EPIDEMIOLOGY OF OSTEOPOROSIS AND PREDICTION OF FRACTURES

A 9-year population based follow-up study

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EPIDEMIOLOGIE VAN OSTEOPOROSE EN PREDIKTIE VAN FRAKTUREN

Een 9-jarig vervolg onderzoek in de algemene bevolking

PROEFSCHRIFT

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Promotoren : Prof. Dr. J.P. Vandenbroucke
Prof. Dr. H.A. Valkenburg

Overige leden: Prof. Dr. J.C. Birkenhäger
Prof. K. Hoornstra

In a word, then, every effect is a distinct event from its cause. It could not, therefore, be discovered in the cause, and the first invention or conception of it, **a priori**, must be entirely arbitrary. And even after it is suggested, the conjunction of it with the cause must appear equally arbitrary: since there are always many other effects, which to reason, must seem fully as consistent and natural. In vain, therefore should we pretend to determine any single event, or infer any cause or effect, without the assistance of observation and experience.

David Hume (1711-1776)
Enquiries concerning the human understanding, 1777

For Hanneke and Steven

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Chapter 1.

Introduction

1.1. Osteoporosis as a public health problem

The investigation that is the subject of this thesis intended to evaluate the clinical value of risk factors of osteoporosis for prediction of fractures.

Osteoporosis and related fractures constitute a frequently occurring and expanding medical problem in the elderly population. The occurrence of skeletal fractures is approximately five times more frequent in women aged 85 years as compared to women aged 45 years.[1] Osteoporosis, a condition characterised by a reduced amount of bone tissue in the skeleton, may be a major cause of the age related increase in fracture risk.

Although osteoporosis is by no means a new disease, it has become a significant public health problem only recently. In the past decade, the absolute number of elderly fracture patients has grown considerably. In 1972 approximately 6000 subjects aged 65 years and over were admitted to Dutch hospitals for treatment of a limb fracture. Ten years later, in 1982 the number of hospital treated fracture patients of this age had increased by 65 per cent, to more than 10.000 patients.[2] These figures represent only a small fraction of all fracture patients, since the majority of fractures will have been treated in outpatient facilities. The rise in the absolute number of fractures may be explained from two factors. Firstly, there has been some increase in the age specific incidence of (hip) fractures.[3] Secondly, the size of the population with a high risk of fractures, has grown considerably. Between 1972 and 1982, the size of the Dutch population of subjects aged 65 years and over increased by 20 per cent; the population aged 75 years and over increased by 35 per cent; and the female population aged 75 years and over increased by more than 45 per cent. In the latter group the risk of fractures is particularly high.[4,5] For the future it is expected that the absolute number of elderly subjects will continue to increase.[6] As a consequence the "epidemic" of fractures among the elderly will further expand. The financial consequences of the large number of fractures may be considerable. For the USA, the financial costs of osteoporosis has been

estimated at 6.1 billion dollar in 1983.[7]

In the past few years osteoporosis has become a major health issue for the general public. The condition has been frequently discussed: both in the professional and in the lay press. News papers and popular magazines have regularly devoted their pages to inform the public about the disease. For the same reason several popular books have been published, some of which had provoking titles such as: "Osteoporosis: your head start on the prevention and treatment of brittle bones".[8] All this publicity may add to the impression of an epidemic disease threatening the integrity of our bones.

1.2. Aim and background of the investigation

The medical professional interest in the subject of osteoporosis has been remarkably high. In the three years between 1984 and 1987, at least three consensus conferences have been organised on the subject.[9,10,11] This high consensus activity may be a reflection of the increasing magnitude of the problem. It may also reflect the difficulty among experts in the field of osteoporosis, to agree on matters of substantial importance. The experts do agree about the importance of osteoporosis prevention. The process of bone loss proceeds only slowly, but it may continue over a long period of time. In due time, thirty per cent or more of an individual's total amount of bone tissue may be lost. This will result in a significant reduction in the mechanical strength of the skeleton. Once the bone loss has occurred, little or nothing can be done to restore the initial skeletal mass. Therefore, it makes sense, to start with prevention of bone loss long before osteoporosis manifests itself in the form of fractures.

For postmenopausal women, who are the major risk group, oestrogen substitution therapy is accepted by the majority of experts as the most promising intervention strategy in this respect. It has been suggested that women with a high risk of developing osteoporosis could be treated prophylactically with this kind of therapy, shortly after menopause. There is very little agreement, however, among the experts about the identification of a high risk group.[12] One approach that has been suggested for this purpose is the use of the risk factor

status.[13] In the medical literature many risk factors of osteoporosis have been described. For example, factors such as low body mass, early menopause, a diet low in calcium and lack of physical exercise have all been related to osteoporosis. It has been suggested that individuals with many risk factors should be selected for fracture prevention programmes. The study described in this thesis was designed to test the validity of this concept. In a longitudinal population based investigation among 1167 women initially aged 45 to 64 years, baseline risk factor status was related to the occurrence of fractures during a nine year follow-up period. The simultaneous influence on fracture risk of a combination of risk factors was expressed for each individual in a Fracture Risk Score, indicating the personal risk of fractures.

Next to the main question concerning fracture prediction, two additional questions were addressed. Firstly, the existence of differences in the rate of bone loss between individuals was evaluated longitudinally. From cross-sectional investigations it has been inferred that bone loss is a frequently occurring phenomenon in postmenopausal women as a group. Longitudinal data concerning the rate of bone loss may be helpful to further define a population at risk for osteoporosis. Secondly, the role of endogenous oestrogen activity was evaluated as a potential contributing factor in the etiology of osteoporosis.

1.3. The structure of the thesis

In chapter two a selective review of the literature is presented. The development of the concept of osteoporosis is described in a historical perspective, and the literature concerning the epidemiology of osteoporosis is described. In chapter three, the study population and methodology are described. In the chapters four to six the results of the investigation are presented. Chapter four deals with prediction of fractures; chapter five with differences in the rate of bone loss; and chapter six with the role of endogenous oestrogen activity as a potential cause of postmenopausal osteoporosis. In chapter seven the results of the investigation are discussed and some recommendations are made for prevention of osteoporosis and for further epidemiological research.

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Chapter 2.

Osteoporosis since Albright

2.1. Introduction

In this review of the literature the development of the concept of osteoporosis is described in a historical perspective. A distinction is made between osteoporosis as a clinical syndrome and osteoporosis as a phenomenon in the general population. This distinction was thought to be useful, because the manifestation of osteoporosis may appear different in clinical observations of individual patients or in epidemiological observations of the general population. The epidemiological view, being the subject of this thesis, will be discussed in further detail. The clinical and epidemiological literature on osteoporosis has been recently reviewed by Thomson,[1] Cummings,[2] and Riggs.[3]

2.2. The concept of osteoporosis

Osteoporosis can be considered as a condition in which the amount of bone tissue in the skeleton is reduced to an extent that fractures can easily occur.[4] The osteoporotic condition may occur in relation to a multitude of diseases and syndromes that are known to influence bone metabolism. A classification of osteoporosis is presented in Table I. Osteoporosis occurs most frequently as a primary condition among women in the menopause or among men and women at old age (i.e. postmenopausal or senile osteoporosis). In women, the distinction between the two conditions is often vague. Idiopathic osteoporosis -which is a form of osteoporosis of unknown etiology that occurs in young or middle aged subjects- and osteoporosis as a secondary condition are both relatively rare.

Skeletal wasting is held responsible for many of the fractures that occur in elderly people. Although the condition has been recognized as a clinical syndrome comparatively recently, it has probably existed for at least 3000 years. Perzigian described reduced amounts of bone tissue in the skeletons of the elderly members of an indian population, who lived between 2500 and 2000 BC

Table I A classification of osteoporosis.[4]

I. Common forms of osteoporosis of unknown cause not associated with other disease.
   A. Idiopathic osteoporosis (juvenile and adult)
   B. Postmenopausal osteoporosis
   C. Senile osteoporosis

II. Disorders or conditions in which osteoporosis is a common feature or pathogenesis partially understood.
   A. Hypogonadism
   B. Hyperadrenocorticism
   C. Thyrotoxicosis
   D. Malabsorption
   E. Scurvy
   F. Calcium deficiency
   G. Immobilization
   H. Chronic heparin administration
   I. Systematic mastocytosis
   J. Adult hypophosphatasia
   K. Associated with other metabolic bone disease

III. Osteoporosis as a feature of heritable disorders of connective tissue.
   A. Osteogenesis Imperfecta
   B. Homocystinuria due to cystathionine synthase deficiency
   C. Ehlers-Danlos syndrome
   D. Marfan syndrome

IV. Disorders in which osteoporosis is associated but pathogenesis not understood.
   A. Rheumatoid arthritis
   B. Malnutrition
   C. Alcoholism
   D. Epilepsy
   E. Diabetes
   F. Chronic obstructive pulmonary disease
   G. Menke's syndrome

on the northeastern bank of the Green river in Ohio, Kentucky.[5]

Early clinical descriptions of bone wasting have been given by several authors in the 19th century.[6,7] Sir Astley Cooper, for example, observed in 1824 that in old age bones "become thin in their shell and spongy in their texture". On an autopsy, on a lady who had suffered a hip fracture, William Porter noted in 1836 that "The entire osseous system was weak and fragile; the fibula gave way under the pressure of the finger and thumb and was crushed as easily as an egg shell".

The first formal description of osteoporosis has been ascribed to Pommer.[8] In 1885, this german pathologist published a monograph on osteomalacia, in which he suggested a classification of those diseases of the skeleton that were characterised by a reduced calcium content of the bone. On the basis of histological criteria he proposed a division in three categories: osteomalacia, osteitis fibrosa (abnormality of the bone tissue in hyperparathyroidism) and osteoporosis. Incomplete mineralisation of the bone matrix was described as the characteristic feature in osteomalacia. In osteitis fibrosa normal bone tissue was replaced by fibrous tissue and in osteoporosis the bone tissue was considered to be histologically normal. The reduced amount of bone tissue was described as the sole abnormality in osteoporosis.

2.2.1. Albright: osteoporosis as a disease

Osteoporosis was not recognized as a distinct disorder in medical practice until Fuller Albright drew attention to the condition around 1940.[9,10,11] Before Albright, the diagnosis osteoporosis was commonly confused with osteomalacia. Albright again made a distinction between osteoporosis, osteomalacia and osteitis fibrosa. He suggested basic metabolic differences between these conditions, with implications for simple clinical diagnostic criteria to discriminate one condition from the other. Furthermore, he proposed a multitude of hypotheses concerning the etiology and pathogenesis of osteoporosis. He described many case histories to illustrate his theories. At the same time these histories served as a clinical description of the condition. Finally, Albright introduced the use of oestrogens as a therapy for the newly discovered syndrome. By and large, the work of

Albright changed the theoretical concept of osteoporosis as described by Pommer into a clinical reality.

In the conception of Albright, osteoporosis was a disease of the bone tissue that was characterised by a deficient amount of bone in the skeleton, because of a defective bone formation. A clinical diagnostic differentiation between osteoporosis, osteomalacia and osteitis fibrosa was suggested on the basis of serum phosphatase, urinary calcium and urinary phosphorous concentrations. These were essentially normal in osteoporosis.

Concerning the etiology of osteoporosis Albright considered a multitude of factors, including the postmenopausal state, disuse, dietary deficiency, gastric hypoacidity, repeated pregnancies, longstanding thyrotoxicosis, senescence, Cushing's disease and acromegaly. He considered postmenopausal and senile osteoporosis as the two most frequent manifestations of the syndrome. The importance of the postmenopausal state as an etiological factor was illustrated in a paper in 1941, in which Albright described all known cases of generalised osteoporosis -without an obvious cause, like infantile paralysis- that could be traced since 1931 in subjects aged less then 65 years. Of 42 cases, 40 were women who had passed the menopause. The patients were invariably characterised by an increased radiotranslucency of the spine and sometimes by an increased translucency of other bones as well. Eighty per cent of the patients had suffered from spinal fractures; five per cent of other fractures and ten per cent had suffered from pain but had no fractures. The remaining five per cent of the patients had an increased skeletal radiotranslucency as the only symptom. The manifestation of osteoporosis as a disease that is characterised by a reduced amount of bone tissue, especially in the axial skeleton, accompanied by the occurrence of vertebral fractures and perhaps back pain still dominates the clinical conception of osteoporosis.[4]

2.2.2. Newton-John: osteoporosis as a general phenomenon in man

After osteoporosis had become established as a disease of clinical relevance, research activity became directed towards the further exploration of its manifestations. Radiological techniques were developed for in-vivo measurement

of the amount of bone tissue in the skeleton. Bone density was quantified both in normal and in supposedly osteoporotic populations. The accumulated data concerning the relationship between ageing, bone loss and fractures was reviewed in 1970 by Newton-John and Morgan.[12] In this review, the concept of osteoporosis as a disease was seriously challenged. An analysis of the available data from 30 unnamed publications concerning the amount of bone tissue in relation to age and sex led Newton-John and Morgan to the following conclusions:

" 1. All persons lose bone with age.

2. There is so far no evidence that osteoporosis in the older population is the result of either an excessive rate of loss or an abnormal total loss of bone.

3. The risk of fractures is largely determined by the amount of bone, and the increase in frequency of fracture with age is largely determined by the normal loss of bone with age."

According to this epidemiological view of osteoporosis, the existence of a subgroup of the population suffering from a disease called osteoporosis was denied. The argumentation was mainly built on the observations of many cross-sectional population based studies, in which -despite a continuous decline of bone density in elderly subjects- the range in the values of bone density (standard deviation) remained constant. The lack of an increasing trend in the standard deviation of bone density between consecutive age groups was interpreted as an argument for the homogeneity of the process of bone loss within the population. The age related increase in fracture incidence was explained from an increase in the number of individuals with a low bone density. Low bone density was considered as a risk factor for all fractures; not just vertebral fractures. It was argued that, as a result of the normal bone loss that occurs at a similar (physiological) rate in all old people, the prevalence of this risk factor does increase as the population grows older, and so does the total fracture incidence.

2.2.3. Riggs: back to Albright ?

In the past decade, the techniques for measuring the amount of bone tissue, particularly of the axial skeleton, have improved and an increasing amount of data on fracture incidence has become available. On the basis of the recent literature, Riggs and Melton III have suggested a solution for the controversy between Albright and Newton-John, by postulating the existence of two distinct syndromes of involutional osteoporosis.[13] Firstly, a syndrome that they labeled Type I osteoporosis, which occurs in a relatively small subset of postmenopausal women who are 51 to 65 years of age. Secondly, Type II osteoporosis, which occurs in a large proportion of women or men who are older than 75 years.

Type I osteoporosis was formerly known as postmenopausal osteoporosis. It is characterised by an accelerated and disproportionate loss of trabecular bone. Fractures of the vertebral bodies and of the forearm are the typical fractures for this type of osteoporosis. These skeletal sites contain predominantly trabecular bone. Oestrogen deficiency has been implicated as an etiologic agent, but other factors have been suggested as well. This syndrome corresponds to the clinical description of osteoporosis according to Albright.

Type II osteoporosis was formerly known as senile osteoporosis. It is characterised by a proportionate loss of both cortical and trabecular bone and the rate of bone loss is similar to that of the general population. Fractures of the hip, proximal humerus, proximal tibia and pelvis are the typical fractures. These sites of the skeleton contain substantial amounts of both cortical and trabecular bone. Impaired bone formation and secondary hyperparathyroidism have been implicated as etiologic factors. The syndrome corresponds to the Newton-John and Morgan concept of bone loss.

At present, the available data on age related changes in axial bone density are still relatively scarce, and it is too early for an evaluation of the clinical value of the distinction between type I and type II osteoporosis.

In summary, Pommer first described a theoretical concept of osteoporosis in 1885. Albright defined the clinical syndrome in 1940, and among others, he made a distinction between postmenopausal and senile osteoporosis. In 1970, the concept of osteoporosis as a disease was challenged by Newton-John and

Morgan, who suggested that -after a certain age- bone loss had to be considered as a physiological process. In 1983, Riggs presented a "new" model of type I and type II osteoporosis, which closely resembled the former distinction between postmenopausal and senile osteoporosis. The value of this distinction remains to be established.

2.3. Epidemiology of osteoporosis

In the following paragraphs a selection of the literature concerning the epidemiology of bone loss and fractures is presented, and the relationship between bone density and the risk of fractures is discussed.

2.3.1. Bone density and bone loss

a. Measurement of bone density:

Since Albright, many radiological techniques have been developed for non-invasive measurement of the amount of bone tissue in the skeleton. Present day technology allows measurement of the mineral content both of the entire skeleton and at particular sites of the skeleton. These measurements range from simple observations on radiographs to the application of sophisticated techniques such as quantitative computer tomography or neutron activation analysis. An overview of techniques has been given by Kimmel in 1984.[14] Techniques for measuring bone tissue in the peripheral skeleton have been available for several decades. Techniques for measuring total body calcium or mineral content of the axial skeleton were developed more recently.

Measurements of the bone mineral content at a single site of the skeleton are commonly used as an indicator of individual bone density on the assumption that the site selected will be representative for the remainder of the skeleton. This assumption is incorrect, as was demonstrated by Aitken et al. in a study of the amount of bone per unit of volume (bone density) at different skeletal sites in male and female cadavers.[15] Bone density at peripheral sites of the skeleton was found to be only moderately correlated to bone density at the vertebral

collumn. For metacarpal bone density, for example, the coefficient of correlation to vertebral bone density was only 0.47 in twenty-one female cadavers. This correlation is too low to characterise individual axial bone density by measuring the bone density at a peripheral site. However, for epidemiological purposes, a peripheral measurement can be used for comparisons between groups with a high or low bone mineral content of the skeleton on average.

b. Measurement of bone loss:

In theory, it is possible to study the actual process of bone loss longitudinally by measuring the bone mineral content of the skeleton at consecutive points in times. In practice, this approach has been seldomly applied, because the amount of bone tissue that is lost over a period of time is only a small percentage of the amount that is present. For detection of a difference in bone mineral content over time, either the measurement technique must be extremely accurate or the time period between the measurements must be rather long. Most inferences about bone loss have therefore been made on the basis of cross-sectional data, by comparing the bone mineral content of groups of individuals in various circumstances, e.g. age groups.

c. Determinants of bone density:

Age and sex are the two most important single determinants of bone density. In general, there is an increase in the amount of bone tissue in the skeleton in early life and a decrease later on, both in men and women. The amount of bone tissue at any given age is the resultant of the amount initially laid down ("peak bone mass"), minus the amount that is lost later on. From cross-sectional investigations of bone density it has been inferred that bone loss occurs as a universal phenomenon in middle aged and elderly individuals. In females the process starts at an earlier age and the rate of loss is larger than in males.[16] It has been suggested that bone loss in the axial and peripheral skeleton occurs in different patterns. In males bone loss from the peripheral skeleton begins between 40 and 55 years of age and the rate of loss has been estimated between 0.3 and 0.5 per cent per year. In females bone loss from the peripheral skeleton begins between 35 and 50 years of age. Before 50 years the rate of loss has been estimated between 0.2 and 0.4 per cent per year and after 50

Table II

Supposed major risk factors of osteoporosis in women.[3]

Postmenopausal (within 20 years after menopause)
White or asian
Premature menopause
Positive family history
Short stature and small bones
Leanness
Low calcium intake
Inactivity
Nulliparity
Gastric or small-bowel resection
Long-term glucocorticoid therapy
Long-term use of anticoagulants
Hyperparathyroidism
Thyrotoxicosis
Smoking
Heavy alcohol use

years of age between 0.8 and 1.2 per cent per year. Bone loss from the axial skeleton may begin at an earlier age and the sex difference may be less pronounced.

Besides age and sex, many other factors have been studied in relation to bone density. A list of supposed major risk factors of osteoporosis in women, as described by Riggs et al., is presented in Table II.[3] A detailed discussion of risk factors has been given in 1985 by Cummings et al..[2]

2.3.2. Epidemiology of fractures

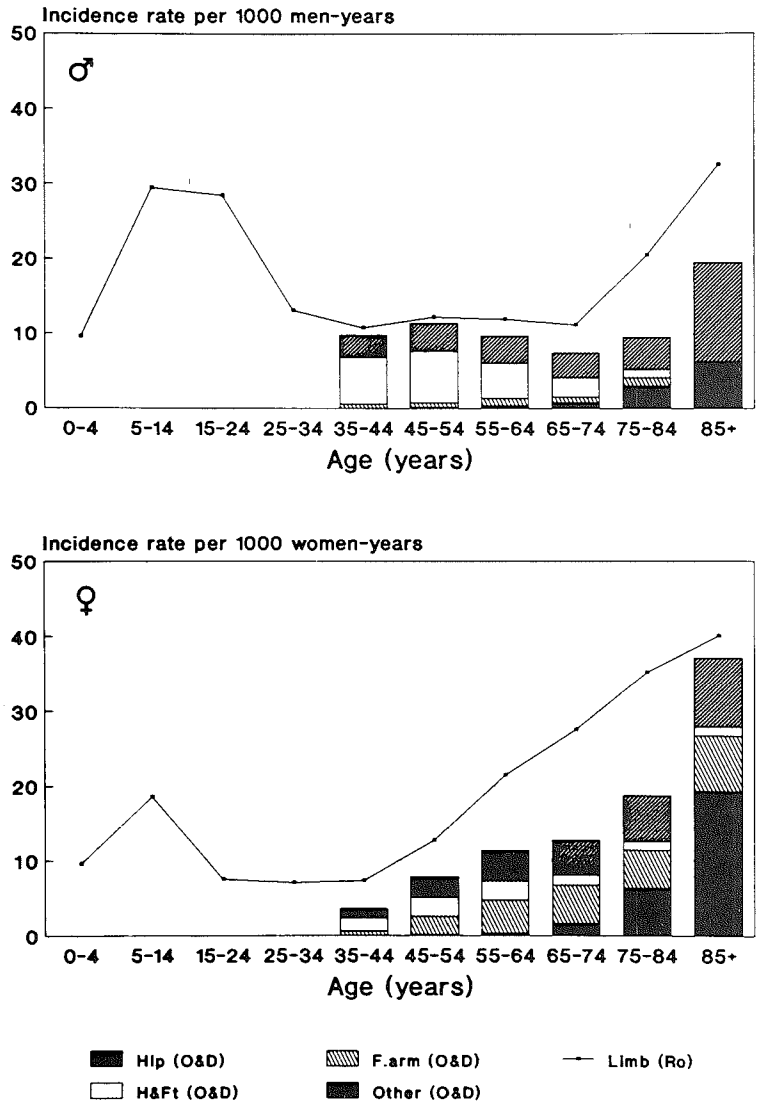
An increased risk of fractures may be considered as the most important clinical feature of osteoporosis. In the present paragraph the epidemiology of fractures will be described in relation to age and sex.

