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Symposium on 'Dietary management of disease'

Session 2: Other diseases
Dietary management of osteoporosis throughout the life course

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Osteoporosis-related fractures have a major impact on health at the individual and societal levels, through associated morbidity and increased mortality. Up to 50% of women and 20% of men at age 50 years may have a fragility fracture in their remaining lifetimes. Nutrition is important throughout the life course. Thus, adequate Ca and vitamin D intake has been shown to reduce risk of fracture in old age. Other factors such as protein and vitamin K may also be important, although the evidence here is less strong. In childhood Ca or vitamin D supplementation trials have demonstrated modest short-term increases in bone mass, but the long-term implications have not been established. Over recent years it has become apparent that maternal nutrition may have critical and far-reaching persistent consequences for offspring health. Thus, reduced maternal fat stores and low levels of circulating 25-hydroxyvitamin D in pregnancy are associated with reduced bone mass in the offspring; placental Ca transport may be key to these relationships. Wider maternal dietary patterns have also been shown to predict offspring bone mass. These data suggest that an interventional approach aimed at specific micronutrients, such as vitamin D, should be complemented by general optimisation of the mother's diet and lifestyle in order to maximise intrauterine bone mineral accrual and postnatal skeletal growth and thus reduce the burden of osteoporotic fractures in future generations.

Osteoporosis: Nutrition and bone health: Conception to old age

Epidemiology of osteoporotic fracture

Osteoporosis is a skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture[1]. These fractures typically occur at the hip, spine and wrist. It has been estimated that at age 50 years the remaining lifetime risk of fracture at one of these sites is 50% among women and 20% among men[2]. Osteoporotic fracture has a huge impact economically, in addition to its effect on health. Osteoporotic fracture costs the USA approximately US$17·9 \times 10^9$/year, with the cost in the UK being £1·7 \times 10^9$/year[3]. Hip fractures contribute most to these costs.

In most populations the occurrence of hip fractures increases exponentially with age. Overall, approximately 98% of hip fractures occur among individuals aged >35 years and 80% occur in women[2]. Hip fracture rates are highest in Caucasian women living in temperate climates and appear to be lower in women from Mediterranean and Asian countries, with the lowest rates in African women[4]. Data from the European Vertebral Osteoporosis Study have shown an age-standardised population prevalence of vertebral fracture across Europe of 12·2% for men and 12·0% for women aged 50–79 years of age[5]. Wrist fractures show a different pattern of occurrence from hip and vertebral fractures, with a plateau in risk after 60 years of age.

Future projections

With life expectancy increasing around the globe, the number of elderly individuals is rising in every geographic region. These demographic changes alone can be expected to increase the number of hip fractures occurring among

Abbreviations: BMC, bone mineral content; BMD, bone mineral density.

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individuals aged >35 years. Osteoporosis is therefore a disease that has a huge effect on public health, with an increasing burden as the elderly population rises. Identifying risk factors for the development of osteoporosis throughout the life course at the level of the population, such as poor nutrition, may have a marked effect on the burden of the disease.

Nutrition throughout the life course

Older age

Poor nutrition is evident in many elderly patients presenting with hip fracture and these patients tend to recover faster from hip surgery when given nutritional supplements[6,7]. These findings suggest that malnutrition may have contributed to the poor bone health of the patients with fractures.

Calcium and vitamin D intake in the elderly. The most important nutrients for bone health are Ca and vitamin D, and most studies of fracture risk in the elderly have tended to focus on these key factors. Intake of Ca and vitamin D in the elderly may be reduced for many reasons including inadequate diet associated with a declining appetite and diminishing alimentary absorption, as well as avoidance of certain foods such as dairy products that are perceived as fattening or causing a rise in their cholesterol level. Additionally, the elderly tend to spend more time indoors and as a consequence lack sunlight exposure, reducing their ability to synthesise vitamin D[8].

Ca is one of the main mineral constituents of bone and an appropriate supply is needed at all stages throughout the life course. Vitamin D is essential for absorption of Ca from the diet. A deficiency of either Ca or vitamin D causes reduced absolute or fractional Ca absorption, resulting in a lower concentration of circulating ionised Ca and a consequent rise in parathyroid hormone levels. This secondary hyperparathyroidism alters bone remodelling and results in a marked loss of bone and an increase in fracture risk. Historically, 25-hydroxyvitamin D insufficiency has been defined as a level of <20 ng/ml (50 nmol/l). Parathyroid hormone levels tend to rise when 25-hydroxyvitamin D levels reach 30–40 ng/ml (75–100 nmol/l). A level of 25-hydroxyvitamin D of 21–29 ng/ml (50–80 nmol/l) corresponds to changes in intestinal Ca absorption[9]. Thus, more recent suggestions are a level of approximately 75–80 nmol/l for 25-hydroxyvitamin D insufficiency[9].

