

Diet, nutrition and the prevention of osteoporosis

A Prentice*

MRC Human Nutrition Research, Elsie Widdowson Laboratory, Cambridge, UK

Abstract

Objective: To review the evidence on diet and nutrition relating to osteoporosis and provide recommendations for preventing osteoporosis, in particular, osteoporotic fracture.

Approach: Firstly, to review the definition, diagnosis and epidemiology of osteoporosis, to discuss the difficulties in using bone mineral density to define osteoporosis risk in a world-wide context and to propose that fragility fracture should be considered as the disease endpoint. Secondly, to provide an overview of the scientific data, the strengths and weaknesses of the evidence and the conceptual difficulties in interpreting studies linking diet, nutrition and osteoporosis. The following were considered: calcium, vitamin D, phosphorus, magnesium, protein and fluorine. Other potential dietary influences on bone health were also discussed, including vitamins, trace elements, electrolytes, acid–base balance, phyto-oestrogens, vegetarianism and lactose intolerance.

Conclusions: There is insufficient knowledge linking bone mineral status, growth rates or bone turnover in children and adolescents to long-term benefits in old age for these indices to be used as markers of osteoporotic disease risk. For adults, the evidence of a link between intakes of any dietary component and fracture risk is not sufficiently secure to make firm recommendations, with the exception of calcium and vitamin D. For other aspects of the diet, accumulating evidence suggests that current healthy-eating advice to decrease sodium intake, to increase potassium intake, and to consume more fresh fruits and vegetables is unlikely to be detrimental to bone health and may be beneficial.

Keywords

Calcium

Vitamin D

Diet

Osteoporosis

World Health Organization

Osteoporosis is a disease that affects many millions of people around the world. It is characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk^{1,2}. Fragility fractures are most common at the wrist, spinal vertebrae and hip, although they can occur throughout the skeleton. The incidence of vertebral and hip fractures increases exponentially with advancing age while that of wrist fractures levels off after the age of 60 years³. Osteoporotic fractures are a major cause of morbidity and disability in the elderly and, in the case of hip fractures, can lead to premature death. In addition, they impose a considerable economic burden on health services, costing many billions of dollars each year⁴.

World-wide variation in the incidence and prevalence of osteoporosis is difficult to determine because of problems with definition and diagnosis. The WHO definition of osteoporosis is a bone mineral content (BMC) or bone mineral density (BMD), measured by techniques such as dual-energy X-ray absorptiometry, that is more than -2.5 SD below the young adult mean for the population⁵. A low

BMC or density in an older person implies a sub-optimal bone mass in young adulthood (peak bone mass) or greater bone loss in later life, or both. Whilst useful as a working definition within populations, it is unhelpful in comparing populations. Both BMC and BMD are strongly influenced by body size, and populations of shorter stature, such as those in the Far East and Africa, have lower bone mineral status than Western populations but do not have higher rates of osteoporotic fracture^{6–10}.

Because of this, the most useful comparison of osteoporosis between populations is fracture rate amongst older people. However, this is not without problems. Many fractures, including those of the spine and wrist, are not life-threatening, can be asymptomatic, and may not come to medical attention. Only population-based screening can accurately determine prevalence rates for these fractures, and few such studies have been conducted. Hip fractures are the exception and many countries have hip fracture registers that can be used to estimate incidence. Even so, definitions vary about what constitutes an osteoporotic (i.e. minimal trauma) fracture, and the exclusion of traumatic fractures may underestimate the prevalence of

*Corresponding author. Email ann.prentice@mrc-hnr.cam.ac.uk

fragility fractures¹¹. In addition, quantitative data from developing countries are scarce, and may be unreliable given the lack of access to medical facilities by older people in these regions, and the uncertainties of determining exact age and cause of fracture in these populations.

Epidemiology of osteoporotic fractures

Despite these caveats, the current consensus is that approximately 1.66 million hip fractures occur each year world-wide, that the incidence is set to increase 4-fold by the year 2050 because of the increasing numbers of older people, and that age-adjusted incidence rates are many times higher in Western countries than in Asia and sub-Saharan Africa^{10,12,13}. The incidence of vertebral and hip fractures in both sexes increases exponentially with age. In countries with a high fracture incidence, rates are greater amongst women by 3–4-fold. In countries where fracture rates are low, men and women are more equally affected^{9,13–15}. Thus, although widely regarded as a disease that affects women, osteoporosis is also a major problem for older men, with 20% of symptomatic spine fractures and 30% of hip fractures in countries with high fracture rates occurring in men¹⁶.

Hip fracture rates are the highest in Caucasian women living in temperate climates, are somewhat lower in women from Mediterranean and Asian countries and are lowest in African women^{9,14,17}. Countries in developmental transition, such as Hong Kong, have seen significant increases in age-adjusted fracture rates in recent decades while those in Western countries appear largely to have reached a plateau^{18,19}.

Differences in fracture rates can occur even within a geographical area. For example, substantial variations in hip fracture incidence have been observed within the Mediterranean region^{14,20}. This pattern is also mirrored in the prevalence of spinal deformities which is greater in Scandinavian than in Mediterranean countries²¹. Urban dwellers tend to have higher fracture rates than those living in rural areas²². Fracture rates also differ between ethnic groups, living in the same region. For example, African-Americans and New Zealand Maoris have lower hip fracture rates than their Caucasian counterparts, whilst, in Singapore, hip fractures are more common among the Indian population¹³.

Scientific interpretation of differences and changes in BMC and BMD

Low bone mass, as measured by BMC and low BMD, is a risk factor for fragility fractures^{3,5}. This has been demonstrated retrospectively, in studies comparing fracture cases with age-matched individuals in the normal population²³, and prospectively, in studies that show that low bone mass can predict future fracture risk^{23–25}. There is an increasing gradient of fracture risk with decreasing

bone mass, such that, for example, one standard deviation below the young adult mean is associated with a 2-fold increase in relative risk of hip fracture^{25,26}. This increase rises to 2.6 if the measurement is made at the femoral neck, but a measurement at any skeletal site has predictive value. At the osteoporosis threshold of -2.5 SD, the relative risk is 5 for a measurement at any site, 6.5 for a measurement at the femoral neck. In addition, BMD typically explains 60–80% of bone strength when bone samples are compared in a laboratory setting under controlled loading conditions²⁷. Consequently, peak bone mass (the maximum bone mass achieved in adulthood) and the rate of subsequent bone loss are regarded as major determinants of osteoporotic fracture risk in later life.

Because of the relationships between bone mass and fracture risk, and because WHO defines osteoporosis in terms of BMC and BMD, there has been a tendency for people to equate differences and changes in BMC and BMD with differences and alterations in fracture risk. There are several reasons why such an interpretation needs to be treated with caution, particularly when considering population-based strategies for prevention or clinical effectiveness of treatment. The following paragraphs outline the main scientific points that need to be considered when interpreting studies and evaluating the evidence.

DXA measurements and relationships of BMC and BMD with size

Absorptiometry permits the precise *in vivo* measurement of bone mineral in healthy individuals²⁸. Single energy absorptiometry is used for measuring the bones of the arms and legs; dual energy instruments are required for axial (spine, hip) and whole-body measurements to correct for overlying soft tissue of variable composition. The technique is based on the attenuation of energy from a beam of penetrating photons as it scans across the skeletal region of interest. Bone edges are identified by software algorithms based on the change in energy reaching the detector. Calibration materials are used to convert the cumulative attenuation between opposing bone edges to mass of mineral within the bone envelope. The measured mineral mass represents an average over all the elements within that region of the skeleton—bony tissue, intraosseous soft tissues and, depending on the region, medullary cavity or spinal canal. Results are expressed as mineral mass per unit length of the limb for single energy absorptiometry; mineral mass per anatomical region (e.g. per vertebra, per whole-body) for dual energy absorptiometry. In dual-energy absorptiometry of skeletal regions that involve the long bones, such as the hip, the anatomical region is arbitrarily defined. All these measures are referred to as BMC although the units differ: g/cm for single energy data, g for dual energy.

Absorptiometric data are often expressed as BMD, in order to minimise measurement errors connected with

positioning, movement and bone edge detection, and to make some adjustment for size differences between individuals. This index is obtained by dividing BMC by the area of the scanned bone envelope; the units are g/cm^2 . For single energy techniques this area is equivalent to the distance between the opposing bone edges (bone width, BW, cm); for dual energy measurements it is the designated bone area (BA, cm^2). Absorptiometric BMD is a mathematical construct and is not a true density measurement. It is useful in fracture risk assessment and long-term patient monitoring, since it is a highly reproducible measure and is simple to use.

However, BMD represents only a partial correction for bone size and, depending on the skeletal site and the nature of the study population, BA can be an influential determinant of BMD as well as of BMC^{7,28}. In epidemiological studies, failure to correct bone mineral measurements fully for BA can lead to spurious or inflated relationships with other variables that are themselves related to size, such as dietary intake, obesity and energy expenditure⁷. An example is given in Table 1. In this group of young British adults, a highly significant relationship between whole-body BMD and calcium intake disappeared after BA was included as an independent variable in multiple regression analysis. This finding can be interpreted as showing that, in this group of young people, the larger individuals (with the greater bone mineral mass and greater BMD) had the greater calcium intake, but when comparing people of the same bone size, there was no association between bone mineral status and the calcium content of the diet. A similar result was obtained using BMC as the dependent variable (mathematically, BMC and BMD are equivalent once BA is included in the regression model, the equations only differing in the value of the BA coefficient).

In the absence of a full correction for BA, proxy information about bone size may be provided by other anthropometric variables such as body weight and height. For instance, in the example given in Table 1, the apparent association between BMD and calcium intake was removed by adding body weight and height as

independent variables to Model 1. However, without testing, it cannot be assumed that apparent correlations between BMD and size-related variables are not due to confounding by BA even when other size-adjustments have been made. In particular, body mass index (BMI, $\text{weight}/\text{height}^2$), used by many researchers to adjust bone mineral data, is usually ineffective in removing BA artefacts^{7,29}.

The potential problem of size-related artefacts in absorptiometric studies has been appreciated only recently and affects the majority of published studies that have investigated lifestyle determinants of bone mineral status, including dietary intake^{7,30}. This limits the usefulness of cross-sectional studies and meta-analyses of epidemiological data in examining the relationships between nutrition and osteoporosis, unless steps are taken to minimise the confounding influence of size. In addition, it should be appreciated that bone health may also be modulated by differences in bone size, or by differential effects on periosteal apposition and endosteal resorption which could affect bone size. It is therefore important to consider the two elements of bone mass (size and density) separately.

