THE EPIDEMIOLOGY OF HIP FRACTURES IN THE ELDERLY

by

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ABSTRACT

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This thesis addresses three issues which are fundamental to the design of preventive strategies for hip fractures in the elderly: the independent contribution of osteoporosis to the risk of hip fracture, the roles of low dietary calcium intake and physical inactivity as risk factors for hip fracture, and the geographic variation in hip fracture incidence within England and Wales.

Femoral neck bone mass was measured in 708 elderly people who had fallen and injured a hip. Bone mass was lower in those who had sustained a hip fracture than in those who did not. There was a steep increase in the risk of fracture with reduced bone mass at younger ages. At older ages, the risk gradient was less steep. The results suggest that osteoporosis contributes to the risk of hip fracture in the elderly independently of the risk of falling. Other age-related factors become increasingly important above the age of around 75 years.

A case-control comparison between 300 elderly men and women with hip fractures and 600 age and sex matched community controls showed that physical inactivity and reduced grip strength were associated with statistically significant ($p<0.01$) increases in fracture risk. In women, dietary calcium intake did not influence the risk of fracture. Men with daily calcium intakes above one gram had lower risks.

Examination of death certification from hip fracture in England and Wales showed major inaccuracies which limit the usefulness of mortality rates as indices of the incidence of the condition.

These studies suggest that the risk of hip fracture in the elderly depends upon an interaction between osteoporosis, the risk of falling and other age-related factors. Physical inactivity and concomitant muscle weakness are important individual risk factors for hip fracture. They may influence fracture risk through an effect on bone mass, the risk of falling or both of these. The results support the maintenance of activity and muscle strength in the elderly. Such a strategy requires prospective evaluation.

THE EPIDEMIOLOGY OF HIP FRACTURES IN THE ELDERLY

CONTENTS

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INTRODUCTION

In this thesis I describe a series of studies which have been aimed at answering three questions relating to the epidemiology of hip fracture. The first of these examines the independent contribution of osteoporosis to the risk of hip fracture. The second assesses the roles of reduced dietary calcium intake and physical inactivity as risk factors for hip fracture. The third explores the usefulness of mortality and hospital discharge data in the study of geographic variation in hip fracture incidence throughout England and Wales.

Following an opening section which reviews the pertinent literature, sections two to four contain the methods used and results obtained from the studies aiming to answer each of these questions. They are followed by a concluding discussion (section five) which also outlines avenues for future research into the aetiology of hip fracture.

SECTION ONE

LITERATURE REVIEW

CHAPTER ONE

THE EPIDEMIOLOGY OF OSTEOPOROSIS AND AGE-RELATED FRACTURES

Fractures of the hip, vertebrae and distal radius are an important cause of ill health and death in the elderly. Osteoporosis, defined as a reduction in bone mass, is thought to have a role in causing these age-related fractures. This review outlines the descriptive epidemiology of hip fractures, the structural and biochemical nature of osteoporosis, the relationship between bone mass and fracture risk, the epidemiology of falling in the elderly and the individual risk factors for hip fracture.

1.1 The descriptive epidemiology of hip fracture

Fractures of the proximal femur are a major public health problem. The cumulative lifetime risk of suffering such a fracture approaches 30 per cent in Caucasian women and 15 per cent in Caucasian men, at age 90 years[1]. The annual cost of their acute care alone in this country is estimated at £165 million[2].

1.1.1 Age and sex

The incidence of hip fracture varies markedly with age and sex. The first accurate measurements of hip fracture incidence were made approximately 30 years ago. These early studies[3-6] showed that the incidence rate rises exponentially with age in both sexes, with a doubling in rate in each successive five year age group. In the United Kingdom, age-specific incidence rates are between two and three times as high in women as in men[6,7]. This marked sex difference is not universal. Age standardised rates are approximately equal for men and women in Negroid populations[8] and in Hong Kong[9]. In Singapore Chinese[10], the overall rate in men is twice that in women and a similar predominance in men has been shown in India[11].

1.1.2 Geography and ethnic group

The measured frequency with which hip fractures occur in different geographic areas and ethnic groups varies enormously. Data is now available from Sweden[12-16], Norway[17], Finland[18], the USA[19,20], UK[6,7,21-29], Israel[30], New Zealand[31], South Africa[8], Hong Kong[9], Singapore[10] and Yugoslavia[32]. In Caucasian populations, the variation of fracture incidence with age and sex is similar, with the highest recorded rates in the USA. Both studies in Oriental populations[9,10] have shown an exponential increase in incidence with age but a similarity between male and female rates at all ages. The New Zealand data are based on a three year study examining hip fracture admission rates for the whole country[31]. The Pakeha population shared the age and sex specific pattern of incidence common to other European populations, whilst Maori men and women had a fracture incidence approximating that of European men. The ethnic difference in fracture incidence is most pronounced in studies of Negroid populations. Solomon examined the Bantu inhabitants of Johannesburg between 1957 and 1963[8]. The fracture rate in the elderly Bantu was less than one-tenth of that in Caucasian South Africans, and men and women were again affected equally. Hip fracture is also less frequent in Negroes in the USA than in Caucasian Americans[33]. Although the study populations have sometimes been poorly defined and incidence estimates are therefore imprecise, it is unlikely that these ethnic variations are attributable to differences in reporting of hip fractures.

1.1.3 Time trends

Changes in hip fracture incidence rates have been studied in the United Kingdom, Scandinavia and the USA.

The first reliable age and sex specific incidence rates for hip fracture in the UK were obtained by the MRC Working Party on fractures in the elderly[6], which analysed all fractures in Dundee and Oxford over the period 1954 to 1958. Both cities had a centralised service dealing with all fractures within their respective boundaries and the study entailed a time consuming retrospective analysis of cases presenting over a five year mid-census period. Since that time, there has been an increase in the number of hip fractures which occur annually[7,22,24-27,29] and most studies have been aimed at resolving whether this increase in incidence can be entirely accounted for by the increasing number of elderly in the population. The majority of studies suggesting a true increase in incidence rate have been based on routinely collected hospital activity data[7,22,24,26,27]. The use of such uncensored data has been criticised on the grounds that they do not account for double recording of transferred patients and are prone to errors from diagnostic misclassification and re-admissions for late complications. Such errors could easily have accounted for the increases in incidence which were observed[34,35]. Convincing evidence for a true secular increase in hip fracture incidence, however, is provided by a study performed in Oxford in 1983, in which Boyce and Vessey[29] prospectively recorded the incidence of such fractures occurring within the city over a one year period, adhering to the diagnostic criteria of the MRC study 28 years previously. Even allowing for a 15 per cent underestimation of the denominator population, they found a 35 per cent increase in incidence over the period between the two studies.

Changes in hip fracture incidence with time have also been studied in Scandinavia and the USA but with inconsistent results[20]. Zetterburg[13] recorded a 60 per cent increase in incidence in Upsaala between 1965 and 1980, but other studies have suggested that secular increases have now ceased[12,14-16].

The reason for this secular trend is unknown. It may reflect either a current increase in one or more environmental risk factors, or a progressive increase in risk in successive generations as a result of an adverse environmental influence in early life.

1.1.4 Seasonality

Although small studies have disagreed over the existence of seasonal variation in hip fracture incidence, larger ones have consistently suggested that a significantly greater number of fractures occur during the winter months of November to February in temperate zones of the northern hemisphere[3,13,24,36]. Two studies have suggested that the winter peak occurs amongst the thinnest individuals and is associated with falls indoors[37,38]. Hypothermia, to which thin people are more susceptible, could increase the likelihood of falls by impairing neuromuscular co-ordination[37]. An association between hip fracture and vitamin D deficiency during winter in northern England provides an alternative explanation[39].

1.1.5 Anatomical site

Hip fractures may be either intracapsular (cervical) or extracapsular (trochanteric). Although further subdivision into subcapital, transcervical, intertrochanteric and basal fractures is possible, it is of doubtful validity as such distinctions often

depend on radiological artefact[40]. The two fracture types have an approximately equal incidence in the UK, with a slight preponderance of extracapsular fractures[3,6,38]. The ratio of extracapsular to intracapsular fractures has been reported to rise with age (becoming 2:1 in patients over the age of 85 years) but no variation is found between the sexes[5,38]. Epidemiological studies of hip fracture in Sweden 30 years ago discovered a significant excess of intracapsular fractures, but a selective increase in the incidence of extracapsular fractures has resulted in more recent studies showing a similar distribution to that of the UK[16]. The side on which the fracture occurs has been reported in some studies; although the distribution is symmetrical in most of these, two have reported an excess on the left[5,9]. In patients who have previously suffered from strokes, the fracture usually affects the paretic limb[41].

1.1.6 Other age-related fractures

Fractures of the vertebrae, distal radius, proximal humerus and pelvis resemble hip fractures in being strongly age-related and more frequent in women.

Vertebral fractures may be classified as partial (or wedge) deformities and complete (or crush) fractures[42]. They usually occur spontaneously or following minimal trauma. Although they may cause back pain, many are asymptomatic. Vertebral fractures show a consistent predilection for two sites in the spine: the dorsal kyphosis (D7-D8) and the caudal thoracic region (D12-L1). The disability and cost resulting from vertebral fractures remain unknown. One of the few epidemiological studies carried out of these fractures was a survey of 2,063 ambulant female hospital out-patients and volunteers from South

Michigan[43]. It suggested that 2.7 per cent of women aged between 55 and 59 years had sustained one or more vertebral fractures. The prevalence rose to 20 per cent at ages 70 to 74 years. A Danish study[44] reported that 4.5 per cent of 70 year old women randomly selected from the general population had crush fractures and an additional 18 per cent had partial deformities. Estimates of crush fracture prevalence in the UK derive from the Leeds female population where prevalences rise from 2.5 per cent at age 60 to 7.5 per cent at age 80 years[45]. Wedge deformities are considerably more frequent with a prevalence of around 60 per cent in women aged over 75 years. The annual incidence of vertebral fractures in the elderly population of this country has not been directly determined. A large radiological survey recently performed in Finland[46] using 17,557 lateral thoracic radiographs from a tuberculosis screening programme, estimated a crude annual incidence of thoracic spine compression fractures in women over the age of 65 years at 1.8/1,000/year, a figure comparable with a North American estimate[47] of 2.3/1,000/year among women aged 45 years and over who had densitometrically normal spinal radiographs.

Distal radial fractures are the most common fractures in Caucasian women up to age 75 years. In the UK[48] and Sweden[49], the incidence in women has been shown to increase linearly from age 40 to 70 years. Thereafter, rates stabilise. In men, incidence remains constant between age 20 and 80 years. As with hip fractures, there is a winter peak in incidence[50]. This is associated with icy weather conditions. Approximately 20 per cent of distal radial fractures

result in hospitalisation and most patients do not require intensive rehabilitation[51].

Hip, vertebral and distal radial fractures occur in the same individuals. Gallagher[52] found that 18 per cent of a series of hip fracture cases had previously sustained distal radial fractures and 25 per cent had evidence of vertebral crush fractures. Brocklehurst[38] and Baker[53] found a greater prevalence of previous distal radial fracture in hip fracture cases when compared with controls of similar age and sex. In the Danish survey[44], the majority of patients with vertebral fractures had also suffered one of the other two fractures.

1.2 Osteoporosis

Osteoporosis may be defined as an absolute reduction in bone mass which increases susceptibility to fracture[54]. More precise definition is difficult as there is, at any particular age and for each sex, a wide and continuously distributed range of bone mass. The public health importance of osteoporosis stems from its association with fractures of the hip, vertebrae and distal radius. This section will review some current concepts of bone structure and function, the methods of measuring bone mass, the patterns of change in bone mass with ageing, and the pathogenetic mechanisms believed to underlie osteoporosis.

1.2.1 Bone structure

The human skeleton consists of two types of bone: cortical and trabecular[55,56]. Cortical bone is the compact layer which predominates in the shafts of long bones. Trabecular bone is comprised of a series of thin plates which form the interior meshwork of bones,

particularly the vertebrae, pelvis and ends of long bones[57]. Overall the adult skeleton is about 80 per cent cortical and 20 per cent trabecular bone. Both cortex and trabeculae contribute to bone strength and each bone has its own normal proportion of cortical and trabecular components[58,59]. The shafts of long bones, such as the radius and ulna, are at least 90 per cent cortical, whereas vertebrae are mostly composed of trabecular bone[42,60]. Trabecular bone, with its greater surface area, is metabolically much more active than cortical bone and therefore more responsive to influences which alter mineral homeostasis. Conditions which predispose to rapid bone loss, such as oestrogen deficiency, thus tend to affect trabecular bone more quickly than cortical bone[57].

Bone is synthesised by the deposition of organic matrix (osteoid) and its subsequent mineralisation. Normal adult bone collagen is deposited in a lamellar fashion, which when examined by polarised microscopy appears as parallel fibres of uniform diameter[61]. The anatomy of skeletal collagen, the principle constituent of osteoid, reflects the rate at which it is synthesized; for example, when skeletal synthesis is markedly accelerated, such as accompanying fracture repair or various states of hyperparathyroidism, the collagen assumes a woven pattern consisting of variously sized, randomly arranged fibres. These patterns of collagen synthesis may contribute to the tensile strength of bone.

Despite their relatively small number in a large organic and inorganic tissue, bone cells dictate the structure of the skeleton. The three major cell types in bone are the osteoblasts, the osteocytes and the osteoclasts[62,63]. Osteoblasts, derived from

fibroblastic stem cells, are responsible for the synthesis of the extracellular bone matrix components. They mature into osteocytes which lie in concentric layers within mineralised bone and serve to control local mineralisation and mineral exchange between bone and plasma. Osteoclasts are multinucleate cells, derived from the monocyte-macrophage series which resorb calcified bone or cartilage. Bone cell functions may be divided into those occurring only prior to cessation of growth, and those ongoing throughout life[61]. Growth and modelling are the processes whereby bone increases in size and is shaped to adult proportions; both of these activities cease with epiphyseal closure. Remodelling, in contrast, continues throughout life; it consists of a programmed sequence of bone formation and resorption at discrete foci known as basic multicellular units[64,65]. At the beginning of each remodelling cycle, osteoclasts appear on a previously inactive surface and, over a period of about two weeks, construct a tunnel in cortical bone or a lacuna on the surface of trabecular bone. The osteoclasts are replaced by osteoblasts which fill in the resorption cavity over a period of three to four months to create a new structural unit of bone. The rate of bone turnover is determined mainly by the frequency of activation of new basic multicellular units. The unique aspect of remodelling is the anatomical and functional coupling of osteoblastic formation and osteoclastic resorption. In normal young adults, the two actions are tightly coupled and bone mass is maintained. Bone loss implies an uncoupling of the phases with a relative or absolute increase in resorption over formation[66]. Bone cell function in vitro can be influenced by several extrinsic agents

including hormones (parathyroid hormone, 1,25-dihydroxy vitamin D and calcitonin), drugs and mechanical effects[62]. The local mechanism, however, whereby bone formation and resorption are coupled remains unknown.

1.2.2 The measurement of bone mass

Early information about adult bone mass was obtained by in vitro analysis of dry, defatted skeletons, expressing results as the ash weight to volume ratio[67,68]. Although confined to autopsy specimens, these studies showed that skeletal weight decreases with age above 40 years in both sexes and in Caucasians and Negroes. A number of methods of bone mass measurement have subsequently been developed (Table 1). These methods can be divided into four broad categories: radiogrammetry, absorptiometry, methods for the overall assessment of skeletal status and bone histology.

Radiogrammetry

Radiogrammetric measurements have been applied to three skeletal sites: the metacarpal, spine and proximal femur[69,70]. The major advantages of these methods are that special facilities are not required and the measurement procedures are straightforward.

Radiographic morphometry of the second metacarpal involves measurement of the total and medullary width at the midshaft[69,71]. The measurements are made on contact radiographs of the hand using needle-tipped vernier calipers[72]. Results are expressed as cortical width, or the ratio of cortical width to total width. Metacarpal morphometry quantifies surface-specific processes such as net endosteal resorption but cannot reveal changes in bone tissue composition or losses

Table 1

Methods of measuring bone mass

Method	Site	Bone type
Radiogrammetry	(1) Metacarpal	Cortical
	(2) Vertebral	Trabecular
	(3) Femoral	Cortical and trabecular
Absorptiometry	(1) Single photon absorptiometry	
	distal radius	Cortical 50% Trabecular 50%
	mid-radius	Cortical 90% Trabecular 10%
	(2) Dual photon absorptiometry	
	vertebral	Trabecular
	femoral neck	Cortical and trabecular
	(3) Computed axial tomography	
	vertebral	Trabecular
Overall assessments	(1) Neutron activation analysis	Cortical and trabecular
	(2) Whole body retention of technetium diphosphonate	
Histology	(1) Iliac crest	Cortical and trabecular

due to intra-cortical resorption. The technique can be used to follow age-related bone loss in individuals and is a commonly adopted tool in population studies[73]. It correlates moderately well with the ash weight to volume ratio at the measured site and is reproducible[73,74]. There are two problems, however, with its use in studies of hip fracture. First, it is solely a measure of cortical bone mass. Second, it measures bone at a site distant from the proximal femur and evidence had mounted that bone loss occurs at different rates at different skeletal sites[42,75-77].

Visual assessment of biconcavity, wedging and collapse of vertebral bodies on lateral spine radiographs is subjective[72]. Biconcavity is easily confused with artefacts due to obliquity and is of uncertain prognostic value. However, the number and degree of wedged and collapsed vertebral bodies can be assessed objectively by a number of morphometric techniques to provide a spinal score[78]. Densitometric modifications of lumbar spine radiographs with the inclusion of an aluminium step wedge have also been attempted in an effort to standardise the procedure[79].

The third site at which radiographic measurements are possible is the proximal femur. The trabecular bone in the femoral neck is normally arranged in a series of arches which correspond to the primary and secondary compressive and tensile stresses in the upper femur. These arches are resorbed with advancing age in an order which is determined by their functional significance. In 1970, Singh[70] suggested a six point scale for grading the trabecular patterns in the upper femur. The validity and reproducibility of the method, however, have not been carefully evaluated.

Absorptiometry

Photon absorptiometry was developed two decades ago as a transmission technique for measuring cortical bone in the appendicular skeleton[80,81]. A beam of radiation from a radionuclide source is passed across a limb and the radiation transmitted is monitored using a scintillation detector. If soft tissue thickness around the measurement site can be made effectively constant, only one form of radiant energy is required (single photon absorptiometry); if not, two energies are required (dual photon absorptiometry).

In single photon absorptiometry[71,72], the usual isotope is iodine-125 and the limb is immersed in water. The amount of bone mineral present is proportional to the change in beam intensity over the bone, and may be expressed as mass per unit length or per unit area. The technique provides an accurate assessment of the amount of mineral present, with correlation coefficients of 0.98 reported with the results of ashing studies at the measured site. The reproducibility of repeated measurements is also good with coefficients of variation of one to two per cent in normal individuals. Although any peripheral bone can be measured, the most widely used sites are the mid-radius (a region composed of 90 per cent cortical bone) and the distal radius, a site containing approximately equal amounts of cortical and trabecular bone. In addition to its accuracy and reproducibility, single photon absorptiometry has the advantage of widespread availability at moderate cost. For measurements made at the radius, there is good correlation with other cortical sites and with total body calcium assessed by neutron activation analysis. The method primarily reflects changes in cortical

bone and is therefore not a good index of changes in axial trabecular bone mass.

Some of the limitations of single photon absorptiometry are overcome by making measurements at two distinct energy levels. This eliminates the need to have a constant thickness of soft tissue around the bone and enables measurement at any body location. Dual photon absorptiometry[82], using high activity gadolinium-153 sources, has been successfully applied to measurements of the lumbar spine and femoral neck. The precision of spinal measurements is typically three to five per cent in vivo, and the method has yielded important information about changes in axial bone mineral content with ageing.

Computed axial tomography (CT) is now widely used in radiology departments for clinical imaging. CT measurements involve making attenuation determinations at many positions in a fixed arc about an object of interest. Quantitative estimates are thus possible of the density of particular skeletal sites[82,83]. Unfortunately, the method measures both bone and marrow when applied to the axial skeleton, reducing its accuracy.

An alternative absorptiometric approach has recently been developed using ultrasound to assess bone mass in the os calcis[84,85]. A beam of broadband ultrasound is propagated through the heel and its attenuation is expressed as a function of frequency.

Assessment of overall skeletal mass and function

The total amount of calcium in the body can be measured in vivo using neutron activation analysis[82]. The major isotopic constituent of calcium is 40-Ca, but small quantities of a rare stable 48-Ca isotope also

occur in uniform concentration. The principle of neutron activation analysis is that following total body irradiation of the subject by a beam of fast neutrons, small amounts of this 48-Ca are converted to a radioactive isotope 49-Ca, which is measured in a total body counter. As calcium is a constant fraction (0.38) of bone mineral, 49-Ca can be interpreted directly as an indicator of skeletal mass in the absence of ectopic calcification. This costly procedure is only available in a few major research centres with irradiation facilities and whole body counters.

The other major method for assessing overall skeletal function involves the measurement of whole body retention of technetium-99c diphosphonate. This bone-seeking compound is believed to adsorb onto the calcium of hydroxyapatite crystals and the major factors which govern this adsorption are osteoblastic activity and skeletal vascularity. Twenty four hours after injection, diphosphonate reaches a stable equilibrium in bone while any remaining isotope in the body has been largely cleared from the soft tissues via the renal tract. It has been shown that whole body retention provides a sensitive means of identifying increased bone turnover in a wide variety of metabolic bone disorders.

Bone histology

Samples of cortical and trabecular bone may be obtained from the iliac crest[61]. Conventional methods of preparing these biopsies for histological analysis entailed decalcification prior to sectioning. The procedure made distinction between mineralised and non-mineralised (osteoid) bone matrix impossible and

limited the method to identification of patients with disorders of skeletal calcification. More recently, non-decalcified sections have been made by embedding the biopsy in plastic and using a heavy duty microtome. The microscopic sections performed in this manner permit easy identification of both calcified bone and osteoid. Various morphological parameters may be quantified which reflect the amount and behaviour of bone in the remodelling surfaces[86,87]. These histomorphometric parameters provide information not only about the total amount of bone present but also about the rate of bone turnover, through quantitation of osteoclastic resorption surfaces and osteoid-covered surfaces. Furthermore, the dynamics of the calcification process can be quantified using double-labelling with tetracycline. This antibiotic binds to newly deposited bone mineral and when examined by fluorescent microscopy, the complex appears as a yellow line at the calcification front. The calcification rate is determined by measuring the distance between two labels, representing sequential doses of tetracycline administered prior to the biopsy.

Bone histomorphometry has little to offer in the diagnosis of osteoporosis, largely because of substantial within-individual variation in measurements of trabecular bone volume. It has, however, provided unique information on the heterogeneity of bone cell behaviour in osteoporosis and this analysis at the level of the basic structural unit of bone permits more critical choice and evaluation of therapeutic regimes in individual cases.

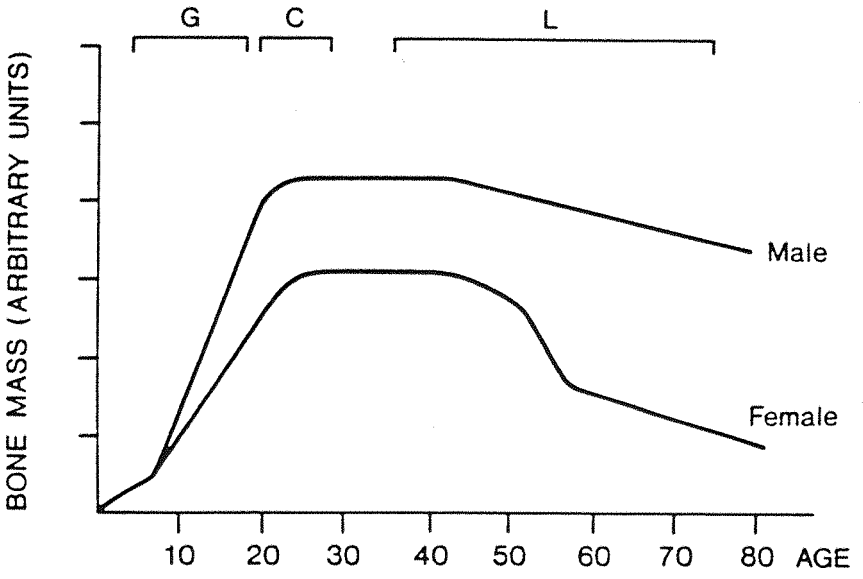
1.2.3 Changes in bone mass with ageing

Alterations in the bone mass of human beings throughout life fall into three phases: growth, consolidation and loss[56,57] (Figure 1). From conception to epiphyseal closure, there is a progressive increase in cortical and trabecular bone mass which is accelerated during the pre-pubertal growth spurt. This growth phase produces 90 per cent of peak bone mass and is followed by a five to 15 year period of consolidation, during which formed trabecular plates become thicker and cortical porosity gradually diminishes. Peak bone mass is attained in the third decade of life[56,73]. Age-related bone loss commences soon after. A biphasic pattern of loss has been identified for both cortical and trabecular bone: a protracted slow phase which occurs in both sexes and a transient accelerated phase which occurs in women after the menopause. For cortical bone, the slow phase of loss begins at about age 40 years in both sexes at an initial rate of 0.3 to 0.5 per cent per year[75,88]; in postmenopausal women, an accelerated phase of cortical loss of two to three per cent is superimposed on this pattern[89]. Data on trabecular bone loss from the axial skeleton are conflicting[75,77,90-95], but this probably commences slightly earlier than cortical loss and the accelerated postmenopausal phase has a greater rate.

Marked ethnic variation has been observed in bone mass. Studies of Negroid populations in the USA have detected higher total bone mass than in Caucasians, whether measured by ashing studies[67] or neutron activation analysis[96]. However, a South African study using metacarpal morphometry failed to find differences in cortical bone mass between these two ethnic groups[97]. Data from Japanese residents in Hawaii have

Figure 1

Changes in bone mass with age in Caucasian men and women.



G = GROWTH

C = CONSOLIDATION

L = LOSS

suggested lower forearm bone mineral content than in US Caucasians of similar age[98], and Polynesian women in New Zealand have been shown to have greater appendicular bone mass than Caucasians[99].

Bone mass in any individual over the age of 40 years depends on the amount of bone made during growth and its subsequent rate of loss. Although the rate of bone loss has received more attention in the study of osteoporosis, it is becoming increasingly recognised that insufficient accumulation of skeletal mass by young adulthood may predispose a person to fractures later in life as age-related bone loss ensues[57]. The effects of heredity, race and sex on the incidence of hip fracture can be explained, in part, by their effects on peak bone mass. Smith[100] found that monozygotic twins had a significantly greater concordance for bone mass of the radius than did dizygotic twins. A genetically determined peak bone mass also explains the tendency to familial aggregation amongst osteoporotic fractures[42].

The greater peak bone mass reported in Negroid populations may explain why these individuals sustain fewer fractures than Caucasians, although Negroes also show a greater resistance to the bone resorptive effects of parathyroid hormone and 1,25 dihydroxy vitamin D[101]. This resistance may allow them to accumulate more bone during growth.

Finally, an accumulation of studies measuring cortical and trabecular bone mass in individuals suggest that women have a 15 per cent lower bone mass than men after completion of skeletal growth[57]. Unfortunately, there are few studies which have attempted to define the interactions between genetic, nutritional, hormonal and mechanical factors which

determine peak bone mass. Risk factors for age-related bone loss will be considered in detail later.

1.2.4 The skeleton and calcium homeostasis

The maintenance of a constant calcium ion concentration in extracellular fluid plays a central role in the control of bone metabolism[102-107]. This is acheived through the actions of three regulatory hormones: parathyroid hormone (PTH), vitamin D and calcitonin.

Parathyroid hormone exerts its action in man on three major organs: bone, kidney and small intestine. The net effect of its action on these organs is to raise the calcium concentration of the extracellular fluid. In turn, the production of PTH is inhibited by an increase, and stimulated by a decrease, in serum calcium through direct effects of calcium on the rate of PTH secretion. PTH is initially synthesised as a larger pro-hormone, which is cleaved to the classical 84 amino acid molecule prior to secretion. The secreted hormone is rapidly degraded to fragments that may be biologically active or inactive. Thus immunoreactive and biologically active PTH concentrations are not necessarily the same. At the cellular level, PTH exerts its effect through activation of the enzyme adenyl cyclase and the formation of 3':5' cyclic AMP in the cells of target tissues. This rapid increase in intracellular cyclic AMP is the initial manifestation of the physiological effects of the hormone. In vitro studies indicate that there are three temporally related responses of bone to PTH. Following an initial fall in serum calcium concentration, there is a prolonged hypercalcaemia, and days later, a general increase in bone remodelling with

increased numbers of histologically detectable osteoclasts and osteoblasts, and an overall reduction in bone matrix and mineral. The hormone exerts two separate actions on mineral ion transport in the kidney: an increase in phosphate excretion and a decrease in calcium clearance. Its effect on the intestine was the last to be recognised and is least well understood. PTH influences the renal production of 1,25 dihydroxy vitamin D through stimulation of renal 1-hydroxylase activity, thereby enhancing calcium absorption.

Vitamin D (cholecalciferol) may be formed in the skin from 7-dehydrocholesterol by the action of ultraviolet light. This is the form found in animal tissues. The term is also applied to ergocalciferol (D2) which can be obtained from plants after artificial ultraviolet irradiation. These vitamins are transported in the blood bound to specific carrier proteins; they are inactive until metabolised. In the liver the molecule is hydroxylated to 25-hydroxy cholecalciferol (25HCC or 25OHD), the main circulating form of the vitamin. Any excess of vitamin D is stored in the organ, or is converted to inactive forms and excreted. Further hydroxylation of 25 HCC by the kidney to 1,25 dihydroxy cholecalciferol (1,25 DHCC) is necessary to confer biological activity on the vitamin. 1,25 DHCC acts on the intestine, increasing calcium absorption and in conjunction with PTH it releases calcium from bone. The rate of production of 1,25 DHCC is controlled by the circulating level of PTH. A reduction in extracellular ionised calcium level stimulates PTH production by the parathyroid glands. PTH stimulates 1,25 DHCC synthesis and the two hormones act synergistically on the bone reservoir releasing

calcium into the circulation; 1,25 DHCC also increases calcium absorption. In short term homeostasis, the skeletal effect is more important; after prolonged hypocalcaemia, more efficient absorption becomes important.

PTH and 1,25 DHCC also have influences on the rates of bone cell function. These effects on bone formation and resorption may be important in the pathogenesis and treatment of osteoporosis. PTH is able to stimulate bone resorption and has a direct inhibitory effect on osteoblastic collagen synthesises. It is becoming increasingly apparent that serum PTH levels increase with age[108-110] and that supranormal levels occur in some patients with symptomatic osteoporosis[111]. Although this age-related rise has been attributed to decreasing renal function, poor dietary calcium intake and defective calcium absorptive mechanisms resulting from impaired hepatic and renal hydroxylation of vitamin D and 25 HCC respectively, the actual cause is unknown[105]. The contribution of this senescent hyperparathyroidism to the normal age-related decrease in bone mass is controversial. It is supported by evidence that the rate of bone loss in postmenopausal women is greater in those with higher levels of circulating PTH[112].

