UNIVERSITY OF SOUTHAMPTON

Water Fluoridation and Osteoporotic Hip Fracture

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ABSTRACT

FACULTY OF MEDICINE

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Doctor of Philosophy

WATER FLUORIDATION AND OSTEOPOROTIC HIP FRACTURE

by Sharon Lee Hillier

Ecological studies suggest a positive association between water fluoridation and hip fracture incidence. However, few studies have been performed to relate water fluoride content to hip fracture risk in individuals. This issue was addressed in a case-control study of hip fracture.

The study was located in the county of Cleveland, comprising three districts: Hartlepool (natural fluoride 1-2ppm) Middlesbrough and Stockton (fluoride 0.15ppm). In each district all patients aged 50 years and over who had sustained a fracture of the proximal femur and able to pass a mental test score were interviewed. Controls were selected from general practice listings for the county. Information on risk factors was obtained using a structured questionnaire. Cumulative exposure to fluoride in water was estimated from a residential history, and data on fluoride content of water supplied by local water companies. Excised femoral heads were collected from cases who had undergone surgery. The fluoride content of the bones were ascertained and used as a biological marker for fluoride exposure.

The study comprised 424 cases and 281 controls. Independent risk factors for hip fracture included body mass index (OR 3.1, 95% CI 2.0 - 4.8, lowest v. highest third of distribution); recent physical inactivity (OR 6.3, 95% CI 3.8 - 10.5); diagnosis of rheumatoid arthritis (OR 2.3 95% CI 1.1 - 5.1) and age at menarche (OR 1.8 95% CI 1.1 - 3.0, 15 years or older v. 13 years or younger). After adjusting for age, sex and these variables, there was no increase risk of hip fracture associated with lifetime exposure to fluoride in water (OR 0.6, 95% CI 0.4 - 1.0). Water fluoride was associated with higher fluoride in the femoral heads

In conclusion, no increase in the risk of hip fracture was observed with water fluoride at levels of up to 2 ppm.

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Acknowledgements

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I am very grateful to Lisa Madhok and Gill Smith, the research nurses who completed an excellent task of data collection, which was made especially difficult as they worked in isolation of the MRC unit.

I must thank Sam Kellingray for her ability to make statistics seem easy and for introducing me to the world of STATA. Indeed I am grateful to all of the friends and colleagues at the MRC unit who have made the last three years so enjoyable.

I must of course acknowledge the support I have received from Alastair and my parents. I am especially grateful to Alastair who tolerated my frequent visits to the North East and provided moral support whilst writing this thesis.

Abbreviations

BMI = Body mass index

CI = confidence interval

dmft = decayed missing and filled teeth

GP = general practitioner

ICD = international classification of disease

NHS = national health service

NS = not significant

NSAIDs = non-steroidal anti-inflammatory drugs

OR = odds ratio

ppm = parts per million

RR = relative risk

Section A : Forward

Outline of thesis

This thesis describes a case-control study set up to investigate the relationship between water fluoride and osteoporotic hip fracture. Caries reduction by water fluoridation has been one of the most celebrated public health measures. However, there have been concerns about the effect of fluoride on bone health, and in particular on osteoporotic hip fracture. The thesis starts by outlining the history of water fluoridation. It then describes the anatomy and physiology of bone, and the clinical and pathological features of osteoporosis. Next the epidemiology of osteoporosis, osteoporotic fracture, and particularly osteoporotic hip fracture is reviewed. This is followed by a discussion of the pharmacokinetics of fluoride and its relation to bone. I then discuss the literature so far published on the relationship between water fluoridation and osteoporotic hip fracture. Section C is concerned with the methodology of the case-control study and this is followed by a description of its findings and a discussion of their implications.

The main aim of the study was to investigate whether fluoride in drinking water at the level advocated for prevention of tooth decay (1ppm) increases the risk of osteoporotic hip fracture and also whether exposure to water containing fluoride at this level increases the fluoride content of the femoral head. In addition, various potential confounders were assessed so that they could be accounted for in the analysis, and it was therefore possible also to investigate these variables as risk factors in their own right. The risk factors in question were body mass index, physical inactivity, calcium intake, previous fracture, previous stroke, diagnosis of rheumatoid arthritis, female reproductive variables and current medication.

Practicalities

I started this PhD in November 1994 and during the first year was concerned with undertaking a literature review, and deciding on the detailed methodology and the study's location. Once Cleveland had been selected as the study area, the local orthopaedic consultants, Tees Health Authority and local general practitioners were invited to participate in the study. I undertook a trial run of the methods of data collection in the summer of 1995. It was then possible to start the main data collection in November 1995 after a research nurse, Lisa Madhok, had been appointed and trained. I visited Cleveland for a number of days each month to ensure everything ran smoothly and to assist with the data collection. In addition, I undertook the administrative support of the project from Southampton. At the beginning of the second year it was possible to appoint Gill Smith, a second research nurse. I was lucky to have excellent research nurses, very helpful ward staff and co-operative subjects.

Due to the time limit imposed by my funding, it was decided to use the data collected over the first 17 months for this thesis. Data entry was completed by staff at the MRC Environmental Epidemiology Unit for which I am very grateful. I validated the data and coded the addresses for fluoride exposure using programs written by Leslie Styles, computer programmer MRC. The data was cleaned and prepared for analysis with the help of Sam Kellingray, statistician MRC. Sam was able to teach me how to use the statistical package, STATA, so that I was able to complete most of the routine analysis myself and she made herself available when problems arose and difficult analyses were needed.

Of course throughout this process my tutors; Professor David Coggon and Professor Cyrus Cooper provided advice and support.

Section B: Background

B.1. Water Fluoridation

The history of water fluoridation dates to 1901 when Dr Frederick McKay arrived in Colorado Springs, Colorado, USA to practise orthodontics. He soon noticed that many of his patients had a permanent stain on their teeth, which he termed "mottled enamel". This was described as: 'minute white flecks, or yellow or brown spots or areas, scattered irregularly or streaked over the surface of a tooth, or a condition where the entire tooth surface is of a dead paper-white, like the colour of a china dish' (McKay, 1916). McKay failed to find any reference to this condition in the dental literature and thus became intrigued as to its cause.

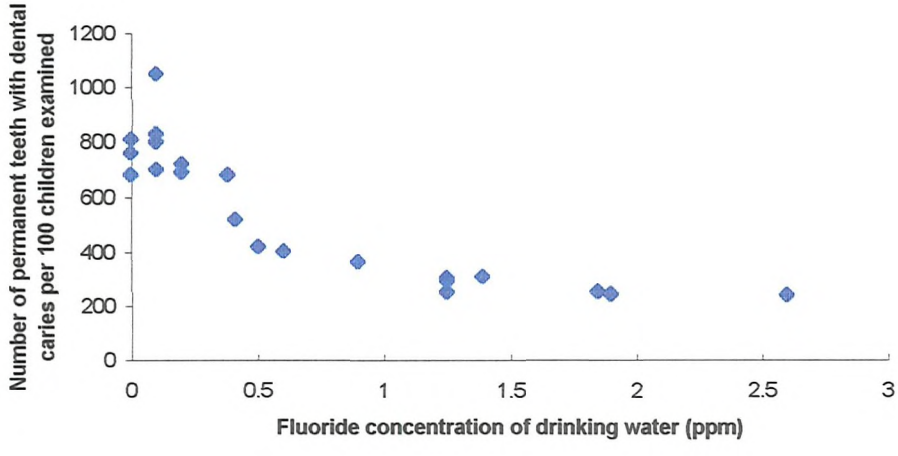
As McKay worked hard to increase the profile of the abnormality, it became apparent that many areas of the USA were similarly affected. As the circumstantial evidence built up, it seemed unlikely that diet was to blame, as mottled teeth occurred in both poor and wealthy children. An unidentified agent in the water seemed a possible candidate, as there had been several communities who had been free of the condition before they altered their water supply. The first analysis of water in an affected area was carried out by an aluminium company who were worried that their aluminium ware for cooking could be to blame. They found an unusually high fluoride concentration of 13.7ppm (parts per million) in the water supplying the town of Bauxite where the young children had badly stained teeth. Samples of water were analysed from other endemic areas of mottled enamel and the fluoride concentrations ranged from 2.0ppm to 12.0ppm.

It was emphasised at this point that no correlation between fluoride content of water and mottled enamel had been established. The confirmation came from subsequent rat experiments. Rats were fed with water from an endemic area, which had been concentrated to one tenth of its original

volume, and within a month the enamel was 'strikingly dull, white in appearance and pitted' (Smith and Smith, 1931). A further experiment was carried out, this time the rats were fed with a solution of sodium fluoride and similar defects in enamel developed. The water from the endemic area was analysed and found to have a fluoride concentration which ranged from 3.8-7.2ppm.

McKay noted during his early studies that mottled teeth had a caries rate no higher than normal teeth. However, a study conducted for the Dental Disease Committee of the Medical Research Council in England and Wales found that children living in Maldon, which had a concentration of 4.5-5.0ppm of fluoride in the water, had a lower prevalence of dental caries than the national average. This development provoked such interest that in 1931 Dr H. Trendley Dean was employed to pursue full-time research on mottled enamel in America. To test further the hypothesis that an inverse relationship existed between endemic dental fluorosis and dental caries, two studies were carried out. The larger investigation examined 7257 12-14 year old children from 21 cities in four states of America and the results are shown in Figure B.1.1

Figure B.1.1: Fluoride content of water supply and caries of experience of 12-14 year old school children (7,257) in 21 American cities (Dean *et al.*, 1942).



The results depict with clarity the negative ecological association between fluoride concentration in the drinking water and caries prevalence in the population. Furthermore, this study showed that near maximal reduction in caries experience occurred at a concentration of 1ppm fluoride. At this concentration, fluoride caused only sporadic instances of the mildest forms of dental fluorosis of no practical aesthetic significance (Dean *et al.*, 1942).

This finding was confirmed in the UK by a study which examined 1000 children on each side of the River Tyne. South Shields had a fluoride concentration of 2ppm as compared with 0.25ppm in North Shields. It was reported that the mean count of decayed missing and filled teeth (dmft) in 5 year old children was 3.9 in South Shields and 6.6 in North Shields; the comparative figures for 12 year old children were 2.4 and 4.3 dmft.

The fluoridation story now entered its final phase. The crucial step was to see if dental caries could be reduced in a community by adding fluoride at 1ppm to a fluoride-deficient water supply. After confirmation in field and laboratory studies that this concentration was the best for caries control and well within the apparent limits of safety (Moulton, 1942), it was decided that Grand Rapids, Michigan would be the experimental town and Muskegon the control town. Baseline studies showed that caries experience in the two towns was similar. On 25 January 1945 sodium fluoride was added to the Grand Rapids water supply. After six and a half years of water fluoridation the results were clear: the caries experience of 6-year-old Grand Rapids children was almost half that of 6-year-old Muskegon children. At this point Muskegon decided to fluoridate its waters (Arnold *et al.*, 1953).

Since 1962, the "optimal" concentration of fluoride in drinking water for the United States has been set at 0.7-1.2ppm, depending on the mean temperature of the locality (0.7ppm for areas with warm climates, where the water consumption is high and 1.2ppm for cool climates where the water consumption is low). This range was considered optimal as it provided a balance between prevention of dental caries and occurrence of objectionable dental fluorosis (National Research Council, 1993).

In 1952, the British Government sent a mission to the USA and Canada to study fluoridation in operation. The mission concluded that fluoridation of water supplies was a valuable health measure, but recommended that in this country fluoride should be added to the water supplies of some selected communities before its general adoption was considered (Report of United Kingdom Mission, 1953). The selected communities were Watford, Kilmarnock and part of Anglesey. Fluoride was added to the drinking water in these areas in 1955-1956. The results after five years showed that fluoridation was a highly effective method of reducing dental decay (Department of Public Health and Social Security, 1962).

Currently over 5 million people in the UK receive water whose fluoride content has been artificially supplemented to the optimum level for dental health purposes of around 1ppm, or whose naturally occurring fluoride content is at this concentration. In addition about half a million people receive water with fluoride levels between 0.7 and 0.9ppm and a further 2.2 million people have water supplies with a fluoride concentration between 0.3 and 0.7ppm. The remaining majority (47 million) receive water with a fluoride concentration less than 0.3ppm. Figure B.1.2 and Table B.1.1 summarise the current fluoridation status of England and Wales.

Figure B.1.2. Areas of England and Wales where 50 percent or more of the population receive water with a fluoride concentration of at least 0.9ppm. Refer to Table B.1.1. for description of areas.

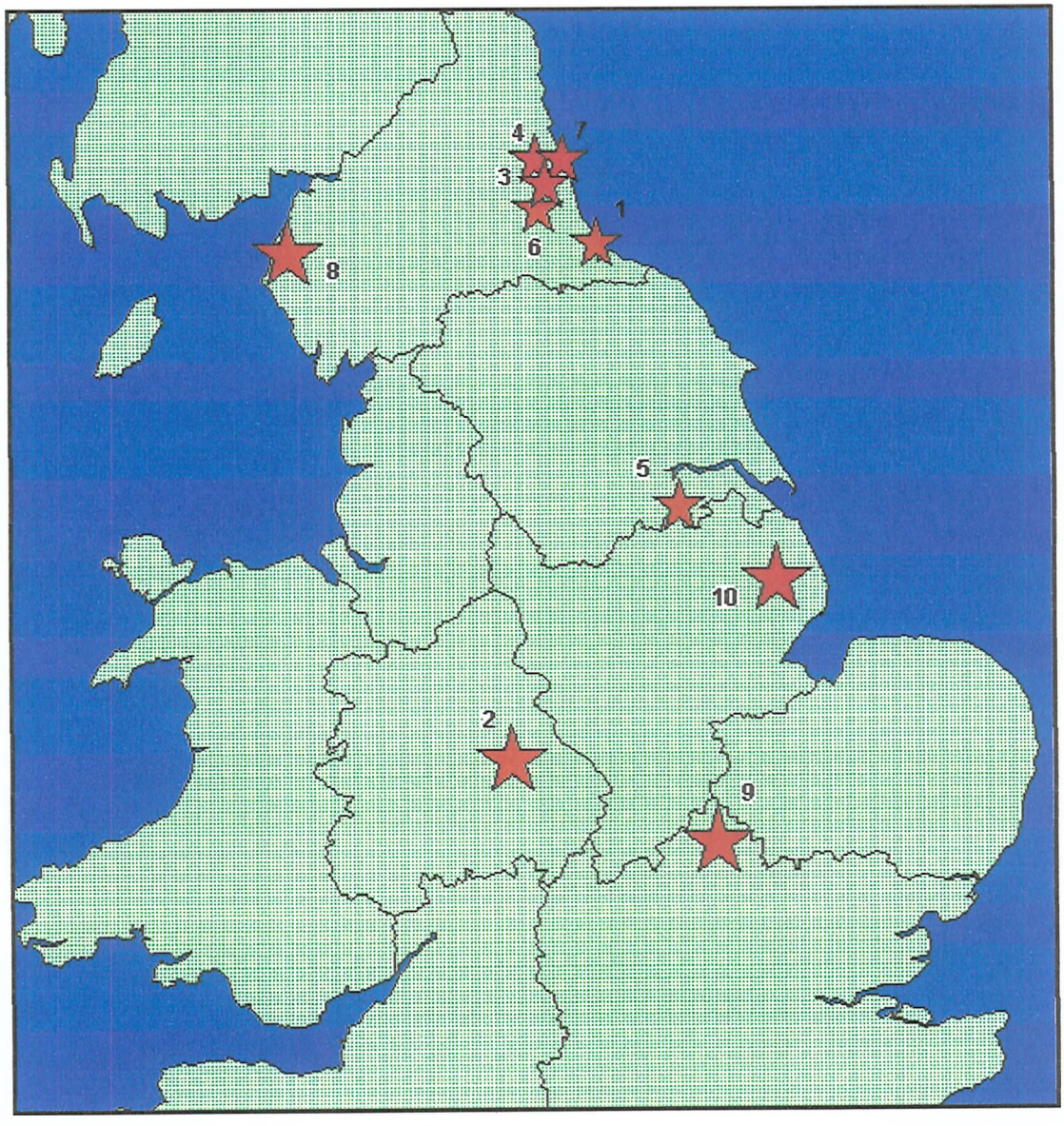


Table B.1.1. Areas of England and Wales where 50 percent or more of the population receive water with a fluoride concentration of at least 0.9ppm (Public Health Alliance and British Fluoridation Society, 1994).

Ref. No.[#]	Location	Total population	Percentage of the population exposed	Year fluoridation scheme initiated
1	Hartlepool	92,000	100	N/A Natural fluoride
2	West Midlands	5,236,363	65	1964-1991*
3	Gateshead	207,000	100	1968
4	Newcastle	277,600	100	1968
5	Scunthorpe	199,300	67	1968/69*
6	North Durham	223,000	57	1968
7	North Tyneside	192,900	50	1968
8	West Cumbria	137,640	87	1969/71*
9	North Bedfordshire	253,780	76	1972
10	Lincolnshire	318,300	76	1980/91*

[#]Refer to Figure B.1.2 * Fluoridation schemes were initiated over several years in these areas

Despite the apparent success of water fluoridation in reducing the incidence of dental caries, the measure remains controversial. Some people believe that fluoride at levels of 1ppm can cause severe dental fluorosis which may lead to psychological problems. Assertions have been made that fluoridation is related to skeletal fluorosis, osteoporotic fractures, cancer and arthritis. The balance of evidence suggests no link with cancer or arthritis (National Research Council, 1993). However its relation to fracture is less certain. This possible association is of special concern as osteoporotic fractures are an increasing problem with high attributable morbidity and cost.

Before considering the epidemiological evidence on osteoporotic fracture and fluoride in water it is helpful first to review the anatomy, physiology and biochemistry of bone and the pathology and epidemiology of osteoporosis and osteoporotic fracture.

B.2. Bone:

Introduction:

The skeletal system is made up of just over 200 bones, joined together to provide a strong movable living framework for the body. It fulfils four main functions: it supports and protects the surrounding soft tissues and organs; it acts as a leverage system to which muscles and tendons can attach; it provides a storage system for mineral salts, particularly calcium and phosphate; and it manufactures blood cells in the red bone marrow.

i. Histology and anatomy:

Bone is a composite tissue whose properties, both mechanical and metabolic, closely depend on its structure and composition (Bonucci, 1989). There are four main components: Osteoid which is composed of collagen (95%), hyaluronic acid and chondroitin sulphate; amorphous calcium phosphate; osteoblast, osteoclast and osteocyte bone cells; and bone marrow.

The osteoid is arranged in the form of a matrix which provides the bone's tensile strength. The calcium and phosphate mineralises the matrix, giving the bone both compressive strength and rigidity. Mineralisation is achieved by amorphous calcium phosphate forming apatite crystals, which become orientated along collagen molecules and produce hydroxyapatite. A layer of water, the hydration shell, is bound to the surface of the crystals.

Osteoblasts are of uniform size and have a high concentration of intracellular alkaline phosphatase. Their function is to synthesise and secrete the organic matrix and to promote mineralisation. Osteocytes are osteoblasts that have become trapped in the bone matrix that they have produced. Osteocytes were once considered to be relatively inactive but, as they show changes with varying levels of parathyroid hormone and calcitonin, it is now thought that they play an important role in maintaining constant levels of calcium in body fluids (Woolf and Dixon, 1988).

Osteoclasts are highly mobile cells which vary greatly in size. They are responsible for resorption of bone in the remodelling process (see below). They have a high concentration of intracellular acid phosphatase and other enzymes that are concerned with lysis.

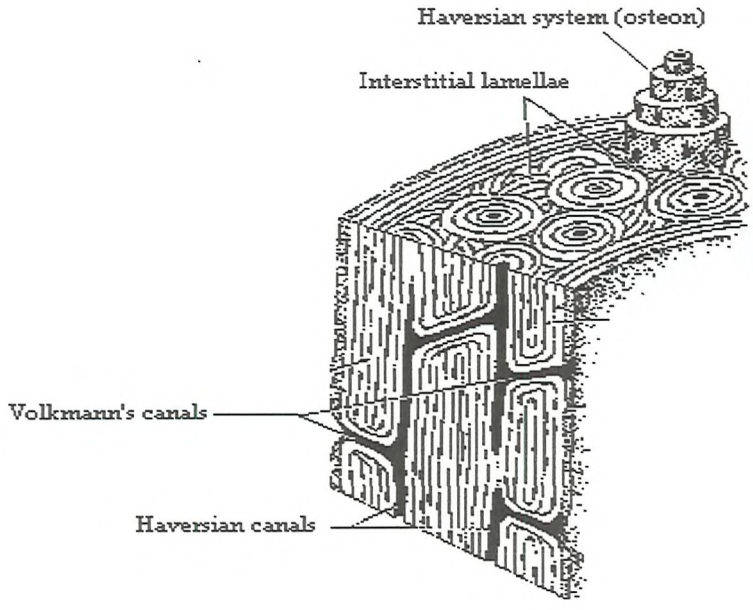
Bone marrow is one of the large organs of the body and the main site of haematopoiesis. It is found in the medullary canals of long bones and in the cavities of trabecular bone. The marrow is a gelatinous material which is highly organised and complex. It comprises the precursors of the erythrocytes, lymphocytes, megakaryocytes, granulocytes and monocytes of the peripheral blood. The main functions of bone marrow are the production of blood cells, destruction of red blood cells, and storage of iron derived from the breakdown of haemoglobin.

Different types of bone:

There are three types of bone; woven, cortical and trabecular. Woven bone is the first bone to appear in embryonic development and in the repair of fractures. The bone is usually more cellular and the lacunae in which the osteocytes reside are not as flattened as they are in mature bone. Immature bone is usually replaced but some may persist, especially near tendon insertions and ligament attachments.

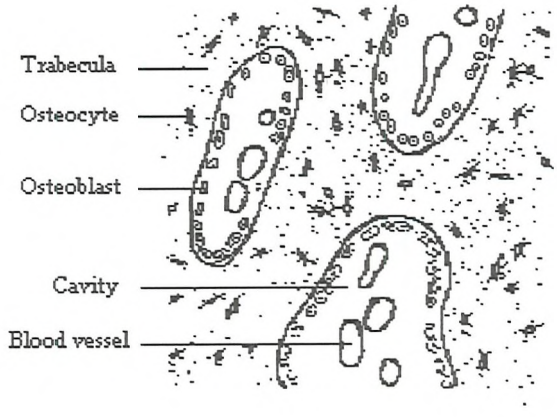
Cortical bone forms the outer layer of all bones. It is found in the shafts of long bones where it encloses the marrow cavity and in the outer and inner parts of flat bones. Cortical bone has a role of support and is compact and very hard. The bone has a very regular, organised structure. Each unit is known as an Haversian system or 'osteon' and consists of an Haversian canal which contains an arteriole, venule, capillary and nerve, around which concentric layers of bone called lamellae form. Osteocytes lie within groves in the lamellae, called lacunae, and adjacent osteocytes communicate via systems of microcanaliculi. Figure B.2.1 illustrates the structure of cortical bone .

Figure B.2.1 The structure of cortical bone (Hinchliff and Montague, 1988)



Trabecular bone is hard like all bone, but has a spongy appearance to the naked eye. The spaces in spongy bone are filled with red bone marrow. It is found in vertebrae, flat bones and at the end of long bones. This bone also contains Haversian systems although there are fewer of them. Trabecular bone is more metabolically active than cortical bone. Figure B.2.2. illustrates the structure of trabecular bone.

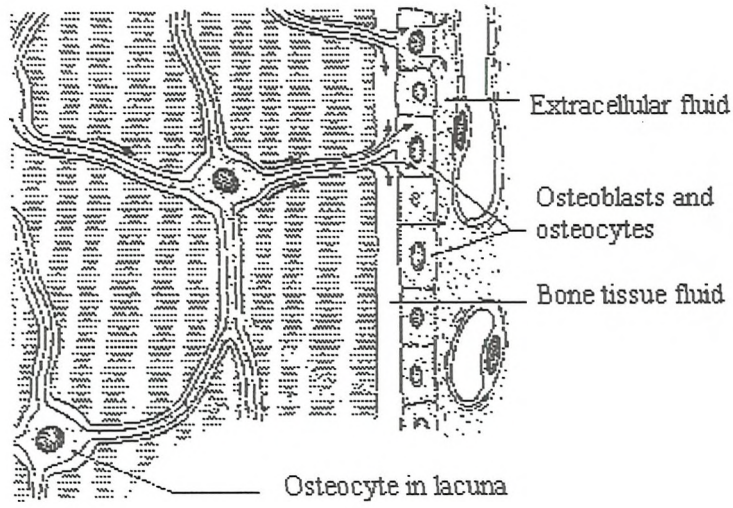
Figure B.2.2 The structure of trabecular bone (Hinchliff and Montague, 1988)



Blood supply to bone:

Bone is a metabolically active tissue with a rich blood supply. Approximately 20% of the cardiac output is delivered to the skeleton in the resting human (Charkes *et al.*, 1980). The pathway of nutrients from the blood into the bone is illustrated in figure B.2.3

Figure B.2.3: Diagrammatic representation of the blood supply to bone (Hinchliff and Montague, 1988)



It has been estimated that trabecular bone has a twofold higher blood flow rate than cortical bone (Whiteside *et al.*, 1977).

ii. Remodelling of bone:

Bone is not a constant stable tissue but changes all the time by undergoing remodelling. Remodelling is the process by which areas of the bone are broken down and reabsorbed and another layer of bone is built up, so that the microanatomy of the bone changes subtly. Remodelling is essential for bone as it enables it to respond to mechanical stresses and increase its strength where needed. Remodelling also has the function of maintaining the biomechanical competence of the skeleton by preventing accumulation of fatigue damage and maintaining a tissue whose components are available for mineral homeostasis.

It has been estimated that at any given time 3.5% of the adult skeleton is being remodelled (Rasmussen, 1968). In adults, rates of remodelling may be 5 to 10 times higher in trabecular bone compared to cortical bone (Parfitt, 1988). The time taken for an area of bone to be remodelled from start to finish is approximately four months.

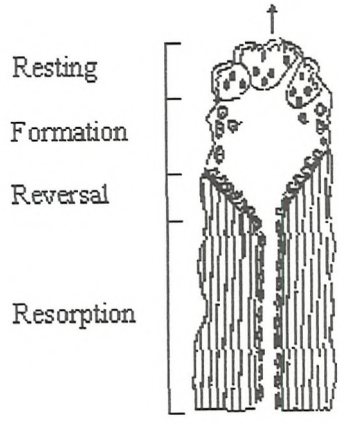
There are three distinct stages in remodelling (refer to figure B.2.4)

Stage 1: Osteoclasts are stimulated (time period hours-days). It is unknown what stimulates the osteoclasts, but parathyroid hormone, thyroxine, oestrogens and metabolites of vitamin A and D are all possible candidates.

Stage 2: Osteoclasts erode tunnels 1mm in diameter through the bone (1-3 weeks). They remove both the mineral and matrix components of bone.

Stage 3 : Osteoblasts deposit new bone inside the tunnels (3 months).

Figure B.2.4 Schematic representation the remodelling sequence of bone (Dempster and Lindsay, 1993)



The mass of bone is maintained constant by a coupling between osteoclast and osteoblast activity (Frost, 1964). Factors that bring about activation at a particular site are not clear. It appears that the remodelling units are activated at random locations throughout the skeleton, but it may be that the stimulation is too subtle to detect. Possibilities include local factors released from ageing bone or stimulation from local stresses (Dempster and Lindsay, 1993).

There is evidence of a relationship between bone blood flow and bone remodelling. Studying dogs with different degrees of remodelling (hypoparathyroidism, hyperparathyroidism, hypothyroidism and hyperthyroidism) showed that osseous blood flow was closely related with remodelling activity (Sim and Kelly, 1970). Whiteside *et al.* (1977) examined the differences in remodelling and blood flow in trabecular and cortical bone and concluded that the two were related

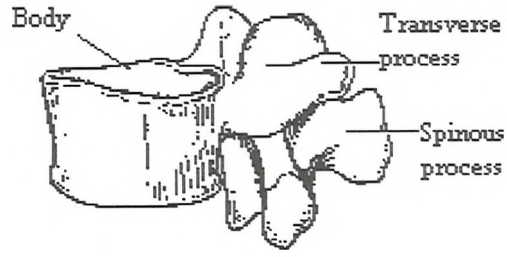
iii. Gross Anatomy of the Skeleton

The skeleton can be divided into the axial skeleton, comprising the head and trunk, and the appendicular skeleton - the arms and legs. The parts of the skeleton particularly pertinent to osteoporosis are the vertebrae, femoral head and radius and ulna.

Vertebrae:

The vertebral column makes up part of the trunk. It consists of a number of irregular bones called vertebrae (Figure B.2.5) which are firmly connected to one another by ligaments, tendons and muscles. The column provides support for the trunk and also protects the spinal cord. Although there is only limited movement between any two adjoining vertebrae, there is considerable movement in the vertebral column as a whole. Vertebrae consist mainly of trabecular bone (66-90%), the remainder being cortical bone (Einhorn, 1992).

Figure B.2.5: A vertebrae (Jackson and Bennett, 1988)



Femur:

The femur is the longest and strongest bone in the body. The upper end of the bone has a hemispherical head which articulates with the acetabulum of the hip. Near its centre is a small depression which gives attachment to the ligament of the head of the femur. The neck of the femur projects at an angle from the shaft. The shaft of the femur is thinnest in the middle and widens considerably at the lower end which ensures that there is a good area for the transmission of the body weight to the tibia through the articulation at the knee. The femur is composed mostly of cortical bone. The trabecular bone content varies at different sites of the femur, with only 25% at the femoral neck and 50% at the intertrochanteric region (Einhorn, 1992). Refer to figure B.2.6 for a diagram of a femur.

Radius and Ulna:

The upper end of the radius is disc-shaped with a hollowed upper surface which articulates with the capitulum of the humerus. The shaft of the bone has a sharp ridge facing the ulna and from it a sheet of fibrous tissue runs to the ulna. The lower end of the radius is the wider part and forms part of the wrist joint.

The ulna lies on the inner side of the forearm. The upper end articulates with the humerus; the shaft, as in the radius, carries a sharp ridge to which the fibrous tissue attaches; and the lower end has a rounded part, which articulates with the ulnar notch of the radius. Figure B.2.7 shows a sketch of a typical radius and ulna. The proportion of trabecular bone is 25% at the distal radius and 1% at the mid radius, the remainder being comprised of cortical bone (Einhorn, 1992).

