Osteoarthritis and Osteoporosis Assessed from Hand Radiographs: Prevalence, Determinants, and Associations with Morbidity and Mortality

Doctoral dissertation

To be presented by permission of the Faculty of Medicine of the University of Kuopio for public examination in Auditorium 2 of Kuopio University Hospital on Saturday 3rd June 2006, at 12 noon

Department of Surgery
Department of Physical and Rehabilitation Medicine
Kuopio University Hospital
Department of Health and Functional Capacity
National Public Health Institute
ABSTRACT

Objectives - Osteoarthritis (OA) is highly prevalent in hand joints and it may be an indicator of systemic OA. However, few studies have focused on hand OA as a predictor of mortality or disability. Osteoporosis (OP) has clinical and public health importance because of increased risk of fractures. To date, a case-finding strategy is recommended to target patients at high risk of fracture, and there is a need for simple and cheap measurement of bone mass. A number of previous studies have reported an inverse relationship between OA and OP, but limited studies are available on longitudinal changes in bone mineral mass in subjects with radiographic OA. Such studies are needed to design effective management for OA and OP. The aim of this study was to investigate OA and OP assessed from hand radiographs and their prevalence, determinants and associations with morbidity and mortality.

Methods - In 1978-80, a representative population sample of 8,000 Finns aged 30 or over were invited to a comprehensive health examination; 7,217 (90%) complied. Hand radiographs were taken from 3,595 subjects to diagnose OA in both hands and to determine the metacarpal cortical index (MCI), a proxy of cortical bone mineral mass. Work disability and mortality of the subjects were systematically followed from registers covering the whole population. Record linkage to the National Hospital Discharge Register identified subjects who had been hospitalised for primary treatment of hip fracture or myocardial infarction by the end of 1994. In 2000, calcaneal broadband ultrasound attenuation (BUA) was measured with the SAHARA sonometer, and clinical re-examination was carried out in 340 of the participants.

Results - The prevalence rates of OA of Kellgren’s grade 2 to 4 in any finger joint (finger OA) and in at least two symmetrical pairs of distal interphalangeal joints (symmetrical DIP OA) and thumb carpometacarpal joints (CMC-1 OA) were 44.8%, 16.0% and 11.0%, respectively. The subjects with body mass index (BMI) over 35 kg/m\(^2\) had a two-fold risk of hand OA of any type as compared to those with normal relative weight (BMI 20.0 - 24.9 kg/m\(^2\)). Symmetrical DIP OA predicted total mortality in women (relative risk (RR) 1.23; 95% confidence interval (CI) 1.01-1.51), and finger OA predicted cardiovascular deaths in men (RR 1.42; 95% CI 1.05-1.92). It appeared that the risk of a new major coronary event was elevated among those with regular analgesic use at baseline (RR 1.51; 95% CI 1.08-2.10). None of the hand OA types predicted work disability or was associated with difficulties in performing ordinary daily activities. High age, low BMI, high stature and smoking showed, independently of each other, statistically significant associations with low MCI. The adjusted relative risk of hip fracture per increment of MCI by a standard deviation (0.1) was 0.69 (95% CI 0.55-0.86). Symmetrical DIP OA and CMC-1 OA showed a statistically significant association with low MCI in proportion to the radiological severity of OA. Symmetric DIP OA predicted low values of BUA at follow-up.

Conclusions - Obesity is a strong risk determinant of all forms of hand OA in both sexes. This indicates that overweight exerts a systemic influence on the risk of OA. The increased cardiovascular mortality in men with finger OA was not explained by the general risk factors of cardiovascular diseases, or by the regular use of analgesics. However, the regular use of analgesics at baseline predicted a major coronary event during follow-up. Even if hand OA is prevalent, its impact on disability in the general population is modest. MCI, easily determined at low cost, can be used to assess bone mineral status and future hip fracture risk. Patients with symmetrical DIP OA might be considered candidates for evaluation of osteoporosis over time.

National Library of Medicine Classification: WE 348, WE 250
Medical Subject Headings: osteoarthritis; osteoarthritis/mortality; osteoarthritis/radiography; osteoporosis; hand joints/radiography; risk factors; hip fractures; bone density; obesity; longitudinal studies; Finland
To my Family
ACKNOWLEDGEMENTS

This study was carried out at the Department of Surgery, and the Department of Physical and Rehabilitation Medicine, Kuopio University Hospital, and the Department of Health and Functional Capacity of the National Public Health Institute in 2000-2006.

I am deeply grateful to Docent Markku Heliövaara, M.D., Ph.D., for giving me the opportunity to use unique data from the Mini-Finland Health Survey, and for instilling in me a wide knowledge of the field of musculoskeletal epidemiology. His professional insight, endless enthusiasm and encouragement have made these studies possible. Also my other supervisors, Professor Heikki Kröger, M.D., Ph.D., Docent Jari Arokoski, M.D., Ph.D., and Pirjo Manninen, M.D., Ph.D., deserve my special gratitude. The central role of Heikki in developing ideas, and his persuasive encouragement have been crucial to my work.

The exceptional expertise of Jari concerning the osteoarthritis has been of great help to me in carrying out this study. Moreover, I want to thank Jari for the scientific and the non-scientific discussions, which have given me strength during these years. Pirjo is acknowledged for her generous help concerning the epidemiological research methods, and for her encouragement in hard times.

I am grateful to the official reviewers of the dissertation, Docent Päivi-Leino Arjas, M.D., Ph.D., and Docent Ville Remes, M.D., Ph.D., for the time they spent reviewing the manuscript, and for their valuable criticism and suggestions, which greatly improved this work.

I am extremely grateful to Olli Impivaara M.D., Ph.D, Professor Paul Knekt, Ph.D., Professor Antti Reunanen, M.D., Ph.D., and Professor Arpo Aromaa, M.D., Ph.D., for their valuable contribution in the preparation of the original articles, not to mention their crucial part in the execution of the survey itself. I owe special thanks to Alpo Kärkkäinen, M.D., Ph.D., who did an enormous amount of work reading the baseline hand radiographs, which were the basis of this study.

I am grateful to Sirkka Rinne and Harri Rissanen of the Department of Health and Functional Capacity from the National Public Health Institute, who have taken care of the survey data, and did the new linkages to the registers at follow-up, which were essential for this study. I would also like to thank all, who has been working in the examination survey at baseline and during these years.

I express my warmest thanks to Marianna Sunnari, Phil. Lic., and Jacqueline Välimäki, M.A., for carefully revision of the language of the dissertation.

I am deeply indebted to Docent Heikki Pekkarinen, M.D., Ph.D., for his encouragement to begin a scientific career.

I would also like to thank my friends Markus, Sami and Tuomas for relaxing moments and discussions throughout these years. The members of KePa are acknowledged for memorable activities during these years. KePa-member Tuomas Rissanen, M.D., Ph.D., is especially acknowledged for his technical assistance.

I wish to express my gratitude to my parents, Matti and Tiina, for all the warm support they have given me. I am grateful to my brothers Taneli, Heikki and Jaakko for their friendship and brotherliness. I also want to express my warmest thanks to my grandparents, Eino and Saara, and Kaarlo and Kaarina, who have supported me throughout my life.

Finally, I wish to sincerely thank my wife Sanna for her love, patience and understanding, and my son Eino, both of whom have taught me that there are more important things in life than science.

Kuopio, June 2006

Mikko Haara

This study was supported by grants from the Finnish Graduate School of Musculoskeletal Diseases, EVO-Funding of Kuopio University Hospital, EVO-Funding of North Karelia Central Hospital, Northern-Savo Cultural Foundation, Finnish Orthopaedics Research Foundation, Kuopio University Research Foundation and Duodecim Foundation.
<table>
<thead>
<tr>
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<tr>
<td>BMD</td>
<td>bone mineral density</td>
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<td>BMI</td>
<td>body mass index</td>
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<td>BUA</td>
<td>broadband ultrasound attenuation</td>
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<td>CCT</td>
<td>combined cortical thickness</td>
</tr>
<tr>
<td>CMC</td>
<td>carpometacarpal joint</td>
</tr>
<tr>
<td>COX</td>
<td>cyclooxygenase</td>
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<tr>
<td>CVD</td>
<td>cardiovascular diseases</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>DXA</td>
<td>dual X-ray absorbtiometry</td>
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<td>DIP</td>
<td>distal interphalangeal joint</td>
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<td>DISH</td>
<td>diffuse idiopathic skeletal hyperostosis</td>
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<td>GOA</td>
<td>generalised osteoarthritis</td>
</tr>
<tr>
<td>HN</td>
<td>Heberden’s nodes</td>
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<tr>
<td>HRT</td>
<td>hormone replacement therapy</td>
</tr>
<tr>
<td>IP</td>
<td>interphalangeal joint</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of the Diseases</td>
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<tr>
<td>IGF-1</td>
<td>insulin-like growth factor-1</td>
</tr>
<tr>
<td>MCI</td>
<td>metacarpal cortical index</td>
</tr>
<tr>
<td>MCP</td>
<td>metacarpophalangeal joint</td>
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<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
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<td>OA</td>
<td>osteoarthritis</td>
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<td>OP</td>
<td>osteoporosis</td>
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<td>PIP</td>
<td>proximal interphalangeal joint</td>
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<tr>
<td>VDR</td>
<td>vitamin D receptor</td>
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<tr>
<td>QCT</td>
<td>quantitative computed tomography</td>
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LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications* which are referred to by their Roman numerals:


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1. INTRODUCTION

Osteoarthritis (OA) is the most common joint disease worldwide. Among patients with OA, 80% have some degree of limitation of movement, and 25% cannot perform the major daily activities of life (WHO 2003). Its high and growing prevalence and its moderate to severe impact on disability, also make OA an important condition in health policy concerns (Yelin 2003). OA is highly prevalent in hand joints and it may be an indicator of systemic OA (Hochberg 1991, Cicuttini et al. 1998). Previous studies have suggested an association between hand OA and OA in hip joint (Hochberg et al. 1995, Riyazi et al. 2004) and OA in knee joint (Hirsch et al. 1996, Sowers et al. 2000, Englund et al. 2004).


Osteoporosis (OP) is also a common age-related disease. Due to the ageing of the population, the incidence of new osteoporotic fractures has been projected to increase rapidly in the future in western countries (Kanis 2002, Cummings and Melton 2002). An estimated 1.7 million hip fractures occurred worldwide in 1990, the figure being expected to exceed 6 million by 2050 (WHO 2003). However, it is difficult to predict who will sustain an osteoporotic fracture. A case-finding strategy has been recommended to target preventive measures to individuals who are at high risk of fracture (Cummings and Melton 2002). In many countries, however, such recommendations cannot be followed to their full potential because of limited possibilities of diagnosis at affordable costs (Bouxsein et al. 2002). There is a need for a simple and cheap measure of bone mass, which would also be widely available in general practice. Recent evidence suggests that the metacarpal cortical index (MCI) measured from hand radiographs might be successfully used to assess bone mass and quality, and also to predict osteoporotic fractures (Dey et al. 2000, Nielsen 2000, Hyldstrup and Nielsen 2001, Bouxsein et al. 2002).

The possibility of an inverse relationship between OA and OP has long been considered in the literature, but the association between them remains contradictory. It seems that the association may be different between localised OA and primary generalized OA, while bone mineral mass seems to be associated differently with OA depending on the joint site (Sambrook and Naganathan 1997, Stewart and Black 2000). Even if there are numerous studies focusing on the association between OA at various sites and bone mineral mass measured by several techniques (Dequeker et al. 1995), limited information is available on longitudinal changes in bone mineral mass in subjects with radiographic OA (Sowers et al. 1996, Arden et al. 1999, Bettica et al. 2002, Hochberg et al. 2004). However, such studies are needed to understand the mechanisms of associations, to plan prevention, and to design effective management of OA and OP.
The aim of this study was to investigate osteoarthritis and osteoporosis assessed from hand radiographs for their prevalence, determinants and associations with morbidity and mortality in a large population sample of Finns aged 30 years or over, who had undergone a comprehensive examination at baseline and were subsequently followed up for 15 years.

2. REVIEW OF THE LITERATURE

2.1. Pathogenesis of osteoarthritis

Previously OA has been considered as a degenerative disease, the inevitable accompaniment of ageing, with wear and tear as the principal pathogenic mechanism (Brandt et al. 2003). However, to date it seems to be a complex combination of both degenerative and regenerative processes, where also muscles, tendons, ligaments, bone, and anatomical variability are involved (Brandt et al. 2003). OA is a disease of the whole joint (Figure 1).

In view of the present theories on the pathogenesis of OA, both systemic and local factors affect the likelihood of OA development in a joint (Felson and Zhang 1998, Arokoski et al. 2000, Arokoski et al. 2001, Felson 2003) (Figure 1). It is thought that the systemic factors (age, gender, genes, hormones etc.) establish the foundation for cartilage properties but that the local biomechanical factors (degree of joint loading, joint trauma, elevated weight-bearing on account of overweight, joint deformity etc.) have a crucial influence on the final qualities of articular cartilage, its well being, or breakdown. Thus, local biomechanical factors determine the site and severity of OA (Figure 1).

2.2. Diagnosis of hand osteoarthritis

**Figure 1.** Schematic representation of the pathogenesis of OA (Dieppe 1995, Arokoski et al. 2001, Felson 2003).

**Table 1.** American College of Rheumatology criteria for the classification and reporting of hand OA (Altman et al. 1990). Modified from (Felson 2003).

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<table>
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<tbody>
<tr>
<td>1</td>
<td>Hand pain, aching, or stiffness for most days of prior month.</td>
</tr>
<tr>
<td>2</td>
<td>Hard tissue enlargement of $\geq 2$ of 10 selected hand joints*.</td>
</tr>
<tr>
<td>3</td>
<td>Fewer than 3 swollen MCP joints.</td>
</tr>
<tr>
<td>4</td>
<td>Hard tissue enlargement of 2 or more DIP joints.</td>
</tr>
<tr>
<td>5</td>
<td>Deformity of 2 or more of 10 selected hand joints*.</td>
</tr>
</tbody>
</table>

* Selected hand joints are the second and third DIP and PIP and first CMC of both hands.

DIP = distal interphalangeal; PIP = proximal interphalangeal; MCP = metacarpophalangeal; CMC = carpometacarpal.

OA is present if items 1,2,3,4 or items 1,2,3,5 are present. Sensitivity and specificity are 92% and 98%, respectively.

Jones et al. 2002). The radiographic features of hand OA based on the most often used radiological grading system developed by Kellgren and Lawrence (1952) and illustrated in the Atlas of Standard Radiographs (Kellgren 1963) include: 1) the formation of osteophytes on the joint margings or in ligamentous attachments; 2) the periarticular ossicles, chiefly in relation to distal and proximal interphalangeal joints; 3) the narrowing of the joint space associated with sclerosis of subchondral bone; 4) the cystic areas with sclerotic walls situated in the subchondral bone; 5) the altered shape of the bone ends.

However, in situations where radiology is not available, clinical examination is a viable substitute for diagnosing hand OA.
(Hart et al. 1994). The most commonly used clinical diagnostic system for hand OA uses the criteria of the American College of Rheumatology (Altman et al. 1990), which is reliable for symptomatic disease (Table 1), and is also usable in clinical practice.

2.3. Prevalence of hand osteoarthritis

OA is highly prevalent in hand joints. The distal interphalangeal (DIP) joints, the proximal interphalangeal (PIP) joints, and the carpometacarpal (CMC) joint of the thumb are those most frequently involved (Acheson et al. 1970, Plato and Norris, 1979a, Butler et al. 1988, Egger et al. 1995, Felson 2003). Cross-sectional studies have estimated that the prevalence of radiographic hand OA in the Caucasian population among those over 65 years are ranging from 64 to 78% in men, and from 71 to 99% in women (Mikkelsen and Duff, 1970, van Saase et al. 1989, Cauley et al. 1993, Felson 2003). Even if the trends for the prevalence of hand OA are similar in these studies, there are variations due to the different methods used. In Finns aged 30 years or over, the age-adjusted prevalence of radiographic hand OA was 39% in men and 40% in women (Kärkkäinen 1985). In the age group 60-69 years, the prevalence was 76% among men and 84% among women (Kärkkäinen 1985). Among American adults aged 30 years and over, the prevalence of radiographic hand OA was approximately 33 % (Lawrence et al. 1998). In Finns aged less than 40 years, the prevalence was higher in men than in women, but in those over 40 years the prevalence was higher in women (Kärkkäinen 1985).

The prevalence of radiological thumb CMC OA in Caucasians has been reported to be from 8 to 12% in the general population (Lawrence et al. 1966), and as high as 33% among postmenopausal women (Armstrong et al. 1994). The prevalence of symptomatic thumb CMC OA among elderly Caucasians was 2% (right) and 3% (left) in men, and 5% in both carpometacarpal joints in women (Zhang et al. 2002).

Even though the variation in the prevalence of hand OA is only minor among different populations, there are some notable exceptions. For example, Blackfeet and Pima Indians have a very high prevalence of radiographic OA of the DIP joints (Bennet and Burch 1963), whereas Bulgarians show a very low prevalence of radiographic OA in DIP joints (Tzonchev et al. 1966). African women from Tswana and Tsikundamalema have a low radiographic thumb CMC joint involvement, but a relatively high prevalence in the DIP joints (Brighton et al. 1985). The age- and sex-adjusted prevalence of radiographic OA in PIP joints, metacarpophalangeal (MCP) joints, and especially the thumb CMC joint in the Japanese population was lower than among Americans (Yoshida et al. 2002). Moreover, elderly Chinese subjects in Beijing had a much lower age- and sex-adjusted prevalence of radiological hand OA than elderly whites in Framingham (Zhang et al. 2003).

Even though the prevalence varies between the populations and between joints, hand OA seems to affect mostly older women (Hirsch et al. 2000). Differences in the prevalence of hand OA among populations suggest site-specific differences in the prevalence of hand OA that may be attributed to genetic and environmental factors.

2.4. Determinants of hand osteoarthritis

The determinants most closely associated with hand OA are high age and female gender. Studies concerning obesity are partially conflicting, but it seems that obesity is as important a determinant for hand OA as for OA in weight-bearing joints (Carman et al. 1994, Cicuttini et al. 1996, Oliveria et al. 1999, Sayer et al. 2003). Determinants of hand OA based on
previous epidemiological and clinical studies are presented in Table 2. These studies are mainly cross-sectional.

2.4.1. Age

The factor most closely associated with the development of hand OA is age (Lawrence et al. 1966) (Table 2). The effect of age on the risk of hand OA is even more evident and faster in women than in men (Kärkkäinen 1985, Hirsch et al. 2000). Even though radiological hand OA first appears at the MCP joints from the age of 25 years, the highest incidence of hand OA occurs after 45 years when OA develops in the IP joints and the CMC joint of the thumb (Allander 1974).

The mechanism for this age-related development of hand OA is partially unknown. However, it is well known that the metabolic activity of the cartilage will decrease with age, limiting the regenerative mechanism of the cartilage (Kempson 1991). On the other hand, the decreasing of the metabolic activity with ageing diminishes the biomechanical properties of the cartilage, and thus the damage risk of the cartilage will increase. Even if getting older does not cause OA per se, disease incidence and prevalence increase dramatically with age. Thus, persons reaching old age with minimal or no radiographic evidence of disease are still at risk of developing OA within a short time (Busby et al. 1991).

2.4.2. Gender and hormonal factors

Female gender is strongly associated with hand OA according to previous studies (Table 2). Above the age of 55 years, hand OA is more common in women, usually involving several joints, mostly the interphalangeals and the first metacarpal (Lawrence 1977). Like severe knee OA (Manninen et al. 1996), symmetrical OA in distal interphalangeal joints has also been suggested to be a women’s disease (Cicuttini et al. 1998). Clinical and population-based studies of generalized OA suggest that the onset of OA is related either to the perimenopausal period or to an episode of hormone imbalance (Spector and Campion 1989).