Vitamin D insufficiency in the elderly has been linked to age-related bone loss and osteoporotic fracture. The mechanism may be through secondary hyperparathyroidism, although muscle weakness associated with vitamin D insufficiency may also be important. Vitamin D insufficiency is common in countries outside the tropics because of the lack of sunlight exposure; this situation is particularly evident in the winter months. Several studies have reported a high prevalence of vitamin D insufficiency or deficiency in the older populations, particularly amongst those who are institutionalised, of several European countries[10,11].

There have been several large randomised controlled trials in the elderly that have investigated the effects of Ca and vitamin D supplementation on the prevention of fractures and bone loss. In 2005 the MRC RECORD trial group studied 5292 patients with low-trauma fracture aged ≥70 years who were mobile pre-fracture. Subjects were randomly assigned to receive: 20 µg daily oral cholecalciferol; 1000 mg Ca; oral cholecalciferol (20 µg/d) combined with Ca (1000 mg/d); placebo[12]. With no difference in fracture incidence between the groups, the study does not support routine oral supplementation with Ca and cholecalciferol, either alone or in combination, for the secondary prevention of further fractures in previously-mobile elderly individuals. In addition, the Wessex Fracture Prevention Study has reported that an annual intramuscular injection of 7·5 mg ergocalciferol is not effective in preventing non-vertebral fractures among elderly men and women resident in the general population[13]. In contrast, previous studies do show an effect of combined Ca and vitamin D on fracture prevention[14–16]; these studies involved older and frailer participants who were mostly institutionalised and therefore more likely to have vitamin D insufficiency and secondary hyperparathyroidism. A recent meta-analysis of twenty-nine randomised controlled trials that included participants aged >50 years suggests that Ca alone or in combination with vitamin D is effective for the prevention of osteoporotic fracture. The fracture-risk reduction is greatest in individuals who are elderly, live in institutions, have a low body weight and have a low-Ca diet or are at a higher baseline risk than in others[17].

Ca is probably a threshold nutrient, i.e. there is a level of intake below which skeletal Ca accumulation is a function of intake and above which skeletal Ca accumulation is constant, irrespective of further increasing intakes[18]. This type of threshold behaviour is important in determining optimal dietary intake and supports targeting nutritional supplements to those whose intake is poor rather than the population as a whole.

Overall, the cumulative evidence suggests that supplementation with Ca and vitamin D in those individuals at high risk of nutritional deficit is an effective strategy in preventing age-related bone loss and osteoporotic fracture. However, routine supplementation of the general population does not appear to be warranted.

Protein intake and bone health. Protein makes up approximately 50% of the volume of bone and about one-third of its mass; this bone matrix protein undergoes continuous turnover and remodelling and thus a daily supply of dietary protein is required for bone maintenance[19]. However, the relationship between dietary protein and bone metabolism remains controversial, as a number of studies have identified protein as being either detrimental or beneficial to bone health. There are good data to show that protein undernutrition is a risk factor for bone loss and in addition is a concern for patients with hip fracture; one study has shown that supplementing with dietary protein post hip fracture is associated with improved clinical outcome and a lower rate of complications[20]. Although high protein intake has also been suggested as a risk factor for osteoporosis through increased acid-load-induced renal Ca loss, this outcome may not actually be associated with increased bone resorption[21]. With the exception of trials

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of dairy products, there are no randomised controlled trials that have specifically tested the effects of protein supplements on bone health and only intervention studies could reliably address this question.

Other nutrients. Various vitamin K-related abnormalities have been described in association with osteoporosis; however, the pathogenesis remains unclear. Three vitamin K-dependent proteins are found in bone matrix, of which osteocalcin is unique to bone. Osteocalcin binds to hydroxyapatite and is chemotactic for bone-resorbing cells[22]. In vitamin K deficiency serum osteocalcin levels decline and may result in detectable skeletal effects. Circulating vitamin K levels have been found to be low in patients with hip fracture, and in addition urine Ca levels have been reported to be high in some patients with osteoporosis, which can be corrected with physiological doses of vitamin K[22]. Vitamin K may be important for bone health; however, further work is needed to investigate this relationship.

Other essential nutrients for bone health include Mg, trace minerals, Cu and Zn, although only limited data are currently available. The role of Mg in bone health will be discussed further in the present review in relation to maternal diet in pregnancy and childhood bone mass.