The age and sex specific incidence of fractures have been estimated in two population based investigations. First, the incidence of fractures of the limbs has been investigated in the United States by Garraway et al. in 1979.[17] It is the only relatively complete study of fracture incidence rates in a population containing all age and sex groups. The case register of the Mayo Clinics was used to identify all cases of fractures of the peripheral skeleton that were treated in the hospitals of Rochester (Ro), Minnesota. In the line diagram in Figure I the age specific incidence rates for males and females are presented. Limb fractures occurred most often in younger males and older females. The average fracture incidence rates were 18.4 per 1000 person-years for males and 14.0 per 1000 person-years for females. For the population aged 35 years and over the incidence rates were 12.5 and 18.9 respectively. An age related increase in fracture incidence rate was present in both elderly males and females, but in females the increase started at an earlier age. In males the fracture incidence started to increase after the age of 75 years, from 11.2 per 1000 person-years, up to 32.6 per 1000 person-years in the group aged 85 years and over. In females the fracture incidence started to increase after the age of 45 years from 7.3 per 1000 person-years up to 40.0 per 1000 person-years in the group aged 85 years and over. In the Rochester study age and sex specific incidence rates were not given for fractures at particular sites of the skeleton.

Site specific incidence rates were studied by Knowelden et al. in the United Kingdom in 1964.[18] Here, the study population had been restricted to individuals aged 35 years and over. The registers of the centralised services dealing with all fractures in Oxford and Dundee (O&D) were used to identify the fracture cases in the two regions. In the stack diagram in Figure I the age specific incidence rates for males and females are presented for various common types of fractures. The top of each bar represents the total age and sex specific fracture incidence rates. In comparison to Rochester the total incidence rates

Figure I

Age specific fracture incidence rates in males and females. The line diagram represents data from the population of Rochester (Ro), USA.[17] The histogram represents combined data from the population of Oxford and Dundee (O&D), UK.[18] Site specific rates are presented for O&D for femoral neck (Hip), forearm (F.arm), hand and feet (H&Ft) and other fractures.



were lower at all ages. The reason for this is unclear, but it has been suggested that the study population had been not so well defined.[18] The incidence rates of all fractures in this population were 10.0 per 1000 person-years for males and 9.3 per 1000 person-years for females. The incidence rates of limb fractures were 9.2 and 8.9 respectively. Fractures of the small bones of hand and feet were more common in males than in females. Conversely, fractures of the distal forearm were more common in females than in males. Up to age 65 the age related increase in fractures rates in women could be largely ascribed to an increase in the incidence of forearm fractures. After the age of 65 years hip fractures became increasingly important, both in males and in females. After the age of 85 years hip fractures were the most frequently occurring single type of fractures.

An age related increase in fracture incidence rates has been described for several other specific sites of the skeleton including the humerus,[19] ankle,[20] and pelvis.[21] Fractures at these sites occur less frequently as compared to forearm and femoral neck fractures.

The epidemiology of vertebral fractures deserves a separate discussion. Vertebral fractures have been considered as the classical type of osteoporotic fractures, but reliable data on the incidence of these fractures in the general population are not available. Incidence data are difficult to obtain, because many of these fractures occur without prominent symptoms. As a consequence, only a limited proportion of all vertebral fractures will come to the attention of medical services. As a further complication, there is no general agreement about the criteria for the diagnosis of vertebral fractures.

Data on the prevalence of vertebral fractures are available from three population based studies. Since it is unlikely for vertebral fractures to heal without leaving traces, these data can be considered as an estimation of the cumulative incidence.

Firstly, the age specific prevalence of vertebral fractures was estimated in 1966 by Smith et al. in a population of 2063 females from Michigan, aged 45 to 90 years.[22] The women were selected from hospital personnel and outpatients. The prevalence of compression fractures of the lumbar vertebral bodies was found to increase in relation to age from 0.7 per cent for women aged 45 to 49 years up to 16.7 per cent for women aged 70 to 74 years. In a follow-up study

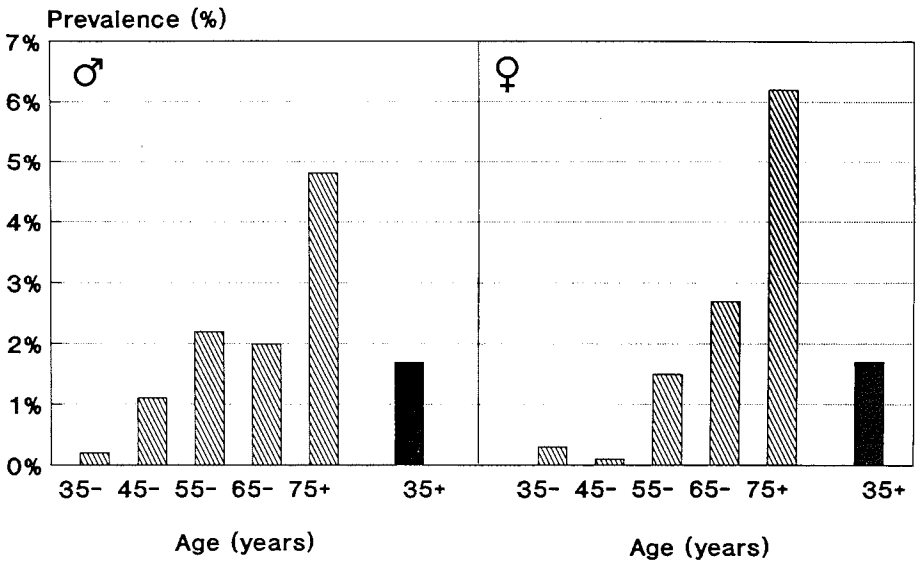
of these women by Iskrant et al. 20 women reported (!) spinal fractures over an average follow-up period of 4.3 years (8831 women-years). The estimated reported incidence of vertebral fractures was 2.3 per 1000 women-years.[23] The true incidence must have been higher.

Secondly, the prevalence of complete (crush) and partial (wedge) compression fractures of the thoracic and lumbar spine was estimated in 1982 by Jensen et al. in a sample from the general population of 285 Danish women aged 70 years.[24] In this study a prevalence of 4.6 per cent was found for complete compression fractures and 18.2 per cent for partial compression fractures.

Thirdly, the prevalence of crush fractures of the lumbar spine was estimated in 1980 by Valkenburg et al. in the EPOZ-investigation in a sample from the general population of 1593 males and 1843 females from a Dutch population aged

Figure II

Age specific prevalence of crush fractures of the vertebral bodies T12 to L5, in a representative sample of 1593 males and 1843 females from a Dutch population. (EPOZ 1975-1978).[25]



35 years and older.[25] At present, these figures represent the only estimation of the prevalence of vertebral fractures among males. The group of females that was 45 to 64 years of age was used as the baseline population in the investigation described in this thesis. The age and sex specific percentages of crush fractures of the vertebral bodies T12 to L5 are presented in Figure II. These results were obtained from routine readings of the films for back disorders. For males and females aged 35 years and older the total prevalence of vertebral crush fractures was similar. In males it appeared that many of the fractures occurred before 65 years of age and after 75 years of age. In females the majority of fractures occurred after 55 years of age. Presumably, some of the vertebral fractures in younger males resulted from accidents at work.

2.3.3. Relationship between bone density and fractures

In the previous two sections an age related decrease in bone density and a parallel increase in fracture rate were described. Since the main clinical characteristic of osteoporosis is an increased risk of fractures due to a decreased bone density, the relationship between the two will be discussed in the present paragraph.

a. Theoretical argumentation:

From a bio-mechanical point of view any bone will fracture if a sufficient force is applied. In laboratory studies a direct relationship has been demonstrated between the bone density of a particular bone and the forces it can withstand. For example, in a postmortem study of 17 radii of female subjects who were 39 to 95 years old at the time of death, the coefficient of correlation between the load necessary to produce a fracture and the bone mineral content was 0.83.[26] In a similar study of 61 femoral neck autopsy specimens the coefficient of correlation was 0.89.[27] Similarly, for trabecular bone the compressive strength has been found to be proportional to the square of the apparent density of the bone.[28] Thus, the risk of a fracture for a particular bone will depend on the actual bone density and on the risk of a sufficient force being applied to that particular bone.

b. Empirical argumentation:

As described previously, it has been established that bone density declines and fracture risk increases in relation to age. In females bone density declines by approximately 30 per cent between 45 and 75 years of age. At the same time, there is an approximate fourfold increase in fracture risk. From the theoretical point of view, it will be very likely that bone loss does contribute to the occurrence of fractures in the elderly. However, besides bone loss, many other age related factors may contribute to an increased fracture risk as well. For example, the quality of the motor system declines with age. The frequency of falls increases and protective reflexes that modify the way of falling become less effective in the elderly.[29] Furthermore, the fat and muscular tissue surrounding the skeleton as a protective shield will become less effective due to atrophy. Also, the mechanical properties of the bone tissue as a material declines in relation to age. For femoral bone specimens it has been found that the tissue becomes more brittle in the elderly in a sense that the material would rather break than bend.[30] Finally, for trabecular bone certain structural factors have been suggested to influence the mechanical strength.[31]

The intermingling of a multitude of factors that are subject to age related change, makes it difficult to make an empirical estimation of the contribution of bone density as a separate factor in fracture causation. The importance of the loss of bone as a cause of the age related increase in fracture risk would be overestimated if these factors were neglected. On the other hand, if an attempt is made to control for these factors by standardising for age, the contribution of age related bone loss will be underestimated, since at a similar age, bone loss will have occurred both in the fracture patients and in the non-fracture controls.

The literature concerning the relationship between bone density and fracture risk has recently been reviewed by Cummings et al. (1986).[32] In two investigations the relationship between bone density and fracture occurrence has been studied prospectively.

Firstly, in a study by Iskrant et al., spinal bone density was rated subjectively on lumbar spine radiographs of 2088 Michigan women aged 45 years and over.[23] The incidence of all fractures was estimated during an average period of 4.2 years of follow-up. The total fracture incidence rate was 37 per 1000

women-years. which is relatively high. In ten year strata of age. the risk of fractures was approximately twice as high for women with a low spinal bone density as compared to women with a high bone density.

Secondly. in 1981 Wasnich et al. have started a prospective investigation among 1098 Japanese-American women from Hawaii. aged 43 to 80 years. Bone mineral content was measured by photon absorptiometry in the proximal and distal forearm. in the os calcis and for a selection of the women in the lumbar spine. An interim report based on 26 incident fractures was presented in 1985.[33] Fractures of the forearm and the ribs occurred most frequently. The estimated incidence rate of non-spinal fractures was 8.3 per 1000 women-years. which is relatively low. The age adjusted fracture odds ratio for the highest and lowest quintiles of bone mineral content was 4.1 for measurements in the distal radius and 10.3 for measurements in the os calcis.

Several case-control studies have been conducted. comparing the bone density in individuals with specific types of fracture to non-fracture controls. For subjects who had forearm fractures the bone mineral content of the contra-lateral forearm has been found (only) 7% lower as compared to age-matched controls.[34] In a critical review of 15 case-control studies for femoral neck fractures. Cummings (1984) concluded that "the most rigorously designed studies observed less bone density in the hips of patients with fractures than in the hips of control subjects. but the differences were small and overlapping."[35] For cases with vertebral fractures the vertebral bone mineral content has been found considerably lower as compared to age-adjusted controls. In a study by Krolner et al. approximately one third of 72 cases with vertebral compression fractures had a mineral content of the spine below the 95% range for age-matched controls.[36] The difference in bone mineral content between vertebral fracture cases and age-matched controls was less pronounced if the measure-ments were made in the forearm.[37]

In conclusion. the relationship between bone density and fracture risk appears to be well established. However. there is considerable reason for doubting the idea that individuals with fractures constitute a separate population of "osteo-porotic" patients. The age related increase in fracture rate may be explained in part by the universal age related bone loss. but most likely other factors do

contribute as well. If these factors are neglected, the influence of age related bone loss will be overestimated. If an adjustment for age is applied, the influence of the universal occurrence of bone loss will be underestimated.

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Chapter 3

Architecture of the investigation

3.1. Introduction

The investigation that is the subject of this thesis can be characterised as a cohort study with a forward directionality and a nine year period of follow-up.[1] A group of 1167 women aged 45 to 64 years was investigated for a first time between 1975 and 1978 as a part of the Epidemiological Preventive Investigation Zoetermeer, which is known by the Dutch acronym EPOZ. The same women were invited for a second investigation in 1985 and 1986.

The investigation permitted several types of evaluation. Firstly, putative risk factors of osteoporosis that were present at the time of the initial investigation were related to the subsequent occurrence of fractures during the period of follow-up. This evaluation constituted the main reason for conducting the investigation. The results are presented in chapter four.

Secondly, the occurrence of age related bone loss was evaluated in a cross-sectional and in a longitudinal way. The longitudinal data were used to evaluate the presence of differences in the rate of bone loss between individuals. The results of the evaluation are presented in chapter five.

Thirdly, the forward study design was inverted to evaluate endogenous oestrogen activity in relation to bone density, bone loss and fractures. Endogenous oestrogen activity was measured at follow-up. It was related to bone density in a cross-sectional analysis, and to the occurrence of bone loss and fractures in a retrospective analysis. The latter approach of a retrospective cohort design with a backward directionality can be compared to the case-control design. The subjects with high bone loss and/or fractures can be conceived as the "cases" and the remaining population as the non-diseased "controls". The approach was considered valid under the assumption that endogenous oestrogen activity was not influenced by bone density, bone loss, fractures or selective non-response at follow-up, nor by an unknown third factor influencing either of these. The results of the evaluation are presented in chapter six.

The cohort design has specific advantages and disadvantages, that are described in more detail in the epidemiological handbooks.[2] In the present situation, the population approach represented a natural imitation of the situation of normal middle-aged females visiting a general practitioner for advise about prevention of osteoporosis. Both the potential efficiency of selection of a "high-risk" group of women for preventive measures and the impact of fracture occurrence could be evaluated. An unavoidable disadvantage of the approach was that information was limited for events of infrequent occurrence.

3.2. Population and methods

The present investigation started with baseline information about risk factors of osteoporosis from the EPOZ survey, which took place between 1975 and 1978.[3] In the EPOZ-survey the inhabitants of two suburbs of Zoetermeer, a Dutch town near The Hague, were medically investigated for a study of prevalence and determinants of chronic disorders, such as cardiovascular, pulmonary, renal and rheumatic disorders. A total number of 13,462 individuals of all ages were invited and 10,532 (78 %) individuals participated in this survey. In 1985 and 1986, the female participants who were 45 to 64 years of age at the time of the EPOZ-survey were invited for a follow-up investigation to obtain information concerning bone loss and incident i.e. newly occurring fractures since EPOZ. This specific study group was chosen for several reasons. Osteoporosis is particularly frequent among middle-aged and elderly females. Age related bone loss starts at an earlier age and proceeds at a higher rate in females than in males.[4] Also, the age specific fracture incidence is considerably higher in elderly females than in elderly males.[5] In addition, the group of middle aged women was chosen for this study, because it is for this group that oestrogen replacement therapy is propagated as an effective strategy for prevention of fractures.

3.2.1. Period of follow-up and response rate

The period of follow-up was calculated for the group of women for whom fracture information was available at the end of the study. The period ranged from 7 to 10 years, with an average and standard deviation of 9.0 ± 0.8 years. At baseline the average age of the women was 53.5 ± 5.8 years. At follow-up, the women were 53 to 76 years of age, with an average and standard deviation of 62.5 ± 5.8 years.

The total number of women aged 45 to 64 years that participated in the EPOZ-survey was 1167 and the response rate among these women was 78 per cent. At the time of follow-up, 71 of these women had died and 87 had moved out of the town of Zoetermeer. Of the remaining 1009 women, 855 (85 %) participated in the complete follow-up investigation. For those women who moved out of the town of Zoetermeer or who refused participation, a fracture history was obtained by telephone. In this way, a fracture history was recovered for 1014 women, which is 93 per cent of the women who were alive at the time of follow-up. The strategy of inviting women for the follow-up investigation is described in further detail in chapter seven.

3.2.2. Information at baseline: EPOZ (1975-1978)

In the EPOZ-survey a variety of information was collected by questionnaire, physical examination, radiological examination and serum analyses. From the questionnaire, information was used concerning chronological age, age and circumstances of menopause, age of menarche and smoking habits. Body height and weight had been measured without shoes, but with indoor clothing; the Quetelet-index (body mass) was calculated as the ratio of body weight and height squared. Radiographs were available for most joints and joint groups. Antero-posterior radiographs of the hands were used for measurement of the diameter of the distal forearm. Bone density was determined in a classical way, by measuring the cortical thickness of the metacarpal bones (Metacarpal Radiogrammetry). Measurements of the outer diameter (D) and medullar diameter (d) were made at the mid-shaft of the metacarpal bones II, III and IV of both

hands, using a 7 times magnifying measurement loupe with an accuracy of 0.01 mm (Figure I). The Metacarpal Cortical Area (MCA) was calculated as the mean value of D^2-d^2 for six metacarpals and the Relative Cortical Area (RCA) was calculated as the mean value of 100 x (D^2-d^2)/D^2 of six metacarpals.[6,7] Considerations for the choice of the metacarpal indices are given below.

Lateral radiographs of the lumbar spine (T12 to L5) were used for detection of osteoporotic deformations of the vertebral bodies.[8] A wedge deformation was considered to be present if the ratio of anterior to posterior height of the vertebral body was less than 0.8 with intact end plates. This definition is relatively conservative.[9] A crush deformation was considered to be present if an end plate was crushed or if the total vertebral body had collapsed. Antero-posterior radiographs of the knees were used for measurement of the diameter of the knees at the level of the femoral epicondyles.

3.2.3. Follow-up (1985-1986)

The follow-up investigation included a questionnaire, a physical examination, a radiological examination and withdrawal of a serum sample. The follow-up investigation was designed to collect information about the occurrence of fractures since the initial EPOZ-survey. In addition, information was collected concerning number of children, history of lactation, age and circumstances of menopause and use of postmenopausal oestrogens. Radiographs of the hands were repeated for the purpose of follow-up Metacarpal Radiogrammetry. Lateral radiographs of the lumbar spine were repeated for detection of incident vertebral fractures. The serum samples that were taken were used for a multitude of biochemical measurements including serum concentration of oestrone, oestradiol, androstenedione and sex hormone binding globulin (SHBG). Additional information that was collected, but not used for the evaluations presented in this thesis, is described in chapter seven. An english translation of the questionnaire that was used for the follow-up investigation is included in the appendix.

a. Fractures:

A history of non-vertebral fractures during the 9-year study period was obtained by questionnaire. The presence of incident deformations of the vertebral bodies of T12 to L5 was detected by comparison of the initial and follow-up radiographs of the lumbar spine. The definition of prevalent vertebral deformations was described above. Incident vertebral fractures were considered to be present during the study period if: 1). a new deformation became apparent, 2). a wedge deformation changed into a crush deformation, or 3). the antero-posterior ratio of a wedge deformation decreased by 0.2 or more.

b. Bone loss:

Antero-posterior radiographs of the hands were repeated for follow-up metacarpal measurements. For the Relative Cortical Area the total loss during the study period was calculated by subtracting the initial measurements from those at follow-up. Since loss in RCA started around the age of menopause in our cross-sectional data, the annual rate of loss in RCA (change-in-RCA) was calculated as the total loss divided by the postmenopausal period during follow-up. For the subjects who were already postmenopausal at the initial investigation (69 per cent of the 799 women for whom both initial and follow-up radiographs were available) this period was equal to the study period. For those who became postmenopausal during the study period (the remaining 31 per cent), this period was shorter. The average and standard deviation of the postmenopausal period during follow-up were 7.9 $\pm$ 2.1 years for the total group.

As an illustration, details of the initial and follow-up radiographs of the left hand of the same subject are reproduced in Figure I. The woman of whom these radiographs were made was 50 years of age at the time of the first examination and 58 years at the time of the second investigation. RCA-1 was 88 mm^2% and RCA-2 was 66 mm^2%; the period of follow-up was 8.2 years; the postmenopausal period during follow-up was similar, since the last menstruation had occurred before the first examination at age 48. The annual rate of loss in RCA (change-in-RCA) was -2.7 mm^2% (-3.0 % of the initial RCA).

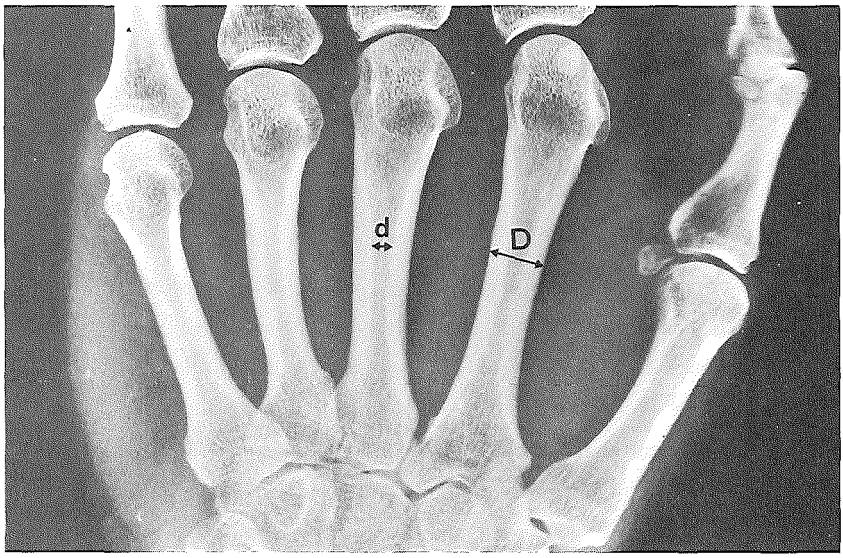
c. Endogenous oestrogens:

Serum samples drawn at follow-up were used for duplicate measurements of

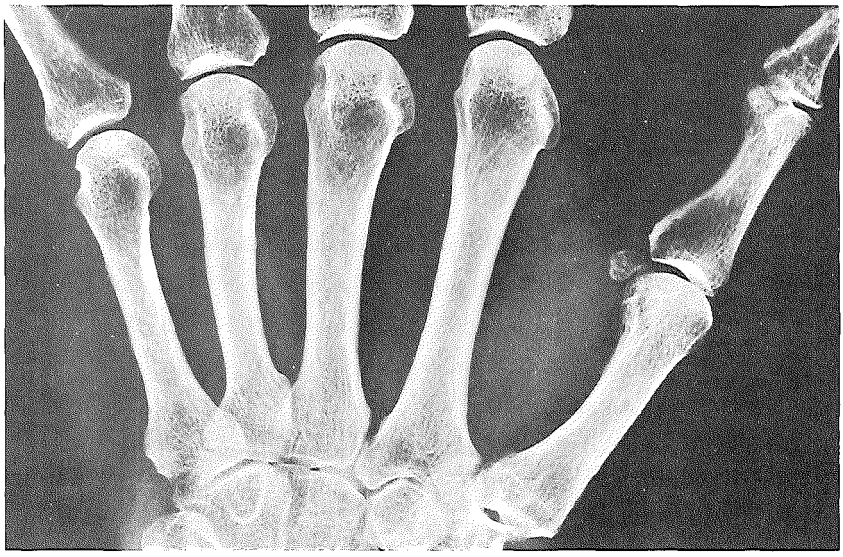
Figure 1

Detail of the initial (A) and follow-up (B) radiograph of the hands of the same individual. The intervening period between the two radiographs was 8.2 years. D = outer diameter; d = medullar diameter at the mid-shaft of the metacarpal bone. (EPOZ Follow-up Osteoporosis).