Calcitonin is a 32 amino acid peptide hormone secreted by the thyroid C-cells, embryologically derived from the neural crest. It is synthesised as part of a large precursor protein which contains flanking peptides, and the calcitonin gene also codes for other molecules which may alternatively be produced by post-transcriptional processing. A marked sex difference is found in circulating calcitonin levels, with higher concentrations found in men than in women.

However, during pregnancy and lactation, times of increased physiological requirement for calcium, this difference is abolished. A major action of calcitonin in humans is to oppose bone resorption by a direct inhibitory effect on osteoclasts, and it thereby has potent calcium-lowering properties. Low and normal calcitonin levels have been observed in osteoporotic patients[107]. It has been postulated that a lifelong relative deficiency of calcitonin in some women could play a role in age-related bone loss, particularly during the post-menopausal decade.

Compared to the calcium regulating hormones, relatively little attention has been paid to hormones which exert their major effects on other systems but also influence bone metabolism. Oestrogen deficiency has been clearly implicated in the pathogenesis of osteoporosis, but it is not clear how this effect is mediated. It has been suggested that reduced amounts of endogenous oestrogen may contribute to greater urinary calcium loss and greater bone loss in thin women[105]. An alternative explanation is that oestrogens increase gastro-intestinal calcium absorption, thereby stimulating calcitonin secretion and reducing bone resorption. Other systemic hormones have direct effects on bone. The growth hormone dependent factor somatomedin C is a potent stimulator of bone cell replication and collagen synthesis. Somatomedin C is lower in old age and has been reported to be low in osteoporotic individuals.

Finally, local factors may be important in determining the pattern of age-related bone loss. These local mechanisms, hitherto undefined, could lead

to an uncoupling of bone formation from bone resorption, in favour of the latter. A number of intercellular mediators such as prostaglandins, interleukins and growth factors are candidates for such functions.

1.2.5 The biochemical assessment of bone turnover

The major biochemical markers of bone resorption and formation are listed in Table 2. Collagen is degraded to small peptides containing hydroxyproline, which contributes to plasma hydroxyproline and urinary dialysable hydroxyproline[113]. Urinary total hydroxyproline (THP) does not differentiate between different collagen types, accounts for less than 20 per cent of total collagen metabolism, is derived from skin and dietary gelatin as well as from bone, and includes a non-dialysable component that is a byproduct of collagen synthesis. Despite these limitations, urinary THP correlates modestly with other biochemical and kinetic indices, especially when resorption and formation are increased as in Paget's disease[114]. The significance of urinary THP in the study of age-related bone loss depends on the choice of referent. Expressed per unit of time, urinary THP in adults falls with age, but expressed per unit of creatinine excretion (an index of muscle mass) or per unit of creatinine clearance (an index of glomerular filtration rate), urinary THP remains unchanged or increases with age especially after the menopause in women[115]. Osteoclasts contain an acid phosphatase which is released into the circulation and can be differentiated from prostatic acid phosphatase by its resistance to inhibition by tartrate[116]. This compound is also a useful marker of bone resorption.

Table 2

Biochemical markers of bone remodelling[113].

Resorption	Formation
Urinary total hydroxyproline (HP)	Serum total alkaline phosphatase (AP)
Urinary dialysable HP	Serum bone-specific AP
Serum total HP	Serum osteocalcin
Serum tartrate resistant acid phosphatase	Urinary non-dialysable HP

The most widely applied marker of bone formation is serum total alkaline phosphatase, which includes several organ-specific iso-enzymes. Serum total alkaline phosphatase increases with age and after the menopause in women[115,117]. It is frequently increased in osteoporosis but correlates poorly with histologically determined bone formation rates or other histological indices of bone remodelling[113]. Bone specific alkaline phosphatase is potentially a more useful marker of total body bone formation but analytical methods for its detection are of uncertain specificity[118].

Osteocalcin is the most abundant non-collagenous protein in bone[119,120]. It contains several glutamic acid residues that are gamma-carboxylated (a process mediated by the vitamin K cycle) and is synthesised exclusively by osteoblasts. Serum levels of osteocalcin are therefore thought to be amongst the most sensitive indicators of bone formation. Although analytical methods are not of uniform specificity, most workers agree that levels rise with age in adults, are higher in women than in men, and correlate better than alkaline phophatase with histological indices of bone formation, both in normal subjects and in patients with osteoporosis. A number of other factors influence serum osteocalcin levels including renal function, calcium ingestion, surgery and circadian variation. Some studies have suggested that osteocalcin levels are higher in patients with vertebral crush fractures than in age-matched controls. The interpretation of this finding is difficult, however, given the number of other factors which might influence bone remodelling in such patients.

1.2.6 Bone mass and bone strength

Bone mass is an important determinant of bone strength. Studies using cores of trabecular bone from lumbar vertebrae have shown a strong positive correlation between compressive strength and the ash weight to volume ratio[121]. However, extrapolation of the correlation between bone mass and bone strength from vertebral bone to the proximal femur may not be justified for two reasons. Firstly, the geometric structure of the femoral neck makes the direction and nature of any force applied an important determinant of internal stress and likelihood of fracture. In this regard, morphological variation in the neck-shaft angle has been suggested as a reason for racial differences in hip fracture incidence[122]. Secondly, the internal architecture of the femoral neck is unique. It is composed of a substantial amount of cortical bone, and bone mineral in its trabecular region is distributed in a series of compressive and tensile arches following the lines of load bearing stress. The sequential loss of these trabeculae has, in fact, been suggested as a method for grading bone loss in the upper femur[70]. Despite these unique structural characteristics of the femoral neck, some investigators have shown close correlations between bone mass in the upper femur and compressive strength. Dalen[123] showed a strong relationship between x-ray spectrophotometric assessment of femoral neck bone mineral content and the ultimate force at fracture in a series of autopsy specimens. Leichter[124], in a detailed study of bone density, mineral content and shearing stress in bending at failure, showed a good correlation between bone density and breaking stress.

In excised cadaveric specimens, the ash weight

predicts only 70 per cent of the variation in bone strength, reflecting the importance of qualitative aspects of bone structure in determining its strength. It has been suggested that there is an age-related decline in bone remodelling with a consequent reduction in repair of microfractures which continually occur in trabecular bone[125]. The accumulation of such microfractures might lead to fracture. Other investigators report that changes in the physical properties of bone are associated with fracture risk. Dickenson and co-workers[126] found a reduction in the energy-absorbing capability of osteoporotic bone that seemed over and above the effects of bone loss per se. It has been suggested that this effect results from altered morphology of hydroxyapatite crystals and local variation in the density of osteoporotic bone[127].

Bone strength is also a function of the integrity of internal bone architecture. Bone trabeculae provide both vertical support and horizontal crossties, especially in vertebrae and at the ends of long bones. The age-related loss of bone trabeculae disrupts this internal structural supporting system and may cause a reduction in strength disproportionate to the loss of bone tissue[128]. Furthermore, although compressive strength in bone may relate largely to mineral content, tensile strength may largely be dependent on the collagenous matrix and our knowledge of changes in the physical properties of bone collagen with age is limited. Finally, osteomalacia - a failure of, or delay in, mineralisation of newly formed bone - may impair bone strength. Fractures sometimes occur in localised areas of reduced bone density, and osteomalacia has been a frequent finding in some British series of patients with hip fractures[39].

In summary, although bone mass is an important predictor of bone strength, many other qualitative and quantitative aspects of bone structure may also contribute to skeletal integrity.

1.3 The relationship between bone mass and fracture

The advent of non-invasive methods for measuring bone mass and the characterisation of patterns of change in bone mass with ageing have led to greater understanding of the relationship between osteoporosis and fracture risk. This understanding is based firstly upon a number of theoretical models to explain fracture incidence on the basis of age-related bone loss, and secondly, upon the results of analytic studies measuring bone mass in fracture cases and non-fracture controls.

1.3.1 Theoretical models to explain the relationship between bone mass and fracture

Newton John and Morgan[129] constructed the first model to explain the age and sex-specific incidence patterns of hip fracture on the basis of bone loss with ageing. They reviewed the results of over 30 studies and concluded that age-related bone loss was universal, that fracture risk was largely determined by bone mass and that no evidence existed for a separate population of rapid bone losers who were at greater risk of fracture. With regard to bone loss with ageing, they analysed the cross-sectional data of Garn[130], Meema[131], Richmond Smith[43] and Nordin[132], as well as the longitudinal data of Garn[73,130], separating measurements of cortical and trabecular bone. The combined results suggested that all bones lose tissue

with age, that this loss begins at 40 to 45 years in women and 50 to 65 years in men, that the rate of loss of bone is greater in women than in men, and that the rates of loss of cortical and trabecular bone are similar in each sex. The values for the amount of bone at each age have a normal distribution and the variation in the amount of bone does not change with age in either sex. The second set of results reviewed were those of studies measuring bone mass in patients with fractures and comparing them to population or control values. In all these studies, the mean bone mass of fracture cases was lower than that of controls but a separate subpopulation with excessive bone loss was not detectable. Finally, by defining fracture thresholds at various levels in the young normal bone mass distribution, they demonstrated that the number of elderly in the population who fell below this threshold showed an age distribution which almost exactly matched the observed incidence data for age-related fractures. These threshold values were -2.5 standard deviations for the hip and -1 standard deviation for the distal radius. They claimed, therefore, that "the increased incidence of fracture with age is explained by the increased incidence of thin bones with age".

Several criticisms have been made of this hypothesis. Doyle[133] argued that only longitudinal data could convincingly demonstrate that all individuals lose bone at a constant rate and the available data from the longitudinal studies of Garn[130], Adams[134] and Dequeker[135] suggested unequal rates of loss amongst individuals. Secondly, he questioned the conclusion that the variance in bone mass remains constant at all ages, using cross-sectional data from quantitative radiology of the ulna.

Thirdly, cross-sectional data might incorporate secular trends which have an effect upon bone mass. Finally, the Newton John and Morgan hypothesis predicts a sigmoid distribution of hip fracture incidence with age, while that observed is exponential, suggesting that aetiological factors other than bone mass have to be invoked to explain the continuing rise in the older age groups.

The original hypothesis was undoubtedly an over-simplification of the cause of age-related fractures and Morgan[136] has modified it to accommodate some of the criticisms and inaccuracies mentioned above. He considers the two extreme models relating bone mass to fracture: the first, in which fracture risk is directly related to the amount of bone present, and the second, in which fracture risk is entirely determined by the initiating traumatic event. These models are considered separately for fractures of the vertebrae, and hip. The bone mass model fits the published data for vertebral fractures but neither model adequately explains the incidence pattern and cross-sectional data available for hip fracture.

Smith et al[38] performed radial single photon absorptiometry on 571 Caucasian women over the age of 50 years. They showed that subjects with vertebral fractures were losing bone mineral at the same rate as those without such fractures. Also in accord with the Newton-John and Morgan hypothesis, they found that bone mineral content (BMC) values showed a normal distribution in each decade age group and the variation in BMC did not increase with age. In order to reconcile these results with those of longitudinal studies showing unequal rates of loss of bone in individuals, they concluded that either the rate of

loss for an individual is not constant over time, or the rate of mineral loss is proportional to the amount of mineral present at maturity. These postulates remain to be confirmed in longitudinal studies.

Riggs[137] further subdivides the age-related fractures into two separate syndromes. Type 1 osteoporosis occurs in a small subset of post-menopausal women between 51 and 65 years of age, whilst type 2 occurs in a large proportion of men and women above 75 years. Using dual photon absorptiometry in 123 normal women they found that lumbar BMC (mainly trabecular bone) decreased linearly by 42 per cent during life, whilst femoral neck BMC (mixed cortical and trabecular) decreased by 58 per cent. At age 75 years all women had BMC values at both sites which were below the putative fracture threshold. In 26 elderly women with hip fractures, the mean value for femoral neck BMC was decreased but all individual values were within the age-specific normal range. In contrast, for 27 women with vertebral fractures, lumbar BMC values were considerably below the age-expected mean and 20 had values outside the normal range. Radial BMC, however, was normal. These data suggested that type 1 osteoporosis was characterised by accelerated and disproportionate loss of trabecular bone, whilst type 2 osteoporosis showed a proportionate loss of both cortical and trabecular bone, with a rate of loss similar to that of the general population. This second syndrome corresponds with Newton-John and Morgan's model and two major pathogenetic mechanisms are proposed: impaired bone formation or secondary hyperparathyroidism.

More recently Horsman[138] has devised a stochastic model to describe quantitatively the association

between bone mass and fracture risk. The model uses a series of individual characteristics of bone mass to characterise a population. Fracture risk is calculated for each individual, increasing as the amount of bone decreases. From individual fracture risks, fracture cases are identified and age and sex specific incidence rates are constructed. A series of independent parameters were assigned to represent the amount of bone in the young adult (M), the age at which bone loss commences (A), the mean rate of decrease of bone mass in the population (R) and the putative fracture threshold, above which the probability of fracture is zero. When the absolute value of M was chosen for females arbitrarily, R set at 0.5 to 1.0 per cent per year, A set at the mean age of the menopause a curve was obtained which closely resembled the Leeds female hip fracture incidence curve. The Leeds male age specific hip fracture incidence rates were mimicked by increasing M by ten per cent, leaving all other parameter values unchanged. The importance of such stochastic models is that they show how closely, even with a simple model postulating linear bone loss, observations of fracture incidence can be reproduced. They may not, however, represent the true influences upon fracture risk; in particular, these models do not account for the age and sex specific incidence of falls which rise roughly in parallel with the incidence of hip fractures.

1.3.2 Case-control studies

Reduced spinal trabecular bone mass has consistently been found in patients with vertebral crush fractures when compared with non-fracture controls[139-141]. Furthermore, a threshold value can be

defined below which crush fractures occur but above which they are rarely found. The prevalence of fractures increases the further bone mass falls below this threshold. A reduction in spinal trabecular bone mass therefore appears to be an important determinant of the risk of vertebral crush fracture.

However the role of osteoporosis in the occurrence of hip fracture remains controversial. The results of 15 case-control studies which have examined bone mass in patients with hip fractures and non-fracture controls have recently been reviewed by Cummings[142]. In six of these[139,143-147], bone mass was measured in the contralateral hip by a variety of methods. All these studies found lower bone mass in the patients with hip fractures than in control subjects. The difference between cases and controls was smallest in the two studies using dual photon absorptiometry[139,144] and largest in those using a radiological grading system of the femoral neck trabecular pattern - Singh index[143,146]. In two studies, the Singh index differentiated between hip fracture patients and controls more effectively than other measurements of femoral or metacarpal cortical thickness[143,148], and in one of these the investigator was blinded to the identity of each subject as a case or control. The results of these studies may also have been affected by bias in the selection and exclusion of subjects. Riggs[139] studied ambulatory patients who had survived for at least one year after the fracture. Approximately 20 per cent of patients with hip fracture die within the first year[149] and their sample may therefore have been a relatively healthy subgroup with greater bone mass than those who died or were unable to walk.

The remaining studies have measured cortical or trabecular bone mass at various skeletal sites in hip fracture cases and controls[92,139,144,150-152]. Three of these[92,139,144] have failed to detect statistically significant differences in lumbar spine bone mineral content by dual photon absorptiometry, and two[139,150] have not detected differences in forearm bone mineral content.

These results have fuelled the argument that the primary determinant of hip fracture in the elderly is falling, and that osteoporosis is merely a correlate of the ageing process, with no causal significance. Hence, it is argued, measures to prevent hip fracture should be directed primarily at the prevention of falling, rather than at retarding the rate of bone loss. They also suggest that measurements of bone mass may not be an accurate way of predicting hip fracture risk in individual patients[153,154].

1.3.3 Cohort studies

There have been few population-based cohort studies examining the role of osteoporosis in the aetiology of hip fracture.

Iskrant[47] classified 2,100 women aged over 45 years into four groups according to vertebral density and followed 95 per cent of them for three years. A total of 325 fractures occurred during this period. When fractures of the radius, hip and ankle were taken together, a significant association was found with bone mass grading. In a Danish retrospective cohort study[44], the patients with hip fractures had lower radial BMC and metacarpal cortical ratios than the non-fracture controls.

In summary, analytical studies have not demonstrated large differences in bone mass between hip fracture cases and controls, although those examining bone mass in the upper femur have more consistently shown a reduction amongst patients with hip fractures. The independent contributions of osteoporosis and the risk of falling to the occurrence of hip fracture remain unknown.

1.4 Falls in the elderly

The epidemiology of falls in the elderly has not been well studied. In the USA and UK accidental falls are a leading cause of death in persons over 65 years of age[155-157] and hip fracture is an important cause of fall-related mortality. About a quarter of people aged over 65 years fall, and two per cent of all elderly come to medical treatment each year as a result of falls.

1.4.1 The elderly at home

In 1948, Sheldon[158] performed an interview study on a random sample of elderly residents in Wolverhampton; 43 per cent of women and 21 per cent of men stated a liability to fall. The proportion of respondents reporting falls increased markedly after age 70 years, with a small fall-off in the over-80 year age group. Twenty per cent of falls resulted from postural instability and 24 per cent from drop attacks; eight per cent of fallers sustained a fracture.

In 1977, Exton-Smith[159] interviewed 963 elderly. Women were more likely to report liability to fall and the rate of falls increased linearly with age. Tripping was the commonest cause of falls in those under 75 years, whilst postural instability and drop attacks became more prevalent above this age. Forty

per cent of falls in the over 75 year old women led to fractures, whilst only 27 per cent of over 75 year old male fallers fractured.

Perry[160] suggested that disability or illness was associated with 75 per cent of falls but could show no relationship of falling to race, sex and marital status. These studies all revealed that 30-50 per cent of the elderly report falling, that falling increased with age, that women were more likely to fall than men, and that the severity of the subsequent injuries varied according to the age and sex of the subjects. As they were all based on interview information, the frequency of falling may have been underestimated.

1.4.2 Out-patient or casualty populations

Most epidemiological studies of falling in the elderly have used readily available patient populations; these studies involve difficulties with selection bias, over-representing the elderly with pre-existing disease or those injured more severely.

In a one year study of 1,544 injuries from accidents in the home, Seiler[161] found that 41 per cent of all such injuries resulted from falls. Falls caused fractures in 42 per cent of the cases and accounted for 58 per cent of home accident-related deaths. The home injury rate for subjects rose with age from 3/1,000/year at age 65 to 74 years to 14/1,000/year in those over 85 years.

Sheldon[162] described 500 falls in 202 persons treated in casualty or by general practitioners. The rate of falling increased with age and 224 of the falls resulted from environmental factors such as obstacles in the home, while 276 were related to illness. There was a high overall occurrence of drop attacks (25 per

cent) and emphasis was placed on host-related factors predisposing to falls such as vertigo, cerebrovascular disease, and vertebrobasilar insufficiency.

MacQueen[163] surveyed all medically treated injuries in Aberdeen over a two year period. He showed an increasing fall rate with age, a higher rate in women and a high prevalence of decreased mobility and decreased visual acuity amongst fallers. Stairs were prominent environmental hazards.

Lucht[164] studied falls in the home which were treated at a community hospital. The annual incidence was 14/1,000 in the elderly and a rapid increase occurred after 75 years. The mortality rate also increased with age, and social isolation appeared to play a role in this. Twenty five per cent of falls occurred on stairs and almost all occurred during the day time, with 39 per cent resulting from illness.

Waller[165] performed a case-control study of 150 persons over the age of 60 years seeking emergency treatment at a university hospital casualty. Controls were obtained by interviewing neighbours of similar age and sex. Thirty per cent reported falling in the previous year. In a third of these, the chief cause was a health problem. Among the healthy elderly, slippery or rough ground accounted for 54 per cent of falls but in the sick elderly this factor accounted for only 14 per cent.

In summary, casualty and out-patient studies confirm the greater frequency of falls in women and in the older elderly. The rates of treated falls range from three to 200 per 1,000 subjects per year, depending upon the population studied. Many elderly who fall do not seek treatment. The well and sick elderly may fall for different reasons.

1.4.3 Institutionalised elderly populations

Homes for the aged have provided further information. Rodstein[166] reported 147 consecutive accidents in 85 subjects in a home. Twenty five per cent of residents fell within a six month period, 20 per cent of falls occurring during an acute illness and 30 per cent in patients with chronic illnesses. The most frequent circumstances surrounding a fall were transfers of position. Only one per cent of falls led to fracture. Gryfe[167] in a five year prospective study of active institutionalised elderly persons found a fall rate of 668/1,000/year. Severity of injuries increased with age. No specific time of day, day of the week or season of the year bore a significant relationship to falling. Other studies[168-170] have confirmed a relatively high frequency of falling in the institutionalised elderly, with falls occurring during normal daily activities or associated with illness.

1.4.4 Falling and hip fracture

Data on the relationship between falls and hip fracture is scarce. Although some studies have suggested an increase in the number of falls during periods of snow and ice[50,171], evidence for an increase in hip fracture incidence during these periods is limited. Further, the majority of fractures occur indoors, dampening any seasonal effect on rates due to ice and snow. Bastow et al[37] observed that thinner hip fracture patients had a higher mortality and a lower core temperature on admission than their heavier counterparts. They suggested that undernutrition predisposes to hypothermia, which in turn causes falling and that this is the cause of seasonal variation in fracture incidence. Evidence conflicts

over whether hip fracture cases fall more frequently than controls. Brocklehurst et al[38] could only identify a significant excess of falls in the previous year in those aged over 85 years, while Evans et al[35] found a history of falls to be significantly more frequent in cases than in a community sample after age standardisation. Although all falls in the community may only rise threefold between the ages of 60 and 90 years, more severe falls may increase by a greater order, as evidenced by the tenfold rise in hospital admissions due to falls between these ages[156]. Several characteristics are known to distinguish fallers from the general population and occasional from habitual fallers[172-178]. Regular fallers are less mobile, less independent individuals who live alone. They have a higher prevalence of dementia, stroke, heart disease and neurological dysfunction, and are more likely to be taking minor tranquillisers and anti-hypertensive medication.

1.5 Individual risk factors for hip fracture

The results from 13 published case-control studies of hip fracture[179-192] are outlined in Table 3. These studies vary in many ways: the number of cases studied, selection criteria for these cases, the number of controls used, the source of these controls and the range of variables studied. These differences in study design limit comparisons of some of the data, but together they have yielded a number of risk factors some of which are thought to exert their influence on bone mass and others on propensity to trauma.

Table 3

Individual risk factors for hip fracture: findings of 13 case-control studies

	Study	Cases	Controls	Factors studied	Positive findings
1.	Brocklehurst et al[38]	384	226	Falls, mental/physical state	Dementia, poor physical state
2.	Wootton et al[179,180]	110	72	Bone mass determinants	Radial BMC, low body weight
3.	Hutchinson et al[181]	157	157	Reproductive variables	Age of menopause, body weight, hormone replacement therapy (HRT)
4.	Baker[53]	189	95	Wide range	Social isolation, sunlight exposure, vitamin D intake, body weight
5.	Paganini Hill et al[182]	91	182	Wide range	Body weight, sunlight exposure, physical activity, age at menopause, smoking, HRT
6.	Wyshak[183]	118	709	Parity	Four children protective
7.	Cook et al[184]	384	DHSS survey	Bone mass determinants	Metacarpal index, osteomalacia
8.	Weiss et al[185-187]	353	576	Smoking, weight, HRT	All
9.	Kreiger et al[188]	98	800	Reproductive variables	Body weight, HRT, breast feeding
10.	Boyce[189]	139	139	Wide range	Functional ability, physical activity, age at menopause
11.	Johnell et al[190]	609	609	Health and social status	Functional state, disability
12.	Rashiq et al[191]	102	204	Drug history	Drugs protective
13.	Ray[192]	Medicaid records		Drug use	Sedative/psychotropic drugs

1.5.1 Risk factors influencing bone mass

REPRODUCTIVE VARIABLES

A major aim of several of these studies has been to investigate the relationship between post-menopausal oestrogen therapy, other reproductive variables and fracture. The summated case-control evidence[181,182,185,188] suggests that five years of treatment with oestrogen following the menopause reduces the incidence of hip fracture by approximately 50 per cent. With regard to other reproductive variables, it has been consistently found that an artificially early menopause through oopherectomy in women is associated with an acceleration in rate of bone loss[89,193] and an increased risk of hip fracture[188].

The influence of age at natural menopause, parity, lactation, age at menarche and use of oral contraceptive preparations is more contentious[5,112,181,182,188,194-196]. Although Paganini Hill[182] found a doubling in relative risk for fracture in women undergoing natural menopause before the age of 59 years as compared with those who were older than 60, three larger studies[53,187,189] have found no difference between the age at menopause of cases and controls. One study of elderly women in a nursing home suggested a protective effect of increased parity on hip fracture risk[183], but other studies have not documented significant differences between cases and controls in either number of pregnancies or age at first pregnancy[187,188]. The three studies which have examined breast feeding have yielded conflicting results[187-189]. In parallel with age at menopause, bone mass has been reported to be lower in women with a history of late menarche[197], but case-control studies

of hip fracture have been unable to detect any such effect. Finally, the use of oral contraceptives has been associated with somewhat greater cortical bone mass[196].

BODY BUILD

Almost all case-control studies of hip fracture have found that women who are thin have a greater risk of fracture than obese women[53,179-183,186,189]. Differences in mean weight between cases and controls are of the order of seven to ten kilograms, and when categorised by body mass indices (such as the Quetelet or ponderal indices) a two to threefold increase in risk is found between the thinnest and most obese tertiles. Women who are thin also have less cortical bone than obese women[195,198,199], and thin body build is a risk factor for vertebral fractures in men[200]. Obesity may protect against bone loss in women after the menopause by increasing the amount of biologically available oestrogen through enhanced peripheral conversion of androstenedione to oestrone in adipose tissue cells[201,202]. Additionally, sex hormone binding globulin levels are lower in obese women, increasing oestrogen availability[203]. Besides these oestrogenic effects, body weight might also be associated with greater bone mass through greater skeletal loading, and adipose tissue may act as a cushion against external trauma[42]. The importance of other aspects of body build is unclear. Some studies have found that fracture cases are taller than controls[182,186]. They have a higher prevalence of edentulousness (a marker of mandibular bone loss), and lower skin fold thickness[38,179,195]. A higher prevalence of scoliosis has also been reported in subjects with vertebral osteoporosis[204].

DIETARY CALCIUM INTAKE

Two basic approaches have been used to study the relationship between calcium requirements and bone health in the elderly: epidemiological methods and balance studies[205].

Epidemiological studies have sought the effects of self-selected differences in calcium intake on bone mass, rate of bone loss, osteoporotic fracture incidence, or, conversely, differences in calcium intake between osteoporotics and age-matched controls.

Several early studies failed to detect a relationship between current calcium intake and current bone mass. Garn[73], in his several studies in North and Central America, found no appreciable effect of calcium intake on bone mass in persons across a broad age range. Similarly, Smith and Rizek[43], and Smith and Frame[206] found no significant relationship between current intake and femoral cortical thickness, metacarpal cortical thickness or vertebral density in women with calcium intakes ranging from 150 to 2,100 mg/day. Hurxthal[207] found a weak positive correlation of lumbar vertebral density with lifetime calcium intake calculated by diet history in 404 subjects and the results of the ten state nutrition survey[205] also showed a weak but significant positive correlation of calcium intake with metacarpal cortical area.

By contrast, Matkovic[32] found clear differences in bone mass and fracture rates in two Yugoslav communities distinguished principally by an approximately twofold difference in calcium intake. In both rural districts, nutritional data on intakes of protein, calories, fat, calcium, and phosphorus were obtained by diet histories in 200 subjects. Bone mass was measured by metacarpal morphometry, and incidence

rates for femoral and forearm fractures were recorded over a six year period. Bone mass was found to be higher at all ages in men and women in the high calcium district. Apparent rate of loss with age was the same in both districts for both men and women, and the principal reason for the mass difference appeared to be the fact that persons in the high calcium district started with a higher peak bone mass than did persons in the low calcium district.

It is noteworthy that the majority of such studies have used radiogrammetric methods of measuring bone mass. Metacarpal morphometry takes no account of intra-cortical porosity, or of trabecular bone, and correlates less well than radial photon absorptiometry with either ash weight at the examined site, or total body calcium. The results of studies which have used more precise measurement methods to study the relationship between customary calcium intake and current bone mass have also been equivocal[197,208,209].

Evidence does exist that calcium nutrition is important to skeletal development in humans[210]. It has long been realised that milk supplements given to schoolchildren increased their gain in height when compared with controls given the same caloric intake. This has been seen recently in Japan, where prior to 1950 calcium intake was very low at about 200 mg/day. After 1960, the Japanese authorities began fortifying school bread with calcium and issuing free milk to schoolchildren. Twenty years later, 12 year old Japanese boys averaged about four inches taller in height. In the Yugoslavian study already outlined, bone mass was greater in the high calcium district by the age of 30 years, suggesting that any nutritional advantage was achieved early in life.

With regard to the relationship between calcium intake and rate of bone loss, Garn's studies[73] of over 5,000 subjects in seven countries showed a similar rate of cortical bone loss in all groups despite wide variation in calcium intake.

A study of international patterns of bone loss used spine radiographs to judge the prevalence of osteoporosis[205]. They suggested an inverse rank order correlation between crush fracture frequency and calcium intakes; for example, Japan with the lowest calcium intake had the highest prevalence, and Finland, with the highest intake, the lowest. However, Gambia and Jamaica, with relatively low calcium intakes, were found to have a low prevalence of osteoporosis. Interpretation of their results is complicated by ascertainment bias, ethnic diversity, and imprecision in method. Indeed, if one looks at the international age-specific incidence rates for hip fracture, the over-riding influence of racial factors can be seen, with extremely low rates in black populations throughout the world and much higher rates in Caucasians. Within cultural comparisons of fracture rates and dietary calcium intake are lacking except for the Yugoslavian study which showed substantially lower hip fracture rates at all ages in both men and women in the high calcium district. No differences were noted in forearm fracture frequency.

The final piece of epidemiological evidence comes from the studies which have compared calcium intakes of patients with age-related fractures and controls. Methods of estimating calcium intake vary widely among these studies and control intakes are variable. Nonetheless, the majority of them conclude that fracture cases give histories of lower calcium intakes

than non-fracture controls. This observation is made more consistently in vertebral crush fracture cases[211-213] than in those with hip fracture[53,179].

The majority of balance performance studies have measured balance response to manipulated calcium intake[205]. Estimated mean requirements from such studies range from 200-1,700 mg/day. However, many of them, particularly those at the lower end of the scale for calcium requirement, were performed in young healthy individuals, and are of uncertain relevance to the elderly.

Very few balance studies have been performed in individuals on their self-selected home calcium intakes. Heaney[214], in 233 balances obtained on 150 oestrogen replete perimenopausal women observed a mean requirement of 990 mg/day, and in 41 balances from oestrogen deprived women of the same general age, a mean requirement of 1,504mg/day. When the relationship between calcium intake and calcium balance was examined under conditions of oestrogen presence and oestrogen deficiency, a linear relationship was found in both groups, but a shift was found in the regression line suggesting an increased calcium requirement for zero balance in oestrogen deficiency.