The bone remodelling transient

Alterations in the mineral content of bone imply differences in the retention of calcium and other minerals in the skeletal pool. This pool corresponds, in adults, to the mineral released and laid down during bone remodelling. Remodelling is the process whereby the skeleton undergoes continual renewal by a phased sequence of bone resorption and formation^{2,31–33}. In the adult, 95% of bone turnover occurs by remodelling and approximately 10–15% of skeletal surfaces are in the process of being remodelled at any one time. Osteoclasts, the cells responsible for bone resorption, dissolve away a small, discrete portion of the surface. The resulting resorption cavity is refilled by the action of osteoblasts, the bone-forming cells. These lay down bone matrix (osteoid) which gradually becomes mineralised to form new bone. There is a strict chronological sequence of events, with recruitment of osteoblasts occurring some time after resorption, and with newly-formed bone mineralising rapidly in the initial stages but more slowly thereafter. As a result, it takes many weeks or months for the entire process to be completed.

During this time, there is a temporary net deficit of mineral in the volume of bone undergoing remodelling and hence in whole-body bone mineral^{2,31,34}. Since bone turnover is most rapid in trabecular bone, the reversible mineral deficit is greatest in regions rich in trabecular bone (about 4%). When resorption conditions vary, there is a transition period where the number or size of new resorption cavities is modified but restoration of existing resorption pits is maintained at the previous rate. This produces a quantitative change in the remodelling space, a

Table 1 Relationship between calcium intake and whole-body BMD in young adults

Variable	Coefficient	SE	t-ratio	P
<i>Model 1: BMD = constant + calcium intake</i>				
Constant	1.13	0.03	44.2	<0.0001
Calcium intake mg/d ($\times 10^{-3}$)	0.06	0.02	2.7	0.009
<i>Model 2: BMD = constant + BA + calcium intake</i>				
Constant	0.89	0.06	14.1	<0.0001
BA (cm^2)	0.13	0.03	4.2	<0.0001
Calcium intake mg/d ($\times 10^{-3}$)	0.02	0.02	0.7	0.47 (NS)

Data from Prentice *et al.*⁷, based on a study of 65 men and women, aged 18–21 years, with whole body bone data obtained by dual energy X-ray absorptiometry (Hologic QDR 1000/w).

corresponding alteration in the reversible mineral deficit, and results in a rise or fall in the total amount of mineralised tissue per unit volume of bone until a new steady state is established.

Absorptiometry is a static measurement which provides a 'snapshot' at any one moment. If bone turnover decreases with no overall change in bone volume, BMC rises by a few per cent because of the smaller number of resorption cavities being excavated. BMC continues to rise for some time until a new steady state is achieved because of the time lag between resorption and completion of the formation phase^{2,31,34}. Similarly, a decrease in reversible mineral space caused by an increase in bone turnover will lead to a decrease in measured BMC. BMD is affected in a similar fashion. This phenomenon is referred to as the bone remodelling transient.

Bone remodelling transients complicate the interpretation of absorptiometric studies^{2,34}. An observed rise in BMC or BMD in an older person after intervention with a particular agent might be due to a bone remodelling transient rather than to an increase in bone mass. In this instance, the decrease in turnover might of itself be beneficial, because high rates of turnover, as indicated by markers of bone remodelling, predict future fracture risk³⁵, and because bone loss might be diminished. The exact interpretation of the bone mineral change could, therefore, be regarded as academic. However, unless there were also a change in the rate of bone loss, the benefit would be of short duration (equivalent to the period of one remodelling cycle) and likely to be fully reversed at the end of the intervention period. In children and adolescents, an increase in BMC or BMD might indicate a bone remodelling transient caused by a decrease in bone turnover rather than an alteration in net bone acquisition. If it were due to a bone remodelling transient, the effect would be seen early in the intervention period, no further increment would accrue with prolonged intervention and the effect would be expected to disappear when the intervention stopped. It is possible that such a decrease in bone turnover could alter the tempo of bone growth and might not be associated ultimately with optimised peak bone mass, even if the intervention were sustained until skeletal maturity. Studies investigating the effects of an intervention on BMC or BMD need to be of sufficient duration, and accompanied by biochemical or stable isotope studies of bone turnover, to gain an insight into the processes involved.

Relationship between BMC, BMD and fracture risk

The indication that BMC and BMD predict bone strength and future osteoporotic fracture risk is based on studies conducted in older adults from populations with a high incidence of fractures. The evidence that these relationships can be extrapolated to young people and to other populations is weak. As mentioned earlier, people in the Far East and Africa have lower bone mineral status than

Western populations but do not have higher rates of osteoporotic fracture^{6–10}.

The relationships between future fracture risk and the bone mineral status of children and adolescents have yet to be firmly established. It has been commonly assumed, that the maximisation of peak bone mass, by optimising factors that influence skeletal development during childhood and adolescence, is an important preventative strategy against future fractures. However, as discussed in the preceding sections, peak bone mass, as defined by BMC or BMD, contains elements related to the size of the skeleton, to the amount of bony tissue contained within it, to the mineral content of that tissue and to the degree to which the bony tissue is actively undergoing remodelling. It is, as yet, unclear which of these aspects is influential in determining future fracture risk.

Small adult skeletal size is a recognised risk factor for osteoporosis, although in Scandinavia, taller women are at greater risk of hip fracture³⁶. Anatomical variations between adults may reflect the impact of environmental effects at different stages of skeletal development and these may influence later predisposition to fractures³⁷. Size in infancy predicts adult BMC, suggesting that the environment *in utero* and early life may be an important modulating factor for fracture risk in old age³⁸. BMC and BMD at age 8–12 years are lower in children born prematurely than those of the same age born at term, paralleling differences in size achieved³⁹. These studies provide evidence to suggest that any effect of bone mass in young people on future fracture risk may be related more to skeletal size or shape rather than to bone mineralisation *per se*. In addition, bone turnover is lower in African-American adolescents compared with Caucasians of the same age, suggesting an influence of remodelling rate on peak bone mass development and later fracture risk⁴⁰, although nothing is known about what an optimal bone turnover rate might be for young people. All these facets need to be considered when considering the role of diet and nutrition of young people in the prevention of osteoporosis.

Alterations in BMC and BMD in relation to fracture risk

Despite the relationships that have been established between bone mass and fracture risk in older people, changes in BMC or BMD may not accurately predict the benefits of an intervention^{27,41–43}. Gains in BMC or BMD have been associated with measurable reductions in fracture incidence with some therapeutic agents but this is not the case in all situations^{27,44}. Improvements in bone quality or non-skeletal functions such as muscle strength or balance, may decrease fracture risk with little or no change in BMC or BMD. Examples include, improvements in vertebral fracture incidence by raloxifene that are more closely related to decreases in markers of bone turnover than to changes in BMD^{45,46}, and effects of calcium and

vitamin D supplementation on decreased body sway and risk of falling⁴⁷. Significant increases in BMC or BMD may produce poor quality bone and result in unchanged or even increased bone fragility. A well-known example of the latter occurs with sodium fluoride, treatment with which increases bone mineralisation but produces mechanically inferior bone and increases fracture incidence⁴⁸. Also, as mentioned earlier, increases in BMC or BMD may reflect bone remodelling transient effects which may or may not have long-term benefits in terms of fracture incidence.

In fact, there is no *a priori* reason why it should be assumed that because fracture risk increases as BMC or BMD decreases, on an epidemiological basis, that the relationship is bi-directional and that, within individuals, an increase in bone mineral will be matched by an equivalent decrease in fracture risk²⁷. In engineering, the force/deformation characteristics of certain materials are different under tension than in compression, a property referred to as hysteresis²⁷. It is plausible that hysteresis effects may also apply to the human skeleton in the relationship between BMD and bone strength. Thus, although there is firm evidence that bone mineral measurements are good predictors of fracture risk, the importance of increasing BMC or BMD for reducing fracture risk is less clear. For all these reasons there is increasing recognition that interventions and clinical trials should use fracture as the primary end-point, rather than rely on evidence from bone mineral measurements^{27,30,41}.

Multiple risk factors

Low bone mass is only one of several risk factors for osteoporotic fracture, and these include both skeletal and non-skeletal factors. Of those that act independently of low bone mass, physical frailty, propensity to fall and a history of fracture appear to be strong predictors^{49,50}. In addition, the risk of fracture at a given BMC or BMD is strongly influenced by age⁵¹. Skeletal factors that may act independently of bone mass include skeletal geometry and aspects of bone quality such as turnover, trabecular connectedness, osteocyte viability and osteonal distribution⁴⁴. Of those risk factors that are associated with a low bone mass, and may be acting through this pathway, family history and genetic susceptibility are especially important. Indeed, heritability studies have indicated that 60–70% of the variation in BMD within a population has a genetic origin⁵². Environmental factors, other than nutritional status and diet, are important determinants of fracture risk. These include cigarette smoking, alcohol abuse, physical inactivity, dependency and use of certain medications⁵³. In epidemiological studies, therefore, exploration of the influence of diet or specific nutrients on bone mass or fracture risk is likely to be confounded by the co-existence of other risk factors, especially where there is the potential for clustering of potentially adverse environmental factors, such as in the frail elderly.

Distinction between prevention and treatment of osteoporosis

Because, in Western countries, osteoporosis is widely prevalent in the older population, especially when implementing the WHO definition, the distinction between prevention and treatment can become blurred. It is important to realise that many studies and intervention trials are conducted in individuals at particular risk of fracture, recruited because of low bone mineral measurements or because of a previous fragility fracture. As such, these studies are useful in providing an indication of the response to treatment but not to the efficacy of population-based preventative measures applicable to the general population or to populations at lower risk of fracture. In addition, response to treatment with a specific agent cannot be interpreted as demonstrating the correction of some underlying inadequacy in the normal supply of that agent. While these precepts are self-evident in the case of pharmaceutical agents, these principles are often forgotten when applied to nutrients and other dietary components.

Evidence relating osteoporosis to diet and nutrition

Calcium

Calcium is one of the main bone-forming minerals and an appropriate supply to bone is essential at all stages of life. In estimating calcium requirements, most committees have used either a factorial approach, where calculations of skeletal accretion and turnover rates are combined with typical values for calcium absorption and excretion, or a variety of methods based on experimentally-derived balance data^{30,54}. There has been considerable debate about whether current recommended intakes are adequate to maximise peak bone mass and to minimise bone loss and fracture risk in later life, and the controversies continue^{2,17,30,54,55}.

Correlations between calcium intake and adult BMC or BMD have been reported from a large number of cross-sectional and retrospective studies, although there are many other studies where no such association has been observed. Meta-analyses have concluded that calcium intake is a significant determinant of BMD^{56,57} but the magnitude of the effect is small, at about 1% of the population variance. Interpretation of this association is difficult, however, because few studies have adjusted adequately for the confounding effects of body size (see earlier).