A case control study showed that in women with OA in hand, knee or hip joints, the rate of hysterectomy was twice as high as that of age-matched women with rheumatoid arthritis or with no joint disease (Spector et al. 1988). On the other hand, in the Chingford Study, there was a significant protective effect of HRT use for knee OA (odds ratio 0.31; 95% confidence interval 0.11-0.93). The effect was similar, but weaker for DIP OA (odds ratio 0.48; 95% confidence interval 0.17-1.42). Opposite results were found in a cross-sectional study of 348 women from 76 families in the Tasmanian population (Cooley et al. 2003). It was noted that both current and ever use of HRT associated with an increased prevalence of Heberden’s nodes (HN) and with severity of HN and DIP OA.

The protective effect of oestrogen is therefore unclear, but has important implications for the etiopathogenesis of OA, and indicates a possible therapeutic role for oestrogen in OA (Felson and Nevitt 1998).
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study subjects</th>
<th>Age</th>
<th>Study setting</th>
<th>Diagnose and joints</th>
<th>Determinants of hand OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acheson et al.</td>
<td>1127 men and women of New Haven, Conn.</td>
<td>21 or over</td>
<td>Cross-sectional Population study</td>
<td>Radiological DIP, PIP, MCP, CMC</td>
<td>Female gender++, age++, mechanical stress+</td>
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<td>Haven, Connecticut</td>
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<tr>
<td>Caird et al.</td>
<td>300 men and women random sample in Glasgow</td>
<td>65 or over</td>
<td>Cross-sectional Clinical study</td>
<td>Radiological DIP, PIP, MCP</td>
<td>Female gender++, age++, occupation 0 bone thickness 0</td>
</tr>
<tr>
<td>Butler et al.</td>
<td>3035 men and women in Tecumseh</td>
<td>32 or over</td>
<td>Cross-sectional Population study</td>
<td>Radiological DIP, PIP, MCP</td>
<td>Female gender++, age++ PIP associated with DIP joints</td>
</tr>
<tr>
<td>van Saase et al.</td>
<td>2168 men and women in Zoetermeer survey</td>
<td>19 or over</td>
<td>Cross-sectional Population study</td>
<td>Radiological DIP, PIP, MCP, CMC</td>
<td>Obesity++</td>
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<tr>
<td>van Saase et al.</td>
<td>6585 men and women in Zoetermeer survey</td>
<td>19 or over</td>
<td>Cross-sectional Population study</td>
<td>Radiological DIP, PIP, MCP, CMC</td>
<td>Female gender++, age++</td>
</tr>
<tr>
<td>Lane et al.</td>
<td>134 men and women in Stanford area</td>
<td>53-75</td>
<td>Cross-sectional Population study</td>
<td>Radiological DIP, PIP, MCP, IP, CMC</td>
<td>Hand OA not prevalent in dominant hand</td>
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<tr>
<td>Davis et al.</td>
<td>1636 men and women HNANES I-survey</td>
<td>35-79</td>
<td>Cross-sectional Population study</td>
<td>Radiological</td>
<td>Obesity 0</td>
</tr>
<tr>
<td>Schouten et al.</td>
<td>690 women in Zoetermeer survey</td>
<td>45-54</td>
<td>Cross-sectional Case-control study</td>
<td>Radiological DIP</td>
<td>Postmenopausal state +, Hysterectomy 0, oophorectomy 0</td>
</tr>
<tr>
<td>Authors</td>
<td>Study subjects</td>
<td>Age</td>
<td>Study setting</td>
<td>Diagnose and joints</td>
<td>Determinants of hand OA</td>
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<tr>
<td>Hart and Spector</td>
<td>1003 women in Chingford Study</td>
<td>45-64</td>
<td>Cross-sectional</td>
<td>Radiological</td>
<td>DIP joints and smoking -, PIP and CMC joints and smoking 0, obesity ++ in DIP and CMC joints</td>
</tr>
<tr>
<td>Cauley et al. 1993</td>
<td>229 white women</td>
<td>mean age 74</td>
<td>Cross-sectional</td>
<td>Radiological hand score index</td>
<td>No associations between serum sex hormone level and hand OA</td>
</tr>
<tr>
<td>Sowers et al. 1996</td>
<td>573 women in Michigan Bone Health Study</td>
<td>24-45</td>
<td>Cross-sectional</td>
<td>Radiological DIP, PIP, MCP, CMC</td>
<td>Age++, low testosterone levels++, high bone mineral density (DXA) ++, BMI++</td>
</tr>
<tr>
<td>Spector et al. 1997b</td>
<td>1003 women in Chingford study</td>
<td>45-64</td>
<td>Cross-sectional</td>
<td>Radiological DIP, CMC</td>
<td>Inverse weak association between DIP joint OA and current HRT use</td>
</tr>
<tr>
<td>Olivera et al. 1999</td>
<td>134 female case-control pairs in Fallon Community</td>
<td>20-89</td>
<td>Cross-sectional</td>
<td>Radiological symptomatic hand OA</td>
<td>Obesity++</td>
</tr>
<tr>
<td>Maheu et al. 2000</td>
<td>711 women in all areas of France</td>
<td>50-75</td>
<td>Cross-sectional</td>
<td>Clinical criteria with x-ray and symptoms</td>
<td>HRT 0</td>
</tr>
<tr>
<td>Jones et al. 2001 and 2002</td>
<td>522 men and women in Tasmania</td>
<td>39-72</td>
<td>Cross-sectional</td>
<td>Radiological DIP, CMC</td>
<td>Female gender++, age++, grip strength-, smoking 0, occupation 0, physical activity 0, sport participation 0, digital fracture ++ with severe DIP joint OA</td>
</tr>
<tr>
<td>Authors</td>
<td>Study subjects</td>
<td>Age</td>
<td>Study setting</td>
<td>Diagnose and joints</td>
<td>Determinants of hand OA</td>
</tr>
<tr>
<td>--------------------</td>
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<tr>
<td>Cooley et al. 2003</td>
<td>349 women from 76 Families in Tasmania</td>
<td>over 35</td>
<td>Cross-sectional</td>
<td>Radiological / Clinical DIP, CMC, / HN</td>
<td>Inverse association between HRT usage and severity of DIP OA and HN-, Breast feeding protective for CMC OA++</td>
</tr>
<tr>
<td>Solovieva et al. 2005b</td>
<td>295 female dentists and female 248 teachers</td>
<td>45–63 years</td>
<td>Cross-sectional</td>
<td>Radiological DIP, PIP, CMC, MCP</td>
<td>Hand use protective for finger joint OA, but joint overload may lead to severe OA</td>
</tr>
<tr>
<td>Plato and Norris 1979b</td>
<td>478 men in Baltimore Longitudinal Study</td>
<td>21-97</td>
<td>Longitudinal population</td>
<td>Radiological DIP, PIP</td>
<td>Age++, incidence of DIP joints degeneration was 2-fold that in PIP joints</td>
</tr>
<tr>
<td>Hochberg et al. 1991</td>
<td>888 men in Baltimore Longitudinal Study</td>
<td>17-102</td>
<td>Longitudinal population</td>
<td>Radiological PIP, DIP</td>
<td>Age++, % body fat ++, waist/hip ratio++, body mass index 0, grip strength -, metacarpal cortical area-</td>
</tr>
<tr>
<td>Bagge et al. 1991</td>
<td>Men and women in Göteborg area</td>
<td>over 70</td>
<td>Longitudinal population</td>
<td>Radiological hand OA</td>
<td>Female gender ++, Obesity++ in men with increasing grades of hand OA</td>
</tr>
<tr>
<td>Hochberg et al. 1993</td>
<td>317 women in Baltimore Longitudinal Study</td>
<td>40 or over</td>
<td>Longitudinal population</td>
<td>Radiological DIP, PIP, CMC</td>
<td>Age++, waist/hip ratio+, % body fat+, body mass index 0 with increasing grades of hand OA</td>
</tr>
<tr>
<td>Authors</td>
<td>Study subjects</td>
<td>Age</td>
<td>Study setting</td>
<td>Diagnose and joints</td>
<td>Determinants of hand OA</td>
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<tr>
<td>Carman et al. 1994</td>
<td>1276 men and women in Tecumseh</td>
<td>50-74</td>
<td>Longitudinal population - Follow-up 23 years</td>
<td>Radiological 32 joints of hands and wrist</td>
<td>Association between weight and hand OA index at follow-up</td>
</tr>
<tr>
<td>Chaisson et al. 1999</td>
<td>453 men and women in Framingham Study</td>
<td>48-59</td>
<td>Longitudinal population - Follow-up 5 years</td>
<td>Radiological DIP, PIP, MCP, CMC</td>
<td>High grip strength in men increased risk for PIP, MCP and CMC joints and DIP joints women</td>
</tr>
<tr>
<td>Sayer et al. 2003</td>
<td>1467 men and women in a British National Survey</td>
<td>0-53</td>
<td>Longitudinal population - Follow-up 53 years</td>
<td>Clinical criteria OA present if at least one hand joint affected</td>
<td>Increased adult weight in men++ Decreased birth weight in men++</td>
</tr>
<tr>
<td>Cicuttini et al. 1996</td>
<td>335 women twin pairs from twin register of Institute of Psychiatry, London</td>
<td>48-70</td>
<td>A twin study</td>
<td>Radiological DIP, PIP, CMC</td>
<td>Risk of CMC OA increase 9-13% per kg with increasing body weight, obesity++</td>
</tr>
<tr>
<td>Kraus et al. 2004</td>
<td>1043 men and women in Genetics of GOA Study</td>
<td>over 80</td>
<td>Family study Siblings studied</td>
<td>Radiological PIP, CMC, MCP</td>
<td>Joint-protective effect of hypermobility in PIP, but not in CMC-joints</td>
</tr>
</tbody>
</table>

OA = osteoarthritis; DIP = distal interphalangeal; PIP = proximal interphalangeal; MCP = metacarpophalangeal; CMC = carpometacarpal; IP = interphalangeal; GOA = generalised osteoarthritis; HN = Heberden’s nodes; HRT = hormone replacement therapy.
++ statistically significant association; + association, but not statistically significant; 0 no association; - statistically significant inverse association.
2.4.3. Genetic factors

Although the multifactor nature of hand OA is well recognized, genetic factors have been found to be strong determinants of the disease (Spector and MacGregor 2004). A strong genetic component in hand OA was suggested to be present in the development already in the 1940s, when Stecher found HN to be three times more common in sisters of hand OA affected women than in the general population (Stecher 1947). Other studies have also suggested that genetic factors have significance particularly in the aetiology of symmetric hand OA (Horton et al. 1998, Spector et al. 1996). Evidence of a genetic influence on hand OA comes from a number of sources, including epidemiological studies of family history and family clustering and twin studies (Spector and MacGregor 2004). One classic twin study has shown a genetic effect for OA of the hand in women, with 65% of the variance in twins being explained by genetic factors (Spector et al. 1996). A similar result was found in one population study, where the heritability estimate for hand OA was 0.56 (95% confidence interval 0.34-0.76) (Bijkerk et al. 1999). Hand OA has also been connected with linkages on chromosome 2q (Leppävuori et al. 1999), but there are also conflicting results (Stankovich et al. 2002). Another chromosome linked to hand OA is 11g (Kalichman et al. 2003). Genes suggested to be associated with hand OA include: aggrecan (Horton et al. 1998), insulin-like growth factor-1 (IGF-1) (Meulenbelt et al. 1998), matrilin-3 (Min et al. 2006, Stefánsson et al. 2003), collagen type XI (Leppävuori et al. 2000) and vitamin D receptor (VDR) (Zhai et al. 2004, Solovieva et al. 2005a).

Genes may operate differently in different genders, at different body sites, and on different disease features within body sites. OA in general is a complex disease, and understanding its complexity should help us find the relevant genes, and new pathways and drug targets (Spector and MacGregor 2004).

2.4.4. Obesity

The effect of obesity on OA has been thought to be mediated through mechanical loading on weight-bearing joints (Schouten et al. 1992a, Heliövaara et al. 1993a, Manninen et al. 1996, Felson et al. 1997, Felson and Chaisson, 1997). On the other hand, there exists a lot of evidence of an association between hand OA and obesity (van Saase et al. 1988, Bagge et al. 1991, Hart and Spector 1993b, Carman et al. 1994, Cicuttini et al. 1996, Sowers et al. 1996, Felson and Chaisson 1997, Sayer et al. 2003). A longitudinal study from Tecumseh Community reported that baseline obesity was associated with the 23-year incidence of hand OA in men (relative risk 1.59; 95% confidence interval 1.10-2.31) and women (relative risk 2.07; 95% confidence interval 1.33-3.24) among subjects who were free of hand OA at baseline (Carman et al. 1994). In a twin study among middle-age women, obesity was an important risk factor for the development of both knee and CMC OA, with significant increases of 9-13% in risk of OA per kg increase in body weight (Cicuttini et al. 1996). Although the mechanism by which obesity may predispose an individual to hand OA is unknown, previous findings strongly suggest that metabolic factors of obesity are of importance in hand OA. In contrast, however, no association was observed between incidence of obesity and hand OA in men in the Baltimore Longitudinal Study of Ageing (Hochberg et al. 1991, Hochberg et al. 1993). Also for women, no association was observed between the BMI and hand OA in the National Health Examination Survey (Davis et al. 1990).

An interesting feature of the association between obesity and OA is that obese
people appear to be at an especially high risk of bilateral as opposed to unilateral OA in the knee or hip joint, of which the latter may be more often associated with injuries and fractures (Spector et al. 1994). Furthermore, one longitudinal study suggested that obese people with knee OA have a higher risk of experiencing disease progression than thinner people (Dougados et al. 1992). On the other hand, women with unilateral disease who are overweight may be at a much higher risk of developing bilateral knee OA than their non-obese controls (Spector et al. 1994).

On the basis of these previous studies, both metabolic and mechanical factors mediate the effects of obesity on joints (Eaton 2004). Furthermore, obesity is one of the few risk factors that appear to be important for both initiation and progression of OA at all joint sites (Cooper et al. 2000).

2.4.5. Mechanical stress and workload

Mechanical stress and workload are not as important risk factors for hand OA as for OA in weight-bearing joints. However, repetitive work loading of the hand joint has been proved to be a risk factor also for hand OA (Stecher 1947). In the classical surveys of coal miners, Lawrence (1977) showed that they had more hand OA than dockers, who in turn had more hand OA than office workers. In three different occupational groups in a Virginia textile mill, women whose jobs required a fine pincer grip, with increased force across the distal interphalangeal joints, had significantly more distal interphalangeal joint OA than those whose work required a repeated power grip (Hadler et al. 1978). In a recent comparative study, the prevalence of moderate finger OA was higher among the female teachers compared with the female dentists, but in severe finger OA, the prevalence was significantly elevated among the dentists compared with the teachers (odds ratio 2.61; 95% confidence interval 1.03-6.59) (Solovieva et al. 2005b). The authors conclude that hand use may have a protective effect on finger joint OA, whereas continuing joint overload may lead to joint impairment (Solovieva et al. 2005b).

One longitudinal study concerning the association between hand OA and grip strength found that maximal grip strength in men increased the risk of OA in the PIP, MCP and CMC joints, but not with DIP-joints (Chaisson et al. 1999). Opposite results were found in a cross-sectional Tasmanian population study, where hand OA associated with low grip strength (Jones et al. 2001). However, further adjustment of the results suggested that the osteoarthritic associations with grip strength were largely mediated by pain. Therefore, it was assumed that OA symptoms were the reason for low grip strength. There is evidence, based on one study, that a paralysed hand has no radiological hand OA at all (Stecher 1947). Furthermore, it has been suggested that hand OA is more common in the dominant hand than in the non-dominant hand (Acheson et al. 1970), but there are also opposite findings (Lane et al. 1989, Solovieva et al. 2005b). Interestingly, hypermobility of the hand joints might also be a mechanical risk factor. In a clinical study by Jonsson and Valtysdottir (1995), a positive association between hypermobility of the CMC-joint and CMC OA was shown. In contrast, a recent family-based study demonstrated a joint-protective effect of hypermobility on radiographic OA of PIP joints (Kraus et al. 2004). Therefore, mechanical stress, workload and joint laxity are thought to be important, potentially modifiable factors in the development of hand OA.
2.4.6. Other factors

A major joint injury can alter the biomechanics of the joint by increasing stress across particular areas of the joint, and often dramatically increases the risk of OA (Felson 2003). Furthermore, joint cartilage and other joint structures are often damaged by sudden injuries such as fractures or ligamentous tears (Felson 2003). Acute major knee injuries including cruciate and meniscal tears are common causes of knee OA especially among men (Roos et al. 1998). The association between injuries and hand OA has been studied less, even though Stecher and Karnosh (1947) observed the role of trauma in the development of hand OA almost 50 years ago. However, in a population-based study in Tasmania, they found that self-reported digital fracture was associated with prevalence of hand OA (odds ratio 2.42; 95% confidence interval 1.22 - 4.83), and particularly with severe DIP joint disease (Jones et al. 2002). There is a clear interplay between systemic factors and local injury factors in the development of OA. Therefore, it is not surprising that those who sustain major knee injuries after the age of 30 are at a much higher risk of rapidly developing knee OA, than persons who sustain similar injuries under the age of 30 (Roos et al. 1998). As a systemic factor, ageing limiting the regenerative mechanism of the cartilage (Kempson 1991) and joint injury as a local risk factor increase the development of the OA process in the elderly.

The effect of smoking in the aetiology of OA is not clear, but in the Framingham study, lower rates of radiological knee OA in male and female smokers compared with non-smokers were reported (Felson et al. 1989). In another population study in Turkey, the rate of symptomatic knee OA was significantly lower in smokers than non-smokers (Kacar et al. 2003). In contrast in the Chingford study, no clear protective effect of smoking on hand or knee OA in women was found (Hart and Spector 1993a). There was no association between hand OA and smoking in the Tasmanian population study, either (Jones et al. 2002). A recent study also found that smoking did not protect against the development of radiologically confirmed OA in the knee, hand, foot and cervical spine (Wilder et al. 2003). It is not known whether smoking affects cartilage, bone, or both.

There is some evidence of a protective effect of vitamins C and D on the progression of OA in weight-bearing joints, but the association between hand OA and these vitamins has been studied less. Vitamin C or ascorbic acid has a multitude of functions within cartilage. For example, it protects against damage by reactive oxygen species and serves as a cofactor for enzymes contributing to type II collagen synthesis (Felson 2003). On the other hand, sufficient vitamin D is necessary for active bone turnover, which may be critical in OA (Felson 2003). In the Framingham study, it was found that a high intake of vitamin C may reduce the risk of cartilage loss and disease progression in people with knee OA (McAlindon et al. 1996). In the same study subjects, a similar protective effect on knee OA progression of high levels and intakes of vitamin D was noticed (McAlindon et al. 1996).

However, one recent genetic study failed to find an association between VDR gene polymorphisms and OA in hand, hip or knee joints (Huang et al. 2000). Further, mutations at the VDR locus did not play an important role as a cause of common OA in the Framingham population (Baldwin et al. 2002). In contrast, in a recent study VDR gene polymorphism was associated with symmetrical hand OA, and the association was modified by calcium intake (Solovieva et al. 2005a). Therefore, it is suggested that vitamin intake may also be beneficial for patients with hand OA, but it is unclear
whether the protective effects are mediated by genes.

2.5. Patterns of osteoarthritis

It is well established that OA at one site in the hand increases the risk of OA at other sites in the hand. The Framingham study showed that OA in any joint in the hand markedly increased the risk of OA in other joints in the same row (Chaisson et al. 1997). The DIP was the joint most frequently affected by OA, followed by the CMC, PIP and MCP joints. In the Chingford study, the pattern of radiographic involvement of hand joints was examined in women aged 45-64 (Egger et al. 1995). Evidence of clustering in joint involvement was found. The major patterns of joint involvement were symmetry, which was the most important, and clustering by row. Similar patterns of joint involvement were reported in a recent Finnish study among teachers and dentists (Solovieva et al. 2005b).