In conclusion, the relation between calcium intake and bone mass remains controversial. The evidence from metabolic balance studies powerfully supports a high calcium requirement in the elderly, but this must be contrasted with the epidemiological data suggesting only a weak correlation between calcium intake and either bone mass or fracture risk. It is noteworthy that the NIH Consensus Conference on Osteoporosis held in the USA in April 1984[54], favoured a high calcium intake in the elderly. This panel recommended a daily

intake of 1,000 mg/day for oestrogen replete perimenopausal women and 1,500 mg/day for oestrogen deprived post-menopausal women. Convincing evidence is still required that inclusion of such a measure in a population-based strategy to prevent hip fractures would be effective.

VITAMIN D STATUS

Some surveys from this country and Northern Europe have reported a high prevalence of histological osteomalacia in elderly patients with hip fractures; this finding has not been confirmed by other studies[215]. Elderly women have lower serum concentrations of 1,25 DHCC than younger women, but there is controversy about whether 1,25 DHCC or 25 HCC levels are lower in vertebral or hip fracture patients than in controls of similar age. When it has been investigated, sunlight exposure in hip fracture cases is lower than in age-matched controls.

WATER FLUORIDE CONCENTRATION

The major effect of fluoride on bone is the stimulation of osteoblastic activity resulting in an increase in new bone formation[216]. Chronic ingestion of fluoride results in its progressive accumulation in skeletal tissue with fluoride ions substituting for hydroxyl ions and the gradual conversion of bone apatite to fluoro-apatite.

The ability of fluoride to induce new bone formation suggested a possible use in the treatment of osteoporosis and early epidemiological studies provided support for this idea. Leone[217] studied residents of two communities in which the water supply contained 0.4 or eight parts per million (ppm) fluoride; radiographic examination was carried out twice in a ten year period.

Fewer cases of age-related fracture developed in the high fluoride area than in the low fluoride area.

A more detailed study of the relationship between osteoporosis and fluoride intake was undertaken by Bernstein[218]. Lumbar spine radiographs were obtained from 300 people living in an area of North Dakota where the fluoride content of the water was high (4-5.8 ppm) and from 715 in an area where the water fluoride was low (0.15-0.30 ppm). Over 50 per cent of the subjects had lived in their respective areas for a lifetime. The incidence of decreased bone density was greater in women from the low fluoride area than from the high fluoride area, although the difference was not significant in the younger age groups. The number of women with at least one collapsed vertebra who were over 55 years of age was also significantly lower in the high fluoride area. In men, no difference was found between the two areas. These data suggest retrospectively that somewhat elevated fluoride intakes might have a significant impact on the incidence of vertebral crush fractures in the elderly. More recent studies in the USA[219,220] have concluded that fluoridation of drinking water to a level of one ppm has little protective effect against age-related fractures. Above this level, a relationship is detectable between water fluoride concentration and both fracture incidence as well as bone mass[42]. They must be contrasted with the findings of a two centre Finnish study[221] in which hip fracture incidence was found to be substantially lower in a town with a fluoride content of one ppm as compared with that in a town with a concentration of 0.1 ppm.

The overall likelihood is that although low fluoride intake might increase the risk of age-related fractures, the increase is unlikely to be a large one.

PHYSICAL ACTIVITY

The idea that mechanical factors influence bone mass is not new: Wolff[222] stated that any bone becomes adapted to the functional forces acting upon it. The need for a rigid skeleton, the specific requirements for its architecture and the necessity for a particular level of bone mass are all related exclusively to the role of bone as a load-bearing organ, rather than as a mineral reservoir. It is thus reasonable to expect that the features of the skeletal environment primarily responsible for determining its mass should be mechanical rather than hormonal.

As an individual grows older, physiological and lifestyle changes often lead to diminished levels of physical activity. Since maintenance of bone depends on adequate muscular and mechanical stress, this gradual decrease in activity leads to bone atrophy. Bone atrophy due to inactivity is most strikingly illustrated in subjects who are immobilised. Initially described in patients immobilised by fracture, spinal tuberculosis or paralytic poliomyelitis, osteoporosis is now known to be an accompaniment of many other diseases requiring prolonged bed rest[223,224]. The use of non-invasive methods of measuring bone mass in such patients has shown a loss of bone mass of about four per cent monthly during the initial period of bed rest. This is considerably greater than the loss predicted from calcium balance studies (0.5 per cent monthly), which in turn, is above the expected age-related loss of 0.1 per cent per month. Few studies have examined the changes in calcium regulating hormones during immobilisation although there is some evidence that despite a tendency towards hypercalcaemia and hypercalcuria, levels of PTH rise. It has also been

demonstrated that healthy adults lose bone mineral during immobilisation. The amount of bone loss is specific to the immobilised area and studies of the Gemini astronauts[225] demonstrated that bone atrophy occurs despite the presence of adequate dietary calcium intake. Once a person is confined to bed options for maintaining bone mass are limited. In a series of studies on young men, Issekutz[226] showed that four hours per day of intensive cycling did not decrease the rapid loss of urinary calcium, but standing for three hours provided sufficient stress to the musculoskeletal system to significantly reduce this excretion rate.

Anatomical studies have clearly demonstrated a relationship between muscle mass and bone mass. Those of Cohn[95,224] showed a constant ratio of total body potassium to total body calcium in Caucasian men and women aged from 30 to 70 years. Their findings suggested that the differences in body composition between ethnic groups might be important in determining the higher incidence of fractures amongst Caucasian than Negro women.

Cross-sectional studies have demonstrated greater bone mass in atnletes than in the general population. These studies are susceptible to selection bias as athletes may be attracted to sports as a result of higher bone mass. Some of this bias is removed in studies comparing bone mineral content in the dominant and non-dominant forearms of tennis players[227].

The response of bone to stress is specific both to the skeletal site which is stressed and to the activity mode. In a study of bone mass in the forearm, lumbar spine and metatarsals of groups of swimmers, tennis players and controls[228], the weight-bearing tennis players had higher metatarsal bone mineral content than

the swimmers, whilst both groups had higher forearm bone mineral content than the controls.

The role of exercise in the prevention or reversal of osteoporosis is a difficult issue to study. However, three of four controlled trials[42,229] which have studied the effects of exercise on the bone mass of post-menopausal women have found a beneficial effect of 30 to 60 minutes exercise three to five days a week on forearm bone mineral content or total body calcium. Only one of these studies had blinded outcome measurements and two had randomised designs. The effectiveness of specific types of therapy such as walking in the prevention of bone loss has not been well studied.

Several theories exist concerning the mechnisms by which bone mineral mass is locally controlled through stress. Bassett[230] reported that electrical charges are induced in the convex and concave surfaces of a bone which is bent. Calcium and phosphorus accumulate on the negatively charged area and are resorbed from the postively charged area. Carter[231] suggested that bone hypertrophy occurs in response to microfractures at the level of the osteon. Lanyon and Rubin[232] have investigated experimental loading systems in animals and found that structurally useful remodelling of bone could be induced by changes in the distribution of strain within the normal range of magnitude. The prime cellular candidate for reception of mechanical signals is the osteoblast[233]. Deforming mechanical stress may stimulate these osteogenic cells by the induction of piezoelectric impulses.

In summary, the weight of evidence supports physical activity as a major determinant of bone mass. However more information is required on the

differential effects of exercise on the appendicular skeleton, the types of activities with most osteogenic potential and the role of exercise as a risk factor for hip fracture.

CIGARETTE SMOKING

Most studies have suggested that men and women who smoke cigarettes have a higher risk of hip and vertebral fractures than non-smokers[42]. The studies of Lindsay[234] and Daniell[195] also suggest that women who smoke have lower cortical bone mass. The apparent effects of cigarette smoking may be mediated or confounded by variables such as weight, age at menopause, diet and physical inactivity, making it hard to establish with certainty that smoking causes bone loss and osteoporotic fractures. For example, female smokers are thinner than non-smokers, and Lindsay reported that the difference in body weight accounted entirely for the differences he observed in cortical bone mass between female smokers and non-smokers. In contrast, Williams[186] found that smoking and low body weight added independently to the risk of hip and distal radial fractures in women, and the Mayo Clinic study of vertebral fractures in men[200] found that smoking remained a risk factor even after allowance was made for differences in body weight. Furthermore, women who smoke undergo menopause at an earlier age than non-smokers and have lower serum concentrations of endogenous oestrogens[42]. Cigarette smoking illustrates well the paucity of information available on interactions between various risk factors which have been identified in analytical studies of age-related fractures.

ALCOHOL CONSUMPTION

Alcohol consumption is another lifestyle variable which has been implicated in the causation of age-related fractures. Hutchinson[181] reported that a history of alcoholism substantially increased hip fracture risk, and Paganini Hill[182] found a doubling of risk in women with alcohol consumption greater than eight measures weekly. Alcoholic men have been shown to have lower bone mass and a greater rate of bone loss than non-alcoholics[235,236]. The key question, however, as to whether moderate consumption of alcohol causes significant loss of bone, is uncertain. Mechanisms for the association between alcohol and osteoporosis include a direct toxic effect of alcohol on the osteoblast, reduced body weight, smoking, poor nutrition, reduced activity and chronic liver disease[42].

MEDICAL CONDITIONS AND DRUGS

Certain diseases, surgical procedures and medications may be associated with the development of osteoporosis[57]. These predisposing factors have been reported in as many as 40 per cent of men and 20 per cent of women presenting with vertebral or hip fractures and include early oopherectomy, hypogonadism, subtotal gastrectomy, hyperthyroidism, stroke, hyperparathyroidism, rheumatoid arthritis and diabetes mellitus. The types of medication which have been suggested as speeding bone loss or adversely affecting calcium metabolism include corticosteroids, thyroxine and anticonvulsants. Conversely, thiazide diuretics are thought to have a protective effect against bone loss.

1.5.2 Risk factors influencing propensity to trauma

Another group of risk factors for hip fracture are thought to exert their influence on fracture risk through an effect on falling. Falls may be the specific result of chronic neurological or cardiovascular disorders such as epilepsy and dysrhythmias, or be a non-specific sequel to cumulative effects of chronic illness and ageing on gait, balance, proprioception, muscle strength, and co-ordination. Individuals who sustain hip fractures are more frequently demented, poorly nourished and functionally impaired than controls of similar age and sex[38,53,179]. They have a greater likelihood of suffering from cerebrovascular accidents, visual impairment and postural instability[35,38]. Although a causal association between the use of certain medications, notably sedatives and hypnotics, and the risk of hip fracture is biologically plausible, the case-control evidence is discrepant[191,192].

It is generally assumed that such factors influence fracture risk through their association with falling, but clear evidence of this is lacking. Furthermore, many of them are inter-related and their independent contribution to the risk of fracture is unknown.

1.6 Objectives of the current study

This thesis addresses three issues which are fundamental to the design of preventive strategies for hip fracture.

(1) The independent contribution of osteoporosis to the risk of hip fracture

This section describes two studies. In the first, a radiological index of bone mass in the upper femur

was evaluated for use in epidemiological research. Its validity was assessed by comparison with the ash density of excised upper femoral bone samples. Assessment of its repeatability entailed measurement of within and between observer variation.

The second study employed this method of estimating bone mass to investigate the contribution of osteoporosis, independent of the risk of falling, to the risk of hip fracture. Bone mass was measured in 708 elderly people who had fallen and injured a hip. The bone mass of those who had sustained hip fractures was compared with that of those who did not.

(2) Calcium intake, physical activity and the risk of hip fracture

This section consists of four chapters. The first two discuss the choice and evaluation of methods for measuring calcium intake and physical activity in the elderly. The third describes a case-control study performed in Southampton, in which risk factors for hip fracture were sought in 300 consecutively admitted fracture cases who had passed a mental test score and 600 age and sex matched community controls. The fourth describes a series of biochemical indices of calcium metabolism in 41 of the female fracture cases, comparing them with elderly in-patient and out-patient control groups.

(3) Geographic variation in the incidence of hip fracture in England and Wales

Two sources of routinely collected data on hip fracture (death certification and hospital activity analysis) were used to examine geographic variation in mortality and hospital discharge rates in England and Wales. The validity of mortality data for hip fracture was assessed by studying assignment and coding of the

underlying cause of death in a series of death certificates of individuals admitted to hospital with hip fractures, who subsequently died.

Ethical approval for these studies was obtained, where applicable, from the Ethical Sub-Committee of Southampton University and Hospitals, the Southampton Division of General Practice and the Division of Orthopaedic Surgery, Southampton General Hospital.

SECTION TWO

THE INDEPENDENT CONTRIBUTION OF OSTEOPOROSIS TO HIP FRACTURE

CHAPTER TWO

EVAULATION OF THE SINGH INDEX AS AN EPIDEMIOLOGICAL METHOD FOR MEASURING BONE MASS IN THE FEMORAL NECK

Epidemiological research into the aetiology of hip fracture requires a validated measure of bone mass, suitable for use on large numbers of subjects. As bone loss does not occur at the same rate throughout the skeleton, inferences about bone mass in the femoral neck based on measurements at other sites are uncertain[57]. Direct observations on the femur are preferable and a swift, inexpensive method for this would allow the study of differences in bone mass between populations. In 1970, Singh and his associates[70] proposed a radiological method for the grading of the trabecular architecture in the femoral neck. The aim of this study was to validate this local radiological index against the results of ashing studies on samples of proximal femoral bone.

2.1 Material and methods

Excised femoral heads were collected at operation from 62 patients undergoing surgery (52 for hip fracture, ten for osteoarthrosis). Fifty one of the patients were women and 11 were men; their ages ranged from 58 years to 99 years. The femoral heads were stripped of soft tissue and their volumes measured by displacement of water. They were ashed in a muffle furnace at 700^{o}C for a period of 16 hours to constant weight.

The bone density of the upper femora of the 62 subjects was assessed from pre-operative pelvic radiographs by a single trained observer. The Singh grading was applied by comparing the trabecular pattern in the proximal femur with the reference scale as published[70]. This pattern is characterised on a six point scale from grade six, where all the major trabeculae are present, to grade one, in which only the

primary compressive group is visible. The repeatability of the Singh grading was assessed using a coded series of radiographs from another 100 patients. Thirty were patients with hip fractures and 70 were hospital out-patients aged 55-90 years, of whom a radiograph showing the upper femur was taken during radiography for non-skeletal indications. To assess within observer variation the observer examined the radiographs on two occasions. On each occasion they were presented to him in random order and the second examination was carried out in such a way that he was unaware of his earlier report on the radiographs. Between observer variation was measured against a second trained observer from the MRC Mineral Metabolism Unit, Leeds, using a further set of 100 radiographs. In a sample of the radiographs collected, which excluded those with hip fractures, the Singh grade was assessed bilaterally.

2.2 Results

Bone density in the femoral neck and head, expressed as the ash weight to volume ratio, was correlated ($r=0.69$, $p<0.01$, Figure 2) with the Singh grade. The mean ash density at each Singh grade showed a linear increase from grade two through to grade six, although within each grade there was wide variation around the mean. This variation was similar in femoral heads excised after fracture and for osteoarthrosis. For 82 of the 100 radiographs re-examined by one observer there was complete agreement on the Singh grade at the two examinations (Table 4). The remaining 18 differed by one grade only. In the test of between observer variation (Table 5) there was agreement in 78 of 100 radiographs. In 20 there was a difference of

Figure 2

Relationship of bone density in the upper femur (ash weight to volume ratio) to Singh grade (●, femoral head excised for osteoarthritis; O, femoral head excised for femoral neck fracture).

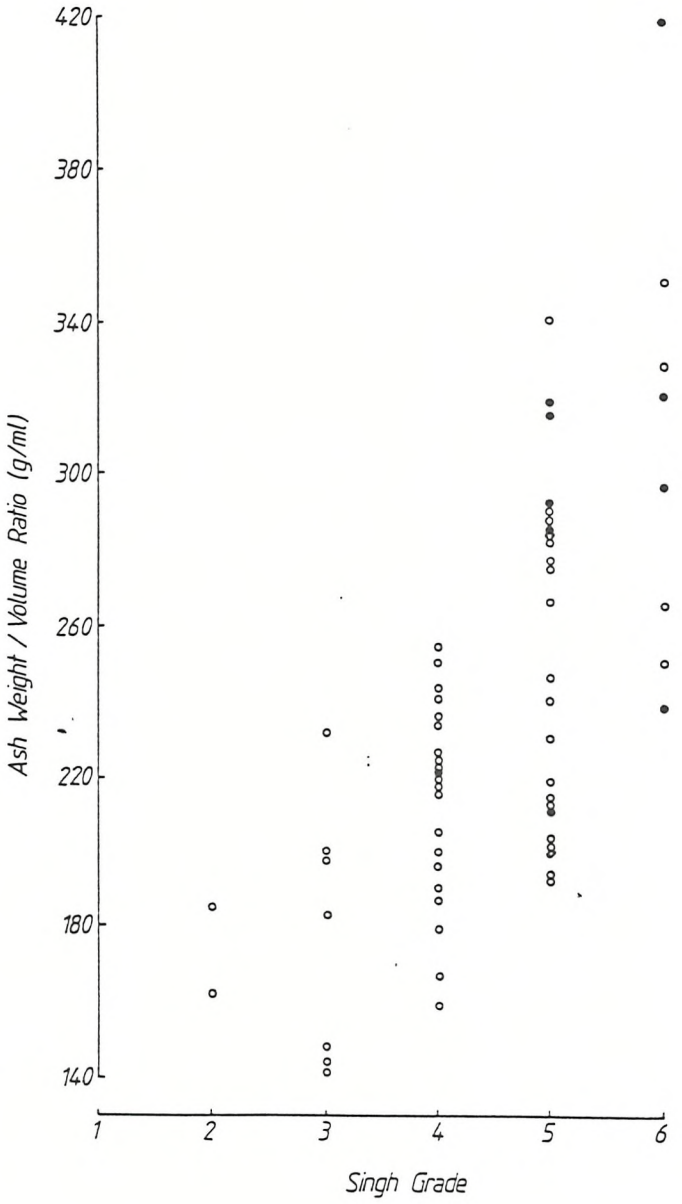


Table 4

Singh gradings in 100 radiographs examined on two occasions by the same observer

		1st EXAMINATION					
		1	2	3	4	5	6
2nd EXAMINATION	1						
	2		1				
	3			18	5		
	4				39	8	
	5				2	22	2
	6					1	2

Table 5

Singh gradings in 100 radiographs examined independently by two observers

		OBSERVER I					
		1	2	3	4	5	6
OBSERVER II	1						
	2		7		1		
	3		1	24	9	1	
	4			5	38	3	
	5				1	9	1
	6						

one grade, and in two cases, a difference of two grades. No major systematic difference in Singh grading between the two observers was detected. Bilateral assessment of the Singh grade in 100 radiographs from non-fracture cases revealed concordance in 80 out of 100, with no difference greater than one.

2.3 Discussion

This study shows that the Singh index of femoral neck trabeculation, when applied to an elderly population, correlates with bone mass in the femoral head as measured by the ash weight to volume ratio. This ratio has been widely used as an expression of absolute bone mass[67,237], and in vertebrae, correlates with compressive strength[121].

Despite its use in several studies, the Singh index has never been validated against a direct measurement of upper femoral bone mass. Singh[70] showed a correlation with iliac crest histology but later studies showed no relationship with either radial bone mineral content as measured by photon absorptiometry[238], vertebral appearance[239] or histological measurement of trabecular bone volume[147]. However, since rates of bone loss vary from one part of the skeleton to another the index is not invalidated by lack of correlation with measures at other sites. In two recent studies[143,148], the Singh index has been shown superior to metacarpal morphometry, vertebral index, iliac crest histology and femoral cortical measurements in its ability to discriminate between hip fracture cases and age and sex matched controls. The results of the present study show that measurements

using the Singh index bear a similar trend to those of actual femoral bone mass.

A range of between observer variation has been described for the index. The concordance of 78 per cent in this survey and the lack of any major systematic difference between observers are reassuring. The within observer concordance of 82 per cent accords with the values reported in two previous studies[146,147]. Observer variability is influenced by the quality of the radiographs and the range of pathology they show. Variability is generally less for normal radiographs or those showing severe pathology than for those showing intermediate changes. Nevertheless, these results support the view that training can reduce observer variability to an acceptable level for large-scale studies. Although Singh, in his original description of the method, stated that there was complete bilateral agreement in 50 out of 50 radiographs, formal correlation between the measurements of both femora has been independently assessed only once[238]. The result was a right-left concordance of 77 per cent, in 35 cases examined, comparable to our result of 80 per cent in 100 cases.

In conclusion, the Singh index is a useful epidemiological tool for the measurement of femoral neck bone mass. Although fallible in the classification of individuals, the method may be used to detect differences between populations or subgroups within populations.

CHAPTER THREE

OSTEOPOROSIS, RISK OF FALLING AND NEUROMUSCULAR PROTECTIVE RESPONSES IN FRACTURE OF THE PROXIMAL FEMUR

The incidence of fracture of the proximal femur in the elderly depends on bone strength and the risk of falling[178]. The relative importance, however, of each of these influences is unknown and the strategy to prevent hip fractures is therefore a matter of conjecture.

In order to address this issue femoral neck bone mass was measured in a consecutive series of elderly people who presented to hospital casualty departments having fallen and sustained a hip injury. Bone mass was compared in those who had fractured their hip and those who had not.

3.1 Patients and methods

The records and radiographs were reviewed of patients aged 50 years and over who presented to casualty departments in Southampton and Salisbury health districts during one year, April 1984 to March 1985, having fallen and sustained a hip injury. Patients who had sustained hip injuries from causes other than falls, such as road traffic accidents, and patients with pelvic fractures were excluded. In each case the injury was sufficiently severe to require pelvic radiography to exclude a fracture. Patients were identified from the casualty registers. Completeness of ascertainment of those with fractures was checked from ward lists and hospital discharge records. Patients not living within the two health districts were excluded. From the pelvic radiographs a single trained observer graded the femoral neck trabecular pattern of each subject according to the Singh scale. The femur on the contralateral side to the injury was examined; the identity of the patient was unknown to the observer, who was presented with a view of a single intact proximal femur.

The association between Singh grade and the risk of fracture was examined by calculating the relative risk of fracture with 95 per cent confidence intervals at each Singh grade[240].

3.2 Results

Seven hundred and eight subjects fulfilled the entry criteria to the study of whom 456 (109 men and 347 women) sustained a hip fracture; 252 of them (72 men and 180 women) did not. Table 6 shows that those without fractures tended to be in the younger age groups. Within each age group there were more women than men.

Among both groups of patients the proportion with lower Singh grades increased with age (Table 7). Within each age group, however, the distribution of grades differed between the two groups of patients. Grades tended to be higher in those without fractures. When expressed as relative risk of fracture according to grade this difference gave an increase in risk from grades five and six up to grades one and two (Figure 3). This gradient was statistically significant ($p<0.01$) in each age group. The increase was steeper at younger ages, the relative risks for grades one and two being 33.0 at ages 50 to 64 years compared with 17.7 at 65 to 74, 5.4 at 75 to 84, and 5.4 at 85 and over. To examine the risks in each sex the age groups were amalgamated (Table 8). The steeper increase in risk at younger ages was found in both sexes (Figure 4). Although it was more pronounced in younger women than younger men, the difference was not significant. Table 9 and Figure 5 show the independent effects of age and Singh grade on the risk of fracture. They demonstrate the presence of an age-related factor which is independent of bone mass, at grades five and six. The interaction between Singh grade and age

Table 6

Number of patients by age and sex according to the presence or absence of hip fracture

Age (years)	Fracture		Non-fracture	
	Men	Women	Men	Women
50-64	19	33	28	54
65-74	37	56	16	45
75-84	42	138	25	44
⩾85	11	120	3	37
Total	109	347	72	180

Table 7

Distribution of Singh grades and relative risks for hip fracture by age

Age (years)	Singh grade	No. of patients with fracture	No. of patients without fracture	Relative risk	95% CI*	P (X^2 test for linear trend d.f. = 1)
50-64	5 + 6	14	66	1	-	
	4	23	13	8.3	3.6 to 19	
	3	8	2	18.9	5.0 to 71	X^2 = 33.8
	1 + 2	7	1	33.0	7.1 to 155	p<0.01
65-74	5 + 6	23	37	1	-	
	4	30	16	3.0	1.4 to 6.6	
	3	29	7	6.7	2.6 to 17	X^2 = 21.8
	1 + 2	11	1	17.7	3.3 to 94	p<0.01
75-84	5 + 6	35	26	1	-	
	4	49	27	1.3	0.7 to 2.7	
	3	52	10	3.9	1.7 to 8.8	X^2 = 17.5
	1 + 2	44	6	5.4	2.1 to 14	p<0.01
≥85	5 + 6	8	6	1	-	
	4	39	17	1.7	0.5 to 5.7	
	3	41	11	2.8	0.8 to 9.5	X^2 = 7.4
	1 + 2	43	6	5.4	1.5 to 19	p<0.01
All ages	5 + 6	80	135	1	-	
	4	141	73	3.3	2.2 to 4.8	
	3	130	30	7.3	4.6 to 12	X^2 = 108.7
	1 + 2	105	14	12.7	7.3 to 22	p<0.01

* CI = confidence intervals

Figure 3

Relative risk of hip fracture in each Singh grade and age group.

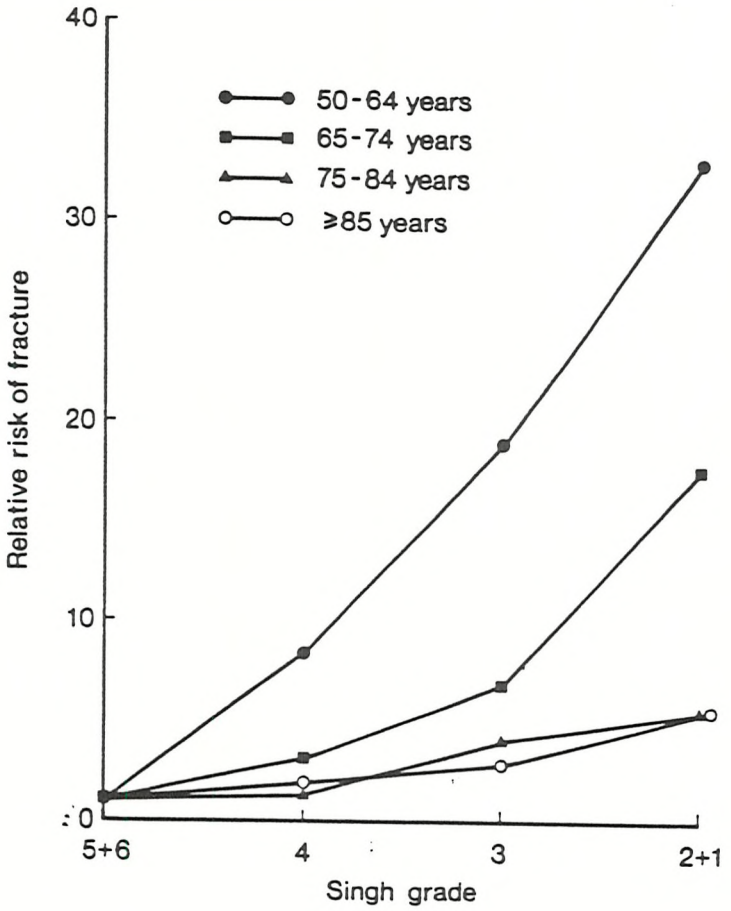


Table 8

Distribution of Singh grades and relative risks for hip fracture by age and sex

Age	Singh grade	No. of patients with fracture	No. of patients without fracture	Relative risk	95% CI*	p (X^2 test for linear trend d.f. = 1)
MEN						
<75	5 + 6	22	34	1	-	
	4	19	8	3.7	1.4 to 9.6	
	3	10	1	15.5	2.8 to 86	X^2 = 12.8
	1 + 2	5	1	7.7	1.1 to 54	p<0.01
≥75	5 + 6	15	10	1	-	
	4	10	13	0.5	0.2 to 1.6	
	3	17	4	2.8	0.8 to 11	X^2 = 5.3
	1 + 2	11	1	7.3	1.0 to 53	p<0.01
All ages	5 + 6	37	44	1	-	
	4	29	21	1.6	0.8 to 3.3	
	3	27	5	6.4	2.4 to 17	X^2 = 19.4
	1 + 2	16	2	9.5	2.5 to 36	p<0.01
WOMEN						
<75	5 + 6	15	69	1	-	
	4	34	21	7.4	3.5 to 16	
	3	27	8	15.5	6.5 to 37	X^2 = 52.0
	1 + 2	13	1	59.8	14.8 to 241	p<0.01
≥75	5 + 6	28	22	1	-	
	4	78	31	2.0	1.0 to 3.9	
	3	76	17	3.5	1.7 to 7.4	X^2 = 18.4
	1 + 2	76	11	5.4	2.4 to 12.1	p<0.01
All ages	5 + 6	43	91	1	-	
	4	112	52	4.6	2.8 to 7.3	
	3	103	25	8.7	5.1 to 15	X^2 = 88.0
	1 + 2	89	12	15.7	8.4 to 30	p<0.01

* CI = confidence intervals

Figure 4

Relative risk of hip fracture in each Singh grade by age and sex.