In populations with a moderate-high risk of osteoporosis, case-control and cohort studies in countries with an average calcium intake close to recommended levels have shown no relationship between calcium intake and risk of hip fracture^{58–62}. Calcium intake, at a mean of 800 mg/d, was not a determinant of longitudinal bone loss over 4 years in the Framingham cohort of older people (mean age 75 years) from the USA⁶³. In contrast, studies in

populations with a lower average intake suggest an increasing risk of hip fracture with declining calcium intake^{64–67}. Studies in Southern Europe^{66,67} observed that the greatest risk of fracture was amongst those with the lowest consumption of milk and cheese, indicative of a very low calcium intake, but no additional risk reduction was afforded by an intake above the average. A recent, frequently quoted, meta-analysis has suggested a decrease in hip fracture incidence with increasing calcium intake such that each additional 300 mg of calcium in the diet is associated with an odds ratio of 0.96 for hip fracture (4% reduction in risk)⁶⁸. The estimate becomes 0.92 (8% reduction) after applying corrections for likely measurement errors⁶⁸. This implies that each 1000 mg/d is associated with a 24% reduction in risk of hip fracture. However, closer inspection of the individual studies shows that this effect appears to be confined to populations with a comparatively low average calcium intake (Fig. 1) and that the assumption that the relationship is linear across the range of calcium intakes is not valid. Taken together, the data suggest that, in populations at risk of osteoporotic fracture, there is a threshold of increasing risk below around 400–500 mg/d³⁰ but that, at a population level, no additional benefit is associated with a customary intake above those currently recommended⁶⁹.

Calcium supplementation of women within 5 years of the menopause has little or no effect on the BMD of trabecular regions of the skeleton, where the greatest loss of bone is occurring at that time^{2,30,70–72}. Where reductions in the rate of bone loss have been noted, they are generally short-lived and occur in skeletal areas rich in cortical bone. In older women, calcium supplementation is associated with a higher BMD, by around 1–3%, and with reductions in bone loss, although, in most studies, it does not prevent some loss from occurring^{30,72–77}.

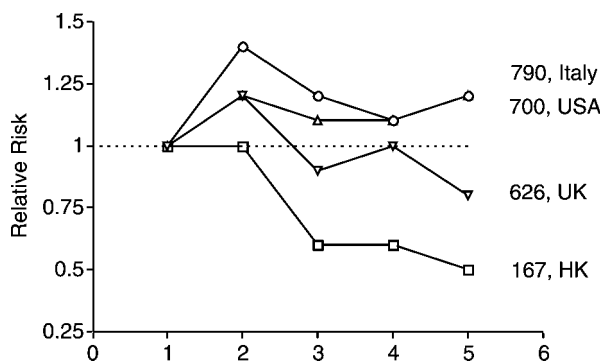


Fig. 1 Relative risk of hip fracture by fifths of calcium intake within each country. The referent in each case is the lowest fifth (#1), the population mean intake is middle fifth (#3) and is given (mg/d) in the label at the right-hand side. Data are selected from Cumming *et al.*⁶⁸, and show studies from Italy, USA, UK and Hong Kong. This illustrates that where average intakes are low, the risk of hip fracture increases at intakes below the average, but with no indication of continued risk reduction at intakes higher than the average. For those with higher average intakes, there is no evidence of a gradient of fracture risk with calcium intake (copyright Ann Prentice)

Long-term studies suggest that the effects of calcium supplementation largely occur in the first 1–2 years, probably due to a bone remodelling transient caused by the anti-resorptive properties of calcium (see earlier). Supplementation of children with calcium salts also results in an increase in bone mineral accompanied by a decrease in bone turnover, possibly indicating fewer remodelling sites at the tissue level, while supplementation with milk appears to increase bone mineral by promoting skeletal growth^{2,78,79}. It is important to note that milk may have different actions to calcium alone, given the fact that much of the epidemiological data linking calcium to bone health has been based on intakes of milk and dairy products.

There have been only a few calcium supplementation trials with fracture as an end-point^{17,30}. All have been in women more than 5 years after the menopause^{73,76,77,80,81} and some have included patients with a history of vertebral fracture^{80,82}. These studies have shown either no effect or a modest reduction in fracture incidence, but sample sizes have been small. Larger trials in elderly people of supplementation with calcium and vitamin D together have demonstrated sizeable reductions in non-vertebral fracture incidence (see under vitamin D). The ongoing MRC RECORD Study in the UK will provide clarification of the utility of calcium supplementation alone or in combination with vitamin D for secondary fracture prevention in elderly men and women (see under vitamin D).

In general, the effect of customary calcium intake on the outcome of calcium supplementation has not been investigated. In those studies where it has, no relationship has been noted, except in a study of American women 6 or more years post-menopause where the effect on BMD and on bone loss was limited to those with a daily calcium intake below 400 mg/d^{30,72}. Taken together with the observational data, this suggests, for women living in Western-style environments, in populations at risk of osteoporotic fracture, that customary calcium intakes below the UK and EU lower reference nutrient intake of 400 mg/d^{30,83} may be associated with an increased risk of osteoporosis. There is, however, no evidence of a beneficial skeletal effect of a customary calcium intake above those currently recommended, although calcium supplementation is a recognised adjunct in the treatment of bone loss and the prevention of fracture in vulnerable individuals^{17,30}.

The Royal College of Physicians (London), in its recent clinical guidelines for the prevention and treatment of osteoporosis¹⁷, does not regard population-based preventative strategies as feasible, and, in the case of calcium, notes that similar small decreases in overall fracture incidence would be expected from a population-wide approach or from targeting those with the lowest calcium intake. A quote from this document exemplifies the clinical perception of the role of calcium in osteoporosis prevention: 'In the context of the menopause, it is

misleading to believe and to inform patients that attention to calcium nutrition will solve the problems of bone loss'. Two recent nutrition committees have taken a similar view after reviewing the evidence and have felt unable to use BMD or fracture outcome as criteria for calculating reference or recommended calcium intakes^{30,54}.

The studies described above have largely been conducted in populations with a medium to high risk of osteoporotic fracture, and may not apply to countries where risk is low. On a world-wide basis, customary calcium intake cannot explain variation in fracture risk, since paradoxically, those countries with a low calcium intake have the lowest hip fracture incidence, while the highest rates of fracture occur in those populations with a high calcium intake (Fig. 2).

The reasons for the large geographical variation in fracture incidence are unknown. Many theories abound, including effects at the genetic, anatomical, biochemical, nutritional and lifestyle level². There is increasing evidence that the variation is not due specifically to differences in the deterioration of bone mineral mass, since bone loss at the menopause and low bone mineral status in old age appear to be universal phenomena^{6,84}. Other aspects of bone health, such as turnover, microstructure and resilience, or propensity to fall, are likely to be more important factors. Recent studies in The Gambia, China and Hong Kong have shown positive effects of calcium supplements on bone mineral of older women and on children and adolescents^{78,85,86} but not on bone mineral status or breast-milk calcium secretion of lactating women⁸⁷. The results were similar to those obtained in studies conducted in the USA, UK and Australia, both in the skeletal regions that responded and in the magnitude of the effects, suggesting that there are no fundamental

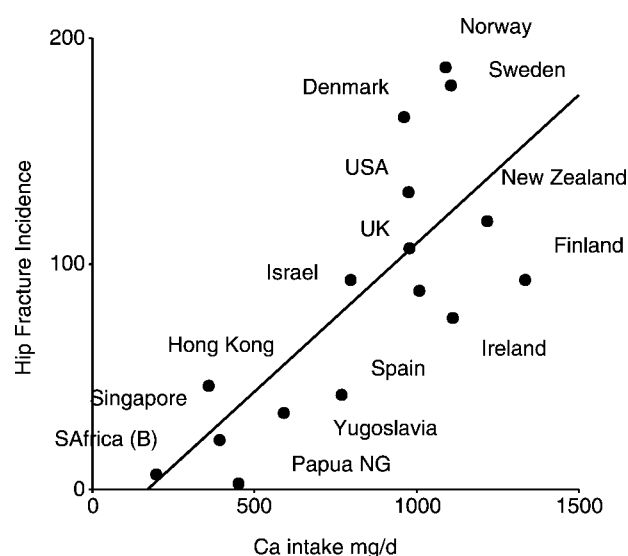


Fig. 2 World-wide variation in hip fracture incidence. Data from Abelow *et al.*⁹⁰ showing age-adjusted hip fracture incidence per 100000 by population calcium intake in mg/caput/d (copyright Ann Prentice)

differences in calcium biology between people in developed and developing countries^{88,89}.

It has long been regarded that obligatory calcium losses, and therefore dietary calcium requirements, are less in countries with a low calcium diet than those with a Western diet because of reduced obligatory urinary and dermal calcium excretion. Reasons cited for this include lower intakes of salt and animal protein, and differences in perspiration rates⁹⁰. None of these assumptions have been tested experimentally, and intakes of sodium in Africa and Asia are often similar to or higher than those in the West. In any case, given the very low calcium intakes recorded in sub-Saharan Africa, which are of the order of 300–400 mg/d, it seems doubtful that differences in calcium bioavailability (i.e. the difference between absorption and excretion) can explain the world-wide difference in fracture rates.

Vitamin D

Overt vitamin D deficiency causes rickets in children and osteomalacia in adults, conditions where the ratio of mineral to osteoid in bone is reduced. Poor vitamin D status in the elderly, at plasma levels of 25-hydroxyvitamin D above those associated with osteomalacia, has been linked to age-related bone loss and osteoporotic fracture, where the ratio of mineral to osteoid remains normal. The mechanism is likely to be through secondary hyperparathyroidism, although muscle weakness and depression associated with vitamin D insufficiency may also be important.

Vitamin D is obtained either from the diet or by synthesis in the skin under the action of sunlight. Older people tend to have reduced endogenous production of the vitamin for a variety of reasons, and they become more dependent on dietary sources to maintain adequate vitamin D status³⁰. In countries at latitudes outside the tropics, this is particularly evident in the wintertime, when sunlight does not contain the wavelengths necessary to activate vitamin D synthesis⁹¹. A high prevalence of plasma 25-hydroxyvitamin D concentrations close to or below the normal range has been reported in the older population of several European countries, particularly amongst the 'oldest-old' and those living in institutions^{30,92,93}. Younger people also have a reliance on dietary sources of vitamin D, if they have limited exposure to sunlight for cultural or medical reasons, or are dark-skinned and living outside the tropics.

Associations have been reported between plasma 25-hydroxyvitamin D and BMD in middle-aged and older women^{94,95}. However, vitamin D intervention trials of older people with either bone loss or fracture as outcome have given inconsistent results^{30,77,95–97}, possibly reflecting differing degrees of vitamin D insufficiency in the various study populations. Trials of calcium and vitamin D in combination have resulted in substantial decreases in incidence of non-vertebral fractures, but not

consistently in the attenuation of bone loss^{17,30,98–101}. In the largest trial of its kind, 3270 women aged 86 (SD6) years in French nursing homes were randomised to 1200 mg calcium and 800 IU (20 µg) vitamin D per day or placebo^{99,100}. After 3 years the incidence of hip fractures in the treated group was 29% lower ($P < 0.01$) and of all non-vertebral fractures 24% lower ($P < 0.01$), than in the placebo group.