A.



B.



Photographs by T. Rijsdijk

oestrone, oestradiol, sex hormone binding globulin (SHBG) and androstenedione concentrations. Oestrone concentrations were measured by means of a radio-immuno-assay (RIA), after extraction of the serum on LH-20 microcolumns, using the antiserum as described by Van Landeghem et al..[10] The intra-assay variability was 13.2 per cent and the inter-assay variability was 18.4 per cent. Oestradiol concentrations were measured by means of a RIA, using a commercial kit supplied by Diagnostic Products Corporation (Los Angeles, California, USA). The intra-assay variability was 14.6 per cent and the inter-assay variability was 18.5 per cent. Androstenedione concentrations were measured by means of a RIA using a commercial kit supplied by Eurodiagnostics (Apeldoorn, The Netherlands). The intra-assay variability was 10.8 per cent and the inter-assay variability was 16.5 per cent. SHBG was measured as described by Hammond et al..[11] The intra-assay variability was 11.4 per cent and the inter-assay variability was 17.8 per cent.

3.3. Metacarpal Radiogrammetry

In the past few decades a multitude of techniques have been developed for non-invasive measurements of the amount of bone tissue in the skeleton.[12] Measurements can be made in the axial or in the peripheral skeleton. Dual Photon Absorptiometry (DPA) or Quantitative Computer Tomography (QCT) can be used for measurements of the amount of (cancellous) bone in the axial skeleton. Both these techniques are not well fit for population surveys, because they are expensive, time-consuming and require specialised equipment. For large scale epidemiological investigation bone measurements will usually have to be limited to the peripheral skeleton. The techniques most commonly used measurements are Single Photon Absorptiometry (SPA) and Metacarpal Radiogrammetry. The latter technique was employed in the present investigation. It offered the unique opportunity to evaluate data from a large population over a long period of follow-up.

The technique of Metacarpal Radiogrammetry is a simple method of quantifying the amount of bone tissue in the metacarpal bones. It requires very little technical facilities.

3.3.1. Metacarpal indices

Once the measurements of the outer (D) and inner (d) diameter of the metacarpal bones have been made, two slightly different approaches can be followed to calculate indices of metacarpal bone mass. The first approach was described by Barnett and Nordin and constitutes of the calculation of the Metacarpal Cortical Thickness (MCT) of the metacarpal bones: D-d .[13] The second approach was described by Garn et al. and constitutes of the calculation of Metacarpal Cortical Area (MCA): D^2-d^2 .[6] As a standardization for differences in body size the Relative Cortical Thickness (RCT) and Relative Cortical Area (RCA) can be calculated for both approaches. This is done by expressing MCT and MCA as a percentage of the size of the metacarpal bone: $100x(D-d)/D$ and $100x(D^2-d^2)/D^2$ respectively.* Thus, the amount of metacarpal bone can be expressed as the thickness or as the cross-sectional area of the cortex; both can be expressed as absolute mass (MCT and MCA) or as relative density (RCT and RCA). The relationship between the indices in our own baseline data is demonstrated in Table I, where the coefficients of correlation between MCT, MCA, RCT and RCA are presented. Baseline data for Metacarpal Radiogrammetry were available for 1134 women.

In the present investigation, MCA was preferred over MCT, because the former has a superior correlation to the amount of bone tissue that is actually present in the metacarpal bones as was demonstrated by Exton-Smith et al..[14] In this post-mortem study, the metacarpal indices were correlated to the mineral content as estimated by ashing the shaft of the metacarpal bone at 600 degrees Celsius. For MCA the correlation to ash content was 0.85; for MCT only 0.31.

The arguments for the choice between the MCA and RCA were not so clear-cut. Absolute cortical area can be interpreted as an indicator of the absolute

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* The two relative indices are mathematically equivalent:

If $RCT' = (D-d)/D$ [1] then $1-RCT' = d/D$ [2]

If $RCA' = (D^2-d^2)/D^2$ then $RCA' = (D-d)/D \times (1+d/D)$ [3]

Through substitution of [1] and [2] in [3] it follows that

$RCA' = RCT' \times (1+(1-RCT')$ or $RCA' = 2RCT'-RCT'^2$

Table I

Coefficients of correlation of Metacarpal Cortical Thickness (MCT), Metacarpal Cortical Area (MCA), Relative Cortical Thickness (MCT) and Relative Cortical Area (RCA) among 1134 women aged 45 to 64 years. (EPOZ 1975-78).

	RCA	RCT	MCA	MCT
MCT	0.79	0.91	0.86	1.00
MCA	0.45	0.59	1.00	
RCT	0.95	1.00		
RCA	1.00			

MCT = D-d, MCA = D^2-d^2, RCT = 100x(D-d)/D, RCA = 100x(D^2-d^2)/D^2
D = Outer diameter, d = Medullar diameter of metacarpal bone

amount of bone that is present (bone mass) and relative cortical area can be interpreted as the amount of bone per unit of volume (bone density). The first will be dependent on body size, whereas the latter is standardized for differences in body size. The influence of body size on MCA and RCA could be demonstrated empirically in our own data. Metacarpal Cortical Area was correlated significantly to body length ($r=0.33$; $p<0.001$). Relative Cortical Area was unrelated to body length ($r=-0.01$; not sign.).

In theory, skeletal strength and fracture risk may depend both on bone mass (size of the skeleton) and on bone density. Therefor, both MCA (bone mass) and RCA (bone density) were used in the analysis of fracture risk as presented in chapter four. However, in a comparison of the amount of bone tissue between individuals, the size of the skeleton will act as a disturbing factor. As a consequence, RCA was preferred for the comparisons between individuals that were made in the chapters five and six.

For comparisons between different studies, RCA will be more informative than MCA, since the latter is very sensitive for variation in the projection of the hand on the radiograph due to variation in the tube-hand-film distances.

3.3.2 Validity of Metacarpal Radiogrammetry

As a method of measuring the amount of bone tissue, Metacarpal Radiogrammetry has been criticised for several reasons.[15]

Firstly, it has been claimed that the measurement precision of Metacarpal Radiogrammetry is unsatisfactory. This may be true for measurements of a single metacarpal bone, for which a precision of 5 to 10 per cent has been reported. However, for multiple measurements of six metacarpal bones the precision is much better. Values between 1 and 3 per cent have been reported.[16] For comparison, the precision of Single Photon Absorptiometry has been reported to be 1 to 2 per cent in laboratory conditions and 2 to 5 per cent in clinical circumstances. In the present investigation, the measurement precision was estimated in 100 duplicate measurements. The mean intra-individual standard deviation of a duplicate measurement was 1.9 mm^2 (4 %) for MCA and 2.5 mm^2% (3 %) for RCA. It is concluded that Metacarpal Radiogrammetry is sufficiently precise to allow for meaningful comparisons of bone density between individuals. For detection of bone loss, the method is only suitable in long-term follow-up studies.

Secondly, the accuracy of the method has been doubted. It has been suggested, that the method does not accurately measure what it intends to measure, i.e. the amount of bone tissue in the metacarpals. This may be true for some of the metacarpal indices, but for the Metacarpal Cortical Area a reasonable correlation to the ash mineral content has been established, as was described in the previous section.

Thirdly, the strength of the correlation between metacarpal bone mass and bone mass at other sites of the skeleton has been questioned. In a post-mortem study, Aitken et al. found moderate to high correlations between ash mineral content of the metacarpals and the ash mineral content of the vertebral bodies (0.47), distal femur (0.84), distal radius (0.75), mid-shaft femur (0.85) and mid-shaft radius (0.96) in females.[17] Thus, metacarpal cortical bone density is not very strongly related to bone density in the axial skeleton, but it is reasonably correlated to bone density at peripheral skeletal sites of cortical bone. More recently, Reinbold et al. compared Metacarpal Cortical Thickness, SPA of the distal forearm and DPA and QCT of the vertebral bodies.[18] Both for Metacarpal

Cortical Thickness and for SPA measurements of the distal forearm the correlation to vertebral mineral density was around 0.50 for healthy women and around 0.25 for women who had axial osteoporosis. In this respect, Metacarpal Cortical Thickness was not of inferior value as compared to SPA. Neither method appeared to be very useful for the detection of axial osteoporosis.

Finally, it has been suggested that the validity of the measurements may be limited by a continuing age related gain of bone tissue at the outer surface of the metacarpal bone, as is reflected in a slow growth of the outer diameter of the bones. Since the outer diameter of the metacarpal bone (D) is considerably larger than the medullar diameter (d), a small increase in D (gain of bone) might compensate a much larger increase in d (loss of bone). In theory, MCA could remain unaltered, while RCA would decrease. The influence of growth of the metacarpal bone in relation to change in MCA and RCA was evaluated in our own longitudinal data. In the baseline data, the mean outer diameter of the six metacarpals was 8.0 mm. The age related increase in D was approximately 0.1% per year. The mean medullar diameter of the six metacarpals was 3.7 mm and the age related increase in d was approximately 1.5% per year. In the correlation matrix in Table II the relationships between changes in D (delta-D), d (delta-d), RCA (delta-RCA) and MCA (delta-MCA) were evaluated. All

Table II

Coefficients of correlation of the change in mean outer diameter of six metacarpals (delta-D), mean medullar diameter of six metacarpals (delta-d), Metacarpal Cortical Area (delta-MCA) and Relative Cortical Area (delta-RCA) over a period of nine years of follow-up among 799 women initially aged 45 to 64 years. (EPOZ Follow-up Osteoporoses).

	Delta-D	Delta-d	Delta-MCA	Delta-RCA
Delta-RCA	-0.09	-0.94	0.86	1.00
Delta-MCA	0.34	-0.76	1.00	
Delta-d	0.23	1.00		
Delta-D	1.00			

coefficients were significantly different from zero. Changes in RCA were predominantly determined by changes in d (bone loss) ($r=-0.94$; $p<0.001$). Delta-RCA was only slightly related to delta-D (bone gain) ($r=-0.09$; $p<0.05$). Delta-MCA was also strongly determined by delta-d ($r=-0.76$; $p<0.001$), but to a lesser extent by delta-D as well ($r=0.34$; $p<0.001$). Apparently, the dynamic of change in both RCA and MCA was predominantly influenced by bone loss (delta-d). RCA was practically unaffected by bone gain (delta-D) and MCA was only moderately affected by bone gain. The significant correlation between delta-D and delta-d ($r=0.23$; $p<0.001$) was of interest, because it suggests that the processes of bone gain at the outer metacarpal surface and bone loss from the medullar metacarpal surface did not occur independently.

In summary, the validity of Metacarpal Radiogrammetry has been questioned for several reasons. From the previous discussion it is concluded, that the precision and accuracy of the method are sufficient. The correlation of metacarpal bone density to bone density at other peripheral sites of the skeleton is reasonable and this correlation is not inferior to that of SPA of the distal radius. An age related growth of the outer diameter of the metacarpals was present in our study population. The growth of the metacarpal bone had practically no influence on delta-RCA and little on delta-MCA. For the purpose of short-term follow-up investigations of bone density in the peripheral skeleton, Single Photon Absorptiometry of the distal forearm may be preferred rather than Metacarpal Radiogrammetry, considering the slightly better precision. For the purpose of the present epidemiological investigation with a long period of follow-up, Metacarpal Radiogrammetry is probably not inferior to Single Photon Absorptiometry of the distal forearm.

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Chapter 4

Prediction of osteoporotic fractures in the general population by a Fracture Risk Score. A 9-year follow-up among middle aged women

4.1. Introduction

The occurrence of skeletal fractures is very common among postmenopausal women. The incidence of limb fractures rises with age, from approximately 7.3 per 1000 women years at age 45 to approximately 40 per 1000 women years at age 85 and over.[1] Reduced bone mass due to postmenopausal bone loss may be a major contributing factor in the propensity of older bones to fracture.

Both the process of bone loss and the occurrence of fractures can be prevented by long-term oestrogen replacement therapy, starting early after the menopause. This may lead to an estimated reduction in fracture occurrence up to 60 per cent.[2,3] However, the question which women would benefit most from oestrogen treatment remains to be answered.[4]

In the past, much effort has been devoted to the search for risk factors of osteoporosis. Factors such as smoking, body size, age and circumstances of the menopause and reproductive history have all been implicated as possible predictors of osteopenia or fractures. It has been suggested that this knowledge may be used to select women for fracture prevention programmes.[5] The present investigation was intended to evaluate the clinical efficiency of this approach among middle aged women from the general population.

Initial information about twelve historical and radiological risk factors of osteoporosis was collected among 1167 women aged 45 to 64 years. For the nine following years information was collected about all newly occurring fractures. The efficiency of initial risk factors in predicting subsequent fractures was evaluated. A Fracture Risk Score (FRS) was assembled from the best combination of risk factors.[6] Detailed information concerning the study design was presented in chapter three.

4.2 Statistics

In the statistical analyses, subjects who had one or more missing values for any of the study variables were excluded. Complete data were available for 742 women. The fracture rate among the subjects that were excluded because of missing data was similar to the fracture rate among the remaining subjects. The analysis was performed for all fractures as a single group and, separately, for the group of type I osteoporotic fractures, (forearm and vertebral fractures). In

Table I

Mean values, standard deviations and 90 per cent ranges for the continuous, and proportions for the categorical risk factors. Data from 742 Dutch women aged 45 to 64 years. (EPOZ 1975-1978).

Continuous risk factors			Percentiles	
	Mean	S.D	5th	95th
Age (years)	53.5	5.2	46	63
Metacarpal Cortical Area (mm^2)	50.6	6.6	40	62
RCA (% mm^2)	78.5	7.6	65	90
Quetelet index (kg/m^2)	25.5	3.3	21	32
Body height (cm)	162.8	6.1	153	172
Diameter of forearm (mm)	49.1	2.8	44	54
Diameter of knee (mm)	85.4	4.1	79	92
Age of menarche (years)	13.5	1.8	11	17
Age of menopause (years)	47.7	4.9	39	54

Categorical risk factors	proportions in percentages		
Smoking (cigarettes/day)	none: 66	$\leq$ 10: 19	$\geq$ 11: 15
Number of children	none: 13	1-4: 66	$\geq$ 5: 21
Period of lactation (months)	none: 32	$\leq$ 12: 43	$\geq$ 13: 26

Table I the mean values and frequency distributions are shown for the risk factors that were studied.

The nine year risk for one or more fractures was calculated in several categories of each risk factor. Age was categorised in 5-year groups of initial age. Smoking was divided in arbitrary categories: none, $\leq$ 10 or more than 10 cigarettes per day. MCA, RCA, Quetelet-index, body height, and diameter of the forearm and knee were categorised in tertiles, indicated as high, middle and low in the Figures. For age and circumstances of menopause the women were arbitrarily divided in the groups older and younger than 45 years; the latter group (early menopause) was further divided according to the cause of menopause: natural, hysterectomy and oophorectomy. Menarcheal age was divided according to conventional age limits: younger then 12 years, 12 to 15 years and 16 years and over. For history of lactation all periods were summed together to a total period, which was divided arbitrarily into categories: none, $\leq$ 12 month and more than 12 months. Chi-Square statistics were used to test the statistical significance of the differences in fracture risk between the categories of each risk factor.

In a multivariate analysis the relationship between risk factors and fracture risk was combined in order to maximize predictive strength. Variables that discriminated best between individuals with and without fractures were selected and these variables were used to calculate an individual Fracture Risk Score. The selection of discriminatory variables was made by a stepwise multiple logistic regression procedure.[7,8] Indicator variables were created for all the variable-categories that were described above. In preliminary analysis initial age demonstrated to be an effect modifier for some of the risk factors. Therefore, interaction variables were created for each variable category and the age category 55 years and over. The principle of logistic regression analyses with indicator variables and the analysis of effect modification with interaction variables have been described in detail by Kleinbaum et al..[9] Each indicator variable was allowed to enter into the model separately, using a stepwise selection procedure. The p-value limit for selection into the model was set to 0.10. In this way a set of indicators with maximum discriminatory power was selected.

A Fracture Risk Score was calculated for each individual by the equation:

FRS = exp(A)/(1+exp(A)). where A represents the sum of the intercept and the logistic regression coefficients of the indicators that were selected in the model. The FRS represents the maximum likelihood estimate of the individual fracture risk. To evaluate the accuracy of the FRS in predicting fractures the observed nine year fracture risk was calculated in quintiles of the score. To evaluate the stability of the prediction a single split-sample test was performed.[6] For this purpose the study population was randomly split in two samples of approximately equal size; The first sample was used to derive the logistic regression coefficients and the second sample was used to calculate the risk score and the observed fracture risk.

4.3. Results

a. Fractures:

The fracture types and numbers are shown in Table II. Among 1014 women a total number of 203 fractures occurred in 161 women. Of all fractures 92 were type I osteoporotic (forearm or vertebral) fractures and these occurred in 83 women. The estimated incidence was 22.2 per 1000 women-years for all fractures and 10.1 per 1000 women-years for type I osteoporotic fractures. More than a single fracture was reported by 32 women. The nine year risk for one or more fractures was 0.16 for all fractures and 0.08 for osteoporotic fractures. Approximately 80 per cent of all fractures and 90 per cent of type I osteoporotic fractures occurred after a minimal trauma (e.g. fall from standing position) or without a known trauma (vertebral fractures).

b. Risk factors:

The nine year risk of one or more fractures in categories of each of the twelve risk factors is presented in the Figures I to III. For most risk factors the patterns of fracture risk were similar for all fractures and for type I osteoporotic fractures.

The fracture risk increased consistently over the 5-year categories of initial age (Figure I). The habit of smoking cigarettes appeared to be unrelated to fracture risk. although the proportion of osteoporotic fractures was relatively

Table II

Type and number of fractures over nine years of follow-up among 1014 middle aged Dutch women. (EPOZ Follow-up Osteoporosis).

Skull	1
Nasal bone	1
Vertebral body	37
Clavicula	3
Scapula	2
Rib	6
Os sacrum	2
Pelvis	4
Upper arm	11
Lower arm	7
Forearm	55
Hand & foot	44
Femoral neck	2
Upper leg	3
Patella	4
Lower leg	7
Ankle	14
Total	203

high among the women smoking 11 or more cigarettes per day. For Metacarpal Cortical Area (MCA), a "dose-response" type of relationship was present, but the contrast between the upper and lower tertiles was not very strong. For Relative Cortical Area (RCA), the contrast in fracture risk was stronger than for MCA, but the dose-response relationship was absent. The contrast between both MCA and RCA tertiles was less pronounced after adjustment for age differences (not shown). In the group of risk factors representing body size (Figure II), Quetelet index and radiological diameter of the knee appeared to be

unrelated to fracture risk. For body height and radiological diameter of the forearm a relatively strong contrast was present between the middle and lower tertiles. Low body height and low (!) diameter of the forearm appeared to offer some protection against the occurrence of fractures. In the group of risk factors representing reproductive history (Figure III), the risk of type I osteoporotic fractures seemed to be slightly increased in women who had a history of a late menarcheal age, a long period of lactation, or no children. For age and circumstances of the menopause, fracture risk was highest among the women who had an oophorectomy before age 45. However, quite contrary to common wisdom, fracture risk was lowest among the women who had an early natural menopause before age 45.

In general, the differences in fracture risk between the various risk categories were small. The differences were statistically significant ($p<0.05$) for age, RCA, body height and diameter of the forearm, both for all and for type I osteoporotic fractures.

Information concerning the use of postmenopausal therapy was collected retrospectively in the follow-up investigation. Of 742 women with complete data, 229 (31%) reported the use of some form of postmenopausal therapy (either oestrogens, progestagens or androgens). The use was predominantly of short duration: less than one year for 123 women and 3 years or more for 54 women. No relationship was found between the use of postmenopausal therapy and the occurrence of fractures. The use of the therapy was significantly more frequent among women who reported a hysterectomy or an ovariectomy. It was not significantly related to the presence of any of the other risk factors. In order to maintain the forward directionality of the study design, the information was not included in the construction of the Fracture Risk Score.

c. Fracture Risk Score:

For the construction of a Fracture Risk Score, variable-categories were selected and combined, using a stepwise logistic regression technique, as described above. The variable-categories selected for all fractures were: low body height, both low and high diameter of the forearm and both low and high RCA. In addition, for women over 55 years only: total period of lactation > 12 months and having no children were selected. The latter two categories were associated with an

Figure I

Nine year risk of all fractures and of Type I osteoporotic fractures in categories of initial age, smoking, Metacarpal Cortical Area and Relative Cortical Area among 742 middle aged women. (EPOZ Follow-up Osteoporosis).

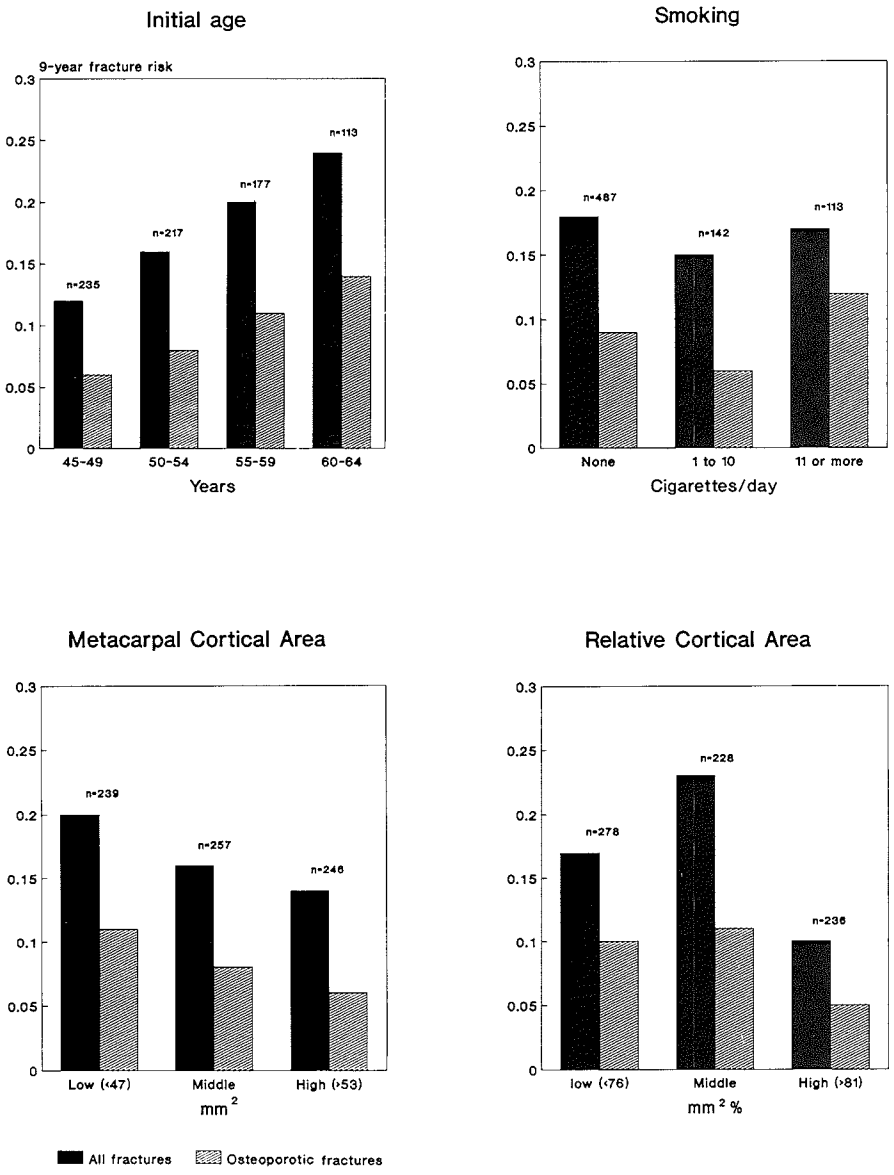


Figure II

Nine year risk of all fractures and of Type I osteoporotic fractures in categories of body size among 742 middle aged women. (EPOZ Follow-up Osteoporosis).