On the other hand, previous reports also suggest strong associations between hand OA and OA in weight-bearing joints. In the Study of Osteoporotic Fractures, an association was found between radiological hand and both unilateral and bilateral hip OA in older women (Hochberg et al. 1995). Furthermore, in the Baltimore Longitudinal Study of Aging there were associations between radiological OA in the DIP, PIP and CMC-joints and knee OA in men and women. The strength of the associations increased with increasing disease severity. Particularly for the PIP site, there was a trend toward an increasing strength of association with increasing numbers of affected joints and bilateral knee OA (Hirsch et al. 1996). Studies concerning the association between hand OA and OA in weight-bearing joints have usually been done using elderly subjects. However, an association was found between radiological OA in the dominant hand and OA in knee joints among Michigan black and white pre-and perimenopausal women aged less than 45 years (Sowers et al. 2000). In a recent Swedish retrospective study of 170 male and female patients, who had undergone isolated meniscectomy on the average 20 years earlier, it was found that the presence of radiographic hand OA was associated with an increased frequency of radiographic knee OA after meniscectomy (Englund et al. 2004). Therefore, it is suggested that hand OA may be a predictor of OA in weight-bearing joints.

Furthermore, previous studies suggest that hand OA and particularly symmetric DIP joint OA are strongly related with generalised OA (GOA) (Cooper et al. 1996, Hirsch et al. 1996, Cicuttini et al. 1998). GOA is a form of osteoarthritis, in which many joints are affected, but the classification is controversial (Cicuttini and Spector 1995). According to Kellgren and Moore (1952), GOA exists if at least 3 joints or a group of joints are affected. Two previous large genetic epidemiological studies have shown that GOA is connected with a strong genetic background and heritability (Felson et al. 1998, Hirsch et al. 1998).

2.6. Hand osteoarthritis and coexisting diseases

There are few studies on the association between hand OA and other musculoskeletal diseases. However, there was a strong association between radiological hand OA and disc degeneration of the spine in a genetic epidemiological study of 1,583 individuals (Bijkerk et al. 1999). One recent longitudinal study of Chingford women found that radiological knee and hip OA are important risk factors for the progression of lumbar spine disc degeneration (Hassett et al. 2003).

There are also few studies on the association between OA and other chronic diseases such as diabetes or cardiovascular
diseases. However, such an association could be expected, because patients with OA seem to have an adverse profile of metabolic risk factors for coronary heart disease and diabetes (Lippiello et al. 1991, Philbin et al. 1996, Cheras et al. 1997). One recent study found that hypertension was associated with OA in the CMC-joints, but not with OA in the IP-joints among 639 patients scheduled for either hip or knee replacement because of advanced OA (Kessler et al. 2003). However, in a large Swedish epidemiological study among the elderly no associations between hand OA and diabetes, ischemic heart disease, hypertension, physical activity, triglycerides, cholesterol or blood glucose levels were found (Bagge et al. 1991). Similarly, there was no association between hand OA and diabetes or hypothyroidism in a clinical study of geriatric patients (Caspi et al. 2001). Therefore, it seems that the association between hand OA and other chronic diseases remains partially unclear.

2.7. Hand osteoarthritis as a cause of disability

Even though the hand is a common site of peripheral OA, it is often underestimated as a cause of disability. In addition, its effect on quality of life may be considerable (Hart and Spector 2000). Recent studies have shown that pain and disability caused by hand OA have an effect on grip and pinch strength, particularly in older people (Hirsch et al. 1999, Jones et al. 2001, Bellamy et al. 2002, Zhang et al. 2002). Therefore, hand OA may cause limitations in performing activities of daily living such as dressing and eating (Hart and Spector 2000). Severe forms of thumb carpometacarpal OA are particularly associated with disability (Staxler et al. 1994, Damen et al. 1996), and CMC OA frequently needs operation to relieve pain (Damen et al. 1996, Poole et al. 2000). However, recent evidence based on a clinical comparative study of disability between CMC OA and DIP joint OA suggests that there are no differences between disabilities in these different forms of hand OA (Spacek et al. 2004).

Even though the association between hand OA and disability has been investigated previously in elderly subjects (Hirsch et al. 1999, Jones et al. 2001, Zhang et al. 2002), the association has been studied less in younger subjects. Neither are there any studies of the effects of hand OA on different occupations or disability pensions at population level. Such studies are, however, needed to better understand the effect of hand OA on the individual and society.

2.8. Osteoarthritis and related mortality

Mortality rates higher than expected have been reported in most rheumatic conditions, particularly in inflammatory rheumatic diseases (Callahan and Pincus 1995). However, there is also evidence that OA in general may be associated with reduced life expectancy (Lawrence et al. 1987, Cerhan et al. 1995). Excess mortality in females with osteoarthritis of the knee was found in the longitudinal study of Lawrence and his colleagues (Lawrence et al. 1987). Moreover, results from a longitudinal study of 296 women suggest that an increasing prevalence of full-body radiographic osteoarthritis is associated with decreased survival, independent of age and several co-morbid conditions related to osteoarthritis (Cerhan et al. 1995). In contrast, a recent very large longitudinal study of 2.37 million patients from the United Kingdom General Practice Research Database found that, compared to patients with clinical OA and those with no arthritis, patients with clinical rheumatoid arthritis (RA) had a higher age- and gender-adjusted all-cause mortality and incidence of major vascular events during almost 5 years of follow-up (Watson et al. 2003). In their study, the
rates of all-cause mortality and the incidence of major vascular events in patients with clinical OA and those with no arthritis were essentially the same.

One explanation for the higher mortality rates among osteoarthritic patients (Lawrence et al. 1987, Cerhan et al. 1995) could be the regular use of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of pain caused by OA. The widely used new COX-2 selective NSAIDs may be prothrombotic and increase the risk of myocardial infarction (Bombardier et al. 2000, Howes and Krum 2002, Solomon et al. 2004, Graham et al. 2005, Levesque et al. 2005). However, traditional non-selective NSAIDs also have complex effects that could prevent or promote coronary heart disease (Ray et al. 2002). Recent results from large population studies show an increased risk of myocardial infarction with current use of all NSAIDs, despite adjustment for many potential confounders (Hippisley-Cox and Coupland 2005, Johnsen et al. 2005). Moreover, the use of NSAIDs or acetaminophen at high frequency or dose was associated with a significantly increased risk of major cardiovascular events in a prospective cohort of 70,971 women (Chan et al. 2006), although moderate use did not confer a substantial risk.

The mechanism behind these associations between NSAID use and cardiovascular risks is partially unknown. Nevertheless, the isozymes, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), are known to catalyze the conversion of arachidonic acid to eicosanoids that play an important role in the maintenance of cardiovascular hemostasis. Thromboxane A2, primarily synthesized by platelet COX-1, causes irreversible platelet aggregation, vasoconstriction and smooth muscle proliferation. In contrast, vascular prostaglandin I2, which appears to be synthesized by COX-2, counteracts most of the effects exerted by thromboxane A2 (Garcia Rodriguez 2001). Inhibition of the COX isozymes by regular use of traditional NSAIDs or new COX-2 selective inhibitors may therefore disturb the balance between these two routes through which vasoactive eicosanoids are formed (Garcia Rodriguez 2001). This results in platelet aggregation, vasoconstriction, myocardial infarction and coronary death. Therefore, regular use of NSAID for the treatment of OA pain can increase the risk of myocardial infarction or even coronary death, especially among persons who have other risk factors of coronary heart disease.

2.9. Pathogenesis and risk factors of osteoporosis

Osteoporosis (OP) is a systemic skeletal disease characterised by low bone mineral mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (Consensus Development Conference 1993). OP has both clinical and public health importance because of these fractures (Cummings and Melton 2002).

To date, well-documented general risk factors for OP are female sex, premature menopause, age, primary or secondary amenorrhea, hypogonadism in men, glucocorticoid therapy, high bone turnover, low body weight, cigarette smoking, heavy alcohol consumption, low physical activity, long-term immobilisation, low dietary calcium intake and vitamin D deficiency (Kröger et al. 1994, Cummings et al. 1995, Kanis et al. 1997, Kanis 2002).

2.10. Diagnosis and assessment of fracture risk of osteoporosis

Diagnosis of OP depends on the measurement of skeletal mass, because there are no satisfactory clinical means to assess bone quality (Kanis 2002). The diagnosis of osteoporosis is currently based on the measurement of bone mineral
density (BMD) using dual x-ray absorptiometry (DXA) (Cummings and Melton 2002), which is regarded as the golden standard for diagnosis (Kanis 2002). Osteoporosis is present in women, if hip BMD is 2.5 SD or more below the mean of young adult females (T score ≤-2.5) (WHO 1994). A similar cut-off value for the hip BMD that is used in women can also be used in men (Kröger et al. 1999, Kanis and Gluer 2000). Moreover, BMD also predicts osteoporotic fractures with a gradient of relative risk ranging from about 1.5 to 3.0 for each standard deviation decrease in BMD (Kanis 2002). In a large meta-analysis of how well measures of BMD predict occurrence of osteoporotic fracture, the relative risks of fracture for a decrease in bone mineral density of one standard deviation below the age-adjusted mean were 1.5 (95% confidence interval 1.4-1.6) for all site fractures, 2.3 (95% confidence interval 1.9-2.8) for vertebral fracture, and 2.6 (95% confidence interval 2.0-3.5) for hip fracture (Marshall et al. 1996). However, DXA does not accurately measure bone at every skeletal site; it is quite expensive, and available mainly at hospitals (Nielsen 2000, Hyldstrup and Nielsen 2001). Moreover, DXA is highly dependent of bone size and it cannot measure cortical and cancellous bone mass differentially. Therefore, many other assessment methods of OP and fracture risk have also been extensively studied. Various methods used to estimate bone mineral content are compared in Table 3.

With quantitative computed tomography (QCT) it is possible to measure the bone mass of the peripheral skeleton and the spine (Genant et al. 1987, Siu et al. 2003). QCT is most useful in the assessment of cancellous bone density, because it provides a measure of the true volumetric density, whereas DXA gives the area-adjusted result (Kanis 2002). Moreover, cancellous bone is more responsive than cortical bone to medical treatment of OP, and therefore QCT is a good method to monitor the effect of treatment (Genant et al. 1996). Moreover, the technique avoids the effect of degenerative disease, such as spondylosis, when measuring bone mineral density at the spine. Disadvantages of QCT are the high dose of radiation, availability, problems in quality control, and high costs as compared to DXA (Kanis 2002).

Calcaneal ultrasound measurement with its output variable broadband ultrasound attenuation (BUA), has also been shown to give a good estimate of bone mineral mass and fracture risk in both sexes (Hadji et al. 2000, Frost et al. 2001, Huopio et al. 2004, Khaw et al. 2004). The strongest evidence of BUA’s ability to predict fractures was reported in a recent large population study of 14,824 men and women aged 42-82 years during a mean follow-up time of 1.9 years (Khaw et al. 2004). Among these subjects of the Norfolk cohort, a fall of about 1 SD in BUA (20db/Mhz) was associated with a relative risk of total fracture of 1.95, independent of age, sex, weight, height, smoking, and history of fractures (Khaw et al. 2004). Therefore, BUA can provide a precise, radiation-free, low-cost and rapid method for fracture risk assessment also in clinical practice. However, the absence of the universal reference values of BUA limits its use in OP screening.

Plain radiography is not the first method of choice for diagnosing OP, because there has to be from 30 to 50% decrease in bone mineral mass before it can be seen in radiographs (Kormano 1998). Radiographic determination of OP had only a specificity of 61% and a sensitivity of 61% when orthopaedic surgeons were using x-rays of the wrist in diagnosing OP (Olschewski et al. 2001). On the other hand, measurement of cortical bone width and geometry from radiographs was among the first methods developed for assessment of skeletal mass (Barnett and Nordin 1960). Even today, plain radiography is readily available in
various health care systems worldwide (Dey et al. 2000). Recent evidence suggests that both the traditional metacarpal index (MCI) and its advanced form, computed metacarpal X-ray radiogrammetry, might be successfully used for assessing bone mass and quality, and for predicting osteoporotic fractures (Dey et al. 2000, Nielsen 2000, Hyldestrup and Nielsen 2001, Bouxsein et al. 2002). Metacarpal X-ray radiogrammetry can also be assessed from old radiographs, thus enabling estimation of cortical bone loss from the time of earlier recordings (Nielsen 2000).

Magnetic resonance imaging (MRI) could also be one method to diagnose OP (Wehrli et al. 1995). However, to date, its use is limited to the research purposes only, because the cost of the equipment is high. Micro MRI-derived structural parameters are shown to be associated with biomechanical properties of bone and fracture resistance (Wehrli et al. 2000). Further, MRI might be useful as a means to evaluate the effects of OP treatment. Currently, the method is confined to peripheral skeletal sites, and its extension to typical fracture sites such as the proximal femur hinges on further advances in detection sensitivity (Wehrli et al. 2002).

2.11. Osteoporosis and fracture risk

Results from large population studies have shown that almost all types of fractures are more frequent in patients of all ages with low bone mineral density (Seeley et al. 1991, Kröger et al. 1994, Kröger et al. 1995, Nguyen et al. 1996). Furthermore, irrespective of the type of fracture, adults who sustain a fracture are 50-100% more likely to have another fracture of a different type than those without any fracture (Klotzbuecher et al. 2000, Wu et al. 2002). The amount of bone mineral density, previous fracture history and general risk factors of OA, together with other factors such as poor visual acuity, neuromuscular disorders and chronic diseases, affect the fracture risk of the individual (Cummings and Melton 2002, Kanis 2002, Huopio et al. 2005).

However, in general, risk factor scores show poor specificity and sensitivity in prediction of either BMD or fracture risk, (Johnell et al. 1995, Cummings et al. 1995, Ribot et al. 1995), and some risk factors, such as those of falling, vary in importance according to age (Kanis 2002). In one study, current anthropometric and life-style factors explained only 19-25 % of the variability of BMD (Kröger et al. 1994). Thus, the risk of fracture is very high when OP is present, but the risk of fracture is not negligible even when BMD is normal. Clinical risk factors that contribute to fracture risk independently of BMD are age, previous fragility fracture, premature menopause, non-use of HRT, a family history of hip fracture, having had three or more chronic illnesses, smoking, and the use of oral corticosteroids (Kanis 2002, Huopio et al. 2000).

Nowadays, a case-finding strategy is recommended to target preventive measures to patients with previous fragility fracture or with some other strong BMD-independent risk factor for fracture (Kanis 2002, Cummings and Melton 2002).

2.12. Association between osteoarthritis and osteoporosis

The association between OA and OP remains partially unclear even after 30 years of research since the first results indicating an apparent inverse relationship between these two common diseases (Foss and Byers 1972). It has been suggested that higher bone mineral densities measured by DXA are found in subjects with knee or hip OA, but that this association is less obvious in subjects with hand OA (Stewart and Black 2000). Furthermore, it seems that the association between OA and OP may differ between localised OA and primary
<table>
<thead>
<tr>
<th>Measure</th>
<th>Dual X-ray absorptiometry (DXA)</th>
<th>Quantitive computed tomography (QCT)</th>
<th>Quantitive ultrasound</th>
<th>Plain radiographs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Output variable</td>
<td>Bone mineral content (g) / measured area (cm²) = BMD</td>
<td>Volumetric density</td>
<td>Bone mass</td>
<td>Cortical bone mineral mass</td>
</tr>
<tr>
<td>Measuring site</td>
<td>Axial skeleton and spine, hip</td>
<td>Appendicular skeleton and spine</td>
<td>Usually heel, but also peripheral skeleton</td>
<td>Metacarpal bones</td>
</tr>
<tr>
<td>Diagnostic for OP</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prediction of fracture</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reference values</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes (digital X-ray radiogrammetry)</td>
</tr>
<tr>
<td>Accurary</td>
<td>Good</td>
<td>Good</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Radiation</td>
<td>Low</td>
<td>High</td>
<td>Radiation free</td>
<td>Moderate</td>
</tr>
<tr>
<td>Availability</td>
<td>Hospitals</td>
<td>University hospitals</td>
<td>General practice</td>
<td>General practice</td>
</tr>
<tr>
<td>Costs</td>
<td>Moderate</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Follow-up of OP treatment</td>
<td>Good</td>
<td>Very good</td>
<td>Moderate</td>
<td>Weak</td>
</tr>
</tbody>
</table>
generalized OA (GOA) (Sambrook and Naganathan 1997), and it is likely that genetics plays a significant role in the mechanism of the relationship between GOA and OP (Sambrook and Naganathan 1997).

Recent evidence shows that the relationship between OA and OP varies between different joint sites (Arden et al. 1999, Sowers et al. 1999, Schneider et al. 2002, Hochberg et al. 2004). Schneider and his colleagues (2002) found in their cross-sectional study that clinically diagnosed OA in the hip or knee did not associate with increased BMD levels in men or women. However, women with clinical hand OA had significantly lower hip BMD. Furthermore, Arden and colleagues (1999) found that older women with radiological hip OA lost bone mass at a lower rate than those without hip OA. Moreover, one twin study found an inverse relationship between OA and OP at the hip, but the relationship was localised to the OA-affected hip (Antoniades et al. 2000). On the other hand, Arokoski and colleagues (2004) did not find any association between hip OA and increase of bone mineral density in the femoral neck or in the head of the femur. However, in another of their studies, increased bone size and shape of the femur were associated with hip OA (Arokoski et al. 2002). Moreover, according to a recent longitudinal study, knee and hip OA can be accompanied by an increase in bone size or changes in shape at baseline and faster loss of BMD at 5 years’ follow-up (Sandini et al. 2005).

Hochberg and colleagues (Hochberg et al. 2004), in their recent longitudinal study found that women with radiographic OA of the hand had a significantly greater adjusted rate of bone loss at the radius than women with normal hand radiographs. Interestingly, in their study there was an inverse association between BMD at the lumbar spine and radiological knee OA (Hochberg et al. 2004). Higher BMD at the lumbar spine was associated with an increased risk of developing incident radiographic knee OA. In the Chingford study of 1,003 women, patients with progressive knee OA had increased bone resorption, but it was not increased in those with non-progressive knee OA (Bettica et al. 2002). They concluded that increased bone resorption seen in patients with progressive knee OA is similar to that observed in patients with osteoporosis (Bettica et al. 2002). Sowers and co-authors (Sowers et al. 1991), in their 23-year follow-up study of radiological OA in the hand and metacarpal bone loss, concluded that the women who later developed hand OA were more likely to have higher baseline bone mass than women who did not. However, these women also had a greater likelihood of bone loss over time.

In addition to the different relationship between OA and OP at various joints sites, there is also evidence of differences between the grade of OA and OP. In the study of Bruno and colleagues (1999), it was found that hips with Kellgren-Lawrence scores of 1 or 2 had increased BMD throughout the proximal femur, but as the disease progressed, the BMD declined. It has been also postulated that women with radiological knee osteophytes (moderate OA) had higher femoral BMD than those with no osteophytes (Hannan et al. 1993), but joint space narrowing (severe OA) had less influence on BMD. An opposite result was reported in a longitudinal study of the women in the Framingham cohort, where femoral neck BMD change was not associated with osteophyte development, but gain in BMD lowered the risk of joint space loss (Zhang et al. 2000). Moreover, a recent longitudinal study of the Chingford population confirmed that in women who developed incident knee OA, defined by osteophytes, both spine and hip BMD were higher, whereas women with previous fractures had
less chance of developing OA, independent of BMD status (Hart et al. 2002).

There are a number of possible mechanisms behind the association between OA and OP. One suggested mechanism is that OA might primarily be a disease of subchondral bone; stiff bone with high bone mineral mass may increase the mechanical stress on cartilage (Radin et al. 1972,Dequeker et al. 1995, Arokoski et al. 2000, Buckland-Wright 2004). On the other hand, it has been postulated that osteoporotic bone might absorb load more efficiently than normal bone, thus transmitting less stress to the overlying articular cartilage (Dequeker 1997). Moreover, the two diseases have common risk factors, such as weight and lifestyle risk factors (Naganathan et al. 2002). Furthermore, systemic factors are also involved in the relationship between OA and osteoporosis, probably including shared genetic factors such as VDR polymorphism (Uitterlinden et al. 1997, Uitterlinden et al. 2000), as well as non-genetic factors related to bone turnover (Sowers et al. 1999, Stewart et al. 1999), and use of nonsteroidal anti-inflammatory drugs (Bauer et al. 1996, Morton et al. 1998). Moreover, serum IGF-1 has also been shown to be associated with body composition, muscle strength and adiposity (Sambrook and Naganathan 1997). These known associations have led to the hypothesis that IGF-1 may be a factor in both OP and OA, because a higher level of a growth factor may account for both a higher bone density and osteophyte formation (Sambrook and Naganathan 1997). However, in OA it is still unclear whether changes in the cartilage precede those in bone or vice versa (Buckwalter and Mankin 1998, Burr 1998, Arokoski et al. 2000).