Middle life

In young adulthood and middle life (third to fifth decade) major nutritional deficiencies are less common and supplementation to maintain bone health may be of less critical importance than in the young or elderly[8]. Consuming a healthy balanced diet and participating in regular weight-bearing exercise are important factors in maintaining bone mass throughout middle life. However, when women approach the menopause these measures may no longer be sufficient, since massive bone loss may occur once the bone-conserving effects of oestrogens are lost.

A number of epidemiological studies have evaluated the relationship between Ca intake and bone density in post-menopausal women with differing results. Several studies have concluded that Ca supplementation within 5 years of the menopause has little or no effect on bone mineral density (BMD)[23]. Where reductions in the rate of bone loss have been noted, the effects are generally short lived and limited to areas of the skeleton rich in cortical bone[10,24,25]. However, a review of over twenty studies in post-menopausal women does conclude that Ca supplementation could decrease bone loss by approximately 1 %/year[26]. In post-menopausal women the positive effect of total Ca intake on BMD seems to be greater at skeletal sites with more cortical bone such as the hip and femoral neck. A study of post-menopausal Chinese women has shown that a Ca intake >900 mg/d is helpful in the prevention of cortical bone loss[27].

Children

Bone mass (a composite measure including contributions from bone size and from its volumetric mineral density) increases throughout childhood and early adulthood to reach a peak in early adulthood. The bone mass of an individual later in life depends on the peak attained after skeletal growth and the subsequent rate of bone loss[28]. Peak bone mass is a major determinant of later osteoporosis risk, accounting for half the variance in BMD at age 70 years[29]. More recent work has demonstrated that peak bone mass is a sixfold more powerful predictor of age of onset of osteoporosis than rate of bone loss or age at menopause[30]. In addition, there are now data available that directly link growth rates in childhood to the risk of later hip fracture[31]. Peak bone mass is determined by a variety of environmental and genetic factors including nutrition, exercise, hormonal factors and the intrauterine environment.

Fractures are common in children, particularly at the wrist. Most childhood fractures occur during play and sport and result from mild to moderate trauma; however, children who have experienced one fracture tend to be at increased risk of repeated fracture and to have a lower BMD than their peers[32,33]. These findings suggest that there may be an underlying tendency in some children that may be related to genetic inheritance, poor nutrition or other environmental factors. Adequate nutrition in childhood is therefore essential to optimise the development of strong healthy bones that have a low risk of fragility fracture during childhood and later life.

Calcium intake in children The earliest data suggesting an influence of dietary Ca on peak bone mass came from a study of two Croatian populations with substantially different Ca intakes. The differences seen in bone mass were found to be present at age 30 years, suggesting that the effects of dietary Ca probably occur during growth rather than adulthood[34]. In addition, some epidemiological studies have shown an increased prevalence of osteoporosis in regions in which dietary Ca intake is low[35].

The nature of infant feeding has been shown to influence bone mineral accrual, with a positive correlation between mineral content in the feed and infant bone mass[36]. Much of this work has been carried out in premature infants, who tend to be small and have reduced BMD. Studies of premature infants randomised to formulas of differing Ca concentrations have shown short-term increases in bone mineral accrual with the higher Ca concentrations[37]. However, at follow up in later childhood there are no differences in bone mass when adjusted for body size between the different feeding regimens[38]. There are very few data for term infants, but one such study has found that, although at 6 months infants fed a high-Ca formula have greater BMD that those fed breast milk, these differences disappear after a further 6 months during which they had all received normal formula[39], which is consistent with postnatal tracking along the growth trajectory. In addition, a recent study of 599 mother–child pairs recruited from the Southampton Women's Survey does not show an association between duration of breast-feeding in the first year of life and 4-year bone size or density[40].

Although it is intuitively reasonable to suppose that increasing Ca intake during childhood and adolescence will be associated with greater accrual of bone mass, the evidence relating dietary Ca intake to bone mass among children and young adults has been inconsistent. The most convincing evidence that Ca consumption influences rates of bone mineral accrual comes from controlled

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supplementation trials in young healthy subjects. These studies have shown that subjects given additional Ca, whether as Ca salts, milk minerals or dairy products for 1–7 years have greater gains than controls[41–45]; however, overall these gains are small. Although bone size increases as a result of added dietary Ca, the response to Ca varies with skeletal site, pretreatment Ca consumption and pubertal stage. Greater bone mineral gains have been reported at cortical skeletal sites in prepubertal subjects and in girls whose habitual dietary intake is <850 mg/d[41,44]. It is not yet known whether these short-term increases will translate into clinically-relevant reduction in osteoporosis risk. Most studies have suggested that the beneficial effect of Ca supplementation does not persist and report that the benefits of intervention cease once the treatment has finished[46,47]. However, in some studies, mainly using milk-derived supplements, benefits have been shown to persist 12 months after discontinuation[48]. Scientifically, there are credible explanations for these observations; a large proportion of bone is protein and milk provides a ready supply. Bone mineral is composed of calcium hydroxyapatite, which contains Ca and phosphate, and milk contains this particular Ca salt. Additionally, milk provides other growth-promoting factors such as insulin-like growth factor 1.