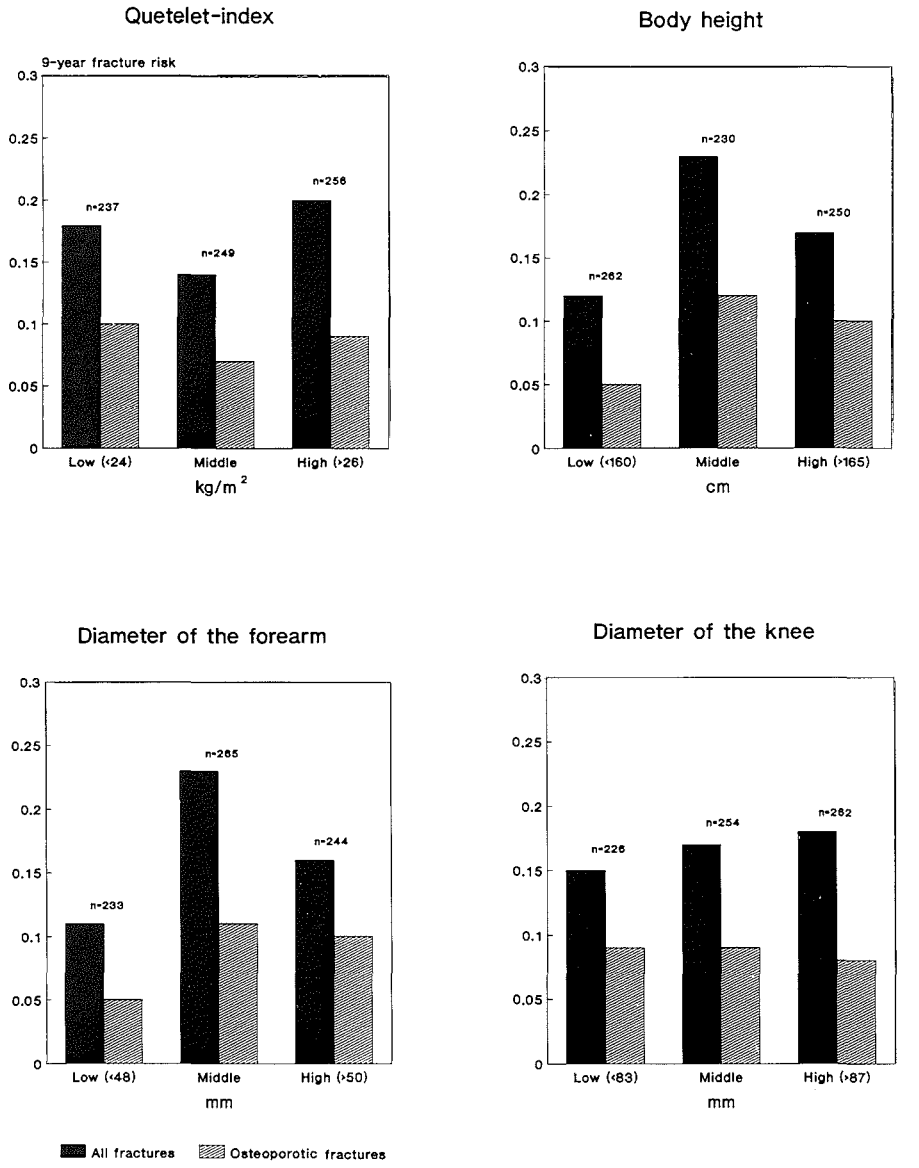
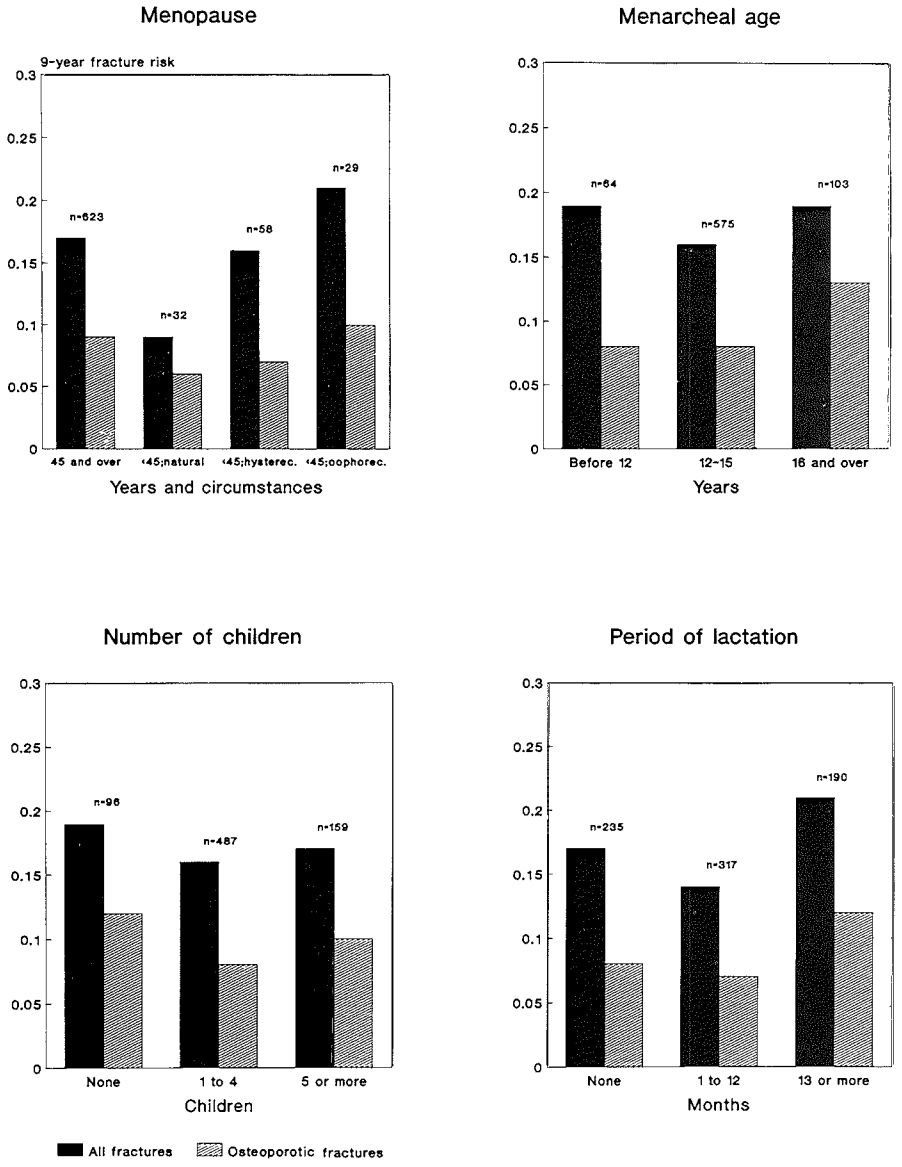


Figure III

Nine year risk of all fractures and of Type I osteoporotic fractures in categories of reproductive history among 742 middle aged women. (EPOZ Follow-up Osteoporosis).



increased risk, whereas the other categories were relatively protective as compared to the referent categories, which were complementary to the categories selected. The variable-categories selected for type I osteoporotic fractures were: low body height and age of menarche $\geq$ 16 years. For women over 55 years only: low MCA, total period of lactation $>$ 12 months and having no children were selected as well. Here, all variable-categories with the exception of low body height were associated with an increased fracture risk.

The variable-categories selected were used to calculate an individual FRS both for all and for type I osteoporotic fractures. The observed nine year fracture risk in quintiles of the FRS is presented in Figure IV. Results of a split sample test (sst) are included in the text in parentheses. The fracture risk ratio between the upper quintile versus the lower quintile was 6.4 (sst: 5.4) for all fractures and 7.0 (sst: 5.7) for type I osteoporotic fractures. The contrast in

Figure IV

Observed nine year risk of all fractures and of Type I osteoporotic fractures in quintiles of a Fracture Risk Score (FRS) among 742 middles aged women. (EPOZ Follow-up Osteoporosis).

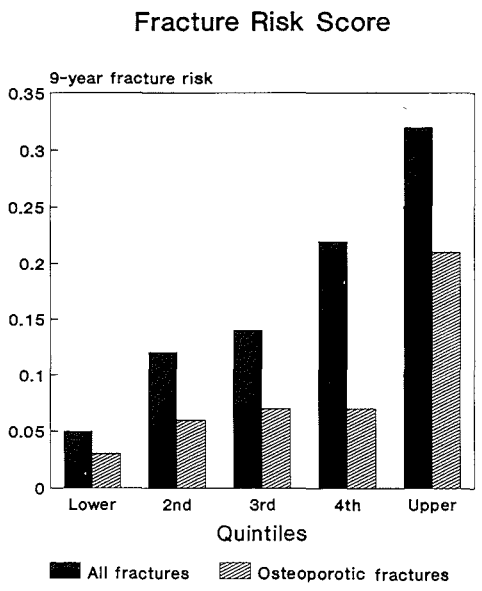


Table III

Number of subjects with and without fractures, in quintiles of the Fracture Risk Score (FRS). FRS 1-4 = Lower 4 risk quintiles; FRS 5 = Highest risk quintile; A. All fractures; B. Type I osteoporotic fractures. (EPOZ Follow-up Osteoporosis).

A. All fractures

	No fractures	All fractures	Total
FRS 1-4	515 (84%)	79 (63%)	594
FRS 5	101 (16%)	47 (37%)	148
Total	616 (100%)	126 (100%	742

B. Type I osteoporotic fractures

	No Type I fractures	Type I fractures	Total
FRS 1-4	560 (83%)	34 (52%)	594
FRS 5	117 (17%)	31 (48%)	148
Total	677 (100%)	65 (100%)	742

fracture risk between the two extreme quintiles was statistically significant ($p < 0.005$). However, if the upper quintile of the FRS were to be considered as a diagnostic test for predicting the occurrence of fractures the score was not very accurate. The number of individuals with and without fractures in the upper quintile versus the remaining quintiles of the Risk Score are presented in Table III. The upper FRS quintile contained no more than 37 per cent (sst: 32 %) of all fracture patients and 48 per cent (sst: 37 %) of type I osteoporotic fracture patients. The corresponding sensitivity and specificity of this prediction was 0.37 (sst: 0.32) and 0.84 (sst: 0.83) for all fractures and 0.48 (sst: 0.37) and 0.83 (sst: 0.82) for type I osteoporotic fractures.

4.4. Comment

The results of the present analyses can be summarised as follows. Information about single historical or radiological risk factors of osteoporosis is of little value in predicting the occurrence of fractures. The influence of several risk factors combined in a Fracture Risk Score resulted in a strong contrast between women with a high and a low risk of fractures. However, if the FRS were to be used to identify a high risk group of women, a selection of 20 per cent of all women between 45 and 64 years would contain less than 40 per cent of the fracture cases that occur in the general population during a nine year period.

To qualify our results we need to discuss the quality of our information and procedures. Information about non-vertebral fractures was obtained by questionnaire, asking participants to remember their fracture history over the past nine years. The reliability of such a fracture history has been shown previously.[10] As a validation of our data we estimated the expected number of limb fractures for our population, using incidence figures from the population of Rochester.[1] The expected number of limb fractures was 173 (95% conf. limits: 148-200), which was not significantly different from the observed number of 149 (95% conf. limits: 125-174).[11] The number of incident, i.e. newly occurring vertebral fractures in our study population could not be compared to other populations, because these figures are not available. In our population we found these fractures to be second in frequency after forearm fractures. The real incidence will be higher, since we assessed the vertebral bodies T12 to L5 only. With the conservative criterion that was used, approximately half of the incident vertebral fractures were wedge in type. The majority of women who had newly occurring vertebral fractures were asymptomatic: only three of the women were attending their general practitioner for this reason.

The limitations of our statistical procedure of constructing the FRS have to be borne in mind. The selection of risk factors was made purely mathematically, from a pool of approximately 60 variable-categories, using the p-value of the association to fracture risk as the selection criterion. With this approach maximum predictive power was selected from the data, including spurious predictive power that could have been present due to coincidental relationships. If this procedure were used for the purpose of risk factor identification it could

be rightly criticised for the fact that "chance" relationships specific to the particular data would be wrongly identified as potential risk factors. However, the present investigation was not intended to identify risk factors, but to evaluate the (maximum) efficiency of the use of risk factors for clinical fracture prediction. At worst, the inclusion of coincidental relationships will result in an estimation of the predictive power that is too optimistic. The importance of these chance effects can be demonstrated in two ways: 1). in a simulated prediction and 2). in a split sample test of the real data. In a set of simulated data with a similar structure as our data, but with variables that were randomly generated, we found a sensitivity and a specificity of 0.35 and 0.81 for "chance" prediction. In the split sample test the influence of coincidental relationships is reduced by deriving the prediction score from one half of the data, while testing it on the other half of the data. For the present data, both the contrast between the upper and lower quintiles of the FRS and the sensitivity and specificity of the predictions were reduced in the split sample test. Considering these limitation it must be expected that the performance of the FRS will be even less if the same scores were used in entirely different populations.

The present investigation demonstrates that the accuracy of fracture prediction on the basis of twelve historical and radiological risk factors of osteoporosis is relatively poor. We may wonder whether a better prediction could be attained if other risk factors were used. A necessary requirement for these risk factors would be that they discriminate well between individuals with and without fractures. A sophisticated technique, like Quantitative CT measurement of the mineral mass of vertebral bodies indeed has some predictive value for the occurrence of vertebral fractures.[12] However, this technique is not appropriate for population screening. For other measurement techniques at different sites of the skeleton, the overlap between fracture patients and normals has invariably been considerable and the use of these techniques for population screening has recently been discouraged.[13]

Next to the risk factors that were studied in the present investigation, other risk factors, such as low calcium consumption and physical activity have been suggested as risk indicators, because of an assumed influence on bone mass. Apart from the practical problem of the accurate measurement of these

variables, it seems unlikely that these factors will be strongly related to the occurrence of fractures, if bone mass is not. In the present investigation no relationship could be demonstrated between fracture occurrence and dietary calcium consumption that was estimated at follow-up.

A multitude of relatively rare conditions such as gastro-intestinal resection, renal insufficiency or hyperparathyroidism may be more strongly related to fracture risk. From a clinical point of view, these relationships could be important, but it can not be expected that these rare conditions will contribute to prediction of the frequently occurring fractures in the general population. It seems unlikely that any of the generally accepted risk factors of osteoporosis will be useful for an effective selection of women for fracture prevention programmes.

In conclusion, we cannot propose an effective selection strategy for women at high risk of fractures. Recently, on the International Symposium of Osteoporosis in Aalborg, Denmark, a panel of experts came to a similar negative result.[4] In a reaction to this disappointing situation an editorial suggested that women and their doctors will have to continue to rely on the traditional risk factors, such as slender, small build and early menopause.[14] The main conclusion of the present investigation is that this approach is not to be recommended. It may be preferable, or at least more economic,[15] to advise oestrogen therapy to all women -if not contraindicated- shortly after the menopause, rather than selecting a subgroup of women on the basis of risk factors which hardly predict future fracture occurrence.

4.5. Summary of the chapter

The possibility to predict the occurrence of skeletal fractures on the basis of risk factors of osteoporosis was evaluated in a follow-up study of 1167 women from the general population initially aged 45 to 64 years. During the nine years of follow-up 16 per cent of the women experienced one or more fractures.

In separate analyses of twelve historical and radiological risk factors which are considered important in the biomedical literature, none were found to be

strong indicators of future fractures; neither of all fractures, nor of type I osteoporotic fractures (fractures of the vertebral bodies and distal forearm).

A Fracture Risk Score (FRS) was calculated for each individual by combining the simultaneous influence of several risk factors in a multivariate analysis. The FRS discriminated relatively well between women with a high and low risk of fractures. The risk ratio between the highest and the lowest FRS quintiles was 6.4 for all fractures and 7.0 for type I osteoporotic fractures. However, if belonging to the highest quintile were to be considered as a screening test for fracture prediction the sensitivity and specificity were relatively poor: 0.38 and 0.84 for all fractures and 0.47 and 0.83 for type I osteoporotic fractures. These results indicate that it might not be efficient to use risk factor status to select women for fracture prevention programmes.

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Chapter 5

Metacarpal bone loss in middle-aged women

5.1. Introduction

Bone loss is a universal age related phenomenon, occurring both in men and women.[1] The loss of bone tissue from the skeleton will eventually lead to osteopenia, which is often held responsible for the increased frequency of fractures in the elderly.

In 1941 Albright et al. defined osteoporosis as a disease characterised by "too little bone in the skeleton". This disease was supposed to originate from a defective function of the osteoblast.[2] The concept of osteoporosis as a disease implies that some individuals are affected while others are spared. In 1970 this concept was challenged by Newton-John et al., who stated that in all individuals after a certain age, the rate of bone loss is of comparable magnitude.[3] According to this view osteopenia at old age is no more than a reflection of the level of bone density at a younger age. The argumentation of Newton-John was based on a review of cross-sectional studies of bone density. Valid longitudinal data were not available at that time and are still scarce.

In the present population based investigation the occurrence of bone loss was investigated longitudinally. The rate of metacarpal bone loss was measured in 799 women aged 45 to 64 years, who were followed for an average period of nine years. The occurrence of osteopenia, bone loss and individual differences in bone loss were evaluated.

5.2. Theoretical considerations

The purpose of the data analyses that were carried out was firstly to evaluate the existence of differences in the rate of bone loss between women and secondly to evaluate whether differences in the rate of bone loss were of relevance for the occurrence of osteopenia. Some theoretical considerations concerning the statistical techniques are presented first.

5.2.1. Analysis of differences in bone loss

Three approaches were used to evaluate the presence of differences in the rate of bone loss between women: a). comparison of standard deviations of bone density, b). estimation of the proportion of the variance in the rate of bone loss that could be ascribed to "true" loss and c). evaluation of the presence of the phenomenon of horse-racing.

a. Comparison of standard deviations:

The presence or absence of an age related change in the standard deviation of bone density has been interpreted by some as an indicator of the homogeneity between individuals of the process of bone loss. In 1972, Doyle described four different models of bone loss with their corresponding age related changes in the standard deviation (Figure I):[4]

I. A model of equal bone loss for all individuals, as was suggested by Newton-John and Morgan.[3] The standard deviation is unrelated to age.

II. A model of a high rate of bone loss for individuals with a high initial bone density and a low rate of loss for individuals with a low initial bone density. This model was inferred from the writings of Albright and Reifenstein.[5] The standard deviation diminishes progressively with age.

III. The opposite model of a high rate of bone loss for individuals with a low initial bone density and a low rate of loss for individuals with a high initial bone density. Here, the standard deviation increases progressively with age.