Even though there are numerous studies on the association between OA at various sites and bone mineral mass measured by means of various techniques (Dequeker et al. 1995), only a few have evaluated the changes in bone mineral mass longitudinally in subjects with radiographic OA (Arden et al. 1999, Sowers et al. 1999, Bettica et al. 2002, Hochberg et al. 2004). Furthermore, only a few studies have concentrated on the associations between different grades of OA and bone mineral mass (Bruno et al. 1999). Such studies would help to clarify the order of onset and association of OA and OP, and how the severity of OA and bone mineral mass relate to each other.
3. AIMS OF THE STUDY

The general aim of this dissertation was to investigate osteoarthritis and osteoporosis assessed from hand radiographs for their prevalence, determinants and associations with morbidity and mortality in a large population sample of Finnish men and women aged 30 years or over. This goal was divided into specific objectives as follows:

to determine the prevalence and risk factors of various types of hand OA, such as any finger OA, symmetrical DIP OA and thumb carpometacarpal OA,

to investigate symptoms, signs, mortality, disability and morbidity related to various types of hand OA, and

to examine cortical bone mineral mass as determined from hand radiographs, and its associations with osteoporosis, various types of hand OA, other coexisting diseases, and fracture risk.

4. MATERIALS AND METHODS

4.1. Study population

The study population was a stratified two-stage cluster sample of 8,000 persons drawn from the population register to represent Finnish adults aged 30 years or over (Aromaa et al. 1989). In the first stage, 40 representative areas were selected. In the second stage, a systematic sample of inhabitants was drawn from each area. The sample consisted of 8,000 persons (3,637 men and 4,363 women) from 69 municipalities. A total of 7,217 persons (90% of the sample) participated (Figure 2).

4.2. Study design

The baseline examinations were carried out from 1978 through 1980 by the Mobile Clinic of the Social Insurance Institution in two phases: a screening phase and a diagnostic (clinical) phase. A total of 7,217 persons (90% of the sample) participated in the screening phase. The distribution of sex, age and level of education among the participants corresponded closely to that of the whole Finnish population (Aromaa et al. 1989) (Figure 2). The examinations included administration of questionnaires, interviews about symptoms, and various measurements and tests. The subjects with a disease history, symptoms or findings suggestive of musculoskeletal diseases were invited to participate in the diagnostic (clinical) phase (Figure 3). The methods for studying musculoskeletal diseases are described in detail in Table 4.
Table 4. The screening procedure for musculoskeletal disorders (Sievers et al. 1985).

A person was considered positive in the screening for musculoskeletal disorders, and invited to the diagnostic examination, if he or she had one or more of the following:

1. Total or partial difficulty in performing one or more of joint function tests. The ten assessed functions were: walking on even ground, walking on tiptoe, climbing on a two step ladder, crouching, abduction of the arm straight up, extension of the elbow, flexion of the elbow, extension of the wrist by pressing the palms together, flexion of the fingers into a fist, and flexion of the thumbs.

2. A report in the basic questionnaire of a chronic disorder in the back, neck, joints or muscles diagnosed by a physician.

3. A report of musculoskeletal symptoms of chronic pain or stiffness in the back, neck, or joints (> 3 months) in the interview.

4. A previous diagnosis of a chronic musculoskeletal disorder found in the registry of disability pensions, or in the national registry of diseases entitling to specially reimbursed drugs.

Of those examined, 3,775 (52%) fulfilled at least one of the screening criteria, and a posterior anterior hand X-ray was taken in 3,595 subjects. Of these, 2,503 had been invited because they were screening-positive for musculoskeletal disease and 1,092 because they belonged to the random subsample (every fifth subject of the whole sample). Of the latter, 627 were also screening-positive whereas 465 were screening-negative. Physical examinations of the subjects were carried out by specially trained physicians according to a standardised written protocol (Aho et al. 1989, Aromaa et al. 1989, Mäkelä et al. 1991, Mäkelä et al. 1993, Heliövaara et al. 1993b, Heliövaara et al. 1993c). These 3,595 subjects constituted the study population that was followed up for disability, mortality, hip fractures and myocardial infarction up to the year 1994.

A follow-up musculoskeletal examination of a sample of study subjects was carried out about one year after the baseline examination to investigate the stability of findings over time (Mäkelä et al. 1993, Heliövaara et al. 1993c). A repeat testing of the joint functions used in the screening procedure was performed in 794 subjects about 3 months later (at the time of the main examination); the kappa coefficients ranged from 0.36 to 0.76 (Heliövaara et al. 1993c).
Figure 2. Geographical location of the study subjects.

1. Salo, Muurla (I 1978)
2. Somero, Somerniemi (II 1978)
3. Karjaa, Pohja (II 1978)
5. Porvoo (V 1978)
7. Luumäki, Ylämaa (IX 1978)
8. Savonlinna (IX 1978)
9. Iitti, Jaala (IX 1978)
10. Kuopio (X 1978)
11. Juva (X 1978)
12. Vihti (XII 1978)
13. Ilomantsi (I 1979)
14. Suonenjoki (I 1979)
15. Lahti (II 1979)
16. Asikkala, Padasjoki (II 1979)
17. Jyväskylä, Jyväskylän mlk, Säynätsalo, Muurame (III 1979)
18. Aänekoski, Konginkangas (III 1979)
19. Karstula, Kyyjärvi (IV 1979)
20. Iisalmi (III 1979)
21. Kajaani, Kajaanin mlk (IV 1979)
22. Oulu, Oulunsalo, Kempele, Hailuoto (IV 1979)
23. Kemijärvi (V 1979)
24. Suomussalmi (V 1979)
25. Nummo (VII 1979)
27. Valvekoski (VII 1979)
28. Kolari (IX 1979)
29. Muhos (X 1979)
30. Kestilä (X 1979)
31. Ylivieska (X 1979)
32. Vaasa (X 1979)
33. Tampere (X 1979)
34. Teuva (XII 1979)
35. Pori (I 1980)
36. Eura, Kiukainen (I 1980)
37. Hämeenlinna (I 1980)
38. Kokemäki (II 1980)
39. Pöytyä (II 1980)
40. Turku, Raisio, Naantali, Kaarina, Rusko, Vahto (V 1980)
**Figure 3.** The flow of the operations during the Mini-Finland Health Survey and the follow-up.

- **POPULATION**
  - Sample of 8000 Finns aged 30 years or over

- **SCREENING EXAMINATION AT BASELINE IN 1978-1980**
  - Screening examination by mobile clinic; questionnaires, symptom interviews and basic measurements
  - 7217 subjects (90%) participated

- **CLINICAL EXAMINATION 3 TO 6 MONTHS LATER,**
  - 3775 musculoskeletal screening-positive

  - Hand radiography was taken in 3595 subjects, of whom 2503 were screening-positive for musculoskeletal diseases
    - 1092 belonged to a random subsample (20%) of whom
      - 627 were screening-positive
      - 465 were screening-negative

  - Osteoarthritis in hand joints was diagnosed and graded based on hand radiographs by a radiologist (I, II, V)
  - Metacarpal cortical index (MCI) and combined cortical thickness (CCT) were measured by another radiologist (IV, V)
  - Diffuse idiopathic skeletal hyperostosis (DISH) was determined from chest radiographs by a third radiologist (VI)

  - Osteoarthritis in knee and hip joints, chronic neck and low-back syndromes were diagnosed by trained physicians (I, II, VI)

- **FOLLOW-UP EXAMINATION IN 2000**
  - 340 participants, in whom broadband ultrasound attenuation (BUA) was measured (V) and chronic neck and low-back syndromes were re-diagnosed (VI)

- **FOLLOW-UP TO YEAR 1994**
  - Linkages to:
    - Social Insurance Institution’s register of work disability pensions (I, II)
    - Central Statistical Office of Finland
      - Mortality and coronary deaths (I, II, III)
    - National Hospital Discharge Register
      - Hospitalisation due to hip fractures and myocardial infarction (III, IV)
4.3. Methods

4.3.1. Definition of the risk determinants

A basic questionnaire was used to obtain information on physical activity by asking whether the person participates in physical activity in his/her spare time and by classifying the answers into three classes: low (in my leisure time I mostly read, watch television, listen to the radio, go to the cinema, go to restaurants, or do other things which do not require much physical exertion); moderate (as my main pastime or in addition to the above, I fish, hunt, do gardening, go on family outings etc. fairly regularly or take some other kind of exercise now and then); and high (as my main pastime or in addition to the above I take some kind of physical exercise regularly or fairly regularly, e.g. running, skiing, cycling, ball games, swimming, gymnastics, weight lifting, etc.; you belong to this group if you do any of these competitively, as a hobby, to improve your condition, etc.).

Self-reported general health was assessed by asking the subjects to rate their present general health status along a five-point scale: “very good” to “quite good” to “average” to “quite poor” to “very poor”. A basic questionnaire was used to elicit information on the present occupation and the previous occupation of longest duration involving exposure to (a) lifting or carrying heavy objects, (b) stooped, twisted or otherwise awkward work postures, (c) vibration of the whole body or the use of vibrating equipment, (d) continuously repeated series of movements, and (e) work paced by a machine. These exposures were recorded as dichotomies (no = 0, yes = 1), and their total number was designated as “the sum index of physical stress at work” (Mäkelä et al. 1993, Heliövaara et al. 1993c).

Overall disability was defined as at least marked difficulty in any of the following activities: moving about in the house, getting in and out of bed, dressing and undressing, walking 400 m, carrying a shopping bag weighing 5 kg, climbing a flight of stairs, managing grocery shopping, clipping toenails, reading a newspaper, travelling on public transport, or performing heavy housework such as cleaning (Mäkelä et al. 1993, Heliövaara et al. 1993c).

Standing height and weight were measured at the screening examination, and body mass index \((\text{weight/height}^2, \text{kg/m}^2)\) was used as a measure of relative weight. Smoking history was obtained in a standard interview and categorised as follows: never smoked; quit smoking; current smoker of cigars, pipe or of fewer than 20 cigarettes a day, and current smoker of 20 cigarettes or more a day. The basic questionnaire inquired about average weekly consumption of beer, wine and strong beverages during the preceding month. The overall alcohol consumption was then calculated and expressed in grams of ethanol per week (Aromaa et al. 1989). The level of education was considered in three categories based on the years of education (<8, 8-12, and >12 years). Socioeconomic class was determined in three categories based on the household income.

Persons were classified as diabetics if they were using insulin or other drugs for diabetes, or if they had clearly elevated fasting blood glucose level (over 130mg/100ml) and / or abnormal glucose tolerance and glucosuria (Aromaa et al. 1989). Serum cholesterol concentrations were determined from serum samples after 1-3 weeks of storage at -20°C with an auto-analyser modification of the Liebermann-Burchard reaction. Systolic and diastolic blood pressures were measured using long cuffs with rubber bags sized 12.5cm x 40cm with the standard protocol (Aromaa et al. 1989).

In basic questionnaires, there was also a question about the use of analgesics:” Have you in the past three months taken any
medicine (prescribed or over the counter) for any of the following reasons?": head pain, back pain, muscle or joint pain, or other pain. In the present study, we classified this question as follows: none; occasional, but not continued; and regular use of analgesics (prescribed or over the counter) for head, back, muscle or joint pain, or other pain during the previous three months (Aromaa et al. 1989).

### 4.3.2. Clinical examinations

In diagnosing OA in knee or hip joints, the doctors took medical histories including the course of various diseases and previous medical examinations and diagnoses. The doctors also investigated all the documents (prescriptions, health records, X-rays and medical reports) that the subjects had been asked to bring with them (Heliövaara et al 1993c).

OA in the knee and hip joints was immediately diagnosed, on the basis of medical history, symptoms and physical examination, during the clinical phase in 3,568 subjects, and was further divided into different diagnostic subcategories: definite OA or possible OA (Table 5). Definite OA was diagnosed if there was either a convincing disease history, such as documentation of previous x-ray findings, or a definitive finding in the physical status of one or both knees or hip joints (Table 5). Possible OA was diagnosed if subjects had less definitive abnormalities in the physical status, or less convincingly documented disease histories, or if the subjects gave a typical symptom history of knee or hip OA (Sievers et al. 1985, Heliövaara et al 1993c).

When diagnosing a chronic low-back syndrome, physicians inspected the back curvature, tested the flexion, extension and torsion of the back and the mobility of the limb joints, and used the straight-leg raising test. Immediately after the examination, the field physicians made their final diagnoses on the basis of the disease history, symptoms, and clinical findings (Heliövaara et al. 1991). A chronic low-back syndrome was diagnosed if the person had a convincing symptom history of chronic low-back pain and symptoms during the preceding month and a major pathological finding on physical examination (i.e. fingertip-floor distance of 25 cm or more at flexion, rotation restricted to 25° or less, objective signs of back pain in motion, scoliosis of 20° or more on inspection, clearly straightened lumbar lordosis on inspection, Laseque’s test positive at 60° or less, or other severe abnormality). If the patient had both a convincing symptom and a disease history of an earlier low-back diagnosis based on convincing clinical findings, the physician diagnosed a chronic low-back syndrome even in the presence of a minor pathological finding in any of the physical tests (Heliövaara et al. 1991).

A chronic neck syndrome was diagnosed if there was 1) a convincing history of severe longstanding neck pain that had manifested symptoms during the previous month; 2) a documented history of a previously diagnosed chronic neck pain with convincing observable signs on physical examination, or 3) mild or moderate neck pain with convincing observable physical signs at the time of the examination (Mäkelä et al. 1991). Current neck pain of short (< 3 months) duration was not considered a chronic neck pain.

To study symptoms and impaired function associated with various forms of hand OA, relevant items from the joint function examination, the symptom interview and the physician’s clinical examination were used as outcomes (Sievers et al. 1985). At the joint function examination, a flexion failure of 1 cm or less in at least one finger from 2 to 4 was defined as restricted flexion.
Table 5. The diagnostic criteria for definite and possible knee and hip OA (Sievers et al. 1985).

**OA of knee or hip was regarded as definite if some of the following conditions were fulfilled:**

1) history of definitely documented diagnosis of knee or hip OA

2) knee or hip arthroplasty performed due to OA

3) evident OA in knee examination: at least moderate limitation of range of motion (flexion contracture over 5 degrees or maximal range of motion under 100 degrees), tenderness and deformations, such as bony enlargement, giving support to diagnosis

4) evident OA in hip examination: at least moderate limitation of range of motion (maximal range of motion) under 30 degrees in medial rotation or under 40 degrees in lateral rotation, or under 60 degrees in abduction-adduction ) and tenderness, giving support to diagnosis

**OA of knee or hip was possible if some of the following conditions were fulfilled:**

1) knee or hip arthroplasty, but disease history not quite clear

2) disease history without documentation or documentation with diagnosis, but without argumentations of diagnosis, and also the typical symptoms of knee or hip OA (morning stiffness, exercise pain or slowly increased pain in knee or hip overtime) but without obvious clinical findings

3) knee or hip OA findings at clinical examination, such as mild limitation of range of motion (<20% decrement from normal range), motion tenderness and deformities, but history gives no indication of diagnosis

The experience of finger joint pain during the previous month was based on the symptom interview. As part of the clinical examination, the field physician recorded swelling, movement restraint, movement tenderness, and palpation tenderness in every joint of both the right and left hand separately, including the CMC joints of the thumbs.

The variation among the examining physicians in the use of the diagnostic criteria was assessed by forty authentic subject documents, reassessed twice by six of the eight examiners over a period of one year. The overall agreement (kappa) was 0.76 for both knee and hip OA, and 0.74 for low-back syndrome, and 0.75 for neck syndrome and 0.67 for hand OA, which were regarded as a moderate agreement (Heliövaara et al. 1993b, Heliövaara et al. 1993c). The stability of the OA diagnosis over time was assessed about one year after the clinical phase by a follow-up examination of 302 subjects performed by a specialist in physical and rehabilitation medicine (Heliövaara et al. 1993b, Heliövaara et al. 1993c). The diagnostic threshold was quite different in the two examinations, the follow-up being much more sensitive and accurate. However, the overall agreement (kappa) between these two examinations was moderate for both knee OA, 0.52, and for hip OA, 0.44; and 0.34 (low) for low-back syndrome and a neck syndrome, 0.40 (moderate); and 0.39 (low) for hand OA (Heliövaara et al. 1993b, Heliövaara et al. 1993c).
Repeated physical status of hand joints was available for 204 subjects. Among these subjects, the prevalence of Heberden's nodes was 10.8% at baseline examination, and 9.8% at follow-up examination. The kappa for agreement between the two examinations was 0.58 and McNemar's test indicated no systematic difference (p = 0.62) (Heliövaara et al. 1993c).

4.3.3. Radiological methods

Posteroanterior hand radiographs of both hands were taken from 3,595 persons who met at least one of the screening criteria for musculoskeletal diseases, or belonged to the random 20% sample (Figure 3). Hand radiographs were read mainly to diagnose OA (Kärkkäinen 1985). Standard criteria (Kellgren et al. 1963, Larsen et al. 1976) were used for assessing the joint space narrowing and osteophytes. The readings of x-rays were carried out by a radiologist without any information about the clinical findings or the metacarpal measurements assessed by another radiologist (Kärkkäinen 1985). Each joint of both hands was graded as follows: Grade 0: No OA, Grade 1: Minimal osteophytosis and possible cyst formation (doubtful OA), Grade 2: Definite osteophytosis and possible cysts (minimal OA), Grade 3: Moderate osteophytes, narrowing of joint space and subchondral sclerosis and deformity of bone ends (moderate OA), Grade 4: Large osteophytes, severe sclerosis and narrowing of joint space (severe OA). OA was considered to be present if the grade was 2 or more in at least one of the joints.

In the subpopulation of 1,092 subjects belonging to the random 20% sample, the prevalence and determinants of hand OA have been described in detail earlier (Kärkkäinen 1985).

Three different kinds of hand OA types were defined for the current study:

1) OA of Kellgren’s grade 2 to 4 in any finger joint (OA in any finger joint) including DIP, PIP, MCP and the thumb interphalangeal joints.

2) OA of Kellgren’s grade 2 to 4 in at least two distal interphalangeal joints symmetrically (symmetrical DIP OA) including all DIP joints except the thumb IP joints.

3) OA of Kellgren’s grade 2 to 4 in carpometacarpal OA of the thumb (thumb carpometacarpal OA)

Examples of these types of hand OA is presented in figures 4-6.

The reliability of the readings of the hand radiographs was estimated by measuring intraobserver and interobserver agreement, using the correlation coefficient kappa (k) as an indicator of agreement (Kärkkäinen, 1985). The reader classified 84.9% of the joints in the same way in the first and the second reading; kappa was 0.71, which is generally regarded as a good agreement. Two readers classified 73.5% of the joints in the same way; kappa was 0.53, which is considered a moderate agreement. When classifying the examinees as “OA present” and “OA absent”, the intraobserver agreement was excellent; kappa was 0.89 (Kärkkäinen 1985). Both interobserver and intraobserver agreements were highest in distal interphalangeal and metacarpophalangeal joints and lowest in wrist joints.
**Figure 4.** Hand radiographs of a 57-year-old woman, who has osteoarthritis of Kellgren’s grade 2-4 in distal interphalangeal joints (I-IV) of both hands (symmetrical DIP OA).

**Figure 5.** Hand radiograph of a 47-year-old woman, who has osteoarthritis of Kellgren’s grade 3 in carpometacarpal joint of the left thumb (thumb carpometacarpal OA).

**Figure 6.** Hand radiograph of a 60-year-old man, who has osteoarthritis of Kellgren’s grade 4 in proximal interphalangeal joint (IV) of the right hand (OA in any finger joint).
Figure 7. Assessment of metacarpal index (MCI) from the midpoint of the second metacarpal bone in the right hand of a 37-year-old healthy woman.