Vitamin D intake in children. Vitamin D is a key hormone for the regulation of bone growth and mineralisation during life and insufficiency may result in rickets or osteomalacia. Breast-fed infants may be prone to vitamin D insufficiency since the breast milk content of vitamin D is related to the lactating mother's vitamin D status. Vitamin D insufficiency is common in women of child-bearing age; in one study of young white Caucasian women in Southampton 31% of women were found to have levels of 25-hydroxyvitamin D <20 ng/ml, with 17% having levels <10 ng/ml[49].

The association between 25-hydroxyvitamin D concentration and bone mineral content (BMC) in infants has been examined in two randomised controlled trials with differing results[50,51]. Both trials involved supplementing breast-fed infants with 10 μg vitamin D or a placebo and then following them for the first 6 months of life. In the smaller study the BMC was found to increase compared with the placebo at 3 months but not at 6 months[50]. However, in the second larger study BMC was shown to be higher in the placebo group than in the vitamin D group[51]. It is difficult to extrapolate recommendations from these results; however, the American Academy of Paediatrics currently recommends daily vitamin D supplements of 10 μg/l for breast-fed infants, which should continue through childhood to maintain serum 25(OH)-vitamin D concentrations ≥50 nmol/l[52]. These data are not based on robust dose–response data and the optimal dose of vitamin D has yet to be determined.

In older children and adolescents lower vitamin D concentrations have been shown to have unfavourable effects on bone mineralisation[53]. A few studies have examined vitamin D supplementation and areal BMD or BMC as a functional outcome. In a retrospective cohort study of 149 healthy prepubertal Caucasian girls (age 7–9 years) who were all breast-fed, those who were supplemented with 10 μg vitamin D/d in the first year of life were reported to have a higher BMC at the hip than those not supplemented[54].

A small placebo-controlled study of Finnish girls aged 10–12 years who were randomised to receive 5 μg vitamin D/d supplements with or without Ca (1000 mg) were not found to have any beneficial effects on BMD[44]. However, the study was limited by the number of subjects. A further Finnish trial has examined the effects of vitamin D supplementation on BMC in 228 adolescent girls (aged 11–12 years) with adequate Ca intake. Subjects were randomised to placebo, 5 μg or 10 μg vitamin D/d. BMC was reported to increase in a dose-dependent manner in both the femur and lumbar spine of participants in the supplemented groups who had consumed ≥80% of the vitamin D supplements[55]. A randomised controlled trial of vitamin D replacement (weekly oral doses of 35 μg, 350 μg or placebo) in 179 girls aged 10–17 years has reported in the overall group of girls an increase in bone area and total hip BMC in the high-dose treatment group[56]. Consistent trends were found in the premenarchal girls for increments in BMD and/or BMC at several skeletal sites, reaching significance at the lumbar spine in the low-dose group and at the trochanter in both treatment groups. It was concluded that vitamin D replacement has a positive impact on musculoskeletal variables in girls, especially during the premenarchal period.

Fruit and vegetable intake in children. Although most studies have focused on the effect of Ca and vitamin D on bone accrual, there is increasing evidence to suggest a role for dietary fruit and vegetable intake. The first reported cross-sectional data that have shown a positive link between the consumption of fruit and vegetables and BMD are from a study of 10-year-old girls[57]. Further work in girls aged 8–13 years has found a positive association between fruit and vegetable consumption and bone area and BMD[58]. A positive association with whole-body BMC has also been seen in a study of boys aged 8–20 years[59]. A possible explanation to account for some of this effect is that fruit and vegetables provide organic salts of K and Mg that have a buffering effect against the acid load from the ingestion of Western-type diets, which is believed to lead to bone loss[60,61]. Natural antioxidants and phytoestrogen compounds in some vegetables may also have some bone protective effects[62]. Alternatively, high intake of fruit and vegetables may be a marker of some other bone-favourable factor.

