understanding of OA, especially a frequently occurring form of OA, hand OA, and its clinical consequences for the patients.

Except for one review, all other studies presented in this thesis were based on data from the Rotterdam study, a large cohort from the open population of persons aged 55 years and older in the Netherlands. Baseline measurements were conducted between 1990 and 1993 on a total of 7983 participants (response rate of 78%). Hand radiographs were made at baseline for each participant, but for feasibility reasons only 3906 radiographs were scored of which the data were used in the following studies.

Chapter 2 investigates in this open population the prevalence and pattern of radiographic OA of the hand joints and their association with self-reported hand pain and disability. Radiographic hand OA is a frequently occurring disease in the elderly, especially in females, with the highest frequency in DIP and CMC1/TS joints of the hand followed by PIP and MCP joints. OA co-occurs more frequently in different joint groups of the hand than it occurs solely. A modest to weak association of radiographic OA of the hand with hand pain and disability was found, which varies with the site of involvement.

In **Chapter 3** the prevalence of hand pain and hand disability in the open population and the contribution of their potential determinants including radiographic hand OA was studied. One-month period prevalence of hand pain in this population was 17% and the prevalence of hand disability was 14%. In the univariate analysis for hand pain, rheumatoid arthritis showed the highest explained variance (R^2) and odds ratio. For hand disability, ageing showed the highest explained variance (R^2), while Parkinson's disease had the highest odds ratio. Contribution of available potential determinants in this study was about 20% for hand pain and about 25% for hand disability. Radiographic hand OA contributed only poorly to the explained variance of hand pain and made no contribution to the explained variance of hand disability.

Chapter 4 presents a systematic appraisal in which we summarized current knowledge on the association between radiographic signs of OA in the hand and

clinical symptoms. This review revealed a positive association between radiographic hand OA and hand pain, but the reported strength of the association ranges from weak to strong. Results on hand function impairment and OA were inconsistent, ranging from no association to moderately associated. A severe form of OA showed a stronger association with hand pain but, again, data on hand function impairment were inconsistent. An increasing number of joints with OA showed a stronger association with both hand pain and hand function impairment. This review revealed a great heterogeneity in terms of measurement of hand pain, hand function impairment and also radiographic hand OA, suggesting that a uniform definition for each of these measurements might reduce the difficulty in comparing the results.

In **Chapter 5** we evaluate the risk of hand OA for future hip/knee OA and also evaluate whether the concurrent presence of hand OA with other risk factors or an OA biomarker (Collagen type II) increase this risk further. Hand OA showed an increased risk for future hip/knee OA, which is higher for hip OA than for knee OA. Concurrent presence of hand OA and other risk factors (overweight or family history of OA) or high CTX-II increased the risk further for future hip/knee OA.

In **Chapter 6** we addressed whether a test for the common C282Y and H63D mutations in the hemochromatosis gene is clinically relevant in patients with OA at atypical joint sites at the hand. We found that persons homozygous for H63D had significantly more often radiographic OA at any hand joints compared to non-carriers, but no relation with hand OA in C282Y mutations was found. The number of subjects with C282Y homozygosity was too low to allow a meaningful statistical analysis. We showed that the chance of identifying H63D homozygotes in persons with MCP OA is higher than identifying this mutation in the total study population especially at a relatively younger age (55-65 years). Thus a genetic test for the hemochromatosis (H63D) mutation in patients with radiographic OA in MCP joint might be clinically relevant, leading to detection of hemochromatosis at early stages.

In **Chapter 7** the role of obesity in hand OA was evaluated. Since hand joints are non-weight bearing, the association between overweight and hand OA is critical to understand how overweight may cause OA apart from axial load. Furthermore, overweight might be associated with the occurrence of OA through other metabolic factors (e.g. diabetes, hypertension, total/HDL cholesterol). In this chapter we showed no intermediate effect of metabolic factors on the association of overweight with hand OA. An additional risk for hand OA, however, seems to be present when overweight occurs together with hypertension and diabetes especially at a relatively younger age (55-62 years).

Chapter 8 addresses the main topics in this thesis, presents some recommendations for future studies, and discusses the clinical implications of our findings in general practice. Further, in this chapter we discuss the difficulties confronting researchers in their aim to identify people at high risk to develop OA.

Acknowledgements

With the manuscript nearly finished, it is time to thank the many people who have contributed to the work presented here.