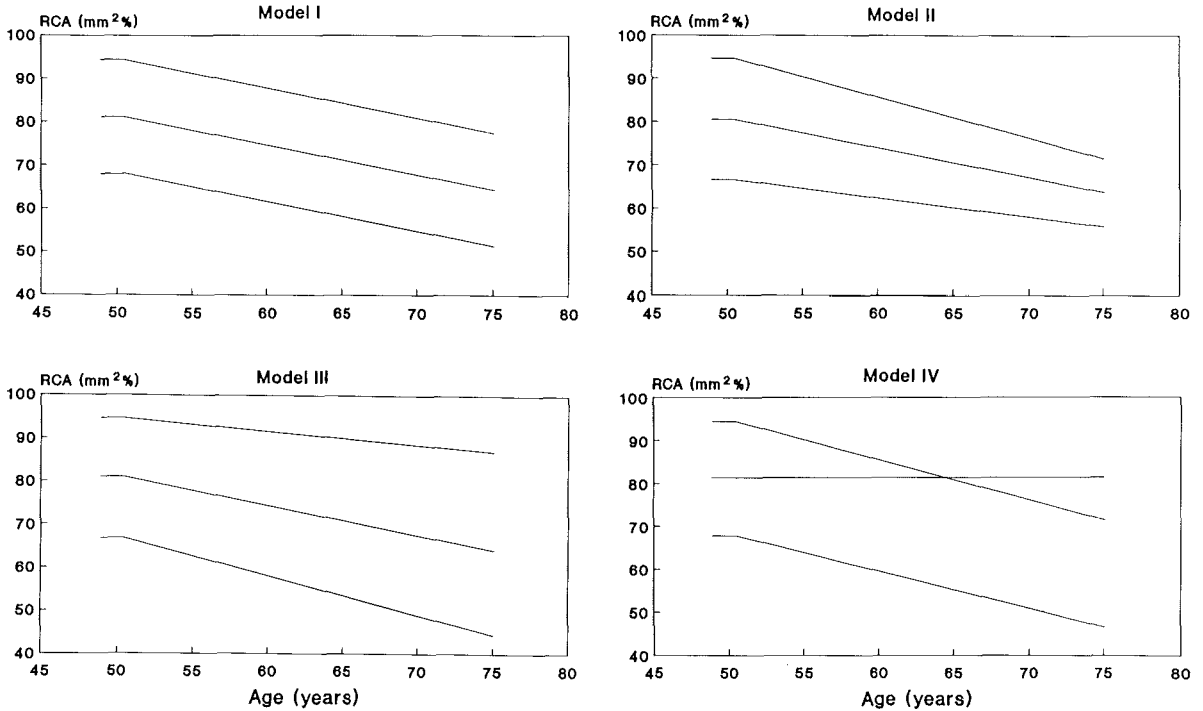
IV. A model of unequal bone loss with some women losing bone and others not losing bone, irrespective of initial level as was suggested by Adams et al..[6] Again, the standard deviation increases progressively with age.

b. Longitudinal rate of bone loss:

An intuitive approach of evaluating differences in the rate of bone loss between individuals is the calculation of the bone loss as it can be observed in a longitudinal investigation. At first sight, these data represent exactly the information needed. However, there is a problem; the difference between an initial and a

Figure I

Four models of bone loss according to Doyle (1972).[4] I. Similar loss for all individuals; II. High loss in relation to high initial bone density; III. High loss in relation to low initial bone density; IV. Loss for some individuals and not for others, irrespective of initial bone density. Each line in the figure represents a hypothetical individual course of age related bone loss.



follow-up measurement is not only determined by bone loss, but also by the measurement error. This problem is particularly relevant if the measurement error is relatively large as compared to "true" loss. As a consequence, direct measurements of individual changes in bone density are of limited value. As an alternative, the presence of "true" differences in the rate of bone loss can be demonstrated in groups, by estimating the "true" variance in bone loss. In the present evaluation this was done by subtracting the error variance, as estimated from 100 duplicate measurements, from the total variance of bone loss that was observed in the study population.[7]

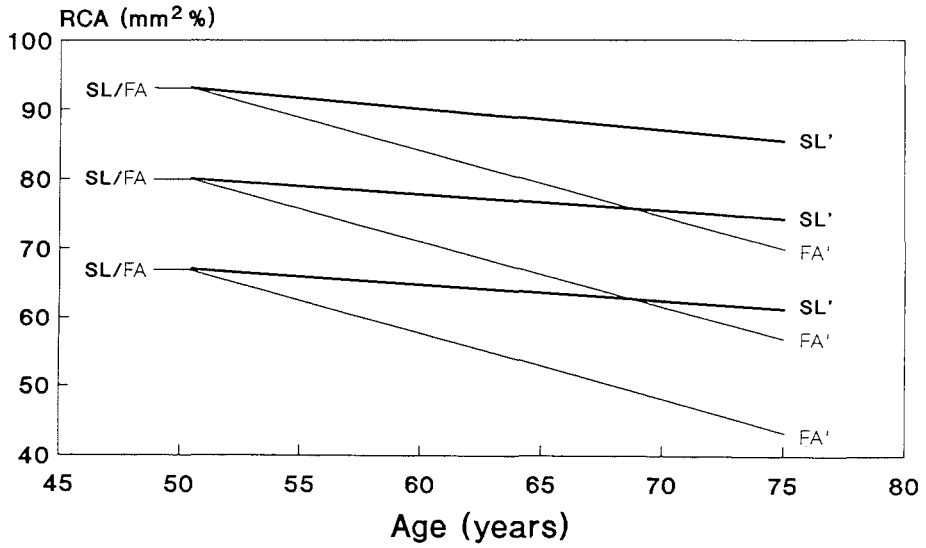
c. Horse-racing:

A third method to evaluate the presence of differences in the rate of bone loss between women is an analysis of the relationship between the level of bone density and the rate of bone loss. With this approach, the influence on bone density of consistent, long term differences in the rate of bone loss can be evaluated. The technique of relating rate of change to initial value has been used previously in pulmonary function and blood pressure research.[8,9,10] The basic idea can be described as follows: if a subgroup of women is consistently losing bone at a relatively fast rate over a longer period of time, this subgroup will "shift down" to the lower part of the frequency distribution of bone density (Figure II). The other way around, if the fast bone loss continues, the women with the lowest bone density will demonstrate the highest loss. This relationship will grow stronger as the period over which the fast loss has occurred has been longer; i.e. in the elderly women. The phenomenon of a drift of individuals with a high level of change to the extreme side of the frequency distribution has been nick-named "horse-racing", to indicate that those who win or lose will separate themselves ever more clearly from the crowd as time goes by.[8]

The presence of the phenomenon of horse-racing can be analyzed by linear regression of the rate of change in bone density on the initial value of bone density (change-in-RCA = a + b x initial-RCA). A positive value of the regression coefficient (b) will indicate horse-racing; i.e. a high rate of bone loss

Figure II

Schematic representation of the hypothetical relationship between rate of bone loss, level of bone density and age. The lines **SL-SL'** represent slow losers and the lines FA-FA' represent fast losers. Before age 50 no loss is present. At age 50 no relationship is present between rate of loss and level of RCA. As a result of horse-racing fast losers (FA') have become over represented at the lower end of the frequency distribution of bone density at age 75.



in relation to low bone density.* A negative coefficient may be the result of a high rate of bone loss at a high level of bone density, but it may also result from an important methodological complication of the analysis: regression towards the mean.

The phenomenon of regression towards the mean has been described among others by Oldham as a statistical pitfall in longitudinal analyses.[11] The problem arises from the presence of a random component in the initial and follow-up

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* Since change-in-RCA has a negative value, a positive value of the coefficient (b) in the regression equation is indicative of a less negative value of change-in-RCA in relation to high initial bone density and a more negative value of change-in-RCA in relation to low bone density. To avoid confusion: a positive association is indicative of high loss in relation to low initial level.

measurements of bone density. A single measurement of bone density can be considered as being composed of "true" bone density and measurement error. For those individual subjects where the measurement error in the initial measurement had been coincidentally high, the follow-up measurement error will be zero on average (assuming that the measurement error is distributed randomly). Also, for those individual cases where the measurement error in the initial measurement had been coincidentally low, the follow-up measurements error will be zero on average. Thus, if "true" bone density remains unchanged, high initial values will be related to lower follow-up measurements and low initial values will be related to higher follow-up measurements on average. In other words, the extreme values of the initial measurements will be closer to the mean at follow-up (regression towards the mean). This is because part of the extreme values were due to coincidental extreme measurement errors. As a result, the rate of bone loss at a high level of bone density would be spuriously overestimated and the rate of bone loss at a low level of bone density would be spuriously underestimated. A regression analysis of rate of change on initial value will result in a regression coefficient that is spuriously negative, or at least too low.

Various statistical techniques have been proposed to adjust for regression towards the mean. Oldham suggested regression of the rate of change on the mean value of initial and follow-up measurements.[11] Feinleib et al. have demonstrated that this technique is equivalent to an analysis of change in standard deviation, as described above.[9] They suggested an alternative method based on analysis of three or more measurements for each individual. Blomqvist et al. suggested a method of adjustment based on an estimation of the magnitude of the random component in the measurements.[12,13] The latter approach was chosen for the present analysis. In an analysis of simulated data this approach resulted in a correct estimation of the regression coefficient, provided that the random variance was not of the same magnitude as the total variance (Correction Factor is 1, resulting in division by zero in the calculation of the adjusted coefficient; see page 78). This condition was clearly fulfilled in the case of bone density measurements (page 82). A disadvantage of the technique as described by Blomqvist is that it depends strongly on an exact estimation of the random error. If the error is underestimated, the regression coefficient may

remain spuriously negative or too low. If the error is overestimated, a spurious conclusion concerning the presence of horse-racing may result. In the present analyses the measurement error was used as estimation of the random variance. This is a conservative estimate, because a possible random component in the measurements due to repeating a radiograph was not included in the error estimation. Finally, it should be noted that, irrespective of the sign of the coefficient, a trend between consecutive age groups can be indicative of the presence of horse-racing if the coefficient becomes more positive in elderly age groups.

5.2.2. Relevance of differences in bone loss

The analytic approaches discussed above were intended for an evaluation of the presence of differences in the rate of bone loss between women. A next step in the analysis aimed at an evaluation of the contribution of differences in the rate of bone loss to the occurrence of osteopenia. This was done by predicting the occurrence of osteopenia at follow-up by rate of bone loss or by initial level of bone density. The sensitivity and specificity of a prediction of osteopenia were compared for high/low rate of loss and high/low initial bone density.

5.3. Statistics

In the analyses, subjects who had one or more missing values for initial or follow-up bone density were excluded. For 56 of 855 women who participated in the complete follow-up investigation, either the initial or the follow-up radiographs were missing, or could not be measured for technical reasons. Complete data were available for 799 women. The mean value and standard deviation of initial RCA were similar for the 799 women that were used in the analyses and for 302 women who were not investigated, but for whom the baseline radiographs were available.

Three year moving averages of RCA were used for graphical presentation of the cross-sectional relationship between RCA and age. The relationship was

quantified by means of linear regression analysis. The frequency distributions of RCA were plotted in 5-year categories of age. To this end, data of the initial and follow-up investigation were combined; the curves were smoothed by sight.

The relationship between the rate of loss in RCA and the level of RCA, which could be indicative of the presence of consistent fast bone losers (horse-racing), was evaluated in linear regression analyses, as described above (change-in-RCA= a + b x initial-RCA). Adjustment for regression towards the mean was performed as described by Blomqvist et al.:[13] the maximum likelihood estimate of the "true" regression coefficient was calculated from the observed coefficients. The necessary correction factor (CF) was calculated as the ratio of the random variance and the observed variance of the measurements (for each age group). The measurement error of RCA was used as a conservative estimation of the random variances. The Adjusted Coefficient (AC) was calculated from the Observed Coefficient (OC) according to the formula: $AC=(OC+CF)/(1-CF)$. The Adjusted Standard Error (ASE) was calculated from the Observed Standard Error (OSE) according to the formula:
$ASE^2/(1+AC)^2 = OSE^2/(1+OC)^2 + (2 \times CF^2/(1-CF)^2) \times (1/f+1/f_1)$, where f and f_1

Table I

Mean values and standard deviations (SD) of Relative Cortical Area (RCA) in 5-year categories of initial age. Data from 799 women; EPOZ (1975-78) and follow-up (1985-86).

Initial Age	Number of Persons	EPOZ RCA-1	EPOZ SD	Follow-up RCA-2	Follow-up SD
		(mm^2%)		(mm^2%)	
45-49	285	81.2	6.4	76.0	6.5
50-54	204	79.9	7.0	73.3	7.3
55-59	182	76.5	7.0	69.8	7.8
60-64	128	72.1	7.7	66.2	8.6
All	799	78.3	7.6	72.3	8.1

were the degrees of freedom for the estimated total and error variance. The division of the crude change in RCA by postmenopausal years during follow-up, was taken into account by multiplying OC and OSE by this number of years prior to the calculation of the adjusted values, and dividing AC and ASE by the same number of years after the calculation.

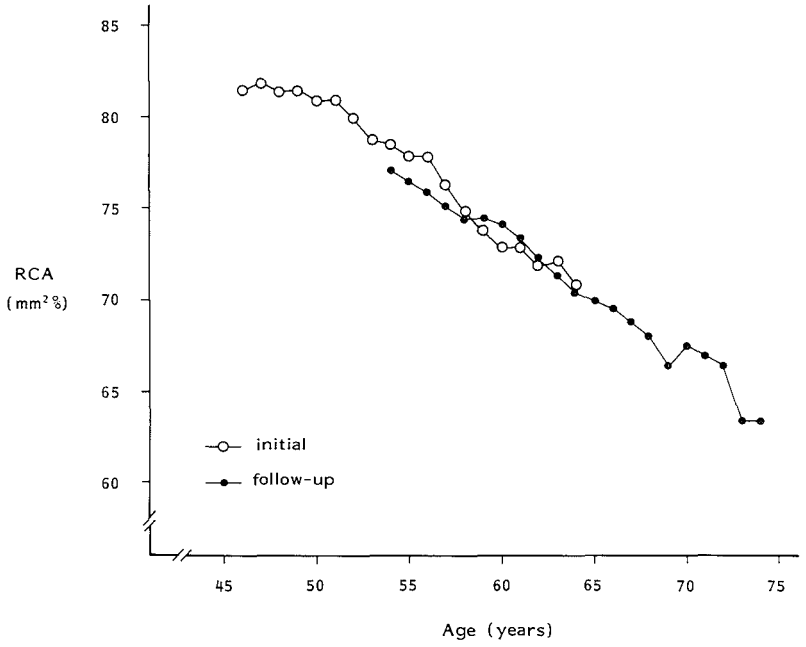
5.4. Results

a. Relative Cortical Area:

The mean values and standard deviations of RCA are presented in 5-year categories of initial age in Table I. The mean values of RCA declined with age, both cross-sectionally (compare age categories) and longitudinally (compare

Figure III

Three year moving averages of Relative Cortical Area (RCA) in relation to age. Data from 799 women from an initial (EPOZ: 1975-1978) and a follow-up (1985-1986) investigation.



RCA-1 to RCA-2). The standard deviation of RCA showed a slight increase both from one age category to the other and over the period of follow-up.

The cross-sectional relationship of RCA and age is shown graphically in Figure III. In linear regression analysis of the cross-sectional data the difference in RCA for women over 50 years of age was -0.80 mm^2% per year of age ($p<0.001$) for the initial investigation and -0.68 mm^2% per year of age ($p<0.001$) at follow-up. Before age 50, the difference in RCA was -0.06 mm^2% per year of age, which was not significantly different from zero. In a similar analysis using years since menopause instead of age the decline in RCA for the premenopausal women was -0.02 mm^2%/yr.

Smoothed drawings of the frequency distribution of RCA are shown in 5-year categories of age in Figure IV. The cross-sectional difference in RCA between age categories was reflected in a shift of the entire range of the distribution towards the lower values. If an arbitrary cutoff level for osteopenia was chosen at 70 mm^2%, the prevalence of osteopenia increased from 5 per cent among the women aged 45 to 49 years, up to 68 per cent among the women aged 70 to 76.

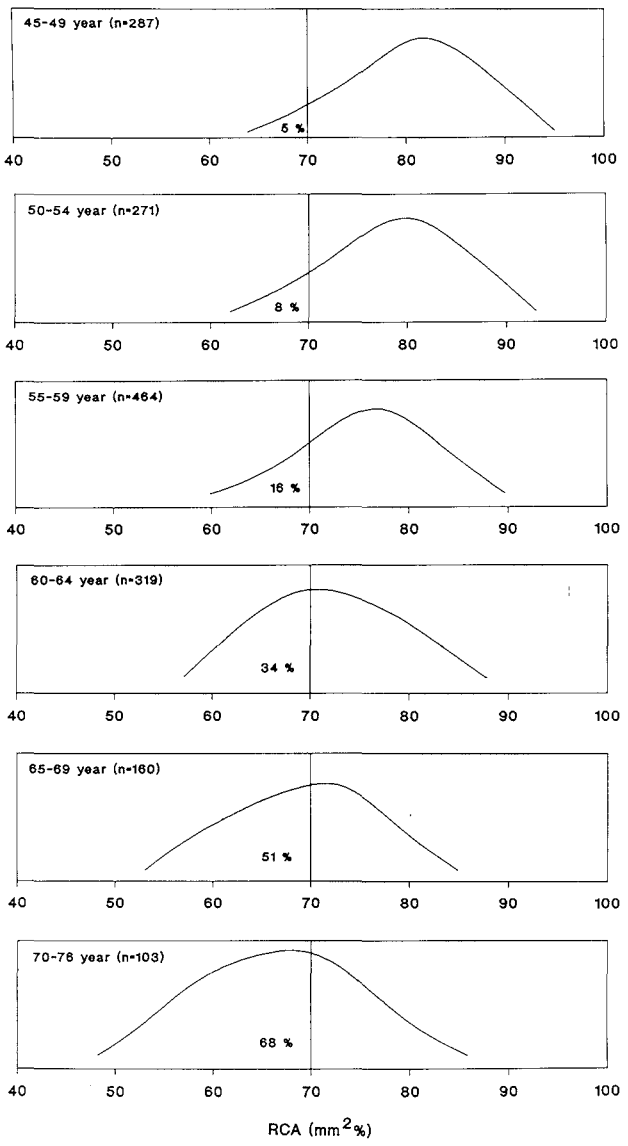
Table II

Mean values, standard deviations (SD) and 90 per cent range of annual rate of change-in-RCA as an absolute value and as a percentage of the initial value of bone density (%-change) in 5 year categories of initial age. Data from 799 women. (EPOZ Follow-up Osteoporosis).

Initial Age	Number of persons	Change-in-RCA (mm^2%/yr)	SD	Percentiles 5th	Percentiles 95th	%-Change (%)
45-49	285	-0.91	0.97	-3.09	+0.16	-1.1
50-54	204	-0.84	0.63	-1.89	-0.10	-1.0
55-59	182	-0.76	0.50	-1.63	-0.10	-1.0
60-64	128	-0.65	0.46	-1.38	-0.10	-0.9
All	799	-0.82	0.73	-2.16	0.00	-1.0

Figure IV

Frequency distribution of Relative Cortical Area (RCA) in 5-year categories of age. Data from 799 women from an initial (EPOZ: 1975-78) and a follow-up (1985-86) investigation were combined.



b. Loss of Relative Cortical Area:

The mean annual rate of change-in-RCA, calculated from the longitudinal data is presented in Table II. The average change-in-RCA was -0.82 mm^2% per year, which is -1.0 per cent of the mean initial RCA. The rate of change became less negative in relation to age, from -0.92 mm^2% or -1.1 per cent per year for the women initially aged 45 to 49 years to -0.65 mm^2% or -0.9 per cent per year for the women initially aged 60 to 64 years. The absolute age related decline in the rate of loss was statistically significant ($p<0.005$) in linear regression analysis. If the rate of loss was expressed as percentages of the initial value of RCA, the decline was not significant ($p<0.12$).

Bone loss was present in 95 per cent or more of the women over 50 years of age. The total variance in change-in-RCA was 0.53 $(mm^2\%)^2$; the estimated error variance was 0.15 $(mm^2\%)^2$; thus an estimate of the "true" variance was 0.38 $(mm^2\%)^2$, or 72 per cent of the total variance.

Table III

Adjusted regression coefficients (b) of linear regression analysis of annual rate of change-in-RCA on initial level of RCA, for 799 women in 5-year categories of initial age. Change-in-RCA was expressed as absolute change and as percentage-change of the initial value. Adjustment for regression towards the mean according to Blomqvist. Standard errors (SE) in parentheses. (EPOZ Follow-up Osteoporosis).

Initial Age	Number of persons	Absolute change b*	(SE)	Percentage-change b*	(SE)
45-49	285	-0.030**	(0.010)	-0.022	(0.014)
50-54	204	-0.012	(0.008)	-0.001	(0.010)
55-59	182	+0.006	(0.007)	+0.021**	(0.009)
60-64	128	+0.010	(0.007)	+0.030**	(0.009)
All	799	-0.012**	(0.004)	-0.001	(0.006)

* Slope of change-in-RCA on initial RCA
** $p<0.05$

c. Horse-racing:

The adjusted coefficients (b) and standard errors of the regression analyses of change-in-RCA on initial RCA are presented in Table III. The analyses were performed separately for change-in-RCA as an absolute value and for change-in-RCA as a percentage of the initial value. For the total group, absolute change-in-RCA was negatively related to the level of RCA and percentage-change was unrelated to level of RCA. The relationship was dependent on age. In 5-year age categories the negative relationship was strongest for the younger women. In elderly women the relationship became positive. For percentage-change a more positive relationship was present in all age categories. Both for absolute and for percentage-change the coefficients increased consistently from the younger towards the older age categories, which is indicative for horse-racing.

d. Prediction of osteopenia at follow-up:

At the time of the initial investigation, RCA was below the arbitrary

Table IV

Cross table of A). Rate of bone loss during a 9-year follow-up period and presence of osteopenia at follow-up (1985-86) and B). Initial bone density (1975-78) and presence of osteopenia at follow-up (1985-86) for 799 middle aged women. (EPOZ Follow-up Osteoporosis).

	Osteopenia at follow-up (RCA < 70 mm^2%)		
A.	No	Yes	Total
Slow Losers (≤ 1%/yr)	343	105	448
Fast losers (> 1%/yr)	186	165	351
Total	529	270	799
B.	No	Yes	Total
Initial RCA > 77 mm^2%	418	32	450
Initial RCA 77-70 mm^2%	110	137	247
Initial RCA < 70 mm^2%	1	101	102
Total	529	270	799

70 mm^2% limit for osteopenia in 12.8 percent of the women. At follow-up this percentage had increased to 33.8 %. The relationship between rate of loss and occurrence of osteopenia is presented in Table IV-A for an arbitrary cutoff level for rate of loss at 1 per cent per year. If the presence of osteopenia at follow-up was predicted by considering a rate of bone loss above 1 per cent per year as a positive "test", the sensitivity and specificity of the prediction were 0.61 and 0.65 respectively. The relationship between initial level of bone density and presence of osteopenia at follow-up is presented in Table IV-B for an arbitrary cutoff level for initial bone density at 77 mm^2%. If the presence of osteopenia at follow-up was predicted by considering a low initial bone density, below 77 mm^2%, as a positive "test", the sensitivity and specificity of the prediction were 0.88 and 0.79 respectively.

5.5. Comment

The results of the analyses can be summarised as follows. Bone loss was present in more than 95 per cent of the women initially aged 50 years and over. On average, the rate of bone loss was 1 per cent of the initial bone density per year. The rate of bone loss was not similar for all women, but the differences in rate of bone loss that were present contributed relatively little to the occurrence of osteopenia.

5.5.1. Differences in bone loss

The presence of differences in the rate of bone loss between individuals was evaluated in three ways. Firstly, the standard deviations of bone density were compared cross-sectionally between consecutive age groups and longitudinally within each age group over the period of follow-up. Secondly, actual differences in the rate of bone loss as measured longitudinally were evaluated; and thirdly the rate of bone loss was related to the level of bone density.

1. Comparison of the standard deviation of bone density in 5-year age groups revealed a small but consistent increase from one age group to the other. Also, an increase in the standard deviation was present over the period of follow-up. This may be interpreted as an indication that individuals were losing bone at different rates. Alternatively, cross-sectional differences in the standard deviation may be explained from historical variation in the presence of bone losing influences (cohort-effect). Some of the longitudinal differences in the standard deviation may have occurred as a result of variation in the period of follow-up.

2. Differences in the rate of bone loss were present between individuals in the longitudinal measurements. Theoretically, these differences may originate from "real" biological differences or from differences due to measurement error. In the present investigation, the measurement error was insufficient to explain the variation in the rate of bone loss between individuals. This again suggests "real" differences in the rate of bone loss between individuals. It should be noted, however, that the range of the differences may be considerably less than the range indicated in Table III. Extreme values are particularly likely to be affected by measurement errors.