Figure B.2.6 The femur (Jackson and Bennett, 1988)

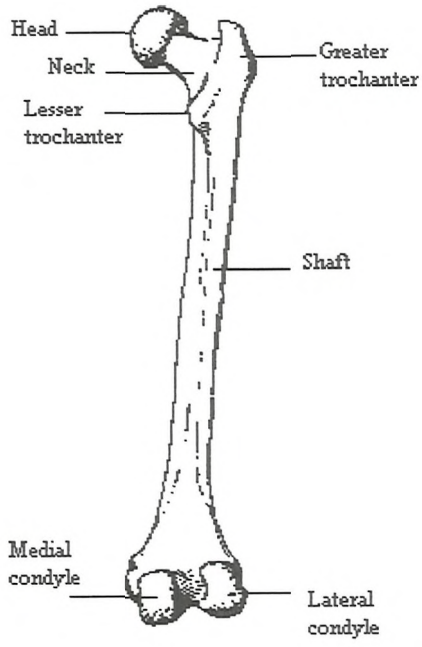
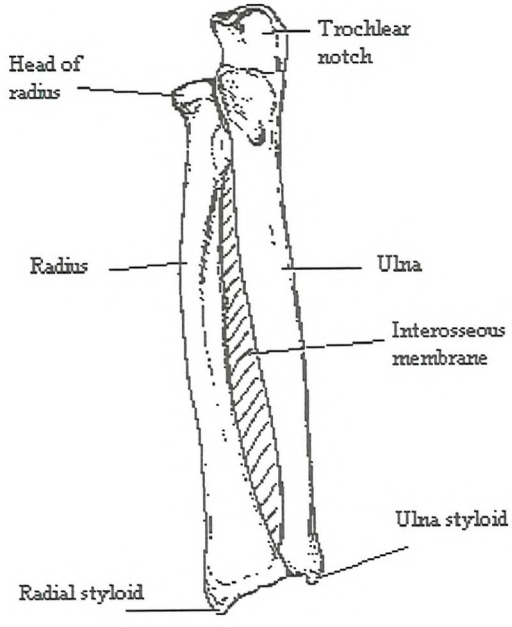


Figure B.2.7 The radius and ulna (Jackson and Bennett, 1988)



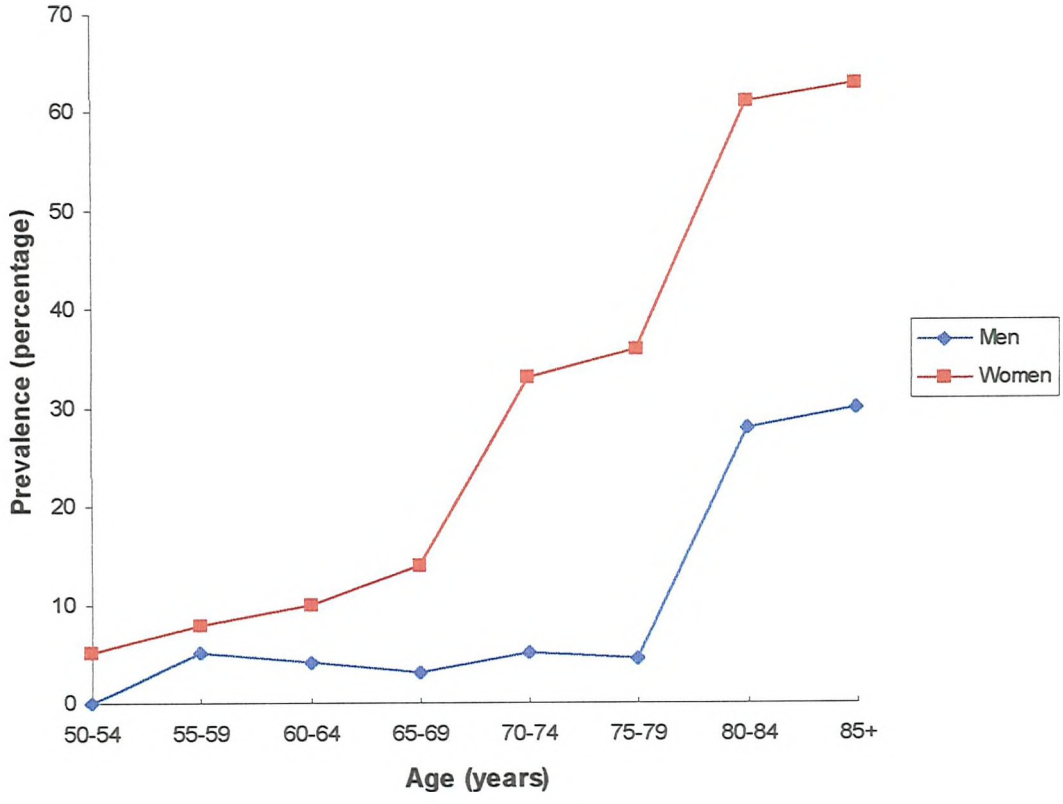
B.3. Osteoporosis:

i. Definition:

Osteoporosis is a systemic skeletal disorder characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility. The disorder is a major health problem through its association with fracture. Osteoporotic fractures typically occur at three skeletal sites; the femoral neck, vertebrae and lower end of radius and ulna.

There has been debate as to whether osteoporosis can be defined simply on the basis of a reduction in bone mass, or whether the occurrence of fracture is necessary before the term can be applied. The difficulty has recently been resolved by the World Health Organisation who have suggested that the notions of low bone mineral density and fracture may be amalgamated in a stratified definition of osteoporosis (WHO Study Group, 1994). According to this classification, there are four categories: (1) normal; where bone mineral density is not more than one standard deviation below the young adult mean, (2) low bone mass (or osteopenia); where the value for bone mineral density lies between one standard deviation and 2.5 standard deviations below the young adult mean, (3) osteoporosis; where the value for bone mineral density lies more than 2.5 standard deviations below the young adult mean, and (4) established osteoporosis; where bone mineral density is reduced below this threshold and one or more fractures have occurred. The prevalence of osteoporosis of the femoral neck in a British population according to the WHO definition (Kanis *et al.*, 1994) is shown in figure B.3.1.

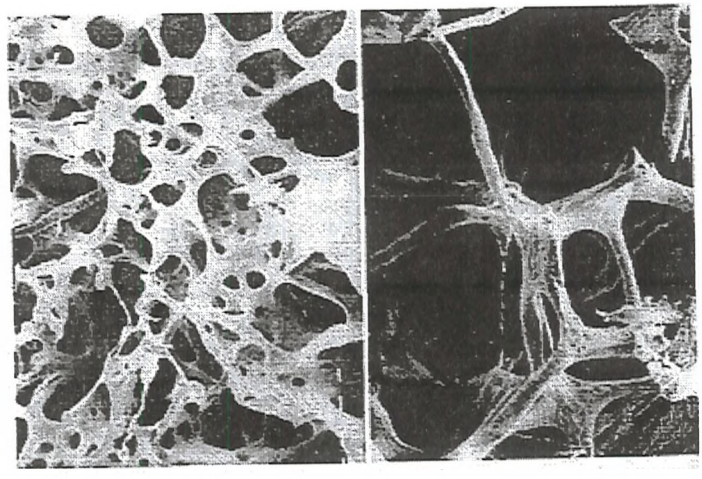
Figure B.3.1: Prevalence of osteoporosis of the femoral neck in a British population according to WHO criteria (Kanis *et al.*, 1994)



ii. Histology of Osteoporosis

Normal trabecular bone resembles a honeycomb as it consists of a highly connected network of vertical and horizontal plates (with respect to the body being in an upright position) called trabeculae. Trabecular bone mass is approximately 35% lower in patients with osteoporosis. When observed the trabeculae are thinner and differ in their spatial arrangement compared to normal bone. There is a reduction in the number of interconnections between trabeculae (see figure B.3.2) and this loss of connectivity may explain some of the exaggerated fragility of the skeleton in osteoporotic patients. Evidence has been presented that loss of horizontal trabeculae occurs earlier and to a greater extent than vertical trabeculae (Atkinson, 1997; Mosekilde, 1997).

Figure B.3.2: Scanning electron micrograph of normal (left) and osteoporotic (right) vertebral trabecular bone (Marcus, 1988).



Osteoporotic bone loss in cortical bone occurs at two sites. Firstly there is removal from the inner cortical surface and secondly removal from within the cortex. There is an increasing trend of porosity from the outer, towards the inner region of the cortex. Spaces in the inner region have the propensity to connect with the marrow cavity which consequently expands in volume (Arnold *et al.*, 1966). Enlargement and coalescence of the cavities transforms the inner third or more of the original cortex into a tissue that resembles trabecular bone.

iii. Pathogenesis of Osteoporosis:

The loss of bone, both the osteoid and mineral components, observed in osteoporosis is recognised as a major risk factor for fracture (Black *et al.*, 1992). The only opportunity for losing bone in the adult human is during the remodelling process. Bone remodelling is defective in osteoporosis in the sense that bone is removed inappropriately or not adequately replaced.

There are several points during the process of remodelling where problems can arise (Dempster and Lindsay, 1993). Increased activation of new remodelling units can lead to

temporary loss of bone since resorption precedes formation and the latter takes several months to complete. Such loss is largely reversible if the remodelling activation frequency returns to normal. Enhanced osteoclast action could result in deeper lacunae, which may be incompletely filled by the osteoblast team. The reversal process could stall, leaving resorption without formation. Finally, the team of osteoblasts could fail to refill even a normal sized resorption lacuna. In all instances bone loss would occur and be irreversible until remodelling was again initiated at the site.

These different scenarios are apparent at different sites. To illustrate, the gradual thinning of the trabeculae mentioned above, is brought about by declining osteoblast function. Thus the osteoblast teams become less and less capable of refilling the resorption cavities created by the osteoclasts, so that the trabeculae become thinner (Lindsay, 1988). In contrast, rapid postmenopausal bone loss (see p 41) is thought to be osteoclast mediated. As oestrogen concentrations fall, the osteoclasts may become hyperactive, penetrate too deeply into the plates and perforate them.

The chief culprit in cortical bone is the osteoclast, and there is evidence for an age and menopause related increase in the extent and depth of resorption cavities on the endosteal surface (Dawson-Hughes *et al.*, 1990). Cortical thinning is accompanied by a gradual increase in cortical porosity, which can be ascribed to decreased osteoblastic recruitment and vigour.

iv. Assessment of osteoporosis and diagnostic criteria

As mentioned above, the reduction of bone mass observed in osteoporotic patients is a major risk factor for fracture. Although the histology of osteoporotic bone is unique, it is not routinely used in the clinical assessment of the disease as non invasive techniques are available

Measurement of bone mass:

Several techniques are available for the assessment of bone mass (World Health Organisation, 1994). Dual energy x ray absorptiometry is widely used because of its ability to assess bone mass at both axial and appendicular sites, its high reproducibility, and the fact that is entails only low doses of radiation (Compston *et al.*, 1995). Single energy photon and x ray

absorpiometry enable measurements only at appendicular sites, usually the forearm; the machines are portable and relatively inexpensive and, like dual energy x ray absorptiometry, have high reproducibility and require very low doses of radiation. Quantitative computed tomography enables differential measurement of cortical and trabecular bone in the spine or peripheral skeleton, but the equipment required is expensive and the radiation dose relatively high.

All the above methods with the exception of quantitative computed tomography generate a linear measurement of bone mineral content (g or g/cm) which can be converted into bone density (g/cm^2) by dividing the bone mineral content by the width of the bone in the forearm or the area of the scan in the spine and hip.

There are some limitations of absorptiometric techniques. Firstly, the absolute bone mineral density of a given bone mass varies with different manufacturers' systems (Laskey *et al.*, 1992), and there are also differences in the reference data provided by the manufactures (Laskey *et al.*, 1992), so that the same measured value may lie within different parts of the reference range depending on the system used. Secondly, measurement of the bone mineral density in the spine may be affected by the presence of extraskeletal calcification, osteophytes, and vertebral deformity, particularly in elderly subjects (Reid *et al.*, 1997).

The Singh Index:

The trabecular pattern in the proximal femur is visible on plain radiographs and shows characteristic changes with ageing and loss of bone mass. Singh *et al.* (1970) described a grading system based on these changes in appearance, in which there are six grades according to the number and density of the trabecular bundles. The use of reference radiographs for comparison is essential for reproducibility. There is increased risk of fracture of the proximal femur in individuals with a Singh index of grade 3 or less but many patients presenting with fracture have normal values (Horsman *et al.*, 1982). The Singh index is therefore not a good predictor of fracture risk for the individual, although it has been of use in epidemiological studies when looking for differences between groups.

Diagnostic Criteria:

Diagnostic classification of osteoporosis is usually based on densitometric criteria (Compston *et al.*, 1995), bone density values being expressed in relation to the mean reference value in premenopausal women (T score). Bone density values are usually expressed in relation to reference data as standard deviation scores: a Z score representing the number of standard deviations above or below the age and sex matched mean reference value and a T score similarly expressed in relation to reference values for young adults. These standard deviation units reduce the problem associated with differences in calibration between instruments.

Osteopenia is defined as a T score between -1 and -2.5 and may constitute an indication for prophylaxis depending on the age of the patient and the risks and benefits of the proposed treatment. Osteoporosis is defined as a T score below -2.5 and includes nearly all women who will sustain a fracture (Kanis *et al.*, 1994). It can be regarded as an indication for intervention.

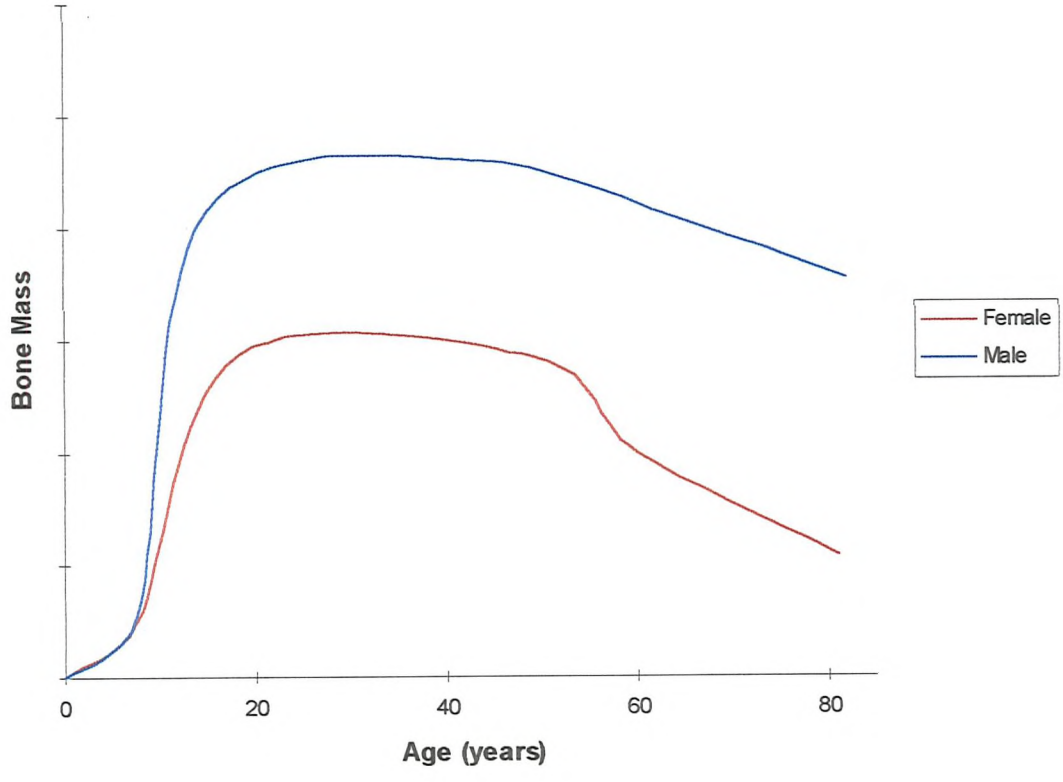
Osteomalacia:

Osteoporosis must be distinguished from osteomalacia in which the amount of bone may be normal but its mineral content is reduced (Nordin, 1983). Osteomalacia is due to delayed mineralisation of new bone. Confusion between osteomalacia and osteoporosis should seldom arise, although it is possible for the two conditions to coexist. The plasma alkaline phosphatase is raised above the normal range in osteomalacia, which is rare in osteoporosis except after a fracture episode. In addition the plasma calcium and phosphate levels are generally low in osteomalacia. Above all, the urine calcium is very low in most forms of osteomalacia, whereas it is normal or high in osteoporosis.

v. Epidemiology of Osteoporosis

Bone mass changes with age and can be categorised into three phases; growth, consolidation and loss (Refer to Figure B.3.3). Through infancy and childhood bones expand and remodel, and during this period bone gain is greater then bone resorption, resulting in a net gain of bone. During adolescence the spurt in bone mineral gain parallels the adolescent spurt in height (Baker *et al.*, 1997). At approximately 18 years of age 95-99% of the peak adult bone mass has been attained (Bonjour *et al.*, 1991). A period of consolidation follows for about 15 years, with further calcium accretion, decreased cortical porosity and increasing cortical thickening. Bone mass subsequently declines with ageing (Woolf and Dixon, 1988b). This is a universal phenomenon, occurring in both sexes and in all races.

Figure B.3.3 Diagrammatic representation of changes in bone mass with ageing.



At all ages women have less mass per unit volume of bone than men, premenopausally they have about 15 per cent less compact bone corrected for bone size. Although both sexes lose bone with ageing, loss of ovarian function, usually at the menopause, results in the most profound alteration in skeletal homeostasis and loss of bone tissue. Although men do not experience an endocrine counterpart of the menopause, some workers have shown a fall in testosterone levels in men over the age of 70 years, which may cause bone loss in later life (Baker *et al.*, 1997; Vermeulen *et al.*, 1972).

American Blacks have significantly greater bone mass than non-hispanic Caucasians (Solomon, 1979; Luckey *et al.*, 1989). It is not well understood whether racial differences in bone mass exist at birth or develop at some point thereafter. Some studies find no distinction in skeletal status between Black and Caucasian children (Prentice *et al.*, 1990; Southard *et al.*, 1991), others described significant differences at all ages during youth (Li *et al.*, 1989; Bell *et al.*, 1991; McCormick *et al.*, 1991). It has been hypothesised that the higher bone mass seen in North American Blacks stems in part from genetic factors. However, investigations of Blacks in South Africa do not support this theory. In fact their bone mass does not exceed that of age-matched South African Caucasians (Solomon, 1979; Patel *et al.*, 1997). In addition, Black children from West Africa- whence originated the majority of African-American forebears- have lower bone mass than their Caucasian peers (Prentice *et al.*, 1990). Therefore differences exist in bone mass within the Black race, with further differences introduced by acculturation in areas to which Black Africans migrated.

vi. Osteoporotic Fracture

The most important clinical consequence of osteoporosis is osteoporotic fracture. Bone fractures when its capacity to absorb energy is exceeded and therefore depends on both the magnitude of the force applied and the energy absorbing capacity of the bone.

Vertebral fractures are classified into three forms: crush, wedge and concave. Crush fractures involve compression of the entire vertebral body. In wedge fractures the posterior height is relatively maintained but there is collapse anteriorly. Concave fractures exhibit collapse of the superior or inferior endplates, or both, with relative maintenance of anterior and posterior heights (Melton *et al.*, 1988).

Forearm fractures are almost always due to a specific episode of trauma. The most usual event is a fall on the outstretched hand. In Colles' fracture there is a metaphyseal fracture through the distal radius with dorsal displacement of the hand (Melton *et al.*, 1988).

Hip fractures are classified by location into three types: femoral neck, intertrochanteric, and subtrochanteric (Heggeness and Mathis, 1996). Femoral neck fracture is also known as subcapital fracture and it lies entirely within the capsule of the hip joint. A fracture in this location often compromises the blood supply to the femoral head so that a high risk of avascular necrosis is associated with this injury. Intertrochanteric fracture is a fracture of the proximal femur at the level of the greater and lesser trochanter. There is often displacement of the trochanters, together with their muscular attachments. As the fracture is extra-articular, substantial loss of blood into the proximal thigh can occur. Subtrochanteric fracture is a fracture of the femur distal to the lesser trochanter It is less common than the aforementioned fractures. However, as with intertrochanteric fracture the injury often leads to comminution.

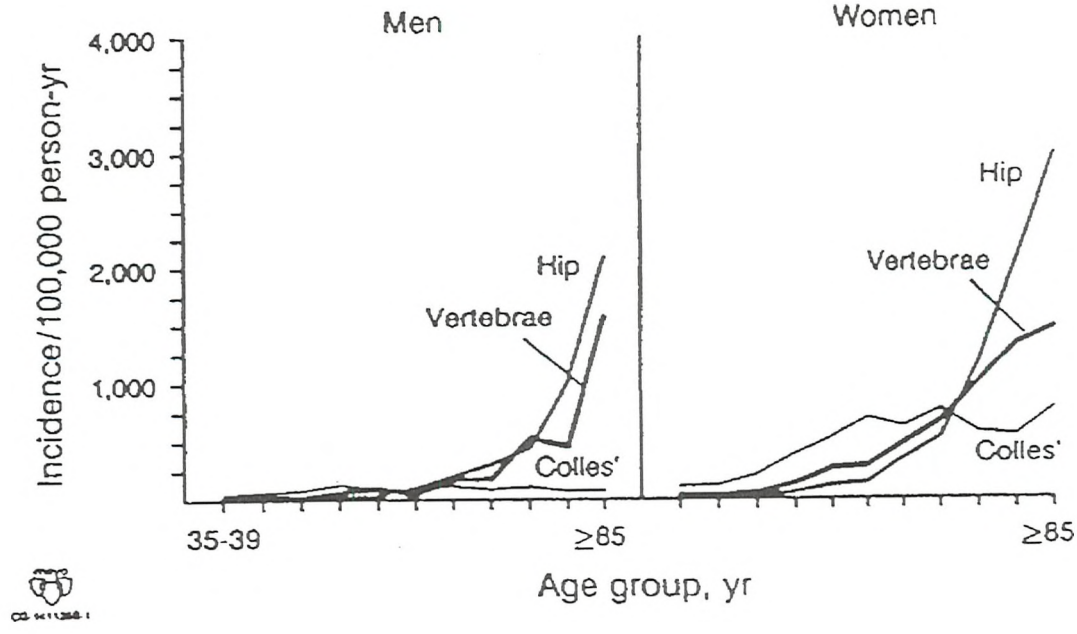
vii. Epidemiology of osteoporotic fracture

Vertebral fractures:

The investigation of the epidemiology of vertebral fractures has been hampered by difficulties in diagnoses. Early epidemiological studies used subjective radiologic assessments of wedge, crush and concave deformities, but these were poorly reproducible (Iskrant and Smith, 1969). These methods gave way to morphometric measurement of vertebral height with fractures defined according to fixed cut-off values. The application of these measurements to various population samples in the United States has permitted estimation of the incidence of new vertebral fractures in the general population. One recent estimate of the age-adjusted incidence among white American women aged 50 years and over was 18 per 1,000 person-years (Cooper *et al.*, 1992a). Although it has long been clear that a proportion of vertebral fractures do not reach clinical attention (Gershon-Cohen *et al.*, 1953), the size of this fraction is unknown.

Figure B.3.4. shows the incidence rate of clinically diagnosed vertebral fractures in men and women. In men, incidence climbs exponentially with age, adopting a pattern similar to that observed for hip fractures in the same population. In women, there is a more linear increase in incidence with age, such that vertebral fracture rates are higher than those for hip fracture before the age of 70 years, but not thereafter.

Figure B.3.4. Age-specific incidence rates for hip, vertebral and Colles' fractures in men and women in population of Rochester, Minnesotta (1985 - 1990) (Cooper *et al.* 1992a)



Colles' Fracture:

In men, the incidence remains constant throughout life. In white women, incidence rates increase linearly from the age 40 to 65 years and then stabilise (refer to figure B.3.4). The reason for this plateau in female incidence remains obscure, but may relate to a change in the pattern for falling with advancing age (Nevitt and Cummings, 1993). The slower gait and impaired neuromuscular co-ordination of elderly women makes them more likely to fall on their hip than on their wrist. The majority of Colles' fractures occur in women, and around half occur among women aged 65 years and over. There is a winter peak in Colles' fracture which is associated with falls outdoors during periods of icy weather (Cooper, 1997).

B.4. Hip Fracture

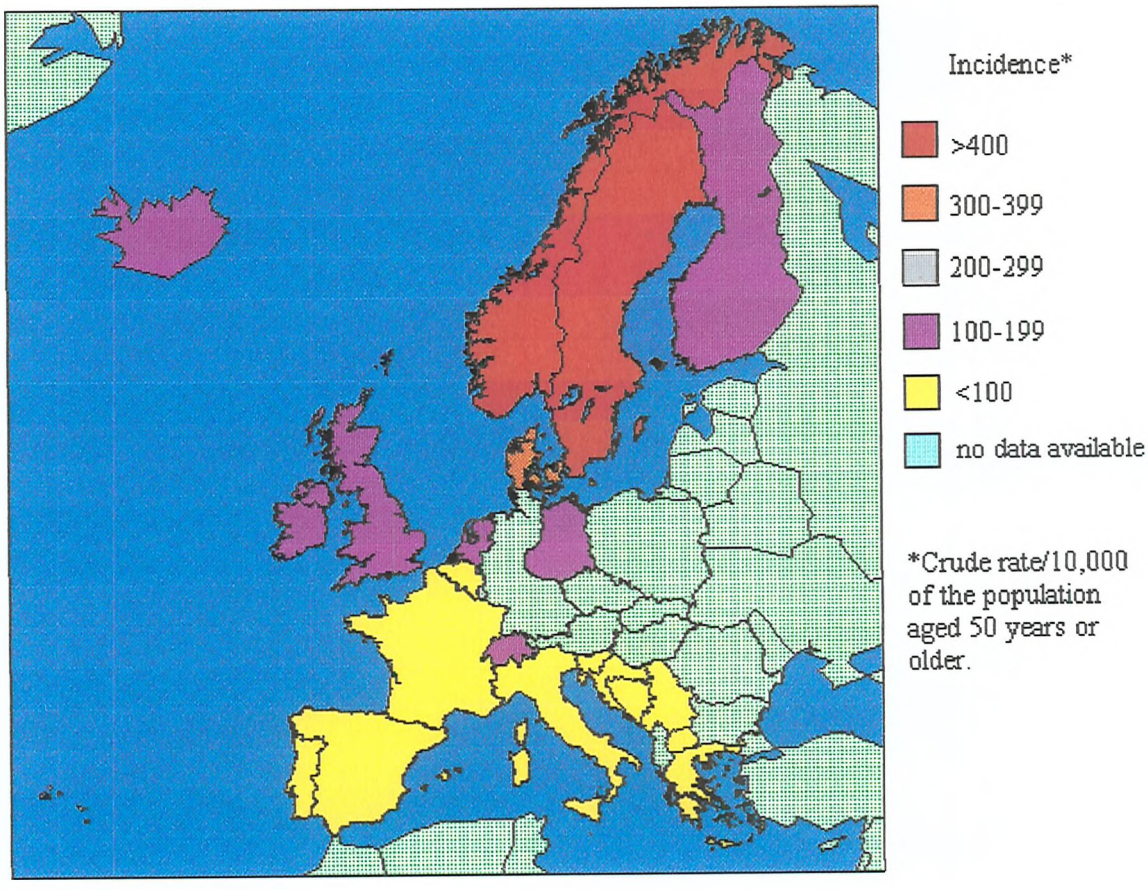
i. Description and epidemiology

The most severe osteoporotic fracture is that of the hip. Typically this results from a fall from standing position, but can occur spontaneously. A hip fracture is usually painful and almost always necessitates hospitalisation. Hip fractures lead to an overall reduction in survival of 10-20% (Melton *et al.*, 1988), with the majority of deaths occurring within the first six months after the fracture. Up to one third of hip fracture victims may become totally dependent (Jensen and Bagger, 1982), and the risk of institutionalisation is greatest among these.

Hip fracture incidence rates increase exponentially with age (Figure B.3.4). In Rochester, Minnesota, USA, rates reach about 3.0% per year among women aged 85 years and over and 1.9% among men in this age group. (Melton *et al.*, 1988). At all ages beyond 50 years, the incidence in women is about twice that in men. Because there are more elderly women than men, however, about 80% of all hip fractures occur in women. World wide, there were an estimated 1.66 million hip fractures in 1990 (Cooper *et al.*, 1992b).

Incidence rates vary substantially from one population to another, and hip fractures are much less frequent among non-whites than whites. However, there is substantial variation even within populations of a given race and gender. Thus, age-adjusted hip fracture incidence rates are higher among white residents of Scandinavia than comparable people in North America or Oceania (Melton, 1991). Even within Europe, hip fracture rates vary more than sevenfold from one country to another (Johnell *et al.*, 1992). Figure B.3.5 displays the differences in incidence of hip fracture in women across Europe

Figure B.3.5. European incidence of hip fracture in females. Data from: Efflors *et al.* (1994), Johnell *et al.* (1992) and Nagant de Deuxchaisnes and Devogelaer (1988).



ii. Risk factors for osteoporotic hip fracture

For a fracture to occur, trauma to the bone must exceed its strength. Risk factors can therefore act either by increasing the impact of the trauma or by decreasing bone strength. They can be further categorised according to frequency of falls, orientation of fall, protective responses, local shock absorbers and bone mass (Cummings and Nevitt, 1989). Some risk factors can have more than one mechanism. Figure B.3.6 summarises the risk factors identified in the literature and their proposed mechanism of action.