The developmental origins of osteoporotic fracture: the role of nutrition

There is now growing evidence for the importance of the intrauterine and early-life environment in the determination of adult health and disease in human subjects. The concept reflects a phenomenon ubiquitous in the natural world, i.e. developmental plasticity, which is the ability of a single genotype to give rise to several different phenotypes, thus allowing the organism to adapt future generations to prevailing environmental conditions. In human subjects the importance of the intrauterine environment

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was initially demonstrated with associations between birth weight and blood pressure, lipid levels and diabetes later in life. This phenomenon was termed 'programming', and defined as 'persisting changes in structure and function caused by adverse environmental influences at a critical stage of early development'[63,64].

Evidence that the risk of osteoporosis might be modified by environmental influences in early life comes from two groups of studies: first, bone mineral measurements undertaken in cohorts of adults whose detailed birth and/or childhood records have been preserved; second, mother–offspring cohorts relating the nutrition, body build and lifestyle of pregnant women to the bone mass of their offspring[65]. Maternal factors that have been shown to influence neonatal bone mass include low maternal fat stores, last-trimester vigorous exercise, maternal smoking in late pregnancy and low maternal birth weight, all of which predict a lower whole-body BMC in the neonate as measured by dual-energy X-ray absorptiometry scanning soon after birth[66].

The key nutrients likely to influence fetal bone development include Ca and vitamin D. Protein nutrition is also likely to be of fundamental importance in bone development, although there are very few data linking this factor directly. The remainder of the present review will summarise the evidence relating maternal nutrition to fetal bone development, focusing mainly on Ca and vitamin D.

The role of maternal Ca and other minerals

The human fetus requires a total of 30 g Ca for bone development, most of which is acquired during the third trimester via active transport across the placenta, resulting in greater Ca concentration in the fetus than maternal plasma[67]. Fetal Ca needs are primarily met by increased maternal intestinal Ca absorption during pregnancy and therefore very low maternal Ca intakes may be a risk for lower bone mass in neonates.

There are only a few trials of Ca in pregnancy and most have been largely focused on preventing pre-eclampsia. Few studies exist with maternal or neonatal bone mass as an outcome. One study of 797 pregnant rural Indian women (for whom vitamin D levels were generally adequate and baseline Ca intake low) has shown that the children of women with a higher frequency of intake of Ca-rich foods during pregnancy have higher total and spine BMC and BMD, independent of parental size and dual-energy X-ray absorptiometry measurements[68]. A further study of eighty-seven pregnant Indian women has shown that babies born to mothers supplemented with 300 and 600 mg elemental Ca daily from the 20th week of gestation onward until term have greater bone density at birth compared with babies of mothers not receiving supplements[69]. In an American study of healthy mothers maternal Ca supplementation of ≤ 2 g/d during the second and third trimesters has been shown to be associated with an increase in fetal bone mineralisation in women with low dietary Ca intake (<600 mg/d). However, the study concludes that Ca supplementation in pregnant women with adequate dietary Ca intake is unlikely to result in major improvement in fetal bone mineralisation[70].

The Avon Longitudinal Study of Parents and Children has assessed the relationship between maternal diet during pregnancy and childhood bone mass at 9 years of age and has found associations between maternal Mg intake and total body BMD and BMD in the offspring[71]. The precise mechanisms by which maternal Mg intake might affect growth in early life are currently unclear, although there is some evidence to suggest it may be a result of effects on fetal Ca homeostasis[72–75]. Increased maternal Mg intake has the potential to lower maternal serum Ca concentration, since Mg is known to compete with Ca for binding to the Ca-sensing receptor, which in turn may lead to a reduction in parathyroid hormone secretion. A reduction in maternal Ca levels may limit the bioavailability of Ca to the fetus and this outcome may cause a compensatory increase in fetal levels of parathyroid hormone-related peptide. Parathyroid hormone-related peptide regulates placental Ca transport and in addition enhances longitudinal growth of the fetus by delaying chondrocyte differentiation[72].

The role of maternal vitamin D

The earliest work yielding an insight into the importance of vitamin D in early life came from a retrospective cohort study of 8-year-old girls. The girls who had been supplemented with vitamin D as babies were found to have a higher BMD at the radial metaphysis, femoral neck and femoral trochanter than those who had not been supplemented[54]. More recent work in a Southampton mother–offspring cohort study has demonstrated that maternal vitamin D insufficiency is common during pregnancy (31 %) and is associated with reduced bone mineral accrual in the healthy term offspring at age 9 years (Fig. 1)[76]. This association appears to be influenced, at least in part, by concentrations of umbilical cord venous Ca adjusted for albumin. In other work maternal vitamin D deficiency in pregnancy has been associated with neonatal hypocalcaemia, enamel hypoplasia of the teeth and other adverse birth outcomes such as craniotabes and widened growth plates[77,78]. Similar findings relating maternal 25-hydroxyvitamin D to offspring bone mass have come from the Southampton Women's Survey, a large ongoing cohort study investigating nutrition and growth in pregnancy. In this study of 556 healthy term neonates and their mothers maternal serum 25-hydroxyvitamin D levels were measured in late pregnancy and a positive association with bone size was found in the offspring when assessed by dual-energy X-ray absorptiometry at birth[79].