5.5.2. Horse-racing

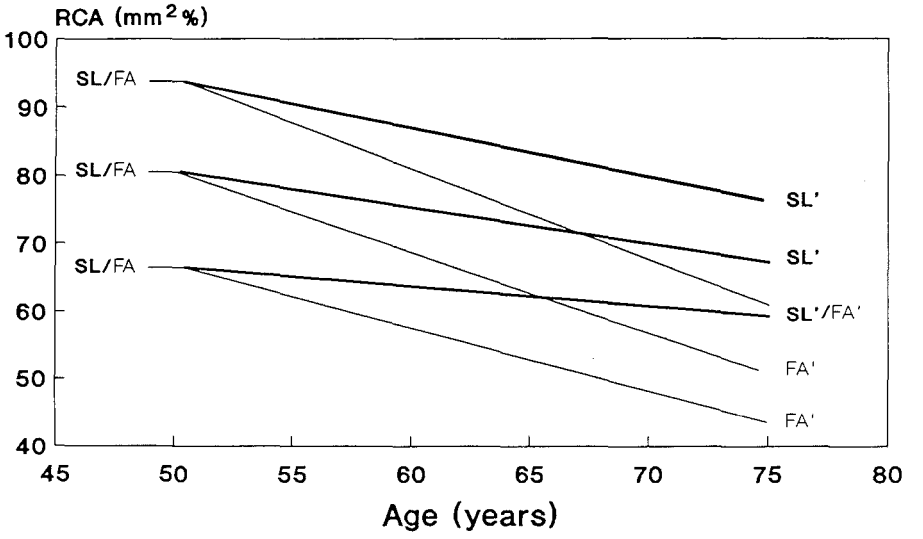
The long term impact of differences in the rate of bone loss was evaluated by relating the rate of change-in-RCA to the level of bone density. If a high rate of bone loss does add to the occurrence of osteopenia, it may be anticipated that in due time, if bone loss continues at a high rate, it will become fastest among the women with a low bone mass (horse-racing). In a regression analysis of the rate of change-in-RCA on level of bone density, a positive regression coefficient will indicate horse-racing (high loss related to low level). A negative coefficient may indicate that bone loss proceeds fastest in individuals with a high bone density, or it may indicate regression towards the mean.

In the present data a negative relationship was present between the absolute rate of change-in-RCA and the initial level of RCA. In consecutive 5-year

categories of initial age the coefficient was more positive in each next age group. The latter observation is indicative of horse-racing. A similar relationship has been found previously for change in blood pressure.[10] The interpretation of these results is complicated, because it can not be excluded that the negative sign of the coefficients are the result of an underestimation of the random error component in the measurements, which would result in insufficient adjustment for regression towards the mean. If this possibility is left aside, the most likely explanation of the results might be that in the beginning of the process of bone loss, just after the age of 50 years, rate of change-in-RCA is negatively related to bone density (Figure I; Model II). However, at each level of bone density, some individuals are losing bone tissue more rapidly than others and horse-racing does occur (Figure II). As a consequence, the initial proportional relationship between bone loss and bone density (high loss in relation to high level) becomes overshadowed by the subgroup of fast losers shifting down in the distribution of bone density. This hypothetical model of a

Figure V

Hypothetical model of a combination of proportional bone loss (high loss in relation to high level) and horse-racing. The lines **SL-SL'** represent slow losers; the lines FA-FA' represent fast losers.



combination of proportional bone loss and horse-racing is represented graphically in Figure V. The model is only schematic, since in a truly proportional model of bone loss, the lines ought to be curved. Physiologically this interpretation can be supported if it is assumed that bone loss is a result of a disequilibrium between bone formation and bone resorption, as it occurs at the metabolic surface of the bone tissue. The absolute amount of bone that is lost will depend on the magnitude of the disequilibrium and on the size of the metabolic surface. The proportional component of the bone loss (Figure I: Model II), as manifested by the negative association between change-in-RCA and level of RCA in the younger age groups, can be considered as the influence of the size of the metabolic surface. The horse-racing component as manifested in the negative relationship between change-in-RCA and level of RCA being more positive in every next 5-year category of initial age, could be considered the result of a different magnitude of the disequilibrium between bone loss and bone formation. The influence of the size of the metabolic surface was (more or less) controlled in the analysis of percentage-change on initial bone density. As expected the coefficients were more positive (Table III).

An interesting feature of the model that is presented in Figure V is that the standard deviation remains relatively constant over time, despite the obvious differences in the rate of bone loss between individuals. In fact, the model illustrates that an evaluation of the presence of differences in the rate of bone loss between individuals on the basis of age related changes in the standard deviations may be of limited value. The model may explain some of the conflicting statements in the literature concerning the absence or presence of fast losers.

5.5.3. Relevance of differences in the rate of loss

Considering these results, we may wonder whether the occurrence of a fast rate of loss among some individuals contributes practically to the occurrence of osteopenia in the population. This question has become of clinical importance recently, since Christiansen et al. reported about a simple and sensitive test to select women with more than average bone loss, without measuring bone

density. They suggested the use of the test for selection of women for prophylactic oestrogen therapy.[14] In the present data initial bone density was a better predictor of osteopenia at follow-up than rate of bone loss. Apparently, the differences in the rate of loss between individuals were not sufficiently large to contribute importantly to the occurrence of osteopenia over a nine year period. The range between an initial high and low bone density is of such magnitude, that it may be doubted whether relative small differences in the rate of loss between individuals will contribute much more to the occurrence of osteopenia over a longer time period. In a clinical sense, the idea of Newton-John that bone density at old age is predominantly determined by bone density at a younger age may still be valid.

5.6. Summary of the chapter

Age related bone loss and differences in the rate of bone loss, were evaluated in a longitudinal population based study among 799 women initially aged 45 to 64 years. Radiographs of the hands were made twice, over an average follow-up period of nine years. The Relative Cortical Area (RCA) of the metacarpals, and the annual rate of loss of RCA were determined.

Bone loss started around the age of 50 years, presumably after the menopause. The average annual rate of loss was approximately 1 per cent of the initial value. If osteopenia was defined as a level of RCA below the fifth percentile of women aged 45 to 49 years, the prevalence of osteopenia increased from 5% (by definition) for women aged 45 to 49 years, up to 68 percent for women aged 70 to 76.

Bone loss was present in more than 95 per cent of women over 50 years of age. The rate of loss was not similar for each individual. The data indicated the presence of a consistent subgroup of fast bone losers. The occurrence of osteopenia at the time of follow-up, however, was more accurately predicted from initial bone density than from differences in the rate of loss. The occurrence of osteopenia was more strongly determined by bone density at a young age than by differences in the rate of bone loss.

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Chapter 6

Sex Hormone Binding Globulin in postmenopausal women: a predictor of osteoporosis superior to endogenous oestrogens

6.1. Introduction

In postmenopausal women oestrogens are known to be related to bone loss and risk of fractures.[1] Postmenopausal bone loss can be prevented by oestrogen substitution therapy[2,3], and women who have had such therapy suffer less fractures of the vertebrae,[4] forearm[5] and femoral neck.[5,6] The importance of endogenous oestrogen activity in preserving bone density after the menopause is illustrated from the loss of bone tissue in relation to oophorectomy[7] and from the well documented positive correlation between body mass and bone density.[8] After the menopause, when the ovarian oestrogen production has ceased, body mass becomes the main determinant of endogenous oestrogen activity.[9] Androstenedione produced in the adrenal glands may be converted in peripheral tissues to oestrone, which in turn may be further converted to the more potent oestradiol.[10]

In two recent investigations forearm mineral density and forearm mineral loss were found to be related directly to postmenopausal serum oestrone and oestradiol concentrations.[11,12] In the present investigation the role of (lack of) endogenous oestrogen activity as a contributing factor in the etiology of postmenopausal osteoporosis was elaborated in further detail. In a population based investigation among 746 postmenopausal women aged 53 to 76 years, body mass, serum oestradiol, oestrone, androstenedione and sex hormone binding globulin (SHBG) levels, were investigated cross-sectionally in relation to metacarpal bone density and retrospectively in relation to annual rate of metacarpal bone loss (change-in-RCA; chapter 3, page 43) and occurrence of fractures. The size of the study population allowed an estimation of the influence of each of these variables while adjusting for correlation to the others.

6.2. Statistics

In the statistical analyses, subjects who had one or more missing values for any of the study variables were excluded. Complete data were available for 763 women, of whom 17 were excluded from the analyses, because they had premenopausal oestradiol levels above 100 pmol/l. The mean values, standard deviations and 90 per cent ranges of the study variables are summarised in table I. The frequency distributions of some of the variables, especially for oestradiol, were considerably skewed. The results of the analyses were not essentially different if the distributions were normalised by logistic transformation.

Univariate and multivariate linear regression analyses were used to evaluate the relationship between either RCA at follow-up or change-in-RCA and the study variables (hormone levels, body mass and age at follow-up). Multivariate analyses were used to adjust for interdependency between the study variables.

Table I

Mean values, standard deviations (S.D.) and 90 per cent ranges of study variables in 746 Dutch postmenopausal women aged 53 to 76 years. (EPOZ Follow-up Osteoporosis).

			Percentiles	
	Mean	S.D.	5th	95th
Age at follow-up (years)	62.3	5.6	54.7	72.2
RCA at follow-up (mm^2%)	72.2	8.0	57	84
Change-in-RCA (mm^2%/yr)	-0.82	0.69	-2.16	0.00
SHBG (nmol/l)	78.4	49.3	16.7	158.3
Oestradiol (pmol/l)	28.2	20.6	5	69
Oestrone (pmol/l)	140.9	52.7	69	238
Androstenedione (nmol/l)	3.5	1.9	1.2	7.1
Body mass (kg/m^2)	26.3	3.9	20.7	32.9

To facilitate mutual comparisons within the study population, regression coefficients were standardized by multiplication with the standard deviation of the variable concerned. These standard deviations, as estimated from a sample of the general population were considered as the natural range of the variables. For comparisons to different populations it may be wise to check for the similarity of standard deviations.[13] The value of these standardized coefficients represents the mean difference in the dependent variable (RCA or change-in-RCA) with 1 standard deviation difference in the independent variable (e.g. hormone levels). For example, a difference in serum SHBG level of 49.3 nmol/l (1 standard deviation; Table I) corresponds to a mean difference in RCA of -1.85 mm^2% (standardized regression coefficient; Table II).

A t-test was used to evaluate the differences in the mean values of the study variables for the women who had no fractures, those who had type I osteoporotic fractures (forearm or vertebral fractures) and those who had other, non-osteoporotic fractures.

Table II

Standardized regression coefficients of univariate and multivariate analyses of study variables on RCA at follow-up in 746 Dutch postmenopausal women aged 53 to 76 years. Standard errors in parentheses. (EPOZ Follow-up Osteoporosis).

	Univariate	p <	Multivariate	p <
Age at follow-up	-3.64 (±0.26)	0.001	-3.57 (±0.25)	0.001
SHBG	-1.85 (±0.29)	0.001	-1.15 (±0.26)	0.001
Oestradiol	1.14 (±0.29)	0.001	0.82 (±0.28)	0.005
Oestrone	1.11 (±0.29)	0.001	0.44 (±0.31)	ns
Androstenedione	0.53 (±0.29)	ns	0.01 (±0.28)	ns
Body mass	0.81 (±0.29)	0.001	0.65 (±0.28)	0.05

6.3. Results

The standardized regression coefficients of the analyses for Relative Cortical Area (RCA) are presented in Table II. In the univariate analyses, RCA was positively related to body mass, serum oestrone, oestradiol and androstenedione and negatively to age and serum SHBG. All relationships were statistically significant, with the exception of that for androstenedione. In the multivariate analysis the relationship was no longer significant for serum oestrone and the regression coefficient for androstenedione decreased virtually to zero. Apart from age, the standardized regression coefficient for SHBG was largest (as an absolute value), followed by oestradiol and body mass.

The standardized regression coefficients of the analyses for the annual rate of change-in-RCA are presented in Table III. In the univariate analyses, change-in-RCA was less negative at a high body mass, serum oestrone, oestradiol, androstenedione and age. Change-in-RCA was more negative at a high serum SHBG. Again, all relationships were statistically significant with the exception of that for androstenedione. In the multivariate analysis the regression coefficients for age and SHBG remained statistically significant. If the rate of bone loss was expressed as percentage of the initial value (standardization

Table III

Standardized regression coefficients of univariate and multivariate analyses of study variables on change-in-RCA in 746 Dutch postmenopausal women aged 53 to 76 years. Standard errors in parenthesis. (EPOZ Follow-up Osteoporosis).

	Univariate	p <	Multivariate	p <
Age at follow-up	0.107 (±0.025)	0.001	0.113 (±0.025)	0.001
SHBG	-0.092 (±0.025)	0.001	-0.090 (±0.026)	0.005
Oestradiol	0.077 (±0.025)	0.005	0.047 (±0.027)	ns
Oestrone	0.070 (±0.025)	0.01	0.042 (±0.030)	ns
Androstenedione	0.019 (±0.025)	ns	-0.018 (±0.028)	ns
Body mass	0.068 (±0.025)	0.01	0.013 (±0.027)	ns

Table IV

Mean value of study variables for subjects with and without fractures in 746 Dutch postmenopausal women aged 53 to 76 years. Standard errors in parentheses. (EPOZ Follow-up Osteoporosis).

Total group								
	Osteop. frac. (n=62)		t-test	no frac. (n=620)		t-test	other frac. (n=64)	
Age at follow-up	64.7	(±0.7)	*	61.8	(±0.2)	*	63.5	(±0.8)
RCA at follow-up	69.2	(±1.0)	*	72.5	(±0.3)	ns	71.3	(±0.8)
Change-in-RCA	-0.76	(±0.08)	ns	-0.83	(±0.03)	ns	-0.81	(±0.08)
SHBG	87.3	(±6.3)	ns	77.9	(±2.0)	ns	75.0	(±5.9)
Oestradiol	29.4	(±2.6)	ns	28.2	(±0.8)	ns	27.0	(±2.5)
Oestrone	151.8	(±6.4)	ns	140.6	(±2.1)	ns	133.5	(±6.4)
Androstenedione	3.8	(±0.2)	ns	3.5	(±0.1)	*	3.0	(±0.2)
Body mass	27.0	(±0.5)	ns	26.2	(±0.2)	ns	27.0	(±0.5)
Age ≥ 65 years								
	Osteop. frac. (n=31)		t-test	no frac. (n=191)		t-test	other frac. (n=27)	
Age at follow-up	69.5	(±0.5)	ns	68.9	(±0.2)	ns	69.8	(±0.6)
RCA at follow-up	66.8	(±1.4)	ns	68.0	(±0.6)	ns	67.3	(±1.3)
Change-in-RCA	-0.71	(±0.07)	ns	-0.68	(±0.03)	ns	-0.79	(±0.08)
SHBG	102.9	(±10.0)	*	81.9	(±3.8)	ns	79.5	(±12.1)
Oestradiol	34.7	(±4.2)	ns	29.6	(±1.5)	ns	32.9	(±4.8)
Oestrone	153.9	(±6.6)	ns	142.4	(±4.2)	ns	133.0	(±11.3)
Androstenedione	3.9	(±0.3)	ns	3.6	(±0.2)	*	3.0	(±0.2)
Body mass	26.1	(±0.7)	ns	26.4	(±0.2)	*	27.6	(±0.5)

* $p<0.05$

for metabolic surface; chapter 5. page 87) the relationships were essentially similar.

The mean values of the study variables for fracture patients and controls are presented in Table IV. Statistically significant differences were found for age. RCA and serum androstenedione (Table IV-upper panel). Women who had one or more fractures in the previous nine years were older than women without fractures. RCA was lower for women with type I osteoporotic fractures and androstenedione was lower for women with non-osteoporotic fractures. In the subgroup of elderly women, aged 65 years and older, statistically significant differences were found for serum SHBG, body mass and serum androstenedione (Table IV-lower panel). SHBG levels were higher for women with type I osteoporotic fractures. Body mass was higher and serum androstenedione lower for women with other fractures. The differences between cases and controls were not substantially influenced by multivariate adjustments.

6.4. Comment

a. Bone density and bone loss:

The influence of endogenous oestrogen activity on bone density and bone loss has been found in several studies. Murakami et al. have demonstrated a positive correlation between serum oestradiol and forearm mineral density in postmenopausal women[14] and Cauley et al. have found a similar relationship for serum oestrone.[11] Riis et al. have demonstrated lower levels of both serum oestradiol and oestrone in postmenopausal women characterized as rapid bone losers as compared to slow bone losers.[12] None of the previous studies have investigated the independent influences of oestrone, oestradiol, SHBG or body mass in relation to bone mass or bone loss.

In the present study bone density was positively related to the serum concentration of oestradiol and negatively to the concentration of SHBG. The negative influence of SHBG on bone density was confirmed by its relation to the rate of bone loss. The serum concentration of oestrone was not an important determinant of bone density or bone loss. The results of the multivariate analyses demonstrated that the influence of oestrone as a single variable was

explained by its correlation to the other variables. Oestrone was especially correlated to oestradiol (r=0.40) and body mass (r=0.34). The serum concentration of androstenedione was unrelated to either bone density or bone loss.

In the multivariate analysis, body mass was positively related to bone density, but not to bone loss. The relationship between body mass as a single variable and bone loss, was explained by the correlation of body mass to the other variables. Body mass was especially correlated to oestrone (r=0.34), oestradiol (r=0.23) and SHBG (r=-0.28). Apparently, the relationship between body mass and bone loss was mediated by the positive association of body mass with oestrogen level and the negative association of body mass with SHBG. The latter association has been previously described by de Moor et al..[15] The persistence of an association between body mass and bone density, in the multivariate analysis may suggest an independent premenopausal positive influence of body mass on (peak) bone density.

b. Fractures:

Low bone density or high rate of bone loss are no pathologic conditions as long as the skeleton remains intact. The pathology of these conditions lies in the increased likelihood of fractures. The role of endogenous sex steroid activity in relation to fracture risk has been investigated in several small case-control studies. For women with vertebral fractures normal, increased and decreased levels of oestrogens have been found and levels of SHBG, androstenedione or testosterone were normal in the majority of studies.[16,17,18,19,20] For women with femoral neck fractures Davidson et al. demonstrated increased levels of SHBG, decreased levels of free oestradiol and testosterone and normal levels of androstenedione and oestrone.[21] It must be noted that in most studies the subjects with vertebral fractures were roughly 10 years younger than those with femoral neck fractures. This is important because bone loss is a process which proceeds relatively slow. It will take a considerable period of time before fast bone losers differentiate themselves from slow bone losers in terms of an increased fracture risk. As a consequence, a contrast in sex hormone activity between fracture cases and healthy controls is most likely to be found in elderly women.

The present investigation was based on a large unselected sample of postmenopausal women. No differences were found between fracture cases and controls for serum levels of oestrone and oestradiol. For androstenedione serum levels were decreased in women with other than type I osteoporotic fractures. This relationship may be coincidental, since no relationships were found between androstenedione levels and bone density or bone loss. For SHBG no differences were found for the total study population, but an increased level of SHBG was demonstrated for the subgroup of elderly women with type I osteoporotic fractures. This suggests an increased risk of these fractures after an extended period of exposure to high levels of SHBG.

In conclusion, the role of endogenous oestrogens was investigated in relation to the level of bone density, the rate of bone loss and the risk of fractures in a large population based study. The level of serum SHBG was found to be a stronger determinant of bone density and bone loss than either serum oestradiol or oestrone levels and among these, SHBG was the only factor which was also related to fracture risk. Most likely, these findings should be explained from a dominant negative influence of SHBG on free (active) oestradiol and possibly on free (active) testosterone. Probably, the variance in free oestradiol in postmenopausal women is determined more strongly by the variance in SHBG than by the variance in total oestradiol. The results support the hypothesis that endogenous oestrogen activity in general, and serum SHBG in particular, may play a significant role in the etiology of postmenopausal osteoporosis.

6.5. Summary of the chapter

To quantify the role of endogenous oestrogen activity in osteoporosis body mass, Relative Metacarpal Cortical Area (RCA) serum oestrone, oestradiol, androstenedione, and Sex Hormone Binding Globulin (SHBG) were measured in 746 postmenopausal women aged 53 to 76 years. The occurrence of fractures and the rate of loss of RCA (change-in-RCA) were determined over the previous nine years.

Both RCA and change-in-RCA were significantly related to body mass, serum oestrone, oestradiol, and SHBG. The influence of the first three variables appeared to be bone preserving, whereas the latter appeared to be bone wasting. Serum oestradiol, SHBG and body mass proved to have an independent relationship with RCA in a multivariate regression analysis. The relationship to change-in-RCA was statistically independent for serum SHBG only. Serum androstenedione was unrelated to either RCA or change-in-RCA.

In the total study population, body mass, serum oestrone, oestradiol and SHBG were unrelated to the occurrence of fractures. Androstenedione levels were lower for women with non-osteoporotic fractures, as compared to controls without fractures. In the subgroup of 249 elderly women, aged 65 to 76 years, SHBG levels were significantly higher for women with type I osteoporotic fractures as compared to controls.

These results suggest a substantial bone wasting influence of SHBG in postmenopausal women, possibly resulting in an increased risk of type I osteoporotic fractures in elderly women.

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Chapter 7

A reflection on the methods and some recommendations

7.1. Introduction

The investigation that is the subject of this thesis can be characterised as a longitudinal population based investigation, that was intended to evaluate the accuracy of fracture prediction on the basis of known risk factors of osteoporosis. In addition, the pattern of metacarpal bone loss in middle-aged women and the possible role of endogenous oestrogen activity in the pathogenesis of osteoporosis were investigated. From the point of view of epidemiologic methodology, chapter four is an example of a clinical prediction study for the evaluation of the efficiency of one particular approach of selecting patients for fracture prevention programmes. Chapter five is an example of a mathematical analysis of the homogeneity of a process of change within a population. The existence of differences in the rate of bone loss between individuals and the relevance of these differences for the occurrence of osteopenia were evaluated. Chapter six is an example of an evaluation of the relationship between a potential pathogenetic factor (endogenous oestrogen activity) and the occurrence of a disease (osteoporosis).

The results of the investigation can be summarised as follows:

a. Prediction of fractures (chapter 4):

1) Fractures occurred frequently in middle-aged women and the risk of fractures increased with age.
2) Fractures of the forearm and of the vertebral bodies (Type I osteoporotic fractures) were most frequent, next to fractures of the small bones of hands and feet.
3) The majority of the vertebral fractures had been undiagnosed before the investigation, presumably because the majority of these fractures were asymptomatic.
4) Prediction of the occurrence of fractures on the basis of risk factors of osteoporosis was inaccurate.

b. Pattern of metacarpal bone loss (chapter 5):

5) Bone loss occurred in more than 95 per cent of the women over 50 years of age.
6) The rate of bone loss was approximately 1 per cent of the initial bone density per year.
7) The rate of bone loss was not similar for all women; in some the loss was consistently more rapid than in others.
8) At a younger age the rate of bone loss was fastest for women who had a high bone density; at older age the rate of bone loss was fastest for women who had a low bone density.
9) Differences in the rate of bone loss between individuals were of limited value for the prediction of metacarpal osteopenia at follow-up. The level of initial bone density was more informative.

c. Endogenous oestrogen activity (chapter 6):

10) Body mass (Quetelet-index), serum oestrone, serum oestradiol and sex hormone binding globulin (SHBG) levels were all related to osteoporosis; the serum androstenedione level was not.
11) The relationship between body mass and osteoporosis was in part explained from the relationship between body mass and endogenous oestrogen activity. An independent relationship of low body mass to low bone density remained unexplained.
12) The relationship to osteoporosis was stronger for serum oestradiol than for oestrone and it was strongest for SHBG.
13) As an independent factor (i.e. standardized for correlation to the other factors) a high level of SHBG was related to a low bone density, a high rate of bone loss and an increased risk of fractures. A low level of oestradiol was related to a low bone density.