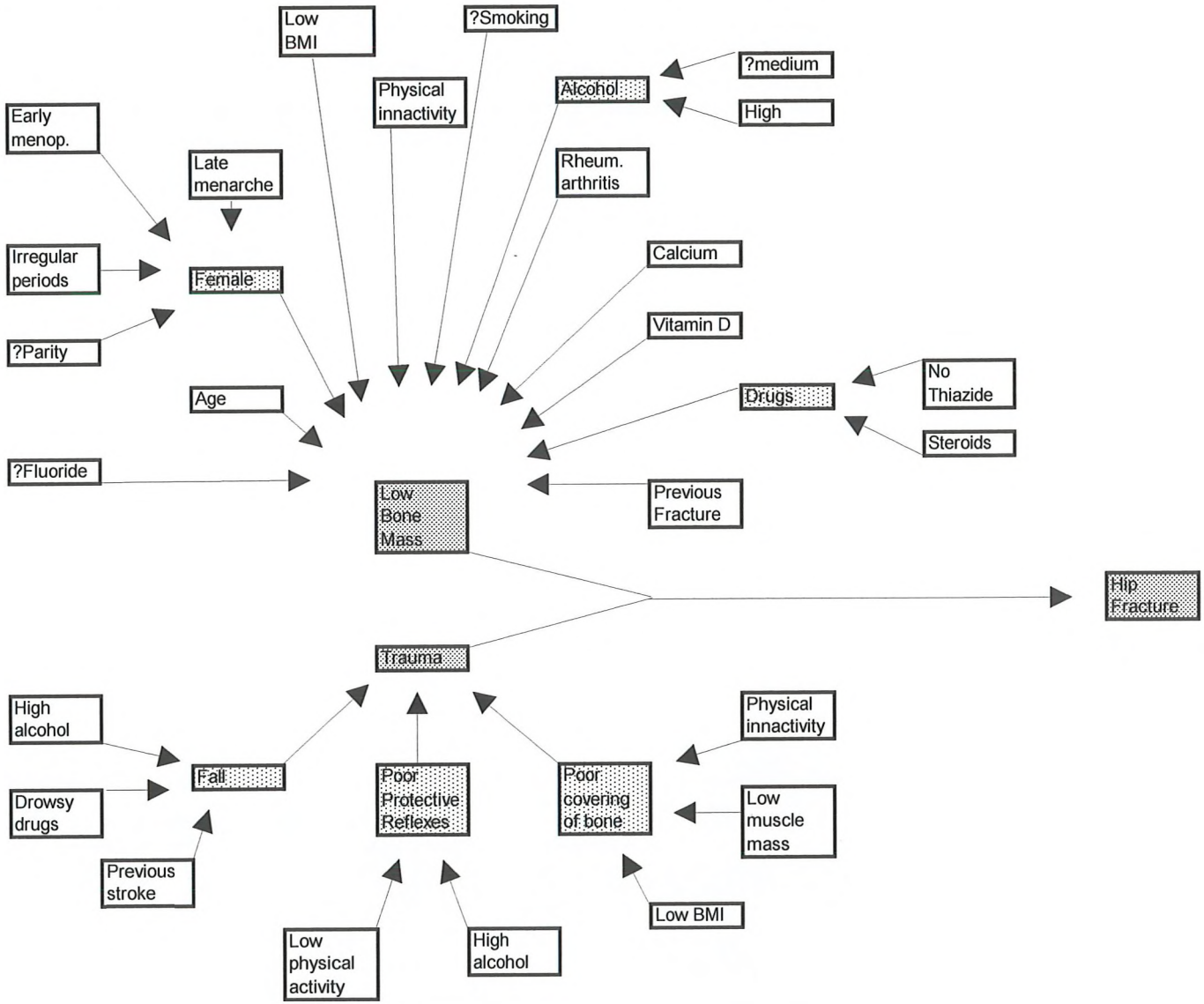
Frequency of falls:

Falls are a relatively common event among the elderly. Although fall rates are difficult to ascertain, population-based surveys and prospective studies indicate that around 30% of community-dwelling elderly fall at least once each year. However, most falls do not result in serious injuries. About 3-5% of falls in the elderly result in a fracture; about 1% result in hip fracture.

Stroke is associated with a risk of falling in the elderly and hence predisposes to hip fracture. Forster *et al.* (1995) found that 73% of elderly patients who had suffered a stroke fell in the six months after discharge from hospital. People who have experienced a stroke have an asymmetric stance with about 70% of the total body weight shifted to the unaffected leg and the gait is characterised by slower, shorter steps, lack of smoothness and asymmetry.

An increased incidence of hip fracture in people in long-term care compared with those living at home was suggested by the Mediterranean Osteoporosis (MEDOS) study in France (Piette *et al.*, 1983). Mivavet *et al.* (1993) re-analysed the findings, this time adjusting for urban background, activity and morbidity and found that living in an institution remained an independent risk factor. It is known that fractures often happen in the first months of institutionalisation and Miravet and colleagues postulated that the explanation could be the change in physical surroundings which may increase the likelihood of falling.

Figure B.3.6. Summary of risk factors identified in published literature and their proposed mechanisms of action



Orientation of fall:

The point of impact of a fall influences the type and extent of injury. Risk of hip fracture is reported as significantly increased in women falling sideways, straight down, or those who fall on or near the hip; falling backward may be associated with decreased risk of hip fracture (Cummings, 1993; Hayes *et al.*, 1993). Falling during a displacing activity, such as turning, is more likely to result in a serious injury than falling while walking in one direction (Cummings and Nevitt, 1989; Speechley and Tinetti, 1991).

Protective responses:

Several reflexes and postural responses are initiated during a fall which potentially prevent or reduce injury. These responses are protective if they can 'change the orientation of the faller or reduce the energy of a fall' (Cummings and Nevitt, 1989). The effectiveness of reflex actions depends on speed of execution and strength of the muscles initiating the protective movement (Cummings and Nevitt, 1989).

The sedating effect of certain drugs can impair protective responses. Cummings *et al.* (1995) found that therapy with long-acting benzodiazepines and anticonvulsant drugs increased the risk of hip fracture. Alcohol use has been postulated to increase the risk of falls and has been evaluated in a range of studies (Carlson, 1993). However, most studies, including community-based prospective studies, have not found an association (Campbell *et al.*, 1989; Tinetti *et al.*, 1988; Nevitt *et al.*, 1989).

Local shock absorbers:

Impact of falls can be potentially absorbed by surrounding soft tissue (skin, fat and muscles), thereby reducing the likelihood of an injury. A lower prevalence of injury occurs in fallers with more skinfold thickness (Brocklehurst *et al.*, 1978) or overall higher body weight (Grisso *et al.*, 1991; Nevitt and Cummings, 1993; Wooten *et al.*, 1982) Gissso *et al.* (1996) found a decreased body mass index in men who fell and suffered a hip fracture than elderly fallers who had also landed on their hip but did not sustain a fracture. The strength of hip abductors, the largest group of muscles surrounding the hip, is postulated to affect absorption on impact (Cummings and Nevitt, 1989).

Factors affecting bone strength:

Low bone mass independently increases the risk of osteoporotic fracture (Hui *et al.*, 1988; Cummings *et al.*, 1989; Melton *et al.*, 1993). Adjusted for age, a one standard deviation decline in bone mineral density in the hip is associated with a 2.6-fold increase in the risk of fractures of the proximal femur (Cummings *et al.*, 1993). The factors that affect bone mass are discussed.

Body Mass Index:

There is little disagreement that body weight plays a significant role in determining bone mineral density, particularly at the axial skeleton. Reid and colleagues demonstrated in postmenopausal women that total fat mass, was a consistent predictor of femoral neck bone mineral density (Reid *et al.*, 1992). From prospective cohort studies, such as the Framingham cohort's biennial examination (1988 - 1989) of 693 postmenopausal women, body mass index explained a substantial proportion of the variance in bone mineral density in the femoral neck (Felson *et al.*, 1993). From a cross-sectional evaluation of the Rancho Bernardo cohort, current body mass index explained more than 29% of the variance in bone mineral density at the total hip (Greendale *et al.*, 1995).

Physical Activity:

A number of epidemiological studies have indicated that lack of physical activity is a risk factor for osteoporotic fracture (Lau *et al.*, 1988; Wickham *et al.*, 1989; Cooper *et al.*, 1988). Greendale *et al.* (1995) studied a cohort of community-dwelling California adults (1,014 women and 689 men) with a mean age of 73 years, and found that bone mineral density at all hip sites were greater in current and lifelong recreational exercisers than in those who engaged in mild or no exercise.

Cummings *et al.* (1995) concluded from a large prospective cohort study of risk factors for hip fracture, that women who currently spent four hours per day or less on their feet had twice the risk of women who spent more than four hours per day on their feet. Women who regularly walked for exercise had a 30 percent lower risk of hip fracture than women who did not walk regularly. Risk tended to decrease as the distance walked per day increased.

Coupland *et al.* (1993) found that physical inactivity was an independent risk factor for hip fracture in the elderly. Subjects who did not regularly weight-bear, perform muscle loading activities such as climbing stairs, and perform productive activities such as gardening, were all more than twice as likely to sustain hip fracture, when compared with subjects at the higher end of the spectrum. In a study of young Asian women, Hirota *et al.* (1992) found that those who reported the longest prior history of physical activity exhibited the highest radial bone mineral density. Conversely those with the lowest bone mineral density were more likely to dislike sports.

The problem with this research is that it is difficult to estimating past activity as it relates to skeletal loading; some routine behaviours such as housework and occupational activity may not be included; and perception of exercise intensity is subject to considerable bias when activity is self-reported. In addition it is difficult to distinguish whether a high level of physical activity is a marker of a healthier person who is less likely to fall and fracture for reasons other than their participation in physical activity, or whether physical activity actually protects against fracture.

Calcium :

It has been suggested that the most primitive function of the skeleton is to buffer the internal milieu of critical minerals such as calcium (Urist, 1962). This skeletal reserve is vast compared to the cellular and extracellular metabolic pools of calcium. As a result dietary insufficiency virtually never impairs tissue function that are dependent upon calcium. However since bone strength is a function of bone mass, it follows, that any decrease is the size of the calcium reserve will decrease bone strength. Calcium functions as a threshold nutrient, which means that above a certain intake, no further benefit will accrue. There has been much uncertainty and confusion in recent years about what intake may be for various ages and physiological states.

Cooper *et al.* (1988) found in a case control study in southern Britain there was no relation between calcium intake and hip fracture in women, but men with daily intakes above 1g had lower risks. A further prospective study by the same workers confirmed that a reduced intake of dietary calcium was not a risk factor for hip fracture (Wickham *et al.*, 1989) Another prospective study, this time conducted in California, found the dietary calcium was inversely related to risk of hip fracture (Holbrook *et al.*, 1988 ,Welton *et al.* 1995) discovered a positive association between

calcium intake and bone mass in a meta-analysis. Thirty three studies were performed in adults between 18 and 50 years of age and the authors advised a calcium intake of 1500 mg/day throughout life.

Vitamin D:

Vitamin D is important for absorption of calcium from the diet. This function is particularly important for adaptation to low intakes of calcium and is relatively unimportant at high calcium intakes.

Vitamin D status, monitored by the measurement of the storage form of the vitamin 25-hydroxyvitamin D (25 (OH) D), commonly deteriorates in the elderly. The rate of age-related loss of bone has been found to be inversely correlated to dietary vitamin D (Lukert *et al.*, 1992). Low 25(OH)D levels in the elderly are partly due to decreased solar exposure, partly to decreased efficiency of skin vitamin D synthesis, and partly to decreased intake of milk, the principal dietary source of the vitamin. Moreover, the elderly exhibit other abnormalities of the Vitamin D endocrine system which may further impair their ability to adapt to reduced calcium intake. Heikinheimo *et al.* (1992) carried out a randomised, controlled trial and found that a single injection of 150,000 - 300,00 IU vitamin D each autumn resulted in a reduction in hip fractures in an elderly Finnish population. For all these reasons there is a growing body of opinion that the requirement for vitamin D increases with age (Suter and Russell, 1987; Parfitt *et al.*, 1982).

Smoking:

In most but not all studies, tobacco use is associated with an increased risk of hip fractures in women and in men (Seeman, 1996). Various mechanisms have been postulated including a direct toxic effect on bone, reduction of calcium absorption, reduction of body mass index, and for women; reduction of endogenous oestrogen and advancement of the age of menopause (Law and Hackshaw, 1997). The relative risks for hip fracture associated with tobacco use are about 1.2 to 1.5 with confidence intervals that include or almost include unity. The increased risk for fractures associated with tobacco use is likely to be partly conferred by a reduction in bone density. Tobacco users often start smoking by 10 to 12 years of age, so that reduced peak bone density may contribute to any deficit in bone density in adulthood.

Alcohol:

In women only a small proportion of hip fractures are attributable to alcohol abuse. In contrast Johnell and colleagues found that 25% of all men, and 37% of men over 30 years of age, admitted to hospital for lower extremity fractures had a history of alcohol abuse (Johnell *et al.*, 1985). Alcoholism is associated with reduced bone mineral density, Dalen and colleagues found that well nourished alcoholics had a deficit in the bone density of 4.7% at the proximal femur (Dalen and Lamke, 1976). Chon and colleagues reported reduced bone density by about 0.5 to 0.7 standard deviations in chronically alcoholic, but otherwise healthy, men abstinent from alcohol for a median period of 4 months (Chon *et al.*, 1992). The picture is complicated as alcoholism is associated with other risk factors for osteoporosis such as poor nutrition, leanness, malabsorption, vitamin D deficiency, tobacco use and an increase risk in falling.

The evidence for an association between moderate alcohol intake and fractures is contradictory. Felson and colleagues examined the association between alcohol consumption and hip fracture using a retrospective cohort design (Felson *et al.*, 1988) and found relative risk of 1, 1.34, 1.54 for light, moderate and heavy drinkers respectively for women and 1, 0.78 and 1.54 for men. All confidence intervals included unity. Hememway and colleagues studied 96,508 nurses ages 35-59 years (Hemenway *et al.*, 1994) and found an interaction between body weight and alcohol intake. Increased fracture risk was found in women who drank more than 15 g of alcohol per day and had a relative weight of less than 21 kg/m^2. Thus moderate alcohol consumption may be a risk factor for fractures, but available data are inconclusive. A risk associated with alcohol consumption may be seen primarily among those with lower body weight.

Previous fracture:

It is commonly recognised that patients with one type of age-related fracture often have an other. Patients with hip fracture are about twice as likely as expected to have had a prior fracture of the proximal humerous (Gallagher *et al.*, 1980) or distal forearm (Alffram, 1964) and 3 to 10 times more likely (depending on age) to have had a prior vertebral fracture (Pogrund *et al.*, 1977). Similarly, patients with a Colles' fracture seem to be at about twice the usual risk for a subsequent hip fracture (Owen *et al.*, 1982). Cummings *et al.* (1995) found that history of any type of fracture since the age of 50 was associated with increased risk of hip fracture. The relative risk was 1.5, (95% confidence interval 1.0 to 2.1).

Rheumatoid Arthritis:

Patients with rheumatoid arthritis have been cited as a group with increased risk of osteoporosis as they can exhibit rapid bone loss due to active disease and immobility. In addition, rheumatoid arthritis is commonly treated with oral steroids which have a well-documented deleterious effect on bone turnover (Riggs *et al.*, 1966; Gennari and Imbimbo, 1985; Hahn *et al.*, 1979). Hall *et al.* (1993) demonstrated a reduction in bone mineral density at the hip in postmenopausal women with rheumatoid arthritis. Treatment with steroids resulted in further lowering of bone density.

Diabetes:

Low bone mineral density has been found in the majority of investigations of patients with insulin-dependent diabetes mellitus (Bouillon, 1991). However, the picture is less clear in non-insulin dependent diabetes mellitus (Levin *et al.*, 1976; Weinstock *et al.*, 1989; Seino *et al.*, 1985).

The incidence of insulin-dependent diabetes mellitus peaks around puberty, a time that corresponds to rapid skeletal growth and to the achievement of peak bone mass. A detrimental effect of insulin deficiency on bone formation at this critical juncture might be expected to interfere with attainment of normal adult bone mass. In contrast, the peak incidence of non-insulin-dependent diabetes occurs after the fourth decade of life and after peak bone mass has been attained. Ninety percent of non-insulin dependent diabetics are obese, which may protect against osteoporosis.

A pooled estimate of the increased risk of fracture in diabetes is approximately twofold (Bouillon, 1991). However, a retrospective case-control study from the Mayo Clinic failed to show any increase in the incidence in either types of diabetes (Health *et al.*, 1980).

Medication:

Some medication can alter bone mineral density. Corticosteroids have a well-documented deleterious effect on bone turnover (Riggs *et al.*, 1966; Gennari and Imbimbo, 1985; Hahn *et al.*, 1979). Hall *et al.* (1993) found that treatment with steroids in rheumatoid arthritis sufferers further lowered the bone density at the hip. Cauley *et al.* (1993) found that women who had been using

thiazide diuretics for more than 10 years had significantly higher bone mass then women who had never been prescribed these drugs ($p<0.001$). It is proposed that thiazides induce hypocalciurea which may protect against bone loss (Rashiq and Logan, 1986).

Prostaglandin inhibition by nonsteroidal anti-inflammatory drugs (NSAIDs) may inhibit bone loss and preserve bone mineral density. Bauer *et al.* (1996) assessed the risk factors for osteoporosis and the use of NSAIDs in 77786 white women over age 65 by measuring axial bone mineral density and documenting fractures. Although there was an increase in bone mineral density of the hip of 2.3-5.8% which was reduced to 1.0 - 3.1 % after adjustment for confounders, there was no difference in fracture risk between the two groups.

Teeth:

Postmenopausal women with osteoporosis have a higher than expected number of dentures and fewer teeth (Groen *et al.*, 1968; Kribbs, 1990). It has also been reported that increased tooth loss with age is associated with an increased risk of hip fracture (Astrom *et al.*, 1990). Both loss of bone and adult tooth loss may reflect common systemic metabolic effects. Histological studies have shown that low bone mineral content of the mandible is associated with low bone mineral content of the femoral neck (Dyer and Ball, 1980). May *et al.* (1995) investigated a cohort of participants from general practices in the Cambridge health district and found a consistent decrease in bone mineral density with increasing numbers of teeth lost in men, independent of age, body mass index and smoking habits but not in women.

A Swedish study of 14,375 men and women over the age of 64 years, had their number of teeth documented by dentists and the number of hip fracture sustained over the next 3 years was observed. Women in the tertile with the fewest remaining teeth had a risk of fracture twice that of the women in the other tertiles. The risk of hip fracture for men in the tertile with the fewest remaining teeth was three times that of the other men (Astrom *et al.*, 1990).

Female reproductive variables:

The hormonal status of females is a major factor with respect to their bone mineral density. The hormonal history from menarche through to menopause is of relevance and will be discussed.

Age at menarche can be related to bone mineral density in at least two aspects. First, women with an earlier age at menarche are likely to have a longer time between menarche and the menopause, a time frame during which oestrogen resources are available to support and maintain bone mineralisation. Secondly, events which precipitate earlier menarche may be associated with characteristics which have been reported to produce greater bone density, for example body mass index .

Frank amenorrhea is reported to have a prevalence of 2% in young adult women (Bachmann and Kemmann, 1982). Reported menstrual cycle changes in women who exercise strenuously include delay in menarche (Nelson *et al.*, 1986), shortened luteal phase of the menstrual cycle (Prior *et al.*, 1990), menstrual irregularities, oligomenorrhea and amenorrhea (Drinkwater *et al.*, 1990; Henley and Vaitukaitis, 1988). In addition amenorrhea is a recognised complication of anorexia nervosa.

Pregnancy and lactation are two stages of the reproductive cycle which are characterised by significant alterations in the maternal hormonal environment. During the third trimester of pregnancy maternal oestrogen levels rise as the placenta produces large quantities of oestradiol to facilitate growth (Jaffe and Dell'Acqua, 1985). In contrast, lactation represents a hypoestrogenic state in response to elevated prolactin (Speroff *et al.*, 1989). In this fluctuating hormonal environment, there is substantial calcium transfer from the mother to the foetus. There is obvious concern that foetal demand might outstrip the calcium available from intestinal absorption forcing the reservoir of the maternal skeleton to be accessed.

Thus, the relationship of parity to bone mass is complicated as on one hand pregnancy and lactation decreases the available calcium to the maternal skeleton and on the other there may be an increase due to the greater oestrogen levels in the third trimester and the increased bone-loading that occurs with the weight increases in pregnancy.

Two studies, a longitudinal study (Paganini-Hill *et al.*, 1991) and a case-control study (Hoffman *et al.*, 1993), provide evidence of a protective effect for parity in relation to hip fracture. In both studies, women with three of more children had an approximate 30-40% reduction in risk for fracture as compared to nulliparous women. There have been at least five studies of parity and fracture which have shown no association with parity (Kreiger *et al.*, 1992; Alderman *et al.*, 1986; Ribot *et al.*, 1993; Cumming *et al.*, 1993; Laskey *et al.*, 1990).

Loss of ovarian function, usually at the menopause or after surgical ovariectomy, results in the most profound alteration in skeletal homeostasis and loss of bone tissue. Oophorectomy is commonly cited as an example of hypoestrogenism with an impact on measures of calcium metabolism (Gallagher *et al.*, 1972), fracture (Krieger *et al.*, 1982), and bone mineral content (Richelson *et al.*, 1984; Aitken *et al.*, 1976). As women become oestrogen deficient there are significant changes in the remodelling process. First there is a clear increase in the frequency at which new remodelling cycles are created and a deficit in the amount of new bone formed within each remodelling unit (Parfitt, 1988).

The loss of bone after menopause follows an exponential pattern (Hedlund and Gallagher, 1989; Nordin *et al.*, 1989). Bone resorption increases more suddenly after an artificial menopause than after a natural menopause, probably because the levels of oestrogen decline more rapidly. Several case control and cohort studies have compared oestrogen use in hip fracture cases with that of controls, and have shown reductions in fracture risk of 20-60% (relative risk 0.4-0.8) (Hutchinson *et al.*, 1979; Ettinger *et al.*, 1985; Cauley *et al.*, 1994). There has been only one long-term prospective study which showed that prolonged oestrogen treatment maintained bone density in the hip (Lindsay *et al.*, 1980).

The impact of oral contraceptive use on bone mineral density remains uncertain with a proliferation of recent studies reporting either no effect or a positive relation (Sowers, 1996). The number of studies of oral contraceptives and fracture are limited mostly because wide spread use started in 1960s and therefore those women are only now reaching an age where fractures are more common. Copper *et al.* (1993) examined the fracture experience of the 46,000 enrolees in Royal College of General Practitioners Oral Contraception Study which began in 1974. The risk of subsequent fractures was significantly greater among the oral contraceptive users than among the nonusers.

B.5. Fluoride and bone

i. Distribution of fluoride

Fluoride is the ionic form of fluorine, a halogen and the most electronegative of the elements of the periodic table. It is the 13th most abundant element in the crust of the earth.

Fluoride concentration in soils varies enormously from place to place, the published figures ranging from 10 to 1070ppm, with average values between 200 and 300ppm (Vinogradov, 1970). The amount of free fluoride ions in the soil is governed by the natural solubility of the fluoride compound in question, the acidity of the soil, the presence of other minerals or chemical compounds and the amount of water present. The fluoride concentrations also increase with depth (National Research Council, 1993).

Due to the universal presence of fluoride in the earth's crust, most surface and ground water contains fluoride. Sea water contains concentrations in the range of 0.8 - 1.4 ppm. In Britain the fluoride content of water obtained from lakes, rivers and wells is mostly below 0.5 ppm. See above (pages 7-9) for details of the fluoride concentration of drinking water in the UK.

Fluorides are also widely distributed in the atmosphere, originating from the dusts of fluoride-containing soils (Noguchi *et al.*, 1963), from gaseous industrial waste (MacIntire *et al.*, 1952) and from the burning of coal fires (Cholak, 1959).

ii. Sources of intake:

Dietary:

The two most important sources of fluoride in the diet, apart from drinking water, are tea and fish. The tea plant takes up fluoride from the soil and stores it in the leaves, which when dried may contain between 50 and 350ppm. As the fluoride is readily soluble in water, an infusion of tea leaves may contain 1-3ppm (Duckworth and Duckworth, 1978). Concentrations of fluoride are high in the bones (500ppm) and the skin (8ppm) of fish (Jenkins and Edgar, 1973) and therefore it is only when eating the whole fish, for example, tinned sardines, that its contribution is noteworthy. A typical helping may contain 1-2mg.

The average dietary intake of fluoride in the United Kingdom is estimated to be 1.82mg daily (Sherlock, 1984). Around 70% of this value is obtained from beverages. An above average consumption of tea may result in an intake as high as 8-9 mg daily. It has been estimated that extreme tea drinkers may have daily intakes as high as 12mg (Walters *et al.*, 1983).

Non-Dietary:

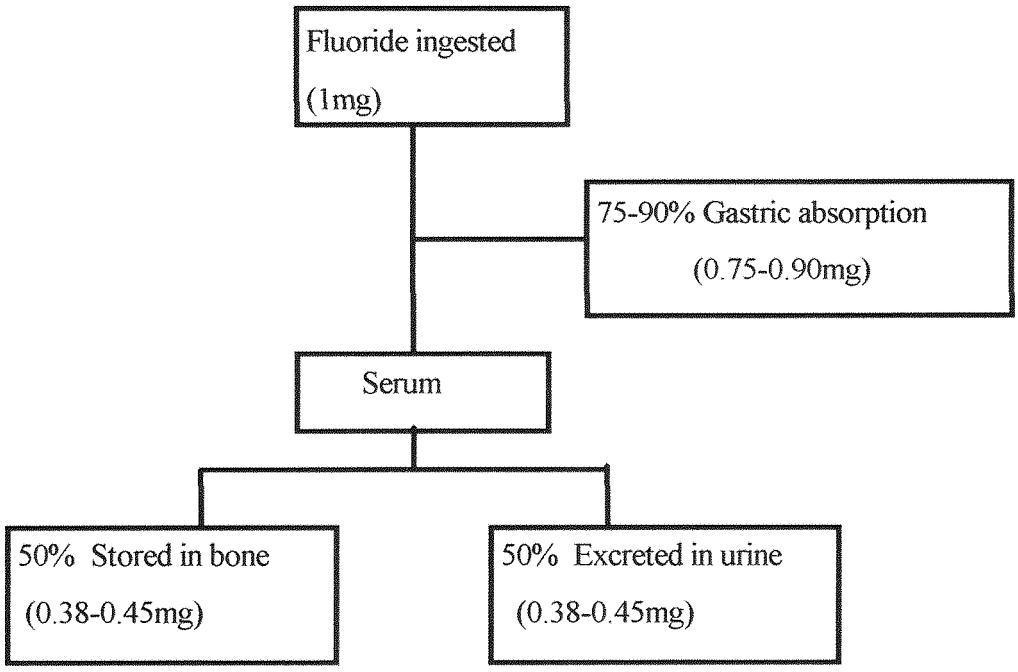
In the developed world most people have been exposed to high concentrations of fluoride in the form of tablets, toothpastes, mouthrinses and less frequently topical dental applications such as solutions and gels. Each episode of brushing with fluoridated toothpaste is associated with an exposure of 1mg of fluoride. If the person then spits the toothpaste out without rinsing, 30% of the fluoride is retained. The fluoride retained has 80% bioavailability (M. Davies oral communication).

Fluoride inhalation from the atmosphere accounts for just 0.01 mg per day of the intake of fluoride (Hodge and Smith, 1977).

iii. Fluoride pharmacokinetics

Fluoride is absorbed and enters the plasma via the gastrointestinal tract. Approximately 50% of an absorbed amount will be excreted in the urine during the following 24 hours, while most of the remainder will become associated with calcified tissue. The major features of fluoride metabolism are shown in figure B.5.1.

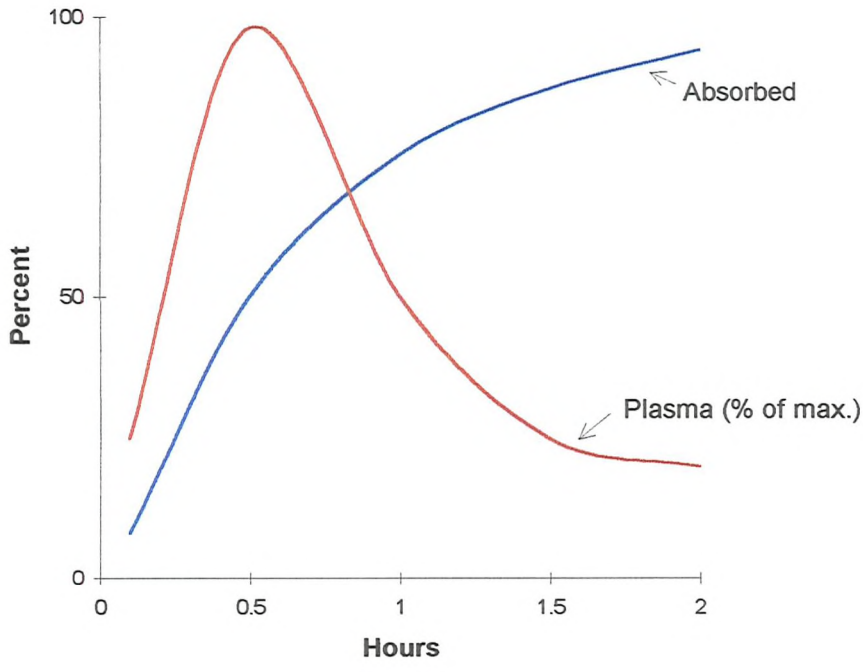
Figure B.5.1: Summary of the pharmacokinetics of ingested fluoride



Absorption:

Fluoride combines with hydrogen ions to form a weak acid, hydrogen fluoride. Hydrogen fluoride has a pKA of 3.4 and it is in this form that fluoride is able to pass through biological membranes (Ekstrand and Spak, 1990). In the absence of high levels of ions that can combine with fluoride to form insoluble salts, the rate of absorption is rapid. The half-time for absorption is about 30 min and the peak plasma concentration usually occurs within 30-60 min (Whitford, 1996). The general relationship between the rate of absorption and plasma fluoride levels is shown in figure B.5.2.

Figure B.5.2 Displays the relationship between the rate of absorption and plasma fluoride levels



The absorption of fluoride is by passive non-ionic diffusion, its rate being dependent on the concentration gradient, and not involving metabolic activity (Ekstrand and Whitford, 1988). The extent of absorption from the stomach is inversely related to the pH of the contents and may account for up to 40-50% of the amount ingested. Most of the remainder is absorbed from the upper small intestine.

Distribution:

Within the various soft tissues, fluoride rapidly establishes a steady-state distribution between extracellular and intracellular fluids. Steady-state means that, while the fluoride levels within these two compartments are not identical, they do parallel each other, rising and falling proportionately and simultaneously (Whitford, 1996). To illustrate the steady state achieved in extracellular fluids, the mean concentration of fluoride ions in a series of random blood samples was found to be approximately 0.01 ppm in areas with low fluoride concentrations in the drinking water (0.25ppm), compared with 0.02ppm in areas with higher levels in the water (1.2ppm) (Ekstrand, 1978).

As is evident from figure B.5.2, the rapid rise of plasma fluoride after absorption of hydrogen fluoride lasts only for an hour or so and therefore there must be a mechanism that allows for rapid

elimination of most of the absorbed dose. The removal of fluoride from the plasma occurs via two processes; uptake and accumulation in the bone and elimination via the kidneys.

Uptake of fluoride by bone:

The main constituent of skeletal tissue is hydroxyapatite. An important property of hydroxyapatite is that several different ions can occupy positions in the crystal by either hetero-ionic or iso-ionic exchange. The resulting crystal's form and dimension are only changed slightly. The dimensions of fluoride are such that it can occupy a position within the structure and form hydrogen bonds with nearby OH ions. As a result, the crystal, now termed fluroapatite, is more stable and will dissolve less readily (Kay *et al.*, 1964).