Correction of a bone mineral deficit caused by hyperparathyroidism secondary to vitamin D and/or calcium insufficiency has been postulated as the mechanism involved¹⁰². However, those trials where an effect of vitamin D has been noted, with or without calcium, have shown a divergence of cumulative fracture incidence within 6–18 months of supplementation. This is regarded as too rapid an effect to be mediated by changes in BMD and bone strength, raising the possibility that part of the benefit arises from improved neuromuscular co-ordination and reduced fall rates³⁰. Calcium and vitamin D supplementation is now advocated as the basic minimum for treatment of osteoporosis and secondary fracture prevention in women several years after the menopause, and it is now common for this regimen to be used as the placebo in trials of new pharmacological therapies¹⁷. The question of whether vitamin D or calcium is the active agent is moot, however, given the inconsistency of the trials with these factors given separately. In addition, it has yet to be demonstrated that consumption of vitamin D supplements or foods rich in vitamin D by older people, with or without additional calcium, is useful for the primary prevention of osteoporosis. However, the ongoing MRC RECORD Study is designed to answer this question with respect to secondary fracture prevention. This trial involves 6000 men and women over the age of 70 years who have presented with a fragility fracture who have been randomised receive calcium and vitamin D alone or in combination or a double placebo.

Phosphorus

Phosphorus is an essential bone-forming element and, as with calcium, an adequate supply of phosphorus to bone is necessary throughout life. Both calcium and phosphorus are required for the appropriate mineralisation of the skeleton and a depletion of serum phosphate leads to impaired bone mineralisation and compromised osteoblast function¹⁰³. However, there is little evidence that, in healthy individuals, the dietary intake of phosphorus influences the risk of osteoporosis, except in the special case of very-low-birthweight infants. Although there is a constant proportion of calcium and phosphorus in bone, the ratio of calcium to phosphorus in the diet can vary over a wide range with no detectable effects on the absorption and retention of either mineral, or on the ability of bone to mineralise appropriately^{54,104}. Reports of correlations between phosphorus intake and

BMD are inconsistent³⁰ and likely to be affected by size-confounding (see earlier).

Concerns have been expressed about the possible adverse effects of the increasingly high intake of phosphorus in Western-style diets, especially in relation to the consumption of carbonated drinks. A high phosphorus intake in combination with a low calcium intake has been shown to alter calcium metabolism and increase parathyroid hormone secretion in short-term studies¹⁰⁵, but these effects are also observed with low calcium diets alone. A doubling of phosphorus intake has no effect on bone turnover^{54,106} and phosphorus-rich carbonated drinks appear to have a negligible effect on calcium excretion¹⁰⁷. There are no studies that have used osteoporotic fracture incidence as an outcome.

Magnesium

Magnesium is involved in bone and mineral homeostasis and is important in bone crystal growth and stabilisation. It also plays a role in the vitamin D-parathyroid hormone axis. The influence of magnesium on osteoporotic fracture risk is unknown. In a limited number of studies, magnesium intake has been reported to be positively associated with both BMD and bone resorption markers in middle-aged women¹⁰⁸ and short-term increases in BMD have been observed with magnesium supplementation¹⁰⁹. Size effects and bone remodelling transients may confound interpretation of these results (see earlier). Magnesium is one of a number of nutrients found in fruits and vegetables, which contribute to an alkaline environment (see later) and may promote bone health by a variety of mechanisms, making it difficult to examine the effects of magnesium alone.

Protein

On a world-wide basis, high protein intakes have been linked with hip fracture because the consumption of protein, particularly in the form of meat and dairy products, is greatest in countries where hip fractures are common¹¹⁰. Protein intake is a determinant of urinary calcium excretion, and animal protein, which is rich in sulphur-containing amino acids, contributes to an acidic environment (see later). There are concerns, therefore, that high protein intakes, especially those rich in animal protein, are inadvisable for long-term bone health. However, evidence of adverse consequences is lacking. For example, when meat is the protein source, the hypercalciuric effect of protein is offset by the hypocalciuric effect of meat phosphorus, and calcium balance is not affected by high meat diets¹¹¹. A high animal protein intake was not associated with deleterious effects on bone in the Framingham longitudinal study of older men and women. In fact, the greatest bone loss over 4 years was observed in those with the lowest animal and total protein intake¹¹². In the Study of Osteoporotic Fracture (SOF) cohort, a high animal protein to vegetable protein ratio

was associated with a greater rate of bone loss at the hip and increased hip fracture risk, whereas total protein intake was not¹¹³. It has been suggested that the potential effects of animal protein may be related to possible differences in net endogeneous acid production¹¹³, although this interpretation has been disputed¹¹⁴. The results are controversial and no consensus has yet been reached^{115,116}.

Conversely, a low protein intake in the elderly may contribute to the risk of osteoporotic fracture. A substantial proportion of elderly patients in Western countries show signs of clinical protein-energy malnutrition on admission^{117,118}, falls are more likely in older people with malnutrition¹¹⁹ and patients with hip fracture have less bone loss and require hospitalisation for shorter periods when given protein supplementation¹²⁰. As described above, a low protein intake was associated with the greatest bone loss over 4 years in the Framingham cohort¹¹². The long-term consequences of protein-energy malnutrition earlier in life have not been studied, but, given that most countries with high childhood malnutrition rates also have low rates of fragility fractures amongst their older population, it would seem unlikely that there are consequences for long-term bone health. Protein intakes in childhood and adolescence may alter the tempo of growth, and possibly the ultimate shape and strength of bones^{79,121}. However, the direction of this relationship is difficult to judge, since it can be argued that a low protein intake during rapid growth may jeopardise bone health, and conversely, that slow rates of growth may ultimately produce a more resilient skeletal structure. At present, there is no firm evidence on which to base recommendations about optimal protein intake for bone growth or the prevention of osteoporosis.

Fluorine

Fluorosis occurs in several parts of the world, such as South Africa, Tanzania and India, because of naturally high fluoride concentrations in drinking water. Fluorosis causes joint stiffness, limb deformities and staining of the teeth. There may be osteopenia of the long bones, and signs of rickets in children. Osteosclerosis and joint calcifications occur in the axial skeleton. Because of its effects on stimulating osteoblastic activity and inhibiting bone crystal dissolution, there has been considerable interest in the use of pharmacologic doses of sodium fluoride for the treatment of osteoporosis. As noted earlier, this agent can produce increases in BMD but its efficacy in reducing fractures is questionable (see earlier). At levels below those associated with fluorosis and when combined with a low calcium intake, high fluorine intakes have been associated with widened bones, reduced BMD and osteoporosis of cortical regions of the skeleton¹²², possibly due to excessive urinary calcium excretion. It is considered unlikely that the levels of fluoride obtained

from fluoridated water supplies have an influence on bone health¹²³.

Other nutrients and dietary constituents

Many other nutrients and dietary factors may be important for long-term bone health and the prevention of osteoporosis. Among the essential nutrients, plausible hypotheses for involvement with skeletal health, based on biochemical and metabolic evidence, can be made for zinc, copper, manganese, boron, vitamin A, vitamin C, vitamin K, the B-vitamins, potassium and sodium³⁰. Evidence from physiological and clinical studies is largely lacking, and the data are often difficult to interpret because of potential size-confounding or bone remodelling transient effects (see earlier).

Among the vitamins, thinning of the cortices and loss of trabecular architecture are common features of frank vitamin C deficiency (scurvy). Vitamin C (ascorbic acid) is a cofactor in the hydroxylation of lysine and proline, and is therefore important in the cross-linking of collagen fibres in bone. At levels of intake in the normal range, in a limited number of studies, a relationship between BMD and vitamin C intake has been shown by some researchers but not others³⁰. Vitamin K is a cofactor in the gamma-carboxylation of glutamic acid which is important in the production of osteocalcin, one of the main non-collagenous proteins of bone. Inverse relationships have been reported between low vitamin K intake in older people, BMD and risk of fragility fractures, possibly through an increase in the amount of osteocalcin produced in its undercarboxylated, and less fully functional, form^{124,125}. A high intake of vitamin A as retinol has been associated with hip fracture in Sweden¹²⁶. There are studies linking low intakes of vitamin B₆ and other B-vitamins with low BMC and hip fracture³⁰.

Among the minerals and trace elements, zinc nutrition is important in infant bone growth¹²⁷, and associations with BMD have been noted in middle-aged premenopausal women³⁰. Copper supplementation has been associated with a reduction of bone loss in one study of peri-menopausal women¹²⁸. A combined supplement of calcium, zinc, manganese and copper produced increases in BMD in a small study of postmenopausal women¹²⁹. Boron has effects on urinary calcium excretion and associations with BMD have been reported¹³⁰.

There has been considerable interest in the possible role of the electrolytes sodium and potassium in the development and prevention of osteoporosis. The movements of calcium and sodium through the renal tubules are intimately linked and a direct relationship exists between urinary sodium and calcium excretion in free-living populations³⁰. Sodium intake is a stronger determinant of urinary calcium excretion than calcium intake⁹⁰ and a high sodium intake is considered deleterious to bone health. Some individuals show more pronounced effects

of sodium intake on calcium excretion than others. The evidence that sodium is important in the aetiology of osteoporosis or that sodium restriction may be a beneficial strategy for fracture prevention, however, is inconclusive³⁰. Data are limited to a small number of studies that have shown effects of sodium intake on calcium homeostasis and bone turnover in post-menopausal women^{131,132}, and a study that has demonstrated a weak but significant association with BMD and age-related bone loss¹³³. Changes in sodium intake do not effect bone turnover in either salt sensitive or non-salt sensitive pre-menopausal women^{132,134}.

Conversely, a higher BMD has been associated with a higher dietary potassium intake, along with other nutrients associated with fruits and vegetable intake^{108,135}. In addition to supplying specific nutrients that may promote bone health, fruits and vegetables promote an alkaline environment by reducing the potential renal acid load (PRAL) and net endogenous acid production (NEAP)¹³⁶. The skeleton acts as a reservoir of alkaline salts for maintenance of adequate acid–base homeostasis, and foods such as fruits and vegetables may diminish the demand for skeletal salts to balance acid generated from foods such as meat^{135,137}. Supplementation of post-menopausal women with potassium bicarbonate has been shown to neutralise endogenous acid, reduce urinary calcium excretion and alter bone remodelling in such a way as improve calcium balance, at least over the short-term^{138,139}.