In organizing the investigation, many considerations were made concerning the study design, the information to be collected, the procedure of data collection, the statistical analyses and the presentation of the data. Some of the considerations concerning the study design and the choice of the three major analyses will be discussed here.

7.2. study design

The follow-up investigation as it actually took place was the result of a development of ideas that began long before the field work started. In the beginning there was a basic idea: with the 1975-78 EPOZ-survey for baseline data, information concerning incident fractures that occurred after this initial survey was to be collected in a mailed questionnaire among the middle aged women. This information might have been sufficient to answer the initial question concerning the clinical value of risk factors of osteoporosis for the prediction of fractures. The most important characteristic of this approach was the forward directionality of the study design with a long period of follow-up among a large group of middle aged women from the general population. Given the potentials of such a design, it was judged to be useful to collect information on additional variables as well. It was decided to include follow-up radiographs of the hands for the purpose of a longitudinal evaluation of bone loss. This was an important step in the development of the investigation, because it implied that the respondents had to visit the EPOZ-research centre in Zoetermeer. A pure administrative follow-up was no longer possible. A next step in the development of the investigation was the inclusion of a radiograph of the lumbar spine to detect newly occurring (asymptomatic) fractures of the vertebral bodies. Also, serum samples were included to create the possibility of investigating potential biochemical factors in relation to observed bone loss. Finally, for further items to be included in the follow-up investigation, a balance was made between the potential interest of the variable versus the practical consequences of inclusion. For example, a food questionnaire, several antropometric measurements and measurement of blood pressure were included in the design. For practical reasons, the collection of data concerning physical activity had to be limited to a simple questionnaire only.

In the final design a questionnaire and a request to visit the research centre were sent to all women who were 45 to 64 years of age at the time of the initial EPOZ-survey. If the request remained unanswered, the women were approached by telephone and invited again. In this way, at least a fracture history could be obtained from the women who refused further participation. The women who were not reached at all in a first round were contacted in a

similar fashion in a second round after addresses had been checked.

The complete investigation consisted of: 1). A questionnaire, for which the information was checked in a physician interview (appendix). Additional questions concerning a history of starvation during world war II and during the economic crisis of the thirties were asked during the interview. 2). A standardized food questionnaire concerning the consumption of Calcium and vitamin D. 3). Various antropometric measurements, including body height and weight, arm span width, diameter of the knees at the level of the femoral epicondyles and skinfold thickness at three sites. 4). Blood pressure measurements. 5). Radiographs of the hands and of lumbar spine: for the first special precautions were made to allow radiographic densitometry.[1] 6). Serum and plasma samples. For each individual several samples were taken. Part of the samples were frozen for future use and part of the samples were used for biochemical measurements, including oestrone, oestradiol, androstenedione, sex hormone binding globulin (SHBG), LH, FSH, total PTH (including fragments), intact PTH and SMA-12 measurements of calcium, phosphate, alkaline phosphatase, total globulin, albumin, creatinine, bilirubin, sodium, potassium, chloride, SGOT and SGPT. For the selection of women who had type I osteoporotic fractures and for a control group, the serum concentration of 25-OH-cholecalciferol (25-OH-Vitamin D) was measured.

As a consequence of the divergent approach that was used in the collection of the data, a large data set was available for further analyses after the field work was finished. In the analyses of the data a convergent approach was chosen, starting from the questions to be answered. The first questions to be answered were those that were formulated before the actual investigation started (chapter 4 and 5), but many more potential questions could be addressed. In this thesis it was chosen to further explore the relationship between endogenous oestrogen activity and the occurrence of osteoporosis. The choice was partly based on the observation from the literature on the subject, which demonstrated that postmenopausal oestrogen substitution therapy is the most promising and effective intervention for prevention of osteoporosis. It was also based on positive results from preliminary analyses and in this respect the choice to further analyze this relationship is an example of research being biased towards positive results.

Besides the relationships that were evaluated in this thesis, the data-set offers a multitude of opportunities for further analyses. Some of these potentials have already paid off [2,3,4,5] and results from various further analyses are to be expected. (For example: relationship between parameters of calcium metabolism and occurrence of osteoporosis; endogenous oestrogen activity and bone density as measured with SPA, DPA and QCT; serum concentration of FSH, LH and inactive LH-fragments in relation to deficient oestrogen stimulation of the hypophysis; biochemical indicators of atherosclerosis; psychological factor as measured in EPOZ as a predictor of medical consumption at follow-up).

7.3. Prediction of fractures

In the first analysis an evaluation was made of the clinical efficiency of using information about risk factors of osteoporosis for prediction of fractures. This evaluation constituted the main reason for conducting the investigation. The study design, statistical analysis and presentation of results were all tailored towards this goal. The study population of middle aged women from the general population was chosen, because this might be an important target population for fracture prevention programmes.[6] Baseline information about risk factors was related prospectively to fracture occurrence over a relative long period of follow-up; a strategy which is optimal to give insight in the potential efficiency of fracture prevention programmes if selection for participation were based on risk factor information. Follow-up information was collected about the occurrence of all fractures, including fractures of the vertebral bodies (which are often asymptomatic).

The statistical analysis was chosen to obtain maximum predictive power from the data. The stepwise logistic regression procedure was used as a discriminant analysis for optimal separation of fracture patients and normals. The possibility of overestimating the strength of the relationship between presence of risk factors and occurrence of fractures was taken for granted.

In the presentation of the results, the strength of the prediction was expressed in terms of sensitivity and specificity, as is usual in clinical practice. In addition, these measures have a practical application in Bayesian medical

decision making.[7]

The choices that were made in the study design and analysis unavoidably brought along certain limitations. The investigation was made possible by the availability of the EPOZ-data. A disadvantage of the use of secondary data for a longitudinal investigation is that the information concerning the specific purpose of the study may be limited. For example, the EPOZ-survey had not been designed to measure the amount of bone in the skeleton. From a clinical point of view the application of techniques such as Single or Dual Photon Absorptiometry might have been preferable over Metacarpal Radiogrammetry. However, Metacarpal Radiogrammetry was an acceptable alternative (chapter 3).

A disadvantage of the choice of the study population from the general population was that rare manifestations of osteoporosis had a low frequency in the study. For example, the serious kind of vertebral osteoporosis as it may be encountered in clinical practice was uncommon in the study population. Only three women out of the 855 investigated suffered from progressive collapses of multiple vertebrae. Also, the study population was still too young, to study fractures of the femoral neck. These fractures may have major consequences both for the victim and for medical costs.[8] However, the frequency of these fractures is only high among subjects aged 70 years and older. In the Netherlands, in 1982 the incidence of femoral neck fractures was 1.3 per 1000 women-years for women aged 45 to 69 years, and 9.7 per 1000 women-years for women aged 70 years and older.[9]

A disadvantage of the choice of the statistical analysis was that it did not guard for the presence of chance relationships. As a consequence, caution is required in interpreting the relationship between separate risk factors and fracture risk.

Finally, the simultaneous use of many variables in a single analysis sets high demands to the completeness of the data for each variable. As a result of a small percentage of missing values for each variable, mostly because of technical reasons, the complete data set was considerably reduced. Of 1014 women for whom a fracture history was available, only 742 women had complete data for all variables that were used. The introduction of a bias that could have resulted from this problem was checked in a comparison between the data-set with and without missing values.

7.4. Metacarpal bone loss

In the second analysis the occurrence of bone loss in the study population was evaluated. The investigation was especially well fit for this purpose. It was the first population based longitudinal study of reasonable size with a long period of follow-up. A basic question in osteoporosis research is whether differences in the rate of bone loss between individuals really exist (Albright) or whether the rate of bone loss is of similar magnitude for all elderly subjects (Newton-John). If the first hypothesis comes closest to reality, it might be useful to early detect the subgroup of fast bone losers for prevention of osteoporosis. If the second hypothesis offers a better description of reality, it might be more useful to gear preventive measures towards all subjects or towards individuals who have a low bone density to begin with.

A problem in the evaluation of the presence of differences in the rate of bone loss between individuals is that the amount of bone tissue that is lost per year is relatively small in comparison to the measurement error. Ordinary bone loss in postmenopausal women will proceed at an average rate of approximately 1 per cent per year. The precision of the most precise measurement techniques is of the same magnitude. As a consequence, a long period of follow-up is required for reliable measurements of bone loss. But even with the nine year period of follow-up of the present investigation, special precautions were required to avoid confusing differences in measurement error with actual differences in the rate of bone loss.

In the statistical analysis of differences in the rate of bone loss between individuals three different approaches were used. Firstly, similar to Newton-John, the standard deviations of bone density were compared in different age groups and within age groups over the period of follow-up. Secondly, direct inferences were made from the bone loss that was actually measured, together with an estimation of the measurement error. Thirdly, the shift of individuals within the frequency distribution of bone density (horse racing) was evaluated in an analysis of the relationship between rate of loss and initial level of bone density in consecutive age groups.

From these analyses it was inferred that differences in the rate of bone loss between individuals were present. A model was proposed for the pattern of bone

loss as it occurs in the general population. This model was based, both on the empirical data and on the (biological) assumption that rate of bone loss was determined by two factors: 1). the magnitude of the disequilibrium between bone formation and bone resorption and 2). the size of the metabolic surface that is present within the bone tissue. The influence of the second, a large metabolic surface, makes that at a younger age, shortly after bone loss has started, the rate of bone loss is fastest for individuals with a high bone density. The influence of the first, differences in the magnitude of the disequilibrium, makes that individuals with a high rate of loss shift down in the frequency distribution of bone density, resulting in high rate of loss for individuals with a low bone density at an older age. The model illustrates the limited validity of a description of the homogeneity of a process of change, just on the basis of changes in standard deviations.

The principle of the analysis of horse-racing has been applied previously in different research areas such as pulmonary function and hypertension research. The approach is new to the field of osteoporosis. A disadvantage of the technique may be its statistical complexity. However, we knew of no alternative way to extract the same kind of information. Since the analysis has not been performed previously on the same kind of data, the results can not be compared to different populations.

Next to the question concerning the presence of differences in the rate of bone loss between individuals, an attempt was made to evaluate the clinical relevance of differences in the rate of bone loss for the occurrence of osteopenia. In this analysis, a comparison was made between the prediction of osteopenia at follow-up on the basis of initial bone density and on the basis fast rate of bone loss. Here, the analysis was kept simple and straightforward. The results were expressed in terms of sensitivity and specificity, is clinically interpretable measures. Of course, bone density at old age will be most correctly described as a function of initial bone density, rate of bone loss and time. However, if a choice has to be made between information bone density or bone loss, to predict bone density over a 9 year period, the first would be the more informative. The model of equal bone loss for all individuals may not be correct in an academic sense, but it may be the more pragmatic view for clinical practice.

7.5. Endogenous oestrogen activity and osteoporosis

In the third analysis the relationship between endogenous oestrogen activity and osteoporosis was evaluated. This relationship has been studied previously by various investigators. However, the present investigation represented the first study in which all components of postmenopausal endogenous oestrogen activity: oestradiol, oestrone and sex hormone binding globulin (SHBG) could be related to the three major constituents of the osteoporotic syndrome: low bone density, high rate of bone loss and increased risk of fractures in a multivariate analysis. In addition, the independent contribution of the theoretical "precursors" of postmenopausal endogenous oestrogen activity: body mass and androstenedione concentrations could be included in the analysis. The population had a sufficient size to allow the use of a multiple linear regression analysis to evaluate the independent relationship of the various components of endogenous oestrogen activity in relation to osteoporosis.

The results suggested that high level of SHBG and perhaps low level of oestradiol could be responsible for some of the differences in the rate of bone loss between individuals. Since all women were postmenopausal and oestrogen levels were in general low, these results may serve as an indication of the sensitivity of bone tissue for oestrogen deficiency.

The study design of this part of the investigation warrants some additional discussion. The relationship between oestrogen activity and bone density was analyzed cross-sectionally. This approach is similar to the majority of other risk factor studies in this field. For the part of the study of bone loss and fractures in relation to endogenous oestrogen activity, the investigation could be characterised as a retrospective cohort study with a backward directionality. Although some frozen serum samples from the initial EPOZ-survey were still available, we had some doubts whether measurements of a globulin substance such as SHBG would be reliable in 10-year old serum. Therefore, the oestrogen activity as was measured at follow-up was related to the bone loss and fractures that occurred during the previous nine years. The approach may be compared to the usual case-control design. An advantage of the present design was that the control group may be conceived as being selected exactly from the source population of the cases. The approach would give biased result if fractures or bone loss would

have an influence on the endogenous oestrogen levels, or if a third factor would influence both variables independently. The existence of such biases were considered to be unlikely, with the exception of a possibility of some women using exogenous oestrogens as a therapy for osteopenia or fractures. Of the nine women who reported current use of some kind of postmenopausal substitution therapy (oestrogens, progestagens or androgens) four were excluded from the analysis because of premenopausal oestrogen levels above 100 pmol/l. The remaining five had average levels of oestrogens and did not in any way influence the results. Although the approach of a retrospective cohort design may be somewhat unusual the associations were nevertheless considered to be valid. In the judgement that was made concerning the causality of the relationship between endogenous oestrogen activity and osteoporosis, the criterion of directionality of cause and effect could not be used. In the present analysis, however, the consistency of the association of high concentrations of serum SHBG to low bone density, high rate of bone loss and increased risk of fractures was striking. Furthermore, the findings were in line with the general hypothesis of an etiologic role of oestrogens activity in relation to osteoporosis. The results encourage further -preferably prospective- investigations, with specific attention for the role of SHBG.

7.6. Recommendations

This investigation intended to evaluate the accuracy of fracture prediction based on known risk factors of osteoporosis. The reason for the evaluation was a suggestion from the literature that strategies for prevention of osteoporosis should be directed at subjects who have a high risk of fractures. One approach to select these subjects could have been the risk factor status. The results of described in chapter four suggest that this approach of fracture prediction is inaccurate from a clinical point of view. Furthermore, the results described in chapter five suggest that bone loss is present in the majority of postmenopausal women, yet, differences in the rate of bone loss were of relatively little importance for prediction of osteopenia. As a consequence, it may be doubted whether any determinants of bone loss will be useful for prediction of

osteopenia related fractures. The results indicate that selection of women for fracture prevention programmes, either on the basis of risk factors or on the basis of fast bone loss is most likely to be inefficient. As an alternative approach it has been suggested that a high-risk group of women might be selected on the basis of bone density measurements around the age of the menopause. In the present investigation the efficiency of this approach could only be tested for Metacarpal Radiogrammetry. The relationship of metacarpal bone density to fracture risk was far too weak to be of any value in this respect. However, many different techniques of measuring bone density may be applied to various locations in the skeleton and without the empirical data the possibility that some technique could be useful for selection of subjects at high risk of fractures can not be excluded. At present no such technique is available.

Apart from age and sex, few factors appear to be useful in guiding the allocation of preventive efforts that are aimed at reducing the number of fractures in the elderly population. Considering these disappointing results, it seems more appealing to direct our efforts towards the total population, or at least towards the total group of postmenopausal women, instead of selecting specific high risk groups. Several measures of intervention that might be advised to the whole population of postmenopausal women have been suggested again and again in the literature ever since Albright first drew attention to the clinical syndrome of osteoporosis. These measures include advice about sufficient consumption of calcium, vitamin D and perhaps fluor, advice about adequate physical activity and about the use of postmenopausal oestrogen substitution therapy. The latter intervention is the only measure for which the effectiveness has been positively demonstrated and accepted in the consensus conferences that were previously mentioned (chapter 1). The results described in chapter six lend further support to the potential beneficial influence of oestrogens on the preservation of the skeleton. However, the debate concerning the possible side effects of postmenopausal oestrogen substitution therapy still continues. Final judgement whether this therapy could be safely advised to the population as a general health measure will depend on the outcome of this discussion.[10]

From the previous discussion it seems that the time has come for properly designed intervention research, measuring the effect of interventions on both the rate of bone loss and the risk of fractures. With the present state of

knowledge, this kind of research is most likely to be of value if interventions to be tested are suitable for application to the total population, or at least to the total group of postmenopausal women.

Next to "preventive" intervention research it seems useful to obtain a better understanding of factors that determine the peak bone density, since it appears that bone density at old age is strongly determined by bone density at a younger age. Perhaps, an effective prevention of osteoporosis should start at an age when the skeleton is still growing.

As a final remark it may be worth considering that, although this thesis dealt with low bone density as a supposed cause of fractures, few fractures occur without at least a minor accident. Despite the neglect of this factor in osteoporosis research, the potential value of accident prevention among the elderly should not be underestimated.

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Chapter 8

Samenvatting

Een groep van 1167 vrouwen van middelbare leeftijd werd gedurende een periode van negen jaar gevolgd. Nagegaan werd of een kombinatie van risikofaktoren voor osteoporose praktisch bruikbaar zou kunnen zijn om een groep vrouwen met een verhoogd fraktuur risiko op te sporen. Daarnaast werd het optreden van botverlies in een normale populatie bestudeerd en de natuurlijke oestrogeen aktiviteit na de menopauze werd in verband gebracht met het optreden van botverlies, lage botmassa en frakturen.

In hoofdstuk twee wordt de historische ontwikkeling van het concept van osteoporose beschreven. Er wordt een onderscheid gemaakt tussen het concept van osteoporose vanuit een klinisch en vanuit een epidemiologisch gezichtspunt. De epidemiologie van osteoporose wordt besproken.

De methode van het onderzoek wordt beschreven in hoofdstuk drie; de resultaten worden beschreven in de hoofdstukken vier, vijf en zes. Een bespreking van de methode van onderzoek volgt in hoofdstuk zeven, te samen met enige aanbevelingen voor verder onderzoek.

Fraktuur prediktie (Hoofdstuk 4)

Tijdens de 9 jaar durende vervolgperiode traden 203 frakturen op bij 163 vrouwen (Tabel II; pagina 57). Dit komt overeen met een gemiddelde incidentie van 22.2 frakturen per 1000 vrouw-jaren. De kans op één of meer frakturen gedurende de onderzoeksperiode was 0.16. Frakturen van de distale onderarm en van de wervels vormden samen ongeveer de helft van alle frakturen (n=92). Deze frakturen worden vaak als typisch beschouwd voor postmenopauzale osteoporose (type I osteoporotische frakturen).

Twaalf risikofaktoren (Tabel I; pagina 54) werden prospektief in verband gebracht met het risiko van alle frakturen of van type I osteoporotische frakturen. De gegevens van 742 vrouwen waren volledig voor alle faktoren. Een significant verhoogd fraktuur risiko werd gevonden voor hoge leeftijd en laag

Relatief Corticaal Oppervlak. Enige bescherming tegen frakturen werd gevonden voor geringe lichaamslengte en geringe (!) breedte van de pols. Geen van de risikofaktoren was sterk gerelateerd aan het risiko van frakturen. De relatie tussen risikofaktoren en fraktuurrisiko was niet essentieel verschillend voor de groep van alle frakturen of voor de subgroep van type I osteoporotische frakturen.

De voorspellende waarde voor het optreden van frakturen werd nagegaan voor een kombinatie van risikofaktoren. De informatie over risikofaktoren werd gecombineerd met behulp van een stapsgewijze logistische regressie techniek. Voor ieder individu werd zo een Fraktuur Risiko Score (FRS) berekend, die laag was voor vrouwen met weinig risikofaktoren en hoog voor vrouwen met veel risikofaktoren. Het risiko van frakturen in quintielen van de FRS wordt weergegeven in Figuur IV (pagina 62). De FRS was sterk gerelateerd aan het risiko van frakturen. Het relatief risiko van het hoogste ten opzichte van het laagste quintiel was 6.4 voor alle frakturen en 7.0 voor type I osteoporotische frakturen. Echter, het gebruik van de FRS met het oog op selektie van een groep vrouwen voor fraktuur preventie zou onbetrouwbaar zijn. Indien het hoogste quintiel van de FRS zou worden beschouwd als een test voor fraktuur voorspelling, dan zou de sensitiviteit en specificiteit in het huidige onderzoek 0,38 en 0,84 bedragen voor de prediktie van alle frakturen en 0,47 en 0,83 voor de prediktie van type I osteoporotische frakturen (Tabel III; pagina 63). In de praktijk zou dit betekenen dat in een selektie van 20 procent van alle vrouwen op basis van deze score, minder dan 40 procent van de frakturen zou vóórkomen. Andersom zou ongeveer 70 procent van geselekteerde vrouwen in de daarop volgende negen jaar geen fraktuur krijgen. Deze schatting van sensitiviteit en specificiteit zal aan de optimistische kant zijn, omdat de score op één zelfde data set werd berekend en getest. Het klinische gebruik van informatie over risikofaktoren van osteoporose bij de selektie van vrouwen voor fraktuurpreventie programma's lijkt niet aan te bevelen.

Botverlies (Hoofdstuk 5)

Handfoto's van 799 vrouwen waren aanwezig voor zowel het initiële als het vervolgonderzoek. De verandering van het Relatief Corticaal Oppervlak (botdichtheid) met de leeftijd wordt weergegeven in Figuur III (pagina 79). Voor het 50^{e} jaar, of vóór het optreden van de menopauze, werd geen noemenswaardige afname in RCO vastgesteld. Na het 50^{e} jaar trad een verlies op van ongeveer 1% van het gemiddelde niveau per jaar. De frequentieverdeling van RCO wordt weergegeven in Figuur IV (pagina 81) in 5-jaars leeftijd categorieën. In de oudere leeftijdsgroepen lag de gehele verdeling van botdichtheid lager, in vergelijking met de jongere leeftijdsgroepen. Wanneer een arbitraire grens voor lage botdichtheid (osteopenie) werd gelegd bij 70 mm^2%, dan nam de prevalentie van osteopenie toe van 5% voor vrouwen tussen 45 en 49 jaar oud tot 68% voor vrouwen van 70 tot 76 jaar oud.