The indicators of cortical bone mineral mass, combined cortical thickness (CCT) and metacarpal index (MCI) were determined during the baseline examination in the period 1978-1980 from hand radiographs by a radiologist, other than the one who diagnosed and graded hand OA (Figure 7). The measurements of the outer and inner cortical diameter were made at the midpoint of the second metacarpal bone of the right hand, with a digital calliper to the nearest 0.1 mm (Figure 7) (Kärkkäinen 1985). The coefficients of intraobserver reliability were 0.91 for both the outer and inner cortical diameter (Kärkkäinen 1985). CCT was calculated as the difference between the outer and inner cortical diameter (Kärkkäinen 1985). MCI was further calculated by dividing the value of CCT with the outer cortical diameter. (Figure 7) (Barnett and Nordin 1960).

Chest radiographs were read mainly to diagnose heart and chronic pulmonary diseases (Aromaa et al. 1989, Julkunen et al. 1981). Diffuse idiopathic skeletal hyperostosis (DISH) was determined from lateral chest radiographs from a random sample of the whole sample at baseline (n=6,167) using the criteria of Forestier and Lagier (1971) by an experienced rheumatologist (Julkunen et al. 1981). Reliability coefficients (kappa) in the repeat reading of 1,025 films ranged between 0.60 and 0.76 (Julkunen et al. 1981). Diffuse idiopathic skeletal hyperostosis (DISH) is an ossifying systemic enthesopathy which mainly involves the thoracic vertebrae and is strongly related to spondylosis, which is a prerequisite for hyperostosis (Forestier and...
4.3.4. Follow-up

The mortality, disability and morbidity of the subjects were systematically followed up between the baseline examination and late 1994 (Figure 3).

To identify new cases of work disability, data on new national disability pensions were collected from the Social Insurance Institution's register. The follow-up was continued from the baseline examination until death, permanent disability pension, age of 65 years (general retirement age in Finland) or the end of the observation period (31.12.1994), which ever occurred first.

The mortality information was obtained from the Central Statistical Office of Finland. The principal causes of death were coded according to the eighth edition of the International Classification of Diseases (ICD-8). The follow-up was continued from the baseline examination until death. When examining cause-specific cardiovascular mortality, ICD-8 codes 391.00-458.00 were used for cardiovascular deaths.

Record linkage to the National Hospital Discharge Register identified subjects in the cohort who were hospitalised for hip fracture by the end of 1994. Hip fractures as primary or secondary diagnoses were also defined according ICD-8. The three-digit code 820 includes both collum and pertrochanteric fractures of the femoral neck, but no diaphyse fractures of the femur (ICD 821).

A major coronary event was defined as either myocardial infarction or coronary death. Non-fatal cases of myocardial infarction (ICD-8 code 410) were identified by linking the study population to the National Hospital Discharge Register, using the unique personal identification number (Heliövaara et al. 1984). The fatal coronary heart disease cases (ICD-8 codes 410-414) were identified from death certificates, which were obtained for all the deceased from Statistics Finland. For a person with several coronary heart disease events, the first major event was registered.

In 2000, 340 of the participants who had undergone the clinical examination including radiography of hands and chest, were re-examined in the Health 2000 survey (Aromaa and Koskinen 2002). The same diagnostic criteria in diagnosing chronic neck and low-back syndromes were used as in the baseline examination. The mean follow-up time of the subject was 21 years. The sample consisted of 131 men and 209 women aged 30-71 years at baseline and living in or around the five largest cities in Finland (Helsinki, Turku, Tampere, Oulu and Kuopio).

4.3.5. Broadband ultrasound attenuation (BUA) measurements

In 2000, Broadband ultrasound attenuation (BUA; db/MHz) was measured by trained nurses from the right calcaneus with a SAHARA sonometer (Hologic Inc. Waltham, USA) from 340 subjects, who had undergone clinical examination, including radiography of hands at baseline (Figure 3).

To evaluate the reliability and validity of field examinations proper, 42 men and 88 women aged 42-92 years were invited to the Department of Physical and Rehabilitation Medicine, Kuopio University Hospital, for a comprehensive re-examination; 81% complied. Intraobserver variation was assessed on the basis of four measurements at both calcanea in 9 men and 14 women. The intra-class correlation coefficients of BUA for the right and left calcaneal measurements was 0.80. Validity was investigated by comparing the BUA measurements with dual X-ray
absorbtimetry (DXA) (Lunar Expert, Lunar Radiation Corporation, Madison, WI, USA) values of the spine (L2-L3), with femur neck bone mineral density (BMD) (g/cm²), and with the peripheral DXA (Peripheral Instantaneous X-Ray Imager, (PIXI), General Electric Company, Fairfield, USA) value of calcaneal BMD (g/cm²) in 130 persons. The Pearson correlation coefficients for BUA were R = 0.48 for spine (L2-L3) BMD, R = 0.49 for femoral neck BMD, and R = 0.72 for calcaneal peripheral DXA measurements.

Among the 899 subjects who were re-examined in the Health 2000 survey (Aromaa and Koskinen 2002), age- and sex-adjusted BUA values at the follow-up examination in those who had and who had not participated in the hand x-ray examination were 77.4 and 75.5, respectively (p = 0.15). Among those who had undergone the hand x-ray examination 20 years earlier, the baseline metacarpal index (odds ratio 1.11; 95% confidence interval 0.98-1.26), thumb carpometacarpal OA (odds ratio 0.81; 95% confidence interval 0.47-1.42) or non-symmetrical DIP OA (odds ratio 0.76; 95% confidence interval 0.49-1.17) did not significantly predict subsequent selection for re-examination. However, symmetrical DIP OA predicted a decreased likelihood of re-examination (odds ratio; 0.45; 95% confidence interval 0.25-0.81).

4.4. Statistical methods

SAS software (SAS Institute Inc., Gary, NC, USA) was used for the statistical analysis. The adjusted prevalence rates and cross-sectional associations, as well as multiple partial correlations between continuous variables were estimated using a general linear model (Searle 1971).

Both cross-sectional and longitudinal associations between alleged risk determinants and dichotomized outcomes and their first-degree interaction terms were analysed with a logistic regression model (Cox 1970). Relative risks were estimated as adjusted odds ratios. The Cox's life-table regression (proportional hazards) model was used to estimate the associations between baseline variables and mortality, incident work disability, hip fractures, and major coronary events during follow-up (Cox 1972).

Potential confounding and effect-modifying factors were also entered into the models. The significance of the interaction was tested by entering interaction terms into the models. The 95 % confidence intervals of the relative risk estimates and the likelihood ratio statistics (chi-squared values expressed as P values) were based on the models. Winer's unbiased estimates of the intra-class correlation coefficient (r) (Winer 1971) were computed to study agreement in the calcaneal BUA measurements between repeated examinations and between the right and left foot. Correspondingly, kappa statistic (Landis and Koch 1977, Fleiss 1981) were computed to estimate agreement in the case of dichotomous measurements, such as clinical findings and radiological diagnoses.
5. RESULTS

5.1. Population

The baseline sample of this dissertation included 1,560 men and 2,035 women whose age range was 30 to 95 (mean 54.4; SD 13.7) years. The characteristics of the subjects of this dissertation (n = 3,595) has been presented in Table 6.

Among subjects who belonged to the random subsample (n = 1,092), there was no significant difference in the prevalence of finger joint OA between screening-negative and screening-positive subjects, whereas subjects with thumb carpometacarpal OA were overrepresented in the group screening-positive for musculoskeletal disease. The age- and sex-adjusted odds ratios (with 95% confidence intervals) of screening positivity were 1.28 (0.83-1.99) for symmetrical DIP OA, 1.34 (0.95-1.89) for OA in any finger joint, 1.25 (0.85-1.85) for non-symmetrical finger OA, and 2.59 (1.45-4.63) for thumb carpometacarpal OA.

Further, among these 1,092 subjects, there was no significant difference in the values of MCI between screening negatively and screening positively (p = 0.82). The age- and sex adjusted mean values of MCI were 0.580 and 0.581, respectively.

Table 6. Characteristics of the subjects included in the sample (n = 3,595).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of subjects (%)</th>
<th>Variable</th>
<th>Number of subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td><strong>Alcohol intake</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1560 (43)</td>
<td>Not at all</td>
<td>1822 (51)</td>
</tr>
<tr>
<td>Women</td>
<td>2035 (57)</td>
<td>1-49 grams per week</td>
<td>1410 (39)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50-249 grams per week</td>
<td>122 (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 250 grams per week</td>
<td>241 (7)</td>
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<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td><strong>History of smoking</strong></td>
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<tr>
<td>30-44</td>
<td>986 (28)</td>
<td>Never smoked</td>
<td>2034 (57)</td>
</tr>
<tr>
<td>45-54</td>
<td>834 (23)</td>
<td>Quit</td>
<td>792 (22)</td>
</tr>
<tr>
<td>55-64</td>
<td>824 (23)</td>
<td>Cigars, pipe or &lt;20</td>
<td>486 (14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cigarettes/day</td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>662 (18)</td>
<td>≥20 cigarettes/day</td>
<td>283 (8)</td>
</tr>
<tr>
<td>75-</td>
<td>289 (8)</td>
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<td></td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
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<td><strong>History of workload</strong></td>
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<tr>
<td>≤20.0</td>
<td>141 (4)</td>
<td>(items of physical exposure)</td>
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<td>20.0-24.9</td>
<td>131 (37)</td>
<td>0</td>
<td>1047 (29)</td>
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<tr>
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<td>1483 (41)</td>
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<td>704 (20)</td>
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<td>30.0-34.9</td>
<td>544 (15)</td>
<td>2</td>
<td>709 (20)</td>
</tr>
<tr>
<td>≥35.0</td>
<td>112 (3)</td>
<td>3</td>
<td>311 (9)</td>
</tr>
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<td>4</td>
<td>200 (6)</td>
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<td></td>
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<td>5</td>
<td>55 (2)</td>
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<td><strong>Educational level</strong></td>
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<tr>
<td>&lt;8 years</td>
<td>2654 (74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-12 years</td>
<td>654 (18)</td>
<td></td>
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<tr>
<td>&gt;12 years</td>
<td>287 (8)</td>
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</tr>
</tbody>
</table>
5.2. Prevalence of radiological hand osteoarthritis (I,II)

The age-adjusted prevalence rates of OA in any finger joint for men and women were 44.3% and 48.1% respectively, and the corresponding rates of symmetrical DIP OA were 10.2% and 20.6%, respectively, and 7% and 15% of thumb carpometarcal joint OA, respectively. The prevalence rates of Heberden’s nodes were 4.6% for men and 13.4% for women. Such as other forms of hand OA also symmetric thumb carpometacarpal OA was more common among women (6.0%) as compared with men (2.6%). The prevalence of OA in any finger, symmetrical DIP OA, and thumb carpometacarpal OA, increased with age in both sexes (Figure 8).

Figure 8. The prevalence rates and 95% confidence intervals of OA of Kellgren grades 2 to 4 in any finger joint (grey columns), OA in at least two distal interphalangeal joints symmetrically (dark grey columns), and OA in the carpometacarpal joint of the thumb (white columns) in Finnish men and women 30 years of age or over.* (I,II)

*The age-adjusted prevalence rates of OA of Kellgren grades 2 to 4 in any finger joint (solid line), OA in at least two distal interphalangeal joints symmetrically (broken line), and OA in carpometacarpal joint of the thumb (dotted line)

5.3. Determinants of hand osteoarthritis (I, II)

Female sex and age were strong risk determinants of all forms of hand OA (Table 7). There was also a positive gradient between BMI and the prevalence of both OA in any finger joint and symmetrical DIP OA (Table 7). The subjects with BMI over 35 kg/m² had a roughly two-fold risk of OA in any finger joint or symmetrical DIP OA as compared to subjects with normal BMI (20.0-24.9kg/m²). The associations were similar in men and women, and adjustments for age, sex, educational level, workload and smoking did not markedly affect the odds ratios (Table 7).
The sum index of physical stress at work showed different associations with OA in any finger joint between men and women (p-value for interaction = 0.04): there was a positive gradient in women but no association in men (Table 7). The association was mainly due to close associations between workload and OA in proximal interphalangeal and metacarpophalangeal joints among women (data not shown). The physical stress index did not show any relation to symmetrical DIP OA in either sex (data not shown).

There was a decreased prevalence of symmetric DIP OA in male smokers compared with never smokers, but such an association could not be observed in women (p-value for interaction = 0.03). In men who smoked 20 cigarettes or more a day, the odds ratio of symmetrical DIP OA was 0.40 (95% confidence interval 0.18-0.86). For any finger OA, smoking also showed a weak negative association in men but not in women.

Table 7. Odds ratios (OR) with 95% confidence intervals (CI) for OA of Kellgren’s grade 2 to 4 in any finger joint (OA in any finger joint), its subcategory OA in at least two distal interphalangeal joints symmetrically (Symmetrical DIP OA), and OA in thumb carpometacarpal joint CMC-1 joint (CMC-1 OA) by age, sex, educational level, body mass index (BMI), history of workload and history of smoking (n =3,595). Logistic regression model. (I, II)

<table>
<thead>
<tr>
<th></th>
<th>OA in any finger joint</th>
<th>Symmetrical DIP OA</th>
<th>CMC-1 OA *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td><strong>Age (years)</strong>†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-44</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>45-54</td>
<td>6.6 4.87-8.87</td>
<td>8.3 3.2-21.4</td>
<td>10.5 3.7-29.6</td>
</tr>
<tr>
<td>55-64</td>
<td>30.6 22.7-41.3</td>
<td>47.28 19.3-115.8</td>
<td>36.13 13.3-98.5</td>
</tr>
<tr>
<td>65-74</td>
<td>80.1 57.4-111.7</td>
<td>119.05 48.8-290.7</td>
<td>72.6 26.7-197.1</td>
</tr>
<tr>
<td>75-</td>
<td>128.5 81.5-202.4</td>
<td>60.42 64.65-398.02</td>
<td>115.7 41.9-319.1</td>
</tr>
<tr>
<td><strong>Sex ‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Women</td>
<td>1.29 1.08-1.53</td>
<td>2.85 2.28-3.57</td>
<td>1.99 1.54-2.54</td>
</tr>
<tr>
<td><strong>Education</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8 years</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>8-12 years</td>
<td>1.15 0.90-1.47</td>
<td>1.07 0.78-1.48</td>
<td>1.30 0.93-1.81</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>0.98 0.60-1.44</td>
<td>1.44 0.84-2.45</td>
<td>1.31 0.73-2.37</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20.0</td>
<td>0.50 0.31-0.83</td>
<td>0.61 0.31-1.20</td>
<td>0.57 0.25-1.33</td>
</tr>
<tr>
<td>20.0-24.9</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>1.17 0.96-1.43</td>
<td>1.45 1.13-1.86</td>
<td>1.37 1.03-1.82</td>
</tr>
<tr>
<td>30.0-34.9</td>
<td>1.78 1.37-2.33</td>
<td>1.75 1.29-2.36</td>
<td>1.46 1.04-2.03</td>
</tr>
<tr>
<td>≥35.0</td>
<td>1.98 1.19-3.27</td>
<td>1.99 1.18-3.37</td>
<td>2.19 1.24-3.84</td>
</tr>
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</table>
Table 7. Continued

<table>
<thead>
<tr>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>History of workload, men § (items of physical exposure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.30</td>
<td>0.87-1.96</td>
<td>1.53</td>
<td>0.82-2.84</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>1.18</td>
<td>0.81-1.72</td>
<td>0.95</td>
<td>0.51-1.76</td>
<td>0.84</td>
</tr>
<tr>
<td>3</td>
<td>1.23</td>
<td>0.82-1.84</td>
<td>1.40</td>
<td>0.73-2.70</td>
<td>0.77</td>
</tr>
<tr>
<td>4</td>
<td>1.41</td>
<td>0.81-2.46</td>
<td>1.71</td>
<td>0.68-4.33</td>
<td>0.78</td>
</tr>
<tr>
<td>5</td>
<td>1.75</td>
<td>0.78-3.91</td>
<td>2.72</td>
<td>0.86-8.58</td>
<td>0.13</td>
</tr>
</tbody>
</table>

| History of workload, women § (items of physical exposure) | | | | | | |
| 0  | 1.00   | 1.00 | 1.10 | 0.76-1.61 | | |
| 1  | 0.97   | 0.68-1.38 | 1.45 | 1.06-2.00 | | |
| 2  | 1.54   | 1.12-2.10 | 1.37 | 0.84-2.22 | | |
| 3  | 1.63   | 1.03-2.59 | 1.81 | 0.90-3.62 | | |
| 4  | 1.21   | 0.66-2.22 | 1.46 | 0.33-6.51 | | |
| 5  | 10.97  | 1.25-95.90 | 1.10 | 0.76-1.61 | | |

| History of smoking, men** | | | | | | |
| 0  | 1.00   | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1  | 0.72   | 0.52-0.99 | 0.51 | 0.33-0.81 | 0.53 | 0.33-0.85 |
| 2  | 0.70   | 0.48-1.03 | 0.48 | 0.27-0.87 | 0.40 | 0.21-0.75 |
| 3  | 0.72   | 0.48-1.09 | 0.40 | 0.18-0.86 | 0.65 | 0.32-1.31 |

| History of smoking, women** | | | | | | |
| 0  | 1.00   | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1  | 0.99   | 0.65-1.52 | 0.36 | 0.19-0.69 | 0.73 | 0.39-1.35 |
| 2  | 0.77   | 0.48-1.22 | 1.32 | 0.75-2.34 | 1.97 | 1.12-3.43 |
| 3  | 0.81   | 0.32-2.04 | 0.66 | 0.18-2.45 | 1.38 | 0.39-4.94 |

* Also adjusted for alcohol consumption
† Unadjusted
‡ Adjusted for age only
§ There was a significant interaction between sex and workload for OA in any finger joint (p = 0.04)
| 0 = never smoked; 1 = quit; 2 = cigars, pipe or < 20 cigarettes / day; 3 = > 20 cigarettes/day
** There were significant interactions between sex and smoking for symmetric DIP OA (p = 0.03) and for CMC-1 OA (p = 0.004)

In addition to age and female sex, body mass index was also a strong determinant of thumb carpometacarpal OA (Table 7). After adjusting for age, sex, and other alleged risk determinants, body mass index was directly proportional to the prevalence of thumb carpometacarpal OA in both sexes. The adjusted odds ratio was 1.29 (95% confidence interval 1.15-1.43) per 5 kg/m² increment in body mass index. Thus, the subjects with body mass index over 35 kg/m² had an over 2-fold risk of having any thumb carpometacarpal OA, as compared to those with normal relative weight (body mass index 20.0 - 24.9 kg/m²) (Table 7). However, body mass index showed a weaker association with advanced thumb carpometacarpal OA (Kellgren's grade 3 to
4). In these analyses, the adjusted odds ratio per 5 kg/m$^2$ increment in body mass index was 1.14 (95% confidence interval 0.92-1.37). Neither level of education nor history of physical workload showed a clear-cut association with the prevalence of thumb carpometacarpal OA.

As in finger OA, there was a significant difference in the associations of smoking and thumb carpometacarpal OA between men and women (p-value for interaction 0.004). Among women there was a positive association, whereas among men both past and current smoking was negatively associated with the prevalence of thumb carpometacarpal OA (Table 7).

Alcohol consumption showed no significant association with the prevalence of OA in any finger joint, symmetrical DIP OA or thumb carpometacarpal OA of Kellgren’s grade > 2. Thumb carpometacarpal OA of Kellgren grade >3, however, was associated with intakes of >250 grams of ethanol per week among men (odds ratio 1.32; 95% confidence interval 1.03-1.69).

5.4. Association between radiological and clinical hand osteoarthritis (I, II)

There was a moderately increased association of restriction in the flexion of fingers 2 to 4 (odds ratio, 1.59; 95% confidence interval 1.08-2.34) and in the opposing movement of the thumb (odds ratio, 1.42; 95% confidence interval 1.00-2.03) with OA in any finger joint, but not with symmetrical DIP OA. Finger pain associated positively with both OA in any finger joint (odds ratio, 1.38; 95% confidence interval 1.14-1.67) and symmetrical DIP OA (odds ratio, 1.68; 95% confidence interval 1.34-2.10). Heberden’s node seemed to associate more often with a risk of symmetrical DIP OA (odds ratio, 4.97; 95% confidence interval 3.81-6.50) than with OA in any finger joint (odds ratio, 3.47; 95% confidence interval 2.51-4.80).