Approximately 99% of the body burden of fluoride is found in bone. Fluoride uptake into bone is in three stages (Neuman and Neuman, 1958): fluoride ions exchange with one of the ions or polarised molecules present on the hydration shell; fluoride ions exchange from the hydration shell with an ion group at the surface of the apatite crystal which becomes fluorapatite; and then fluoride ions present in the crystal surface migrate slowly into vacant spaces in the interior of the crystal during recrystallization.

Fluoride uptake in the bone is dependent on the concentration gradient between the blood and the bone. To illustrate, Zipkin *et al.* (1960) looked at how the concentration of fluoride in bone compared to the concentration of fluoride in the drinking water with the following results:

Table B.5.1: Comparison of concentration of fluoride in drinking water and bone (Zipkin *et al.*, 1960).

Fluoride in drinking water	Fluoride in bone (% of ash weight)
<1.0ppm	0.08
1.0ppm	0.22
2.6ppm	0.40
4.0ppm	0.69

Alhava *et al.* (1980) also explored this issue. They measured the fluoride content of iliac bone in post-mortem cases from Kuopio, Finland (water fluoridated to 1ppm) and outside Kuopio (fluoride level 0.1ppm). They found that men and women who had lived in Kuopio had an average bone fluoride level of 901ppm and 1280ppm respectively. Subjects who had resided outside Kuopio had much lower levels; men 319ppm and women 384ppm. They also found that the fluoride content of the bone increased with age. These data compare with a bone concentration of 3500 ppm in preclinical skeletal fluorosis (Riggins *et al.*, 1974).

Further evidence of the effect of the concentration gradient is that in the young fluoride uptake by the bone is high as the bone is low in fluoride and a higher concentration gradient exists (Evans and Wood, 1994).

It is important to note that fluoride in bone is not irreversibly bound. In the longer time frame fluoride in the deeper regions of bone can be released during the process of normal bone remodelling (Whitford, 1996). Thus, if the intake of fluoride were to increase or decrease on a chronic basis, the concentration in the calcified tissues would eventually reflect the change. To illustrate, when the fluoride in the water supply in Bartlett, Texas, was reduced from the excessive 8ppm to approximately 1 ppm, urinary fluoride excretion was over 4ppm for about 20 weeks after defluoridation and continued to fall, although more slowly. It was suggested that the rapid initial drop occurred as the fluoride in superficial parts of the fluoride-rich bone exchanged with hydroxyl

ions and approached a new equilibrium. The later slower loss probably occurred from the replacement of old bone by new, low in fluoride, in the course of remodelling (Litkins *et al.*, 1956).

Deposition of fluoride in bone

Fluoride is not deposited uniformly in bone. Using x-ray microprobe analysis fluoride accumulation was found around Haversian systems (Bang, 1978). Also there is a higher fluoride content in trabecular bone compared to cortical. Singer *et al.* (1974) investigated the fluoride concentration of different regions of the human rib and found that fluoride made up 1.15% ash weight of the cortical bone and 1.50% of the trabecular bone. The explanation may be that trabecular bone is more metabolically active than cortical and therefore the blood supply is greater (see p13); as more fluoride comes into contact with trabecular bone, its uptake into the bone is increased compared to cortical bone.

Elimination:

The principal route of elimination of fluoride is via the kidneys. It has been shown that the clearance of fluoride is less than that of inulin, which indicates that some of the fluoride filtered through the glomerulus is reabsorbed by the tubules (Carlson *et al.*, 1960). 35-45% of the fluoride is reabsorbed in the proximal tubule, but this percentage is increased if the pH falls in the proximal tubule as this results in more fluoride being converted to hydrogen fluoride which diffuses into the cells (Whitford *et al.*, 1979). A substantial part of the fluoride that is ingested is rapidly excreted from the body. This has been illustrated by tracing a 1mg dose of fluoride through the body and it was found that 30% of the dose had been excreted in 4 hours (Whitford *et al.*, 1979; Ericsson, 1958).

In addition, 10-25% of the daily intake of fluoride is not absorbed and is therefore expelled, unchanged, in the faeces. It is not known if biliary excretion of fluoride is an important factor.

iv. Fluoride and Osteoporosis:

Fluoride accumulation in the bone is known to change both the metabolism of bone and its structure. Studies in humans and several animal models have shown that sodium fluoride stimulates bone formation. It appears that sodium fluoride promotes recruitment of active, normally functioning osteoblasts, independent of osteoclastic activity. There is an increase in osteoid thickness and the rate at which the matrix is made.

In addition it has been shown that fluoride delays the initiation of mineralisation of newly formed bone matrix and decreases the rate at which mineralisation proceeds on previously calcified matrices (Baylink *et al.*, 1983; Harrison *et al.*, 1984).

The substitution of fluoride ions for hydroxyl ions has consequences on the shape and structural stability of the apatite crystals, as well as on their kinetics of precipitation and dissolution (Grynpas, 1990). The structure of flurorapatite is simpler and more stable than that of hydroxyapatite as the fluoride occupies a different position in the lattice.

As hydroxyapatite is a complicated crystal it tends to have imperfections, one of which occurs in relation to the hydroxyl (OH) groups which form a column running through the middle of each crystal. The orientation of the OH ions is reversed at intervals and this results in a vacancy, as two OH ions cannot point towards each other as the hydrogen ions would repel each other and would not fit in the lattice. The dimensions of fluoride are such that it can fill the vacancy and also be attracted to the nearby hydrogen bonds. Therefore the crystal is more stable and will dissolve less readily (Moreno *et al.*, 1997). Another effect of the fluoride ion on the lattice of apatite is to cause a contraction in the size which produces a smaller unit cell volume compared with hydroxyapatite (LeGeros *et al.*, 1997; Moreno *et al.*, 1997). This enhanced stability makes the skeletal system more resistant to osteoclastic resorption.

In summary, fluoride promotes osteoblasts and also alters the structure of the apatite crystals by increasing crystallinity, reducing crystal strain, reducing unit cell size, reducing solubility and reducing surface area (Grynpas, 1990) which makes the structure more resistant to osteoclastic resorption. This can profoundly affect bone mineral deposition and dissolution.

v. Fluoride and osteoporotic fracture

In this discussion of fluoride and osteoporotic fracture, the extreme situation of fluorosis will be reviewed first, followed by the effects of fluoride as a treatment of osteoporosis, and finally the evidence that has accumulated from ecological and individual studies of fluoride and fracture.

Intake of fluoride at relatively high levels for protracted periods leads to changes in the structure and physical characteristics of bones. The condition, known as skeletal fluorosis, has been defined in terms of a preclinical stage and 3 clinical stages (Hodge and Smith, 1977).

In the preclinical stage, patients have no symptoms but a slight increase in bone mass is apparent radiographically, particularly in the trabeculae of the lumbar spine; bone ash fluoride concentrations are generally between 3,500 and 5,500ppm. Patients with stage 1 skeletal fluorosis experience occasional pain and stiffness of some joints and some degree of osteosclerosis of pelvic and vertebral bones is apparent; bone ash fluoride concentrations are usually in the range of 6,000-7,000ppm. Stage II is characterised by chronic joint pain, slight calcification of ligaments, increased osteosclerosis of cancellous bones and, in some cases, osteoporosis of long bones; bone ash fluoride concentrations are 7,500-9,000ppm. Stage III is a severely debilitating condition called crippling fluorosis, in which bone ash fluoride concentrations generally exceed 9,000ppm. Calcification of ligaments often precludes joint mobility and numerous exostoses may be present. These effects may be associated with muscle wasting and neurological problems due to spinal cord compression. Most estimates indicate that crippling skeletal fluorosis occurs when 10-20 mg of fluoride have been ingested on a daily basis for at least 10 years (Whitford, 1996).

Although fluorotic bone is sclerotic, in the sense that there is more of it than normal, it is not as strong, weight for weight, and spontaneous fractures have been described (Nordin, 1973).

Fluoride as treatment for osteoporosis:

Sodium fluoride (NaF) has been used to treat established osteoporosis for at least 30 years. This therapy originated from the thought that skeletal fluorosis may be the antithesis of osteoporosis (Bernstein *et al.*, 1966).

It is widely agreed that treatment with fluoride increases trabecular bone mass in the axial skeleton. Sodium fluoride therapy has therefore been used in patients with established osteoporosis, typically vertebral deformities, in an effort to reduce further bone loss or add to the existing bone mass and to prevent further fracture (Gordon and Corbin, 1992). The minimum dose of sodium fluoride with a demonstrable effect on bone mass is about 40 mg daily.

However the striking increase in trabecular bone mass induced by sodium fluoride therapy is not accompanied by an increase in the cortical bone of the appendicular skeleton. On the contrary, sodium fluoride therapy may decrease cortical bone mass (Ringe *et al.*, 1978; Riggs *et al.*, 1990).

To investigate the value of fluoride therapy for osteoporosis, five clinical trials have been performed. These have provided information on exposure to relatively high concentrations of fluoride amongst groups at high risk for vertebral fractures related to osteoporosis. The daily intake in these trials ranged from 50 to 80mg of sodium fluoride.

Dambacher *et al.* (1986) followed a relatively small number of subjects for 3 years. The treatment group received 80mg of slow release sodium fluoride daily and were compared to patients without fluoride treatment. During the first year of the study patients receiving fluoride treatment had significantly more vertebral fractures than the control group. In addition, 47% of patients in the treated group had experienced osteoarticular pain and swelling in the lower extremities, attributed to stress fractures.

Two large prospective randomised controlled trials of high dose sodium fluoride (75mg daily) in the United States (Riggs *et al.*, 1990; Kleerekoper *et al.*, 1990) suggested that despite a marked improvement in lumber spine bone mineral density, fluoride treated individuals showed no reduction in spine fracture over a 4-year period and had a loss of bone mineral from the

appendicular skeleton. The results of these two studies have led to the large scale abandonment of high dose sodium fluoride in the treatment of established osteoporosis.

Data on the use of lower doses (25-50mg daily) have been more encouraging. In a French study (Mamelle *et al.*, 1988), spinal fracture incidence was clearly reduced amongst 257 patients prescribed sodium fluoride compared with 209 patients given other therapy over a 2 year period. A more recent randomised controlled trial from the United States, which used slow release sodium fluoride (25mg twice daily) gave similar findings (Pak *et al.*, 1994).

The only randomised controlled trial using sodium fluoride (25mg daily) as primary prevention for fracture reported a doubling of hip fracture incidence among 460 elderly nursing home residents over eight months when compared with controls (Inkovaara *et al.*, 1975).

Thus treatment with sodium fluoride, despite being able to increase trabecular bone volume, may not be able to restore the original, biomechanically competent architecture. Osteoblasts can only deposit newly synthesised bone matrix on existing bone surfaces. Therefore only the existing trabeculae can be strengthened and connectivity of the trabeculae is unchanged. Consequently, even though the bone mass is increased it may not follow that the mechanical strength is increased to the same extent as would be expected in normal bone.

In summary, while the use of high doses of sodium fluoride in established vertebral osteoporosis suggests that bone strength may be compromised and that hip fracture incidence might be increased, the studies of lower dose therapy are more encouraging

Water Fluoride and Hip Fracture:

The risk of bone fracture in the elderly has been studied in people exposed to naturally occurring or added fluoride in drinking water and compared with that in people exposed to low concentrations of fluoride in drinking water. Both population-based (ecological) studies and individual-based studies have been carried out.

Ecological Studies:

Refer to Table B.5.2 for a summary of the ecological studies.

The first authors to address this issue were Alffram *et al.* in 1969. They used data from three studies, each of which had investigated the incidence of hip fracture in a different Swedish city. The cities differed in their water fluoride concentration; Gothenburg (<0.1ppm), Malmo (0.2-0.4ppm), and Eskilstuna (0.8 - 1.2ppm), but no statistically significant differences in the hip fracture rates were observed. Information on the sample size was only available for Malmo where there were 1,625 fractures in 210,000 inhabitants.

In the United States, two early ecological studies also suggested no effect of water fluoride concentration on hip fracture rates. Korns (1969) investigated two neighbouring towns in the USA which differed in fluoride status; Newburgh (1.0-1.2ppm) and Kingston (0.05ppm). The community of Newburgh had been continuously exposed to this fluoride level since 1945. They recorded the number of hip fractures that occurred in each town (excluding those secondary to metastatic disease) over three years. No differences were observed between the two towns with respect to hip fracture rates. As there were a total of 93 hip fractures observed in the population of 14,092, the statistical power of the study was rather limited.

Madans *et al.* (1983) used data from the 1973-1977 US National Health Interview Surveys (NHIS) to investigate whether water fluoridation was related to osteoporotic hip fracture. Cases were white people admitted to hospital with a hip fracture. This information was obtained from the NHIS hospital episode record and there was no information how hip fracture was coded. Information with respect to ICD codes would have provided a more accurate picture.

As there was no method for the individual measurement of fluoride in the water available, the Centres for Disease Control provided information on the percent of the population in each county served with water containing at least 0.7ppm fluoride. This value was then interpreted as the probability that the respondent was exposed to a water fluoride content of at least

Table B.5.2. Summary of ecological studies investigating the relationship between water fluoride and hip fracture.

Author	Location	No. fractures (population at risk)	No of centres	Duration	Association	
					Direction*	Significance
Alffram et al. (1969)	Sweden (Malmo and Billesholm)	1,625 (210,000)	2	Not stated	Negative	NS
Korns et al. (1969)	U.S.A. (Kingston and Newburgh, N.Y.)	93 (14,092)	2	3 years	-	NS
Madans et al. (1983)	U.S.A	574 (313,352)	388	5 years	-	NS
Simonen et al. (1985)	Finland (Kuopio and Jyvaskyla)	395 (21,536 - 32,292)	2	12 years	Negative	p<0.001
Arnala et al. (1986)	Finland (Kuopio and Kotka)	61 (not stated)	3	Not stated	-	NS
Jacobsen et al. (1990)	U.S.A.	514,985 (not stated)	Not stated	4 years	Positive	p<0.009
Cooper et al. (1991)	U.K.	20,393 (not stated)	39	5 years	Positive	p<0.001
Danielson et al. (1992)	U.S.A. (Utah)	246 (4,999)	3	7 years	Positive	R.R.**1.27 (CI 1.00 - 1.46)
Jacobsen et al. (1992)	U.S.A.	218,951 (approx 30 million)	323	4 years	Positive	R.R.**1.08 (1.06-1.1)
Suarez-Almazor et al. (1993)	Canada (Alberta)	4,915 (not stated)	2	7 years	-	NS
Jacqmin-Gadda et al. (1995)	South West France	70 (3,777)	75	Not stated	Positive	O.R. ***1.86 (1.02 - 3.36)

* Direction is direction of association; positive implies higher hip fracture risk in fluoridated area and vice-versa.

0.7ppm. There was no statistically significant difference between areas of low fluoride probability (below 0.2) and high probability (above 0.8) regarding rates of hospitalisation. As there were a total of 574 fractures observed from a population of 313,352 the statistical power of the study was good.

The first evidence for a protective effect of water fluoridation came from Simonen *et al.* (1985) who found a lower hip fracture incidence rate in a Finnish town (Kuopio) which fluoridated its drinking water to 1ppm compared to another (Jyvaskyla) which did not. All cases of femoral-neck fracture, coded as 820.0 to 820.10 using ICD, were recorded from the hospital discharge data (there was no information on which ICD revision was used). Relative risks in Javaskyla were 2.5 (men) and 1.5 (women) times those in Kuopio ($p<0.001$ and $p<0.05$, respectively).

Arnala *et al.* (1986) also studied the incidence of fracture in Finland. This time three communities with different fluoride concentrations in the drinking water (0.3ppm, 1.0-1.2ppm and >1.5ppm) were compared. However, the exact population and time period of study and the method of ascertaining hip fracture rates are poorly described in the published report. The authors concluded that the incidence of hip fracture did not differ between the three areas. There is insufficient information in the published report to gauge the power of the study.

The first study to suggest a higher risk of hip fracture in fluoridated areas was published in 1990 by Jacobsen *et al.* This was a large national analysis of over 3,000 USA counties using data from the Health Care Financing Administration, which compiles data on all hospital discharges for persons covered under the Medicare program, between 1984 and 1987. They found a statistically significant positive correlation between the county-specific age-adjusted incidence of hip fracture in white women aged 65 or older and the percentage of the county's population served with fluoridated water. When adjustment was made for other potentially confounding variables this positive relationship remained strong ($p=0.009$). When the study was repeated in 1992 using the same hip fracture data and more up to date and reliable fluoride data (Jacobsen *et al.* 1992), the results were in agreement with the original study.

In the only UK study, Cooper *et al.* (1991), hip fracture rates in 39 county districts of England and Wales were obtained for 1978-82 from hospital activity analysis data. The drinking water

fluoride concentrations of these districts had been measured between 1969 and 1973 as part of the British Regional Heart Study. The correlation between water fluoride content and hospital discharge rate for hip fracture was positive, but non-significant, both for total (r=0.16, p=0.34) and natural (r=0.01, p=0.09) water fluoride. However, when the data were analysed in a weighted least squares regression to allow for differences in the size of individual county districts there was a significantly positive correlation between fluoride levels and discharge rates for hip fracture (r=0.41, p=0.009).

In Utah a small but significant increase in the risk of hip fracture in people exposed to 1ppm fluoride compared to <0.3ppm was found (Danielson *et al.*, 1992). Brigham which had fluoridated its drinking waters for approximately 21 years was compared to two communities, Logan and Ceder City, which had not fluoridated their water. Cases of hip fracture requiring hospitalisation were ascertained from the Utah Peer Review Organisation (UPRO) for the years 1984 to 1990. UPRO is an organisation with computerised records of all Medicare admissions and discharges in Utah since 1984. Medicare provides medical insurance to citizens 65 years of age and older. All cases in their files with an ICD-9 code of 820.0 to 820.9 were included. There was a significantly higher rate of fractures in the fluoridated area in people over 65 years of age with relative risks of 1.27 (95% CI = 1.00 to 1.46) in women and 1.41 (95% CI = 1.00 to 1.81) in men.

A criticism of this study was that Brigham differed from the control communities in other ways apart form water fluoride concentration. In particular it had more nursing home beds. People residing in nursing homes are more likely to fracture their hips as they are frailer, have more illness and are less active than their independent counterparts. This may have caused the apparent effect of fluoridation to be overestimated. In addition 70% of Brigham's population were members of the Latterday Saints Church and as such may have had a different risk of hip fracture for reasons other than their fluoride intake. For example, insofar as they refrained from smoking and drinking alcohol there may have been a tendency to underestimate the effect of fluoridation.

Suarez-Almazor *et al.* (1993) also compared two North American cities, Edmonton (1ppm) and Calgary (approx. 0.33ppm).The water in Edmonton had been fluoridated for more than 20 years. The two communities were chosen as they were very similar in aspects other than

fluoridation, except that Edmonton was more 'white collared' than Calgary and therefore probably had a lower physical activity level. Patients aged 45 years and older who were discharged from hospital between January 1981 and December 1987 and whose diagnosis were coded as 820.0 - 820.9 to ICD-9 were ascertained. Age-sex standardised admission rates were calculated for Calgary using the direct method of standardisation with 5-year age groups. The standardisation rates were calculated by applying the age-sex specific Calgary rates to the Edmonton standard population.

There were no significant differences in the rates for women or for both sexes combined [rate ratio 0.95 (95%CI= 0.89 to 1.01) and 1.00 (95%CI = 0.95 to1.06) respectively]. However, for all men aged 45 and older and the subgroup of men aged 65 and older, the differences between the Edmonton and Calgary standardised rates were statistically significant [rate ratio 1.12 (95%CI =1.01to 1.24) and 1.13 (95%CI =1.00 to1.27) respectively].

Most recently a study, of 3,777 men and women aged 65 years or older and living at home in Southwest France, (Jacquimin-Gadda *et al.*, 1995) revealed that the risk of hip fracture was significantly greater in civil parishes where the water fluoride was higher than 0.11 ppm [odds ratio 1.86 (CI 1.022 to3.36)] compared to between 0.05 and 0.11 ppm (Jacquimin-Gadda *et al.*, 1995).

The results are striking as the difference was observed at such a low fluoride concentration. Although the authors attempted to measure some of the confounding factors such as quetelet index, smoking status and sports activity, information was not provided on whether parish boundaries matched those of water distribution.

It is plain that the ecological studies are discordant in their results. An attempt to put the studies into context and discuss their differences will be made.

Firstly, in the early studies, fluoride was seen to have either a protective effect or no effect, whereas the later studies indicate an increased risk with higher fluoride. This pattern may reflect a publication bias in later years with papers that indicated a problem with fluoridation being selectively published because they contrasted with the earlier papers.

As mentioned previously ecological studies should be interpreted with caution as they lack assessment of individual risk. The problem which most of the above studies encountered was lack of information about confounders, as there was a dearth of information about the differences between the populations investigated. This may help to explain the discordant results, as a counfounder may have been exerting its influence by either overestimating or underestimating the effect of fluoridation.. Possible candidates are physical activity, BMI, female hormonal status, calcium and vitamin D intake and smoking and alcohol habits.

The studies used a variety of exclusion criteria and this makes it difficult to compare the results. Also the minimum age to enter the study ranged from 45 to 65 years. It is possible that fluoride exposure has varying impact at different ages, as several of the studies indicate differences in fracture rate at different ages.

Finally, although confidence intervals are rarely reported, the studies are mostly based on large numbers of fractures and therefore it is unlikely that the differences found are due simply to chance.

Time Trends:

Two North American studies have examined time trends in hip fracture rates before and after water fluoridation. One of these revealed no alteration in hip fracture rates (Goggin *et al.*, 1965), while the other found a decline in hip fracture incidence after fluoridation (Jacobsen *et al.*, 1993). Although studies examining time trends are more robust than simple geographic correlations, the steep secular trends in hip fracture incidence which have occurred in various parts of the world over the last 50 years complicate their interpretation.

Conclusion:

In conclusion although a number of ecological studies have indicated a positive association between fluoride and the risk of hip fracture this finding has not been consistent across all investigations. In general the studies have shown relatively small effects and/or been limited in their statistical power.

Studies of Individuals:

There is a dearth of information relating fluoride ingestion to osteoporosis and fracture risk in individuals. Only two North American studies, have begun to address this issue.

Sowers *et al.* (1991) studied cohorts of women in three communities in Iowa which had different water sources, with different levels of calcium and fluoride. Postmenopausal women in the higher fluoride community (4ppm fluoride) had significantly more fractures than their counterparts in the control community (1ppm fluoride) (Table B.5.3). Although individual measures of fracture and risk factors for osteoporosis were ascertained, the fluoride estimates were essentially ecological in nature. It was not reported whether the data had been explored for a possible interaction between fluoride and calcium and a power calculation was not stated.

Table B. 5. 3 Risk of Osteoporotic Fracture among Iowa, US Women Resident in Areas with High Water concentration of Calcium and Fluoride (Sowers *et al.*, 1991).

	Relative Risk (95% CI)	
Community	Any Fracture	Osteoporotic Fracture
Control	1.0	1.0
High Calcium (375 mg/l)	1.5 (0.7-3.4)	1.6 (0.7-3.4)
High Fluoride (4 mg/l)	2.1 (1.0-4.4)	2.2 (1.1-4.7)

The study demonstrated a mean relative risk of 2.1 (95% confidence interval, 1.2-4.4) for any fracture in postmenopausal women residing in the high fluoride community. Residence in the higher-fluoride community was also associated with significantly lower radial bone mass in premenopausal and postmenopausal women, and an increased rate of radial bone mass loss in premenopausal women. Estimates of risk were adjusted for age and body size.

Cauley *et al.* (1995), studied a cohort of women and estimated individual person-years of fluoride exposure. Individuals were asked to list each address from 1950-1990, the duration of residence at each address and the source of water. The fluoride exposure for each individual, was estimated by summing the total number of years a woman was exposed to residential fluoridated public water. Bone mineral density was measured at three sites: distal and proximal radius and calcaneus, and a history of fracture was obtained. No relation was found between years of fluoride exposure and bone mineral density and there was no relation with history of fracture. A total of 369 fractures occurred among 2076 women and therefore the statistical power was limited

Overall Conclusion:

Although several studies have indicated a positive association between water fluoride concentration and the risk of hip fracture, the effects observed have been small and the ability to adjust for the effects of potential confounding variables (such as physical activity, body build, smoking, alcohol consumption, dietary calcium intake and reproductive variables in women) has been severely limited. An MRC Working Group reviewed this evidence in 1993 and concluded that further information was urgently required. One of the specific recommendations was a case-control study in which the lifetime fluoride intake of hip fracture cases would be compared with that of age and sex-matched controls.

Section C: Design of study

i. Method

The study used a case-control design. Patients presenting to hospital with hip fracture were compared with controls selected from the general population.

Study population:

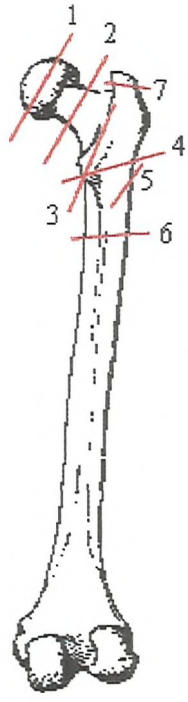
The study population comprised residents of Cleveland aged 50 years and older. The county of Cleveland was selected for study because it comprised Hartlepool (total population 92,000) which throughout this century has been supplied with water from boreholes containing in excess of 1ppm fluoride, and Middlesbrough and Stockton (total population 465,000) where water supplies have never been fluoridated and fluoride levels have always been less than 0.3ppm. Apart from the difference in fluoride, residents of Hartlepool, Middlesbrough and Stockton were thought to be broadly similar in their exposure to other risk factors for hip fracture.

Selection of Cases:

Patients from Cleveland with hip fracture are treated by the orthopaedic departments at Hartlepool General, North Tees General and Middlesbrough General Hospitals. Members of the study population who were admitted to these departments with hip fractures over a 17 month period were identified at least once a week by review of ward admission books. After exclusion of patients younger than 50 years of age, with fractures wholly below the lesser trochanter (Figure C.1.1.) or secondary to malignant deposits, these men and women compromised the eligible case group. See Figure C.1.2 for flow chart summarising how cases were selected.

Each case was visited in hospital by a trained nurse interviewer who obtained informed consent to participation in the study. Those who agreed and who achieved a Hodkinson Abbreviated Mental Test Score of 6/10 or higher were interviewed using a structured questionnaire (Appendix F.1.).

Figure C.1.1 : Inclusion criteria according to type of hip fracture



Include

1. Subcapital
2. Transcervical
3. Intertrochanteric
4. Pertrochanteric
5. Subtrochanteric

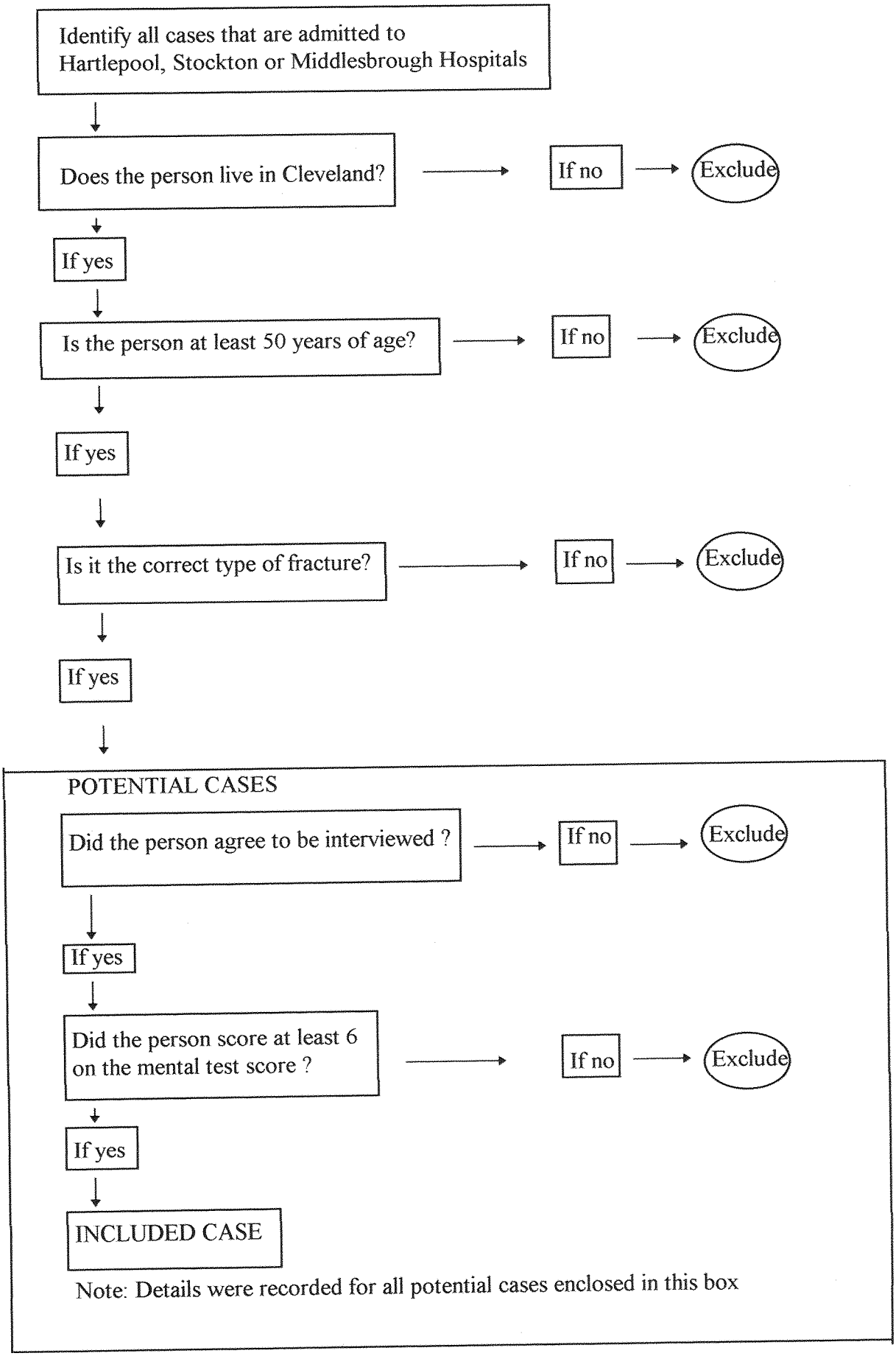
Exclude

6. Shaft of femur
7. Greater trochanter

The questionnaire (Appendix F.1), which was piloted in a series of elderly patients in Southampton, covered demographic data, residential history, occupational history (including past physical activity at work), current activity, history of fracture, medical history and current medication, smoking, alcohol consumption, dietary sources of calcium and fluoride, and reproductive variables among women. Most of the questions had been used previously in studies of hip fracture or osteoporosis and the sections on calcium intake and exercise had been compared against external criteria (Cooper *et al.* 1988). If the case was unable to pass the mental test, information on their age, sex, current address, and current medication was recorded.