Uit het longitudinale gedeelte van het onderzoek bleek dat een verlies in RCO was opgetreden bij 95% of meer van de vrouwen die bij aanvang van het onderzoek ouder waren dan 50 jaar. Het tempo van botverlies was niet gelijk voor iedereen. Er waren aanwijzingen voor verschillen in het tempo van botverlies, die over langere tijd voortduurden. Op jongere leeftijd, kort nadat het botverlies was begonnen, was het tempo van botverlies het hoogste bij vrouwen met een hoge botdichtheid. Op oudere leeftijd, wanneer het botverlies mogelijk al langere tijd bestond, was het botverlies het hoogste bij vrouwen met een lage botdichtheid. De bijdrage van een hoog of een laag tempo van botverlies aan het optreden van osteopenie was echter gering. De individuele verschillen in het niveau van botdichtheid op jongere leeftijd waren van meer invloed. Een voorspelling van het optreden van osteopenie bij het vervolgonderzoek op basis van een hoog botverlies was onnauwkeurig (sensitiviteit: 0.61 en specificiteit: 0.65). Eenzelfde voorspelling op basis van de botdichtheid bij het eerste onderzoek was veel nauwkeuriger (sens.: 0.88 en spec.: 0.79). Blijkbaar had de botdichtheid op jongere leeftijd nog steeds een overheersende invloed op de botdichtheid op oudere leeftijd.

Endogene oestrogeenaktiviteit en osteoporose (Hoofdstuk 6)

Bij het vervolg gedeelte van het onderzoek werd de endogene oestrogeen-aktiviteit bepaald door het meten van de serum concentratie van oestradiol, oestron, androsteendion en sex hormoon bindend globuline (SHBG). Deze faktoren, en ook de Quetelet-index, werden gerelateerd aan het niveau van het Relatief Corticaal Oppervlak ten tijde van het vervolgonderzoek, aan het verlies in RCO dat in de voorafgaande periode sinds het EPOZ-onderzoek was opgetreden en aan het risiko van frakturen gedurende dezelfde periode. De gegevens waren kompleet voor 746 postmenopauzale vrouwen.

Met uitzondering van androsteendion waren alle parameters als afzonderlijke faktoren significant gerelateerd aan botdensiteit en aan botverlies. In een multipele lineaire regressie analyse bleek botdensiteit positief gerelateerd aan serum oestradiol en aan de Quetelet-index en negatief aan serum SHBG (Tabel II; pagina 93). Botverlies was negatief gerelateerd aan serum SHBG (Tabel III; pagina 94). Serum oestron had geen onafhankelijke relatie van enige omvang met botdensitiet of botverlies. De relatie tussen de Quetelet-index als afzonderlijke factor enerzijds en het botverlies anderzijds werd in de multivariate analyse geheel verklaard uit de positieve korrelatie van de Quetelet-index met het serum oestradiol en de negatieve korrelatie met het serum SHBG. De ongunstige invloed van serum SHBG op botdensiteit en botverlies was sterker dan de gunstige invloed van serum oestradiol. Waarschijnlijk moet deze werking van SHBG worden verklaard door een invloed op het vrije oestradiol en mogelijk ook op het vrije testosteron. Beide hormonen worden geinaktiveerd door binding aan SHBG.

Naast de relatie van SHBG met botdensiteit en botverlies bestond er voor SHBG ook een relatie met het risiko van frakturen. Voor de groep oudere vrouwen, boven de 65 jaar, werd gevonden dat het gemiddelde niveau van SHBG hoger lag bij vrouwen met een voorgeschiedenis van type I osteoporotische frakturen in vergelijking met vrouwen die geen frakturen hadden gehad (Tabel IV; pagina 95).

De resultaten suggereren een invloed van endogene oestrogeen aktiviteit bij het ontstaan van postmenopauzale osteoporose. Inaktivering van postmenopauzaal endogeen oestradiol, en mogelijk ook van testosteron, door binding aan SHBG

kan hierbij een rol spelen. Het is mogelijk dat langdurige blootstelling aan een hoge serum concentratie van SHBG uiteindelijk bijdraagt tot een verhoogd risiko van type I osteoporotische frakturen.

Konklusies (Hoofdstuk 7)

1) Frakturen kwamen frequent voor bij vrouwen van middelbare leeftijd en het fraktuurrisiko nam toe met de leeftijd.
2) Frakturen van de pols en van de wervels (Type I osteoporotische frakturen) waren samen met frakturen van de kleine beentjes van handen en voeten het meest frequent.
3) Het merendeel van de wervelfrakturen was voorafgaande aan het onderzoek niet gediagnostiseerd, waarschijnlijk doordat deze frakturen vaak asymptomatisch waren.
4) Voorspelling van het optreden van frakturen op basis van risikofaktoren van osteoporose was onbetrouwbaar.
5) Verlies van botweefsel trad op bij meer dan 95 procent van de vrouwen boven de vijftig jaar.
6) Het tempo van botverlies bedroeg ongeveer 1 procent van de initiële botdichtheid per jaar.
7) Het tempo van botverlies was niet gelijk voor alle vrouwen; bij sommigen verliep het verlies sneller dan bij anderen.
8) Op jongere leeftijd was het tempo van botverlies het hoogste bij de vrouwen met een hoge botdichtheid; op oudere leeftijd was het tempo van botverlies het hoogste bij de vrouwen met een lage botdichtheid.
9) Verschillen in het tempo van botverlies waren van betrekkelijk weinig belang voor het optreden van osteopenie. De initiële botdensiteit had een overheersende invloed.
10) Lichaamsmassa (Quetelet-index), serum concentratie van oestron, oestradiol en sex hormoon bindend globuline (SHBG) waren allen gerelateerd aan het voorkomen van osteoporose; serum androsteendion was dat niet.

11) De relatie tussen lichaamsmassa en osteoporose werd gedeeltelijk verklaard door de relatie tussen lichaamsmassa en endogene oestrogeen aktiviteit. Een onafhankelijk relatie tussen een lage lichaamsmassa en een lage botdichtheid bleef onverklaard.

12) De relatie met osteoporose was sterker voor oestradiol dan voor oestron; de relatie was het sterkste voor SHBG.

13) Als onafhankelijke faktor (na standaardisatie voor de overige faktoren) was een hoge serum SHBG concentratie gerelateerd aan een lage botdichtheid, aan een hoog tempo van botverlies en aan een hoog risiko van frakturen. Een lage oestradiol concentratie was gerelateerd aan een lage botdichtheid.

De konklusies hebben betrekking op een normale populatie vrouwen van middelbare leeftijd, die vergelijkbaar is met een populatie die bijvoorbeeld een huisarts zou kunnen bezoeken om advies te vragen over preventie van osteoporose. Botverlies blijkt op te treden bij praktisch alle vrouwen na de menopauze, onder andere onder invloed van de natuurlijke oestrogeendeficientie. Het selekteren van een subgroep van vrouwen voor fraktuur preventie, op basis van risikofaktoren van osteoporose, of op basis van een hoog tempo van botverlies lijkt niet bijzonder efficiënt.

Appendix

EPOZ Follow-up Questionnaire

An english translation of the questionnaire that was used for the follow-up part of the investigation is reproduced here. The purpose of the questionnaire was to collect information concerning the occurrence of fractures and accidents during the period between the initial and the follow-up investigation. In addition, information was collected concerning factors that were potentially related to bone density, bone loss or risk of fractures. This included simple information concerning physical activity, medical history, age and circumstances of the menopause, use of postmenopausal oestrogen substitution therapy, smoking, and consumption of alcohol and coffee. The questions that were included as indicators of physical activity were chosen from the initial EPOZ-questionnaire, with the exception of question 30 (page 132). This question was inspired on a publication by Sallis, who suggested that a question like this could serve as a rough, but useful estimate of the physical activity.[1] The questions concerning joint pain (page 138), were also selected from the initial EPOZ-questionnaire. These questions were included, because a comparable version of the questionnaire was used for a longitudinal investigation of progression of osteoarthrosis in a population that was overlapping with the population studied in the present investigation.[2]

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EPOZ

(EPIDEMIOLOGICAL PREVENTIVE INVESTIGATION ZOETERMEER)

THIS QUESTIONNAIRE IS BOUND FOR:

name :
street :
postal code :
residence :
date of birth :

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

name :

street :

postal code :

residence :

date of birth :

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

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

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

DATA IN THIS DOSSIER ARE SUBJECT TO MEDICAL PROFESSIONAL SECRECY

EXPLANATION OF THE QUESTIONNAIRE

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

EXAMPLES:

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

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

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

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

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

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

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

---

The following questions concern fractures of the bones and accidents

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

If NO, please continue with question 7.

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

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

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

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

   .....

5. What was your opinion of the accident ?

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

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

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

   ☐ General practitioner Name: .....

   ☐ Hospital Name: .....

   Name doctor: .....

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

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

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

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

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

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

☐ stumbling or slipping

☐ dizziness

☐ fainting

☐ sudden weakness in the legs

☐ other (please describe) .....

10. Do you have difficulties with walking ? Yes ☐ No ☐

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

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

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

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

.....

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

The following questions concern pain in the back

---

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

If NO, please continue on the next page.

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

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

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

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

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

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

If YES, please describe .....

The following questions concern your work and daily activities

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

If NO, please continue on the next page.

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

   ☐ by foot ..... minutes
   ☐ by public transport ..... minutes
   ☐ by bicycle ..... minutes
   ☐ by autocycle ..... minutes
   ☐ by car or taxi ..... minutes

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

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

   .....

5. How many hours per day do you work ?
   ☐ 1-4 hours (half days or less)
   ☐ 5-9 hours (half to full days)
   ☐ full days
   ☐ more than 9 hours (more than full days)

6. How many days per week do you work ?
   ☐ 1 or 2 days ?
   ☐ 3 or 4 days ?
   ☐ 5 days ?
   ☐ 6 or 7 days ?

7. Are you physically active at your work ?
   ☐ No, I sit virtually all the time
   ☐ Not very active, some walking and/or lifting
   ☐ Yes, I am on the move all the time during work

8. Do you perform your own domestic work ?

- ☐ Yes, I do all my domestic work on my own
- ☐ Yes, and everyone in the house gives a hand
- ☐ Yes, and I have help for ... hours per week
- ☐ No, my domestic work is done by someone else

If NO, please continue with question 11.

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

.... persons

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

11. How many hours per day do you cycle ?

- ☐ None
- ☐ Less than half an hour per day
- ☐ More than half an hour per day

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

- ☐ None
- ☐ More than half an hour
- ☐ More than half an hour, but less than an hour
- ☐ More than an hour per day, namely ... hour

13. Do you climb the stairs daily ? Yes ☐ No ☐

If YES, how often ?

- indoors usually .... times per day
- outdoors usually .... times per day

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

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

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

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

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

If NO, please continue with question 20.

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

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

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

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

    .... hours

19. Do you participate in sport competitions ? Yes ☐ No ☐

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

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

If NO, please continue with question 26.

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

    .....

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

    ☐ by foot ..... minutes
    ☐ by public transport ..... minutes
    ☐ by bicycle ..... minutes
    ☐ by autocycle ..... minutes
    ☐ by car or taxi ..... minutes

23. How many hours per day did you work ?

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

24. How many days per week did you work ?

    ☐ 1 or 2 days ?
    ☐ 3 or 4 days ?
    ☐ 5 days ?
    ☐ 6 or 7 days ?

25. Were you physically active at your work ?

☐ No, I sat virtually all the time

☐ Not very active, some walking and/or lifting

☐ Yes, I was on the move all the time during work

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

If NO, please continue with question 30.

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

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

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

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

.... hours

29. Did you participate in sport competitions ? Yes ☐ No ☐

The following questions concern your activities in the past month

---

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

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

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

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

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

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

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

Have you had any of the following diseases or conditions

INFECTIOUS DISEASES

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

CARDIOVASCULAR DISEASES

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

OTHER DISEASES

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

The following questions concern physician treatment now and in the past

OPERATIONS

16. Have you ever been operated ? Yes ☐ No ☐

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

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

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

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

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

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

19. If YES, please indicate what for.

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

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

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

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

MEDICATION AND CURRENT TREATMENT

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

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

    If YES, please indicate what medication.

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

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

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

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

Please bring along all your current medication to the centre!

Now, some questions will follow concerning children, the menstrual periods, and use of "the pill"

1. Do have children of your own ? (including children from a possible previous marriage). Yes ☐ No ☐

   If YES, when were your children borne ?

   1st child 19... 4th child 19... 7th child 19...

   2nd child 19... 5th child 19... 8th child 19...

   3rd child 19... 6th child 19... 9th child 19...

If NO, please continue with question 3.

2. Did you breast feed one or more of the children ? Yes ☐ No ☐

   If YES, how long has that been ?

   1st child .... 4th child .... 7th child .... months

   2nd child .... 5th child .... 8th child .... months

   3rd child .... 6th child .... 9th child .... months

3. Has there ever been a longer period (three months or more) during which the menstruation ceased and than came back again, without a pregnancy ? Yes ☐ No ☐

   If YES, how long did this period last ? ..... months

   What was the cause of it ? .....

4. Did you use "the pill" after january 1st 1975 ? Yes ☐ No ☐

If NO, please continue on the next page.

5. If YES, for what reason did you use "the pill" ? (more than one answer is possible).

   ☐ As a contraceptive.

   ☐ To regulate the menstruation.

   ☐ For another reason, namely .....

6. Could you indicate as accurately as possible, when since january 1st 1975 you used "the pill" ? (Please give month and year). For example FROM january 1975 UNTIL may 1978

	FROM		UNTIL	
	Month	Year	Month	Year
1.	.....	.....	.....	.....
2.	.....	.....	.....	.....

The following questions apply only if the menstrual periods are still coming

7. Do the menstrual periods come regularly ? Yes ☐ No ☐

If YES, you can skip question 8.

8. Have your menstrual periods been regular in previous time ? Yes ☐ No ☐

   If YES, how old were you, when your periods became irregular ?

   .... years old

The following questions apply only if the menstrual periods have ceased

9. How old were you when your menstrual periods ceased altogether ? .... years old

10. Please indicate how your periods came to an end ?

   ☐ on its own

   ☐ through medication

   ☐ after stopping "the pill"

   ☐ after an operation of the uterus and/or ovaries

   ☐ other reason (please specify) .....

The following questions only apply if you have had an operation of the uterus or of the ovaries

11. Has the uterus been removed ? Yes ☐ No ☐ Don't know ☐

    Have the ovaries been removed ? Yes ☐ No ☐ Don't know ☐

12. How old were you at the time of the operation ? .... years old

13. Have you been treated with feminine hormone or "the pill" after the operation ? Yes ☐ No ☐

14. Did you ever have menopausal complaints after the operation (for example hot flushes) Yes ☐ No ☐

    If YES, how old were you when you had these complaints ?

    .... years old

The following questions concern the use of feminine hormone other than "the pill". These are commonly used for the treatment of menopausal complaints (for example hot flushes) or for irregular or superfluous menstrual bleeding. Some names of preparations that are often used for menopausal complaints are: Premarin, Synapause, Ovestin, Lynoral, Dagynil, Progynova and Estrovis. Other hormones that are used to regulate the menstrual periods are: Primolut, Duphaston and Orgametril.

---

15. Have you ever been treated with feminine hormone other than "the pill" ? Yes ☐ No ☐

If NO, please continue on the next page.

16. If YES, how were you treated ?
(more than one answer is possible)

☐ Tablets

☐ Internal ointment or cream

☐ Injection

☐ Subcutaneous implant

☐ Other (please specify) .....

17. What was the reason for treatment ?
(more than one answer is possible)

☐ Menopausal complaints

☐ Irregular or superfluous menstrual bleeding

☐ Disease (please specify) .....

☐ Other (please specify) .....

18. Could you indicate as accurate as possible in what period of your life you used these hormones ? (Pleas, give month and year).
For example FROM may 1975 UNTIL march 1978

	FROM		UNTIL	
	Month	Year	Month	Year
1.	.....	.....	.....	.....
2.	.....	.....	.....	.....
3.	.....	.....	.....	.....

19. If you remember the name of the preparation, please write it down below ?

.....

20. Did you get these hormones from the general practitioner or from a medical specialist ?

☐ Gen. Pract. ☐ Specialist

The following questions concern rheumatic and skeletal diseases

Have you ever had one of the following diseases ?

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

   1. .....
   2. .....
   3. .....
   4. .....

9. If YES, is the pain worse than at daytime ? — Yes ☐ No ☐

The following questions concern the smoking of cigarettes and shag

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

If NO, please continue with question 7.

2. Do you still smoke currently ? Yes ☐ No ☐

If NO, please continue with question 6.

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

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

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

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

The following questions concern the use of alcohol and coffee

7. Have you ever used alcoholic beverages ? Yes ☐ No ☐

If NO, please continue on the next page.

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

If NO, please continue with question 12.

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

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

11. Do you drink coffee regularly ? Yes ☐ No ☐

If NO, please continue with the next section.

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

..... cups

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

.... years

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

☐ less

☐ same

☐ more

Finally, we have some general questions

---

1. Do you currently have a pension ? Yes ☐ No ☐

   If YES, since 19...

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

   If YES, since 19...

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

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

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

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

   .....

5. Did you find it difficult to complete this questionnaire ? Yes ☐ No ☐

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

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE!

Epiloog

Een onderzoek zoals beschreven in dit proefschrift kan slechts tot stand komen dankzij de bereidwillige samenwerking met velen. Op deze plaats wil ik mijn erkentelijkheid betuigen aan een ieder die op enigerlei wijze heeft bijgedragen aan de voltooiing van dit werk.

Het onderzoek kon slechts worden uitgevoerd dankzij alle inspanningen die in het verleden door Professor Dr. Hans A. Valkenburg en zijn medewerkers zijn geleverd bij de tot stand koming van het EPOZ-onderzoek. De medewerking van de respondenten van het initiële onderzoek en van de 1014 vrouwen die bereid waren hun medewerking bij het vervolg onderzoek opnieuw te verlenen vormde de ruggegraat van het onderzoek.

Professor Dr. Jan P. Vandenbroucke was de geestelijk vader van het onderzoek zoals het hier is beschreven. Uit zijn kreativiteit werd het plan voor het onderzoek geboren en dankzij zijn voortdurende begeleiding kon het projekt uiteindelijk voltooid worden. Professor Dr. Hans A. Valkenburg was de geroutineerde epidemioloog, die steeds bij praktische en bij theoretische problemen zijn verhelderend licht deed schijnen. Zijn bank heeft ook voor mij de funktie gehad die binnen het Instituut Epidemiologie vermaard is. De analytische geest van Professor Dr. Albert Hofman vormde de drijvende kracht achter de tot stand koming van hoofdstuk vijf.

Professor Dr. Jan C. Birkenhäger en mevrouw Dorie H. Birkenhäger-Frenkel initieerden mij in de wereld van de osteoporose. Als mijn kennis van osteoporose is gegroeid boven een rudimentair niveau dan is dat hieraan te danken. De voortdurende stimulans van professor Birkenhäger heeft belangrijk bijgedragen aan inhoudelijke aspecten van het onderzoek.

Op het gebied van de röntgenologie heb ik veel te danken aan de vruchtbare samenwerking met Dr. Willem Th. Trouerbach en zijn medewerkers Andries W. Zwamborn, Wiebeke J. van Leeuwen en Marjolein J. van Kints.

Bij een epidemiologisch onderzoek van enige omvang vergen de uitvoering van het veldwerk en de verwerking van de gegevens steeds de grootste inspanning. Deze werkzaamheden werden met bewonderenswaardige werkkracht uitgevoerd door de medewerkers van het Instituut Epidemiologie. Het veldwerk werd verricht door Helen de Bruijn, Marijke ter Haar, Ria Rijneveldshoek en

Carlie Valkenburg. Het leeuwedeel van het administratieve werk werd verricht door Hanny Leezer en Joke Burger.

Vele laboratorium medewerkers in en buiten het Instituut Epidemiologie hebben bijgedragen aan de biochemische bepalingen. Binnen het Instituut wil ik met name Ton de Bruijn en Jeanette Drop danken voor de plezierige samenwerking, ook in niet-biochemische zaken. Buiten het Instituut waren het met name Dr. Frank H. de Jong, Dr. Will H.L. Hackeng, Dr. Huib A.P. Pols en Dr. Bert G. Blijenberg die de bepalingen mogelijk hebben gemaakt.

Een komputer is een machine die vele complexe werkzaamheden snel en efficiënt kan uitvoeren. Helaas is het apparaat zeer kieskeurig bij het aannemen van opdrachten. Een enkel verkeerd woord maakt dat de machine zijn medewerking weigert. Naast hun andere verdiensten, is het te danken aan de begeleiding van Bram van Laar, Leo Muller, Ton Evers en Dick Tensen dat mijn kommunikatie met de PDP, de VAX en de PC niet is uitgemond in een weigering van deze apparaten om hun diensten te verlenen.

Het Instituut epidemiologie en haar karakteristieke mogelijkheden voor een vrij wetenschappelijk discourse vormde de stimulerende werkomgeving waarbinnen het onderzoek kon gedijen. De persoon van mevrouw Cilia Kuynders staat voor mij symbool voor de warme gastvrijheid van het Instituut. Met Jan van Saase heb ik gedurende twee jaar een kamer, een lichtkast, het EPOZ-centrum en vele praktische werkzaamheden gedeeld. De gesprekken die wij voerden over de wetenschapsfilosofische status van medische kennis en over de praktische gang van zaken in de gezondheidszorg vormden voor mij een onmisbare achtergrond bij de uitvoering van het onderzoek.

Bij het schrijven van een proefschrift bestaan er vaak tegengestelde belangen. Het is één van de verdiensten van mijn gezin, Hanneke en Steven, dat zij niet alleen bereid waren om met regelmaat van hun belangen af te zien, maar daarbij ook steeds hun ondersteuning bleven bieden.

Toen ik in januari 1985 begon aan het onderzoek dat hier is beschreven, was mijn kennis van de epidemiologie en haar methoden niet groter dan die van de gemiddelde co-assistent. Als ik in de loop van de vier jaar waarin het proefschrift tot stand is gekomen iets heb bijgeleerd, dan is dit de verdienste van velen; ook van diegenen die hier niet bij name zijn genoemd. De tekortkomingen van het werk zoals het nu is voltooid komen geheel voor mijn rekening.

About the author

Albertus Marinus van Hemert was born on February 7th, 1959 in Hengelo, The Netherlands. He attended secondary school at the Dr. W.A. Visser 't Hooft Lyceum in Leiden. In 1977 he commenced his medical study at the Erasmus University Rotterdam. In 1980 he spent five month working on a research project on the induction of cytochrome p-450 at the department of Clinical Pharmacology of the Hammersmith Hospital in London, England. In 1984 he obtained his medical degree. In the same year he spent a year at the philosophical school of the Erasmus University. In 1985 he started a training in Epidemiology at the Department of Epidemiology of the Erasmus University (Head: Prof. Dr. H.A. Valkenburg). Here, the investigation that was described in this thesis was started under the supervision of Prof. Dr. J.P. Vandenbroucke. In 1987 he attended a year of Psychiatric training at the department of Psychiatry of the Municipal University Hospital in Amsterdam (Head: Prof. Dr. F.E.R.E. de Jonghe). In 1988 he was appointed in his current function as research-associate at the department of Psychiatry of the State University Hospital in Leiden.