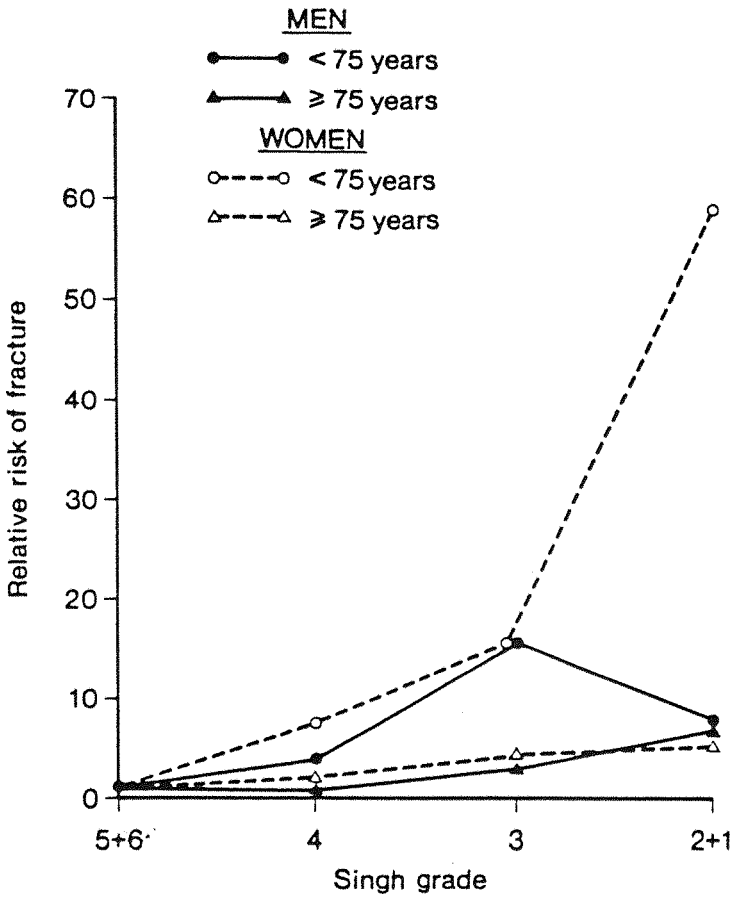


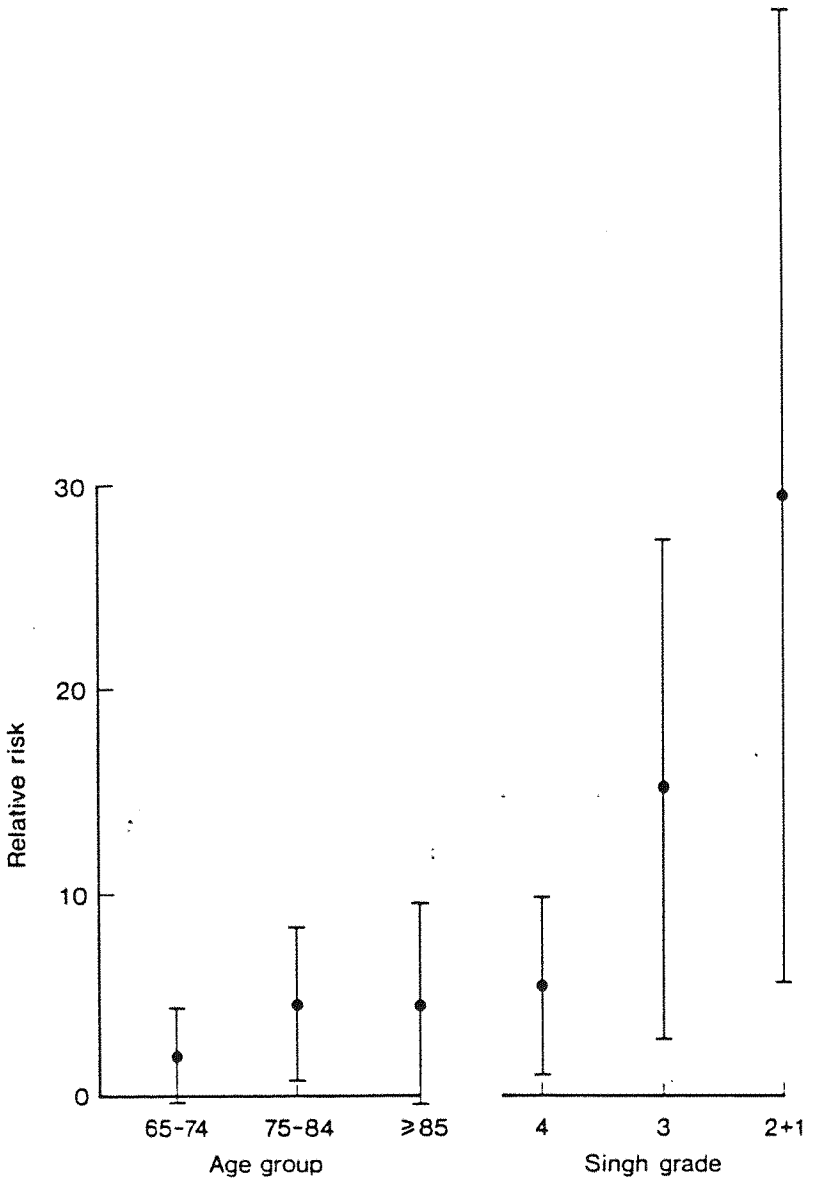
Table 9

Risk of hip fracture, relative to the group with youngest age and greatest bone mass

		Age (years)			
		50-64	65-74	75-84	⩾85
Singh grade	5 + 6	1.0	2.9	6.3	6.3
	4	8.3	8.8	8.6	11
	3	19	20	25	18
	1 + 2	33	52	35	34

Figure 5

Relative risk estimates and 95% CI's for each age and Singh grade fitted from an additive risk model.



closely fitted that predicted by an additive risk model (deviance 2.71, df=9, $p<0.01$).

Two hundred and twenty one of the fractures were intracapsular and 235 extracapsular (Table 10). The relationship between age, Singh grade and the risk of fracture was similar for the two fracture types (Table 11).

A check of hospital records showed that 92 per cent of all patients admitted to the two hospitals with hip fractures during the study period had been included in the study.

3.3 Discussion

Among people aged 50 years and over who presented to hospital casualty departments having fallen and injured their hips, femoral neck bone mass, measured by the Singh grade, was less among those who sustained a fracture at this site than among those who did not. This was seen consistently in each age group and in both men and women. The relative risks of fracture associated with reduced bone mass were large, especially among younger women.

Most previous studies of bone mass in patients with hip fracture have measured sites other than the hip, including the metacarpals, distal radius and lumbar spine[142]. As age-related bone loss does not occur at the same rate throughout the skeleton inferences about bone mass in the femoral neck based upon measurements at other sites are uncertain. Three case-control studies using controls from the general population, rather than people who had fallen, showed an increase in risk of fracture with reduced Singh grade[143,148,241]. In contrast, two similar studies using dual photon absorptiometry showed only small differences in the bone mineral content of cases and

Table 10

Age distribution of patients with intracapsular and extracapsular fractures

Age (years)	Intracapsular (no.)	Extracapsular (no.)
50-64	29	23
65-74	39	54
75-84	103	77
⩾85	50	81

Table 11

Relative risk of fracture by Singh grade in intracapsular and extracapsular groups

Age (years)	Singh grade	Fracture type			
		Intracapsular		Extracapsular	
		Relative risk	95% C.I.	Relative risk	95% C.I.
50-64	1 + 2	22.0	3.7-129	52.8	11 -260
	3	14.7	3.3- 68	26.4	6.1-115
	4	7.3	2.8- 19	10.2	3.4- 30
	5 + 6	1.0	-	1.0	-
65-74	1 + 2	20.6	3.4-123	15.9	2.7- 94
	3	7.0	2.3- 22	6.4	2.3- 18
	4	3.3	1.2- 9.2	2.8	1.1- 7.0
	5 + 6	1.0	-	1.0	-
75-84	1 + 2	5.4	2.0- 15	6.9	2.3- 21
	3	3.9	1.6- 9.6	4.8	1.8- 13
	4	1.3	0.6- 3.0	1.7	0.7- 4.1
	5 + 6	1.0	-	1.0	-
≥85	1 + 2	8.5	1.5- 47	4.3	1.1- 17
	3	4.4	0.8- 24	2.3	0.6- 8.5
	4	2.6	0.5- 15	1.4	0.4- 5.1
	5 + 6	1.0	-	1.0	-

controls[139,144]. One interpretation of these findings is that the trabecular architecture of the femoral neck reflects an aspect of bone morphology that contributes to its strength.

The study population comprised a consecutive series of elderly patients with hip injuries resident in two adjacent health districts. The cases included 92 per cent of all patients in the districts who underwent in-patient treatment for hip fracture during the one year study period. The controls were subject to selection by those factors that determine attendance at the casualty department by elderly people who fall and injure their hips. It is unlikely that these factors are sufficiently closely related to bone mass to produce the observed differences in the bone mass of cases and controls.

These results suggest a third, age-related risk factor for hip fracture which is independent of bone mass and the risk of falling. Biochemical studies in vitro and in vivo have shown that the forces generated during a fall from the standing position are considerably greater than the breaking strength of the femoral neck[178]. They emphasise the importance of neuromuscular co-ordination in protecting the skeleton from injury. These neuromuscular protective mechanisms range from the use of an outstretched arm to break the impact of a fall, through to the contraction of muscles inserting into the upper femur which modulate the forces transmitted to the bone itself. They become progressively blunted with advancing age and constitute a likely candidate for this third age-related factor.

It is concluded that reduced bone mass, or osteoporosis, is a strong independent risk factor for

fracture. The importance of other age-related factors, such as the impairment of neuromuscular protective responses, increases with age. Public health strategies to reduce the incidence of hip fractures should not, therefore, be confined to measures which retard the loss of bone with ageing, but should also be directed at maintaining the neuromuscular responses which protect the skeleton against trauma.

SECTION THREE

CALCIUM INTAKE, PHYSICAL ACTIVITY AND HIP FRACTURE

CHAPTER FOUR

THE ASSESSMENT OF DIETARY CALCIUM INTAKE IN THE ELDERLY

Epidemiological studies relating calcium intake to bone mass or the occurrence of age-related fractures have been hampered by the lack of a suitable tool for assessing calcium intake in the elderly. This chapter describes a new frequency and amount questionnaire for measuring calcium intake in the elderly. Its validity was tested against two commonly used standards of dietary assessment, five-day duplicate diets and seven-day weighed dietary inventories[242]. Calcium intake was assessed by asking about the usual consumption of six major dietary sources of calcium: milk, bread, cheese, puddings, cakes and biscuits. A Department of Health and Social Security survey of nutrition in the elderly has suggested that 82 per cent of calcium intake is derived from these food products[243].

4.1 Subjects and methods

STUDY ONE

Home metabolic balance studies were carried out in a group of 28 elderly residents in Southampton (age range 72 to 90 years, median 78 years) randomly chosen from local general practitioner lists; 13 were men and 15 women. As part of these studies, a complete five-day duplicate diet was collected by a research nurse who visited each subject at home several times daily and ensured completeness of collection. The duplicate dietary portions were combined and homogenised. Triplicate samples of homogenate were dry ashed[244] and the calcium content determined by flame atomic absorption spectrophotometry[245], after dilution in lanthanum chloride.

Following completion of the series of balance studies, the subjects were visited by a different interviewer who administered the calcium intake questionnaire (Appendix 1). To assist in the

estimation of portion size, subjects were shown colour photographs of three serving sizes of each food or drink. The calcium content of the various portion sizes (based on standard food composition tables) and the formulae for calculating present and past calcium intake (mg/day) from the questionnaire responses are shown in Appendix 1.

STUDY TWO

Thirty healthy women aged 65 to 74 years, randomly selected from the list of a general practice, completed the questionnaire on two occasions eight weeks apart. In the intervening period, each woman carried out a seven-day weighed dietary inventory. Each subject was provided with a diary and a battery-operated spring balance with a large digital read-out, and was carefully instructed on how to keep her record. Subjects were visited as often as necessary to ensure accurate records. Nutrient intakes were calculated from the dietary records using standard food composition tables[246].

4.2 Results

Table 12 shows that in the 28 subjects in study one, there was no significant difference between mean calcium intakes, based on duplicate diet analysis and questionnaire responses. The questionnaire value, however, was 126 mg/day lower. There was a strong correlation ($r=0.76$, $p<0.01$) between the intakes estimated by the duplicate diet analysis and by the questionnaire (Figure 6). When subjects were grouped by thirds according to calcium intake (Table 13), 19 of 28 were classified in the same third by questionnaire and duplicate diet analysis. Adjacent misclassification occurred for eight subjects and

Table 12

Estimated mean daily calcium intake in 28 elderly subjects based on duplicate diet analysis and questionnaire responses

Method of measurement	Mean intake* (mg/day)	95% C.I. (mg/day)	Range (mg/day)
Duplicate diet	896	790-1002	424-1441
Questionnaire	770	672- 868	362-1435

*The difference between the means (paired 't' test) is not statistically significant ($p>0.05$).

Figure 6

Mean daily calcium intake in 28 elderly men and women estimated by questionnaire and five day duplicate diet.

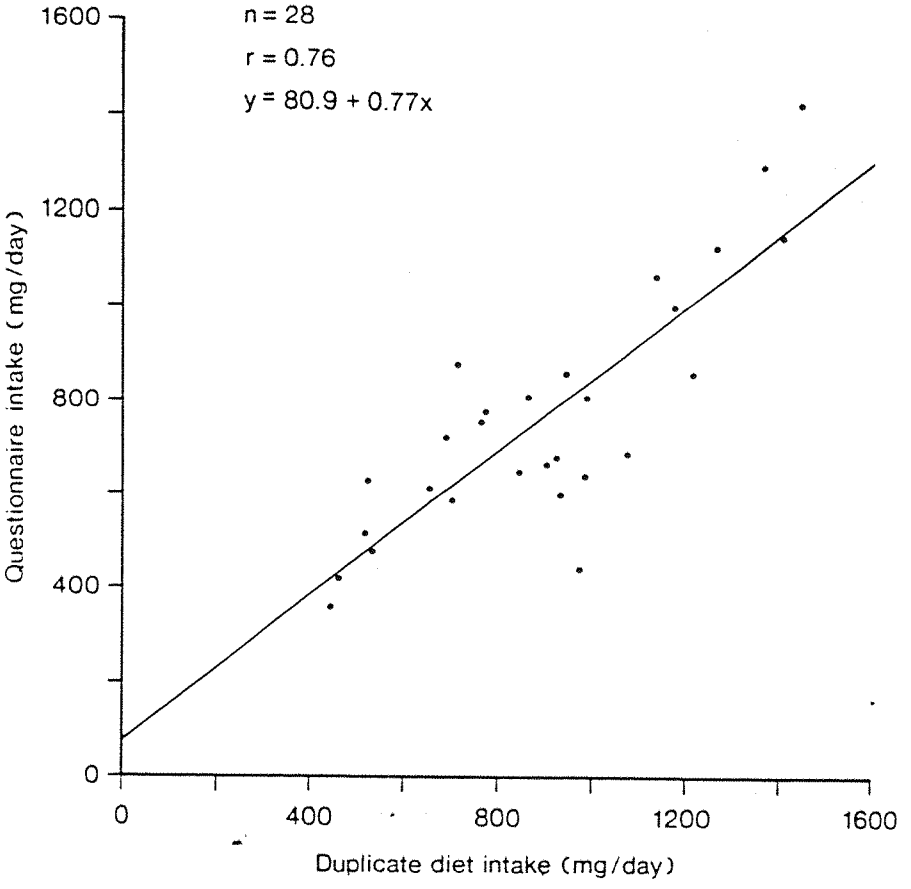


Table 13

Classification of 28 elderly men and women by thirds according to calcium intake estimated by duplicate diet analysis and questionnaire

		Duplicate diet (thirds)		
		Low (444-730 mg)	Middle (731-980 mg)	High (981-1441 mg)
Questionnaire (thirds)	Low (362-628 mg)	7	3	0
	Middle (629-843 mg)	2	5	2
	High (844-1435 mg)	1	1	7

gross misclassification into opposite thirds for only one.

Table 14 shows that in the 30 women in study two there was no statistically significant difference between the mean calcium intakes based on seven-day weighed inventory and questionnaire, although the questionnaire value was lower by 125 mg/day. There was a good correlation ($r=0.69$, $p<0.01$) between calcium intake assessed by diet record and by questionnaire (Figure 7). Classification of subjects by thirds according to calcium intake (Table 15) showed that 14 subjects were classified in the same third by both methods, 16 were classified in adjacent thirds and none were grossly misclassified.

There was a small difference between the mean estimates of calcium intake based on the two administrations of the questionnaire (Table 16), but a strong correlation ($r=0.84$, $p<0.01$) between the estimated individual intakes on the two occasions. Of the 30 subjects, 23 (77 per cent) were classified in the same third on both occasions and only one subject was grossly misclassified.

4.3 Discussion

This study shows that customary calcium intake in the elderly calculated from a frequency-amount questionnaire correlates well with calcium intake measured by both duplicate diet analysis and seven-day weighed inventory. The estimates of calcium intake based on the questionnaire may have been lower than duplicate diet or weighed values because the questionnaire asked about foods which contribute only about 82 per cent of calcium intake.

Nutrients which are concentrated in relatively few

Table 14

Estimated mean daily calcium intake in 30 elderly women based on seven-day weighed record and questionnaire responses

Method of measurement	Mean intake* (mg/day)	95% C.I. (mg/day)	Range (mg/day)
Dietary record	794	690-898	291-1577
Questionnaire	669	574-764	235-1342

*The difference between the means (paired 't' test) is not statistically significant ($p>0.05$).

Figure 7

Mean daily calcium intake in 30 elderly women estimated by questionnaire and seven-day weighed inventory.

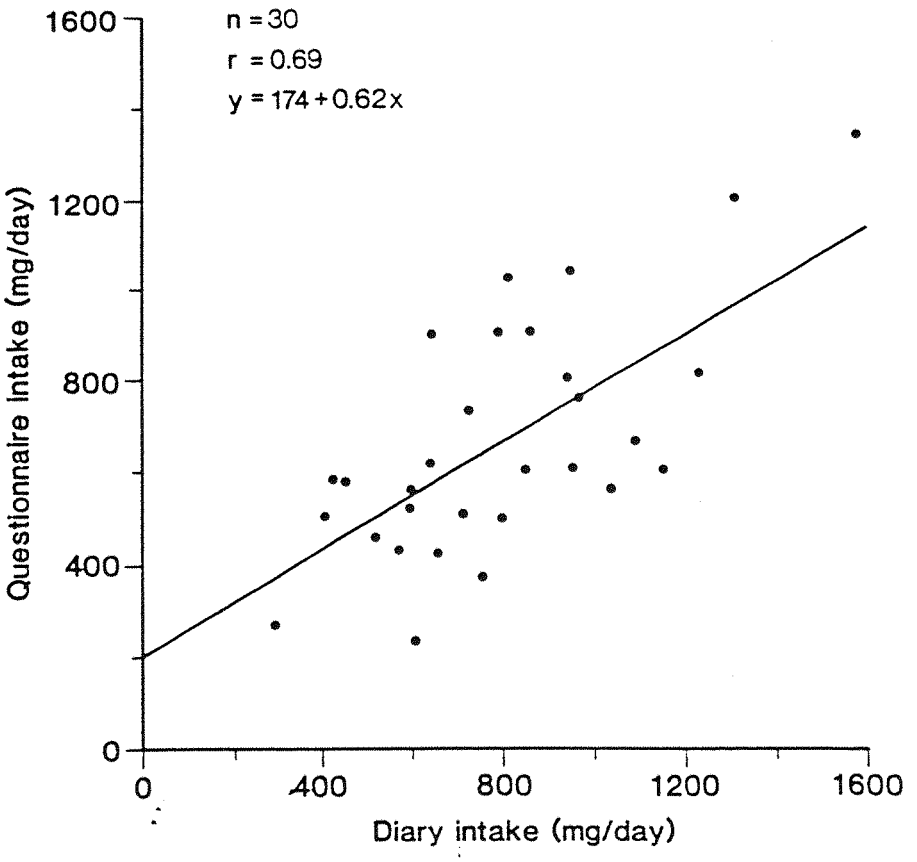


Table 15

Classification of 30 elderly women by thirds according to calcium intake estimated by seven-day weighed inventory and questionnaire

		Weighed inventory (thirds)		
		Low (291-639 mg)	Middle (641-856 mg)	High (939-1577 mg)
Questionnaire (thirds)	Low (235-522 mg)	6	4	0
	Middle (562-732 mg)	4	2	4
	High (760-1342 mg)	0	4	6

Table 16

Mean daily calcium intake in 30 elderly women estimated by questionnaire on two occasions eight weeks apart

	Mean intake* (mg/day)	95% C.I. (mg/day)	Range (mg/day)
First occasion	669	576-762	235-1342
Second occasion	682	594-770	170-1160

*The difference between the means (paired 't' test) is not statistically significant ($p>0.05$).

foods whose portion sizes can be readily assessed lend themselves to accurate estimation of intake using a frequency-amount questionnaire. The validity of the questionnaire was tested against two commonly used standards of dietary assessment. Chemical analysis of duplicate diets is widely accepted as the most accurate method of estimating nutrient intake in individuals. However, the degree of supervision required for successful collection and the expense of carrying out the biochemical analysis limit its use in large nutritional surveys[242]. The alternative method which gives most precision is the weighed dietary inventory. Neither of these methods can be effectively used in a retrospective case-control study of hip fracture as the fracture itself might alter the subsequent diet of an individual. The questionnaire was able to categorise subjects into thirds of the distribution of calcium intake with almost no gross misclassification and showed good repeatability. It therefore fulfills the criteria suggested by Marr[242] and Block[247] for nutritional survey methods and provides an effective method of estimating customary calcium intake in epidemiological studies.

CHAPTER FIVE

THE ASSESSMENT OF PHYSICAL ACTIVITY IN THE ELDERLY

Physical activity is defined as any bodily movement produced by skeletal muscles which results in energy expenditure above basal levels[248]. It may be categorised on the basis of the identifiable portions of daily life during which the activity occurs: sleeping, occupational and leisure time. A number of measurable components contribute to physical activity: cardio-respiratory performance, body composition, muscular strength, endurance and flexibility. These measures vary in their relationships to disease. Cardio-respiratory performance, assessed by oxygen uptake during ergometry, is the relevant aspect to the study of ischaemic heart disease. Skeletal status, on the other hand, relates more closely to muscular loading and it is likely that indices of muscle strength and endurance will be of greater importance in the study of osteoporosis.

As age-related bone loss commences during the fifth decade of life[57], physical inactivity in youth and middle life may also contribute to osteoporosis. However, few methods have been validated for the assessment of either current or previous activity in the elderly, and the relationship between the two remains unknown. This chapter describes the methods available for the assessment of physical activity in epidemiological studies and discusses the choice of methods for a case-control study of hip fracture.

5.1 Current physical activity

Four main methods are available for the estimation of customary physical activity[249] (Table 17). Little is known of the validity and repeatability of all these methods or about inter-relationships between them. Questionnaires obtain structured information about a subject's recent physical activity. They have four

Table 17

The main methods of measuring customary physical activity

1. Questionnaire; interview

2. Diary annotation by: (a) subject
   (b) observer

3. Body-borne instruments (ECG; V_{O_2}; movement of trunk or limbs)

4. Energy intake measurement

components. The first is the time frame, which may vary from five minutes to over one year. Second, the nature and detail of the activities; participants may be asked to provide the frequency, duration and intensity of activities or may merely be asked if they have performed an activity. Third is the mode of data collection, whether by personal interview, telephone or self administration. Fourth, the summary index of activity, based on a calculated estimate of kilocalories expended, an addition of weighted scores, or an ordinal ranking by activity level.

Several epidemiological studies have used recall surveys of activity. Morris and co-workers[250] used a two day recall of specific activities in their studies of British civil servants. The results correlated with caloric intake from weighed dietary inventories, and the repeatability was found to be high in a subset of subjects tested on four occasions. A recall survey by Paffenbarger and associates[251] probed for the distance walked, stairs climbed and sports or recreational activities undertaken during the previous week. The survey asked about major contributors to the weekly activity pattern. Although simple, the validity and repeatability of this approach remain untested. A different recall procedure was adopted at Stanford University[252] in which individuals were asked to recall the time spent doing activities of several levels of intensity over the previous week, rather than providing detailed time estimates for specific activities. This seven-day recall was indirectly validated against the results from a community health survey.

Some recall questionnaires have time frames greater than one week, and request detailed information on specific activities. In those of Taylor[253] and Montoye[254], persons recall over the previous year their activity patterns for a list of specific activities. The Taylor questionnaire has been indirectly validated against treadmill work performance in 175 men and against estimated caloric intake in a group of female college students.

Recall questionnaires are simple, convenient and enable large numbers of subjects to be studied. However, they tend to exaggerate the duration of physical activity undergone and the recall of elderly people is poor. Prospective methods of assessing various types of activity are also available including diary annotation, body-borne devices to measure heart rate, oxygen uptake, ventilation, chest movement and calorimetry. Such methods are inapplicable, however, to the retrospective study of patients with hip fracture, in whom the very event of fracturing might dramatically alter their activity level. A further problem arises in the assessment of physical activity in the elderly. In younger age groups, employment and participation in active sports are likely to be the most relevant factors maintaining physical capacities. Among the elderly, walking and other day to day activities appear to be more relevant[255].

Workers at the Department of Physiology at the University of Nottingham Medical School have recently devised and evaluated a recall tool for the assessment of customary physical activity in the elderly[256]. Activities were divided into five categories: walking, indoor and outdoor productive activities such as gardening and housework, muscle loading activities such as climbing stairs and carrying loads, and leisure

activities. In administering the questions on productive activities, the interviewer first determined whether it was appropriate to ask about the activity and then ascertained whether the respondent's participation was customary (activity performed for at least three minutes, at least weekly, for at least the previous six weeks). If the activity met the criteria for 'customary', than the interviewer asked in detail about the frequency and duration of participation. Muscle loading activity was categorised as the frequency with which the subject climbed stairs or carried loads equivalent to a shopping bag. A different approach was taken in the assessment of walking. The interviewer asked in detail about the walking done yesterday, unless yesterday's walking had been atypical, in which case the respondent was asked about an earlier day (up to a maximum of six days previously). Using a diary recall method the interviewer went through the day in blocks of time, asking whether, and if so how much, the respondent had walked on the sample day. The precision of the activity inventory was demonstrated in a study of 16 elderly women interviewed on two occasions separated by a period of two weeks. Calibrated mechanical pedometers were used to validate the questionnaire assessment of walking. Twenty four female members of a keep fit class (mean age 67 years) each wore two pedometers for a period of six days, after which they were interviewed. A statistically significant correlation was found between reported minutes of walking on the sample day and the mean six-day pedometer score ($r=0.53$, $p<0.01$).

This method of assessing customary physical activity in the elderly is easily learned and can be

applied to large numbers of subjects. In Nottingham, it has been used in a study of 1,400 elderly people resident in the local community. It was therefore adapted for use in a case-control study of hip fracture. The questionnaire was shortened after a pilot study and sections were included on self-reported walking speed and time spent standing on a typical day. The version employed in the case-control study is shown in Appendix 2. It enabled the assessment of five aspects of customary physical activity: daily time spent standing, self-reported walking speed, daily time spent walking, weekly time spent in productive activities and frequency of muscle loading activities.

5.2 Past physical activity

Detailed retrospective activity questionnaires are only valid if applied within a short period of the measured activity. Boyce[189], however, has constructed a questionnaire comprising a series of questions which provide circumstantial evidence of greater than average activity at the age of 50 years. These included the use of a car or bicycle, dog ownership, means of going shopping or to work, participation in gardening, walking for leisure, dancing and sports (Appendix 3). The responses to these questions were scored and summated to give a leisure time past activity score (range 0 to 25 units). The subjects were also asked about their occupations at the age of 50 years. These were then scored from 0 to ten according to the proportion of time spent standing in the job. The scoring was performed by an occupational physician and an occupational hygienist who were presented with a list of the occupations of cases and controls. The occupational activity level was assigned as

predominantly sedentary (0 to three units), intermediate (four to six units) and predominantly weight-bearing (seven to ten units). The scores for individual occupations are shown in Appendix 3. A total past activity score was obtained by summating the occupational and leisure time components.

The validity of recall of previous physical activity is unknown. Although difficult to assess, an opportunity became available to examine the recall of certain leisure time activities over a ten year period in a small group of men of retirement age. Between 1975 and 1977 a series of 105 men aged between 60 and 65 years who were employed at a steelworks in Derbyshire took part in a study of the effects of retirement on body composition and customary physical activity[257]. As part of this study, a questionnaire was administered providing background information on their current pursuits. Seventeen of the individuals were retraced in 1986 and re-interviewed about the aspects of their activity which were previously recorded. For each individual the responses obtained to the questions in 1977 were compared with those obtained in 1986. Table 18 shows that a high level of concordance was found between the original responses and those obtained ten years later for the closed questions about various activities. Car driving and participation in gardening were infallibly recalled, while walking to shops and to friend's houses were least well remembered. Inquiry about continuous variables, such as the duration and distance of various types of walking revealed considerable individual variation in recall (Table 19) Group mean differences, however, between original and recalled values, were small. Although the group of men studied was small and

Table 18

Proportion of subjects giving concordant replies to closed question regarding previous physical activity

Item of activity	Subjects giving concordant replies	
	No.	%
Driving a car	17	100
Doing gardening	17	100
Partaking in outdoor sports	15	88
Riding a bicycle	14	82
Walking a dog	14	82
Mowing the lawn	14	82
Walking for pleasure	13	76
Walking to a public house	13	76
Swimming	13	76
Walking to work	12	71
Dancing	12	71
Walking to the shops	11	65
Walking to a friend's house	11	65

Table 19

Reliability in recalling the frequency and duration of activities after a ten year period

Item of activity	Difference between initial and recalled value		
	Mean	95% CI	Range
Walking for pleasure			
- duration (minutes)	7.65	-16.7 to 31.9	-90,120
- distance (miles)	-0.22	-0.98 to 1.42	-5,3
- frequency (times per month)	-1.0	-6.2 to 4.2	-26,14
Walking to shops			
- duration (minutes)	-1.97	-7.8 to 5.0	-30,30
- distance (miles)	0.0026	-0.3 to 0.9	-1.5,2
Walking to public house			
- duration (minutes)	1.44	-3.4 to 5.4	-15,20
- distance (miles)	0.13	-0.02 to 0.28	-0.5,1
Walking to friends			
- duration (minutes)	-6.18	-15.6 to 3.3	-60,15
- distance (miles)	-0.31	-0.8 to 0.2	-3.5,1

may have been a biased sample, the results are encouraging.

They suggest that despite considerable inaccuracy in the recall of past physical acitivity in individuals, such recall in groups of subjects is sufficient for the purposes of epidemiological studies. A simple interviewer-administered questionnaire containing such questions would provide a useful tool in studies examining the relationship between past physical activity and disease.

CHAPTER SIX

CALCIUM INTAKE, PHYSICAL ACTIVITY AND HIP FRACTURE: A CASE-CONTROL STUDY

Despite the enormous public health importance of hip fracture, there remains a paucity of information on the individual risk factors which predispose to this condition[258]. Among demographic characteristics, the important factors are increasing age, female sex and white race. Bilateral oopherectomy before natural menopause and low body weight have also been consistently detected. Here the consensus stops. A host of other variables has been suggested but the evidence is inconclusive. Among these are possible protection from a high dietary calcium intake, moderate physical activity, thiazide diuretics, oral contraceptives, fluoride in drinking water, pregnancies and lactation. Increases in risk have been attributed to cigarette smoking, alcohol consumption, deficiency of vitamin D and calcium, caffeine and protein intake. In addition to the possibility that the effects of some of these factors are slight, the difficulty of measuring many of them makes it difficult to interpret observational epidemiological studies. Furthermore, many of the factors cluster together in the same individuals, making it difficult to disentangle their individual effects.

Regular exercise and high calcium intake, two measures which are suspected to preserve bone mass in the elderly[259], offer the main immediate population-based strategy for the prevention of osteoporosis. There is, however, little information about their role in the prevention of hip fracture and hence no scientific basis for recommending them as part of a national preventive campaign.

In this study, physical activity and calcium intake, measured using the previously described methods, were compared in a series of elderly patients

with hip fractures and community controls. The independent contribution of each of these two factors to the risk of hip fracture was determined after allowing for the confounding effects of other known risk factors, including low body mass, cigarette smoking and alcohol consumption.

6.1 Patients and methods

Three hundred patients with hip fractures were recruited from 473 patients who were aged 50 years and over, were resident in Southampton Health District and were admitted sequentially to the orthopaedic wards of Southampton General Hospital. Patients with fractures wholly below the lesser trochanter, or through malignant deposits, were excluded. Two hundred and forty of the patients were women and sixty were men. It was estimated that a study of this size had 90 per cent power to detect a relative risk of 1.7 or more in women and 3.0 or more in men, at the five per cent level of statistical significance, assuming 30 per cent exposure of controls to a dichotomous risk factor.

Fifteen of the 473 patients had died before they could be approached and 12 declined to participate. The remaining 446 completed a ten point Hodkinkson abbreviated mental test score[260]. One hundred and forty six scored less than six points. Their demographic details and previous medical histories were obtained from their case notes. The three hundred who scored six or more became the study group.