First I would like thank my two promoters, Prof. Bart Koes and Prof. Mieke Hazes. Dear Bart, I sincerely appreciate your great help in starting me off at Erasmus MC. During my time here, I have received your excellent professional insights into epidemiology, your wise motivating advice, and experienced your wonderful way of working. Your valuable remarks have consistently helped me to develop my work. Dear Mieke, I always admire you for being so dedicated to your work. You have generously provided me with valuable comments, even when other things were making enormous demands on your time and attention.

My deepest gratitude also goes to my boundlessly cheerful co-promoter, Associate Prof. Sita Bierma-Zeinstra. Dear Sita, I have enjoyed all the time I spent working with you! There was hardly a day when I didn't visit you to discuss my results. Your scientific advice, brilliant ideas and enthusiasm for discussing new findings always encouraged me. Your rich experience and enthusiastic advice helped me incredibly during the publication of the manuscripts.

I deeply thank Prof. H.A.P Pols as a member of the PhD committee and also as a head of the Rotterdam Study. Dear Huib, with you as a co-author in many of the manuscripts, I have benefited greatly from your clinical point of view. Of course, I thank all other members of the PhD committee and co-authors in the manuscripts.

Dear Roos, thank you for your outstanding solution to our statistical problems, not to mention our very enjoyable collaboration.

It is a great pleasure to thank not only Dr. A. Ginai, who generously trained us to score hand radiographs, but also Mr. U. Cimon for his work scoring hand radiographs. Neither can I forget the supportive fever of Max and Frank, who provided me with the information and data necessary for these studies.

Dear Dr. Arianne Verhagen, my experience and learning as a researcher at Erasmus MC all started with you. It was really enjoyable to perform the systematic review and to profit from your great knowledge.

I wish to thank my dear roommates, Bionka and Rianne, who also honoured me by being my *paranimfs* in the PhD ceremony. Bionka and Rianne, you both made our office a warm, pleasant, cheering place to work. Over the last two years we have spent wonderful moments together, enthusiastically discussing the results of our work, exchanging ideas, learning from each other and sharing various stories.

It is a great pleasure to thank David Alexander for your high-quality teaching on writing English (and sometimes for your help with reading between the lines!).

Even if I do not name them individually, I would also like to thank all the people in the research group with whom I spent longer or shorter periods of time, chatting during work, social events, or wonderful lunch breaks. Many thanks, especially for always coming forward when help was needed.

Thanks are also due to my colleagues in the Department of General Practice, who helped make it a wonderful place to work; and to people who support me with administrative and technical matters. And of course dear Trudy at the Department of Rheumatology, for always being so warm and friendly when I was trying to reach Mieke!

This is an opportunity to send my deepest gratitude to my dear parents for all their love and faith. You have done your best for your family. My dear Mother, you are my symbol of endless love and ceaseless activity.

And finally I must thank my kind and very patient husband, Mehdi, who has been very understanding and has supported me unconditionally with genuine love. My lovely son Amir, who always visits me at the end of the day, and always asks me whether I will be at home tomorrow, even when the answer is likely to be in the negative. Dear Amir, I gain enormous energy when we read books or play games together. Without you and Mehdi making a nice, warm house at the end of the working day, this work would not have been possible.

Curriculum Vitae

Saeede Dahaghin was born on 11 September 1966 in Tehran. After graduating from high school in 1984, she spent one year studying Technology Radiology at the University of Esfahan before starting medicine at Shahid Sadoughi University, Yazd, in 1986. She did her internship at the University of Tehran medical school. Her research on chronic diarrhoea and malabsorption in children at the Children's Hospital Medical Centre (University of Tehran) led to her thesis and to her graduation as a Medical Doctor in 1993.

After her graduation she started to practice medicine at the East Tehran Medical Centre (Razmi Clinic) and continued working as a medical doctor until she left Iran in 1998. In April 2001, she started her research activity on the systematic review of repetitive strain injury (RSI) according to the rules of Cochrane collaboration at Erasmus Medical Centre, Rotterdam**,** the Netherlands. In 2002 she started on the project on hand osteoarthritis at Erasmus, which developed into a PhD degree. She has also trained in various programmes and courses in epidemiology, statistical analysis, quantitative medicine and health sciences offered by the Netherlands Institute for Health Sciences (Nihes), an institute in which Erasmus Medical Centre participates.

In June 2004, her work was selected as one of the six best clinical research abstracts at the congress of the European League against Rheumatism (EULAR), Berlin, Germany, where it received an International Research Award (Abbott Award).

She is married to Mehdi Afshar-Payam and has one son, Amir.