There was a strong association between thumb carpometacarpal OA and the physical status of the ipsilateral thumb carpometacarpal joint, including movement restraint, movement tenderness, swelling and palpation tenderness in both hands. Subjects with any of these findings had a three-fold risk of having radiological thumb carpometacarpal osteoarthritis in the right hand (odds ratio 3.29, 95% confidence interval 2.03-5.33), and a two-fold risk of having radiological thumb carpometacarpal OA in the left hand (odds ratio 2.16, 95% confidence interval 1.34-3.51).

Also, the presence of at least one Heberden’s node was closely associated with finger pain (odds ratio, 2.56; 95% confidence interval, 2.00-3.27), with restricted flexion of fingers 2 to 4 (odds ratio, 2.36; 95% confidence interval, 1.54-3.62), and with restricted opposing movement of the thumb (odds ratio, 2.11; 95% confidence interval, 1.34–3.32).

5.5. Hand osteoarthritis and coexisting diseases (I, II)

We found no relationship between radiological hand OA types and clinically diagnosed knee OA or hip OA. Nor was there any relationship between radiological hand OA types and chronic neck or low-back syndromes, diabetes or cardiovascular diseases (myocardial infarction or stroke) at baseline.

There was a slightly increased risk of having one or more Heberden’s nodes in the finger, if the person also had knee OA (odds ratio, 1.31; 95% confidence interval 1.01-1.69) or hip OA (odds ratio, 1.14; 95% confidence interval 0.82-1.59). Chronic neck or low-back syndromes were not associated with the prevalence of Heberden’s nodes.

Thumb carpometacarpal OA had a strong association with other types of hand OA. When adjusted for age and sex, having OA in any finger joint (Kellgren’s grade >2)
showed an odds ratio of 8.35 (95% confidence interval 5.30-13.2) for having thumb carpometacarpal OA. A weaker comorbidity with an odds ratio of 3.66 (95% confidence interval 2.85-4.70) was found between thumb carpometacarpal OA and symmetrical OA in the distal interphalangeal joints.

5.6. Hand osteoarthritis as a cause of disability (I, II)

At baseline, none of the hand OA types was associated positively with overall disability to perform daily activities. After adjustment for sex and age, the odds ratio for inability to perform ordinary daily activities due to OA in any finger joint was 0.87 (95% confidence interval 0.72-1.05). Nor did OA in any finger joint or symmetrical DIP OA predict incidence of work disability; after adjustment for age and sex, the relative risks of work disability during the follow-up were 1.07 (95% confidence interval 0.87-1.33) and 1.25 (95% confidence interval 0.89-1.77) in OA in any finger joint and symmetrical DIP OA, respectively. In the presence of thumb carpometacarpal OA, after adjustment for age and sex, the odds ratio for inability to perform ordinary daily activities was 0.80 (95% confidence interval 0.63-1.01). Nor did thumb carpometacarpal OA predict work disability; adjusted for age and sex, the relative risks of work disability during the follow-up were 0.91 (95% confidence interval 0.61-1.38) and 1.47 (95% confidence interval 0.65-3.31) in thumb carpometacarpal OA of Kellgren's grades >2 and >3, respectively. However, a significant negative association was noted between symmetrical DIP OA and inability to perform ordinary daily activities (odds ratio 0.68; 95% confidence interval 0.55-0.84). The result remained significant in both sexes even after adjustment for education, BMI, smoking history and workload (data not shown).

5.7. Hand osteoarthritis and related mortality (I, II, III)

During the follow up, 462 out of 1,560 men, and 435 out of 2,035 women, died. Of the deaths, 261 (56%) and 236 (54%), respectively, were due to cardiovascular causes. A significant difference was observed between men and women for symmetrical DIP OA in its prediction of overall mortality (p-value for interaction = 0.001). Adjusting for age, education, physical stress at work, BMI and smoking, the relative risk of death in women was 1.23 (95% confidence interval 1.01-1.51), whereas in men the association seemed even inverse (relative risk 0.89, 95% confidence interval 0.68-1.16). For non-symmetrical DIP OA among women the corresponding relative risk was 1.02 (95% confidence interval 0.73-1.42).

The presence of OA in any finger joint did not significantly predict total mortality. In men, however, OA in any finger joint significantly predicted cardiovascular deaths (Table 8). No other significant association was found between OA in any finger joint and cause-specific mortality (data not shown). The associations between finger OA and mortality were similar in strata of body mass index. For total mortality in women, the p-value for interaction of body mass index and symmetrical DIP OA was 0.50. For cardiovascular mortality in men, the p-value for interaction of body mass index and OA in any finger joint was 0.75. After adjusting for other potential confounding factors, no significant association was found between thumb carpometacarpal OA Kellgren's grade 2 to 4 and total or cardiovascular mortality. However, a slightly increased risk of total mortality was observed in men who had advanced thumb carpometacarpal OA of Kellgren's grade >3; the adjusted
Table 8. Relative risks of total mortality and cardiovascular mortality (RR) and 95% confidence intervals (CI) during follow-up in men and women by OA of Kellgren's grade 2 to 4 in any finger joint (OA in any finger joint) and its subcategory, OA in at least two distal interphalangeal joints symmetrically (symmetrical DIP OA). Adjusted by age, education, history of workload, smoking, and body mass index (n = 3,595). Cox’s regression model. (I)

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Symmetric DIP OA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>YES</td>
<td>0.89</td>
<td>0.68-1.16</td>
</tr>
<tr>
<td>OA in any finger joint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>YES</td>
<td>1.02</td>
<td>0.83-1.27</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Symmetric DIP OA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>YES</td>
<td>0.96</td>
<td>0.68-1.36</td>
</tr>
<tr>
<td>OA in any finger joint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>YES</td>
<td>1.42</td>
<td>1.05-1.92</td>
</tr>
</tbody>
</table>

relative risk was 1.32 (95% confidence interval 1.03-1.69).

The association between OA in any finger joint and cardiovascular deaths was further studied among subjects who were free of cardiovascular diseases at baseline (n = 2,187) (Haara et al. 2003). After further adjustments for physical activity, educational level, history of workload and household income, for systolic and diastolic pressures, serum HDL and total cholesterol, body mass index, diabetes and smoking history the risk of cardiovascular mortality in men remained significant (Table 9). It was hypothesised that this was a result of frequent use of NSAIDs, but such an effect was not observed. Further adjustment with regular use of analgesics did not notably affect the relative risks (Table 9).

However, among the 4,824 subjects from the whole sample (n = 7,217) who were free of cardiovascular disease at baseline the risk of a new major coronary event was significantly elevated among those who had used analgesics regularly. When adjusted for known risk factors of coronary heart disease such as age, sex, diastolic blood pressure, serum HDL, level of education, smoking, and physical activity at leisure, the relative risk of a coronary event during the whole follow-up period from 1978-1994 was 1.51 (95% confidence interval 1.08 - 2.10) in those having reported regular use of analgesics compared with non-users. During the first two years of follow-up it was as high as 5.27 (95% confidence interval 2.13-13.11) but levelled off thereafter.
Table 9. Relative risks (RR) and 95% confidence intervals (CI) of cardiovascular death by OA in any finger joint in 945 men (72 deaths during 11,972 person-years) and 1,242 women (48 deaths during 16,343 person-years) who had been free of cardiovascular diseases at baseline (n = 2,187). Cox’s regression model. (Haara et al. 2003)

<table>
<thead>
<tr>
<th>Model</th>
<th>Men</th>
<th>Women</th>
<th>Both sexes*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>2.01</td>
<td>1.09-3.68</td>
<td>1.98</td>
</tr>
<tr>
<td>Further adjusted for educational level, history of workload, and household income</td>
<td>2.06</td>
<td>1.12-3.79</td>
<td>1.92</td>
</tr>
<tr>
<td>Further adjusted for physical activity at leisure</td>
<td>2.10</td>
<td>1.14-3.89</td>
<td>1.92</td>
</tr>
<tr>
<td>Further adjusted for systolic and diastolic pressures, serum HDL and total cholesterol, body mass index, diabetes, and smoking history</td>
<td>2.52</td>
<td>1.34-4.74</td>
<td>2.02</td>
</tr>
<tr>
<td>Further adjusted for use of analgesics</td>
<td>2.53</td>
<td>1.34-4.76</td>
<td>2.00</td>
</tr>
</tbody>
</table>

*also adjusted for sex

5.8. Determinants of bone mineral mass (IV)

At baseline, a multitude of potential confounders independently of each other, were significantly associated with a low MCI: high age, low body mass index, high body height and smoking (Table 10).

5.9. Cortical bone mineral mass and hip fracture (IV)

The MCI was inversely proportional to the incidence of hip fracture (Table 11). The unadjusted relative risk of hip fracture per increment of MCI by a standard deviation (0.1) was 0.36 (95% confidence interval, 0.30 - 0.43) and after adjustment for age and sex only, 0.67 (95% confidence interval 0.54-0.84). After further adjustment for all the potential confounders, i.e. age, sex, body mass index, body height, educational level, smoking, alcohol intake, physical activity at leisure, and self-rated general health, the relative risk was still 0.69 (95% confidence interval, 0.55 - 0.86, P for trend = 0.001). In multivariate analysis, only age seemed to carry as a significant interaction (data not shown).
Table 10. Adjusted means of the metacarpal cortical index (MCI) by age, sex, body mass index, body height, and smoking status. Adjusted for age, sex, body mass index, body height, educational level, smoking, alcohol intake, physical activity at leisure and self-rated general health (n = 3,561). General linear model. (IV)

<table>
<thead>
<tr>
<th>Determinant</th>
<th>SD*</th>
<th>MCI</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-44</td>
<td>0.091</td>
<td>0.631</td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>0.091</td>
<td>0.611</td>
<td></td>
</tr>
<tr>
<td>55-64</td>
<td>0.085</td>
<td>0.554</td>
<td>0.0001</td>
</tr>
<tr>
<td>65-74</td>
<td>0.088</td>
<td>0.497</td>
<td></td>
</tr>
<tr>
<td>&gt;75</td>
<td>0.089</td>
<td>0.452</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20.0</td>
<td>0.130</td>
<td>0.573</td>
<td></td>
</tr>
<tr>
<td>20.0-24.9</td>
<td>0.101</td>
<td>0.563</td>
<td></td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>0.108</td>
<td>0.568</td>
<td>0.0001</td>
</tr>
<tr>
<td>30.0-34.9</td>
<td>0.110</td>
<td>0.583</td>
<td></td>
</tr>
<tr>
<td>≥35.0</td>
<td>0.091</td>
<td>0.573</td>
<td></td>
</tr>
<tr>
<td>Body height (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;160</td>
<td>0.110</td>
<td>0.572</td>
<td></td>
</tr>
<tr>
<td>160-180</td>
<td>0.100</td>
<td>0.570</td>
<td>0.011</td>
</tr>
<tr>
<td>&gt;180</td>
<td>0.089</td>
<td>0.555</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>0.113</td>
<td>0.573</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>0.092</td>
<td>0.575</td>
<td>0.001</td>
</tr>
<tr>
<td>Pipe or cigars per/day</td>
<td>0.097</td>
<td>0.557</td>
<td></td>
</tr>
<tr>
<td>&gt;20 cigarettes per/day</td>
<td>0.096</td>
<td>0.561</td>
<td></td>
</tr>
</tbody>
</table>

*SD = unadjusted standard deviation of metacarpal index
† p for heterogeneity of the adjusted means of MCI

Table 11. Adjusted relative risks (RR) and its 95% confidence intervals (CI) of hip fracture by the metacarpal index (MCI). Adjusted by age, sex, body mass index, body height, education, smoking, alcohol intake, physical activity at leisure and self-reported general health (n = 3,561). Cox’s regression model. (IV)

<table>
<thead>
<tr>
<th>MCI decile</th>
<th>n*</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.44</td>
<td>42</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&lt;0.49</td>
<td>20</td>
<td>0.62</td>
<td>0.36-1.08</td>
</tr>
<tr>
<td>&lt;0.52</td>
<td>14</td>
<td>0.59</td>
<td>0.31-1.11</td>
</tr>
<tr>
<td>&lt;0.54</td>
<td>10</td>
<td>0.54</td>
<td>0.26-1.13</td>
</tr>
<tr>
<td>&lt;0.57</td>
<td>11</td>
<td>0.64</td>
<td>0.31-1.32</td>
</tr>
<tr>
<td>&lt;0.60</td>
<td>7</td>
<td>0.49</td>
<td>0.21-1.14</td>
</tr>
<tr>
<td>&lt;0.63</td>
<td>7</td>
<td>0.39</td>
<td>0.17-0.92</td>
</tr>
<tr>
<td>&lt;0.66</td>
<td>2</td>
<td>0.20</td>
<td>0.05-0.86</td>
</tr>
<tr>
<td>&lt;0.70</td>
<td>3</td>
<td>0.31</td>
<td>0.09-1.05</td>
</tr>
<tr>
<td>≥0.70</td>
<td>1</td>
<td>0.16</td>
<td>0.02-1.21</td>
</tr>
</tbody>
</table>

* n = number of subjects with hip fracture

5.10. Osteoarthritis and bone mineral mass (V)

After adjusting for age, sex, BMI, smoking, education, and workload, radiologically diagnosed non-symmetrical DIP OA, symmetrical DIP OA, and thumb carpometacarpal OA were associated with low MCI and low CCT (Table 12). Interestingly, the association was proportional to the severity of OA. Subjects with possible clinical knee OA had higher values of MCI and CCT than subjects with definitive knee OA or no knee OA (Table 12). There was a similar association between clinically diagnosed hip OA and CCT, but hip OA did not show a statistically significant association with MCI (Table 12). As a logical consequence, the metacarpal core thickness showed opposite associations with different OA types compared with the MCI and CCT.

In the longitudinal setting, female sex, high age, and low BMI at baseline significantly predicted low calcaneal BUA values at the follow-up examination (Table 13).
Figure 9. The values of the metacarpal cortical index (MCI) (grey) and subjects with hip fractures (black), according to age in Finnish women (n = 2,014) aged 30 years or over.

Figure 10. The values of the metacarpal cortical index (MCI) (grey) and subjects with hip fracture (black), according to age in Finnish men (n = 1,547) aged 30 years or over.
Table 12. Adjusted means of the metacarpal cortical index (MCI), thickness of the metacarpal core (CORE) and combined cortical thickness (CCT) by radiological OA of Kellgren grades 2 or 3-4 in DIP joints symmetrically and non-symmetrically (DIP OA), by radiological OA of Kellgren grades 2 or 3-4 in thumb carpometacarpal joint (CMC-1 OA) and by clinical possible or definite knee and hip OA. Adjusted for age, sex, body mass index, history of workload, smoking status, and educational level (n = 3,568). General linear model. (V)

<table>
<thead>
<tr>
<th>OA type</th>
<th>MCI</th>
<th>CORE</th>
<th>CCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIP OA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>0.58</td>
<td>3.87</td>
<td>5.20</td>
</tr>
<tr>
<td>Non-symmetric gr2</td>
<td>0.57</td>
<td>3.93</td>
<td>5.13</td>
</tr>
<tr>
<td>Non-symmetric gr3-4</td>
<td>0.56</td>
<td>3.99</td>
<td>4.99</td>
</tr>
<tr>
<td>Symmetric gr2</td>
<td>0.55</td>
<td>4.12</td>
<td>5.02</td>
</tr>
<tr>
<td>Symmetric gr3-4</td>
<td>0.54</td>
<td>4.10</td>
<td>4.80</td>
</tr>
<tr>
<td>p for heterogeneity</td>
<td>&lt;0.0001</td>
<td>0.0007</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>CMC-1 OA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>0.57</td>
<td>3.90</td>
<td>5.16</td>
</tr>
<tr>
<td>Kellgren gr2</td>
<td>0.56</td>
<td>4.03</td>
<td>5.12</td>
</tr>
<tr>
<td>Kellgren gr3-4</td>
<td>0.54</td>
<td>4.16</td>
<td>4.79</td>
</tr>
<tr>
<td>p for heterogeneity</td>
<td>&lt;0.0001</td>
<td>0.006</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Clinical knee OA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>0.57</td>
<td>3.92</td>
<td>5.14</td>
</tr>
<tr>
<td>Possible</td>
<td>0.59</td>
<td>3.78</td>
<td>5.28</td>
</tr>
<tr>
<td>Definite</td>
<td>0.56</td>
<td>4.02</td>
<td>5.03</td>
</tr>
<tr>
<td>p for heterogeneity</td>
<td>0.0004</td>
<td>0.0072</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>Clinical hip OA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>0.57</td>
<td>3.92</td>
<td>5.14</td>
</tr>
<tr>
<td>Possible</td>
<td>0.58</td>
<td>3.85</td>
<td>5.31</td>
</tr>
<tr>
<td>Definite</td>
<td>0.56</td>
<td>3.99</td>
<td>5.06</td>
</tr>
<tr>
<td>p for heterogeneity</td>
<td>0.16</td>
<td>0.52</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Workload, smoking, education, and leisure-time physical activity at baseline did not predict BUA at follow-up (data not shown). Symmetrical DIP OA at baseline significantly predicted low values of BUA 20 years later (Table 13). This finding remained significant even when adjusted for age, sex, BMI, smoking, and MCI at baseline. However, the proportion of the variance in BUA that could be explained by the symmetrical DIP OA was small ($r^2 = 0.02$). Similarly, one or more Heberden’s nodes in hands at baseline significantly predicted low values of BUA at follow-up (Table 13). Thumb carpometacarpal OA and non-symmetrical DIP OA, on the other hand, did not significantly predict BUA values at follow-up (data not shown). Clinically diagnosed hip or knee OA did not predict low BUA values at follow up, either (data not shown). In the longitudinal setting, when adjusted for age and sex only, low MCI significantly predicted low BUA values 20 years later ($r = 0.16$; $p = 0.0001$). According to the final model, including age, sex, BMI and smoking, however, the association was not statistically significant. There was an association between baseline
CCT and BUA at follow-up after adjustment for age and sex ($r = 0.11; p = 0.04$), but after further adjustment for BMI and smoking, the association was not statistically significant ($r = 0.10; p = 0.08$).

**Table 13.** Adjusted mean of broadband ultrasound attenuation (BUA) by baseline age, sex, body mass index (BMI), symmetrical DIP OA, and one or more Heberden’s nodes. Adjusted for age, sex, BMI, smoking, and the metacarpal cortical index ($n = 340$). General linear model. (V)

<table>
<thead>
<tr>
<th>Determinant</th>
<th>BUA</th>
<th>r*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.17</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.15</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.34</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>84.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>70.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symmetrical DIP OA</td>
<td>0.14</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>76.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>63.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heberden’s nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>76.2</td>
<td>0.12</td>
<td>0.03</td>
</tr>
<tr>
<td>YES</td>
<td>66.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$r = \text{partial correlation co-efficient}$

5.11. Bone mineral mass and spinal disorders (VI)

In the cross-sectional setting, a high MCI was statistically significantly associated with chronic neck syndrome and diffuse idiopathic skeletal hyperostosis (DISH), but there was no association between the MCI and chronic low-back syndrome. Adjusted odds ratios for chronic low-back and neck syndromes and DISH per increment of MCI by a standard deviation (0.1)* (n = 3,568). Logistic regression model. (VI)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-back syndrome</td>
<td>1.0</td>
<td>0.95-1.13</td>
</tr>
<tr>
<td>Neck syndrome</td>
<td>1.33</td>
<td>1.21-1.47</td>
</tr>
<tr>
<td>DISH</td>
<td>1.29</td>
<td>1.04-1.60</td>
</tr>
</tbody>
</table>

*adjusted for age, sex, body mass index, diabetes, smoking history, alcohol consumption, education, and history of physical workload
6. DISCUSSION

6.1. Study population

One of the strengths of this study was that we used the population of the Mini-Finland Health Survey, including a clinical examination that applied standardised diagnostic criteria in a subpopulation screened for positive musculoskeletal disorders (Aromaa et al. 1989). The Mini-Finland Health Survey is one of the biggest national health examination surveys in the world, and represents well the Finnish population over 30 years of age (Aromaa et al. 1989).