They were compared with 600 community controls, also resident in Southampton Health District, who were randomly selected from the Southampton Family Practitioner Committee register. Controls were individually matched to the cases by sex and age within

four years. The response rate among controls was 71 per cent of those contacted. The reasons for lack of response were refusal (21 per cent) and failed mental test score (eight per cent). When a control declined to participate or failed the mental test score, a substitute was selected. All cases and controls were interviewed by one of three trained interviewers. Each case control set was seen by the same interviewer. Controls were interviewed within three months of the corresponding case (68 per cent) or during the corresponding quarter one year later (32 per cent).

Physical activity in the period immediately before interview and at age 50 years was estimated using the questionnaires described in chapter five. Five indices of current activity were derived: self reported walking speed, time spent standing indoors, time spent walking outdoors, frequency of muscle loading activity such as climbing stairs or carrying loads, and time spent in productive activities such as gardening and housework. Information on physical activity at age 50 years was classified as occupational or leisure time. Current calcium intake was measured using the frequency amount questionnaire described in chapter four.

Other information obtained included current reported height and weight, previous medical history, reproductive history, cigarette smoking, socio-economic status and family history of fracture. Alcohol consumption was assessed using the method of the General Household Survey[261] and dependence in daily living activities using the Katz assessment of daily living activities[262].

Grip strength was measured with a calibrated isometric dynamometer. The maximum of three readings on each hand was adopted for subsequent analysis. The

data were analysed using a conditional logistic regression for matched case-control studies[263]. The statistical significance of gradients of relative risk was assessed using chi-squared tests for linear trend. Relationships between variables were studied using multiple linear regression or analysis of covariance.

6.2 Results

Table 20 shows the age and sex distribution of the 300 patients who passed the MTS and the 146 who did not. The patients who failed were older than those who passed and the female to male ratio was greater. More of them were resident in supervised accommodation (warden controlled flats, rest homes and nursing homes).

Table 21 shows the distribution of selected variables among cases and controls, expressed as relative risks of fracture associated with them. There was a progressive fall in risk with increasing body mass index. An increased risk was associated with cigarette smoking, alcohol consumption, a history of stroke, current use of corticosteroids, a fall during the previous nine months, previous hip or wrist fractures and inability to walk unaided. Risk fell progressively with rising mental test score and increasing independence in daily living activities.

No difference was detected in the mean age at menarche or menopause of cases and controls. Eighteen of the women with hip fractures (eight per cent) and 22 female controls (five per cent) recalled a previous oopherectomy, giving a relative risk of 1.5 (95 per cent confidence intervals 0.9 to 3.2). The previous use of post-menopausal hormone replacement therapy was reported by six cases (three per cent) and 23 controls

Table 20

Distribution of patients with hip fracture by age, sex and mental test score

Age (years)	Mental test score					
	>5		⩽5		All	
	Women	Men	Women	Men	Women	Men
<55	3	6	-	-	3	6
55-64	11	8	1	1	12	9
65-74	50	16	5	2	55	18
75-84	99	22	43	8	142	30
>84	77	8	78	8	155	16
Total	240	60	127	19	367	79

Table 21

Risk factors for hip fracture

Variable	Number of		Relative risk	95% CI
	Cases	Controls		
Body mass index - weight/height^2 (fifths of distribution)				
- lowest	88	84	6.7	3.8-11.7
- second	67	94	4.3	2.4-7.4
- third	60	112	3.3	1.9-5.8
- fourth	40	128	2.1	1.2-3.8
- highest	24	144	1.0	-
Cigarette smoking (ever and never)	145	223	1.7	1.2-2.3
Alcohol consumption				
- moderate/heavy	28	12	7.5	3.3-16.8
- light	108	205	1.3	1.0-1.8
- occasional/abstainer	163	382	1.0	-
History of stroke	34	39	1.8	1.1-2.9
Current use of corticosteroids	16	13	2.7	1.2-5.8
History of a fall in the previous nine months	112	153	1.3	1.3-2.5
Previous hip fracture after age 50 years	37	14	6.8	3.4-13.8
Previous wrist fracture after age 50 years	48	52	2.3	1.4-3.6
Gait abnormality				
- walks only with help of another person	32	23	4.3	2.4-7.9
- walks with stick	126	199	1.9	1.4-2.6
- walks unaided	142	377	1.0	-
Mental test score 6-7	62	62	3.1	1.9-4.8
8	36	60	1.6	1.0-2.5
9	53	113	1.2	0.8-1.7
10	149	365	1.0	-
Dependence in daily living activities				
- requires help in three or more activities	28	21	4.4	2.3-8.4
- requires help bathing and dressing	38	34	3.4	2.0-5.8
- requires help bathing	77	124	1.9	1.3-2.8
- fully independent	157	420	1.0	-

(five per cent) giving a relative risk of 0.5 (95 per cent confidence intervals 0.2 to 1.3).

PHYSICAL ACTIVITY

The risk of hip fracture was analysed in relation to each of the five indices of current physical activity (Table 22). Among women, the risk of fracture increased with reducing level of standing time, self-reported walking speed, muscle-loading activity and productive activity. These increases in risk were statistically significant at the five per cent level. Among the smaller number of men in the study, similar increases in risk were found with reducing activity but these were not statistically significant. Body mass index, cigarette smoking, alcohol consumption, history of a stroke and use of corticosteroids (Table 21) were thought to be possible confounding variables, that is, independently associated with physical activity and hip fracture. The relation was therefore examined between physical activity and fracture risk after adjusting for these variables (Table 22). The trends were little affected.

The risk of hip fracture also fell with increasing levels of recalled physical activity at age 50 years. Division of past physical activity into occupational and leisure time components (Table 23) showed that a statistically significant decline in fracture risk was only found with increasing occupational activity. There was no significant relationship between fracture risk and past leisure time physical activity.

MUSCLE STRENGTH

Figure 8 shows the variation of grip strength with age and sex. In both cases and controls, it fell

Table 22

Physical activity and the risk of hip fracture

Activity	Level	Women					Men				
		Number of		Relative risk			Number of		Relative risk		
		Cases	Controls	Non-adjusted	Adjusted*	95% CI	Cases	Controls	Non-adjusted	Adjusted*	95% CI
Standing time (mins/day)	None	15	21	2.9	1.6	0.5-4.6	0	2	-	-	-
	1-29	84	102	3.1	2.9	1.7-4.9	16	123	1.9	2.1	0.6-7.5
	30-59	76	152	1.9	1.8	1.1-2.9	18	30	1.6	1.9	0.7-5.0
	60	65	205	1.0	1.0	-	26	65	1.0	1.0	-
Self-reported walking speed	Very slowly	132	207	2.4	2.6	1.3-5.2	23	36	1.5	1.6	0.5-5.7
	Easy pace	46	114	1.4	1.5	0.7-3.0	17	34	1.2	0.9	0.3-2.9
	Normal speed	40	90	1.5	1.5	0.7-3.1	10	27	0.9	0.9	0.2-3.4
	Brisk/fast	22	68	1.0	1.0	-	10	23	1.0	1.0	-
Walking time (mins/day)	None	126	236	1.4	0.8	0.4-1.8	24	43	2.5	3.4	0.8-15.1
	1-29	79	154	1.3	0.9	0.4-2.0	23	35	2.8	2.7	0.7-10.8
	30-59	21	57	0.9	0.8	0.3-2.0	7	16	1.9	4.2	0.8-23.1
	60	14	33	1.0	1.0	-	6	26	1.0	1.0	-
Muscle loading activity (frequency)	Never	89	131	2.0	1.7	1.0-3.1	13	22	4.6	2.5	0.5-13.2
	Less than weekly	63	112	1.6	1.7	1.0-3.1	19	19	7.9	5.6	1.3-23.9
	Weekly to daily	42	117	0.9	1.0	0.6-1.8	18	32	3.5	3.6	1.0-12.9
	Several times a day	46	120	1.0	1.0	-	10	47	1.0	1.0	-
Productive activity (hours/week)	None	66	212	2.7	2.0	1.1-3.7	10	13	2.7	2.4	0.5-12.0
	1,2	52	105	3.4	3.3	1.9-5.7	15	13	4.2	3.8	1.1-13.6
	3-5	66	77	1.8	1.8	1.0-2.9	14	31	1.8	3.2	0.9-11.3
	5	56	86	1.0	1.0	-	21	63	1.0	1.0	-

*Adjusted for body mass index, smoking, alcohol, stroke and steroid treatment.

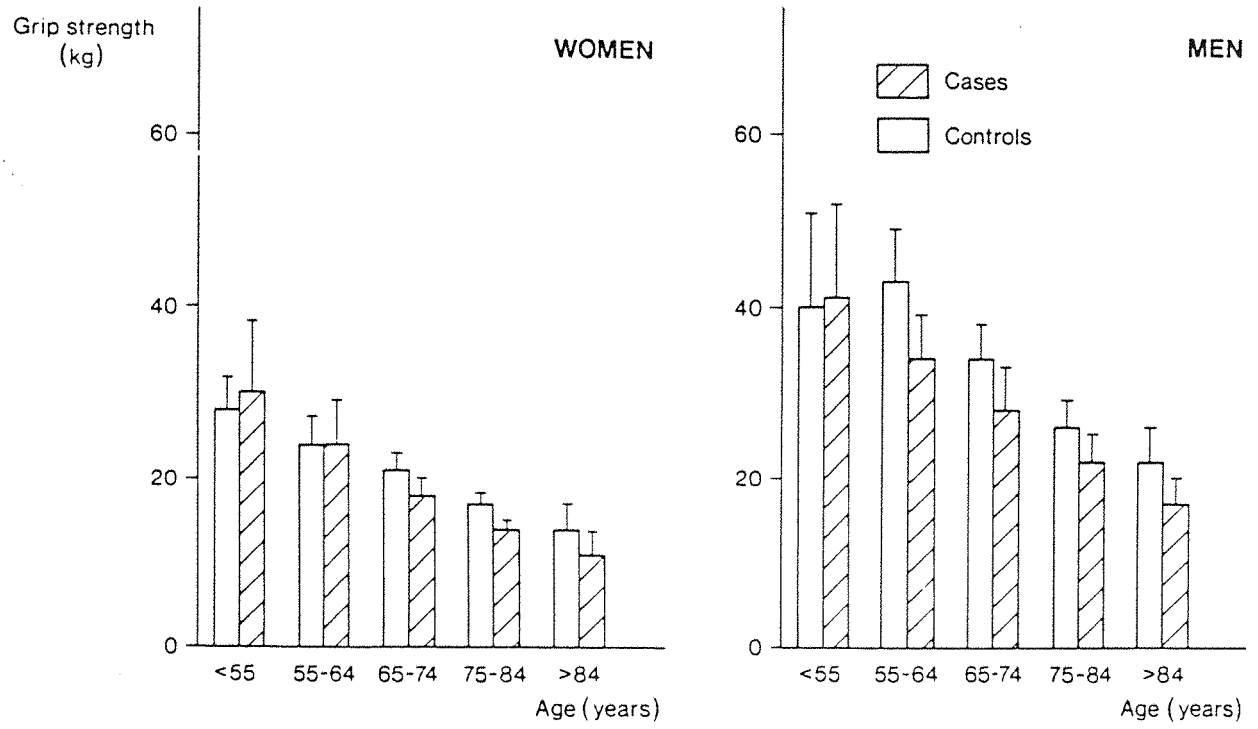
Table 23

Past physical activity and the relative risk of hip fracture

Activity	Level	Number of		Relative risk	95% CI
		Cases	Controls		
Total past activity (units)	<14	78	105	1.0	-
	14-18	176	394	0.6	0.5-0.9
	>18	46	91	0.6	0.4-0.8
Occupational activity (% of time spent standing)	<40	54	51	1.0	-
	40-70	180	355	0.4	0.2-1.0
	>70	66	194	0.4	0.2-1.0
Leisure activity (units)	<9	111	241	1.0	-
	9-11	95	189	0.9	0.6-1.3
	>11	94	170	0.8	0.6-1.2

Figure 8

Changes in grip strength (mean and 95% CI) by age and sex in cases and controls.



sharply with age. In each age group, the mean strength was greater in men than in women. Fracture risk was calculated for men and women in each fifth of the distribution of grip strength (Table 24). There was an almost five-fold increase in risk between the lowest and highest fifths of strength. This increase was statistically significant ($p<0.01$) for both men and women. The risk of fracture remained statistically significantly elevated ($p<0.05$) in women with reduced grip strength after allowance for all five of the possible confounding variables. Although an increased risk with reduced grip strength remained in men, it was not statistically significant.

In both the cases and controls, there were statistically significant ($p<0.01$) positive relationships, after allowance for age and sex, between grip strength and standing time, walking speed, walking time, muscle loading activity, and productive activity.

CALCIUM INTAKE

The mean daily calcium intake of the cases (660 mg/day, 95% confidence intervals 632-688 mg/day) did not differ statistically significantly from that of the controls (mean 689 mg/day, 95% confidence intervals 667-711 mg/day). When the sexes were analysed separately (Figure 9), the male cases had a significantly lower mean intake (701 mg/day, 95% confidence intervals 637-765 mg/day) than the male controls (843 mg/day, 95% confidence intervals 775-911 mg/day). Table 25 shows the relative risks of fracture in men and women in each fifth of the distribution of calcium intake. There was no change in risk with increasing calcium intake amongst women. In men there was a fall in risk with increasing intake. This trend did not remain after adjusting for the five confounding

Table 24

Grip strength and the risk of hip fracture

Sex	Fifths of distribution of grip strength (kg)	Number of		Relative risk of fracture			
		Cases	Controls	Non-adjusted	95% CI	Adjusted*	95% CI
Women	<10	60	64	4.9	2.7- 9.0	2.7	1.4- 5.5
	10-14	64	82	4.3	2.4- 7.7	3.1	1.6- 5.9
	14-18	51	99	2.5	1.4- 4.5	1.7	0.9- 3.2
	18-23	33	116	1.3	0.7- 2.3	1.0	0.5- 1.8
	>23	30	118	1.0	-	1.0	-
Men	<18	15	20	4.9	1.3-18.9	1.9	0.4- 9.5
	18-25	16	17	6.7	1.7-26.1	2.4	0.5-12.0
	25-31	13	27	2.1	0.7- 6.7	1.4	0.4- 5.5
	31-39	7	28	0.9	0.3- 3.3	0.7	0.2- 3.1
	>39	9	28	1.0	-	1.0	-

*Adjusted for body mass index, smoking, alcohol, stroke and steriod treatment.

Figure 9

Dietary calcium intake (mean and 95% CI) in cases and controls.

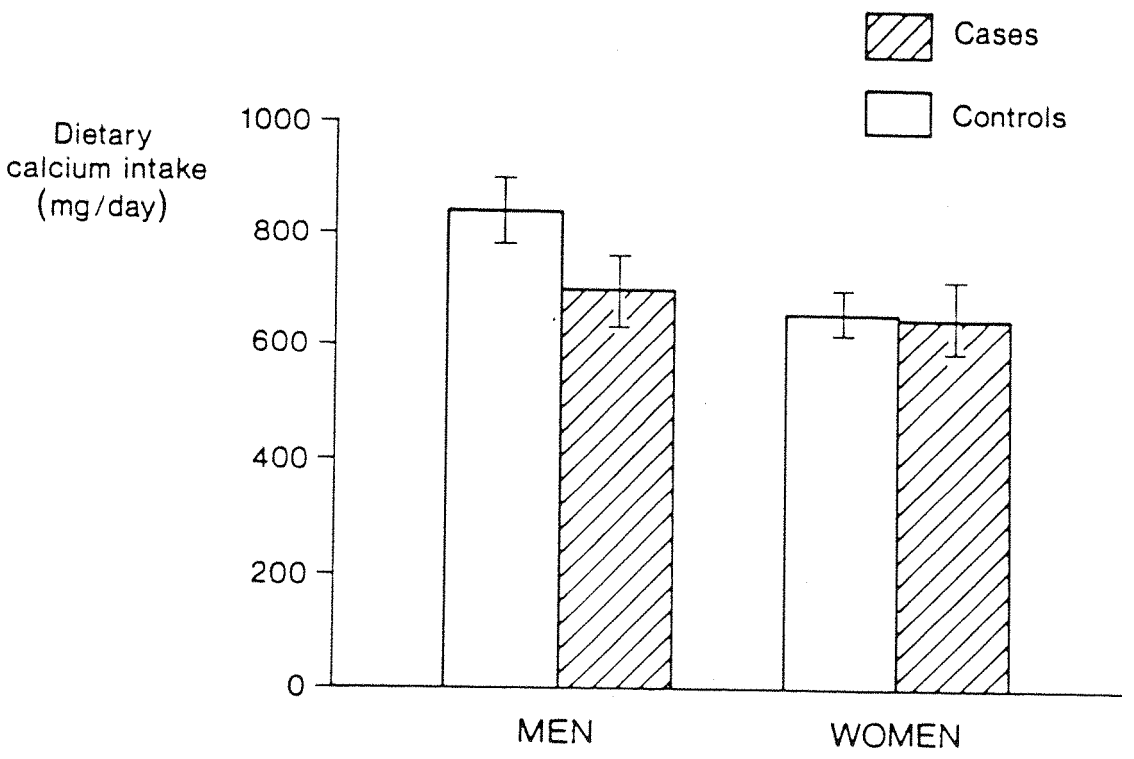


Table 25

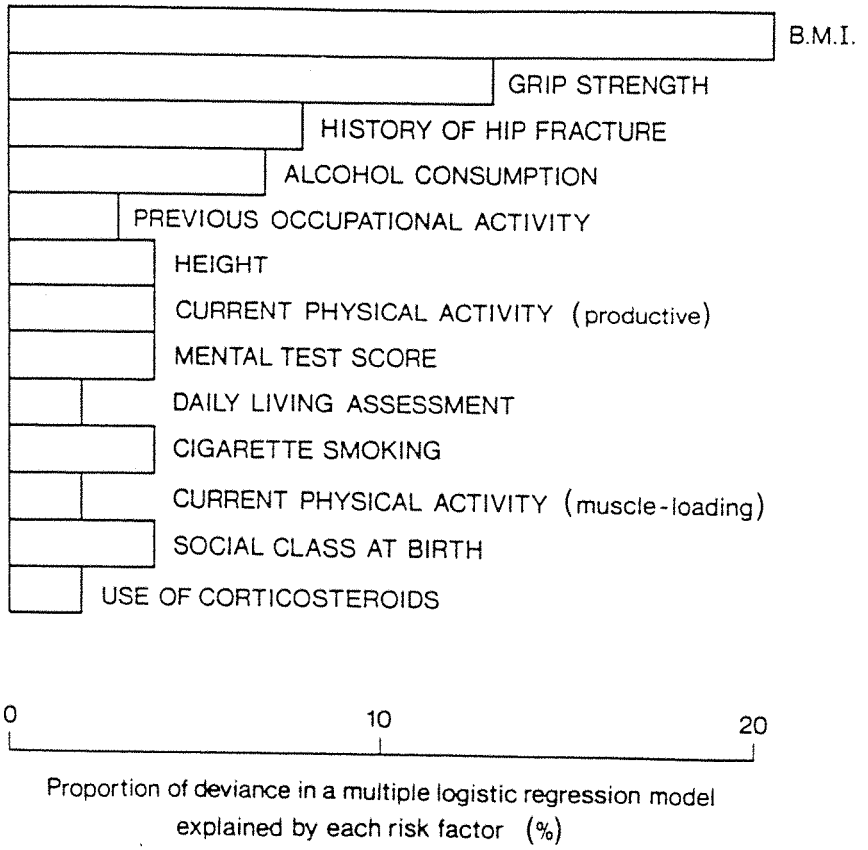
Dietary calcium intake and the risk of hip fracture

Sex	Fifths of the distribution of calcium intake (mg/day)	Number of		Relative risk of fracture			
		Cases	Controls	Non-adjusted	95% CI	Adjusted*	95% CI
Women	<433	47	97	1.0	0.6-1.6	1.2	0.7- 2.2
	433-567	51	93	1.1	0.7-1.8	1.4	0.8- 2.5
	567-684	48	96	1.0	0.6-1.7	1.1	0.6- 2.0
	684-838	47	97	1.0	0.6-1.6	1.2	0.7- 2.1
	>838	47	97	1.0	-	1.0	-
Men	<500	15	21	4.6	1.4-15.0	6.2	1.3-29.7
	500-668	14	22	4.0	1.2-13.0	5.8	1.1-29.0
	668-841	14	22	3.6	1.2-11.1	3.3	0.8-14.1
	841-1041	12	24	3.2	0.9-11.3	6.2	1.2-32.7
	>1041	5	31	1.0	-	1.0	-

*Adjusted for body mass index, smoking, alcohol, stroke and steroid treatment.

Figure 10

Independent risk factors for hip fracture



variables, but the adjusted risk among men with the highest intakes, more than 1,041 mg/day, remained statistically significantly lower than the remainder. The number of pints of milk consumed per week was almost identical in cases (mean 4.35, 95% confidence intervals 4.27-4.43) and controls (mean 4.34, 95% confidence intervals 4.27-4.41). A history of usually taking a milk drink at night was obtained in 102 cases (34 per cent) and 214 controls (36 per cent).

When all the variables included in the study were included in a multiple regression model, 13 factors contributed significantly and independently to reduction in deviance in the model. These are shown diagrammatically in Figure 10. The greatest two effects were attributable to reduced body mass index and reduced grip strength. More detailed results are provided in Appendix 6.

Discussion

This case-control study shows that inactivity and muscle weakness are associated with an increased risk of hip fracture in elderly people. The cases, 80 per cent of whom were women, were a sequential series of all patients in one district and the matched controls were drawn from the community. People with a mental test score of five or less, who would have been unable to reply to the questions, were excluded. This led to exclusion of around one third of cases but fewer controls. Although patterns of activity are likely to be different in people with low mental test scores, it is unlikely that this would create a false association between inactivity and fracture risk.

Four of the five indices of current physical activity were associated with fracture risk in both

sexes (Table 22). Among women, risk was lowest in those who stood for more than one hour a day, walked at a brisk pace, climbed stairs or carried loads more than once a day, or spent more than five hours a week in housework and gardening. Among men there was also a lower risk in those who walked for more than one hour a day. At lower levels of activity the risk was around double. The associations were independent of body mass, cigarette smoking and alcohol consumption.

The present study also provides some evidence for an association between physical activity at the age of 50 years and the risk of hip fracture. This is in accord with the findings of a previous case-control study[189]. The result must be interpreted with caution, however, as recall of previous activity by elderly people may be variable and influenced by current activity levels.

There was a steep increase in fracture risk with reducing grip strength in both sexes (Table 24). Although the occurrence of a hip fracture may lead to loss of muscle strength, the grip strengths of cases and controls correlated with their levels of physical activity. This suggests that part of the reduced strength of the cases antedated the fracture. A relation between muscle strength and activity in the elderly has been shown before[264].

Activity and muscle strength could protect against hip fracture either by preserving bone mass or by reducing the risk and severity of falls. Evidence from several sources suggests an association between exercise and bone mass. People who are immobilised through illness[265] or during space flight lose bone at an accelerated rate[225]. Athletes who use one limb in strenuous physical activity have greater bone mass in

that limb than in the contralateral one[227] and controlled trials of exercise in the elderly are effective in retarding their rate of bone loss[229]. Evidence relating activity, strength and falling comes from a national sample of 1,000 elderly people in Britain[266]. Lower levels of both mobility and grip strength were associated with an increased frequency of reported falls.

Among women there was no relationship between fracture risk and the intake of calcium (Table 25). Among men, after adjusting for confounding variables, risk was lower in those in the highest fifth of calcium intake. Evidence for a relationship between dietary calcium intake and hip fracture is inconsistent. Of two populations within Yugoslavia, that with the lower calcium intake had the higher incidence of hip fracture[32]. Two case-control studies, however, have not shown associations between calcium intake and fracture risk[53,179]. Metabolic balance studies show an age-related decline in the efficiency of mechanisms which maintain calcium balance; this is particularly marked in post-menopausal women[214]. Trials of calcium supplementation, in contrast, have shown little if any beneficial effect on the rate of bone loss[267]. Whether or not low dietary calcium intake is associated with osteoporosis, our results suggest that in elderly women in southern Britain it is not a risk factor for hip fracture. The results in men, however, could support a protective effect of calcium intake above one gram a day, an intake recorded in only 7.5 per cent of the women studied.

It is concluded that physical inactivity and muscle weakness increase the risk of hip fracture in the elderly independently of other influences. This

points to the importance of maintaining physical activity in the day to day lives of old people in Britain.

CHAPTER SEVEN

BIOCHEMICAL INDICES OF CALCIUM METABOLISM IN ELDERLY WOMEN WITH HIP FRACTURES

The pattern of bone loss which culminates in hip fracture (type 2 osteoporosis) might stem from two abnormalities in bone metabolism: impaired bone formation and secondary hyperparathyroidism[137]. There is little experimental evidence, however, to support either mechanism.

Certain biochemical indices of calcium metabolism were therefore examined in a series of elderly women with hip fractures and two groups of controls.

7.1 Patients and methods

The study included 41 women (mean age 77.4, range 50-93 years) admitted consecutively to the orthopaedic wards of Southampton General Hospital, over a three month period between May and July, having sustained a hip fracture. All of them had been admitted within 24 hours of the fracture. Twenty two of the fractures were trochanteric and 19 were cervical. The first control group comprised 20 female geriatric patients admitted acutely to hospital (mean age 73.3, range 55-87 years). They suffered from a variety of disorders including bronchopneumonia, cardiac failure, Parkinson's disease, stroke and urinary tract infection. The second group comprised 20 elderly female out-patients (mean age 66.9, range 51-89 years) attending a rheumatology clinic for a variety of mechanical or soft tissue disorders such as frozen shoulder and cervico-lumbar spondylosis. Patients were excluded from the study if they suffered from thyrotoxicosis, rheumatoid arthritis, chronic liver disease, malignant diseases, or if they were being treated with corticosteroids. Controls with a previous history of hip fracture were also excluded.

Morning blood samples were taken from all the subjects. Those from the hip fracture cases were

obtained within 48 hours of admission, and prior to surgical intervention. Those from in-patient controls were obtained within a week of admission, and, those from the out-patient controls at clinic attendance. Samples were stored at $4^{o}C$ and centrifuged within one hour of collection. Serum was aliquoted and stored at $-20^{o}C$ for a period of three months, prior to assay of albumin, calcium, alkaline phosphatase, creatinine, 25-hydroxy vitamin D (25OHD), parathyroid hormone (PTH) and osteocalcin.

Serum albumin, calcium, alkaline phosphatase and creatinine concentrations were estimated using standard methods on an SP 120 autoanalyser. Calcium concentration was corrected for albumin concentration by the formula: corrected serum calcium = estimated calcium + 0.02 (40 serum albumin).

Serum concentrations of 25OHD were measured by a radioimmunoassay using pig antiserum from Bioanalysis, Cardiff and tritiated 25OHD tracer from Amersham International. The limit of detection was 1.2 ug/l. Intra-assay and interassay coeffients of variation were 8.2 per cent and 12.4 per cent respectively.

Serum concentration of immunoreactive PTH was carried out using NIBSC antiserum at a final dilution of 1:300,000. The limit of detection of the assay was 0.25 ug/l. Intra-assay and interassay coefficients of variation were 5.3 per cent and 12.0 per cent respectively. The assay is primarily directed to the C terminal of the PTH molecule.

Serum osteocalcin concentration was measured by a radioimmunoassay procedure using a rabbit antibody to purified calf osteocalcin as a standard and tracer[268]. The limit of detection was 0.5 ng/ml. The intra-assay and interassay coefficients of variation were ten per cent and 15 per cent respectively.

Early morning urine samples were obtainable from 18 fracture patients and 18 out-patient controls on the day of venesection. Hydroxyproline (OHPr) was assayed using hydrolysis, organic extraction and spectrophotometry. Intra-assay and interassay coefficients of variation were 8.1 per cent and 8.7 per cent respectively. Urine creatinine concentrations were measured by colorimetry after complex formation with picrate (Jaffe reaction). The assays of albumin, calcium, alkaline phosphatase, creatinine, 25-hydroxy vitamin D, parathyroid hormone and hydroxyproline were carried out by Dr. P. Woods, Department of Chemical Pathology, Southampton General Hospital. Those of osteocalcin were carried out by Dr. L. Coulton, Department of Orthopaedic Surgery, Royal Hallamshire Hospital, Sheffield.

Differences between the biochemical measurements of patients and controls were compared using analysis of variance with age as a covariate. The distribution of osteocalcin concentrations was appreciably skewed and values were therefore log transformed.

7.2 Results

Biochemical data from the hip fracture patients and control subjects are shown in Table 26. The serum concentrations of albumin and 25OHD were significantly lower in the fracture group than in the control group ($p<0.01$, Figures 11 and 12). For both variables, concentrations were higher amongst the out-patient controls than the in-patient controls ($p<0.01$). These relationships remained after allowance was made for the age differences between the three groups. A positive correlation was observed between the albumin and 25OHD concentrations of the study subjects as a whole

Table 26

Biochemical values (mean and 95% CI) in patients with hip fractures and control groups

	Hip fracture	In-patient controls	Out-patient controls	Laboratory reference range
Number	41	20	20	
Age (years)	77.4 (74.7-80.1)	73.3 (68.7-77.9)	66.9 (61.7-72.1)	
Albumin (g/l)	30.1 (29.0-31.2[a])	34.7 (33.2-36.2)	38.1 (37.0-39.2)	32-50
Serum creatinine (umol/l)	110 (98-122)	105 (93-117)	84 (74-84)	60-125
Calcium (mmol/l)	2.28 (2.23-2.33)	2.35 (2.28-2.42)	2.35 (2.29-2.41)	2.15-2.55
Alkaline phosphatase (IU/l)	234 (177-291)	192 (175-209)	190 (149-231)	100-350
25OHD (ug/l)	9.4 (7.6-11.2)[a]	14.3 (10.1-18.5)	19.4 (15.0-23.8)	4-40
PTH (ug/l)	0.39 (0.33-0.45)	0.41 (0.32-0.50)	0.33 (0.28-0.38)	<0.5
Osteocalcin (ng/ml)	11.8 (7.7-15.9)[b]	15.9 (12.5-19.3)	13.6 (8.0-19.2)	8-36
Urine* OHPr/Cr (umol/mmol)	14.8 (11.0-18.6)		15.7 (9.8-21.2)	<30

a = significantly lower in fracture patients ($p<0.01$) after ANOVA with age as covariate.

b = when log transformed, significantly lower in fracture patients than in-patient controls after ANOVA with age as covariate ($p<0.02$).

* = based on 18 hip fracture patients and 18 controls

Figure 11

Serum concentrations of albumin in women with hip fractures and controls (lines indicate group mean values).