At each hospital, patients discharged with a diagnosis of hip fracture were listed from hospital discharge data and checked against our records to ensure that all patients had been identified. Only four cases were missed in the first 12 months of the study. This was because they had all been admitted to different speciality wards as they had other serious illnesses. If a person presented for a second time with a fracture of the other hip, this was recorded but they were not interviewed again.

Figure C.1.2 Flow chart depicting the inclusion criteria of cases



Selection of Controls:

At the beginning of the study a pool of potential controls was selected with help from Tees Health (FHSA). The expected numbers were derived using the proportional age and sex distribution of cases in an earlier study and the age and sex distribution for the population of Cleveland. Tees Health produced a stratified, random list of potential controls which was arranged into 5 year age bands and separated by sex.

Figure C.1.3 presents a flow chart summarising how the controls were selected.

Although not a matched study, for practical reasons and to ensure similar distribution with regards age and sex, one control, within the same age bracket and sex, was randomly selected per case. The surname and NHS number was then sent to Tees Health to verify that the person was still on the GP register. This was because the original lists were prepared at the beginning of the study and it was important that we did not try to contact anyone who had recently died. Tees Health also supplied the actual date of birth for those controls selected.

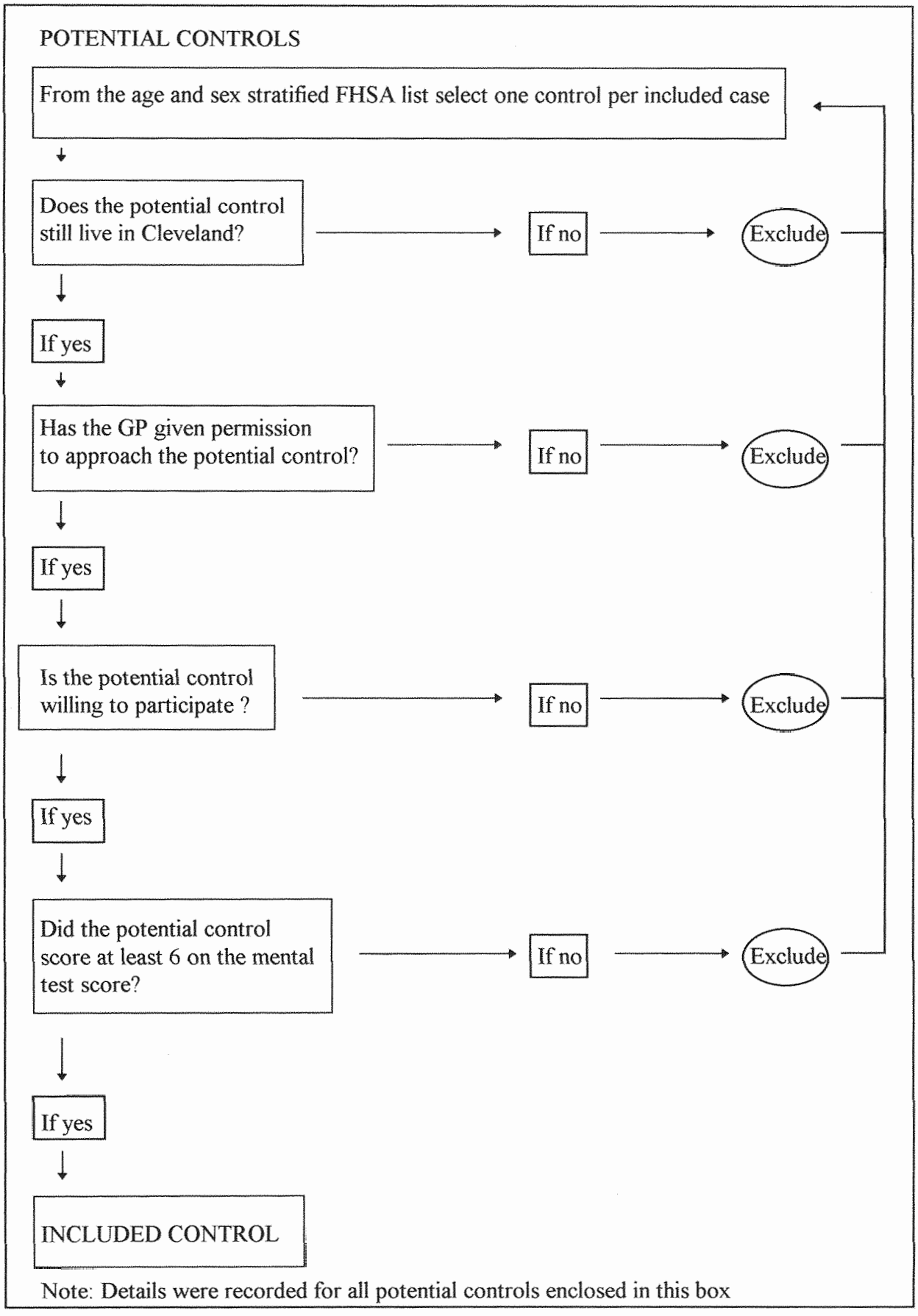
With permission from his/her general practitioner (Appendix F.2.), we wrote to each of these controls asking if our nurse could make a home visit (Appendix F.3.). Those who agreed and who scored at least 6 on the Hodkinson Abbreviated Mental Test Score were interviewed at home, using the same questionnaire as for the cases.

If there was no response from the control to the first letter, the nurse attempted to phone them just before the interview date. If there was no response to the phone call or the number was ex-directory, then the letter was sent again. If there was still no response, the control was excluded and a replacement control selected by the same method.

Sample size:

The aim was to recruit final numbers of 500 cases and 500 controls. From experience in previous case-control studies of hip fracture it was estimated that 70% of cases would pass the mental test score. Assuming that there was one control per case and that 20% of controls had a lifetime average water fluoride >1ppm and 50% <0.2ppm, with these numbers there would be a 70% power to detect an odds ratio of 1.5 between these exposure categories and 99% power to detect an odds ratio of 2.0.

Figure C.1.3. Flow chart depicting the inclusion criteria of controls



ii. Description of the subjects:

Table C.1.1. describes the age and sex of the interviewed cases on which the main analysis was based and also of the eligible cases who were not interviewed. As expected, there were nearly four times as many females in the case group as men and there were more cases in the older age bands. In addition the older age bands had a higher rate of non-interviews compared to the younger age bands.

Table C.1.1. Distribution by age and sex of the eligible cases according to whether they were interviewed.

Age Bands	Cases not interviewed		Cases interviewed	
	Female	Male	Female	Male
50-59	5	4	5	11
60-64	7	3	19	10
65-69	8	6	36	8
70-74	19	8	51	18
75-79	36	10	52	20
80-84	51	6	70	12
85+	127	23	101	11
Total	253	60	334	90

Table C.1.2. describes the age and sex distribution of the controls which were interviewed and also of the eligible controls who were not interviewed. As expected proportionately more controls failed to complete interviews in the older age groups.

Table C.1.2. Distribution by age and sex of eligible controls according to whether or not they were interviewed.

Age band	Controls not interviewed		Interviewed controls	
	Female	Male	Female	Male
50-59	3	6	4	10
60-64	8	5	13	3
65-69	13	2	25	9
70-74	23	9	33	13
75-79	32	10	45	12
80-84	68	7	40	15
85+	114	13	53	5
Total	261	52	213	67

*It was not possible to calculate the exact age of 111 of the non-interviewed controls (17 males and 94 females) as although the age band was known no actual date of birth was available.

Table C.1.3. shows the reasons why controls were excluded. The reasons for exclusion were broadly similar for Hartlepool (high fluoride) and Middlesbrough and Stockton (low fluoride).

Table C.1.3. Reasons why potential controls were excluded according to current address.

Reason	Hartlepool		Middlesbrough / Stockton	
	Number	%	Number	%
Control Refused	35	43.8	162	47.1
GP refused	8	10.0	49	14.2
Dementia reported	9	11.2	11	3.2
Unable to contact	8	10.0	57	16.6
Died	17	21.2	51	14.8
Other	3	3.8	14	4.1
Total	80	100.0	344	100.0

It was important to look to see if there were differences in overall response rates between the two areas for both cases and controls. Table C.1.4. shows that Hartlepool had slightly higher proportion of cases included compared to Middlesbrough and Stockton. The response rate of the controls was very similar between the two areas.

Table C.1.4. Proportion of interviewed cases and controls according to current address

Current Address	Cases		Controls	
	Number	%	Number	%
Hartlepool	81	63.3	51	38.9
Middlesbrough or Stockton	343	56.1	229	40.0

There were three interviewers; LM (interviewer throughout), GS (started November 1996) and myself (intermittent). An attempt was made to ensure that all three interviewers visited similar numbers of cases and controls. Table C.1.5. displays the proportion of cases and controls with respect to the different interviewers.

Table C.1. 5: Distribution of interviewed cases and controls according to interviewer

Interviewer	LM		GS		SLH	
	Number	%	Number	%	Number	%
Cases	322	75.9	66	15.6	36	8.5
Controls	186	66.4	52	18.6	42	15.0

iii. Data entry, validation and coding:

Questionnaires were double punched in batches of approximately 150 onto a multinp file. The two versions were then compared to ensure that they were consistent. A program was written (Mr Leslie Styles) to validate the data on the multinp file, to check for inconsistencies within the data, for example if a job started before the previous one had finished. The validation program was run three times for each batch and a code was entered for missing data. Once the data was clean, the answers to open questions were coded to a form suitable for analysis.

Protocol for assigning fluoride codes

The questionnaire asked subjects to report each address at which they had lived with dates. This information was printed out and fluoride coding was carried out, blind to the subjects case/control status. Fluoride in water was estimated from the following information.

For Hartlepool addresses the local water company supplied a map displaying supply zones, together with the following information.

Previous to 1957 all zones were supplied with water containing 2.0 ppm fluoride. During the period 1957 - 1980, Zones A & B were supplied with water containing 1.3-1.6ppm fluoride and Zone C 1.8-2.0 ppm. From 1980 onwards Zones A & B received 1.2ppm fluoride and Zone C 0.9-1.0 ppm.

Thus Hartlepool addresses were coded according to date and zone supply. The average value was used, for example, if the address was in Zone C in the period of 1957 - 1980 then the

fluoride code was assigned as 1.9ppm. If the address was on the border of two zones then the average of two zones was assigned. Similarly if the address only stated Hartlepool then the average fluoride over all three zones was assigned.

The situation for Middlesbrough and Stockton was much simpler as no artificial fluoridation scheme had ever been implemented and the natural fluoride levels were between 0.1ppm and 0.3ppm. Therefore any address in Cleveland other than Hartlepool was assigned 0.15ppm.

After Cleveland addresses, the next most popular area was Tyne and Wear and Northumberland. As some areas of Newcastle and environs had been fluoridated at different times, more accurate information was obtained from the local water companies. The water companies sent maps with zones of fluoridation and dates implemented and also details of natural fluoride. Other places in the United Kingdom were coded using the British Fluoridation Society report published in 1993.

Two problems were experienced coding the data. Firstly addresses in the county of Durham were unable to be coded as the area has a very complicated history with respect to fluoride. There are areas which have natural fluoride above 0.3ppm and certain areas have received artificially fluoridated water. However, the areas have changed over time and on some occasions water was mixed from different sources. As there are no reliable records available, these addresses have been coded as missing. Secondly, if the address was outside the United Kingdom this was also coded as missing as insufficient information was available to make an accurate decision.

Figures C.1.4. and C.1.5. display algorithms for fluoride assignment.

Figure C.1.4. Algorithm for assigning fluoride levels to address in Hartlepool

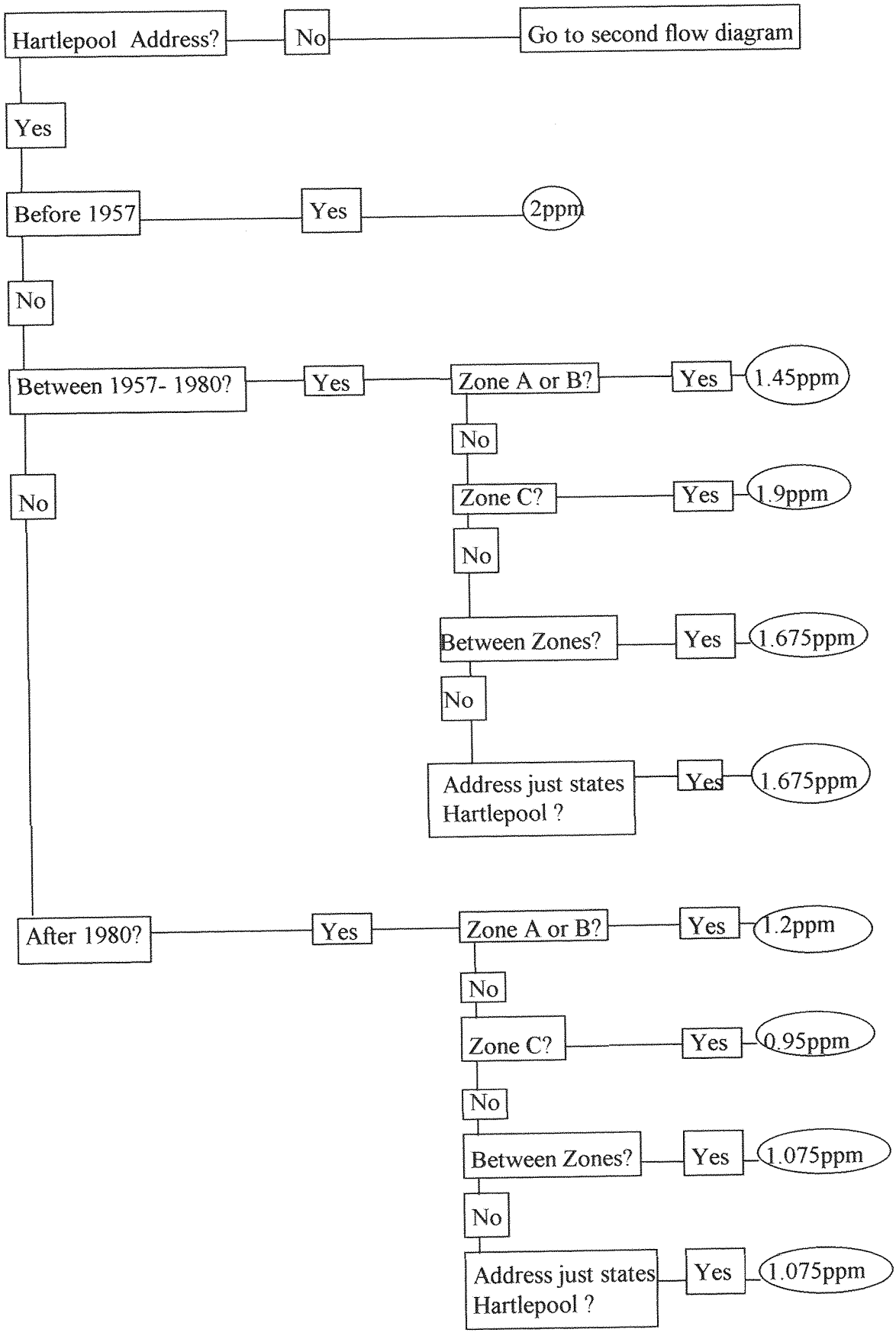
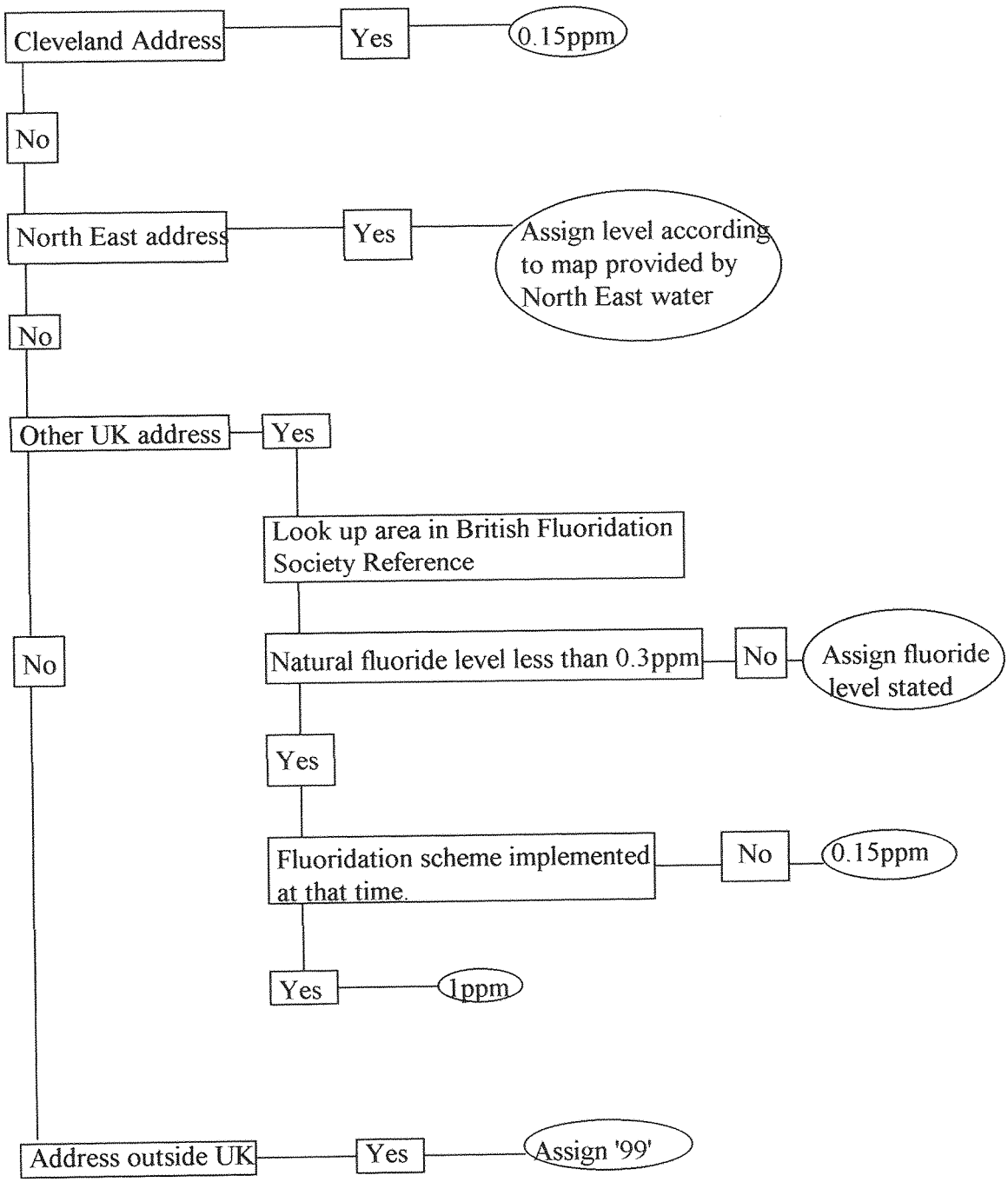


Figure C.1.5. Algorithm to assign fluoride levels to addresses other than Hartlepool



iv. Analysis:

The data which was in a multinp file and contained the coding necessary, was converted into a SPSS file. This was then transferred to STATA and this statistical package was used for all of the analysis.

Firstly, the data was split into the subjects who passed the mental test and those who failed. Only the people who passed the mental test and therefore interviewed were used in the main analysis. Then the variables of interest were categorised. If the variable was continuous then it was sorted into ascending order and split into either two or three equal sized groups. If the variable was already categorised in the raw data then the groups were amalgamated to increase their size or make more sense of the data.

Logistic regression was used throughout the analysis and all odds ratios were adjusted for age and sex as these variables had been matched in the study design. This analysis was appropriate as although a control was sought from the same age and sex stratum as each case, this could be considered as frequency matching rather than individual matching. In addition the analysis was interim and at this point many cases did not have matched controls. Conditional logistical regression is used when cases are individually matched to cases and relationships within matched sets are evaluated.

v. Discussion of the methodology:

A case-control design was chosen in preference to other possibilities because it offered the maximum efficiency. An alternative option would have been a cohort study, but if carried out prospectively this would have been impractical, as the latent period would have been at least 50 years. A partially retrospective cohort might have been possible, but information relating to previous addresses of a large sample of residents of Cleveland would have had to be collected.

The county of Cleveland was by far the best place to undertake this study in the United Kingdom, as it provided the greatest contrast with respect to fluoride in a defined population. Hartlepool has

received natural fluoridated water for the whole of the century which has been in excess of 2ppm fluoride at times, and Middlesbrough and Stockton have always received water with a low natural fluoride concentration. Therefore, if fluoride increased the risk of hip fracture it would be exhibited in this population. In addition, the population in Cleveland were thought to be broadly similar in other risk factors for hip fracture. Another advantage was that the population was quite static which made both the recall of addresses by the participants easier, and coding the addresses for fluoride exposure.

The ascertainment of cases was undertaken thoroughly and precisely, as the potential cases were identified both from the admission book and also by confirmation with the ward staff. As noted above, only four cases were missed in the first year and these patients were admitted to other wards because of other medical problems. The participation rate was good for the cases as they welcomed the distraction.

The main reason that cases did not complete the interview was that they failed the mental test, this was especially true for the older age groups. This was to be expected and unavoidable as a reasonable score was essential for the recall of addresses to be reliable. It appears that a higher proportion of cases compared to controls were lost because they failed the mental test score. This is not surprising as dementia may predispose to falls and recent injury. Moreover, undergoing a major operation may impair mental function in the elderly. In addition many of the controls with dementia were probably excluded from the study by their general practitioner. Table C.1.4. shows that the inclusion rate of cases was higher for Hartlepool than for Middlesbrough and Stockton and this could lead to overemphasis of the effect of fluoride.

The controls were taken randomly from the population as it was important not to match on GP practice as this would eradicate the effect of fluoride. As discussed above, Tees Health produced a random lists of potential controls. The lists were further randomised in the event that they had been listed according to GP practice which would bias the selection of controls by geographical area.

Table C.1.2 compares controls who were interviewed and those who were not. The reasons why eligible controls were not interviewed are illustrated in table C.1.3. The proportions of controls who were not interviewed were broadly similar to the proportions of the cases. It can

be postulated that similar factors prevailed, such as failing the mental test, illness, difficulty in communicating and refusal to take part. The difference between the cases and control was that the interviewer ascertained the reason why the cases were excluded whereas with the controls the reason was sometimes not forthcoming or otherwise it was given by the general practitioner or carer. It was fair to assume that from the random list of controls there was a certain proportion who were able to be interviewed and that it did not matter when in the study they were invited to participate.

As with similar case-control studies, controls from the general population are generally more healthy and active than the cases who are currently in hospital. One advantage of this study was that the cases are interviewed within a few days of being in hospital and should have been leading typical lives up until then. However a disadvantage was that the cases were being interviewed just after a major operation and their powers of recall and concentration may not have been as good as the controls.

Another inherent problem with the design is that cases are trying to identify why they are ill and may overestimate factors they identify as being important. However in this study it was highly unlikely that the patients would associate where they have lived in the past with why they were in hospital.

Table C.1.3. shows that approximately 40 % of the controls approached agreed to participate. This was unavoidable as controls are not as committed to a study as cases, as they do not have the disease and so do not think that it is relevant to them. In addition the cases were approached personally by the nurse whereas the controls were approached by letter which probably made a difference in participation rate. The proportion of controls was similar in Hartlepool and Middlesbrough and Stockton so therefore there was no bias introduced which could mask the effect of fluoride. However controls who were more willing to participate may already have osteoporosis or may have a close family member with the disease. This may mask the effect of fluoride.

As mentioned above there were three interviewers for the study which although not ideal, as there may be consistent differences between their techniques, was required for practical reasons. Both interviewers were trained by myself and I listened to their interview techniques

over the period of the study. I also went through each questionnaire to ensure that they appeared consistently thorough and table C.1.5 shows that all three interviewers interviewed similar proportions of cases and controls.

It was important that the person coding the fluoride did not know if the address was for a case of control so to prevent them introducing bias and this was upheld throughout.

Finally, there was a difference in data collection between cases and controls with respect to current medication. This information was obtained from the hospital notes for the cases and controls were asked to produce the medicine bottles. If the hospital notes were based on the cases' repeat prescription then they may (due to human nature) not actually be taking all of them whereas the control may only produce the medicines which they routinely take.

In summary it was felt that, although there were some limitations to the design of the study, it was carried out as well as possible and was sufficiently robust to explore the issue of the effect of water fluoridation on osteoporotic hip fracture.

Section D: Results

Section D.1 Body mass index and physical inactivity.

Introduction:

Body mass index (BMI) and physical inactivity, both recent and past, have been identified as important risk factors for hip fracture (refer to p34). They have several modes of action, (refer to figure B.3.6) as they can influence both the bone mass attained and conserved and also the protection of the hip from the impact of trauma. It seemed possible that both BMI and inactivity might confound other risk factors that were of interest in the subsequent analysis. BMI and inactivity were therefore investigated first so that the effects of other risk factors could be appropriately adjusted.

Method:

Information on BMI was collected by asking all participants for their current weight and height. If both were available then BMI was calculated as weight in kg/(height in m)^2.

Information on recent inactivity was obtained by asking the participants about their usual activities, cases being prompted to recall a typical week before they came into hospital. A 'typical' week was asked about as it was thought that most of this population would normally follow a regular routine. The interviewers prompted the interviewees as to when they visited the shops, walked the dog or went to the day hospital etc. .It was postulated that within the population there were subjects who were generally inactive or active in many ways. The correlation between various indices of inactivity was investigated to see if this was true. If the different indices were related to each other, then it would be possible to construct a summary score of overall recent inactivity. This could be created by assigning a score to each individual inactivity variable, the most inactive category being assigned the highest score, and the most active the lowest score. The amalgamated score could then be divided into thirds of its distribution.

The information that was gathered on past activity related to activities at work. This was divided into three periods of life, whole life, first 50 years and after 50 years of age. The period of working life was 15 - 59 for women and 15 - 64 for men. When information was missing on specific activities in a job, an experienced occupational hygienist estimated the exposure to the activity from the job title. This was carried out blind to the case/control status of the subject. For the person to be included in the analysis they had to have 80% complete information for the time period investigated.

Results:

Table D.1.1. shows the association of hip fracture with BMI. Low BMI (≤ 21.1) was associated with a three-fold increase in the risk of hip fracture which was statistically significant.

Table D.1.1. Association of hip fracture with BMI

Variable	Categories	No. of Cases	No. of Controls	*OR (95% CI)
BMI	High (≥ 24.7)	108	109	1.0 (-)
	Medium (21.2 - 24.6)	100	96	1.0 (0.7 - 1.6)
	Low (≤21.1)	143	48	3.1 (2.0 - 4.8)

*adjusted for age and sex

Table D.1.2. shows the relation of hip fracture to recent activity. There was a consistent increase in the risk of hip fracture in people who were recently inactive for each of the measures of inactivity. When the odd ratios were adjusted for BMI the relationships remained.

Table D.1.2.: Association of hip fracture with indices of recent inactivity

Variable	Categories	No. of Cases	No. of Controls	*OR (95% CI)	**Adjusted OR (95% CI)
Walking Problems	None	228	203	1.0 (-)	1.0 (-)
	Needs aid/cannot walk	196	77	2.4 (1.7 - 3.4)	2.7 (1.8 - 4.0)
Time walked per day	≥ 1 hour	117	127	1.0 (-)	1.0 (-)
	< 1 hour	117	97	1.4 (0.9 - 2.0)	1.5 (1.0 - 2.2)
	None	190	56	4.0 (2.6 - 6.2)	3.4 (2.2 - 5.5)
Walking speed	Normal/fast	97	120	1.0 (-)	1.0 (-)
	Strolls	79	75	1.4 (0.9 - 2.1)	1.5 (1.0 - 2.4)
	Very slow	247	85	4.0 (2.7 - 5.9)	4.6 (3.0 - 7.1)
Gardening per week	≥ 1 hour	78	117	1.0 (-)	1.0 (-)
	< 1 hour	345	163	3.2 (2.2 - 4.5)	2.9 (2.0 - 4.3)
Housework per week	≥ 1 hour	275	247	1.0 (-)	1.0 (-)
	< 1 hour	148	33	4.3 (2.8 - 6.5)	4.4 (2.7 - 7.1)
Climbing stairs	Several times a day	145	151	1.0 (-)	1.0 (-)
	Once a day - once a week	53	50	1.1 (0.7 - 1.8)	1.2 (0.7 - 1.9)
	Never	226	79	3.1 (2.2 - 4.5)	2.9 (2.0 - 4.4)
Carry loads	Ever	84	97	1.0	1.0 (-)
	Never	340	183	2.1 (1.5 - 3.0)	1.8 (1.2 - 2.7)

* adjusted for age and sex * *adjusted for age, sex and BMI

Table D.1.3. shows that all of the individual measures of recent inactivity correlated with each other and it was therefore justified to amalgamate the individual activities into an overall score.

Table D.1.3.: Association between individual indices of recent inactivity.

Associations were summarised by odds ratios (with 95% confidence intervals) for being in the least active category of an index if a person was in the least active category of another index.

Walking problems						
4.6 (3.6 - 5.8)	Time spent walking					
5.1 (3.9 -6.6)	5.3 (3.8 - 7.2)	Walking speed				
7.6 (4.7 - 12.2)	10.5 (5.2 -21.1)	6.5 (3.8 - 10.9)	Gardening			
4.9 (3.4 -7.0)	7.0 (4.4 - 11.1)	4.6 (2.8 - 7.4)	12.1 (5.8 - 25.2)	Housework		
5.2 (3.6 -7.4)	6.5 (4.2 -10.2)	4.7 (3.0 - 7.4)	4.9 (3.3 - 7.4)	4.8 (3.2 - 7.2)	Climbing stairs	
8.0 (4.8 -13.3)	15.9 (6.2 - 20.6)	11.3 (6.2 - 20.6)	4.7 (3.2 - 6.7)	9.4 (4.7 - 18.9)	6.2 (4.0 -9.4)	Carrying loads

Scores were therefore assigned to each individual inactivity variable, the most inactive category the highest score and the most active the lowest score, and an amalgamated score created. None of the individual scores were weighted in the analysis.