There have only been a small number of studies examining the effects of vitamin D supplementation in pregnancy and so far only one has examined bone mass at birth. In this small study of nineteen Asian mothers who had taken 25 μg vitamin D/d no difference was found in radial BMC of the offspring compared with controls[80]. However, the study is limited by the small numbers and also because of the poor sensitivity of the single-photon absorptiometry in measuring the tiny amount of bone mineral in the baby's distal radius.

The mechanism underlying the association between maternal 25-hydroxyvitamin D, umbilical cord Ca concentration and offspring bone mass is unclear but is an area

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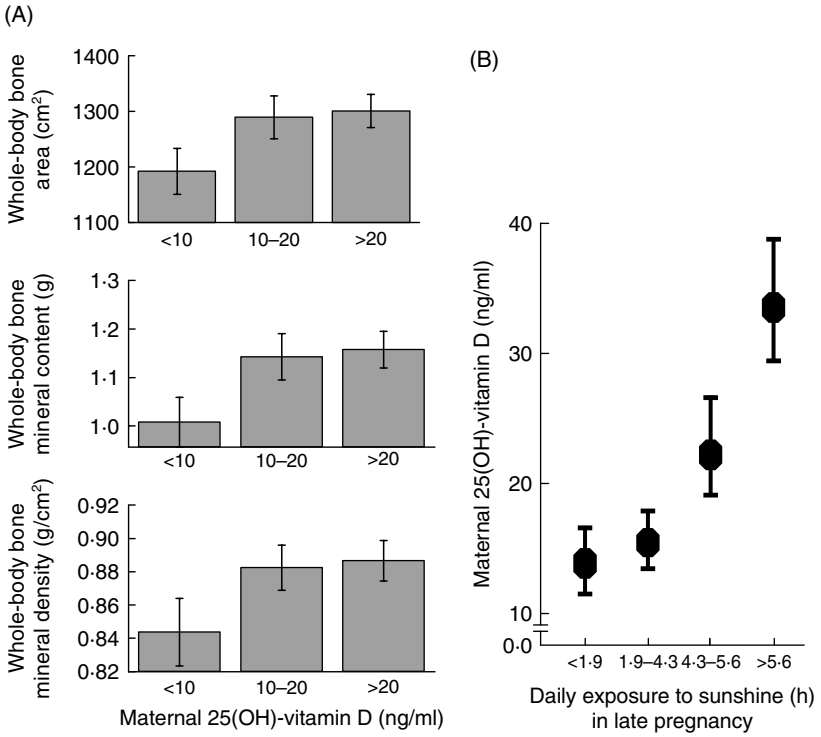

Fig. 1. (A) Maternal 25-hydroxyvitamin D (25(OH)-vitamin D) status in pregnancy and offspring whole-body bone area, bone mineral content and areal bone mineral density at 9 years old. Values are means and 95% CI represented by vertical bars. (B) Period of sunshine (h) per d and maternal 25(OH)-vitamin D status in late pregnancy. Values are means and 95% CI represented by vertical bars. Spearman's rank r 0·60, $P<0·001$. (From Javaid *et al.*[49].)