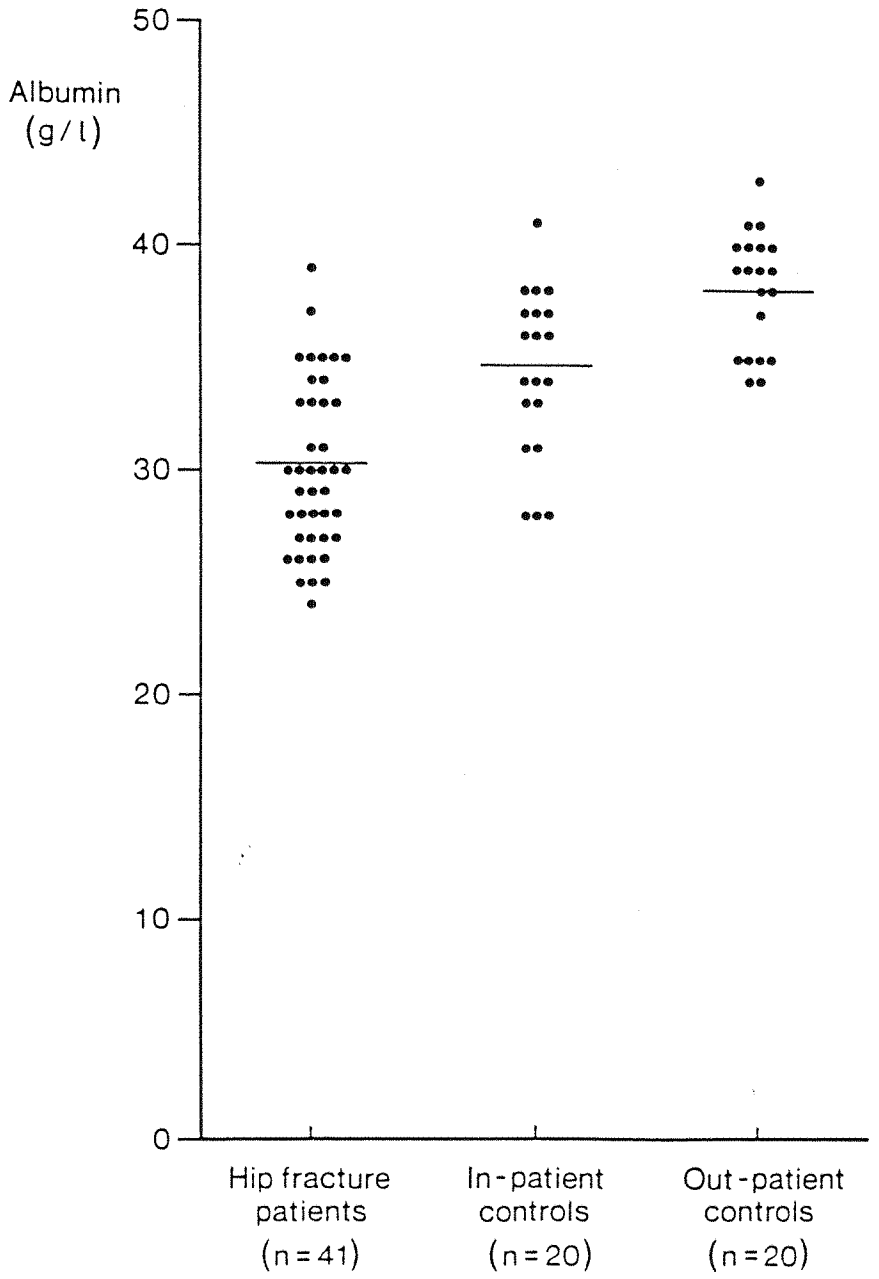
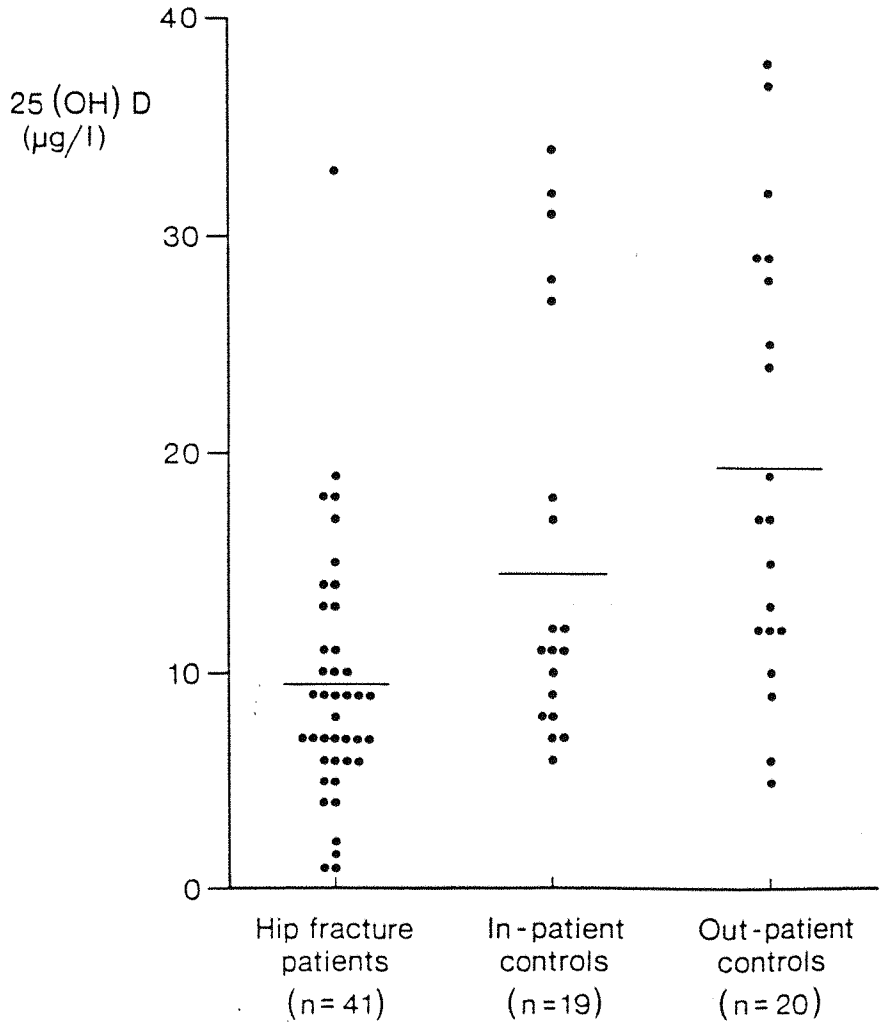


Figure 12

Serum concentrations of 25 hydroxyvitamin D in women with hip fractures and controls (lines indicate group mean values).



($r=0.44$, $p<0.01$), as was a negative relationship between each variable and age. Amongst the fracture patients, 25OHD concentration showed a positive correlation with physical activity score ($r=0.47$, $p<0.01$). When both age and albumin were used as covariates in the ANOVA, no residual difference in serum 25OHD concentration was detectable between the three groups.

The log transformed concentrations of osteocalcin were significantly lower in the fracture patients than in the in-patient controls, after allowance for age ($p<0.05$, Figure 13). No difference, however, was detected between the log transformed values of the fracture patients and the out-patient controls. A significant positive correlation was found in the fracture series between osteocalcin concentration and serum alkaline phosphatase activity ($r=0.32$, $p<0.01$).

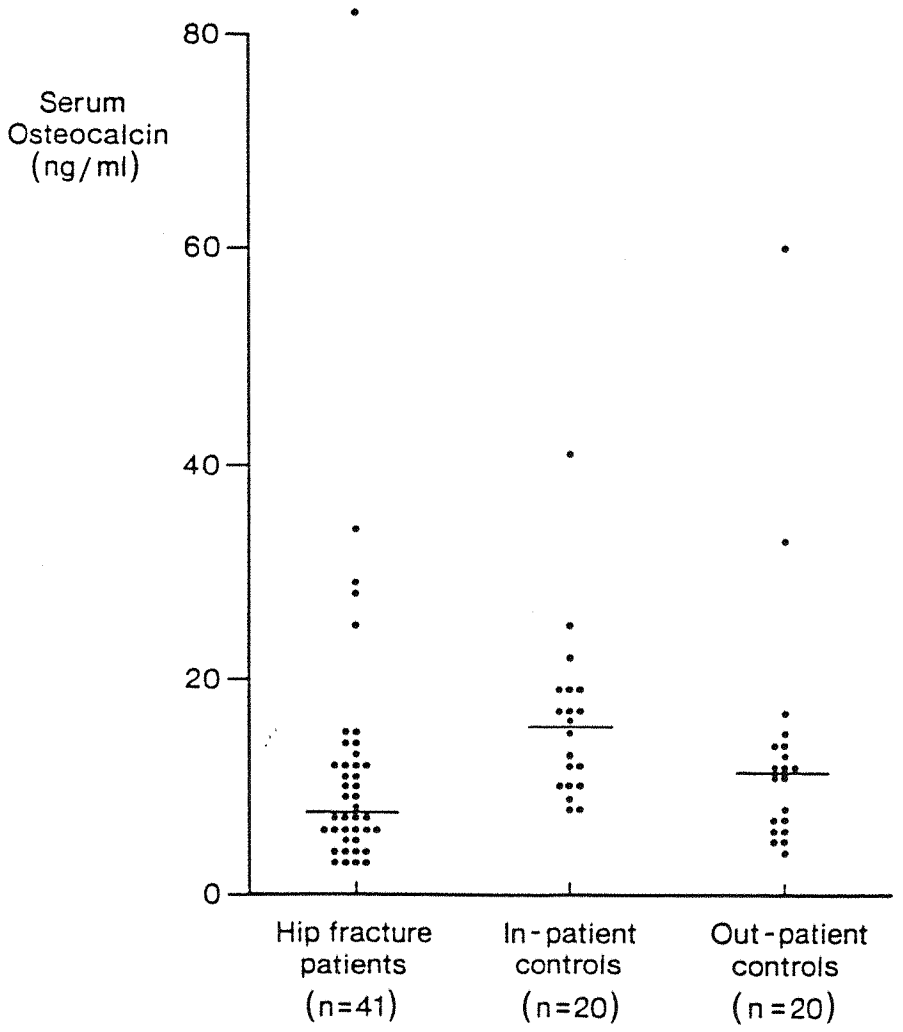
The serum concentrations of PTH, calcium, alkaline phosphatase and urinary OHPr/creatinine ratio did not differ significantly between the three groups. Age ($r=0.31$, $p<0.01$) and alkaline phosphatase ($r=0.42$, $p<0.01$) were significant correlates of PTH concentration.

Serum creatinine concentration was significantly lower ($p<0.05$) in the younger out-patient control group than in the older hip fracture cases and in-patient controls. Allowance for age, however, removed this effect. Serum PTH concentrations showed no statistically significant differences between the three groups of patients after allowance for age and serum creatinine.

Three fracture patients had serum alkaline phosphatase concentrations greater than 350 IU/l with normal hepatic function. In one of these 25OHD

Figure 13

Serum concentrations of osteocalcin before log transformation in women with hip fractures and controls (lines indicate group median values).



concentration was low (1.4 ug/l), osteocalcin was elevated (82 ug/l) and there was evidence of secondary hyperparathyroidism (PTH 3.6 ug/l). In another, an elevated serum osteocalcin without other abnormalities was found, whereas in the third, the elevated alkaline phosphatase concentration occurred in isolation.

7.3 Discussion

The results of this study show that elderly women who have sustained hip fractures have lower serum concentrations of albumin and 25OHD than in-patient or out-patient controls of similar age. A lower circulating concentration of osteocalcin was also found in those women with hip fractures when compared with acutely admitted in-patient controls, but not when compared with ambulatory elderly out-patients.

The interpretation of biochemical data in elderly patients who have sustained hip fractures must be guarded for two reasons. First, several studies have drawn attention to changes in the concentrations of alkaline phosphatase, calcium, phosphate and PTH which follow fractures or surgically induced trauma[269-273]. Changes in these four variables become apparent in the second week following fracture[269,270]. Serum concentrations of osteocalcin, albumin and vitamin D binding protein, however, may fall earlier[271,272,274,275]. Second, many biochemical variables are depressed in sick elderly individuals as compared with the healthy elderly[110,276].

Whether the observed differences between hip fracture patients and in-patient controls might be entirely accounted for by bone trauma in a sick elderly group of subjects is difficult to answer. Most studies have shown lower serum albumin concentrations in hip

fracture patients than in other elderly control groups[179,274]. The results of 25OHD estimations have been less consistent, however. Those of Baker[277] and Lips[274] have suggested reduced concentrations of 25OHD in women with hip fractures. Other studies have failed to confirm this observation, perhaps as a result of biased values in the control groups which were adopted[179,278].

The circulating concentration of osteocalcin may be a sensitive indicator of bone turnover in patients with various metabolic bone disorders[279]. Although primarily synthesised by the osteoblast, the actions and metabolism of this protein remain unknown[280]. Investigations of women with post-menopausal osteoporosis have generally revealed normal or elevated serum osteocalcin concentrations[119,279,281]. In the only published study to measure osteocalcin in patients with hip fractures, concentrations were found to be elevated in a series of 24 patients with hip fractures, who required operative reductions and insertion of a pin, but normal in 13 individuals requiring a prosthesis[282]. The finding in the present study, of a slightly lower serum osteocalcin concentration in hip fracture patients than in the in-patient controls, although possibly resulting from bone trauma, is compatible with the hypothesis that such fractures are associated with a "low-turnover" osteoporosis.

The results do not support an association between hip fracture and secondary hyperparathyroidism. Despite a significant increase in PTH concentrations with age, no relationship was detectable between PTH and 25OHD concentrations, and mean PTH values did not differ significantly between the case and control groups. The interpretation of radioimmunoassays for

PTH is notoriously difficult, however, and studies using the more recently developed bioassays for the hormone are required[283].

In conclusion, few biochemical abnormalities to suggest persisting alterations in bone metabolism are detectable in elderly women with hip fractures. The observed differences in serum albumin and 25OHD status between such patients and controls of similar age are open to various interpretations. Vitamin D deficiency might be important in the pathogenesis of hip fracture in the elderly. Alternatively, the differences could be a consequence of the generally poor physical state of these patients which has been documented in other studies[37,38]. Finally, they may be explained by the trauma and immobilisation which accompany such fractures. The small reduction in osteocalcin concentration observed in these women is in accord with the hypothesis that reduced osteoblast function is an important contributor to the risk of hip fracture.

SECTION FOUR

THE GEOGRAPHY OF HIP FRACTURE INCIDENCE IN ENGLAND AND WALES

CHAPTER EIGHT

THE USEFULNESS OF MORTALITY AND HOSPITAL DISCHARGE DATA TO STUDY GEOGRAPHIC VARIATION IN THE INCIDENCE OF HIP FRACTURES IN ENGLAND AND WALES

Several studies have suggested differences in hip fracture incidence and mortality between various regions in England and Wales but no systematic attempt has been made to study the geography of the condition in detail[7,25,156]. Analysis of mortality data for England and Wales by usual place of residence of the deceased demonstrates considerable geographic variation in rates of deaths certified as due to accidental falls[284]. Most of the deaths occurred in people over the age of 65 years and in this age group, the commonest condition resulting in death from accidental falls is hip fracture.

The geographical pattern of mortality from hip fracture might provide clues about environmental agents relevant to the aetiology of the condition. Mortality, however, may be an uncertain indicator of hip fracture incidence for two reasons. First, mortality reflects case fatality as well as incidence. Second, the certification of death from hip fracture may not be consistent throughout the country. This section therefore describes a study in which the geography of hip fracture was examined in four stages:

1) Standardised mortality ratios (SMR's) for death from hip fracture were calculated for each of the 403 county districts in England and Wales between 1974 and 1985, excluding 1979.
2) Age and sex standardised hospital discharge rates for hip fracture were calculated in 299 of the 403 county districts in England and Wales for which data were available between 1978 and 1982.
3) The SMR's and discharge rates for each county district were compared, as a preliminary attempt to validate the mortality data.

4) In seven selected health districts, a series of death certificates were obtained of individuals recorded on hospital activity analysis (HAA) data as having been admitted with hip fractures, whose disposal was coded as death. The causes to which death was ascribed were analysed in each district.

8.1 Methods

MORTALITY DATA

The Office of Population Censuses and Surveys (OPCS) made available extracts of all 26,918 death certificates in England and Wales during the period 1974 to 1985 (excluding 1979) on which either osteoporosis or fracture of the proximal femur were recorded as the underlying cause of death (ICD 8th Revision codes 733, 820). Deaths attributed to osteoporosis were included because a pilot study had suggested that substantial numbers of deaths following hip fracture were coded to osteoporosis in certain parts of the country, most notably East Anglia. Mortality rates for individuals aged 45 years and above in each sex were calculated for each county district using 1981 Census data. Mortality rates were expressed as standardised mortality ratios.

MORBIDITY DATA

Hospital activity analysis data on admissions with fracture of the proximal femur during 1978 and 1982 were obtained for each health region in England and Wales other than the four Thames regions, which comprise London and the Home Counties. In the data, a patient's residence was coded by county district. Hip fracture rates were calculated from the number of

patients resident in the areas who had (a) been discharged from hospital with the diagnosis of fracture of the proximal femur (ICD 8th Revision code 820), (b) been admitted as emergencies, and (c) not undergone a revision of arthroplasty. Use of these criteria was intended to reduce the number of patients with late complications of hip fracture and those transferred between hospitals. Discharge rates were standardised by sex and age over 45 years.

COMPARISON OF MORTALITY AND MORBIDITY DATA

In the 299 county districts for which SMR's and standardised discharge rates were available, the relationship between mortality and morbidity data was examined. The total number of deaths between 1974 and 1985 (excluding 1979) in each county district was compared with the mean annual number discharged from hospital between 1978 and 1982, and SMR's for each district were compared with standardised discharge rates.

VALIDITY OF DEATH CERTIFICATION

HAA listings were obtained from seven health districts of individuals who had been admitted following a hip fracture and whose subsequent disposal was coded as death. The seven districts (Table 27) were chosen so as to include a wide range of SMR from hip fracture. In Newcastle listings were only available for a one year period, while the other districts provided listings over at least five years. OPCS made available copies of the death certificates of these individuals. They were examined for mention of osteoporosis or hip fracture in Parts Ia, b, c, II or as the coded underlying cause of death.

Table 27

Health districts from which death certificates were obtained of patients who died following hip fracture

District	Period for which death certificates available	Number of death certificates	SMR (1974-1985)
Newport	1978-1982	255	218
Stoke-on-Trent	1978-1983	366	188
Newcastle-upon-Tyne	1981	71	131
Southampton	1979-1983	238	89
Fulham	1979-1983	107	35
Nottingham	1978-1982	227	23
Harrow	1979-1983	47	13

8.2 Results

Tables 28 and 29 show the age and sex distributions of the people included in the mortality and hospital discharge study samples respectively. There were greater numbers of women than men in both samples at all ages over 60 years.

The SMR for osteoporosis and hip fracture varied from eight in Gillingham to 363 in Castle Morpeth. Figure 14 shows the county districts of England and Wales in which the SMR among people aged 45 years and over was in the upper or lower tenth of the distribution. Districts with high SMR's were found in the North East of England, South Yorkshire, Merseyside, the West Midlands and South Wales. SMR's were low in most of London and the South East.

The standardised hospital discharge rate for hip fracture varied from 3.3/10,000/year in Barrow-in-Furness to 37.7/10,000/year in Copeland. Figure 15 shows the county districts in which standardised hospital discharge rates for hip fracture were in the upper or lower tenths of the distribution. The four Thames regions for which discharge rates were not available are hatched. High discharge rates were found in certain districts in the North of England and South Wales. The most prominent feature, however, was the uniformly low discharge rate throughout most of East Anglia.

We explored the relationship between mortality and hospital discharge rates in the 299 county districts for which both sets of data were available. Figure 16 shows that there was a strong correlation ($r=0.80$, $p<0.01$) between the number of deaths recorded in each district and the number of cases discharged each year. No relationship was found, however, between the SMR for

Table 28

Age and sex distribution of individuals aged 45 years and over certified as dying from osteoporosis or hip fracture in England and Wales between 1974 and 1985

Age (years)	Number of	
	Men	Women
45-49	8	8
50-54	27	26
55-59	35	62
60-64	110	173
65-69	246	479
70-74	573	1358
75-79	1058	3211
80-84	1459	5382
85+	2135	10568
Total	5651	21367

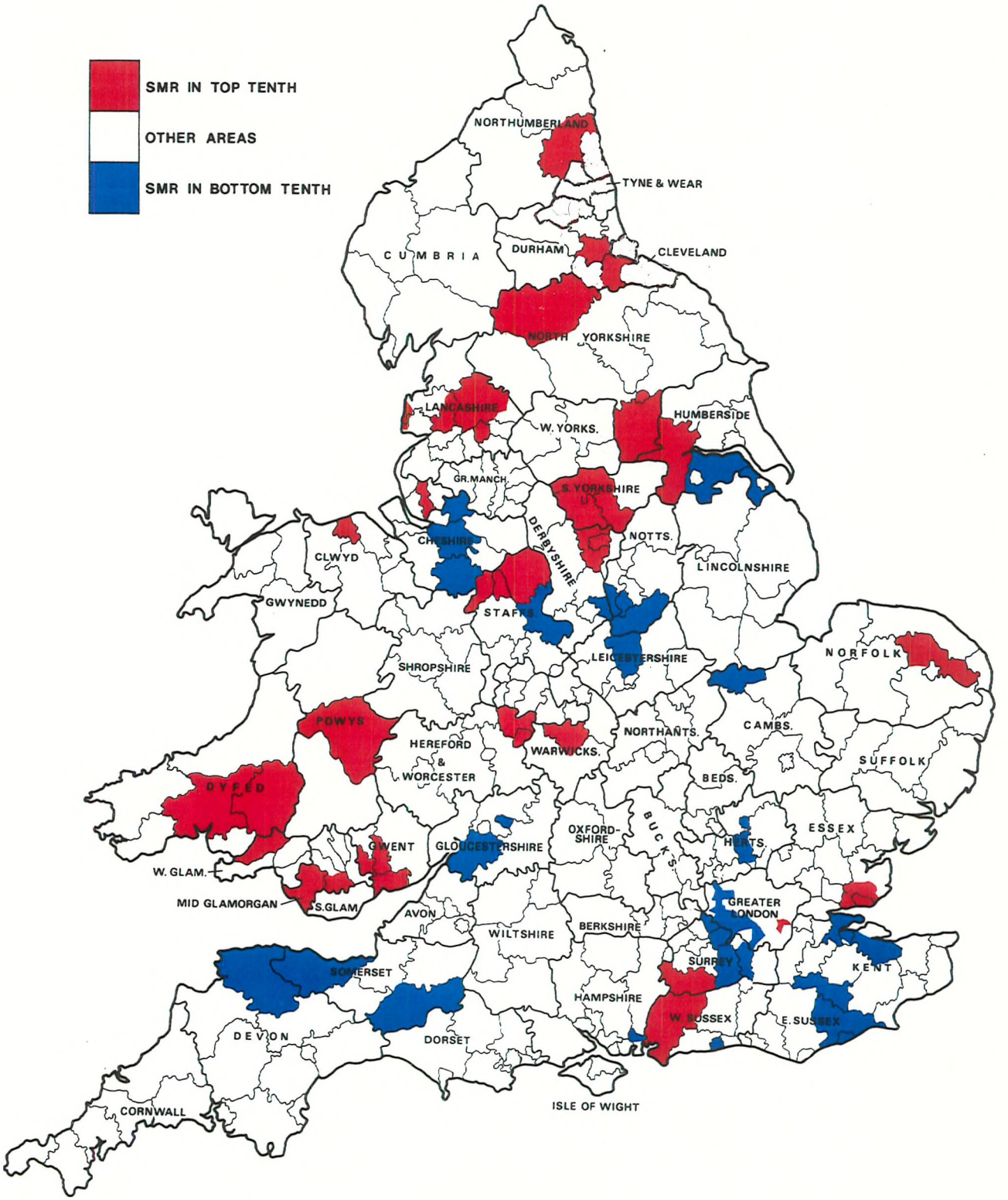
Table 29

Age and sex distribution of people aged 45 years and over discharged from hospital in 299 county districts of England and Wales with a diagnosis of hip fracture between 1978 and 1982

Age (years)	Number of	
	Men	Women
45-49	428	353
50-54	717	897
55-59	1078	1872
60-64	1359	2782
65-69	1961	5099
70-74	2626	8909
75-79	3202	13273
80-84	2930	16173
85+	3271	21223
Total	17572	70581

Figure 14

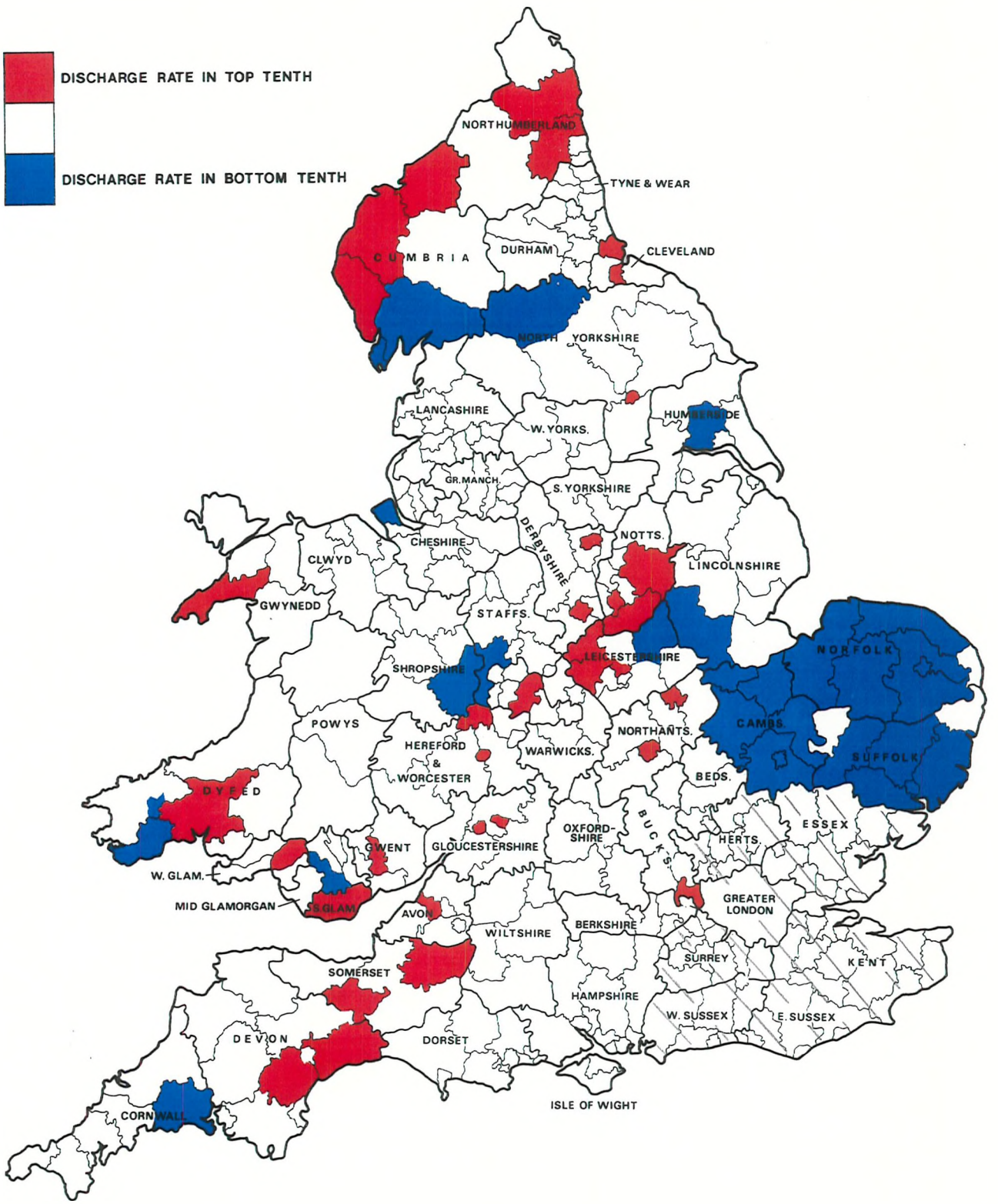
Mortality from osteoporosis and fracture of the proximal femur in England and Wales



MEN AND WOMEN AGED 45 YEARS AND OVER 1974-1985 (EXCLUDING 1979) BY COUNTY DISTRICT

Figure 15

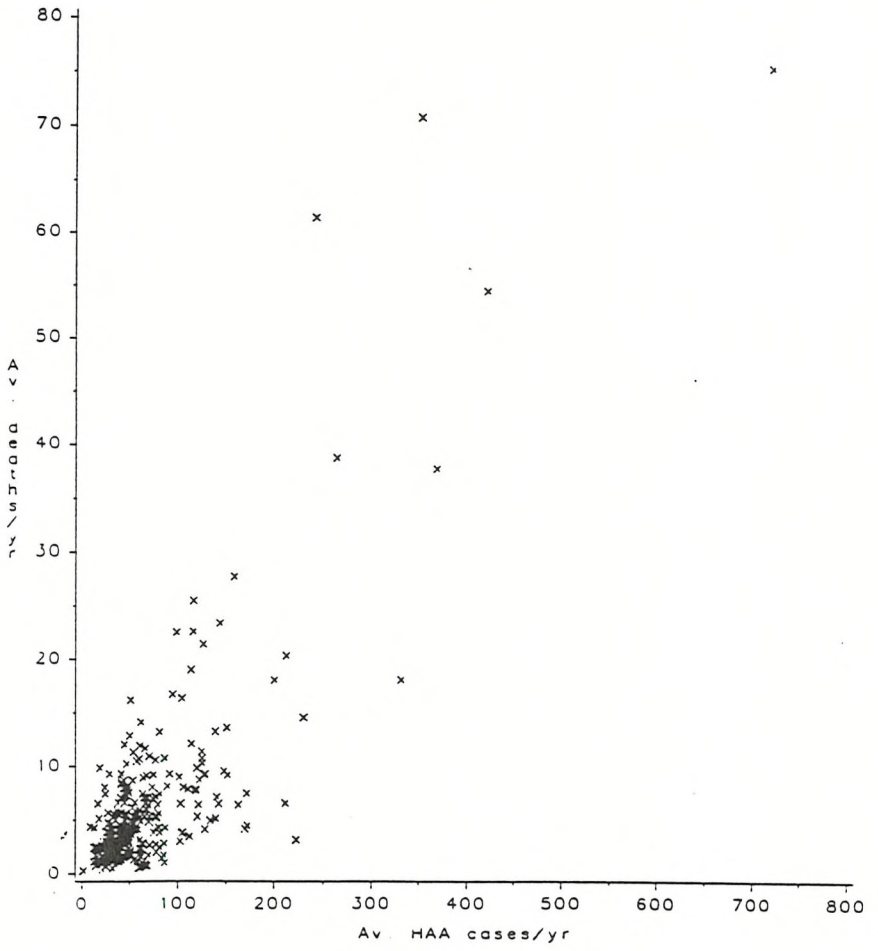
Hospital discharge rate for fracture of the proximal femur in England and Wales



MEN AND WOMEN AGED 45 YEARS AND OVER 1978-1982 BY COUNTY DISTRICT

Figure 16

Relation between average number of deaths and average number of patients discharged following hip fracture, in 299 county districts of England and Wales.



each of these districts and the standardised discharge rate (Figure 17).

To assess the validity of death certification from osteoporosis and hip fracture 1,311 death certificates were obtained of individuals who had been admitted following a hip fracture and died from the seven districts chosen to represent a wide range of SMR. Table 30 shows the proportion of these certificates in which hip fracture was mentioned as a cause of death in Parts Ia, b, c, or II. This varied widely, from none of 47 deaths in Harrow, to 166 (73 per cent) of 227 deaths in Nottingham. The diagnosis was rarely found in Part Ia, usually occurring in Part Ib or II. Osteoporosis was mentioned infrequently on these certificates (Table 31). There was also wide variation in the assignment of underlying cause of death between the seven districts (Table 32). The proportion of certificates in Newport in which the cause of death was coded to ICD 733 or 820 was 38 per cent as compared with none in Harrow. There was a statistically significant positive correlation ($r=0.94$, $p<0.01$) between the proportion of deaths coded to ICD 820 or 733 and the estimated SMR from hip fracture in each of the seven districts (Figure 18).