A high recent inactivity score was associated with a more than six times increased risk of having a hip fracture. (Table D.1.4.)

Table D.1.4. Association of hip fracture recent inactivity score

Variable	Categories	No. of Cases	No. of Controls	* OR (95% CI)	**Adjusted OR(95% CI)
Recent Inactivity Score	Low	104	143	1.0 (-)	1.0 (-)
	Medium	149	91	2.6 (1.7 - 3.8)	2.7 (1.8 - 4.1)
	High	171	46	6.3 (4.0 - 10.0)	6.3 (3.8 - 10.5)

* adjusted for age and sex * *adjusted for age, sex and BMI

Table D.1.5. shows the association of hip fracture with past occupational activities. Having spent over 4 hours of the day either standing or walking tended to be protective. However, this was only statistically significant when assessed over whole life, and with adjustment for BMI and recent inactivity the significance was lost. Spending over 8 hours of the day either walking or standing was also associated with a reduced risk of hip fracture but this did not reach statistical significance. Although the mean recent inactivity score was higher for participants who did not walk or stand for over 4 hours a day at work, this was not the case for walking or standing over 8 hours a day at work. The unadjusted odd ratios were very similar to the adjusted odd ratios, which suggests that neither recent inactivity or BMI were strongly associated with past occupational activity measured in this way.

Although not statistically significant there was a tendency for a reduction in hip fracture risk in participants who had walked over one mile a day for at least 10 years of their working life (Table D.1.6.). There was a hint of an increase in hip fracture risk for participants who had walked over four miles a day. However the confidence intervals were wide and no clear patterns emerged. Again, when adjusted for BMI and recent inactivity, odd ratios were little changed, suggesting that BMI and recent inactivity were not strongly associated with past walking at work.

When past activity was re-analysed using only activities reported by the subjects and not those inferred from job title, the results were similar.

Table D.1.7. shows associations between hip fracture and occupational lifting. Although there was a tendency for an increase in risk of hip fracture if the person lifted 25 lbs or more in an average working day for 10 years or longer, this was not statistically significant.

Table D.1.5. Association of hip fracture with past occupational activities.

Type of Activity	Time of life	Categories	No. of Cases	No. of Controls	Mean recent activity score	*OR (95% CI)	**Adjusted OR (95% CI)
Walking or standing per day for at least 10 years in total	Over all working life	Never	21	8	10.0	1.0 (-)	1.0 (-)
		4-8 hours	52	50	8.3	0.3 (0.1 - 0.9)	0.4 (0.1 -1.1)
		Over 8 hours	62	49	9.2	0.4 (0.2 - 1.2)	0.5 (0.2 - 1.4)
	Before 50 years of age	Never	22	14	9.4	1.0 (-)	1.0 (-)
		4-8 hours	56	50	8.3	0.6 (0.3 - 1.4)	0.8 (0.3 - 2.0)
		Over 8 hours	68	50	9.3	0.8 (0.4 - 1.8)	0.9 (0.4 - 2.1)
	After 50 years of age	Never	56	34	9.0	1.0 (-)	1.0 (-)
		4-8 hours	54	61	8.7	0.5 (0.3 - 0.9)	0.6 (0.4 - 1.2)
		Over 8 hours	38	30	9.3	0.8 (0.4 -1.6)	0.8 (0.4 - 1.8)

* adjusted for age and sex * *adjusted for age, sex , BMI and recent activity

Table D.1.6. Association of hip fracture with distance walked at work.

Type of Activity	Time of life	Categories	No. of Cases	No. of Controls	Mean recent activity score	*OR (95% CI)	**Adjusted OR (95% CI)
Distance walked at work per day for at least 10 years in total	All working life	Never	60	38	9.3	1.0 (-)	1.0 (-)
		1-4 miles	56	55	8.6	0.7 (0.4 - 1.2)	0.9 (0.4 -1.6)
		>4 miles	19	14	8.7	0.9 (0.4 -2.1)	1.1 (0.4 -2.7)
	Before 50 years of age	Never	66	44	9.2	1.0 (-)	1.0 (-)
		1-4 miles	62	55	8.7	0.7 (0.4 -1.3)	0.9 (0.5 -1.6)
		>4 miles	18	15	8.7	0.7 (0.3 - 1.6)	0.7 (0.3 - 1.8)
	After 50 years of age	Never	90	60	9.3	1.0 (-)	1.0 (-)
		1-4 miles	43	55	8.5	0.5 (0.3 -0.9)	0.6 (0.3 -1.1)
		>4 miles	15	10	8.6	1.1 (0.5 - 2.8)	1.3 (0.5 - 3.5)

* adjusted for age and sex **adjusted for age, sex, BMI and recent activity

Table D.1.7. Association of hip fracture with occupational lifting

Type of Activity	Time of life	Categories	No. of Cases	No. of Controls	Mean recent activity score	*OR (95% CI)	**Adjusted OR (95% CI)
Lifted weights over 25lbs in an average working day for at least 10 years in total	All working life	Never	63	49	9.1	1.0	1.0 (-)
		Ever	72	58	8.7	1.0 (0.6 - 1.8)	1.2 (0.6 - 2.2)
	Before 50 years of age	Never	66	57	8.9	1.0	1.0 (-)
		Ever	80	57	8.9	1.3 (0.8 - 2.1)	1.3 (0.7 - 2.4)
	After 50 years of age	Never	93	90	9.0	1.0 (-)	1.0 (-)
		Ever	55	35	8.9	1.7 (1.0 - 2.8)	1.4 (0.8 - 2.5)

* adjusted for age and sex **adjusted for age, sex, BMI and recent activity

Discussion

BMI:

There was a three-fold increase in the risk of hip fracture for participants who had a low BMI (≤21.1) compared to those with a high BMI (≥24.7). This was highly significant statistically, and unlikely to be due to chance.

The BMI calculated was based on self reported measurements as it was impractical for the bed ridden cases to be measured. To avoid bias, information was collected from the controls in the same manner. This method of data collection raises two issues; firstly how many people knew their recent weight and height, and secondly, the accuracy of the estimate.

It was possible to calculate a BMI for 82.8% of the cases and 90.4% of the controls which were adequate proportions of the population. There is a tendency for overweight people to underestimate their weight and underweight people to overestimate it (Schlichting *et al.*, 1981; Stewart, 1982). This tendency of error towards the mean also exists for self reported heights. However, if non-differential, such errors would bias the results towards the null and lead to an underestimate of the effect of BMI on the risk of hip fracture.

The increase in the risk of fracture with a decrease in BMI found in this population accords with the published literature. Cooper *et al.* (1988) found a relative risk of 6.7 (CI 3.8 - 11.7) for the lowest fifth of the distribution of BMI in a case-control study undertaken in Southampton. BMI can be used as a proxy for fat mass and Reid and colleagues (Reid *et al.*, 1992) demonstrated that total fat mass was a consistent predictor of femoral neck bone mineral density. From prospective cohort studies, such as the Framingham cohort's biennial examination (Felson *et al.*, 1993) of 693 postmenopausal women, BMI explained a substantial proportion of the variance in bone mineral density in the femoral neck. From a cross-sectional evaluation of the Rancho Bernardo cohort, recent body mass index explained more than 29% of the variance in bone mineral density in the total hip (Greendale *et al.*, 1995). A higher BMI

is thought to influence bone mass by increasing overall body weight or load. In addition, fat and muscle could help to disperse the force applied to the hip in the event of a fall (Grisso *et al.*, 1996; Brocklehurst *et al.*, 1978; Cummings and Nevitt, 1989).

Recent inactivity:

The individual measures of recent inactivity were all associated with an increase in the risk of hip fracture. The fact that they all correlated with each other, and that the risk of hip fracture increased when the amalgamated inactivity score was used, conferred confidence in the data. The relationship remained statistically significant when adjusted for BMI.

One issue to consider was whether the cases and controls were interviewed at similar times of the year. The recall of activity of gardening or walking may be different during summer months compared to winter months. However this was not a problem as during the spring and summer months controls made up 42% of all participants and 38% during the autumn and winter.

As a tool to estimate physical activity the questionnaire was necessarily crude but apparently effective. Other techniques such as activity diaries or pedometers were not possible as information had to be collected retrospectively for the cases. If the estimates of physical activity were inaccurate then as long as they were non-differential between cases and controls, any bias would have been to the null. It seem unlikely that cases would have grossly underestimated their usual activities as compared with controls.

Another possible bias was that the controls who agreed to participate may have been healthier, more independent and more active than the controls who declined to participate. If this occurred it would lead to an overestimate of the effect of recent inactivity on the risk of hip fracture. It is unlikely that this bias could explain all of the

association as cohort studies, which are not subject to control participation rate biases, have produced results which agree with our findings (see below).

A number of epidemiological studies have indicated that physical inactivity is a risk factor for osteoporotic fracture (Lau *et al.*, 1988; Wickham *et al.*, 1989; Cooper *et al.*, 1988). Cummings *et al.* (1995) concluded from a large prospective cohort study of risk factors for hip fracture, that women who recently spent four hours per day or less on their feet had twice the risk of women who spent more than four hours per day on their feet. Women who regularly walked for exercise had a 30 percent lower risk of hip fracture than women who did not walk regularly.

Coupland *et al.* (1993) found that physical inactivity was an independent risk factor for hip fracture in the elderly. Subjects who did not regularly weight-bear, perform muscle loading activities such as climbing stairs, or perform productive activities such as gardening, were all more than twice as likely to sustain hip fracture, when compared with subjects at the higher end of the spectrum.

Greendale *et al.* (1995) studied a cohort of community-dwelling California adults (1,014 women and 689 men) with a mean age of 73 years, and found that bone mineral density at all hip sites were greater in recent exercisers than in those who engaged in mild or no exercise.

Past activity:

The results in relation to past occupational activity were less consistent. There are several points to discuss.

Firstly, it was a difficult task for the participants to recall past activities at work. This may have been more difficult for the cases as they had just undergone major surgery and might have been still feeling poorly. For the majority of people we were seeking information on activities undertaken up to 60 years earlier. It was especially difficult to estimate the distance walked in the jobs. This was in contrast to time on feet as most people could remember the length of their working day. An educated guess was made

by an experienced hygenist where data were missing (146 out of a total of approximately 11,264 jobs). When the analysis was run with the educated guesses and without them, the results were broadly the same. Nevertheless the data were not complete and may have contained inaccuracies which would probably result in a bias towards the null.

Another problem was that no information was available on activity outside paid employment. Almost all of the female subjects had been housewives for a substantial part of their lives. The activities of a housewife vary greatly depending on whether there are young children to care for etc. An attempt was made at the beginning of the study to collect information about activities related to housework but this proved impossible to implement. There were therefore large gaps in the data which again would tend to obscure associations.

Although none of the adjusted odd ratios were statistically significant, they suggested that walking or standing for over 4 hours a day for at least 10 years was protective against hip fracture. There was no further increase in the odds ratio for over eight hours of walking or standing which could either be due to the small number of people in this category and chance variation, or to the absence of any extra benefit from the extra activity. Similarly with the lifting, although there was a tendency for an increase in risk of hip fracture if the person lifted 25 lbs or more in an average working day for 10 years or longer, this was not statistically significant.

Cooper *et al.* (1990) reported a three fold increase in the risk of hip fracture for men and women who had a sedentary job at age 50. In a study of young Asian women, Hirota *et al.* (1992) found that those who reported the longest prior history of physical activity exhibited the highest radial bone mineral density. Conversely those with the lowest bone mineral density were more likely to dislike sports.

The problem with this research is that it is difficult to estimate past activity as it relates to skeletal loading and perception of exercise intensity is subject to considerable bias when activity is self-reported. In addition it is difficult to distinguish whether a high level of physical activity is a marker of a healthier person who is less likely to fall and fracture for

reasons other than their participation in physical activity, or whether physical activity actually protects against fracture.

Conclusion

In this population a low BMI was associated with a three-fold increase in the risk of hip fracture which reached statistical significance. The study design was sufficiently robust to be confident about this conclusion as the biases identified would have led to an underestimate of the effect of BMI on the risk of fracture. The result was consistent with the published literature on the subject.

In this study the most inactive group of participants were at six times the risk of experiencing a hip fracture. This large effect was based on large numbers, exhibited a dose response relation and was statistically significant. In addition, the result agreed with the published literature.

The published literature suggests a protective effect of past activity on the risk of hip fracture. Although no overall conclusion can be drawn from the results of this study, the findings do not contradict the published literature. Problems encountered in the study were inaccuracies and gaps in the data, which are common problems in studies based on recall of exposure design and if non-differential would bias the results to the null hypothesis, and the small numbers of subjects in some analyses. A prospective study would be a better study design to examine the issue of activity throughout life and risk of hip fracture but would be expensive.

Section D.2: Female reproductive variables

Introduction

Although female reproductive histories have many facets, it is the period of time during which oestrogen is available to support and maintain bone mineralisation that is thought to be of primary relevance to hip fracture. The effects of age at menarche and menopause (both natural and surgical) on the risk of fracture were therefore explored. The effect of parity on the risk of hip fracture is less well defined and this was also investigated.

Method

As part of the questionnaire, female participants were asked to recall details of their reproductive history. Number of children was classified into four categories; none, one, two and three or more. Age at menarche, age at menopause and fertile period were continuous variables and were therefore listed and categorised into thirds of their distributions. For both oopherectomy and hysterectomy, the variables were dichotomised into whether the surgical procedure was before the woman's natural menopause or after.

Results

After adjustment for BMI and recent inactivity, the only reproductive variable that showed a significant association with fracture was age at menarche (Table D.2.1). There was nearly a two-fold increase in risk of hip fracture for onset of menses at 15 years or older. Although not significant there was also a tendency towards an increased risk for menarche at 14 years as compared to 13 years or younger.

If anything, risk of hip fracture was higher in women with a later age at menopause, although those who had an oophorectomy before their natural menopause had a higher risk. No association was found with the total fertile period, which was defined as number of years between menarche and menopause. Giving birth to three or more children was associated with nearly a two-fold increase in risk, although this was not statistically significant.

Table D.2.1 Association of hip fracture with female reproductive variables

Variable	Categories	No. of cases	No. of controls	*OR (95% CI)	**Adjusted OR (95% CI)
Number of children	None	54	37	1.0 (-)	1.0 (-)
	One	57	37	1.1 (0.6 - 2.0)	1.1 (0.6 - 2.2)
	Two	91	68	1.0 (0.6 - 1.7)	1.0 (0.5 - 1.8)
	Three or more	132	71	1.4 (0.8 - 2.3)	1.6 (0.9 - 2.9)
Age at menarche	13 or younger	102	87	1.0 (-)	1.0 (-)
	14	95	62	1.3 (0.8 - 2.0)	1.2 (0.7 - 1.9)
	15 or older	124	57	1.8 (1.2 - 2.8)	1.8 (1.1 - 3.0)
Age at menopause	44 or younger	86	64	1.0 (-)	1.0 (-)
	45 - 49	86	50	1.3 (0.8 - 2.0)	1.5 (0.8 - 2.6)
	50 or older	127	87	1.0 (0.7 - 1.6)	1.2 (0.8 - 2.0)
Fertile period (menopause - menarche)	31 years or less	111	68	1.0 (-)	1.0 (-)
	32 - 35 years	79	54	0.8 (0.5 -1.2)	1.0 (0.6 - 1.7)
	36 years or more	105	77	0.8 (0.5 - 1.2)	1.0 (0.6 - 1.6)
Ovary/ovaries removed at or before menopause	No	290	177	1.0 (-)	1.0 (-)
	Yes	25	15	1.0 (0.5 - 2.1)	1.7 (0.8 - 3.8)
Hysterectomy at or before menopause	No	277	179	1.0 (-)	1.0 (-)
	Yes	44	31	1.0 (0.6 - 1.6)	1.5(0.8 - 2.6)

*adjusted for age and sex, **adjusted for age, sex, bmi and recent activity

Discussion:

In this population there was nearly a two-fold increase in fracture risk associated with a late age of menarche. The relationship remained after adjusting for both current BMI and recent inactivity. In addition, there was a dose-response effect as, although this did not reach statistical significance, there was a tendency for an increase in risk for age of menarche of 14 years compared to 13 years or younger. Of the 547 women, 527 reported their age at menarche which was a sufficient proportion to be representative of the population.

Age at menarche could be related to risk of hip fracture in at least two ways. Firstly, events which precipitate earlier menarche may be associated with characteristics which have been reported to produce greater bone density, for example BMI. Secondly it has been suggested that women with an earlier age at menarche are likely to have a longer time between menarche and the menopause, a time frame during which oestrogen resources are available to support and maintain bone mineralisation. However, when we looked at total fertile period no association was found with risk of hip fracture.

Also in agreement with the literature, although not reaching statistical significance, was an increase in risk if oophorectomy or hysterectomy was performed before the natural menopause. A problem encountered was that of the 128 women who had undergone a hysterectomy, 31 did not know if their ovaries had also been removed. There might therefore have been some misclassification which would probably bias the results towards the null.

The overall results for age at menopause contrasted with those in other studies which have indicated that the risk of hip fracture is greater with an earlier age of menopause (Krieger *et al.*, 1982; Richelson *et al.*, 1984; Aitken *et al.*, 1976). Women had difficulty remembering their age at menopause accurately in the current study, and this may have contributed to the apparent discrepancy. Of the 547 women only 500 recalled their age at menopause and often they reported their age to the nearest decade, for example 'sometime in my 50s' for which the average of 55 years was recorded. This potential misclassification again would probably have biased the results towards the null. It is likely that the direction of the effect of menopause explains why no protective effect of an increase in the length of the fertile period was observed.

Although there was a tendency for an increase in the risk of hip fracture with an increase in number of children, this did not reach statistical significance. Most studies investigating the issue have found no association between risk of hip fracture and parity, (Kreiger *et al.*, 1992; Alderman *et al.*, 1986; Ribot *et al.*, 1993; Cumming and Klineberg, 1993; Laskey *et al.*, 1990) although two studies (Paganini-Hill *et al.*, 1991; Hoffman *et al.*, 1993) suggested a protective effect of increasing parity. Failure to account for potential confounders such as ability to conceive and ability to reach term may account for the different outcomes.

Information was also requested on hormone replacement and oral contraceptive use but the number of women who had used them was too small to analyse. This was to be expected in this age group. In addition, very few women stated that they had experienced ammenorrhoea but this could have resulted from poor design of the question.

Conclusion

In this study a later age at menarche (>=15yrs v.<=13yrs) was associated with nearly a two-fold increase in risk of hip fracture which was statistically significant. As 96% of the women were able to recall their age of menarche and no obvious bias could be identified, there can be confidence in this finding.

The expected relationship of increase in hip fracture for an earlier age at menopause was not observed, although oopherectomy before natural menopause was associated with a nearly two fold increased risk of fracture but this was not statistically significant. The main limitation of this analysis was the inaccuracies and gaps in the recall of age at menopause. An improvement would be to undertake a prospective study as then the age at menopause could be determined more accurately.

Giving birth to three or more children was associated with an odds ratio of 1.6, which contradicts previous studies that have found either no increase in risk or a protective effect. However, the association did not reach statistical significance and may have occurred by chance.

Section D.3: Other Risk Factors for Hip Fracture.

Introduction

In addition to BMI, physical inactivity and reproductive variables, other risk factors for hip fracture have been identified in the literature. These include type of current residence; previous fractured hip or wrist; high alcohol intake; smoking; diagnosis of diabetes; rheumatoid arthritis or stroke; number of teeth; low calcium intake; low sunlight exposure and current medication.

All of these risk factors have been discussed in the introduction (p 31). Figure B.3.6.(p.32) summaries the risk factors and their proposed mode of action. They were investigated to see if they were also risk factors in our population.

Method

With the exception of current residence and medication, information on the risk factors was obtained by using the nurse administered structured questionnaire. Both current type of residence and medication were recorded from the medical notes of the cases and by directly asking the controls. The controls were asked to produce their current medications as confirmation. For the three controls who failed the mental test, residence was known as the nurse had interviewed them at home but current medication was unavailable.

Results

Table D.3.1 shows that living in one's own home was associated with a 70% reduction in the risk of hip fracture.

Table D.3.1: Association of hip fracture with living in one's own home. The analysis included all eligible cases(including those who did not complete the interview)and interviewed controls.

Category	No. of Cases	Cases who passed MTS (%)	No. of Controls	Controls who passed MTS (%)	*OR (95% CI)
Living in warden controlled/ residential home/ nursing home	313	37.4	44	95.4	1.0 (-)
Living in own home	424	72.4	240	99.6	0.3 (0.2 - 0.4)

*adjusted for age and sex

Table D.3.2 shows that when risks were adjusted for age, sex, BMI and recent inactivity, living in one's own home was associated with a 20% reduction in risk of hip fracture, but this was no longer statistically significant. This analysis was restricted to subjects who passed the mental test.

Table D.3.2. Association of hip fracture with living in own home. The analysis only included interviewed cases and controls.

Category	No. of Cases	No. of Controls	* OR (95% CI)	**Adjusted OR (95% CI)
Living in warden controlled/ residential home/ nursing home	117	42	1.0 (-)	1.0 (-)
Living in own home	307	239	0.5 (0.3 - 0.7)	0.8 (0.5 - 1.3)

*adjusted for age and sex **adjusted for age, sex, BMI and recent inactivity

Table D.3.3 shows that previous fracture was associated with an increased risk of subsequent hip fracture. Overall there was approximately a two fold increase with past wrist fracture, which was statistically significant for 'ever broken wrist', 'broken wrist once' and 'broken wrist at 40 year or older'. Previous hip fracture was associated with an increase in risk but this was not statistically significant.

Table D.3.3 : Association of hip fracture with previous fracture.

Variable	Category	No. of Cases	No. of Controls	*OR (95% CI)	**Adjusted OR (95% CI)
Broken hip (other hip if subject a case)	Never	388	268	1.0 (-)	1.0 (-)
	Ever	36	12	2.0 (1.0 - 3.9)	1.3 (0.6 - 2.7)
Broken wrist	Never	303	233	1.0 (-)	1.0 (-)
	Ever	121	47	2.0 (1.3- 2.9)	2.1 (1.3 - 3.2)
Times broken wrist	Never	302	233	1.0 (-)	1.0 (-)
	Once	106	42	1.9 (1.3 - 2.9)	2.0 (1.3 - 3.2)
	Twice	16	5	2.6 (0.9 - 7.1)	2.4 (0.7 - 8.0)
Broken wrist before 40 years of age	No	394	263	1.0 (-)	1.0 (-)
	Yes	22	12	1.3 (0.6 - 2.6)	1.8 (0.8 - 4.0)
Broken wrist at 40 years of age or older	No	325	245	1.0 (-)	1.0 (-)
	Yes	91	30	2.3 (1.5 - 3.6)	2.2 (1.3 - 3.7)
Broken wrist or hip	Never	281	225	1.0 (-)	1.0 (-)
	Ever	143	55	2.1 (1.4 - 3.0)	1.9 (1.2 - 2.9)

*adjusted for age and sex **adjusted for age, sex, BMI and recent inactivity

Table D.3.4 reveals that smoking did not affect the risk of hip fracture. However, among ex-smokers, having stopped smoking for over 30 years was associated with a decreased risk of hip fracture.

Table D.3.4 : Association of hip fracture with smoking.

Variable	Category	No. of Cases	No. of Controls	*Unadjusted OR (95% CI)	**Adjusted OR (95% CI)
Ever smoked regularly	Never	178	111	1.0 (-)	1.0 (-)
	Ever	246	169	1.0 (0.7 - 1.4)	0.9 (0.6 - 1.3)
Type of smoker (No. of cigarettes per day)	Never (<1)	184	119	1.0 (-)	1.0 (-)
	Light (1-19)	135	92	1.0 (0.7 - 1.5)	1.0 (0.6 - 1.5)
	Heavy (≥20)	105	69	1.1 (0.7 - 1.7)	1.0 (0.6 - 1.7)
Current smoking status	Never	178	111	1.0 (-)	1.0 (-)
	Ex smoker	147	113	0.9 (0.6 - 1.3)	0.9 (0.6 - 1.4)
	Current smoker	99	56	1.2 (0.8 - 1.9)	0.9 (0.5 - 1.4)
Ex smoker (number of years stopped)	Less than 15 years	59	32	1.0 (-)	1.0 (-)
	15 - 29 years	43	34	0.7 (0.3 - 1.3)	1.0 (0.4 - 2.1)
	30 Years or more	46	47	0.5 (0.2 - 0.9)	0.4 (0.2 - 1.0)

*adjusted for age and sex **adjusted for age, sex, BMI and recent inactivity

Table D.3.5 shows that there was slight decrease in risk of hip fracture for participants consuming over 4 units of alcohol a day, but this was not statistically significant.

Table D.3.5 : Association of hip fracture with alcohol intake.

Variable	Category	No. of Cases	No. of Controls	*OR (95% CI)	**Adjusted OR (95% CI)
Amount of alcohol drunk per day	None	252	136	1.0 (-)	1.0 (-)
	0.05 - 4 units	90	74	0.7 (0.5 - 1.0)	1.0 (0.6 - 1.5)
	4.1 units or more	82	70	0.6 (0.4 - 1.0)	0.8 (0.5 - 1.2)

*adjusted for age and sex **adjusted for age, sex, BMI and recent inactivity

Table D.3.6 confirms that a previous diagnosis of rheumatoid arthritis was a risk factor for hip fracture. There was a two fold increase in risk which was statistically significant.

Table D.3.6 : Association of hip fracture with previous illness

Variable	Category	No. of Cases	No. of Controls	*OR (95% CI)	*Adjusted OR (95% CI)
Diabetes	Never	392	262	1.0 (-)	1.0 (-)
	Ever	32	18	1.2 (0.7 - 2.2)	0.8 (0.4 - 1.5)
Rheumatoid Arthritis	Never	382	269	1.0 (-)	1.0 (-)
	Ever	42	11	2.7 (1.4 - 5.4)	2.3 (1.1 - 5.1)
Stroke	Never	366	250	1.0 (-)	1.0 (-)
	Ever	58	30	1.3 (0.8 - 2.1)	0.8 (0.4 - 1.4)

*adjusted for age and sex **adjusted for age, sex, BMI and recent inactivity

Table D.3.7 shows that still having some of one's own teeth was associated with a decrease in the risk of hip fracture, but that this was not statistically significant.

Table D.3.7: Association of hip fracture with retention of own teeth

Variable	Category	No. of Cases	No. of Controls	*OR (95% CI)	**Adjusted OR (95% CI)
Number of own teeth	None	309	170	1.0 (-)	1.0 (-)
	Any	115	110	0.6 (0.4 - 0.8)	0.8 (0.5 - 1.1)

*adjusted for age and sex **adjusted for age, sex, BMI and recent inactivity

Table D.3.8 shows that there was a non-significant trend towards a reduced risk of hip fracture with moderate or high intake of dietary calcium.

Table D.3.8: Association of hip fracture with dietary calcium intake

Variable	Category	No. of Cases	No. of Controls	*OR (95% CI)	**Adjusted OR (95% CI)
Calcium intake mg per day	574 or less	140	71	1.0 (-)	1.0 (-)
	575 - 807	123	96	0.7 (0.4 - 1.0)	0.7 (0.5 - 1.2)
	808 or more	161	113	0.8 (0.5 - 1.1)	0.8 (0.5 - 1.2)

*adjusted for age and sex **adjusted for age, sex, BMI and recent inactivity

Exposure to sunlight for more than an hour per day did not effect the risk of hip fracture. (Table D.3.9)

Table D.3.9: Association of hip fracture with sunlight exposure

Variable	Category	No. of Cases	No. of Controls	*OR (95% CI)	**Adjusted OR (95% CI)
Hours of sunlight a day	≤ 1 hour	221	124	1.0 (-)	1.0 (-)
	> 1 hour	201	156	0.8 (0.6 - 1.0)	1.1 (0.8 - 1.5)

*adjusted for age and sex **adjusted for age, sex, BMI and recent inactivity

Table D.3.10 summarises the associations of hip fracture with six types of medication. Oral steroids were associated with an increase in risk which contrasted with a reduced risk associated with use of inhaled steroids. Vitamin D supplements were associated with an 80% reduced risk of hip fracture. Medication which caused drowsiness was associated with nearly a two fold increase in risk. Both analgesics and NSAIDs (non-steroidal anti-inflammatory drugs) were associated with a lower risk of hip fracture.

Table D.3.10 : Association of hip fracture with current medication..

Variable	Category	No. of Cases	No. of Controls	*OR (95% CI)	**Adjusted OR (95% CI)
Oral Steroids	No	401	275	1.0 (-)	1.0 (-)
	Yes	23	5	3.1 (1.2 - 8.4)	1.7 (0.6 - 4.8)
Inhaled Steroids	No	400	260	1.0 (-)	1.0 (-)
	Yes	24	20	0.8 (0.4 - 1.5)	0.5 (0.2 - 1.0)
Vitamin D supplements	No	414	243	1.0 (-)	1. 0 (-)
	Yes	10	37	0.2 (0.1 -0.3)	0.2 (0.1 - 0.5)
Medication which can cause drowsiness	No	306	246	1.0 (-)	1.0 (-)
	Yes	118	34	2.8 (1.8 - 4.2)	1.8 (1.1 - 2.9)
Analgesia	No	383	228	1.0 (-)	1.0 (-)
	Yes	41	52	0.4 (0.3 - 0.7)	0.4 (0.2 - 0.6)
NSAID[#]	No	323	204	1.0 (-)	1.0 (-)
	Yes	101	76	0.8 (0.6 - 1.2)	0.7 (0.4 - 1.0)

*adjusted for age and sex **adjusted for age, sex, BMI and recent inactivity [#]Non-steroidal anti-inflammatory drugs

Discussion

When type of residence was investigated, including all eligible cases (including those who failed to complete the interview) and interviewed controls, presently living in one's own home was associated with a statistically significant 70% reduction in the risk of hip fracture. However, when the analysis was restricted to those participants who completed the interview and adjusted for BMI and recent activity, the risk although remaining in the same direction, was no longer significant. This was not surprising as it is known that people who have relocated to a nursing home, residential home or warden controlled flat are generally frailer, more unwell and hence less active than people who can still live independently.

The type of residence was well documented in the hospital notes and if there was a query then the case was asked for clarification. The controls were visited in their homes and therefore it was very unlikely that there were inaccuracies.

The main problem with the analysis of the whole data set was that the controls were probably not representative of the population. All eligible cases (including those who failed the mental test) were included in the analysis, but, a large proportion of potential controls who currently lived in a nursing home or residential home probably would have failed the mental test score and therefore did not participate. It is likely that this would lead to an overestimate of the relationship between current residence and risk of hip fracture. However this bias would not have affected the second analysis in which only participants who completed the interview were included.