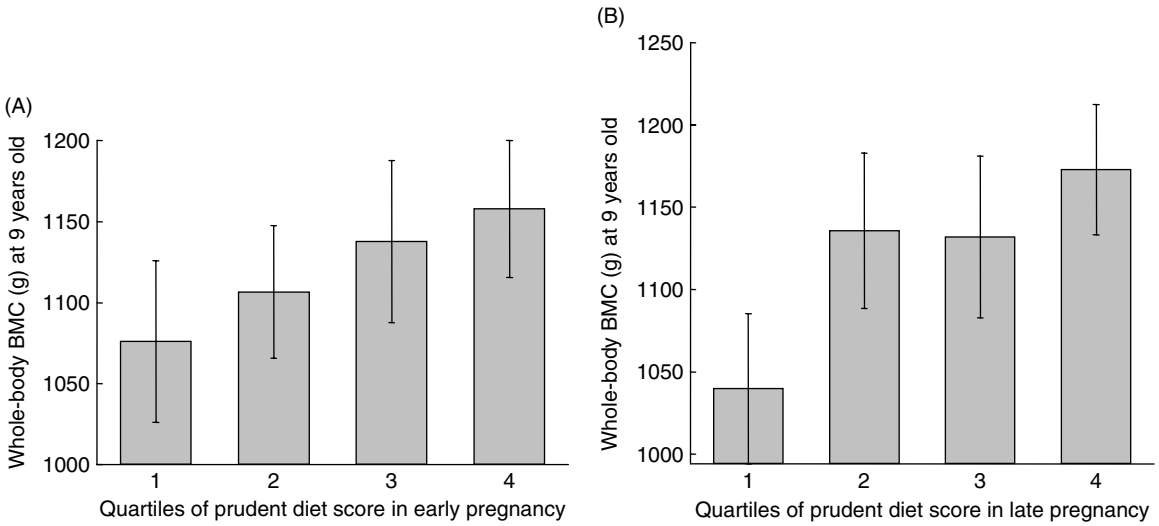

Fig. 2. Maternal prudent diet score in early (A) and late (B) pregnancy and offspring whole-body bone mineral content (BMC) at age 9 years (a high maternal prudent diet score represents high intakes of fruit and vegetables, wholemeal bread, rice and pasta, yoghurt and breakfast cereals and low intakes of chips and roast potatoes, sugar, white bread, processed meat, crisps, tinned vegetables and soft drinks). Values are means and 95% CI represented by vertical bars. (A) R 0·17, $P = 0·01$; (B) R 0·25, $P = 0·001$. (Adapted from Cole *et al.*[82].)

of ongoing research. One study has demonstrated that the expression of placental Ca transporter PMCA3 mRNA predicts neonatal whole-body BMC[81]. Modified expression of the genes encoding placental Ca transporters might represent the means whereby maternal 25-hydroxyvitamin D status could influence bone mineral accrual in the

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neonate. The Maternal Vitamin D Osteoporosis Study is a randomised controlled trial of vitamin D supplementation during pregnancy (ISRCTN82927713) and is currently recruiting participants. The study aims to test the hypothesis that vitamin D supplementation of pregnant women who have low levels of vitamin D will result in improved neonatal BMC. In addition, sub-studies of the Maternal Vitamin D Osteoporosis Study will help to gain further understanding into the mechanism of placental Ca transfer and the influence of vitamin D.

Other maternal dietary factors

In most studies maternal diet has been considered in terms of intake of specific nutrients, such as Ca and vitamin D. However, these nutrients comprise parts of broader dietary patterns and one recent study has explored maternal diet in more detail in relation to skeletal health in the offspring (Fig. 2). The study utilised the Princess Anne Cohort, Southampton, UK and examined dietary patterns in 198 pregnant women aged 17–43 years[82]. Dietary pattern was assessed using principal component analysis from a validated FFQ. The offspring underwent measurements of bone mass using dual-energy X-ray absorptiometry at age 9 years. The results of the study suggest that the pattern of maternal diet during pregnancy is an independent determinant of bone mineral accrual in the offspring. A high maternal prudent diet score (high intakes of fruit and vegetables, wholemeal bread, rice and pasta, yoghurt and breakfast cereals and low intakes of chips and roast potatoes, sugar, white bread, processed meat, crisps, tinned vegetables and soft drinks) was found to be associated with greater bone size and areal BMD in the offspring. The observed effect was shown to be independent of social class, education, maternal height, maternal smoking status and late pregnancy vitamin D levels as well as childhood height, weight and exercise. These findings further strengthen the importance of a healthy balanced diet during pregnancy.

Conclusions

Osteoporosis constitutes a major public health problem through its association with fragility fractures. There is now convincing longitudinal evidence that a reduction in bone density is an important determinant of fracture risk. The main determinants of bone density include peak bone mass and the subsequent rate of bone loss, and both these factors can be influenced by nutrition. The most important nutrients for adequate bone health include Ca and vitamin D; however, other dietary factors such as vegetable and protein intake may also have a role, although there is less evidence available. Recent work has demonstrated that maternal nutrition, particularly circulating 25-hydroxyvitamin D status during pregnancy, may lead to reduced intrauterine bone mineral accrual in the offspring[76], and poor infant growth has been associated with increased risk of hip fracture in later life[31]. Thus, adequate nutrition is essential for optimal bone health at all stages of the life course, from conception to old age.