Hand x-rays were taken for practical reasons in a random subsample of the participants and in those who had screened positive for musculoskeletal diseases. It was not possible to take hand x-rays from all participants, because the resources of the Mobile Clinic were simultaneously needed for taking chest x-rays.

Moreover, only subjects with a possible musculoskeletal disease were included in the hand x-ray examination. The prevalence rates of OA may be slightly overestimated as a result of the use of the screening procedure. However, there were no significant differences between those who screened positive or negative in the prevalence of finger OA among subjects who belonged to the random subsample (n = 1,092). Therefore, it is thought that the use of screening procedure at baseline did not affect the risk factors of finger OA in the whole sample (n = 3,595). Only thumb carpometacarpal OA showed an association with screening positively, but this association is unlikely to affect the risk factors of thumb carpometacarpal OA, which were found in this study.

Further, the values of the MCI did not show difference between those who screened positive or negative of musculoskeletal disease among 1,092 subjects from random subsample. Therefore, the use of screening procedure did not confuse the results concerning the determinants of low MCI or its association with hip fractures.

Moreover, due to the screening procedure at baseline, it is possible that the proportional number of subjects with various risk determinants might be different compared to a representative population sample. However, the OA and OP assessed from hand radiographs for their prevalence, determinants and associations with morbidity and mortality at baseline and 15 years follow-up have never been investigated in a more representative population sample than that used in this study. Consequently, generalisations can certainly be made on the basis of our results.

6.2. Methods

6.2.1. Definition of risk determinants

Imprecision in the measurement of risk indicators tends to produce risk estimates closer to the null value. In the case of odds ratios and relative risks from logistic regression and Cox’s proportional hazards models it towards unity and in multivariate models, it can also bias an ad hoc estimate. In the baseline surveys of this study, training was given to the nurses and physicians and other quality assurance measures were taken to improve the quality of various measurements of risk determinants (Sievers et al. 1985, Aromaa et al. 1989, Heliövaara et al. 1993c). Most of the reliability estimates were good or at least satisfactory, including physical stress at work (Mäkelä et al. 1991), smoking (Korpilähde et al. 2004), self-reported general health (Martikainen et al. 1999, Heistaro et al. 1996) and even moderate levels of alcohol consumption (unpublished results of the Mini-Finland Health Survey,
Willet et al. 1987). Therefore, the risk estimates in the models including these determinants can be assumed to be rather accurate. Nevertheless, since most measurements carried some error, as in observational studies in general, some degree of caution is necessary in the interpretation of the results.

A general limitation in the study of risk determinants for hand OA was the cross-sectional design. Ideally, a risk factor should be defined in terms of incidence rather than prevalence. Even if determinants such as physical stress at work and history of smoking were assessed retrospectively, their temporal relation to the development of hand OA cannot be demonstrated. Thus, comparison bias remains possible.

One limitation of our study was that we do not know the specific names or amounts of the analgesic preparations, when examining how the use of analgesics affects the association between finger OA and cardiovascular mortality. However, it is possible to estimate these on the basis of sales statistics of analgesics. At the time of the baseline study the most sold plain NSAID preparations in Finland were acetylsalicylic acid, indometacin, ibuprofen, naproxen, and ketoprofen (Nordic Council on Medicines 1982). The use of paracetamol was low in Finland at the time of the baseline study (Nordic Council on Medicines 1982). Moreover, selective COX-2 inhibitors did not influence the results, because they were not on sale during the follow-up. On the basis of this information from the sales statistics of analgesics, it seems likely that most of the preparations used regularly for treatment of OA pain were traditional, prescribed or over the counter NSAIDs.

### 6.2.2. Clinical examination

Another limitation of our study was the clinical diagnosis of hip and knee OA, even though the radiological diagnosis is nowadays the golden standard in epidemiological research on OA. Furthermore, we did not use the criteria of the American College of Rheumatology, which are nowadays the most widely used criteria in clinical diagnosis of knee and hip OA (Altman 1991). These criteria did not exist at the time of our baseline survey. Therefore, we were forced to use our own criteria. They have been proved to be valid and reliable (Mäkelä et al. 1993, Heliövaara et al. 1993c, Sievers et al. 1985). However, agreement between clinical and radiological diagnoses of knee OA is shown to be only moderate (Toivanen et al. 2006). Therefore, it is possible that our results concerning the clinical knee OA could be different if the diagnosis of knee OA were radiological. However, the subjects identified by any diagnostic method as having OA in either knee reported significantly more symptoms and disability than the other subjects (Toivanen et al. 2006). It is, therefore, assumed that both clinical and radiological methods are valid enough to find persons with severe knee OA.

The variations among the examining physicians in the use of the diagnostic criteria, and the stability of the diagnosis of OA in knee and hip joints, low-back syndrome, and neck syndrome over time, were assessed about one year after the clinical phase. The results showed that the overall reliability of the diagnostic decisions was adequate (Heliövaara et al. 1993c).

Even though the clinical diagnosis of hand OA was not the main focus of this study, radiological OA in both any finger joint and thumb carpometacarpal OA had clear associations with clinical findings, such as movement restraint and tenderness, swelling, and palpation tenderness. Further, Heberden’s node associated strongly with symmetrical DIP OA. Thus, if radiology is not available, these clinical findings strongly suggest the presence of hand OA.
6.2.3. Radiological methods to assess osteoarthritis and osteoporosis

Radiology is useful in epidemiological studies, especially in the biological determinants of OA because it objectively reflects cartilage degradation, especially when trying to test for systemic influences. However, defining hand OA still leads to problems (Hart et al. 1994) because there is no absolute clinical, radiological or pathological standard with which the occurrence of hand OA can be compared (Spector and Cooper 1993). The Kellgren-Lawrence radiological grading system (Kellgren and Lawrence 1952) has mostly been used, even though it has a number of problems (Hart and Spector 2000). The main difficulties include inconsistencies in the interpretation of the grading system, and the prominence given to the osteophytes at all joint sites (Hart and Spector 2000). Despite the difficulties, we used the Kellgren-Lawrence system so that our results are readily comparable with those of other studies.

We used metacarpal cortical measurements to estimate OP and bone mineral mass at baseline. Recent evidence shows that the MCI measured from hand radiographs might be successfully used for assessing bone mineral mass and quality (Nielsen, 2000, Hyldstrup and Nielsen 2001). The reference values of the MCI have also been determined in previous studies (Black et al. 2001, Hyldstrup and Nielsen 2001), and also the values of the MCI founded in this study were consistent with these.

It is well-known that bone mineral density measured by DXA is proportional to bone size and body surface area (Nielsen 2000, Hyldstrup and Nielsen 2001). This is a simple consequence of the fact that tall people have big bones, and big bones have high bone mineral mass (Nielsen 2000). MCI eliminates this by dividing the combined cortical thickness with the outer bone diameter. Therefore, the MCI is less affected by bone size than DXA (Nielsen 2000, Hyldstrup and Nielsen 2001). Moreover, the MCI is devoid of problems associated with differences in calibration and measurement scales between instruments. Therefore, we assume that the MCI was a suitable measurement of cortical bone mineral mass for this study.

Moreover, since MCI measures the cortical width it is assumed to indicate the changes in the subchondral bone, which has been proved to be an important structure in the etiopathogenesis of OA (Radin et al. 1972, Dequeker et al. 1995, Arokoski et al. 2000, Buckland-Wright 2004). Therefore, the MCI can be used as an estimation of bone mass, when examining the association between OA and OP.

6.2.4. Calcaneal ultrasound measurement

Calcaneal ultrasound measurement and its output variable BUA have been found to be a good estimate of bone mineral mass and fracture risk (Frost et al. 2001, Khaw et al. 2004, Huopio et al. 2004). These results are also supported by the results of the present study, where BUA correlated with BMD values measured by DXA and peripheral DXA. Therefore, it is evident that the calcaneal BUA values are associated with both OP and total bone mineral mass.

Among the roughly one thousand subjects who were re-examined in the Health 2000 survey, there may be some selection bias, because there is evidence that the most severely disabled subjects could not participate in the health examination. It is well known that OA in weight-bearing joints often causes disability and therefore some osteoarthritic persons may have been excluded from the calcaneum ultrasound measurements.
6.2.5. Linkages to registers and follow-up

Current ethical principles were followed in the data collection in 1978-80. However, at that time there were no official ethics review committees. Instead, the steering committee of the project also assessed its ethical aspects. All record linkages are based on permissions from the authorities (the National Board of Health and its successor Stakes, the Ministry of Social Affairs and Health and the Social Insurance Institution of Finland). The study precedes current legislation on medical research. Thus, participants were fully informed about the study, they participated in it on a voluntary basis, and the use of the information for medical research was explained to them. However, there was no written informed consent, which is a later development. Finnish legislation has accepted the principle that in research preceding the current legislation, participants have given their implicit permission to using the data for research by participating voluntarily in the study.

The Finnish National Hospital Discharge Register operating since 1967 contains information on admissions to and discharges from every hospital in the country. This information includes, along with a personal identification code, the primary and secondary diagnoses according to the International Classification of Diseases. By means of these data we were able to identify those study subjects who had been hospitalised for hip fracture, myocardial infarction or stroke since the baseline examination.

Because hip fracture is severely incapacitating and painful, practically all patients with this condition are likely to be admitted to hospital for acute care. In severe injuries leading to hospitalisation, 92% to 97% of the diagnoses have been correctly registered at the three-digit level in the National Hospital Discharge Register, as compared with those in the original hospital documents (Honkanen 1990, Luthje et al. 1995). In view of the above, we feel justified in making generalisations from our results when estimating the hip fracture risk by the metacarpal index.

In myocardial infarctions leading to hospitalisation, 84.7% of the diagnoses have been correctly registered at the three-digit level in the National Hospital Discharge Register, as compared with those in the original hospital documents (Heliövaara et al. 1984). Therefore, hospital discharge information is sufficiently valid to study predictors of myocardial infarction.

In national pension registers maintained by the Social Insurance Institution, the main diagnosis and the two following diagnoses are registered. In general, only the first diagnosis is used in disability statistics. Furthermore, assessing work disability is problematic because disability usually results from many disorders, and many non-medical factors also contribute. Therefore, in work disability due to musculoskeletal diseases such as hand OA, the type of work and non-medical factors may have more impact on the pension decision than they do for other diseases.

Since only a minority of the initial sample (n = 340) was re-examined in BUA measurements at follow-up, selection bias is possible. However, neither MCI, CMC-1 OA, non-symmetrical DIP OA nor baseline screening for musculoskeletal conditions suggested any association with subsequent participation in the re-examination survey. Unexpectedly, symmetrical DIP OA significantly predicted decreased likelihood of re-examination. If symmetrical DIP OA were to predict an increased likelihood of re-examination, its association with low BUA 20 years later could be explained by selection. Since the reverse proved true in the current study, the question of influences of selection remains unanswered. In general, however, our results suggesting an increased risk of OP in the presence of
symmetrical DIP OA are not likely to have resulted from systematic selection.

The follow-up time in our study extended beyond 15 years when examining the associations between hand OA and mortality and morbidity, and the association between the metacarpal cortical index and hip fractures. The follow-up time was even longer when examining the associations between hand OA and MCI at baseline and calcaneal broadband ultrasound measurements, extending beyond 20 years, so this leads to some speculation of causality.

6.3. Main findings

6.3.1. Associations of age and gender with prevalence of hand osteoarthritis

In the present study, the prevalence of all types of hand OA was clearly higher in women compared with men in all age groups. In particular, symmetric DIP OA was more common in women than in men, suggesting an effect of genetic background. Moreover, there was a clear increase in the prevalence of all types of hand OA in both sexes after the age of 45. Overall, our results on the prevalence of hand OA are consistent with previous studies (Mikkelsen and Duff 1970, Allander 1974, Kärkkäinen 1985, van Saase et al. 1989, Busby et al. 1991, Cauley et al. 1993, Felson 2003). One possible explanation for the increase in the prevalence of hand OA after middle age could be that, after this age, the amounts of endogenous sex hormones begin to decrease (Spector and Campion 1989, Cooley et al. 2003). As the level of these hormones diminishes in the body, the balance between degenerative and regenerative factors in cartilage and other joint structures is assumed to disturb, and this may accelerate the progression of OA.

6.3.2. Body mass index, physical workload and smoking as risk factors for hand osteoarthritis

One of the main results of this study was a linear association between BMI and different types of hand OA. Obesity has been amply studied as an eventual risk factor for a multitude of musculoskeletal complaints and disorders (Vissher et al. 2003). It has proved a strong risk factor for OA, especially in lower limbs (van Saase et al. 1988, Felson et al. 1988, Heliövaara et al. 1993a, Felson et al. 1997, Manninen et al. 1996). The association has been found to be stronger in women than in men (Hartz et al. 1986, Schouten et al. 1992a, Felson et al. 1997), and has been assumed to be mediated through mechanical factors. However, it seems likely that mechanical factors alone do not explain the association, as obesity has shown a positive association even with hand OA in several earlier studies (Bagge et al. 1991, van Saase et al. 1988, Hart and Spector 1993b, Carman et al. 1994, Cicuttini et al. 1996, Sowers et al. 1996, Felson and Chaisson 1997, Sayer et al. 2003), although not all (Davis et al. 1990, Hochberg et al. 1991, Hochberg et al. 1993).

Basically, two different mechanisms have been proposed to explain these findings (Felson 1992). According to the mechanical theory, obesity causes osteoarthritis by increasing the load and impact on the joint, which, in turn, promotes degeneration of the cartilage. On the other hand, hormones and other biological factors, such as cartilage growth factor or a bone factor related to obesity, may damage joint structures in a similar fashion (Felson 1992). Insulin-like growth factor and sex hormones might exert a favourable effect on the metabolism of the articular cartilage (Denko et al. 1990, Lloyd et al. 1996, Spector et al. 1997b, Felson and Nevitt 1998). Nevertheless, contrasting results have also been reported (Cauley et al. 1993,
Moreover, it is well known that obesity is an important risk factor of vascular disease, and it is hypothesized that vascular disease in subchondral bone may accelerate the OA process (Conaghan et al. 2005). Furthermore, some preliminary studies have suggested that high levels of serum lipids can accelerate the degradation of articular cartilage (Lippiello et al. 1991 (Philbin et al. 1996, Cheras et al. 1997). Therefore, it seems possible that the association between obesity and OA is mediated by decreased nutrition of the articular cartilage because of atherosclerotic cardiovascular disease.

The present study also found an association between BMI and OA in any finger joint, symmetrical DIP OA, and thumb carpometacarpal OA, supporting the view that overweight is also a systemic risk factor for OA. BMI showed a weaker association with advanced thumb carpometacarpal OA of grade >3 as compared with thumb carpometacarpal OA of grade >2. Thus, obesity might cause thumb carpometacarpal OA through biological mechanisms, whereas mechanical factors would probably be required to initiate more advanced forms of thumb carpometacarpal osteoarthritis.

Previously, rest and inactivity seemed to be the prevailing treatment strategy until it was recognized that this approach was ineffective and contributed further to the patient’s disability and loss of function (Clyman 2001). In addition, it is suggested that the obese who were overweight could have gained weight after developing OA, because of their joint pain and low level of activity. It is also well established that obesity and low physical activity are linked together, and low physical activity is also a risk factor for OA (Clyman 2001). Low physical activity also decreases the muscle strength, which causes the increased instability of the joint (Cicuttini et al. 2005). Therefore, exercise and weight reduction are important for prevention and treatment of OA (Messier et al. 2004, van Gool et al. 2005). Losing weight decreased both the effect on mechanical loading and the effect on the disadvantageous metabolic factors, which are related to obesity, thus decreasing cartilage degeneration.

An interesting possible link between obesity and OA is the inflammatory process reflected by increased CRP levels. An increased CRP level has been found in women with early knee OA, while higher CRP levels predicted progress of disease over 4 years (Spector et al. 1997a). On the other hand, CRP is strongly related to total and central abdominal obesity, blood pressure, and lipid levels, independent of genetic influences (Greenfield et al. 2004). Increased inflammation related to obesity may also be involved in the progression of OA.

No previous studies have focused on the difference between the genders in the effect of physical load as a risk factor of hand OA. In our study, physical workload was associated with the risk of OA in any finger joint in women, but not in men. In symmetrical DIP OA, physical workload also showed an association, but the low number of cases makes it impossible to draw reliable conclusions. One possible explanation for the difference between genders is that women may have inherently more vulnerable joint cartilage than men. Furthermore, the joint structures apparently are weaker and more susceptible to joint wear and tear in women than in men.

Mechanical stress is considered to be a risk factor particularly of thumb carpometacarpal OA, although there is no direct evidence of this (Staxler et al. 1994, Hart and Spector, 2000). However, in the present study, the risk of thumb carpometacarpal OA was not associated with physical workload in either sex. Similarly, no association was found between thumb carpometacarpal OA and occupation or past physical activity in one previous clinical study (Jones et al. 2002).
Thus, mechanical stress apparently contributes to the development of osteoarthritis in most joints, but not necessarily in thumb carpometacarpal OA. Interestingly, there was also another sex difference in the determinants of hand OA in the present study. Smoking was associated with decreased risk of symmetrical DIP OA in men, but not in women. However, the low number of women smokers limits the reliability of conclusions here. As in symmetrical DIP OA, the associations between smoking and thumb carpometacarpal OA showed significantly different patterns in men and women. In a previous study, no clear protective effect of smoking on hand and knee OA in women was found (Hart and Spector 1993a), but another study reported lower rates of radiological knee OA in male smokers compared with non-smokers (Felson et al. 1989). A recent study also found that smoking did not protect against the development of radiologically-confirmed OA in the knee, hand, foot and cervical spine (Wilder et al. 2003). Despite the result that smoking can be protective from OA in men, smoking cannot be recommended as a means of prevention of OA.

6.3.3. Hand osteoarthritis and coexisting diseases

No clear associations could be observed in this study between hand OA and OA in weight-bearing joints. One possible explanation for this is that hand OA may be a separate disease entity rather than one form of generalised OA (GOA). On the other hand, the weak associations between hand OA and GOA in our study may be explained by the rarity of GOA. Furthermore, the diagnosis of knee and hip OA in our study was only clinical. Thus, our attempt to establish systemic OA (systematically influenced cartilage degradation) may also have been hampered by the absence of radiological data on knee and hip joints. Previous reports suggest strong associations between hand OA and OA in weight-bearing joints. In the Study of Osteoporotic Fractures, an association between radiological hand and both unilateral and bilateral hip OA in older women was found (Hochberg et al. 1995). In the Baltimore Longitudinal Study of Aging, associations were found between radiological OA in DIP, PIP and CMC-joints and the knee in men and women. The strength of the associations increased with increasing disease severity. Particularly, for the PIP site, there was a trend toward an increasing strength of association for increasing numbers of affected joints and bilateral knee OA (Hirsch et al. 1996). Studies concerning the association between hand OA and OA in weight-bearing joints have usually concerned elderly subjects. However, there was an association between radiological dominant hand OA and OA in the knee joints among Michigan black and white pre- and perimenopausal women aged under 45 (Sowers et al. 2000). In a recent Swedish retrospective study among 170 male and female patients who had undergone isolated meniscectomy an average of 20 years earlier, it was found that the presence of radiographic hand OA at baseline was associated with an increased frequency of radiographic knee OA after meniscectomy at follow-up (Englund et al. 2004).

On the basis of previous studies, it is suggested that hand OA and particularly symmetric DIP joint OA are strongly related to GOA (Cicuttini et al. 1998, Cooper et al. 1996, Hirsch et al. 1996). Two previous large genetic epidemiological studies have shown that GOA has a strong genetic background (Felson et al. 1998, Hirsch et al. 1998). Therefore, it may be that symmetrical OA in the presence of Heberden’s nodes (nodal OA) in women represents a more restricted definition of systemic OA. In line with this assumption,
we found an association between Heberden’s nodes and symmetrical DIP OA. Therefore, some nodal OA patients definitely have a tendency to develop a familial form of systemic OA.