8.3 Discussion

This study shows that there is considerable geographic variation in the standardised mortality ratios for hip fracture among the county districts of England and Wales when these are calculated from routine mortality data. The pattern of distribution of mortality ratios, however, bears little relation to that of hospital discharge rates. More than 80 per cent of the variation in mortality between seven

Figure 17

Relation between standardised mortality ratios (SMR) for osteoporosis and hip fracture, and standardised hospital discharge rate (HAA-DSR) for hip fracture, in 299 county districts of England and Wales.

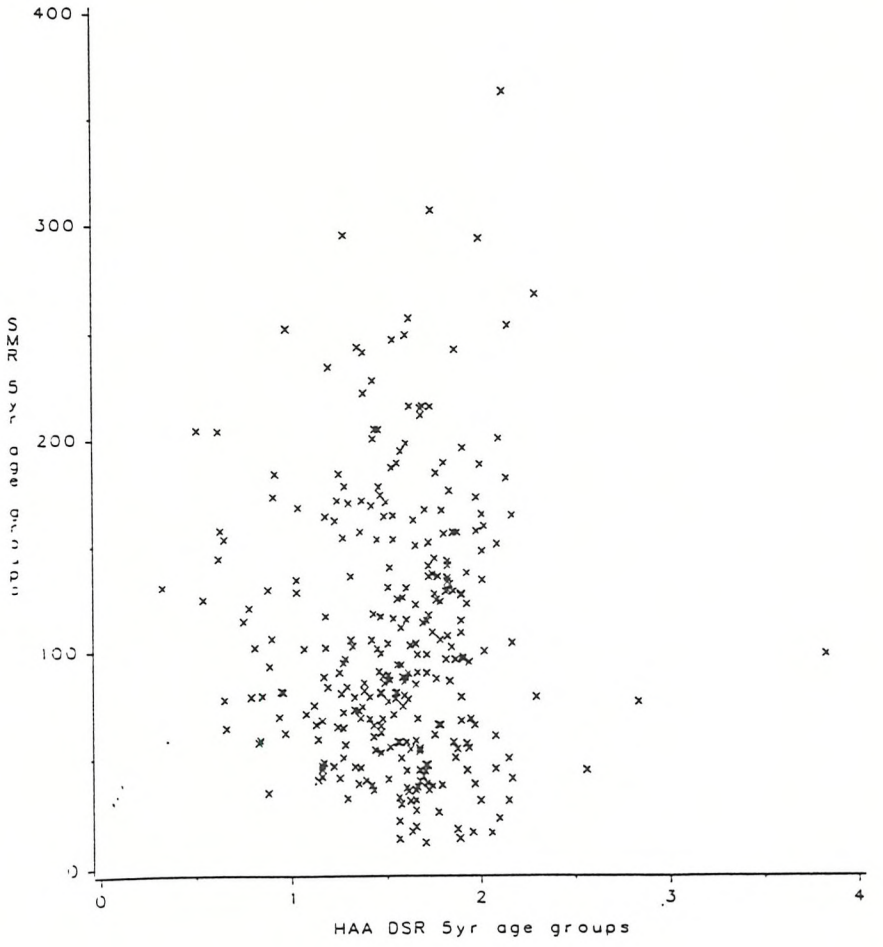


Table 30

Proportion of death certificates in which hip fracture was included as a cause of death

District	Total number of certificates	Number of certificates which list hip fracture in Part				Number of certificates listing hip fracture
		1a	1b	1c	II	
Newport	255	0 (-)	62 (24)	41 (16)	14 (6)	117 (46)
Stoke-on-Trent	366	4 (1)	170 (46)	31 (8)	52 (14)	257 (70)
Newcastle-upon-Tyne	71	1 (1)	1 (1)	7 (10)	10 (15)	19 (27)
Southampton	238	4 (2)	32 (13)	30 (13)	39 (16)	105 (44)
Fulham	107	1 (1)	6 (6)	5 (5)	2 (2)	14 (13)
Nottingham	227	1 (-)	0 (-)	2 (1)	163 (72)	166 (73)
Harrow	47	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)
Total	1311	11 (1)	271 (21)	116 (9)	280 (21)	678 (52)

Figures in parentheses are percentages of total number of certificates in each district

Table 31

Number of death certificates in which osteoporosis was included as a cause of death

District	Total number of certificates	Number of certificates which list osteoporosis in Part				Number of certificates listing hip fracture
		1a	1b	1c	II	
Newport	255	-	-	-	1	1
Stoke-on-Trent	366	-	1	17	12	30
Newcastle-upon-Tyne	71	-	-	-	-	-
Southampton	238	1	2	23	17	43
Fulham	107	-	-	-	-	-
Nottingham	227	-	-	-	-	-
Harrow	47	-	-	-	-	-
Total	1311	1	2	40	30	73

Table 32

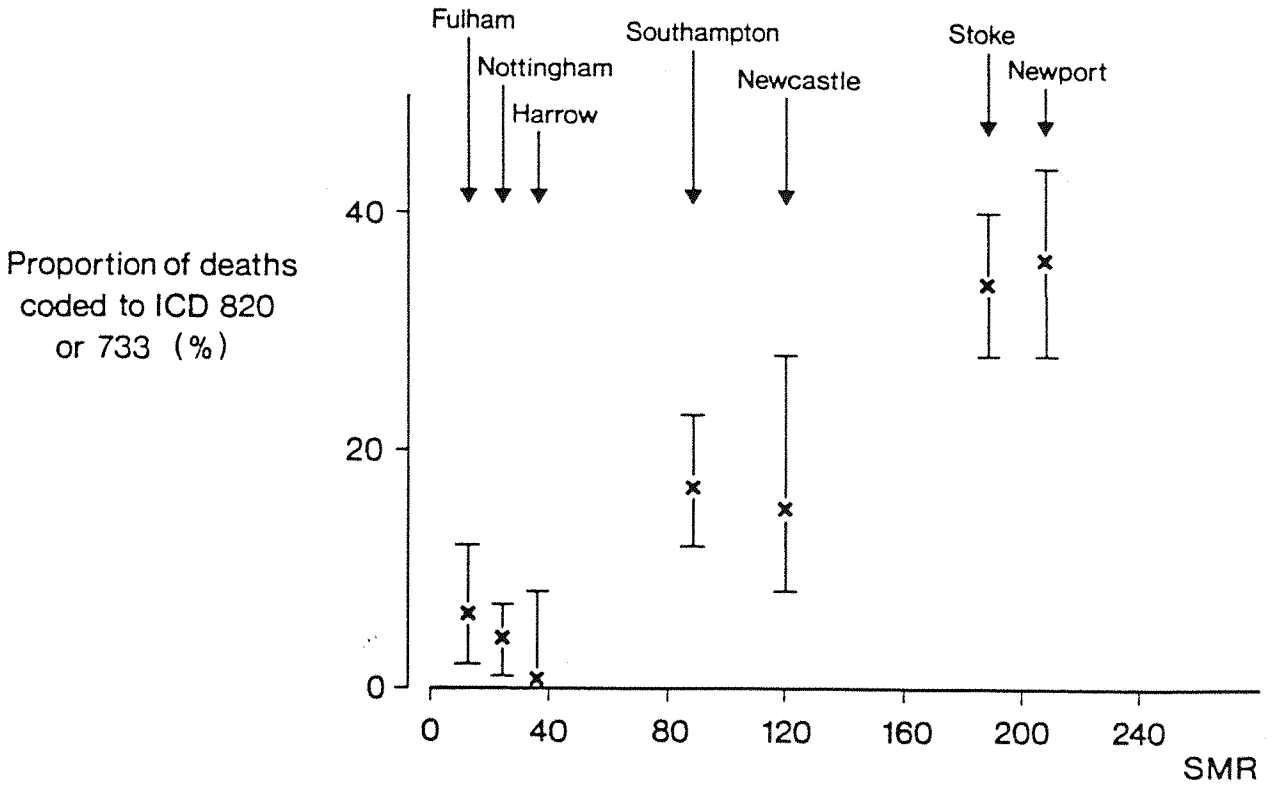
Proportion of death certificates in which the underlying cause of death was coded to ICD 820 or ICD 733

District	Total number of certificates	Underlying cause of death coded to ICD		
		820	733	820 or 733
Newport	255	91 (36)	0 (-)	91 (36)
Stoke-on-Trent	366	118 (32)	7 (4)	125 (34)
Newcastle-upon-Tyne	71	11 (15)	0 (-)	11 (15)
Southampton	238	11 (5)	27 (11)	38 (16)
Fulham	107	6 (6)	0 (-)	6 (6)
Nottingham	227	7 (4)	1 (-)	8 (4)
Harrow	47	0 (-)	0 (-)	0 (-)
Total	1311	237 (18)	35 (3)	272 (21)

Figures in parentheses are percentages of total number of certificates in each district

Figure 18

Relation between proportion of deaths coded to ICD 820 or 733 and estimated standardised mortality ratio (SMR) from hip fracture in seven health districts. Bars indicate 95% CI's for each proportion.



districts from which samples of death certificates were available could be explained by differences in the assignment and coding of causes of death. These observations suggest that routinely derived mortality statistics are unlikely to provide a useful indicator of the incidence of hip fracture within the districts of this country.

Deaths following hip fracture are regarded as accidental deaths and as such should be reported to the coroner who would normally require an autopsy and carry out an inquest. Coroners are known to vary in the extent to which they adhere to this practice[285]. In many elderly patients who die following hip fractures, the cause of death is regarded as natural, providing violence and negligence are excluded. By this means, an unnecessary inquest is avoided which might cause distress to relatives[285]. Our results suggest that reporting of death following hip fracture is also biased through the assignment of causes of death by hospital medical staff, who perhaps wish to avoid referrals to a coroner.

All coding of the underlying cause of death is carried out by coders in the OPCS who follow a set of guidelines[285]. Until 1984, any disease mentioned in Part II of a death certificate would have been ignored for the purposes of coding the underlying cause of death. It was noticed, however, that in a large number of certificates a terminal event such as bronchopneumonia appeared in Part I of the certificate as the only cause of death, while a major disease appeared in Part II as a contributory factor. Incorrect assignment of the underlying cause to terminal events was therefore occurring for an appreciable number of deaths. In 1984, the coding

rules were altered[286] so that certificates where the cause of death under Part Ia was bronchopneumonia, but had a major disease in Part II, were coded to this latter disease. As bronchopneumonia is a frequent terminal event in patients with hip fracture, the number of deaths attributed to hip fracture prior to 1984 may have been underestimated.

The validity of hospital discharge data as indicators of hip fracture incidence has been studied by others[34,35]. Sources of error include patients transferred from one hospital to another during treatment, diagnostic misclassification and the inclusion of duplicate admissions for late complications. A study in Newcastle-upon-Tyne[35] suggested that HAA based estimates of hip fracture incidence would miss seven per cent of cases allocated to multiple fracture codes but include nine per cent of incorrect codes or late complications. In this study, it was hoped to limit such errors by restricting entry to emergency admissions and patients who did not undergo a revision of arthroplasty. Caution must be exercised, however, in interpreting HAA data from smaller areas in which varying error rates may become more important[34].

The reason for the geographic distribution of hip fracture discharge rates in England and Wales which were found is not apparent. It might represent the current distribution of one or more risk factors, either for osteoporosis or for falling. Alternatively, it could reflect the pattern of historical risk factors which might have played a part in the attainment of peak skeletal mass in the earlier part of this century. Finally, it may result from some hitherto unforeseen bias in the recording of routine hospital discharge data.

In conclusion, these results suggest that national mortality statistics do not provide an effective means of studying the geographic variation in hip fracture incidence in England and Wales. The study of such variation might provide clues about environmental agents relevant to the aetiology of hip fracture. Hospital discharge data may be more useful for this purpose.

SECTION FIVE

CONCLUSION

CHAPTER NINE

AETIOLOGICAL AND PUBLIC HEALTH IMPLICATIONS

This thesis has examined three aspects of the epidemiology of hip fractures in the elderly. The conclusions reached from these studies, their implications for preventive strategies and future avenues of inquiry are outlined here.

9.1 The contribution of osteoporosis to hip fracture

The risk of hip fracture depends upon at least two factors: osteoporosis and the risk of falling. The independent contribution of each of these factors is unknown. Some studies have found that patients with hip fractures have lower bone mass than controls of similar age and sex. They conclude that osteoporosis is an important risk factor for fracture and that preventive strategies should be primarily directed at retarding age-related bone loss. Others, failing to find differences in bone mass, have suggested that falls are the important determinant of fracture. There are two problems in interpreting these studies. First, those which have not detected differences in bone mass between fracture cases and controls have measured bone at sites distant from the upper femur and it is recognised that changes in bone mass do not occur at the same rate throughout the skeleton. Second, no previous studies have allowed for falling in their study design.

Femoral neck bone mass was therefore measured in 708 elderly people, all of whom had fallen and injured a hip. Bone mass was measured using a radiographic grading system of the trabecular architecture in the upper femur, the Singh index, which had been validated against a gold standard: the ash weight to volume ratio in a series of excised femoral heads. Although the method was prone to considerable between and within

observer variation, such variation was random rather than systematic and did not preclude its use in epidemiological studies. Below around 75 years of age, there was a steep increase in the relative risk of fracture with reduced bone mass. Above that age, the increase in risk was small and some other factor, independent of bone mass but related to age, became more important. There are biomechanical grounds for believing that an important candidate for this factor is the progressive impairment of neuromuscular responses which protect the skeleton against trauma. Public health measures to reduce the incidence of hip fractures should not, therefore, be confined to measures which retard the loss of bone with ageing, but should also be directed at maintaining neuromuscular function.

9.2 Calcium intake, physical activity and the risk of hip fracture

A high calcium intake and regular exercise have been widely proposed as immediate population-based strategies to combat osteoporosis. There is, however, little evidence to associate these measures with the risk of hip fracture and hence no rational basis for including them as part of a national preventive campaign aimed at reducing the incidence of these fractures. The roles of reduced calcium intake and physical inactivity as risk factors for hip fracture were therefore examined in a case-control study.

Valid methods were obtained for the assessment of the two variables. For calcium intake, a questionniare was devised which was validated against two gold standards for calcium estimation: duplicate diets and seven day weighed inventories. For current physical

activity, the method adopted was developed at the Department of Physiology at Nottingham University. Information was obtained on various indices of customary activity and detailed information on walking had been validated against pedometry. Past physical activity was assessed using a questionnaire developed in the Department of Community Medicine at Oxford University which obtained information about occupational and leisure activity at the age of 50 years. A limited validation of this questionnaire was attempted in 17 elderly men.

Having obtained these methods calcium intake, physical activity and other factors were compared in 300 elderly people admitted with hip fractures and 600 age and sex matched community controls randomly selected from the Family Practitioner Committee register of the same health district. There was a statistically significant increase in the risk of fracture with reducing levels of current physical activity. Individuals who did not walk out of doors on a typical day, did not perform muscle-loading activities and did no gardening or housework, were all approximately twice as likely to fracture as individuals who typically spent an hour each day walking out of doors, performed muscle loading activities more than once a day and spent five or more hours each week doing gardening or housework. Reduced grip strength was also associated with higher risk of fracture. These increases in the risk of fracture with declining activity and grip strength remained statistically significant after allowing for potential confounding variables such as body mass index, cigarette smoking and alcohol consumption. Physical

activity at the age of 50 years was also associated with fracture risk. This resulted from an increased risk of fracture in people who had sedentary occupations at that time of their lives, when compared with those who spent more than 70 per cent of their time at work on their feet. Leisure time activity at age 50 years had little effect on the risk of fracture. These findings support the importance of maintaining exercise and muscle strength in the elderly population.

In women, dietary calcium intake did not influence the risk of hip fracture. In men, daily intake above one gram was associated with lower risk. This increased risk remained when allowance was made for body mass, smoking and alcohol consumption. Although further evidence is required, these results are compatible with a protective effect of very high calcium intakes in men.

Several other statistically independent risk factors were identified. These included reduced body mass index, a previous history of hip fracture, heavy alcohol consumption, tall stature, mental impairment, dependence in daily living activities, cigarette smoking, high social class at birth and the use of corticosteroids. Many of these factors have been previously reported.

Indices of calcium metabolism were assessed in 41 women with hip fractures and two elderly control groups. The women with hip fractures had lower serum concentrations of albumin, 25 hydroxyvitamin D and osteocalcin than the controls. Serum concentrations of calcium, alkaline phosphatase and parathyroid hormone, as well as urinary hydroxyproline/creatinine ratios were similar in the three groups of women. Reduced concentrations of albumin and 25 hydroxyvitamin D have

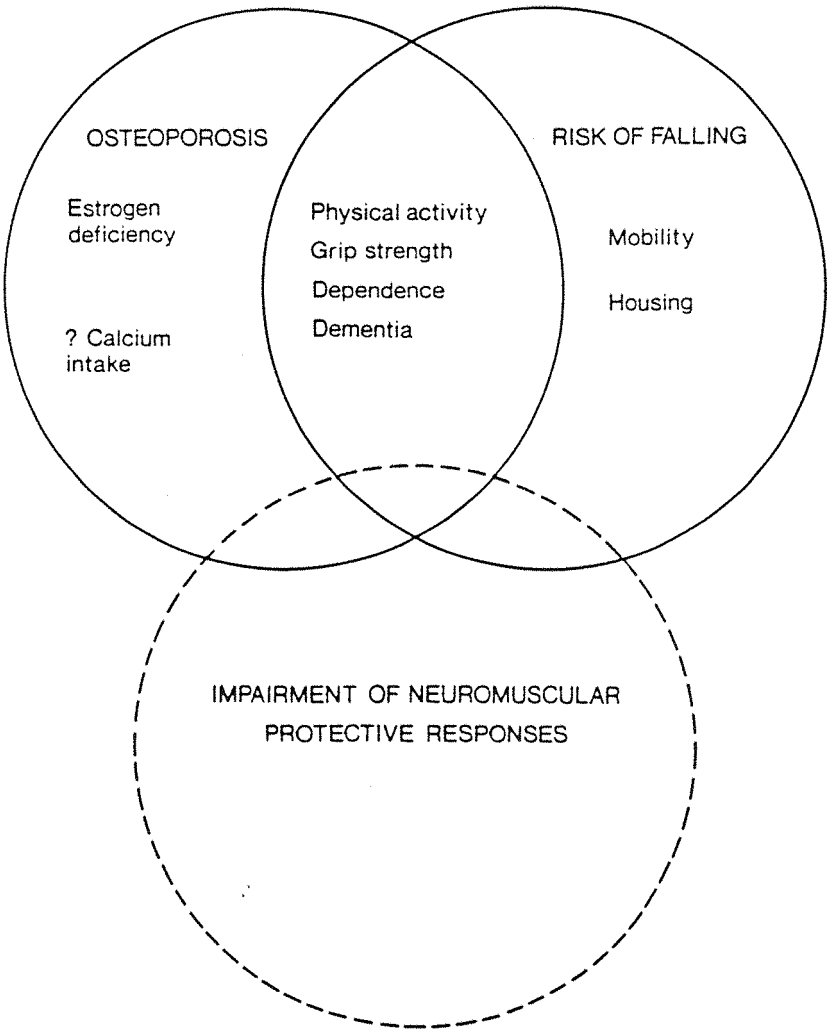
been previously reported in women with hip fractures. They are open to various interpretations. Vitamin D deficiency might be important in the pathogenesis of hip fracture in the elderly. Alternatively, the differences could be a consequence of the generally poor physical state of these patients. Finally, they may be explained by the trauma and immobilisation which accompany such fractures. The small reduction in serum osteocalcin concentration in the fracture patients is consistent with the hypothesis that reduced osteoblast function, rather than secondary hyperparathyroidism, is the major mechanism contributing to the osteoporosis which results in hip fracture.

9.3 Aetiological implications

The results of these studies enable the construction of a working model for the aetiology of hip fracture in the elderly (Figure 21). Fracture risk depends ultimately on bone strength and the magnitude of the force applied to the bone. Bone mass is an important determinant of bone strength but other qualitative aspects of bone structure may also contribute to its mechanical properties. The ability of a crude grading system of the femoral neck trabecular architecture to discriminate between hip fracture cases and non-fracture controls more effectively than sensitive indices of bone mineral content suggests that the Singh grade may be measuring an aspect of bone structure which is more closely related to strength than is purely its mineral content. The forces applied to the upper femur depend not only on the risk and severity of falling but also on the effectiveness of endogenous neuromuscular responses which protect the skeleton against trauma.

Figure 19

The aetiology of hip fracture.



Individual risk factors for hip fracture may influence any, or all, of bone mass, the risk of falling and neuromuscular protective responses. Oestrogen deficiency, low body weight, cigarette smoking and alcohol consumption are known to influence bone mass. Much less is known about risk factors for falls in the elderly. In 1973-74, the Department of Health and Social Security carried out a detailed survey of the health status of approximately 1,000 elderly people randomly selected from eight places in Britain. As part of the information recorded on each subject, a history of falling was obtained. Comparison of the people in the survey who reported ever having had a fall with those who did not, revealed a number of statistically significant factors which increased the risk of falling[266]. These included immobility, reduced grip strength, general ill health, social isolation, poor housing and use of non-phenothiazine tranquillisers. Other studies have suggested that dementia and dependence in daily living activities are also associated with the risk of falling[173]. Physical inactivity and muscle weakness might influence any or all of osteoporosis, the risk of falling and the impairment of neuromuscular protective responses.

9.4 Preventive strategies

Preventive strategies for hip fracture may be targeted at different periods of life: the elderly, the postmenopausal period in women and youth.

THE ELDERLY: The results of these studies suggest an association between physical inactivity, muscle weakness and fracture risk in the elderly. There are two reasons for caution, however, in extending them to

a conclusive recommendation of exercise in the elderly. First, the cross-sectional study design and the comparison of hospitalised cases and community controls may have led to bias. Second, the lower activity levels of many elderly people might be the result of illness or disability, and therefore not amenable to improvement by exercise regimes. There is some support for this view in the results, as many of the inactive cases were also dependent in daily living activites. Nevertheless, even when these individuals were excluded a rising gradient of risk was found with declining activity level. Although inconclusive, therefore, it would seem prudent to encourage moderate day to day exercise in our elderly population. Other preventive approaches in the elderly would be directed at reducing the risk of falls, for example by encouraging more rational prescribing of medication and improving accommodation. Recommendation of a high dietary calcium intake in this age group appears unlikely to have a dramatic influence on the risk of hip fracture.

POSTMENOPAUSAL WOMEN: Measures which reduce bone loss are more appropriate to the postmenopausal decade during which women lose bone at an accelerated rate. The two prophylactic measures to be considered in this period are hormone replacement therapy and a high calcium intake. Hormone replacement therapy has been convincingly shown to retard bone loss in women after the menopause[259]. The adverse effects of hormone replacement, however, make it unlikely to be adopted as a population-based measure for the foreseeable future. The evidence in favour of widespread calcium supplementation is also unclear and more rigorous trials in postmenopausal women are required.

Modification of other lifestyle characteristics such as cigarette smoking and alcohol consumption would appear to be supported by this study which detected statistically significant increases in hip fracture risk attributable to each of these. The mechanism through which their effect is mediated remains a subject for further study. Cigarette smoking might act through an association with low body weight, early menopause, inactivity or poor diet[42]. Heavy alcohol consumption might influence both bone mass and the risk of falling.

YOUTH: The third period at which preventive strategies might be targeted comprises the phase of skeletal growth from birth to the third decade of life. Little is known of the genetic, mechanical, nutritional and hormonal factors which together determine peak adult bone mass. As more information on these factors becomes available, improving the peak bone mass of the entire population might become an integral part of any population-based strategy to reduce hip fracture incidence. An interesting finding of the case-control study was that the fracture cases reported greater height than controls and were of higher social class at birth. Both variables were independently associated with the risk of fracture. One interpretation of this association is that the two factors are merely markers of people who are physically inactive in middle and later life. Alternatively, it might indicate an increased later liability to fracture among people whose childhood and adolescence is prosperous. As childhood environment is known to influence the long term development of certain metabolic and endocrine pathways, it is tempting to speculate that children

attaining greater skeletal size might be at increased risk of a critical reduction in bone mass later in life on encountering adverse environmental circumstances.

9.5 Future research

Avenues for further research are apparent for each of these three periods of life.

THE ELDERLY: In the elderly population, the relationship between physical inactivity and the risk of hip fracture requires confirmation. Similar case-control studies to the one carried out in Southampton are currently in progress in Newcastle upon Tyne and in Hong Kong. Newcastle upon Tyne was chosen as areas of the North East of England were found to have high hospital discharge rates for hip fracture. Hong Kong provides an opportunity to study the condition in a unique epidemiological setting. The Chinese population is characterised by a diet low in calcium and a changing pattern of activity with recent urbanisation.

In the 1973-74 Department of Health and Social Security survey, mobility level and grip strengh were assessed in most of the subjects. Approximately 200 of these people will have sustained hip fractures over the ensuing 15 years. This cohort provides an opportunity to examine the effects of inactivity and muscle weakness on fracture risk longitudinally.

Further evaluation of the roles of activity and muscle strength could then be sought in an intervention study: a randomised controlled trial of exercise in the elderly using as end-points hip fracture, bone mass and fall frequency.

Another area requiring investigation in the elderly population is that of neuromuscular protective

mechanisms[287]. Methods are now available for assessing postural sway, ataxia, gait abnormalities, reflex time and visual depth perception. None of these have been adopted in studies of hip fracture. Futhermore, little is known about the influence of regular exercise on these indices of neuromuscular function in the elderly.

POSTMENOPAUSAL WOMEN: Further research in middle life would appear to be best directed at peri- and postmenopausal women. A clearer understanding is required of the patterns of bone loss in individual women studied longitudinally. If a group of rapid bone losers can be convincingly identified, the adoption of a high risk strategy would be prudent. Such a strategy would aim to select those women at risk of rapid bone loss for subsequent intervention with hormone replacement therapy. Potential methods for such selection include historical risk factor profiles, non-invasive measurements of bone mass and biochemical indices of bone turnover.

YOUTH: Finally, studies are required of the factors which determine the attainment and conservation of peak bone mass. Investigation of geographic variation in hip fracture incidence throughout Britain provides a useful epidemiological tool with which to study the relationship between childhood conditions and the later risk of fracture. Such a model has shed light on the aetiology of ischaemic heart disease[288] and chronic bronchitis[289]. The relationship between childhood nutrition and subsequent hip fracture might be reflected in correlations between the incidence of hip fracture in the county districts of England and Wales today, and the distribution of indices of childhood

poverty such as infant mortality, earlier in this century. The uniformly low hospital discharge rate from hip fracture in East Anglia warrants further investigation. It might be explained on the basis of some current environmental factor such as water fluoride concentration, or a historical factor such as childhood environment earlier in this century.

9.6 Conclusions

The main findings of these studies into the epidemiology of hip fractures are:

1. Osteoporosis contributes to the risk of hip fracture in the elderly independently of the risk of falling.

2. Other age-related factors contribute to fracture risk. These become particularly important over the age of around 75 years. The impairment of neuromuscular protective responses to trauma may be one such factor.

3. Physical inactivity and muscle weakness are risk factors for hip fracture in the elderly.

4. In women in southern Britain, dietary calcium intake does not influence fracture risk. In men, intakes above one gram daily may be protective.

5. Elderly women with hip fractures have lower serum concentrations of albumin, 25 hydroxyvitamin D and osteocalcin than elderly non-fracture controls. The low osteocalcin concentration is consistent with a low bone turnover state in these women.

6. Routinely derived mortality statistics are not a useful indicator of hip fracture incidence in the county districts of England and Wales.

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Appendices

1. Questionnaire for assessment of calcium intake.

2. Questionnaire for assessment of current physical activity.

3. Questionnaire for assessment of past physical activity.

4. Information obtained on hip fracture patients scoring less than six points on a ten point abbreviated mental test score.

5. Questionnaire used in case-control study.

6. Detailed results of case-control study.

7. List of publications included in this thesis.

Appendix 1a

Questionnaire for assessment of current calcium intake

Think about your usual eating habits over the last year.

1. How much milk do you usually use in an average day? (Probe: Do you have milk delivered? Think about milk used in tea and coffee, on breakfast cereals or puddings, and in cooking.) Give your answer to the nearest ½ pint.

   ___ ___ pt. ½pt.

2. Next, I would like to ask you about a number of different foods. Please tell me whether or not you eat the food, how often you have it if you do eat it, and how much you have on the days when you eat the food. (Ring the correct answers and fill in amounts.)

	Not eaten	1/3-4wks	1/1-2wks	1-2d/wk	3-5d/wk	6-7d/wk	Amount per day	Milk?
Tea	1	2	3	4	5	6	___cups ___mugs	1 None 2 Liquid* 3 Tinned milk 4 Powdered milk ___g+
Coffee	1	2	3	4	5	6	___cups ___mugs	1 None 2 Liquid*, ½ or less 3 " ; ½ 4 " , ½ 5 " , all 6 Tinned 7 Powdered milk ___g+ 8 Coffeemate
Other milky drinks (Horlicks, Bournvita, Ovaltine, Hot chocolate, Cocoa, Complan, Build-up, etc.)	1	2	3	4	5	6	___cups ___mugs	1 None 2 Liquid*, ½ or less 3 " , ½ 4 " , ½ 5 " , all 6 Tinned 7 Powdered milk ___g+ 1 Horlicks, other milk-powder based drinks 2 Ovaltine, cocoa, other drinks not milk-powder based 3 Complan etc

* Liquid milk: Whole, semi-skim, skim, UHT, sterilized, powdered made-up. + Level tsp=2g; rounded=3g; heaped=4g=¼ cup liquid.