Other components of the diet could also influence bone health. Of these, phyto-oestrogens are exciting interest in that they are naturally-occurring plant chemicals with weak, oestrogenic properties¹⁴⁰. Phyto-oestrogens include soy-derived isoflavones, such as genistein and daidzein and lignans derived from cereals, fruits and vegetables. These compounds are able to bind to both the α and β oestrogen receptors, and may act as receptor agonists or antagonists depending on the tissue. Studies in animal models after ovariectomy suggest that phyto-oestrogens may prevent bone loss but, as yet, data from human studies are limited^{141,142}. In the past, a high caffeine intake was regarded as a risk factor for osteoporosis because of its effects on urinary mineral excretion but recent population-based studies have not shown caffeine to be associated with either a low BMD or an increased rate of bone loss^{63,143–145}. A recent study has suggested that a high caffeine intake (>300 mg/d) by elderly women may be associated with a higher rate of bone loss, but only in those with a *tt*VDR genotype¹⁴⁶. Heavy alcohol consumption is associated with decreased BMD and moderately increased fracture risk, and alcoholism is a major risk factor for osteoporosis. There is no consistent evidence, however, that moderate alcohol consumption is detrimental and there are some studies that suggest that it may be protective in post-menopausal women³⁰.

Other diet-related issues: body weight and composition, vegetarianism and lactose intolerance

Body weight is a major determinant of BMC and BMD⁷. Low body weight, especially in connection with anorexia nervosa and the frailty of old age, is associated with an increased risk of fractures, and being overweight with a reduced risk³⁰. In young people and older men, after adjusting for differences in body mass, leanness (a higher lean-to-fat ratio) is associated with higher bone mineral status¹⁴⁷ whereas in post-menopausal women, it is fatness (a lower lean-to-fat ratio) that is positively related to bone mineral¹⁴⁸. Various interpretations have been advanced to explain this dichotomy, including the osteogenic effects of muscle in younger people, the shock-absorbing effects of adipose tissue in older people, and the possible endogenous production of oestrogens by adipose tissue, which may be particularly important in women after the menopause.

There is no evidence that a lactovegetarian diet is associated with differences, either detrimental or beneficial, in BMD or fracture risk³⁰. There have been few investigations of individuals consuming vegan or macrobiotic diets, but there is some evidence that these may be associated with low BMD. However, interpretation of studies is difficult because of other differences that may be associated with a vegetarian lifestyle which may affect bone health, such as body weight, smoking habits and physical activity patterns.

Lactose intolerance is associated with a low calcium intake, because of avoidance of milk and milk products, and is regarded as a likely risk factor for osteoporosis. On a global basis, however, lactose intolerance is more prevalent among Asians and Africans, populations that are less at risk of hip fracture. Studies with fracture or bone loss as outcome have produced an inconsistent picture, with some suggesting a modest risk for those with lactose intolerance¹⁴⁹ but not others^{150,151}.

Levels of evidence on nutrition and diet-related factors associated with osteoporosis (with fracture as the outcome) are summarised in Table 2.

Conclusions and policy implications

The review of the scientific data, the strengths and weaknesses of the evidence and the conceptual difficulties in interpreting studies linking diet, nutrition and osteoporosis have been described in detail. There is insufficient knowledge at the present time linking alterations in BMC (or BMD), the tempo of growth or bone turnover rates in children and adolescents to long-term benefits in terms of either enhanced peak bone mass or reduced fracture incidence, for these indices to be used as markers of risk of osteoporotic disease in old age. For adults, the evidence of a link between intakes of any

Table 2 Levels of evidence, with fracture as outcome

	Positive	None	Negative
Convincing			
Older people*	Vitamin D + calcium		High alcohol Low body weight
Probable			
Older people*	Calcium Vitamin D	Fluoride†	
Possible			
	Fruit and vegetables‡,§ Moderate alcohol	Phosphorus	Sodium Low protein High protein

*In populations with high fracture incidence only. Applies to men and women older than 50–60 years, with a low calcium intake and/or poor vitamin D status.

†At levels used to fluoridise water supplies. High fluoride intakes cause fluorosis.

‡Several components of fruit and vegetables are possibly positively linked at levels within the normal range consumed (e.g. alkalinity, vitamin K, phyto-oestrogens, potassium, magnesium, boron).

§Osteoporosis is a feature of vitamin C deficiency (scurvy).

dietary component and bone health is not sufficiently secure to make firm recommendations, with the exception of calcium and vitamin D (see below). For other aspects of the diet, the accumulating picture suggests that current healthy-eating advice to decrease sodium intake, to increase potassium intake, and to consume more fresh fruits and vegetables is unlikely to be detrimental to bone health and may be beneficial³⁰.

For calcium, the evidence to date would suggest that there is a threshold of increasing fracture risk for older men and women at calcium intakes below around 400–500 mg/d but there is no additional benefit in terms of prevention of osteoporosis of a customary dietary calcium intake above those currently recommended. Given the evidence, emphasis would be best placed on minimising the numbers of people with calcium intakes below 400 mg/d, rather than on increasing the calcium intake of those already consuming higher amounts.

Whether this applies to populations with low fracture incidence is not known. In these countries, the calcium intake of the majority is generally below 400–500 mg/d but there is little evidence that this compromises bone health in terms of fracture risk. It is possible that the ability of the human body to adapt to differing levels of calcium intake is sufficiently powerful that calcium intake is largely irrelevant in this context. It is also possible that early life exposure to differing amounts of calcium, or nutrient–gene, nutrient–nutrient or nutrient–lifestyle interactions may alter calcium requirements, rendering some populations at more risk from a low calcium intake than others.

Answers to these questions are urgently needed. Dietary recommendations for calcium have tended to increase over the last decade, largely because of concerns about the potential link with osteoporosis. Many countries have an average calcium intake that is considerably below

these recommended levels, due largely to the scarcity of milk and milk products in those regions^{17,110}, and the potential within these countries to increase the calcium supply is severely limited. Unless there is firm scientific evidence of a health benefit of increasing calcium intake for these populations, it would seem unlikely that the economic, agricultural and industrial investment that will be needed to increase calcium intakes to match recommended intakes would be worthwhile for these populations. In addition, it is important to consider possible deleterious effects of a high calcium intake, especially with respect to the absorption of other minerals, such as iron².

With respect to vitamin D, the evidence has shown that various groups are vulnerable to vitamin D insufficiency and, among adults, this may place them at risk of osteoporosis at levels of plasma 25-hydroxyvitamin D above those associated with osteomalacia. These are older people who are housebound or who live in institutions, and who eat no meat or oily fish, dark-skinned people who live at latitudes away from the tropics, and people who rarely go out of doors or who, when they do so, wear clothes which fully conceal them³⁰. Current dietary targets for vitamin D aim to cover the needs of vulnerable groups such as these. Variations in recommendations from different advisory bodies largely reflect the philosophy used to take account of endogenous production of vitamin D, but in general a dietary recommendation of between 5 and 10 µg/d is given for the vulnerable groups. Some committees have recently advocated a higher target intake for the elderly, in recognition that this group is at high risk of vitamin D deficiency, secondary hyperparathyroidism and poor skeletal health⁵⁴. However, there is little evidence that a higher intake (e.g. 15 or 20 µg/d) is superior to lower target values. There is, however, evidence that, despite these recommendations, average vitamin D intake and status amongst many elderly people are poor. Urgent consideration needs to be given to ways of addressing this problem, including the promotion of greater awareness amongst the public and health professionals of the importance of achieving adequate vitamin D status and the use of vitamin D supplements in those most at risk of deficiency^{54,69}. However, whether improving vitamin D status in these vulnerable groups would be effective as a strategy for osteoporosis prevention is not known.

In conclusion, although calcium and vitamin D supplementation plays a recognised role in the treatment of established osteoporosis, the importance of diet and nutrition in the prevention of osteoporotic fracture is debatable. A good case can be made for targeted approaches, in countries most at risk for fracture, to improve calcium and vitamin D intakes in sub-groups of the population. There is no evidence that measures encompassing entire populations would be effective.

Recommendations

In trying to unravel the complexities of different rates of osteoporosis, and the dietary implications of these, it was decided to use the clinical outcome of the disease, i.e. fragility fracture, rather than an intermediate marker of risk such as BMC or BMD. This was largely predicated on the evidence that BMC and BMD are not well related to fracture risk across different populations and that changes in BMC and BMD do not necessarily translate into alterations in fracture risk.

It was apparent that the incidence of fracture varies greatly by geographic region and this variability is, presumably, an outcome of some lifestyle factor, such as diet or physical activity, and/or ethnicity. The recent FAO/WHO Report on Mineral and Vitamins also identified the role of environment, geography and ethnicity. However, the report implied that because African-Americans have greater bone density and fewer hip fractures that this greater bone density also applied to Africans. Data from Gambia, Nigeria and South Africa indicate that this is not the case and that this cannot account for the low fracture risk of Africans.

Because the disease outcome (i.e. fracture) is not clearly related to BMC or density, dietary recommendations that address BMD or calcium stores will not necessarily impact on fractures. Therefore, increases in BMD and thereby calcium stores, in childhood or at peak bone mass, may not have an impact on later fractures.

With respect to calcium, in countries with a low fracture incidence, intakes above those normally consumed are not associated with decreased fracture risk. The routine intake of calcium in these societies is often less than in many other populations, generally due to a lower consumption of dairy products. In countries with high fracture incidence, usually westernised, there is evidence that older men and women (over 50–60 years) with a low calcium intake (≤ 400 mg/d) are at greater risk and that an increase in their calcium intake may reduce risk. An increase in calcium intake is also useful in the treatment of patients with established osteoporosis. There is inadequate evidence for children, and young adults.

Vitamin D is a surprisingly common problem throughout the world, including countries with plenty of daylight time when the sun is shining, e.g. the Middle East. Groups who avoid sunshine exposure for a variety of reasons are at particular risk. Rickets and osteomalacia continue to be public health problems in many countries. There is evidence that poor vitamin D status in older men and women increases the risk of osteoporotic fracture. In countries at high risk of fracture, increases in vitamin D and calcium intake by elderly men and women have proved beneficial.

Consequently, if general recommendations were to be made, there is a need to address those at risk of vitamin

D deficiency. There is also a need to separately address populations at higher risk of fracture and those historically at lower risk, particularly with respect to calcium intake. Some countries or areas, such as Hong Kong, are in transition from one to another.

Physical activity could be recommended throughout the lifecourse. Likewise, other 'prudent' dietary and lifestyle recommendations, for instance lower salt, high fruit and vegetable intakes, maintaining a healthy body weight, moderating alcohol intake and avoiding smoking are likely to be helpful, but there is insufficient evidence to make firm recommendations with respect to osteoporosis.