Mivavet *et al.*(1993) re-analysed the findings of the Mediterranean Osteoporosis (MEDOS) study and found that living in an institution remained an independent risk factor after adjusting for urban background, inactivity and morbidity. It is known that fractures often happen in the first months of institutionalisation and the authors postulated that the explanation could be the change in physical surroundings which may increase the likelihood of falling. However, when type of residence was treated as a potential risk factor in our population and adjusted for BMI and recent inactivity, living in one's own home was associated with a reduced risk but this was not statistically significant.

There was a consistently higher risk of hip fracture for participants who had previously broken their hip or wrist. Overall, breaking a wrist was associated with a two fold increase in risk. Previous broken hip carried an increase in risk (OR= 1.3) but this was not statistically significant. There was a trend of increasing risk with the number of times that a participant had broken a wrist which suggests a dose-response effect and confers confidence in the data, although the variable 'broken wrist twice' was not statistically significant. This was probably due to the small number in this category.

Breaking a wrist before 40 years of age was not a statistically significant risk factor and was associated with a smaller odds ratio than wrist fracture after 40 years. The cut-off of 40 years was chosen as fractures before this age could not confidently be categorised as osteoporotic (refer to figure B.3.4). In fact, most of these early fracture were in the participants' formative years.

It is commonly recognised that patients with one type of age-related fracture often have an other. Indeed the presence of osteoporosis at one site is associated with osteoporosis at another. Cummings *et al.* (1995), found that history of any type of fracture since the age of 50 was associated with an increased risk of hip fracture. The relative risk was 1.5 with a 95% confidence interval of 1.0 to 2.1. Patients with hip fracture are about twice as likely as expected to have had a prior wrist fracture (Gallagher et al., 1980, Alffram, 1964 and Owen et al., 1982). It follows that the risk factors present at the time of the first fracture will persist and in fact this fracture may further worsen the risk profile. For example, if a person experiences a hip fracture it is likely that the morbidity associated with this fracture would result in the person being less active and thus more at risk of another hip fracture.

There was no conclusive relationship between alcohol intake and hip fracture, although it tended to be protective. There were several problems with the data. Firstly, alcohol intake is generally under reported and it is possible that the cases were trying to work out why they had had a fracture and underestimate their intake because they expected it to be perceived as being wrong. Also there were a few known alcoholics among the cases, and they were generally uncooperative and included some who refused to respond to that question. These factors would bias the results towards an apparent protective effect.

The evidence from other studies for an association between moderate alcohol intake and fracture is contradictory. Felson and colleagues examined the issue using a retrospective cohort design (Felson *et al.*, 1988) and found relative risks of 1, 1.34 and 1.54 for light, moderate and heavy drinkers respectively among women and 1, 0.78 and 1.54 in men. All confidence intervals included unity. Hememway and colleagues studied 96,508 nurses ages 35-59 years (Hemenway et al., 1994) and found an interaction between body weight and alcohol intake. Women were only at increased risk of hip fracture if they were thin and drank more than 15mg of alcohol a day.

Alcoholism has been associated with reduced bone mineral density, (Dalen and Lamke, 1976 and Chon et al., 1992) but the picture is complicated as alcoholism is associated with other risk factors for osteoporosis such as poor nutrition, leanness, malabsorption, vitamin D deficiency, tobacco use and an increased risk of falling.

No relationship was observed between smoking and hip fracture in this study except that stopping smoking for over 30 years was protective compared to having stopped for less than 15 years. This may be a spurious result based on small numbers. As with alcohol (see above) cases may perceive that they are doing wrong by smoking and underestimate their smoking habits. This would bias the results towards a protective effect and might mask a true adverse effect of smoking.

In most, but not all studies, tobacco use has been associated with an increased risk of hip fractures both in women and in men (Seeman, 1996). Law and Hackshaw (1997) published the results of a meta-analysis of 19 cohort and case-control studies reporting risk of hip fractures in smokers relative to non-smokers. They found that the risk for women was similar at age 50 but greater thereafter by an estimated 17% at age 60, 41% at 70, 71% at 80 and 108% at 90. The increased risk for fractures associated with tobacco use is likely to be partly conferred by a reduction in bone density. Tobacco users often start smoking by 10 to 12 years of age, so that reduced peak bone density may contribute to any deficit in bone density in adulthood.

Of the illnesses that were noted in the literature as being risk factors, only rheumatoid arthritis was identified as a risk factor in this study. In fact, the risks associated with both diabetes and stroke, although not statistically significant, were in the opposite direction to that expected. Care was taken during the data collection to differentiate between osteoarthritis and rheumatoid arthritis.

Patients with rheumatoid arthritis have been cited as a group with increased risk of osteoporosis as they can exhibit rapid bone loss due to active disease and immobility. In addition, rheumatoid arthritis is commonly treated with oral steroids which have a well-documented deleterious effect on bone turnover (Riggs *et al.*, 1966; Gennari and Imbimbo, 1985; Hahn *et al.*, 1979). This study found that over 10% of the cases and almost 5% of the controls had been diagnosed with

rheumatoid arthritis, whereas a recalled cumulative prevalence of 1-1.5% would have been expected in this population. This suggests over-reporting of rheumatoid arthritis even though care had been taken to differentiate between osteoarthritis and rheumatoid arthritis when questioning the participant. It is possible that the cases over-reported more than the controls as they were looking for a reason why they had broken their hip and this would exaggerate any relationship between rheumatoid arthritis and osteoporotic hip fracture.

In agreement with the literature, still having any of one's own teeth was associated with a decrease in risk of hip fracture, although this did not reach statistical significance. There was confidence that the participants would know if they had any of their own teeth and the data were regarded as accurate. It was possible that if fluoride intake affected hip fracture, this could confound associations with tooth retention. This association is explored in Section D.6.

When the group with the highest third of calcium intake per day and the middle third were compared to the lowest third there was a non-significant 30% and 20% reduction in the risk of hip fracture respectively. This agreed with the literature reporting that there is a threshold of calcium intake for its effect on hip fracture.

Food frequency questionnaires are fraught with problems and this was no exception. The questionnaire used was a quick and easy way to estimate calcium intake and had previously been shown to correlate well with estimates derived from more robust methods such as duplicate diet analysis and six day weighed inventories (Nelson *et al.*, 1988). It had been shown that compared to the other methods there was a tendency to underestimate intakes, but that the calcium questionnaire did not grossly misclassify subjects. As calcium intake was a potential confounder and not the primary focus of the study, and the method used was able to rank the subjects confidently, it was considered appropriate. Any misclassification that resulted is likely to have been non-differential, with the effect of obscuring associations with fracture. If calcium intake had turned out to be an important confounder, the errors could have meant this its confounding effects were not fully controlled, but this did not appear to be a problem.

Cooper *et al.* (1988) found in a case control study, using the same calcium questionnaire, that there was no relation between calcium intake and hip fracture in women, but men with daily intakes above 1g had lower risks. A further prospective study by the same workers confirmed that a reduced intake of dietary calcium was not a risk factor for hip fracture (Wickham *et al.*, 1989). Another prospective study, this time conducted in California, found the dietary calcium was inversely related to risk of hip fracture (Holbrook *et al.*, 1988). Welton *et al.* (1995) discovered a positive association between calcium intake and bone mass in a meta-analysis. Thirty three studies had been performed in adults between 18 and 50 years of age. The authors advised a calcium intake of 1500 mg/day throughout life.

Thus, although low calcium intake has not been identified as a risk factor in all studies, none of the studies have found an increased risk of hip fracture with high calcium intake. It would seem prudent to treat low calcium as a risk factor for osteoporotic hip fracture as adequate calcium intake seems a logical requirement for healthy bone metabolism.

Duration of sunlight exposure influences the amount of vitamin D manufactured by the skin. The unadjusted odd ratios showed a significant protective effect of sunlight, but this disappeared when adjusted for recent inactivity and BMI. This was to be expected, insofar as sunlight exposure is likely to be associated with higher levels of current activity. Participants found the question on sunlight difficult to answer and tended to concentrate on sunbathing rather than other activities undertaken outside. It is possible, therefore, that the absence of an association with sunlight occurred because of misclassification of exposure.

There was a non-significant increase in the risk of fracture with use of oral steroids. This was in the direction expected as steroids are known to have a deleterious effect on bone mineral density. It was possible that some participants taking oral steroids had rheumatoid arthritis which was confounding the effect of the steroid. However, when the analysis was adjusted for a diagnosis of rheumatoid arthritis (5 of the 28 participants currently taking oral steroids had been diagnosed with rheumatoid arthritis) the odds ratio was only slightly reduced 1.6 (CI 0.6 -4.6).

Inhaled steroids appeared protective against hip fracture. There was a 50% reduction in risk of hip fracture in participants currently taking oral steroids which was statistically significant.

One explanation could be that asthmatics prescribed inhaled steroids may be more active than asthmatics not taking the medication.

Participants taking vitamin D supplements experienced a statistically significant 80% reduction in risk of hip fracture. This was in the direction expected from the literature. The association may have been confounded by the occurrence of osteoporosis which would be an indication for prescribing vitamin D, but this would have biased the results towards an underestimate of the protective effect of vitamin D.

Medications which are known to have the potential to cause drowsiness increased the risk of hip fracture nearly two fold and this reached statistical significance. The drugs were identified by reference to the 'British National Formulary', which states the drugs that require the warning 'may cause drowsiness' on their label when the drug is dispensed. Cummings *et al.* (1995) found that therapy with long-acting benzodiazepines and anticonvulsant drugs increased the risk of hip fracture. One hypothesis is that these drugs may increase the propensity to fall, another is that they can impair protective responses.

Presently taking analgesia was associated with a statistically significant 60% decrease in risk of hip fracture. One explanation may be that participants who were not in pain may have been more active than those experiencing pain or the relationship could simply be a chance finding. A literature search revealed no relevant studies of the relationship between hip fracture and analgesia.

Currently taking non-steroidal anti-inflammatory drugs also conferred protection on the risk of hip fracture. It is thought that prostaglandin inhibition by NSAID may inhibit bone loss and preserve bone mineral density (Bauer *et al.*, 1996).

Overall there were several problems with the collection of data on current medication. As described in the methodology, information for the cases was collected from their hospital notes and controls were asked to produce their medication as confirmation. It was possible that some items of medication were missed by the controls especially if they were not taken on a routine basis. This could underestimate any protective effect of the medication and overestimate any harmful effect.

More generally doctors in Hartlepool may have different prescribing habits than those in Middlesbrough and Stockton. If fluoride was found to exert an effect on the risk of hip fracture then it may be that fluoride was confounding the effect of the medication. The relationship between fluoride and fracture risk is explored in Section D.4.

Conclusion

In this population previous wrist fracture and a diagnosis of rheumatoid arthritis were confirmed as a risk factors for osteoporotic hip fracture. Both variables produced odds ratios in the same direction and magnitude as observed in the literature.

When type of residence was adjusted for BMI and recent inactivity no statistically significant association was evident with risk of hip fracture. This was in contrast to the published literature, but other studies have not always taken BMI into account.

There was no confirmation from this population that alcohol or smoking increased the risk of hip fracture as suggested in the literature. This may have been because of problems with the data collection as discussed.

The relationship between calcium intake and risk of hip fracture confirmed the results of previous workers in this country. There was a non-significant reduction in risk of hip fracture for moderate intake of calcium which did not further reduce for the high intake category. Exposure to sunlight was not reliably reported, and it was unsurprising that no relationship with hip fracture was observed.

Retention of one's own teeth was associated with a non-significant reduction in risk of hip fracture as expected from the literature.

There were some interesting findings in relation to current medication which warrant further investigation as the published literature on the subject is limited.

Section D.4: Fluoride as a risk factor for hip fracture

Introduction

The prime purpose of the study was to investigate the association between hip fracture and fluoride in drinking water. Information on the link between fluoride exposure and increased risk of hip fracture has been presented from drug trials, ecological studies and studies of individuals. The results have been discordant and one criticism was that fluoride exposure had been poorly measured. The main advance in the current study was the painstaking attempt to estimate fluoride exposure. Both past exposure to fluoride in the drinking water and current intake of fluoride, estimated from tea, fish, drinking water and fluoride toothpaste, were investigated. Also, many of the other studies did not collect such detailed information on possible confounders.

Method

Residential history was used to assign a water fluoride concentration for each year of the person's life (refer to p.65). These data were then amalgamated into an average for the first 20 years of life, the last 20 years and over the person's whole life. Only people for whom at least 90% of the residential history could be coded were used in the analysis.

Obviously, only participants who completed the interview could be used in the above analysis. Current address, however, was available from the hospital notes for all subjects, including those who failed the mental test. To see if current address could be used as a proxy for fluoride exposure, the relationship between lifetime average fluoride concentrations and current address was examined in those subjects whose fluoride exposures could be estimated.

Four indices of current fluoride intake were investigated, namely fish, tea, tap water containing in excess of 0.9ppm and toothpaste use. Intake of fish was dichotomised according to whether it was eaten less than once a week or at least once a week. The amount of tea drunk was split into thirds of its distribution to create a low, medium and high category. Tap water intake was classified according to whether participants drank water which contained less than 0.9ppm, or at least 0.9ppm. The second category was then split into two according to the

daily volume of tap water consumed (low intake was ≤ 1583 mls a day and high intake was >1583 mls a day).

Finally, the odd ratios associated with fluoride exposure were adjusted for the other variables which were found significant in the analysis to date and thought to be possible confounders of the effect of fluoride.

Results

Table D.4.1. shows that there was no relationship between high fluoride exposure, as estimated from residential history, and osteoporotic hip fracture.

Table D.4.2. confirms that most people who were currently residents of Hartlepool were categorised in the high fluoride group.

Table D.4.3. shows that when current residence in Hartlepool was used as a proxy for high fluoride exposure, again fluoride exposure was not associated with an increased risk of hip fracture.

Table D.4.4. in keeping with the above results, displays no increase in the risk of hip fracture for other indices of current fluoride consumption. In accordance with above, current high intake of drinking water, which contained in excess of 0.9ppm, was not associated with an increase in the risk of hip fracture. There was, however, a non-significant reduction in the risk of hip fracture among people using fluoride toothpaste. (Table D.4.5.)

Table D.4.1 : Associations of hip fracture with water fluoride concentration at place of residence.

Time period	Fluoride concentration	No. of Cases	No. of Controls	*OR (95% CI)
Average over life	Less than 0.9ppm	330	200	1.0 (-)
	0.9ppm or more	67	44	1.0 (0.7 - 1.5)
Average over first 20 years	Less than 0.9ppm	349	220	1.0 (-)
	0.9ppm or more	65	40	1.0 (0.7 - 1.5)
Average over last 20 years	Less than 0.9 ppm	339	212	1.0 (-)
	0.9 ppm or more	71	48	1.0 (0.7 - 1.5)

*adjusted for age and sex

Table D.4.2 : Association of current address in Hartlepool with lifetime exposure to fluoride in drinking water as estimated from residential history

Time period	Fluoride Concentration	Number with Hartlepool address	Percentage
Average over life	0.9ppm or more	105	91.3
Average over first 20 years	0.9ppm or more	94	75.8
Average over last 20 years	0.9ppm or more	119	94.4

Table D.4.3 : Associations of hip fracture with current residence in Hartlepool. This analysis included all eligible cases and interviewed controls.

Variables	Category	No. of Cases	No. of Controls	*OR (95% CI)
Current address	Stockton or Middlesbrough	609	230	1.0 (-)
	Hartlepool	128	53	0.9 (0.6 - 1.3)

*adjusted for age and sex

Table D.4.4 : Associations of hip fracture with dietary sources of fluoride.

Variable	Categories	No. of Cases	No. of controls	*OR (95% CI)
Fish consumption	< once a week	344	232	1.0 (-)
	≥ once a week	80	48	1.2 (0.8 - 1.7)
Tea intake	Low	151	95	1.0 (-)
	Medium	135	93	0.9 (0.6 - 1.3)
	High	138	92	1.0 (0.7 - 1.4)
Tap water intake	Tap water with <0.3ppm	342	230	1.0 (-)
	Low intake of tap water with ≥0.9ppm fluoride	42	25	1.1 (0.6 - 1.8)
	High intake of tap water with <0.9ppm fluoride	39	26	1.0 (0.6 - 1.7)

*adjusted for age and sex

Table D.4.5 : Association of hip fracture with use of toothpaste containing fluoride. Analysis excluded subjects with no teeth.

Variable	Categories	No. of Cases	No. of controls	*OR (95% CI)	**Adjusted OR (95% CI)
Toothpaste	Do not use	17	5	1.0 (-)	1.0 (-)
	Use	98	105	0.3 (0.1 - 0.8)	0.3 (0.1 - 1.1)

* adjusted for age and sex **adjusted for age, sex, bmi and current activity

Table D.4.6. displays the culmination of the analysis. After adjustment for age, sex, BMI, recent inactivity, rheumatoid arthritis and age at menarche, there was no increase in the risk of hip fracture for participants exposed to higher levels of fluoride in water. Rather, if anything, there was a tendency towards a protective effect of fluoride.

Table D.4.6: Associations of hip fracture with water fluoride concentration at place of residence. All odds ratios are adjusted for age, sex, BMI, current activity, rheumatoid arthritis and age at menarche.

Time Period	Fluoride Concentration	No. of Cases	No. of Controls	Adjusted OR (95 % CI)
Average over lifetime	Less than 0.9 ppm	330	200	1.0 (-)
	0.9 ppm or more	67	44	0.6 (0.4 - 1.0)
Average over first 20 years	Less than 0.9 ppm	349	220	1.0 (-)
	0.9 ppm or more	65	40	0.7 (0.4 - 1.2)
Average over last 20 years	Less than 0.9 ppm	339	212	1.0 (-)
	0.9 ppm or more	71	48	0.5 (0.3 - 0.9)

Discussion

None of the indicators of higher fluoride intake resulted in a statistically significant increase in the risk of hip fracture. If anything, it appeared that participants who were exposed to higher concentrations of fluoride in the drinking water had a lower risk of hip fracture than those exposed to lower concentrations of fluoride. Indeed for the variables 'average over lifetime' and 'average over last 20 years' participants with exposure to fluoride in the drinking water of at least 0.9ppm had a reduced risk of hip fracture of 40% and 50% respectively. In addition the confidence intervals of the odds ratios were narrow and did not include unity. It was encouraging that all of the results (although they did not all reach statistical significance) were in the same direction.

The fact that the results not only suggested that high concentrations of fluoride in the drinking water did not increase the risk of hip fracture but in fact inferred that fluoride exposure may protect against the risk of hip fracture will be important if confirmed in the analysis of the whole data set. It is interesting to think about this apparent protective effect of fluoride in the drinking water. This result could be due to bias or confounding, although no major sources of either effect were identified (as discussed below). It could be a chance effect which is a possibility especially at this stage of the analysis, although the numbers were sufficient to produce statistically significant results with narrow confidence intervals. The other explanation is that it is a true causal relationship which is biologically plausible but needs to be confirmed in the analysis of the whole data set.

When looking at fluoride in water, different stages of life were investigated as it was postulated that fluoride might exert more influence at certain times, such as when the bones were actively growing in youth, but no evidence was found to support this theory.

The residential histories were surprisingly complete and very few people were excluded from the analysis. Even with a high cut-off of 90% of the residential history to be complete and coded, only 30 people were excluded from analysis of first 20 years (4.4%), 34 from last 20 years (5.1%) and 63 from analysis for whole life (9.8%).

Two problems were experienced when coding the data. Firstly addresses in the county of Durham could not be coded as the area has a very complicated history with respect to fluoride. There are localised areas which have natural fluoride in water at concentrations above 0.3ppm and certain areas have received artificially fluoridated water. However, these areas have changed over time and on some occasions water has been mixed from different sources. As there are no reliable records available, these addresses were coded as missing. Secondly, if the address was outside the United Kingdom this was also coded as missing because insufficient information was available to make an accurate classification. However it is unlikely to have affected the validity given that so few people were excluded as a result.

The study population proved to be relatively stable. In essence, the time that people were away from the study area was during the second world war. In fact, when women moved into their marital home it was often in the same street as their parents. This meant that recall of residential histories and coding was easier than if the population had been highly mobile. In addition, the participants would not have expected that were they had lived might have influenced their risk of hip fracture and therefore their responses should not have been biased.

Another potential source of bias was the participation rate of cases and controls. If, for example, Hartlepool cases had a much higher inclusion rate than those in Middlesbrough and Stockton, then this would lead to misrepresentation of the effect of fluoride exposure and vice versa for controls. Table C.1.3. in the method section (p.64) confirmed that this was not an issue.

Table D.4.3 is reassuring with respect to non-response bias influencing the results. This analysis used current residence in Hartlepool as a proxy of high fluoride exposure and it was therefore possible to include all of the eligible cases including those who were unable to complete the interview. The results were in agreement with those which only included cases who completed the interview, in that current residence in Hartlepool did not increase the risk of hip fracture.

When the analyses of fluoride exposure were adjusted for the possible confounding effects of age, sex, BMI, current activity, age at menarche and rheumatoid arthritis, no increase in the

risk of hip fracture was observed. In fact, there was a tendency towards a protective effect of fluoride in water.

It was decided to adjust for BMI, current inactivity, age at menarche and diagnosis of rheumatoid arthritis, as well as for age and sex, since all of these variables had been identified as risk factors in the earlier analysis and it was possible that they might confound any effect of water fluoridation. Although earlier fracture of the wrist was also identified as a risk factor, it was not added to the list of possible cofounders as, if fluoridation were associated with osteoporotic fracture in general, adjustment might obscure a real effect of fluoridation.

When other indices of fluoride intake were investigated, in keeping with above, no association of hip fracture was observed. There are inherent problems with recalled dietary information and this study was no exception. When information was sought on dietary habits such as consumption of tap water, tea and fish, only recent habits were assessed. This did not necessarily reflect the person's intake in the past and therefore only provided a snapshot of the person's fluoride exposure.

In addition, subjects may distort their reported diet for several reasons. Firstly, they may not want to confess to the consumption of certain types of food; they may more generally wish to report a diet that they believe will be acceptable in the eyes of the interviewer; or they may idealise their consumption by reporting a diet that they believe reflects what they usually do, or would like to achieve, but which in fact only represents their activity for a small proportion of the time. However, the food groups that we asked about in this section would not have been perceived as being good or bad foods and would not be subject to these potential biases.

Another problem was the variable concentration of fluoride in tea. The amount of fluoride in tea depends on where the tea was grown, the type of tea, and how it was prepared. Therefore at best the data on frequency of tea consumption provided a very crude estimate of fluoride intake. The potential misclassification would bias the results towards the null.

There was a 70% lower risk of hip fracture if the participant used fluoridated toothpaste, although this association was not significant when the odds ratio was adjusted for possible

confounders. This was in the same direction as the fluoridated drinking water, in that fluoridation tended towards being protective of hip fracture.

As discussed in the introduction (p.52) the ecological studies that have investigated the relationship between fluoride in drinking water and osteoporotic hip fracture have produced discordant results. In the only UK study, Cooper *et al.* (1991), obtained hip fracture rates in 39 county districts of England and Wales and found a significantly positive correlation between fluoride levels and discharge rates for hip fracture ($r=0.41$, $p=0.009$). However each of the ecological studies has basic flaws that make the interpretation of the results difficult. In particular, they may not have controlled adequately for confounding variables.

Better information is available from the few studies that have been based on individuals. Sowers *et al.* (1991) studied cohorts of women in three communities in Iowa which had different water sources, with different levels of calcium and fluoride. The study demonstrated a mean relative risk of 2.1 (95% confidence interval, 1.2-4.4) for any fracture in postmenopausal women residing in the high fluoride community. However, the high fluoride group had approximately 4ppm of fluoride in the water and thus much higher exposure than in our population.

Cauley *et al.* (1995), studied a cohort of women and estimated individual person-years of fluoride exposure. Bone mineral density was measured at three sites and a history of fracture was obtained. No relation was found between years of fluoride exposure and bone mineral density and there was no relation with history of fracture.

Most recently, Phipps *et al.* (1997a) investigated the issue in a population of women enrolled in a cohort study of osteoporotic fractures. Bone mineral density was measured and incident hip fractures were ascertained every four months and confirmed by radiographic report. Variables known to influence bone mineral density were measured using an interviewer administered questionnaire and exposure to fluoridated water was determined using a residential history questionnaire. After adjustment for potential confounders, women with continuous exposure for the last 20 years had bone mineral density values which were 3% higher at the femoral neck ($p<0.001$) and a 28% reduction in hip fracture risk ($RR=0.72$, 95%CI=0.53-0.99).

In another study (Phipps et al., 1997b) the authors; compared the bone mineral density between long-term residents (≥ 20years) of three rural communities in the USA. The authors recorded other variables known to influence bone mineral density. They found no relationship between the ingestion of high levels of fluoride and femoral bone mineral density.

Conclusion:

Water fluoride was not associated with an increase in risk of hip fracture in this study. Rather, if anything there was a trend towards a protective effect of fluoride in water. After adjustment for potential confounders, this reduction in risk was statistically significant when water fluoride exposures were averaged over a lifetime and over last 20 years.

As explained in the discussion, it is difficult to assess the results of this study in relation to previous ecological studies as their results were discordant and confounders could not be accounted for. All of the studies of individuals to date have been carried out in the US. Sowers et al. (1991) compared a community which had 4ppm of fluoride in the water and found a deleterious effect. However, it is difficult to compare this study with ours as at most there was only 2ppm of fluoride in the water in Hartlepool. In three other studies (Cauley *et al.* (1995), Phipps *et al.* (1997a) Phipps et al., 1997b) fluoride was not identified as a risk factor for hip fracture.

In conclusion, water fluoride did not increase the risk of hip fracture in this study. It is unlikely that this finding can be explained by bias and the result is consistent with other studies that have looked at the effect of similar levels of fluoride exposure in individuals.

Section D.5: Fluoride measurements in bone

Introduction

Using the residential histories of participants to estimate their fluoride exposure, although executed as precisely and comprehensively as possible, could be subject to inaccuracies. Similarly, the assessment of current fluoride intake from dietary and non-dietary sources failed to take quantity and concentration of fluoride into account.

The pharmacokinetics of fluoride are well described in the literature (refer p. 43) and it is known that approximately 50% of fluoride absorbed from the alimentary canal is taken up and retained in bone. Thus, analysis of the fluoride concentration in bone should provide an estimate of long-term total fluoride uptake.

It was possible to collect the excised femoral heads of some of the hip fracture cases. This meant that an estimate of the body burden of fluoride could be made for these participants and related to their estimated fluoride exposure. This would help interpretation of the findings in relation to water fluoride. When the study was being planned several possible outcomes were identified.

Firstly, exposure to fluoride in water might be associated with fracture risk and with higher fluoride in femoral heads. This would support the hypothesis that fluoride in drinking water influences the level of fluoride in the proximal femur, making a causal relation to fracture more plausible. Secondly, water fluoride might be associated with fracture risk but not with higher fluoride in femoral heads. The absence of a relation between water fluoride and level of fluoride in the proximal femur, would cast doubt on the causal nature of the association between water fluoride and fracture. Thirdly, water fluoride might be associated with higher fluoride in femoral heads but not with fracture risk. The positive relation between water fluoride and fluoride in the proximal femur would encourage confidence in the validity of the water fluoride estimates, and in the conclusion that water fluoride does not have a major effect on fracture risk. Finally, water fluoride might not be associated either with fluoride in femoral heads or with fracture risk. This would suggest that the lack of association between water fluoride and fracture might be explained by the

fact that exposure to fluoride in water, as measured, does not have an important impact on fluoride in the proximal femur.

Method

Excised femoral heads were collected when possible from hip fracture cases at Hartlepool General, North Tees and Middlesbrough General hospitals. They were stored, unfixed, in clean plastic pots and frozen within 24 hours. The bone samples were then transported, on dry ice, to Dr H Hughes, (Human Metabolism/Clinical Biochemistry, Royal Hallamshire Hospital, Sheffield) for analysis.

The analysis was undertaken blind to fluoride exposure status. To prepare a trabecular bone sample, a slice of bone was sawn from the femoral head approximately 1cm in width. The cortical bone sample was obtained from the femoral neck and hence if there was no femoral neck on the bone sample, no cortical bone sample was available. The femoral neck was sawn off and all the trabecular bone removed, leaving the cortical bone.

The bone samples were then freeze dried, then put into solution with defatted ether. Next, slivers of approximately 50mcg were dissolved in 1 molar perchloric acid. The fluoride was measured using the fluoride electrode for which the pH had to be between 4 - 8. The fluoride was expressed as nmol/dry weight.(Dr H. Hughes, personal communication using the method described in Ishiguro et al., 1993).

The associations of fluoride concentration in the bone samples and the indicators of fluoride exposure used in Section D.4. were investigated. For variables with two categories the average bone fluoride in each category was compared, the 95% CI found and a t-test was undertaken. For variables with three categories a test for trend was applied.

Results

Table D.5.1. shows the number and percentage of trabecular and cortical bone samples that were available for each area of the study. Although there were little differences in the percentage between the two areas overall they were low.

Table D.5.1 Number and percentage of trabecular and cortical bone samples according to current address.

Current address	Total no. of cases	No. of trabecular samples	%	No. of cortical samples	%
Middlesbrough or Stockton	343	61	17.8	27	7.9
Hartlepool	81	20	24.7	3	3.7

No strong relationship between fluoride concentration in trabecular bone and estimated fluoride exposure can be observed from figure D.5.1.

Table D.5.2. shows that although not statistically significant, a higher mean fluoride concentration was found in trabecular bone in all of the higher categories of water fluoride exposure as compared to the low categories.