	Not eaten	1/3-4wks	1/1-2wks	1-2d/wk	3-5d/wk	6-7d/wk	Amount per day	
Milk alone	1	2	3	4	5	6	___small glasses ___large glasses ___cups ___mugs	Milk?
Breakfast cereal (Probe for porridge made with milk)	1	2	3	4	5	6	___ number of portions	1 None 2 small 3 medium 4 large
Bread, toast, and rolls	1	2	3	4	5	6	___ slices	1 White 2 Brown 3 Wholewheat 1 Sliced 2 Unsliced 3 Rolls 1 small 2 large
Cheese	1	2	3	4	5	6	___ number of portions	1 small 2 medium 3 large
Cakes, scones, and biscuits	1	2	3	4	5	6	___ number of portions	sm med lg p:$\frac{1}{10}$'s Cakes + scones 1 2 3 ___ Biscuits 1 2 3 ___
Desserts made with milk (Probe for custard or ice-cream on other desserts)	1	2	3	4	5	6	___ number of portions	sm med lg p:$\frac{1}{10}$'s Custard, blancmange, milk puddings, yog. 1 2 3 ___ Jelly made with milk, angel delight, mousses 1 2 3 ___ Ice cream 1 2 3 ___

Appendix 1b

Guide to calculating calcium intakes per day

Basic formula: Calcium intake (mg/day) = $\frac{\sum(FxNxCaxp)}{7}$

summed over all food groups,
where F = frequency
N = number of portions
Ca = calcium content of portion
p = proportion of food in category (cakes, biscuits and desserts only)

If frequency code is	1	2	3	4	5	6
then F =	0	0.3	0.75	1.5	4.0	6.5

	milk code	Ca/cup	Ca/mug
Tea	1	0	0
	2	42	51
	3	42	51
	4	12 mg/g	12 mg/g
Coffee	1	0	0
	2	49	58
	3	108	147
	4	162	220
	5	216	294
	6	49	58
	7	12 mg/g	12 mg/g
	8	1	1
Other milky drinks	1	0	0
	2	49	58
	3	108	147
	4	162	220
	5	216	294
	6	49	58
	7	12 mg/g	12 mg/g

	Measure	Ca
Milk alone	small glass	192
	large glass	348
	cup	216
	mug	294

	Milk code	
Breakfast cereal	1	0
	2	72
	3	144
	4	216

Bread	type	slice/roll	size	Ca
	1	1	1	24
	1	2	1	20
	1	1	2	33
	1	2	2	37
	1	3	-	65
	2	1	1	25
	2	2	1	22
	2	1	2	38
	2	2	2	44
	2	3	-	65
	3	1	1	6
	3	2	1	5
	3	1	2	9
	3	2	2	10
	3	3	-	15

Cheese	size	Ca
	1	160
	2	320
	3	480

Cakes etc. (95% cake + 5% scones and rock cakes yields 100mg Ca/100g food)		Cakes + scones	Biscuits (av. 106mg Ca/100g)
	1	28	16
	2	55	32
	3	83	53

Desserts made with milk		Custard	Jelly etc.	Ice cream
	1	81	44	60
	2	162	88	90
	3	243	132	120

Portion sizes in Calcium questionnaire photographs

Tea, coffee, milky drinks	cup	175 ml
	mug	270 ml

Milk alone	small glass	160
	large glass	290
	cup	175
	mug	270

Breakfast cereal	small	medium	large
cornflakes	14	28	42
weetabix	19	38	57
milk on cereal	70	120	180
porridge	125	200	275

Bread	small	large
white	24	30
wholewheat	28	34

Cheese	small	medium	large
all pictures	20	40	60

Cakes			
sponge	25	50	75
fruit	30	60	90
scones	32	64	96
Biscuits			
sweet	12(1)	25(2)	48(4)
digestive	18(1)	35(2)	52(3)
Desserts			
rice pudding	60	120	180
custard	60	120	180
ice cream (block and scoop)	50	75	100

Appendix 2a

Questionnaire for assessment of current physical activity

1. Which of the following best describes your walking speed?

   a) Very slowly ___
   b) Stroll at an easy pace ___
   c) Normal speed ___
   d) Fairly briskly ___
   e) Fast ___

2. Walking: choose a sample day within the last week; record all walking lasting more than three minutes.

   a) Did you go out before 9 am?

   Level _____ mins
   Uphill _____ mins
   Downhill _____ mins

   b) Did you go out between 9 am and 12 noon?

   Level _____ mins
   Uphill _____ mins
   Downhill _____ mins

   c) Between 12 noon and 2 pm?

   Level _____ mins
   Uphill _____ mins
   Downhill _____ mins

   d) Between 2 pm and 6 pm?

   Level _____ mins
   Uphill _____ mins
   Downhill _____ mins

   e) Between 6 pm and 7 am?

   Level _____ mins
   Uphill _____ mins
   Downhill _____ mins

   TOTAL WALKING TIME

   Level _____ mins
   Uphill _____ mins
   Downhill _____ mins

3. Standing: on that typical day

7am - 9am	_____	mins
9am - 12pm	_____	mins
12pm - 2pm	_____	mins
2pm - 6pm	_____	mins
6pm - 7am	_____	mins
TOTAL STANDING TIME	_____	mins

4. Outdoor productive activity.

	Allocation of units
a) Heavy (digging, shovelling, mowing lawn, hedge cutting, carpentry).	
< 1 hr per week	0
1-4 hrs per week	2
> 4 hrs per week	4
b) Light (raking, triming, weeding, washing car, light decoration).	
< 1 hr per week	0
1-4 hrs per week	2
> 4 hrs per week	4

5. Indoor productive activity.

a) Heavy (polishing furniture, brass, scrubbing floors, hoovering).	
< 1 hr per week	0
1-4 hrs per week	2
> 4 hrs per week	4
b) Light (dusting, wiping, ironing).	
< 1 hr per week	0
1-4 hrs per week	2
> 4 hrs per week	4

6. Leisure activities.

Bowls	YES/NO	_____	mins/wk	
Cycling	YES/NO	_____	mins/wk	1 unit per
Swimming	YES/NO	_____	mins/wk	hour of
Golf	YES/NO	_____	mins/wk	activity
Fishing	YES/NO	_____	mins/wk	
Dancing	YES/NO	_____	mins/wk	

7. Muscle loading activities.

	Allocation of units
a) Do you climb stairs?	
Never	0
Occasionally	1
Once-several times a week	2
Daily	3
Several times a day	4
b) Do you carry loads?	
Never	0
Occasionally	1
Once-several times a week	2
Daily	3
Several times a day	4

Appendix 2b

Calculation of current physical activity from questionnaire

Five aspects of current physical activity were used in the subsequent analysis. They were derived as follows:

1. Walking speed: five levels as recorded.

2. Walking time: summated number of minutes on the sample day. Subsequent breakdown was by quarter hours per day spent walking.

3. Standing time: summated number of minutes on the sample day. Subsequent breakdown was into four levels - none, 1-30 minutes, 31-60 minutes, greater than 60 minutes.

4. Productive and leisure activities: a number of units were assigned to each activity level, such that each unit corresponded approximately to one hour per week spent in that category of activity. These units were summated and added to the number of hours per week spent in leisure activities. This yielded a productive activity score for the number of hours spent weekly in productive and leisure activities.

5. Muscle loading activities: each frequency level for climbing stairs and carrying loads was allocated a score in units. The summated score was then analysed in four levels of increasing participation in muscle loading activity.

0 units = never

1-2 units = less than once a week

3-4 units = more than once a week to daily

>4 units = several times a day

Appendix 3a

Questionnaire for assessment of past physical activity
A = occupational, B = leisure time

A. At the age of 50 years what was your occupation?

_____

Describe the job.

_____

_____

Score

Occupational activity intensity grading.

B. a) Did you have a dog? YES/NO
Did you walk it or did someone else usually do it? YES/NO
Someone else/respondent 0-2

b) Did you have a car? YES/NO
If YES, did you drive it yourself? YES/NO 0-2

c) Did you use a bicycle? YES/NO 0-1

d) How did you get to the shops? (Walk/bicycle/bus/car/other) .....

If walk/bicycle,
- how far away were the shops? ...miles

If bus,
- how far did you need to walk to and from the bus stop? ...miles 0-4

e) Did you do the gardening? YES/NO
Did you mow the lawn? YES/NO 0-2

f) Did you work at that time in your life? YES/NO
If YES, how did you get to work? (Walk/bicycle/bus/train/other) .....

If walk/bicycle, how far was it?

<½ mile
½-2 miles
>2 miles

If bus/train, how much walking did you have to do each journey?

<½ mile
½-2 miles
>2 miles 0-4

g) Did you ever go swimming? YES/NO
How often did you swim when you were 50?
Never/yearly/monthly/weekly 0-3

h) Did you ever walk for leisure? YES/NO

If YES, how often
less than once a month
more than once a month 0-4

i) Did you ever go dancing YES/NO 0-1

j) Did you ever play sport? YES/NO 0-2

If YES, what sports? .....

1. Sport .....

How many times per month? .....

How many months per year? .....

2. Sport .....

How many times per month? .....

How many months per year? .....

Total = 25

Appendix 3b Assignment of occupational physical activity in case-control study

Largely sedentary (0-3 units)	Intermediate (4-6 units)	Largely standing (7-10 units)
Accountant	Army officer	Animal sanctuary assistant
Alteration hand in fashion shop	Book binder	Assistant warden
Ambulance driver	Braider	Auxiliary nurse
Architect	Cake packer	Badminton instructor
Bank clerk	Children's nanny	Bakery assistant
Bank manager	Detective	Barmaid
Bank official	Fireman	Beer bottler
Banker	Fire chief	Boiler maker
Book keeper	Floral arranger	Builder
Bookshop manager	Florist	Builder's mate
Booking clerk	Flower seller	Bus inspector
Bus driver	Housekeeper	Butcher
Calculator operator	Housewife	Cafe proprietor
Cartographer	Machinist	Canteen attendant
Cashier	Manageress	Care attendant
Cashier (transport)	Manager	Carpenter
Catalogue writer	Matron (school)	Carpet weaving factory worker
Civil servant	Missionary	Caterer
Clerk	Nanny	Catering manageress
Company director	Nursing orderly	Catering supervisor
Council telecommunication manager	Packer	Cleaner
Department store manager	Pharmacy dispenser	Cleaning lady
Doctor	Police sergent	Club stewardess
Dressmaker	Post mistress	Convent labourer
Driver	Power machinist	Cook
Fashion buyer	Private nurse	Cook in restaurant
Fashion editor	Process technician	Dancer
Financial consultant	Security officer	Dock worker
Firm manager	Showroom attendant	Docker
Head mistress	Stately home maintenance officer	Dockyard contractor
Hospital receptionist	Storeman	Dockyard smith
Long distance lorry driver	Supermarket manager	Domestic
Lorry driver	Supervisor (transport)	Domestic service
Mining engineer	Teacher	Draper
Music teacher	Tobacco factory worker	Draper's assistant
Naval architect	Trappist brother	Electrician
Old lady's companion	Undertaker	Engineer
Pilot	Watchman	Factory labourer
Power station manager		Factory work on line
Property salesman		Farm hand
Receptionist		Farm labourer
Sales director		Farmer
Secretary		Fishmonger
Shipping office clerk		Fitter
Shorthand typist		Fitter (custom's launches)
Sorting office clerk		Foundryman
Stockbroker		Garage hand
Surveyor		Garage supervisor
Ticket clerk		Gas fitter
Transport records clerk		Greengrocer
Typist		Grocer
University lecturer		Groundsman
Works engineer		Hairdresser
Works manager		Insurance collector
		Labourer
		Laundry worker
		Mariner
		Mason
		Matron (old people's home)
		Mechanic
		Merchant seaman
		Mother's help
		Nurse
		Nursing sister
		Painter
		Paintshop worker
		Parlor maid
		Pipe fitter
		Plumber
		Postman (delivery)
		Press operator at Ford's
		Publican
		Railway engineer
		Railway man
		Rigger
		Sales assistant
		Salesman
		School dinner lady
		Stewardess at sea
		Seaman
		Seaman rigger
		Sheet metal worker
		Ships engineer
		Ship salvager
		Ships cook
		Shop assistant
		Shopkeeper
		Show woman at circus
		Stevedore
		Toolmaker
		Tram conductress
		Upholsterer
		Waitress

Appendix 4

Information obtained on hip fracture patients scoring less than six points on a ten point mental test score

CASES WHO FAIL MTS

Name: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ Age: _ _ _ _ _ Sex : M/F

Date of admission: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Address: _

Fall: Indoors/outdoors

Standing/sitting/lying/height/RTA/other

Time of fall: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Type of fracture: Intracapsular Side of fracture: R/L

Extracapsular

Past medical history: _

_ _

_ _

Drug history: _

_ _

_ _

_ _

Accommodation: Own home/W.C. flat/rest home/nursing home/ hospital

MTS (0-10: _ _ _ _ _ _ _ _ _ _ _

Appendix 5

Questionnaire used in case-control study

NO. _____

STRICTLY PRIVATE AND CONFIDENTIAL

From notes

1. Date of admission
2. Sex M/F
3. Date of birth
4. Address
   (area code)
5. Hospital number
6. X-ray number
7. G.P.
8. Next of kin
   Address

9. Which leg R/L
10. Type of fracture (from x-ray)
    - intracapsular
    - extracapsular

Questionnaire

1. Name
2. Age
3. Address

4. What is your height? .... ft .... ins
5. How much do you weigh? .... st .... lbs
6. What is the most you've ever weighed?

   .... st .... lbs

   How old were you at the time?

Nature of fracture

7. Did it happen — Indoors / Outdoors

8. When you broke the bone did you -
   a) fall from standing/sitting/lying?
   b) fall from a height?
   c) RTA?
   d) other (state) ...?

9. What time of day did it occur?
   (nearest hour) ...

10. Do you remember the accident?
    If yes, was the fall caused by -
    a) blackout?
    b) loss of balance?
    c) other (state) ...?

11. What other injuries did the fall cause?
    a) bruising
    b) severe soft tissue injury
    c) fracture elsewhere

Previous medical history

12. Have you ever broken your hip before? YES/NO
    If yes,
    a) which side? R/L
    b) how old were you when it happened? .... yrs

13. Have you ever broken your wrist? YES/NO
    If yes,
    how old were you? .... yrs

14. Have you ever had?
    a) arthritis YES/NO
    b) diabetes YES/NO
    c) a stroke YES/NO

    If yes,
    i) how old were you? .... yrs
    ii) immediatley after it, did it stop you walking without help from someone else? YES/NO
    d) an overactive thyroid YES/NO

Drug history

15. Are you on any of the following drugs?

a) diuretics (water tablets) YES/NO/DK
If yes, how long for ....

b) thyroid hormone YES/NO/DK
If yes, how long for ....

c) steroids YES/NO/DK
If yes, how long for ....

d) sleeping tablets YES/NO/DK
If yes, how long for ....
What is it called ....

e) drugs on drug chart
i)
ii)
iii)
iv)

Family history

16. Has anyone in your family (first degree relatives only) broken their:

a) Hip? YES/NO/DK
If yes, what relation are they to you?
how old were they at the time? _____ yrs

b) Wrist? YES/NO/DK
If yes, what relation are they to you?
how old were they at the time? _____ yrs

17.

a) Did you have any brothers or sisters? YES/NO
If yes, how many brothers?
how many sisters?

b) Did any of your brothers or sisters suffer from rickets (bow legs) before the age of 20 years? YES/NO/DK

c) Did any of your brothers or sisters die before the age of 1 year? YES/NO/DK
If yes, how many? .....
how old were they? _____ yrs

d) Did any of your brothers or sisters died between the ages of 1 and 10 years? YES/NO/DK
If yes, how many? .....
how old were they? _____ yrs

e) Did your mother have any stillborn children? YES/NO/DK
If yes, how many? .....

Environmental data

18. Type of accommodation
- own home or relative's home
- hotel/boarding house/W-C Flat
- hospital/rest home
- home for old and disabled/nursing home
- hostel
- other (state ...)

Who lives with you in your house ...

19. Marital status
- single
- married
- remarried
- divorced
- widowed

20. Do you use the following community services?
a) home help YES/NO
b) meals on wheels YES/NO
c) district nurse YES/NO
d) day centre YES/NO

21. Occupation You a) occupation (most recent full time job)

b) description of work

Your husband/wife a) occupation (most recent full time job)

b) description of work

22. What was your father's occupation?

Where were you born?

Functional assessment

23. A.D.L. (1-7)

Are you
a) independent in feeding
b) continence
c) transferring
d) going to the toilet
e) dressing
f) bathing

Hormonal

24. How old were you when your periods started?
..... years

25. How old were you when you last had a period?
..... years

26. Did you have hormone treatment
at that time? YES/NO/DK
If YES, what treatment? .....
how long for? ..... years

27. Have you had a hysterectomy? YES/NO/DK
If YES, i) how old were you when
you had the operation? .... years
ii) did they take out
your ovaries as well? YES/NO/DK

28.
a) During the time when you were accustomed to having periods, did they ever stop for longer than six weeks, apart from during pregnancy?
YES/NO/DK

b) If yes, for how long? _____ months
how old were you? _____ yrs

29. Have you any children? YES/NO
If YES, how many? .....
PLEASE FILL IN THE FOLLOWING TABLE FOR YOUR CHILDREN

	Date of birth	Sex	Breast fed	How long breast-fed for (months)
1.		M/F	YES/NO	
2.		M/F	YES/NO	
3.		M/F	YES/NO	
4.		M/F	YES/NO	
5.		M/F	YES/NO	
6.		M/F	YES/NO	
7.		M/F	YES/NO	
8.		M/F	YES/NO	
9.		M/F	YES/NO	

Smoking

30. Do you smoke? YES/NO
If YES, how old when you started? ..... years
how many per day? .....

If NO, have you ever smoked? YES/NO
age started ..... years
age stopped ..... years
number per day .....

Number of packs year

(Smoking=more than one cigarette per day).

Alcohol

31.
a) How often do you drink alcohol?
- never
- less than once a week
- at least once a week

b) Frequency-amount.

	Most days	3-4x per week	1-2x per week	1-2x per month	1-2x per 6 months	1-2x per year	none in yr.	Amt
Shandy								pts
Beer								pts
Spirits								sgl
Sherry								gls
Wine								gls

Sunlight exposure and falls

32. How much time on average do you spend out-of-doors at this time of year, each day?
..... hours

33. Do you ever fall? YES/NO
If YES, how long is it since your last fall ..... months

Present physical activity

34. As shown in Appendix 2

Past physical activity

35. As shown in Appendix 3

Dietary calcium intake

36. As shown in Appendix 1

ABBREVIATED HODKINSON MTS

1) Age
2) Time (to nearest hour)
3) Address for recall at end of test eg. 42 West Street
4) Year
5) Name of institution
6) Recognition of two persons (doctor, nurse etc.)
7) Date of birth
8) Year of first World War
9) Name of present Monarch
10) Count backwards 20-1

MEASUREMENTS

1) Radiological

Singh grade _____

Femoral calcar _____

2) Physiological

Grip strength R. 1) L. 1)

2) 2)

3) 3)

Demi-arm span _____

3) Laboratory

Hb

Albumin

Creatinine

Calcium

Phosphate

Alkaline phosphatase

MRC
Medical Research Council

MRC Environmental Epidemiology Unit
University of Southampton

Please reply to: **Southampton General Hospital**
Southampton
SO9 4XY

Telephone Southampton 777624 Ext.

Your reference

Our reference

Letter to general practitioner

Dear Doctor,

We are conducting a case control study of femoral neck fracture in the Southampton and SW Hants health district, to examine the role of dietary calcium intake and physical activity as risk factors. Some of the subjects are registered at your practice, and we should be most grateful if you would allow us to obtain a full drug history and past medical history from their practice notes. I will contact you shortly to see whether this is possible, and to arrange a time to meet you at the practice to do this .

Thank you.

Yours sincerely,

Dr. C. Cooper
Medical Epidemiologist

MRC
Medical Research Council

MRC Environmental Epidemiology Unit
University of Southampton

Please reply to: **Southampton General Hospital**
Southampton
SO9 4XY

Telephone Southampton 777624 Ext.

Your reference

Our reference

Letter to subject

Dear ,

Doctors at this hospital are working with the Medical Research Council in a study on the diet of people in Southampton and the prevention of bone disease. As part of this I am interviewing a sample of Southampton residents. Your name has been chosen from a list of all people living in the city, and I would be most grateful if you were willing to answer some simple questions.

I would like to call at your home sometime during the next week and ask you these questions, which will take about twenty minutes. I would be very grateful if you would help us with this research. If you DO NOT wish to take part in the study, please complete the tear-off slip below and return it in the prepaid envelope provided.

Thank you.

Yours sincerely,

Dr. C. Cooper
Medical Epidemiologist

Name:

I am unable to help with your research.

Signed: _____

Reasons/remarks (if any): _____

_____

_____

_____

Appendix 6

Detailed results of the case-control study of hip fracture

Variable	Category		Number of		Relative risk	95% CI
			Cases	Controls		
BODY BUILD	M	F				
Current weight (kg)	<61.7	<49.4	72	98	1.0	-
	61.7-66.7	49.4-54.0	65	90	0.9	0.6-1.5
	66.7-72.0	54.0-59.4	64	128	0.6	0.4-1.0
	72.0-76.2	59.4-65.3	43	126	0.5	0.3-0.7
	>76.2	>65.3	39	131	0.4	0.2-0.6
Maximum weight (kg)	<68.9	<57.2	76	101	1.0	-
	68.9-73.5	57.2-63.1	52	64	1.0	0.6-1.7
	73.5-78.8	63.1-66.2	56	99	0.8	0.5-1.2
	78.8-87.5	66.2-76.2	72	113	0.9	0.5-1.4
	>87.5	>76.2	21	91	0.3	0.2-0.6
Weight loss (kg)	<0.001	<2.7	60	93	1.0	-
	0.001-5.9	2.7-6.4	51	94	0.8	0.5-1.3
	5.9-8.1	6.4-9.1	52	94	0.9	0.6-1.5
	8.1-14.2	9.1-12.7	56	94	0.9	0.6-1.5
	>14.2	>12.7	57	86	1.1	0.7-1.7
Height (kg)	<170	<152	16	60	1.0	-
	170-173	152-158	35	130	1.0	0.5-1.9
	173-178	158-163	98	172	2.0	1.1-3.6
	178-180	163-165	44	84	1.7	0.9-3.4
	>180	>165	93	136	2.4	1.3-4.5
Demiarm span (cm)	<211	<193	44	110	1.0	-
	211-218	193-201	73	123	1.5	0.9-2.4
	218-224	201-203	48	78	1.6	0.9-2.6
	224-231	203-211	78	147	1.4	0.9-2.2
	>231	>211	56	140	1.0	0.6-1.4
Body mass index (kg/m^2)	<20.4	<19.2	88	84	1.0	-
	20.4-21.6	19.2-21.1	67	94	0.6	0.4-1.0
	21.6-23.2	21.1-22.9	60	112	0.5	0.3-0.8
	23.2-24.9	22.9-25.6	40	128	0.3	0.2-0.5
	>24.9	>25.6	24	144	0.2	0.1-0.3

Variable	Category		Number of		Relative risk	95% CI
			Cases	Controls		
GRIP STRENGTH	M	F				
(kg)	<18	<10	75	84	1.0	-
	18-25	10-14	80	99	0.9	0.6-1.4
	25-31	14-18	64	126	0.5	0.3-0.8
	31-39	18-23	40	144	0.3	0.2-0.4
	>39	>23	39	146	0.2	0.1-0.4
CURRENT PHYSICAL ACTIVITY						
Standing time (mins/day)	None		15	23	2.5	1.2-5.2
	1-29		100	125	2.9	1.9-4.3
	30-59		94	182	1.8	1.2-2.6
	>60		91	270	1.0	-
Self-reported walking speed	Very slowly		155	243	2.1	1.0-3.1
	Stroll at easy pace		63	148	1.3	1.0-3.0
	Normal speed		50	117	1.3	0.6-2.2
	Fairly brisk/fast		32	91	1.0	-
Walking time (mins/day)	None		150	279	1.7	1.0-3.1
	1-29		102	189	1.7	1.0-3.0
	30-59		28	73	1.2	0.6-2.2
	>60		20	59	1.0	-
Muscle loading activity (frequency)	Never		102	153	2.4	1.5-3.7
	Less than weekly		82	131	2.1	1.3-3.2
	Weekly to daily		60	149	1.3	0.8-1.9
	Several times a day		56	167	1.0	-
Productive activity (hours/week)	None		66	99	2.1	1.3-3.2
	1-3		93	132	2.1	1.4-3.2
	4-6		65	170	1.1	0.7-1.6
	>6		76	199	1.0	-
PAST PHYSICAL ACTIVITY						
Total (units)	<14		78	105	1.0	-
	14-18		176	394	0.6	0.5-0.9
	>18		46	91	0.6	0.4-0.8

Variable	Category	Number of		Relative risk	95% CI
		Cases	Controls		
PAST PHYSICAL ACTIVITY					
Occupational (% of time spent standing)	<4 sedentary	54	51	1.0	-
	4-7 intermediate	180	355	0.4	0.2-1.0
	>7 standing	66	194	0.4	0.2-1.0
Leisure time (units)	<9	111	241	1.0	-
	9-11	95	189	0.9	0.6-1.3
	>11	94	170	0.8	0.6-1.2
REPRODUCTIVE VARIABLES					
Oopherectomy		18	22	1.6	0.9-3.2
Hormone replacement therapy		6	23	0.5	0.2-1.3
Parity	0	77	114	1.0	-
	1-2	120	245	0.7	0.5-1.0
	>2	43	120	0.3	0.3-0.8
Lactation	<0.5	22	83	1.0	-
	0.5-3.0	42	61	2.4	1.2-4.8
	3.0-5.0	32	75	1.5	0.7-3.1
	5.0-7.5	28	72	1.5	0.7-3.1
	>7.5	37	74	1.8	0.9-3.6
Age at menarche	<14	74	158	1.0	-
	≥14	160	301	1.1	0.8-1.6
Age at menopause	<40	8	28	1.0	-
	40-44	29	57	1.9	0.8-4.8
	45-49	89	109	2.8	1.2-6.4
	50-54	95	226	1.4	0.6-3.2
	>54	15	27	2.2	0.8-6.0

Variable	Category	Number of		Relative risk	95% CI
		Cases	Controls		
MEDICAL HISTORY					
Hip fracture		37	14	6.8	3.4- 13.8
Wrist fracture		48	52	2.3	1.4- 3.6
CVA		34	39	1.8	1.1- 2.9
Fall in previous nine months		112	153	1.8	1.3- 2.5
Diabetes mellitus		19	28	1.4	0.8- 2.5
Thyrotoxicosis		4	4	2.0	0.5- 8.0
Rheumatoid arthritis		14	14	2.1	1.0- 4.7
Corticosteroids		16	13	2.7	1.2- 5.8
Anti-Parkinsonian agents		11	7	3.4	1.3- 9.4
Benzodiazepines		32	63	1.0	0.7- 1.6
Other sedatives		40	88	0.9	0.6- 1.3
Thiazide diuretics		47	111	0.8	0.6- 1.2
Thyroxine		11	21	1.0	0.5- 2.2
Total number of drugs	0	117	242	1.0	-
	1-3	156	297	1.1	0.8- 1.5
	>3	27	67	0.8	0.5- 1.4
SMOKING					
Ever		145	223	1.7	1.2- 2.3
Pack years	0	155	377	1.0	-
	1-9	41	82	1.2	0.8- 1.9
	10-19	45	41	2.8	1.8- 4.6
	20-29	21	36	1.6	0.9- 2.9
	>29	38	64	1.6	1.0- 2.6
ALCOHOL					
	Abstainer	73	168	1.0	-
	Occasional	90	214	1.0	0.7- 1.4
	Infrequent light	59	104	1.4	0.9- 2.2
	Frequent light	49	101	1.2	0.8- 2.0
	Moderate	23	11	6.6	2.7- 16.3
	Heavier	5	1	12.4	1.4-108.3

Variable	Category	Number of		Relative risk	95% CI
		Cases	Controls		
DEPENDENCE IN DAILY LIVING ACTIVITIES					
Katz score	1	157	420	1.0	-
	2	77	124	1.9	1.3-2.8
	3	38	34	3.4	2.0-5.8
	>3	28	21	4.4	2.3-8.4
Meals on wheels		44	46	2.5	1.5-4.1
Home help		91	117	2.1	1.5-3.0
District nurse		34	45	1.6	0.9-2.6
Use of day centre		16	23	1.7	0.8-3.5
SUNLIGHT EXPOSURE (mins/day)					
	0	101	193	1.0	-
	1-29	122	229	1.0	0.7-1.3
	>29	77	178	0.8	0.5-1.2
MENTAL STATE					
	10	149	365	1.0	-
	9	53	113	1.2	0.8-1.7
	8	36	60	1.6	1.0-2.5
	6/7	62	62	3.1	1.9-4.8
SOCIAL CLASS					
Social class of individual	1-2	76	115	1.0	-
	3NM	63	109	0.8	0.5-1.3
	3N	79	204	0.6	0.4-4.8
	4-5	82	172	0.7	0.5-1.0
Social class at birth	1-2	64	82	1.0	-
	3NM	24	54	0.6	0.3-1.1
	3M	88	202	0.6	0.4-0.9
	4-5	84	224	0.5	0.3-0.8

Variable	Category	Number of		Relative risk	95% CI
		Cases	Controls		
SOCIAL CLASS con't ...					
Accommodation	Own/relatives home	225	442	1.0	-
	Warden-controlled	41	98	0.8	0.5-1.2
	Rest home	22	40	1.1	0.6-2.0
	Nursing home	12	10	1.3	0.6-2.9
	Hospital	-	1	-	-
Place of residence	Urban	187	383	1.0	
	Rural	107	196	1.1	0.8-1.5
Marital status	Single	30	51	1.0	-
	Married	103	194	0.9	0.6-1.6
	Re-married	6	23	0.4	0.1-1.2
	Divorced	4	5	1.4	0.4-5.8
	Widowed	157	327	0.8	0.5-1.3
Sibship size	0	27	40	1.0	-
	1	44	92	0.7	0.4-1.3
	2	49	101	0.7	0.4-1.3
	3	51	86	0.9	0.5-1.6
	>3	129	279	0.6	0.4-1.1
Sibling mortality	<1 year	51	60	1.8	1.2-2.6
	1-10 years	8	39	0.4	0.2-0.9
	0-10 years	59	99	1.3	0.9-1.8
	Stillbirths	16	23	1.4	0.7-2.6
Sibling history of rickets		14	22	1.3	0.6-2.6
FAMILY HISTORY					
Hip fracture		19	29	1.4	0.7-2.6
Wrist fracture		27	39	1.5	0.9-2.5

Variable	Category		Number of		Relative risk	95% CI
			Cases	Controls		
DIETARY CALCIUM INTAKE	M	F				
Current calcium intake (mg/day)	<500	<433	62	118	1.0	-
	500-668	433-567	65	115	1.1	0.7-1.6
	668-841	567-684	62	118	1.0	0.7-1.5
	841-1041	684-838	59	121	0.9	0.6-1.4
	>1041	>838	52	128	0.8	0.5-1.2
Past calcium intake (mg/day)	<606	<565	59	121	1.0	-
	606-801	565-693	60	120	1.0	0.7-1.6
	801-990	693-834	61	119	1.1	0.7-1.6
	990-1209	834-1025	62	118	1.1	0.7-1.7
	>1209	>1025	58	122	1.0	0.6-1.5
Milk drink at night			102	214	0.9	0.7-1.2
Pints of milk/ person/week	0-3		105	209	1.0	-
	4		92	141	0.6	1.1-2.3
	>4		77	189	1.2	0.9-1.8

Appendix 7

List of publications included in this thesis

1. Cooper C, Barker DJP, Hall AJ. Evaluation of the Singh index and femoral calcar width as epidemiological methods for measuring bone mass in the femoral neck. Clin Radiol 1986; 37: 123-125.

2. Cooper C, Barker DJP, Morris J, Briggs RSJ. Osteoporosis, falls and age in fracture of the proximal femur. Br Med J 1987; 295: 13-15.

3. Nelson M, Hague G, Cooper C, Bunker V. Calcium intake in the elderly: validation of a dietary questionnaire. J Hum Nutr Diet 1988; 1: 104-114.

4. Cooper C, McLaren M, Wood PJ, Coulton L, Kanis JA. Indices of calcium metabolism in elderly women with hip fractures. Bone Min 1988, in press.

5. Cooper C, Barker DJP, Wickham C. Physical activity, muscle strength and calcium intake in fracture of the proximal femur in Britain. Br Med J 1988, in press.