Therefore, the recommendations for osteoporosis can be summarized as follows:

- No case for global, population-based approaches. A case can be made for targeted approaches with respect to calcium and vitamin D in high-risk sub-groups of populations with a high fracture incidence.
- In countries with high osteoporotic fracture incidence, a low calcium intake (≤ 400 mg/d) among older men and women is associated with increased fracture risk.
- In countries with high fracture incidence, a poor vitamin D status in the elderly increases fracture risk.
- In countries with high fracture incidence, increases in dietary vitamin D and calcium in the elderly can decrease fracture risk.
- Prudent dietary and lifestyle recommendations developed in respect of other chronic diseases may prove helpful in terms of fracture risk but firm evidence is lacking. These include:

- increase physical activity
- reduce sodium intake
- increase consumption of fruit and vegetables
- maintain a healthy body weight
- avoid smoking
- moderate alcohol intake

Research recommendations

- More evidence is required in young people to link intermediate outcome measures such as BMC and density, bone turnover and skeletal dimensions to long-term fracture risk.
- The evidence base needs to include males, people in countries at low risk of osteoporotic fracture and ethnic minorities in countries at high risk of fracture.
- Research is needed to determine the biological basis by which dietary interventions alter BMC or density at different stages of the lifecourse and their relative importance in altering future fracture risk, e.g. skeletal size and proportions, bone turnover, tissue mineralisation, bone architecture.
- Research is needed to define the mechanisms by which adaptation to a low calcium intake occurs, and to examine the interaction of genetic make-up, diet

composition and other environmental exposures with calcium regulation and bone health.

Acknowledgements

An earlier version of this paper was prepared as a background paper for the Joint WHO/FAO Expert Consultation on diet, nutrition and the prevention of chronic diseases (Geneva, 28 January–1 February, 2002). The author would like to thank Professor John Kanis from University of Sheffield Medical School, Sheffield, UK; Dr Roger Francis from University of Newcastle, Newcastle Upon Tyne, UK; and Dr Janet King from Western Human Nutrition Center, Davis, CA, USA for their valuable comments on an earlier draft of the manuscript.

References

- 1 Consensus Development Conference. Diagnosis, prophylaxis and treatment of osteoporosis. *American Journal of Medicine* 1991; **90**: 107–10.
- 2 Prentice A. Is nutrition important in osteoporosis? *Proceedings of the Nutrition Society* 1997; **56**: 357–67.
- 3 Compston J. Osteoporosis. In: Crisp A, ed. *The Management of Common Metabolic Bone Disorders*. Cambridge: Cambridge University Press, 1993, 29–62.
- 4 Johnell O. The socioeconomic burden of fractures: today and in the 21st century. *American Journal of Medicine* 1997; **103**: 20S–5S.
- 5 World Health Organization. *Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis*. WHO Technical Report Series 843. Geneva: World Health Organization, 1994.
- 6 Aspray TJ, Prentice A, Cole TJ, Sawo Y, Reeve J, Francis RM. Low bone mineral content is common but osteoporotic fractures are rare in elderly rural Gambian women. *Journal of Bone and Mineral Research* 1996; **11**: 1018–24.
- 7 Prentice A, Parsons TJ, Cole TJ. Uncritical use of bone mineral density in absorptiometry may lead to size-related artifacts in the identification of bone mineral determinants. *American Journal of Clinical Nutrition* 1994; **60**: 837–42.
- 8 Russel-Aulet M, Wang J, Thornton JC, Colt EWD, Pierson RN. Bone mineral density and mass in a cross-sectional study of White and Asian women. *Journal of Bone and Mineral Research* 1993; **8**: 575–82.
- 9 Yan L, Zhou B, Prentice A, Hou J, Wang X, Golden MHN. Epidemiological study of hip fracture in Shenyang, P.R. China. *Bone* 1997; **24**: 151–5.
- 10 Royal College of Physicians. *Fractured Neck of Femur*. London: Royal College of Physicians, 1989.
- 11 Sanders KM, Pasco JA, Ugoni AM, et al. The exclusion of high trauma fractures may underestimate the prevalence of bone fragility fractures in the community. The GEELONG osteoporosis study. *Journal of Bone and Mineral Research* 1998; **13**: 1337–42.
- 12 Cooper C, Campion G, Melton LJ. Hip fractures in the elderly: a world-wide projection. *Osteoporosis International* 1992; **2**: 285–9.
- 13 Melton LJ 3rd. Epidemiology of fractures. In: Melton LJ, ed. *Osteoporosis: Etiology, Diagnosis, and Management*. 2nd ed. Philadelphia: Lippincott-Raven, 1995, 225–47.
- 14 Ellfors L, Allander E, Kanis JA, Gullberg B, Johnell O, Dequeker J. The variable incidence of hip fracture in southern Europe. The MEDOS study. *Osteoporosis International* 1994; **4**: 253–63.
- 15 Maggi S, Kelsey JL, Litvak J, Heyse SP. Incidence of hip fracture in the elderly: a cross-national analysis. *Osteoporosis International* 1991; **1**: 232–41.
- 16 Eastell R, Boyle IT, Compston J, et al. Management of male osteoporosis: report of the UK Consensus Group. *Quarterly Journal of Medicine* 1998; **91**: 71–92.
- 17 Royal College of Physicians. *Osteoporosis. Clinical Guidelines for Prevention and Treatment*. London: Royal College of Physicians of London, 1999.
- 18 Kannus P, Parkkari J, Sievanen H, Heinonen A, Vuori I, Jarvinen M. Epidemiology of hip fractures. *Bone* 1996; **18**(Suppl. 1): 57S–63S.
- 19 Lau EMC, Cooper C. The epidemiology of osteoporosis. The oriental perspective in a world context. *Clinical Orthopaedics and Related Research* 1996; **323**: 65–74.
- 20 Kanis J. The epidemiology of hip fracture in Europe. The MEDOS study. *Revista Clinica Espanola* 1991; **188**(Suppl. 1): 12–4.
- 21 O'Neill TW, Felsenberg D, Varlow J, Cooper C, Kanis JA, Silman AJ. The prevalence of vertebral deformity in European men and women: the European Vertebral Osteoporosis Study. *Journal of Bone and Mineral Research* 1996; **11**: 1010–8.
- 22 Gardsell P, Johnell O, Nilsson BE, Sernbo I. Bone mass in an urban and a rural population: a comparative, population-based study in southern Sweden. *Journal of Bone and Mineral Research* 1991; **6**: 67–75.
- 23 Ross PD, Davis JW, Vogel JM, Wasnich RD. A critical review of bone mass and the risk of fractures in osteoporosis. *Calcified Tissues International* 1990; **46**: 149–61.
- 24 Gardsell P, Johnell O, Nilsson BE. The predictive value of bone loss for fragility fractures in women: a longitudinal study over 15 years. *Calcified Tissues International* 1991; **49**: 90–4.
- 25 Cummings S, Black D, Nevitt M, et al. Bone density at various sites for prediction of hip fractures. *Lancet* 1993; **341**: 72–5.
- 26 Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *British Medical Journal* 1996; **312**: 1254–9.
- 27 Faulkner KG. Bone matters: are density increases necessary to reduce fracture risk? *Journal of Bone and Mineral Research* 2000; **15**: 183–7.
- 28 Prentice A. Application of DXA and other techniques to the assessment of bone and body composition. In: Cole TJ, ed. *Body Composition Techniques and Assessment in Health and Disease*. Society for the Study of Human Biology; vol Soc Study Human Biol Symp Series 36. Cambridge: Cambridge University Press, 1995, 1–13.
- 29 Cole TJ, Prentice A. Bone mineral measurements. *British Medical Journal* 1992; **305**: 1223–4.
- 30 Department of Health. *Nutrition and Bone Health: With Particular Reference to Calcium and Vitamin D. Report of the Subgroup on Bone Health, Working Group on the Nutritional Status of the Population of the Committee on Medical Aspects of Food and Nutrition Policy*. Report on Health and Social Subjects. Number 49. London: The Stationery Office, 1998.
- 31 Parfitt AM. Morphologic basis of bone mineral measurements: transient and steady state effects of treatment in osteoporosis. *Mineral and Electrolyte Metabolism* 1980; **4**: 273–87.
- 32 Frost HM. *Bone Remodelling and its Relationship to Metabolic Bone Disease*. Springfield: Thomas, 1973.
- 33 Kanis JA. Calcium requirements for optimal skeletal health in women. *Calcified Tissue International* 1991; **49**: S33–41.
- 34 Heaney RP. The bone remodeling transient: Interpreting interventions involving bone-related nutrients. *Nutrition Reviews* 2001; **59**: 327–34.
- 35 Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD.

- Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: the OFELY study. *Journal of Bone and Mineral Research* 2000; **15**: 1526–36.
- 36 Gunnes M, Lehmann EH, Mellstrom D, Johnell O. The relationship between anthropometric measurements and fractures in women. *Bone* 1996; **19**: 407–13.
- 37 Bass S, Delmas PD, Pearce G, Hendrich E, Tabensky A, Seeman E. The differing tempo of growth in bone size, mass, and density in girls is region-specific. *Journal of Clinical Investigation* 1999; **104**: 795–804.
- 38 Cooper C, Fall C, Egger P, Hobbs R, Eastell R, Barker D. Growth in infancy and bone mass in later life. *Annals of the Rheumatic Diseases* 1997; **56**: 17–21.
- 39 Fewtrell MS, Prentice A, Jones SC, *et al*. Bone mineralisation and turnover in preterm infants at 8–12 years of age: the effect of early diet. *Journal of Bone and Mineral Research* 1999; **14**(5): 810–20.
- 40 Slemenda CW, Peacock M, Hui S, Zhou L, Johnston CC. Reduced rates of skeletal remodeling are associated with increased bone mineral density during the development of peak bone mass. *Journal of Bone and Mineral Research* 1997; **12**: 676–82.
- 41 Compston JE. Pharmacological interventions for the prevention of vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: does site-specificity exist? *Bone* 2000; **27**: 765–8.
- 42 Wilkin TJ, Devendra D. Bone densitometry is not a good predictor of hip fracture: for. *British Medical Journal* 2001; **323**: 795–7.
- 43 Dequeker J, Luyten F. Bone densitometry is not a good predictor of hip fracture: against. *British Medical Journal* 2001; **323**: 797–9.
- 44 Chesnut CH 3rd, Rosen CJ. For the Bone Quality Discussion Group. Reconsidering the effects of antiresorptive therapies in reducing osteoporotic fracture. *Journal of Bone and Mineral Research* 2001; **16**: 2163–72.
- 45 Bjarnason NH, Sarkar S, Duong T, Mitlak B, Delmas PD, Christiansen C. Six and twelve month changes in bone turnover are related to reduction in vertebral fracture risk during 3 years of raloxifene treatment in postmenopausal osteoporosis. *Osteoporosis International* 2001; **12**: 922–30.
- 46 Riggs BL, Melton LJ 3rd. Bone turnover matters: the raloxifene treatment paradox of dramatic decreases in vertebral fractures without commensurate increases in bone density. *Journal of Bone and Mineral Research* 2002; **17**: 11–4.
- 47 Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism. *Journal of Bone and Mineral Research* 2000; **15**: 1113–8.
- 48 Sogaard CH, Mosekilde L, Richards A, Mosekilde L. Marked decrease in trabecular bone quality after five years on sodium fluoride therapy assessed by biomechanical testing of iliac crest bone biopsies in osteoporotic patients. *Bone* 1994; **15**: 393–400.
- 49 Dargent Molina P, Favier F, Grandjean H, *et al*. Fall-related factors and risk of hip fracture: the EPIDOS prospective study. *Lancet* 1996; **348**: 145–9.
- 50 Nguyen T, Sambrook P, Kelly P, *et al*. Prediction of osteoporotic fractures by postural instability and bone density. *British Medical Journal* 1993; **307**: 1111–5.
- 51 De Laet CE, van Hout BA, Burger H, Hofman A, Pols HA. Bone density and risk of hip fracture in men and women: cross-sectional analysis. *British Medical Journal* 1997; **26**: 221–5.
- 52 Prentice A. The relative contribution of diet and genotype to bone development. *Proceedings of the Nutrition Society* 2001; **60**: 1–8.
- 53 Cooper C, Aihie A. Osteoporosis: recent advances in pathogenesis and treatment. *Quarterly Journal of Medicine* 1994; **87**: 203–9.
- 54 Institute of Medicine Food and Nutrition Board. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*. Washington, DC: National Academy Press, 1997.
- 55 National Institutes of Health Consensus Development Panel. Optimal calcium intake. *Journal of the American Medical Association* 1994; **272**: 1942–8.
- 56 Cumming RG. Calcium intake and bone mass: a quantitative review of the evidence. *Calcified Tissues International* 1990; **47**: 194–201.
- 57 Welten DC, Kemper HCG, Post GB, Van Staveren WA. A meta-analysis of the effect of calcium intake on bone mass in young and middle aged females and males. *Journal of Nutrition* 1995; **125**: 2802–13.
- 58 Kreiger N, Gross A, Hunter G. Dietary factors and fracture in postmenopausal women: a case-control study. *International Journal of Epidemiology* 1992; **21**(5): 953–8.
- 59 Cummings SR, Nevitt MC, Browner WS, *et al*. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *New England Journal of Medicine* 1995; **332**(12): 767–73.
- 60 Wickham CA, Walsh K, Cooper C, *et al*. Dietary calcium, physical activity, and risk of hip fracture: a prospective study. *British Medical Journal* 1989; **299**(6704): 889–92.
- 61 Cooper C, Barker DJ, Wickham C. Physical activity, muscle strength, and calcium intake in fracture of the proximal femur in Britain. *British Medical Journal* 1988; **297**(6661): 1443–6.
- 62 Cumming RG, Klineberg RJ. Case-control study of risk factors for hip fractures in the elderly. *American Journal of Epidemiology* 1994; **139**(5): 493–503.
- 63 Hannan MT, Felson DT, Dawson-Hughes B, *et al*. Risk factors for longitudinal bone loss in elderly men and women: the Framingham Osteoporosis Study. *Journal of Bone and Mineral Research* 2000; **15**(4): 710–20.
- 64 Lau E, Donnan S, Barker DJ, Cooper C. Physical activity and calcium intake in fracture of the proximal femur in Hong Kong. *British Medical Journal* 1988; **297**(6661): 1441–3.
- 65 Holbrook TL, Barrett-Connor E, Wingard DL. Dietary calcium and risk of hip fracture: 14-year prospective population study. *Lancet* 1988; **2**(8619): 1046–9.
- 66 Johnell O, Gullberg B, Kanis JA, *et al*. Risk factors for hip fracture in European women: the MEDOS Study. Mediterranean Osteoporosis Study. *Journal of Bone and Mineral Research* 1995; **10**(11): 1802–15.
- 67 Kanis J, Johnell O, Gullberg B, *et al*. Risk factors for hip fracture in men from southern Europe: the MEDOS study. Mediterranean Osteoporosis Study. *Osteoporosis International* 1999; **9**(1): 45–54.
- 68 Cumming RG, Nevitt MC. Calcium for prevention of osteoporotic fractures in postmenopausal women. *Journal of Bone and Mineral Research* 1997; **12**: 1321–9.
- 69 Prentice A. What are the dietary requirements for calcium and vitamin D? *Calcified Tissue International* 2002; **70**: 83–8.
- 70 Riis B, Thomsen K, Christiansen C. Does calcium supplementation prevent postmenopausal bone loss? *New England Journal of Medicine* 1987; **316**: 173–7.
- 71 Elders PJM, Lips P, Netelenbos JC, *et al*. Long-term effect of calcium supplementation on bone loss in perimenopausal women. *Journal of Bone and Mineral Research* 1994; **9**: 963–70.
- 72 Dawson-Hughes B, Dallal GE, Krall EA, Sadowski L, Sahyoun N, Tannenbaum S. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *New England Journal of Medicine* 1990; **323**: 878–83.

- 73 Riggs BL, O'Fallon WM, Muhs J, O'Connor MK, Kumar R, Melton LJ 3rd. Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. *Journal of Bone and Mineral Research* 1998; **13**: 168–74.
- 74 Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Effect of calcium supplementation on bone loss in postmenopausal women. *New England Journal of Medicine* 1993; **328**: 460–4.
- 75 Prince RP, Devine A, Dick I, *et al.* The effects of calcium supplementation (milk powder or tablets) and exercise on bone density in postmenopausal women. *Journal of Bone and Mineral Research* 1995; **10**: 1068–75.
- 76 Chevalley T, Rizzoli R, Nydegger V, *et al.* Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin D replete elderly patients. *Osteoporosis International* 1994; **4**: 245–52.
- 77 Peacock M, Liu G, Carey M, *et al.* Effect of a calcium or 25OHD vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. *Journal of Clinical Endocrinology and Metabolism* 2000; **85**: 3011–9.
- 78 Dibba B, Prentice A, Ceesay M, Stirling DM, Cole TJ, Poskitt EME. Effect of calcium supplementation on bone mineral accretion in Gambian children accustomed to a low calcium diet. *American Journal of Clinical Nutrition* 2000; **71**: 544–9.
- 79 Cadogan J, Eastell R, Jones N, Barker ME. Milk intake and bone mineral acquisition in adolescent girls: randomised, controlled intervention trial. *British Medical Journal* 1997; **315**: 1255–60.
- 80 Recker R, Hinders S, Davies KM, *et al.* Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *Journal of Bone and Mineral Research* 1996; **11**: 1961–6.
- 81 Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomised controlled trial. *American Journal of Medicine* 1995; **98**: 331–5.
- 82 Orimo H, Shiraki M, Hayashi T, Nakamura T. Reduced occurrence of vertebral crush fractures in senile osteoporosis treated with 1(OH)-vitamin D₃. *Bone and Mineral* 1987; **3**: 47–52.
- 83 Commission of the European Communities. *Nutrient and Energy Intakes for the European Community*. Reports of the Scientific Committee for Food. Luxembourg: Office for Official Publications of the European Communities, 1993.
- 84 Garn SM, Rohmann CG, Wagner B. Bone loss is a general phenomenon in man. *Federation Proceedings* 1967; **26**: 1729–36.
- 85 Lee WTK, Leung SSF, Wang S-H, *et al.* Double-blind, controlled calcium supplementation and bone mineral accretion in children accustomed to a low-calcium diet. *American Journal of Clinical Nutrition* 1994; **60**: 744–50.
- 86 Lau EMC, Woo J, Leung PC, Swaminathan R, Leung D. The effects of calcium supplementation and exercise on bone density in elderly Chinese women. *Osteoporosis International* 1992; **2**: 168–73.
- 87 Prentice A, Jarjou LMA, Cole TJ, Stirling DM, Dibba B, Fairweather-Tait S. Calcium requirements of lactating Gambian mothers: effects of a calcium supplement on breastmilk calcium concentration, maternal bone mineral content, and urinary calcium excretion. *American Journal of Clinical Nutrition* 1995; **62**: 58–67.
- 88 Prentice A. Calcium requirements of children. *Nutrition Reviews* 1995; **53**(2): 37–40.
- 89 Prentice A. Calcium supplementation during breastfeeding. *New England Journal of Medicine* 1997; **337**: 558–9.
- 90 Nordin BEC, Marshall DH. Dietary requirements for calcium. In: Nordin BEC, ed. *Calcium in Human Biology*. London: Springer-Verlag, 1988.
- 91 Bates CJ, Carter GD, Mishra GD, O'Shea D, Jones J, Prentice A. In a population study, can parathyroid hormone aid the definition of adequate vitamin D status? A study of people aged 65 years and over from the British National Diet and Nutrition Survey. *Osteoporosis International* 2003; **14**: 152–9.
- 92 Finch S, Doyle W, Lowe C, *et al.* *National Diet and Nutrition Survey: People Aged 65 years and Over. Volume 1: Report of the Diet and Nutrition Survey*. London: The Stationery Office, 1998, 637.
- 93 Chapuy MC, Preziosi P, Maamer M, *et al.* Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporosis International* 1997; **7**(5): 439–43.
- 94 Khaw KT, Sneyd MJ, Compston J. Bone density, parathyroid hormone and 25-hydroxyvitamin D. *British Medical Journal* 1992; **350**: 263–7.
- 95 Ooms ME, Roos JC, Bezemer PD, Van Der Vijch WJF, Bouter LM, Lips P. Prevention of bone loss by vitamin D supplementation in elderly women: a randomised double blind trial. *Journal of Clinical Endocrinology and Metabolism* 1995; **80**: 1052–8.
- 96 Lips P, Graafman WC, Ooms ME, Bezemer D, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. *Annals of Internal Medicine* 1996; **124**: 400–6.
- 97 Heikinheimo RJ, Inkovaara JA, Harju EJ, *et al.* Annual injection of vitamin D and fractures of aged bones. *Calcified Tissues International* 1992; **51**: 105–10.
- 98 Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *New England Journal of Medicine* 1997; **337**: 670–6.
- 99 Chapuy MC, Arlot ME, Duboeuf F, *et al.* Vitamin D₃ and calcium to prevent hip fractures in elderly women. *New England Journal of Medicine* 1992; **327**: 1637–42.
- 100 Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *British Medical Journal* 1994; **308**: 1081–2.
- 101 Lau EM, Woo J, Lam V, Hong A. Milk supplementation of the diet of postmenopausal Chinese women on a low calcium intake retards bone loss. *Journal of Bone and Mineral Research* 2001; **16**(9): 1704–9.
- 102 Parfitt AM. Osteoporosis: 50 years of change, mostly in the right direction. In: Ralston SH, ed. *Osteoporosis and Bone Biology: The State of the Art*. London: International Medical Press, 2000, 1–13.
- 103 American Society for Bone and Mineral Research. *Primer of the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. In: Favus M, ed. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 1999.
- 104 Department of Health. *Dietary Reference Values for Food Energy and Nutrients for the United Kingdom*. Report on Health and Social Subjects. vol. 41 London: Her Majesty's Stationery Office, 1991.
- 105 Calvo MS, Kumar R, Heath H 3rd. Persistently elevated parathyroid hormone secretion and action in young women after four weeks of ingesting high phosphorus, low calcium diets. *Journal of Clinical Endocrinology and Metabolism* 1990; **70**: 1334–40.
- 106 Bizik BK, Ding W, Cerlewski FL. Evidence that bone resorption of young men is not increased by high dietary phosphorus obtained from milk and cheese. *Nutrition Research* 1996; **16**: 1143–6.
- 107 Heaney RP, Rafferty K. Carbonated beverages and urinary calcium excretion. *American Journal of Clinical Nutrition* 2001; **74**: 343–7.