Table D.5.3. shows that there was a statistically significant increase in the fluoride concentration of cortical bone for the higher fluoride exposure categories. This was true for all four measures of fluoride exposure

Figure D.5.1. Graphical display of fluoride concentration in trabecular bone and fluoride residence

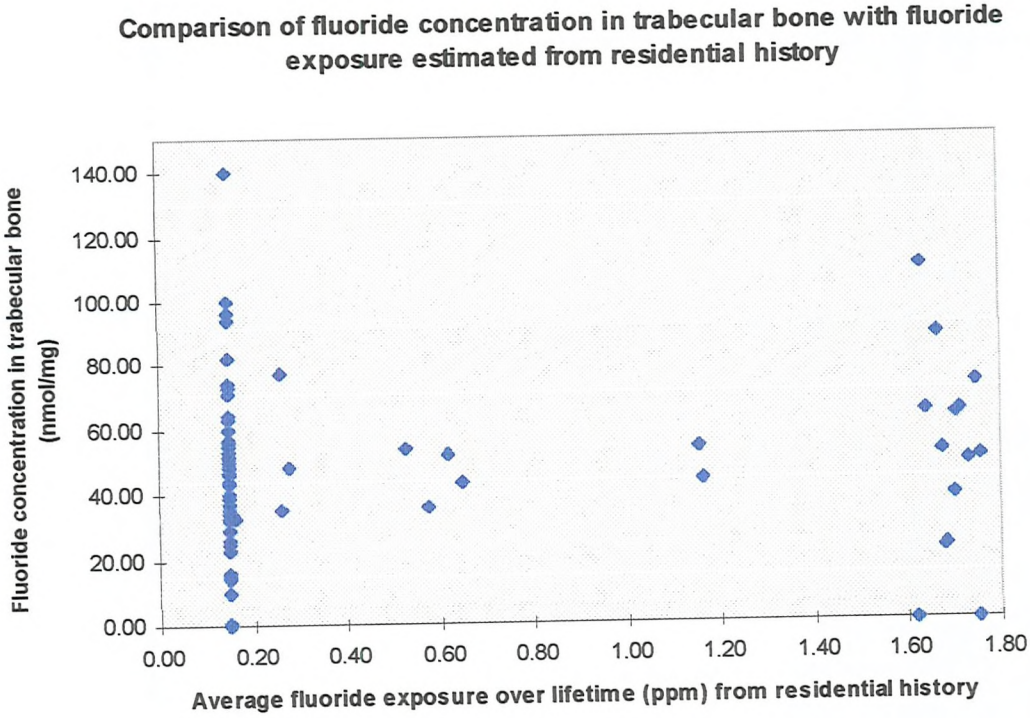


Table D.5.2. Lifetime water fluoride and fluoride concentration (nmol/mg) in trabecular bone

Time Period	Fluoride concentration in water	No. of Samples	Bone fluoride	Difference (95% CI)	Significance
Average over first 20 years	< 0.9 ppm	61	46.5	2.9 (-11.1,16.9)	p=0.7*
	≥0.9 ppm	17	49.4		
Average over last 20 years	< 0.9ppm	63	45.7	4.9 (-9.0,18.8)	p=0.5*
	≥ 0.9 ppm	17	50.5		
Average over life	< 0.9 ppm	62	45.7	3.9 (-10.5,18.3)	p=0.6*
	≥ 0.9 ppm	16	49.6		
Current address	Not Hartlepool	61	45.4	4.8 (-17.9,8.2)	p=0.5*
	Hartlepool	20	50.2		

*t test

Table D.5.3. Lifetime water fluoride and fluoride concentration (nmol/mg) in cortical bone

Time Period	Fluoride concentration in water	No. of Samples	Mean Bone fluoride	Difference in means (95% CI)	Significance
Average over first 20 years	< 0.9 ppm	24	25.3		
	≥0.9 ppm	5	64.2	38.9 (21.2,56.5)	p=0.0001*
Average over last 20 years	< 0.9ppm	27	27.9		
	≥ 0.9 ppm	3	73.0	45.1 (22.5,67.6)	p=0.0003*
Average over life	< 0.9 ppm	26	27.3		
	≥ 0.9 ppm	3	73.0	45.7 (23.0,68.4)	p=0.0003*
Current address	Not Hartlepool	27	27.9		
	Hartlepool	3	73.0	45.1 (22.5,67.6)	p=0.0003*

*t test

All of the cases who were assigned to the ≥0.9ppm fluoride category had a higher fluoride concentration in the cortical bone than any of the cases categorised as ≤0.9ppm (figure D.5.2).

Table D.5.4. summarises the relationship between residential water fluoride and fluoride concentrations in trabecular bone for the sub group of participants who also had cortical bone samples. Although not statistically significant, a higher mean fluoride concentration was found in trabecular bone in all of the high fluoride exposure categories compared to the low fluoride categories.

Figure D.5.2.: Graphical display of fluoride concentration in cortical bone and fluoride residence

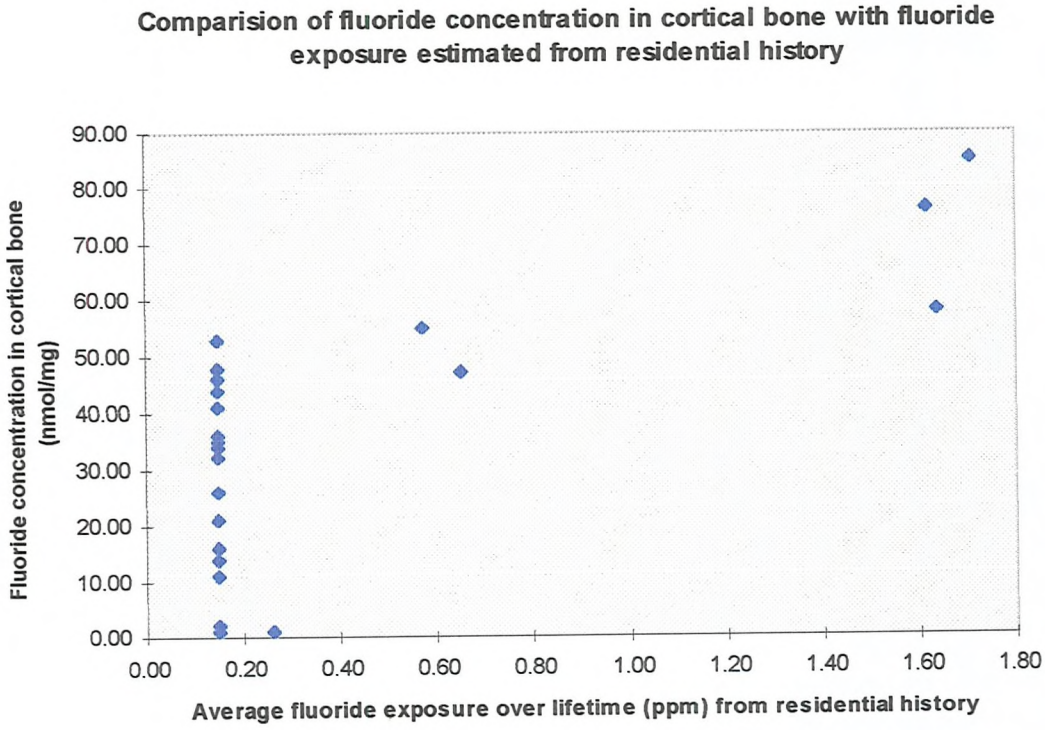


Table D.5.4. Lifetime water fluoride and fluoride concentration (nmol/mg) in trabecular bone for those people who had cortical bone concentrations.

Variables	Category	No. of Samples	Mean Bone fluoride	Difference in means (95% CI)	Significance
Average over first 20 years	< 0.9 ppm	23	45.2	6.3 (-23.7,36.3)	p=0.7
	≥0.9 ppm	4	51.5		
Average over last 20 years	< 0.9ppm	26	44.6	18.9 (-20.3,58.1)	p=0.3
	≥ 0.9 ppm	2	63.5		
Average over life	< 0.9 ppm	25	44.7	18.76 (-21.3,58.9)	p=0.3
	≥ 0.9 ppm	2	63.5		
Current address	Not Hartlepool	26	44.6	18.9 (-20.3,58.1)	p=0.3
	Hartlepool	2	63.5		

Table D.5.5. shows that although none of the current fluoride indices reached statistical significance, both fish and tap water consumption were in the direction expected. In addition both medium and high categories of tea consumption were higher than low tea consumption. No association between bone fluoride concentration and toothpaste use was observed.

Table D.5.5. Current fluoride exposure and fluoride concentration (nmol/mg) in trabecular bone

Variables	Category	No. of Samples	Mean Bone fluoride	Difference in means (95% CI)	Significance
Fish consumption	< Once a week	65	44.3	11.9 (-2.1,25.8)	p=0.09*
	≥ Once a week	16	56.1		
Tea consumption	Low	29	39.7	N/A	p=0.2 **
	Medium	28	52.3		
	High	24	48.3		
Tap water consumption	water with <0.9ppm fluoride	61	45.4	N/A	p=0.5 **
	Low intake with ≥0.9ppm fluoride	11	49.9		
	High intake with ≥0.9ppm fluoride	9	50.7		
Toothpaste	Do not use	61	47.1	2.0 (-11.1, 15.1)	p=0.8*
	Use	20	45.1		

* t test ** test for trend

Table D.5.6. shows there was a statistically significant increase in cortical bone fluoride content and intake of fluoride in drinking water. Although not reaching statistical significance there was a tendency for a increase in bone fluoride for high fish consumption compared to low consumption. No relationship was observed with tea consumption or toothpaste use.

Table D.5.6. Current fluoride exposure and fluoride concentration (nmol/mg) in cortical bone

Variables	Category	No. of Samples	Mean Bone fluoride	Difference (95% CI)	Significance
Fish consumption	< Once a week	25	31.4	6.0 (-16.9,28.8)	p=0.6*
	≥ Once a week	5	37.4		
Tea consumption	Low	11	33.1	N/A	p=0.7 **
	Medium	10	26.8		
	High	9	37.9		
Tap water consumption	water with <0.9ppm fluoride	27	27.9	N/A	p=0.0003**
	Low intake with ≥0.9ppm fluoride	2	67.0		
	High intake with ≥0.9ppm fluoride	1	85.0		
Toothpaste	Do not use	20	34.0	4.8 (-13.2, 22.9)	p=0.6*
	Use	10	29.2		

* t test **test for trend

Discussion

Overall there was a trend for the cases who were categorised in the group that were exposed to at least 0.9ppm, to have higher fluoride concentrations in their bone samples than those in the <0.9ppm group. This was in the direction expected and was statistically significant for the cortical bone but not for the trabecular bone. The main limitation of this analysis was the small number of samples of cortical bone. Only three samples came from people in the ≥0.9ppm exposure category. However, from figure D.5.2. it can be observed that all three samples were above the baseline spread of the low fluoride category.

Except for a statistically significant relationship between high current consumption of fluoridated water and fluoride concentration in cortical bone, no other factor of current fluoride consumption reached statistical significance. However, there was a tendency for a increase in bone fluoride for high fish consumption compared to low consumption in both trabecular and cortical bone. Although there was no relationship observed with tea consumption in cortical bone, both medium and high categories of tea consumption were associated with a higher trabecular bone fluoride. No association was found between bone fluoride and toothpaste use.

It was not surprising that strong relationships were not observed as only recent exposure was investigated. As this was just a snapshot of fluoride exposure it would be highly unlikely to be reflected in the fluoride concentration of the bone. However, the relationship between high intake of fluoridated water agreed with that of the residential histories.

As mentioned above, bone samples were collected only if the femoral head was excised during surgery and was not required for grafting. Thus bone samples were only available for a proportion of the cases. This could have introduced a bias if the concentration of fluoride in the bone affected the type of fracture and subsequent treatment. Whether this was the case is unknown.

The order in which the bone samples were analysed was haphazard, as the bones were stored in a shared freezer and mixed up several times. Although this was not ideal, random ordering proved impractical to implement because of the way the samples were organised.

Another problem was the fact that there were so few cortical bone samples. A sample of cortical bone was identified by eye, which was not ideal. However, the person undertaking the task was experienced in the field.

The main weakness of the analysis was that the fluoride concentration was expressed as nmol/mg of sample weight. There was a lot of blood in some of the samples which suggests that some of the fluoride measured could have been from the blood and not bone. It would have been preferable to have expressed fluoride against calcium or phosphate concentration which would have provided an estimate of the amount of bone present. However the equipment required for this was unavailable.

It was surprising that we had a significant result from the cortical bone and not the trabecular bone. The literature on the subject suggests that the opposite would be more likely as trabecular bone is more metabolically active and its uptake of fluoride higher.

Alhava *et al.* (1980) measured the fluoride content of iliac bone in post-mortem cases (age range 24 to 86 years) from Kuopio and the surrounding area. Kuopio received water fluoridated to 1 ppm and the area outside Kuopio had a fluoride level of 0.1ppm. They found that the fluoride content of bone differed significantly in fluoridated and low fluoride areas ($p<0.001$). To illustrate, the average fluoride concentrations found in trabecular bone (Kuopio v. outside Kuopio) were 2070 v. 622ppm in women and 1360 v. 447ppm in men. The result were similar for cortical bone; 1720 v.443ppm in women and 1290 v. 462ppm in men. This agrees with the trend that was observed in our study, where the fluoride exposure was similar.

Zipkin *et al.* (1960) also found an increase in the fluoride content of bone in populations with higher fluoride in the water. However no attempt was made to distinguish between trabecular and cortical bone and thus it is difficult to compare the results to this study.

There is a dearth of published literature on the relationship between bone fluoride and measures of current fluoride exposure.

Conclusion

There was a trend for an increase in fluoride concentration in the bone for the ≥0.9ppm fluoride group compared to the <0.9ppm group. This was statistically significant for the cortical bone, although based on a small sample size.

In conclusion, water fluoride was associated with higher fluoride in femoral heads but not with fracture risk. This encourages confidence in the validity of the water fluoride estimates, and in the conclusion that water fluoride does not have a major effect on fracture risk

Section D.6: Dental health and exposure to fluoride in water

Introduction

There is little debate as to the effectiveness of fluoridated water to protect against tooth decay. Therefore, it was postulated that more participants who were categorised in the high fluoride exposure group would still have their own teeth than those who had not received fluoridated water. This was investigated, since if it were true it would further support the validity of fluoride exposure estimates.

Method

As part of structured, nurse administered questionnaire the participants were asked if they had any of their own teeth. The group of people who did not have any teeth were compared with those with teeth, with respect to residential history.

Results

Table D.6.1. shows that although the results were not statistically significant, there was a trend for exposure to fluoride in water to be associated with less tooth loss.

Table D.6.1. Lifetime water fluoride and odd ratios of still having one's own teeth

Time period	Fluoride concentration in water	No. without teeth	No. with teeth	*OR (95% CI)
Average over first 20 years	<0.9ppm	396	173	1.0 (-)
	≥0.9ppm	67	38	0.7 (0.4 - 1.1)
Average over last 20 years	<0.9ppm	379	172	1.0 (-)
	≥0.9ppm	81	38	0.9 (0.6 - 1.4)
Average over life	<0.9ppm	370	160	1.0 (-)
	≥0.9ppm	71	40	0.7 (0.5 - 1.2)
Current address	Non Hartlepool	392	180	1.0 (-)
	Hartlepool	87	45	0.8 (0.6 - 1.3)

*adjusted for age and sex

Discussion

The results show that there was a non-significant trend for fluoride exposure to be associated with less tooth loss.

The participants were asked if they had any of their own teeth remaining and there was confidence that the data were accurate. However, various potential confounders could not be taken into account. There are other causes of tooth decay including poor dental hygiene and a high sugar diet. Also, loss of teeth may not be solely due to tooth decay. Gum disease and preference for dentures both by the person and also the dentist are important and these factors were not taken into account. If, for example, there was a vogue for dentist to give a full set of dentures, even if not all of the teeth needed to be removed, then this could bias the relationship between fluoride and tooth retention.

Nevertheless, the indication of a protective effect of fluoroide exposure against tooth loss gave further confidence that the fluoride exposure estimates from the residential histories were meaningful.

Conclusion

There was a non-significant trend for fluoride exposure to be associated with a reduced risk of becoming edentulous. This was in the direction expected and was another indicator that the fluoride exposure estimates from the residential histories were meaningful.

Section E: Conclusion and Further Recommendations

High water fluoride was associated with higher fluoride in femoral head bone and this suggests that fluoride in water does have an important influence on bone biochemistry. After adjustment for potential confounders, high fluoride in water was not associated with any increase in the risk of hip fracture. If anything the risk of hip fracture was reduced in subjects with high fluoride exposure. This negative relationship between fluoride exposure and risk of hip fracture is unlikely to be explained by bias and is consistent with contemporary studies that have looked at the effect of similar levels of fluoride exposure in individuals.

This analysis was based on part of the data that have now been collected for the 'MRC osteoporotic hip fracture and water fluoridation project' and it is intended that extended analysis will be performed on 500 cases and 500 controls. If the analysis of the full data set confirms the findings of the preliminary results then there can be confidence that adding fluoride to water at a concentration of 1ppm does not increase the risk of hip fracture and therefore does not need to be a major consideration when deciding on the fluoridation policy.

It would of course be possible to carry out further studies. One suggestion would be to measure the bone mineral density as an endpoint. Fluoride is proposed to alter the risk of fracture by affecting the bone mineral density and hence bone mineral density measurements would illuminate the proposed mechanism of action. In addition, the study could be repeated in a different population but this would only be worthwhile if it was felt that the results from studying Cleveland could not be extrapolated to the population of the UK in general, which was not felt to be the case. In fact it would be difficult to identify a well defined population who were exposed to varying concentrations of fluoride in the water in the UK.

Of the other findings of the study, the most important are physical activity, nutrition and medication.

Physically active participants were found to be at a reduced risk of hip fracture which was consistent with other studies. It is unclear from the study whether actually undertaking physical activity is protective or whether it is ability to undertake exercise per se which is

associated with the reduction in risk. It would be helpful for a longitudinal study of physical activity and the risk of hip fracture to be conducted.

There were two aspects of nutrition which were of interest. Firstly, the well established relationship of increase in the risk of hip fracture with low BMI was confirmed. This has connotations for recommendations of preventing under nutrition and also as part of a selection criteria for hip fracture prevention.

There was a small protective effect of hip fracture with increase in calcium intake. The association of hip fracture and calcium remains controversial and the question needs further research. A longitudinal study which although would be more expensive would provide better information.

There were some interesting findings with risk of hip fraction and current medication, an area which has little published research. The reduced risk of hip fracture associated with vitamin D makes sense biologically and trials are now in progress to further investigate the association. The reduction in risk found both with analgesia and non-steroidal anti-inflammatory drugs has not been investigated in depth and the mechanism is uncertain. A further study should be undertaken to firstly confirm the relationship and if confirmed the mechanism should then be explored.

Appendix F.1. Questionnaire

STRICTLY PRIVATE AND CONFIDENTIAL

A.1.Serial Number _____

A.2.Date of Interview: _____/_____/_____

A.3.Name: _____ (surname)

_____ (first name)

_____ (title)

A.4.Address:_____

_____

_____

_____Post Code_____

A.5.Type of residence:- 1. Own home
2. Warden controlled flat
3. Rest home
4. Nursing home
5. Hospital _____

A.6.Sex: M / F

A.7.Date of Birth _____/_____/_____

A.8.Consultant : _____

A.9.Hospital Number : _____

A.10.Included in the study ? Yes / No
If No, reason:

_____

_____

B.1. Which medicines and tablets do you currently take ?

PLEASE USE BLOCK CAPITALS. COPY NAMES DIRECTLY FROM BOTTLES IF POSSIBLE. WRITE DOSAGE, FREQUENCY AND REASON FOR TAKING.

NAME	STRENGTH	HOW OFTEN

C. Measurements:

C.1. Height _____ **cms** (from patient)

[_____ **ft** _____ **inches]**

_____ **cms** (actual measurement)

C.2. Weight _____ **kgs** (from patient)

[_____ **st** _____ **lbs]**

_____ **kgs** (actual measurement)

Some of these questions may sound unusual but they are in fact very important.

Mental Ability

D.1. Can you tell me how old you are ? _____

D.2. Can you tell me what the time is ? _____

D.3. I am going to give you an address to remember and will ask you to repeat it back to me in a few minutes time, the address is - 42 West street. _____

D.4. Can you tell me which year it is ? _____

D.5. Can you tell me where we are now ? _____

D.6. Can you tell me what jobs these two people do ? (show photograph of nurse and policeman) _____

D.7. Can you tell me what your date of birth is ? _____

D.8. Can you tell me which year the second world war started? _____

D.9. Can you tell me the name of the present queen ? _____

D.10. Can you please count backwards from 20 to 1 ? _____

REMEMBER TO ASK FOR ADDRESS

Score:_____

Note: If score over 6 - proceed.
If score is less than 6 - terminate the interview.

E1. Residence

Please list the addresses of all the houses where you have lived for three years of more. Do not worry if you cannot remember them all, please tell us what you can.

Year in	Year out	No.	Street	District	Town	County	Postcode	F Code

F.1. Occupation History
Record all jobs/occupations of greater than 1 year duration since the person left school, and how much time is/was spent walking and standing on an average working day. Include housewives.

Job Title	Age Start	Age Stop	Part/ Full time	Time spent on feet-walking & standing (hrs)			Distance walked (miles)			Lift over 25lbs
				< 4	4-8	8 >	< 1	1-4	4 >	Yes/No

Activity at Home

G.1. Establish whether respondent has any mechanical walking problems or gait abnormality:

a) Walks without aid
b) Walks with aid but without help from another person
c) Requires help from another person or cannot walk at all

_____

G.2. Walking out of doors: choose a typical day within the last week; record all walking lasting more than three minutes.

a) Did you go out between 7 am and 9 am? _____ **mins**

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

c) Between 12 noon and 2 pm? _____ **mins**

d) Between 2 pm and 6 pm? _____ **mins**

e) Between 6 pm and 7 am? _____ **mins**

G.3. Which of the following best describes your walking speed?

a) very slow
b) stroll at an easy pace
c) normal speed
d) fairly brisk
e) fast _____

G.4. Gardening: How much time do you spend gardening in a typical week?

a) Less than one hour
b) 1 - 4 hours
c) 5 - 8 hours
d) More than 8 hours _____

G.5. Housework: How much time do you spend doing housework in a typical week?

a) Less than one hour
b) 1 - 4 hours
c) 5 - 8 hours
d) More than 8 hours _____

G.6. Muscle Loading Activities

i) How often do you climb stairs?
   a) Never
   b) Less than once a week
   c) At least once a week but not every day
   d) Once a day
   e) Several times a day _____

ii) How often do you carry loads?
   (equivalent to a shopping bag or 10lbs)
   a) Never
   b) Less than once a week
   c) At least once a week but not every day
   d) Once a day
   e) Several times a day _____

H. Fracture History

H.1. Have you ever broken your hip ? **Yes / No**
(For cases ask if broken other hip)

If **YES**: i) Which side ? a) Right b) Left c) Both _____

ii) How old were you when it happened? _____**years**

(if both) _____**years**

H.2. Have you ever broken your wrist ? **Yes / No**

If **YES**: i) How old were you when it happened ? _____**years**

(if both) _____**years**

I. Clinical History

I.1. Have you ever been told by a doctor that you suffer from a) diabetes ? **Yes / No**

b) rheumatoid arthritis **Yes / No**

Have you ever suffered from :-
c) a stroke **Yes / No**

d) Any other major illnesses ?

_____

J. Reproductive Variables (Women only)

J.1. How many children have you had ? _____

Live births	Breastfed (Yes/No)	How long breastfed (months)
1		
2		
3		
4		
5		
6		
7		
8		

J.2. i) How old were you when your periods started ?

_____**years**

ii) How old were you when you had your last period?

_____**years**

J.3. i) During the time when you were used to having periods, did they ever stop for longer than 6 weeks, apart from during pregnancy ?

Yes / No / Don't know

ii) If **YES**, (i) for how long ? _____**months**

(ii) how old were you ? _____**years**

J.4. i) Have you had a hysterectomy ? **Yes / No**

ii) If **YES**, how old were you at the time ? _____**years**

J.5. i) Have you ever had an ovary removed ?
a) No b) One c) Both d) Do not know _____

ii) How old were you at the time ? _____ **years**

J.6. i) Have you ever taken hormone replacement therapy ?

Yes / No

ii) If **YES**, how old were you when you started _____ **years**

iii) For how long did you take it altogether ?

_____**yrs** _____ **mnth**

J.7. Have you ever taken oral contraceptives ? **Yes / No**

K. Smoking and Alcohol

K.1. Have you ever smoked regularly (ie at least once a day for a year or longer)

Yes / No

If **NO** go to K.5.
If **YES** go to K.2.

K.2. How old were you when you first smoked regularly ?

_____ **years**

K.3. What is the most that you have ever smoked regularly ?

a) Cigarettes _____per day

b) Roll-ups _____per day

c) Tobacco(oz) _____per day

d) Cigars _____per day

K.4. Do you still smoke regularly ? **Yes / No**

If **NO**, how old were you when you last smoked regularly ?

_____ **years**

K.5. I would now like to ask you about your current alcohol consumption ?

K.5.a. Do you ever drink alcohol? **Yes / No**

If **Yes:**

Frequency Codes (FC)					
1 Less than once a month	**2** Once every 3-4 weeks	**3** Once every 1-2 weeks	**4** 1-2 days per week	**5** 3-5 days per week	**6** 6-7 days per week

K.6.a. How often do you currently drink **Shandy** ? _____ (FC)

b. When you drink this how many pints would you normally have? _____

K.7.a. How often do you currently drink **Beer/Stout/Lager/Cider** _____ (FC)

b. When you drink these how many pints would you normally have?

_____

K.8.a. How often do you currently drink **Wine/Sherry/Martini/Cinzano** ? _____ (FC)

b. When you drink these how many glasses would you normally have?

_____

K.9.a. How often do you drink **Spirits/Liqueurs** ? _____ (FC)

b. When you drink these how many measures would you normally have?

_____

L. Sunlight

L.1. In the summer on a typical day, how many hours do you spend out-of-doors?

_____ **hours**

M. Fluoride

M.1.i) Do you have any of your own teeth ? **Yes / No**

If **Yes** :-

ii) How many do you have ? _____

iii) Do you use toothpaste ? **Yes / No**

If **Yes** :-

iv) which brand do you use ?

_____

v) How often do you brush your teeth ?

_____

vi) Do you rinse your mouth after brushing ? **Yes / No**

vii) Do you use any other products with fluoride in e.g. mouthrinses, gels, tablets etc.

Yes / No

If **Yes** :-

viii) please list products used:-

_____

M.2.i) How often do you eat fish such as sardines or pilchards ?

a) Never
b) Less than once a month
c) At least once a month, less than once a week
d) At least once a week

_____

ii) How often do you eat battered fish? (eg. chip shop fish)

a) Never
b) Less than once a month
c) At least once a month, less than once a week
d) At least once a week

_____

N. How much of the following do you drink ?

	Less than once a month	Once every 3-4 weeks	Once every 1-2 weeks	1-2 days per week	3-5 days per week	6-7 days per week	Amount per day		
Tap water	1	2	3	4	5	6	_____ small glasses _____ medium glasses _____ large glasses		
Tea	1	2	3	4	5	6	_____ cups _____ mugs	1.None 2.Milk	A. Weak B. Normal C. Strong
Coffee	1	2	3	4	5	6	_____ cups _____ mugs	1. None 2. Milk (¼) 3. Milk (½) 4. Milk (all) 5. Coffeemate	
Milk alone	1	2	3	4	5	6	_____ small glasses _____ large glasses _____ cups _____ mugs		
Other milky drinks eg. Horlicks, Ovaltine, Cocoa, Complan, Build-up.	1	2	3	4	5	6	1. Small 2. Medium 3. Large		

N. How much of the following do you eat?

	Less than once a month	Once every 3-4 weeks	Once every 1-2 weeks	1-2 days per week	3-5 days per week	6-7 days per week	Amount per day	
Bread	1	2	3	4	5	6	_____ slices	1. Small 2. Large
Cheese	1	2	3	4	5	6	_____ portions	1. Small 2. Medium 3. Large
Cakes	1	2	3	4	5	6	_____ no. of portions	
Scones	1	2	3	4	5	6	_____ no. of portions	
Biscuits	1	2	3	4	5	6	_____ no. of portions	
Green Vegetables	1	2	3	4	5	6	_____ no. of portions	
Breakfast cereal (probe for porridge)	1	2	3	4	5	6	1. Small 2. Medium 3. Large	
Desserts made with milk(inc custard and icecream)	1	2	3	4	5	6	_____ no. of portions	

Appendix F.2. Letter sent to general practitioners

North Tees Health NHS TRUST

SOUTH TEES ACUTE HOSPITALS NHS TRUST

Hartlepool & East Durham NHS Trust

Lisa Madhok, MRC Research Nurse
Mobile Number: [redacted]
or Sharon Hillier [redacted]

Dear

The orthopaedic surgeons at the above hospitals are collaborating with the Medical Research Council in an epidemiological study to investigate the effect of water fluoridation on osteoporotic hip fracture.

Our cases will be hip fracture cases presenting to the above hospitals. Our controls are members of the general population who are the same age and sex as the cases. The study has been approved by all of the Local Research Ethical Committees in Cleveland and by the Local Medical Committee.

The FHSA have given us the names of the possible controls who are your patients, and I am writing to ask permission to approach these patients. I enclose a copy of the letter we would send.

Could I please ask you to complete the slip overleaf and return it in the prepaid envelope provided.

Thank you for your help,

Yours sincerely,

[redacted]
Lisa Madhok
Research Nurse

[redacted]
Dr C Cooper
Epidemiologist

[redacted]
Mr N C Bayliss
Consultant
Orthopaedic Surgeon

[redacted]
Mr I Wallace
Consultant
Orthopaedic Surgeon

[redacted]
Mrs C Lennox
Consultant
Orthopaedic Surgeon

Appendix F.3. Letter sent to controls.

North Tees Health HS TRUST

SOUTH TEES ACUTE HOSPITALS NHS TRUST

Hartlepool & East Durham NHS Trust

Mobile Number: [redacted]
Lisa Madhok, Research Nurse MRC

Dear

Doctors at the above hospitals are working with the Medical Research Council to find out more about the causes of osteoporosis (brittle bones). Your name has been selected from a list of patients registered with GPs in Cleveland, and your doctor, has given me permission to write and ask whether you would help us with this work.

If you agree, I would visit you at home to interview you about where you have lived, your past activities at work and in the home and your diet. The visit would take about 30 minutes.

I would like to arrange an appointment for at
I would be greatful if you could indicate if this time is convenient, or if you do not wish me to visit, on the tear-off slip below and return it in the pre-paid envelope provided as soon as possible. If you prefer, you can telephone the above number and leave a message (between office hours).

I do hope that you will be able to help. We hope that by learning about the causes of osteoporosis, we will be able to prevent it occuring so often. Your name has been chosen to be representative of people living in Cleveland and <u>not</u> because we have any reason to suspect that you have brittle bones.

Yours sincerely,

[redacted]

[redacted]

Lisa Madhok
Research Nurse

Dr C Cooper
Epidemiologist

Mr I Wallace
Consultant Orthopaedic Surgeon

Osteoporosis study

Serial Number _____ Date of interview ____/____/____

I would like to take part in the study at the time you suggest. _____

I would like to take part in the study, but am not available at the time you suggest. Please make a new appointment. _____

I do not wish to take part in the study. _____

Telephone No: _____ Signature _____

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