There were no associations between hand OA and other musculoskeletal disorders, such as chronic low-back or neck syndromes, in this study. However, there is previous evidence of an association between both hand OA (Bijkerk et al. 1999), and knee and hip OA (Hassett et al. 2003), and progression of lumbar spine disc degeneration.

Moreover, none of the hand OA types showed associations between diabetes and cardiovascular diseases at cross-sectional setting. Similar negative associations have also been reported in other studies (Bagge et al. 1991, Caspi et al. 2001). Taken together, these results indicate that the aetiology of hand OA is not associated with that of cardiovascular diseases or diabetes.

6.3.4. Hand osteoarthritis as a cause of disability

An important finding of our study was that, even though the hand is a common site of peripheral OA, this rarely causes disability, whether assessed cross-sectionally or in a longitudinal design. These results disagree with those reported by others (Hirsch et al. 1999, Jones et al. 2001, Bellamy et al. 2002, Zhang et al. 2002), who claimed that pain and disability caused by hand OA affect grip and pinch strength particularly in older people. These discrepancies may be due to differences among study populations. We studied subjects from a national population sample aged 30 years or over, whereas the other studies were based on subjects selected from clinical sources or from elderly age groups. Work disability due to hand OA is likely in jobs with physically high demands on the hands, but such an association can probably not be detected in study populations involving a large variety of different physical demands at work. Particularly severe forms of thumb carpometacarpal OA are associated with disability (Staxler et al. 1994, Damen et al. 1996), and CMC OA frequently needs an operation to relieve pain (Damen et al. 1996, Poole et al. 2000). However, a recent clinical comparative study found no differences in disability between CMC OA and DIP joint OA (Spacek et al. 2004).

This study demonstrates that hand OA has only a minor effect on disability pensions at population level. Moreover, despite the pain and disability which hand OA causes in the individual, patients with hand OA seem to cope well with ordinary daily activities, and hand OA does not seem, on average, to greatly affect the quality of life of persons with the disease. In this study, hand OA was defined as a radiological entity. We cannot exclude the possibility that clinically diagnosed and symptomatic hand OA might show closer associations with disability, and this could explain the difference between this study and the previous studies based on series of patients.

6.3.5. Hand osteoarthritis and related mortality

There was a positive association between symmetrical DIP OA and mortality in women, but not in men. OA in any finger joint showed no association with mortality in either sex. Similar results have also been reported by one previous study (Cerhan et al. 1995), in which an increasing number of OA-affected joints predicted decreased survival in women. The different mortality patterns between men and women in symmetrical DIP OA may reflect a difference between the sexes in the genetic background of hand OA. This result also supports the finding that particularly symmetrical DIP OA is a woman’s disease (Cicuttini et al. 1998). On the other hand, the association between mortality and thumb carpometacarpal OA was rather
weak in our study. Only advanced thumb carpometacarpal OA predicted mortality in men. One explanation for the different mortality patterns between thumb carpometacarpal OA and hand OA at other sites may be the aetiological differences between these forms of hand OA.

An interesting result concerning the association between mortality and hand OA in this study was that OA in any finger joint significantly predicted cardiovascular death (myocardial infarction or stroke) in men (I). Such an association has not previously been reported. The association remained after further adjustment for smoking, physical activity, socioeconomic status, serum lipid profile and blood pressure (Haara et al. 2003). However, when examining subjects who were free of cardiovascular diseases at baseline, there were no relations between hand OA and a new myocardial infarction during follow-up. Nor were there any associations between hand OA and blood pressure, serum cholesterol level, or diabetes. Therefore, some mechanism other than a direct link between hand OA and cardiovascular disease probably mediates the association between hand OA and cardiovascular mortality.

A possible explanatory mechanism for this association could be the regular use of analgesics for OA pain. The regular use of traditional analgesics predicted major coronary event in this study (III). Since almost all analgesics used in Finland at the end of the 1970s were non-steroidal anti-inflammatory drugs (NSAIDs) (Nordic Council on Medicines 1982) the increased risk of major coronary events among regular users of analgesics is likely to be due to traditional NSAIDs. Our results support recent observations (Hippisley-Cox and Coupland 2005, Johnsen et al. 2005, Chan et al. 2006) suggesting that the risk of major coronary events associated with regular use of NSAIDs is not confined to the use of selective COX-2 inhibitors, but also involves traditional analgesics. However, the regular use of analgesics predicted major coronary events predominantly during the first two years after the baseline examination. The risk of these events is therefore likely to be reversible.

In a recent prospective cohort of 70,971 women, it was found that the risk of major cardiovascular events was associated with the use of NSAIDs or acetaminophen at high frequency or dose, particularly among current smokers (Chan et al. 2006). There was no increased risk with less than daily use of NSAIDs or acetaminophen (Chan et al. 2006). These results demonstrated that regular use of high doses of analgesics constitute a risk, particularly for patients with known risk factors for coronary heart disease, such as smoking. However, the regular use of analgesics at baseline explained only a minor part of the association between finger OA and cardiovascular mortality in this study. Otherwise, the mechanism remains unclear.

Earlier data suggest that hypertension, hypercholesterolemia and raised blood glucose are associated with both unilateral and bilateral knee OA, independent of obesity (Hart et al. 1995, Felson and Chaisson 1997). Results from the Ulm Osteoarthritis Study add to the evidence regarding the independent role of serum cholesterol as a systemic risk factor for OA (Stürmer et al. 1998). It was found that hypercholesterolemia and high serum cholesterol levels were independently associated with GOA. Patients with non-insulin-dependent diabetes mellitus also more often had bilateral knee or hip OA than controls (Stürmer et al. 2001). In addition, some studies have suggested that high levels of serum lipids can accelerate the degradation of articular cartilage (Lippiello et al. 1991, Philbin et al. 1996, Cheras et al. 1997). Thus, CVD and OA may have joint risk factors other than body mass index, but further studies are needed to confirm the association between OA and
Hormonal factors could be an explanation for differences between the genders concerning the associations between hand OA and cardiovascular deaths. One study argues that a fall in male testosterone levels coincides with an increasing risk of heart disease (Channer and Jones 2003). The authors concluded that men with heart disease are twice as likely to have reduced testosterone levels than other men. Testosterone is a metabolic hormone and its effect on articular cartilage can be favourable. Therefore, the decrease in testosterone levels in the male menopause might increase the progression of OA.

Altogether, it seems possible that the risk factor profile associated with CVD may also apply to OA. Even though the association between OA and increased risk of death from CVD is not thoroughly understood, this study underlines the importance of a healthy lifestyle. Avoiding becoming overweight by exercising and eating low-fat food may decrease the risk of both OA and CVD.

6.3.6. Cortical bone mineral mass and its determinants and hip fracture risk

In this study, OP was assessed using the MCI as a proxy. There were associations between low MCI and high age, low BMI, high stature and smoking. These results are consistent with previous reports on determinants of OP and bone mineral mass, even when the assessment methods of OP and bone mineral mass have been different (Kröger et al. 1994, Cummings et al. 1995, Kanis et al. 1997, Kanis 2002). Since the MCI is associated with several risk factors of OP, it can also be expected to be associated with OP. Even if the MCI less connected with bone size than DXA, low MCI was associated with high stature in this study. However, this association is maybe connected with the association between low MCI and low BMI, because increasing stature decrease the BMI.

There was a clear decrease in MCI values in women of menopausal age in this study, but such a decrease was not observed in men. Furthermore, in women, all hip fractures but one in this study occurred in subjects after the age of 55. The reduction in cortical bone mass with age and time since menopause in women results from both progressive intracortical porosity and reduction in cortical thickness (Iwamoto et al. 2004). It has also been shown that age-related cortical bone loss is generally more dependent on cortical thinning in women than in men (Maggio et al. 1997). A recent study found that increased bone loss after menopause in women is associated with increased periosteal apposition, which partially preserves bone strength (Ahlborg et al. 2003). However, endocortical resorption is greater in women than in men, but men lose less cortical width, because periosteal apposition during aging is greater in men than in women compensating for endocortical resorption (Seeman 1999). In women, bone loss occurs when a greater volume of bone is removed than is replaced in cortical layers of bone, because oestrogen deficiency inhibits the periosteal apposition (Seeman 2003). Since the MCI measures the width of cortical bone it is subject to changes resulting from bone resorption and remodelling, which either decreased or increased cortical bone mineral mass.

A low MCI strongly predicted hip fractures in men and women during 15 years of follow-up. Similar results have been previously reported (Cooper et al. 1991, Wishart et al. 1993). A clear association was recently shown between low bone mineral density measured by digital X-ray radiogrammetry and hip fractures (Bouxsein et al. 2002). This technique uses automated image analysis of standard hand radiographs to estimate bone mineral density (Bouxsein et al. 2002).

The intracortical porosity has high
importance for mechanical strength of cortical bone (Seeman 1999). In femoral neck biopsies of the person with hip fracture, the cortical bone porosity was greatest in the anterior cortex, being 41% higher in that quadrant than in controls from cadaveric samples (Bell et al. 1999). Moreover, one study examined the bone specimens by peripheral QCT from women with intracapsular hip fracture compared to post-mortem specimens from healthy bone (Crabtree et al. 2001). It was found that the mean cortical width among women with hip fracture was significantly lower in the inferoanterior and in the inferior cortex of the hip (Crabtree et al. 2001). The authors suggest that a key feature in the aetiology of intracapsular hip fracture is the site-specific loss of cortical bone, which is concentrated in the regions maximally loaded during a fall on the greater trochanter. Further, in a recent methodologically similar study, the authors suggest that increasing in hip fragility is due to underloading of the superolateral cortex, which leads to atrophic thinning in ageing women (Mayhew et al. 2005). It is also suggested that the fragile zones in healthy bones may need strengthening, for example with more well-targeted exercise (Mayhew et al. 2005). Even though the proportional contribution of cortical bone mineral mass for bone strength is not clear (Seeman 2003), the association between low baseline MCI and hip fracture during follow-up suggests that high cortical bone mass is important in preserving bone strength and in decreasing a fracture risk.

This study shows that the MCI is a potent predictor of hip fractures, but based on this study only, no limit can be set for the MCI regarding the need for further evaluation in the clinical context. Further, the risk of fracture is increased when the MCI is low, but the risk of fracture is not negligible even when the MCI is normal. Together with the MCI, other possible risk factors of fracture should also be taken into account in estimating the fracture risk. Moreover, in a recent large follow-up study from the Rotterdam population (n = 7,806), only 44% of all non-vertebral fractures occurred in women with a T-score below -2.5, while in men this percentage was even lower (21%) (Schuit et al. 2004). Thus, there is a clear need for the development of more sensitive risk assessment tools, using not only BMD, but also other clinical predictors of fractures. Many other factors, such as female gender, low BMI, smoking, high stature, previous fracture history, high alcohol consumption, and family history of fractures, influence the risk of osteoporotic hip fracture apart from BMD (Cummings and Melton 2002, Kanis 2002, Huopio et al. 2005).

However, since the hand X-ray is cheap and easy to take, measuring the MCI adds valuable information in clinical practice, together with other determinants of osteoporotic fracture. Therefore, the MCI might be usefully applied at low cost both in epidemiological research and in primary care to find patients who should undergo further assessment for diagnosis, risk of fracture, and need of care. To carry out such a screening, further studies are needed to determine appropriate cut-off points.

### 6.3.7. Association between osteoarthritis and bone mineral mass

Some previous studies have reported an inverse association between OA in weight-bearing joints and bone mineral mass (Arden et al. 1999, Antoniades et al. 2000, Hart et al. 2002, Hochberg et al. 2004). These results may be influenced by the fact that different grades of OA were not used. We found that subjects with possible clinically diagnosed knee OA had significantly higher values of both MCI and CCT than subjects with definite knee OA. A similar trend was also seen between clinically diagnosed hip OA and the metacarpal measurements, although this
association was not statistically significant. These results suggest that increased cortical bone formation is an important factor in the early stages of OA development, but that in the later phase with OA progression, cortical bone resorption also increases. In line with these findings, Bruno and colleagues (Bruno et al. 1999) noticed that hips with Kellgren-Lawrence scores of 1 or 2 had increased BMD throughout the proximal femur, but as the disease progressed, BMD declined. It has also been postulated that women with radiological knee osteophytes have higher femoral BMD than those with no osteophytes (Hannan et al. 1993), but that joint-space narrowing has less influence on BMD. Therefore, the assumed inverse association between moderate OA in weight-bearing joints and high bone mineral mass exists because of mechanical factors, which cause osteophyte formation in the joint. When OA progresses towards joint-space narrowing in severe OA, disability and pain will cause low physical activity, which leads to secondary osteoporosis.

In the present study, there was a direct cross-sectional relation between both radiological DIP OA and CMC-1 OA and low cortical bone mineral mass, in proportion to the severity of OA. Therefore, hand osteophytosis seems to have a less specific association with BMD than OA in weight-bearing joints, and it may be that genetic factors predominate in hand OA compared with local mechanical factors in knee and hip OA (Sambrook and Naganathan 1997). Mechanical loading may not be as important a risk factor in hand OA as in knee and hip OA. We also studied hand OA and bone loss over time and found that symmetrical DIP OA diagnosed from hand radiographs at baseline predicted lower values of calcaneum broadband ultrasound attenuation 20 years later. This result suggests that persons with radiographic OA in the hands symmetrically lose bone at different rates than those with normal radiographs. A similar result has been previously reported by Hochberg and colleagues (2004), who found that women with radiographic OA of the hand had a significantly greater adjusted rate of bone loss at the radius than women with normal hand radiographs.

There were no associations between baseline clinically assessed knee or hip OA or radiological OA in any finger joint and low calcaneal BUA values at follow up. This indicates that only symmetrical hand OA has an association with osteoporosis. This is an interesting result, because it has previously been suggested that genetic factors are of significance in the aetiology of symmetric hand OA (Spector et al. 1996, Spector and MacGregor 2004) and that symmetric hand OA is more likely to reflect generalised OA than OA at only one joint site (Hirsch et al. 1996). Over 50 years ago, Kellgren and Lawrence (1952) postulated that Heberden’s nodes in hand joints are associated with generalised OA, but since then it has been claimed that radiological DIP osteophytes are a better marker of knee and multiple joint OA than Heberden’s nodes (Cicuttini et al. 1998). Also in this study, there was a strong association between symmetrical DIP OA and Heberden’s nodes. Moreover, Heberden’s nodes at baseline also predicted lower values of calcaneum broadband ultrasound attenuation 20 years later. We suggest that, since symmetrical DIP joint OA is associated with genetically determined generalised OA, persons with generalised OA seems to lose bone more rapidly than those with no osteoarthritis changes in several joints.

The clinical diagnosis of knee and hip OA compared to the radiological diagnosis of hand OA may confuse the results concerning the different associations between OP and OA at various joint sites in this study. However, the results of this study were comparable with some previous
studies, even though radiology was used in diagnosing both hand OA and OA in weight-bearing joints in the previous studies (Hannan et al. 1993, Bruno et al. 1999). Moreover, the clinical diagnoses of knee and hip OA were not dependent on the radiological diagnosis of hand OA, which can be considered a strength rather than a weakness of the study setting.

6.3.8. Association of cortical bone mineral mass with spinal disorders

There was a cross-sectional association between a high MCI and DISH in this study. Similar results have also been reported previously. Persons with DISH have been shown to have a higher bone mineral density than controls (Di Franco et al. 2000, Sahin et al. 2002), but the mechanism remains partially unknown. However, it has been proposed that increased BMD probably results in hyperostosis of the axial skeleton. On the other hand, DISH is an ossifying systemic enthesopathy which may also be involved in other sites in addition to the spine (Di Franco et al. 2000). Degenerative, inflammatory, and metabolic factors have been reported as having a possible pathogenic role in the new bone growth that characterises DISH (Kiss et al. 2002). Compared with controls, patients with DISH had a higher BMI and an increased risk of diabetes (Kiss et al. 2002). Therefore, both a high BMI and the new bone growth in DISH patients can explain the positive association between bone mineral mass and DISH.

Cortical bone mineral mass estimated by the MCI showed a cross-sectional association with chronic neck syndrome. This result has not been previously reported. Contrary to a recent study that found an association between increasing bone mineral density and low-back pain in middle-aged women (Manabe et al. 2003), there was no association between cortical bone mineral mass and chronic low-back syndrome in the present study. The result suggests the cortical bone mineral mass as a possible etiological factor for chronic neck syndrome, but the absence of a longitudinal association does not confirm the causality. Chronic neck syndrome is common among persons with a heavy workload (Mäkelä et al. 1991, Croft et al. 2001), and a heavy workload increases the bone mineral mass. Therefore, it is possible that other factors, such as the residual confounding effect of heavy manual labour, could explain the association between high cortical bone mineral mass and chronic neck syndrome even after adjustment for the history of physical workload. Even though the mechanism through which high cortical bone mineral mass is associated with chronic neck syndrome is unclear, our results suggest a different association of bone mineral mass with chronic neck vs. low-back syndromes.
Hand OA is prevalent particular in women, and many joints are usually affected. Both radiological OA in any finger joint and thumb carpometacarpal OA have strong associations with clinical findings such as movement restraint and tenderness, swelling, and palpation tenderness. Heberden’s nodes are typical of symmetrical DIP OA.

Obesity is also a strong risk determinant of OA in any finger joint and its subcategory, symmetrical DIP OA, and thumb carpometacarpal OA in both sexes. This indicates that overweight also exerts a systemic influence on the risk of OA. Weight control is, therefore, highly important in the prevention of OA.

A history of high physical workload is a risk factor of OA in any finger joint in women, but not in men. Smoking in men carries protection against symmetrical DIP OA, but not in women. Therefore, the risk factor profiles are different for OA in any finger joint and for symmetrical DIP OA, which suggests that these forms of hand OA probably represent separate disease entities.

Even though hand OA is prevalent, its impact on disability in the general population is modest. Due to the rarity of ensuing disability, hand OA is likely to be under-diagnosed in clinical practice.

Symmetrical DIP OA predicted total mortality in women, but not in men. The different mortality patterns between men and women in symmetrical DIP OA may reflect a difference between the sexes in the genetic background of hand OA.

OA in any finger joint predicted cardiovascular deaths in men. This was hypothesized as resulting from the regular use of analgesics, but such an effect was not observed, and the hypothesis was rejected. Nevertheless, the risk of a new major coronary event was elevated in both sexes among those who had used analgesics regularly at baseline. Therefore, doctors should be aware of the coronary risks involved in the regular use of analgesics, especially when treating patients who have other risk factors for coronary heart disease.

A low metacarpal index shows significant associations with known risk factors of osteoporosis, such as high age, female gender, high stature, and low BMI, and predicts hip fracture at follow-up. Measurement of the MCI might be usefully applied as a low cost method in both epidemiological research and in primary care to identify subjects who should undergo further assessment for diagnosis, risk of fracture, and need of care. To carry out such a screening, further studies are needed to determine appropriate cut-off points.

There are cross-sectional associations between low cortical bone mineral mass and radiological DIP OA and CMC-1 OA in proportion to the severity of OA. Furthermore, symmetrical DIP OA predicts low bone mineral mass estimated by BUA 20 years later. Patients with symmetrical DIP OA might thus be considered candidates for evaluation of a risk of osteoporosis and fracture.

Peripheral cortical bone mineral mass is directly proportional to the prevalence of chronic neck syndrome and DISH. This suggests a joint metabolic factor, which needs to be identified and studied further for its effects on bones and intervertebral discs.
8. CLINICAL IMPLICATIONS

Even though potent risk factors for hand OA were found in this dissertation, the aetiology of hand OA remains unclear. However, doctors have already been advised to tell their patients that weight control and avoidance of obesity is crucial in the prevention of OA. This dissertation extends the instruction from hip and knee OA to hand OA.

Further, the results of this dissertation suggest that when taking hand radiographs from postmenopausal women, it is worth remembering to measure the metacarpal cortical index from the second metacarpal bone. If the value is under 0.5, and the patient has other risk factors for OP, the fracture risk should be evaluated further.

Furthermore, based on the result on this dissertation, doctors should be aware the coronary risks of the regular use of analgesics, especially when the treatment period is long or the dose is high.

Finally, this dissertation shows that all forms of hand OA are quite benign. The good news that a doctor should tell a patient suffering from hand OA is that the disease is unlikely to result in severe disability.
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