- 108 New SA, Robins SP, Campbell MK, *et al.* Dietary influences on bone mass and bone metabolism: further evidence of a positive link between fruit and vegetable intake and bone health? *American Journal of Clinical Nutrition* 2000; **71**: 142–51.
- 109 Stendig-Lindberg G, Tepper R, Leichter I. Trabecular bone density in a two year controlled trial of oreroral magnesium in osteoporosis. *Magnesium Research* 1993; **6**: 155–63.
- 110 Abelow BJ, Holford TR, Insogna KL. Cross-cultural association between dietary animal protein and hip fracture: a hypothesis. *Calcified Tissue International* 1992; **50**: 14–8.
- 111 Hunt JR, Gallagher SK, Johnson LK, Lykken GI. High-versus low-meat diets: effects on zinc absorption, iron status, and calcium, copper, iron magnesium, manganese, nitrogen, phosphorus, and zinc balance in postmenopausal women. *American Journal of Clinical Nutrition* 1995; **62**: 621–32.
- 112 Hannan MT, Tucker KL, Dawson-Hughes B, Cupples LA, Felson DT, Kiel DP. Effect of dietary protein on bone loss in elderly men and women: the Framingham Osteoporosis Study. *Journal of Bone and Mineral Research* 2000; **15**(12): 2504–12.
- 113 Sellmeyer DE, Stone KL, Sebastian A, Cummings SR. For the Study of Osteoporotic Fractures Research Group. A high ratio of dietary animal to vegetable protein increases the rate of bone loss and the risk of fracture in postmenopausal women. *American Journal of Clinical Nutrition* 2001; **73**(1): 118–22.
- 114 Heaney RP. Protein intake and bone health: the influence of belief systems on the conduct of nutritional science. *American Journal of Clinical Nutrition* 2001; **73**(1): 5–6.
- 115 Sebastian A, Sellmeyer DE, Stone KL, Cummings SR. Dietary ratio of animal to vegetable protein and rate of bone loss and risk of fracture in postmenopausal women (letter). *American Journal of Clinical Nutrition* 2001; **74**: 411–2.
- 116 Heaney RP. Reply to A Sebastian *et al.* (letter). *American Journal of Clinical Nutrition* 2001; **74**: 412.
- 117 Mowe M, Bohmer T, Kindt E. Reduced nutritional status in an elderly population (>70 year) is probable before disease and possibly contributes to the development of disease. *American Journal of Clinical Nutrition* 1994; **59**: 317–24.
- 118 Larsson J, Unosson M, Ek A-C, Nilsson L, Thorslund S, Bjurulf P. Effect of dietary supplement on nutritional status and clinical outcome in 501 geriatric patients—a randomised study. *Clinical Nutrition* 1990; **9**: 179–84.
- 119 Lipschitz DA. Nutritional assessment and interventions in the elderly. In: Burckhardt P, Heaney RP, ed. *Nutritional Aspects of Osteoporosis '94*. Rome: Ares-Serono Symposia Publications, Challenges of Modern Medicine vol. 7, 1995 177–91.
- 120 Schurch MA, Rizzoli R, Slosman D, Vadas L, Vergnaud P, Bonjour JP. Protein supplements increase serum insulin-like growth factor-1 levels and attenuate proximal femur bone loss in patients with recent hip fracture. *Annals of Internal Medicine* 1998; **128**: 801–9.
- 121 Rizzoli R, Bonjour JP. Determinants of peak bone mass and mechanisms of bone loss. *Osteoporosis International* 1999; **9**(Suppl 2): S17–23.
- 122 World Health Organization. *Diet, Nutrition, and the Prevention of Chronic Diseases*. WHO Technical Report Series no. 797. Geneva: World Health Organization, 1990.
- 123 Gordon SL, Corbin SB. Summary of workshop on drinking water fluoride influence on hip fracture and on bone health. *Osteoporosis International* 1992; **2**: 109–17.
- 124 Szulc P, Arlot M, Chapuy MC, Duboeuf F, Meunier PJ, Delmas PD. Serum undercarboxylated osteocalcin correlates with hip bone mineral density in elderly women. *Journal of Bone and Mineral Research* 1994; **9**: 1591–5.
- 125 Shearer MJ. Role of vitamin K and Gla proteins in the pathophysiology of osteoporosis and vascular calcification. *Current Opinion in Clinical Nutrition and Metabolic Care* 2000; **3**: 433–8.
- 126 Melhus H, Michaelsson K, Kindmark A, *et al.* Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. *Annals of Internal Medicine* 1998; **129**: 770–8.
- 127 Prentice A, Bates CJ. Adequacy of dietary mineral supply for human bone growth and mineralisation. *European Journal of Clinical Nutrition* 1994; **48S**: 161–77.
- 128 Eaton-Evans J, McIlrath EM, Jackson WE, McCartney H, Strain JJ. Copper supplementation and the maintenance of bone mineral density in middle-aged women. *Journal of Trace Element Experimental Medicine* 1996; **9**: 87–94.
- 129 Strause L, Saltman P, Smith KT, Bracker M, Andon MB. Spinal bone loss in postmenopausal women supplemented with calcium and trace minerals. *Journal of Nutrition* 1994; **124**: 1060–4.
- 130 Meacham SL, Taper LJ, Volpe SL. Effects of boron supplementation on bone mineral density and dietary, blood and urinary calcium, phosphorus, magnesium and boron in female athletes. *Environment and Health Perspectives* 1994; **102**: 79–82.
- 131 Dawson-Hughes B, Fowler SE, Dalsky G, Gallagher C. Sodium excretion influences calcium homeostasis in elderly men and women. *Journal of Nutrition* 1996; **126**: 2107–12.
- 132 Evans CE, Chugtai AY, Blumsohn A, Giles M, Eastell R. The effects of dietary sodium on calcium metabolism in premenopausal and postmenopausal women. *European Journal of Clinical Nutrition* 1997; **51**: 394–9.
- 133 Devine A, Criddle RA, Dick IM, Kerr RA, Prince RL. A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. *American Journal of Clinical Nutrition* 1995; **62**: 740–5.
- 134 Ginty F, Flynn A, Cashman KD. The effect of sodium intake on biochemical markers of bone metabolism in young women. *British Journal of Nutrition* 1998; **79**: 343–50.
- 135 Tucker KL, Hannan MT, Chen H, Cupples LA, Wilson PW, Kiel DP. Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone mineral density in elderly men and women. *American Journal of Clinical Nutrition* 1999; **69**: 727–36.
- 136 Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. *Journal of the American Dietetic Association* 1995; **95**: 791–2.
- 137 Reid DM, New SA. Nutritional influences on bone mass. *British Journal of Nutrition* 1997; **56**: 977–87.
- 138 Wood RJ. Potassium bicarbonate supplementation and calcium metabolism in postmenopausal women: are we barking up the wrong tree? *Nutrition Reviews* 1994; **52**: 278–80.
- 139 Sebastian A, Harris ST, Ottaway JH, Todd KM, Morris RC. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *New England Journal of Medicine* 1994; **330**: 1776–81.
- 140 Bingham SA, Atkinson C, Liggins J, Bluck L, Coward A. Phyto-oestrogens: where are we now? *British Journal of Nutrition* 1998; **79**: 393–406.
- 141 Kardinaal AF, Morton MS, Bruggemann-Rotgans IE, van-Beresteijn EC. Phyto-oestrogen excretion and rate of bone loss in postmenopausal women. *European Journal of Clinical Nutrition* 1998; **52**: 850–5.
- 142 Ho SC, Chan SG, Yi Q, Wong E, Leung PC. Soy intake and the maintenance of peak bone mass in Hong Kong Chinese women. *Journal of Bone and Mineral Research* 2001; **16**: 1363–9.

- 143 Grainge MJ, Coupland CA, Cliffe SJ, Chilvers CE, Hosking DJ. Cigarette smoking, alcohol and caffeine consumption and bone mineral density in postmenopausal women. The Nottingham EPIC Study Group. *Osteoporosis International* 1998; **8**: 355–63.
- 144 Lloyd T, Johnson-Rollings N, Eggli DF, Kieselhorst K, Mauger EA, Cusatis DC. Bone status among postmenopausal women with different habitual caffeine intakes: a longitudinal investigation. *Journal of the American College of Nutrition* 2000; **19**: 256–61.
- 145 Conlisk AJ, Galuska DA. Is caffeine associated with bone mineral density in young adult women? *Preventative Medicine* 2000; **31**: 562–8.
- 146 Rapuri PB, Gallagher JC, Kinyamu HK, Ryschon KL. Caffeine intake increases the rate of bone loss in elderly women and interacts with vitamin D receptor genotypes. *American Journal of Clinical Nutrition* 2001; **74**: 694–700.
- 147 Parsons TJ, Prentice A, Smith EA, Cole TJ, Compston JE. Bone mineral mass consolidation in young British adults. *Journal of Bone and Mineral Research* 1996; **11**: 264–74.
- 148 Baumgartner RN, Stauber PM, Koehler KM, Romero L, Garry PJ. Associations of fat and muscle masses with bone mineral in elderly men and women. *American Journal of Clinical Nutrition* 1996; **63**: 365–72.
- 149 Honkanen R, Kroger H, Alhava E, Turpeinen P, Tuppurainen M, Saarikoski S. Lactose intolerance associated with fractures of weight-bearing bones in Finnish women aged 38–57 years. *Bone* 1997; **21**: 473–7.
- 150 Harma M, Alhava E. Is lactose malabsorption a risk factor for fractures of the elderly? *Annales Chirurgiae et Gynaecologiae* 1988; **77**: 180–3.
- 151 Goulding A, Taylor RW, Keil D, Gold E, Lewis-Barned NJ, Williams SM. Lactose malabsorption and rate of bone loss in older women. *Age and Ageing* 1999; **28**: 175–80.