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References

1. Harvey N, Dennison E & Cooper C (2008) Epidemiology of osteoporotic fracture. In *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, 7th ed., pp. 198–203 [MJ Favus, editor]. Washington, DC: American Society for Bone and Mineral Research.
2. Van Staa TP, Dennison EM, Leufkens HG *et al.* (2001) Epidemiology of fractures in England and Wales. *Bone* **29**, 517–522.
3. Department of Health (1994) *Advisory Group on Osteoporosis – Report*. London: Department of Health.
4. Ellfors L, Allander E, Kanis JA *et al.* (1995) The variable incidence of hip fracture in southern Europe. The MEDOS study. *Osteoporosis Int* **4**, 253–263.
5. O'Neill TW, Felsenberg D, Varlow J *et al.* (1996) The prevalence of vertebral deformity in European men and women: The European Vertebral Osteoporosis Study. *J Bone Miner Res* **11**, 1010–1018.
6. Diamon T, Smerddely P, Kormas N *et al.* (1998) Hip fracture in elderly men: the importance of subclinical vitamin D deficiency and hypogonadism. *Med J Aust* **169**, 138–141.
7. Schurch MA, Rizzoli R, Slosman D *et al.* (1998) Protein supplements increase serum insulin-like growth factor 1 levels and attenuate proximal femur bone loss in patients with recent hip fracture – a randomised, double-blind, placebo-controlled trial. *Ann Intern Med* **128**, 801–809.
8. Goulding A & Grant A (2007) Nutritional strategies to optimize bone health throughout the life course. In *Managing Osteoporosis*, pp. 3–20 [SA Lanham-New, T O'Neill, R Morris, D Skeleton and A Sutcliffe]. Oxford: Clinical Publishing.
9. Holick MF (2007) Vitamin D deficiency. Review article. *N Engl J Med* **357**, 266–281.
10. Department of Health (1998) *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* no. 49. London: The Stationery Office.
11. Chapuy MC, Preziosi P & Mamer M (1997) Prevalence of vitamin D insufficiency in adult normal population. *Osteoporosis Int* **7**, 439–443.
12. Grant AM, Avenell A & Campbell MK (2005) Oral vitamin D3 and calcium for the secondary prevention of low-trauma fracture in elderly people (Randomised Evaluation of Calcium Or Vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet* **365**, 1621–1628.
13. Smith H, Anderson F, Raphael H *et al.* (2007) Effect of annual intramuscular vitamin D on fracture risk in elderly men and women – a population-based, randomized, double-blind, placebo-controlled trial. *Rheumatology* **46**, 1852–1857.

https://doi.org/10.1017/S0029665109991765 Published online by Cambridge University Press

14. Chapuy MC, Arlot ME, Delmas PD *et al.* (1994) Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *Br Med J* **308**, 1081–1082.
15. Chapuy MC, Arlot ME, Duboeuf F *et al.* (1992) Vitamin D3 and calcium to prevent hip fractures in elderly women. *N Engl J Med* **327**, 1637–1642.
16. Chapuy MC, Pamphile R, Paris E *et al.* (2002) Combined calcium and vitamin D3 supplementation in elderly women: confirmation of the reversal of secondary hyperparathyroidism and hip fracture rick: the Decalyos II study. *Osteoporosis Int* **13**, 257–264.
17. Tang BM, Eslick GD, Nowson C *et al.* (2007) Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years or older: a meta analysis. *Lancet* **370**, 657–666.
18. Matkovic V & Heaney RP (1992) Calcium balance during human growth: evidence for threshold behaviour. *Am J Clin Nutr* **55**, 992–996.
19. Heaney RP & Layman DK (2008) Amount and type of protein influences bone health. *Am J Clin Nutr* **87**, 1567S–1569S.
20. Delmi M, Rapin CH, Bengoa JM *et al.* (1990) Dietary supplementation in elderly patients with fractured neck of femur. *Lancet* **335**, 1013–1016.
21. Kerstetter JE, O'Brien KO, Caseria DM *et al.* (2005) The impact of dietary protein on calcium absorption and kinetic measures of bone turnover in women. *J Clin Endocrinol Metab* **90**, 26–31.
22. Heaney RP (2001) Nutrition and risk for osteoporosis. *Osteoporosis*, 2nd ed., vol. 1, pp. 669–700 [R Marcus, D Feldman and J Kelsey, editors]. San Diego, CA: Academic Press.
23. Royal College of Physicians (1999) *Osteoporosis. Clinical Guidelines for Prevention and Treatment*. London: Royal College of Physicians.
24. Elders PJM, Lips P & Netelenbos JC (1994) Long-term effect of calcium supplements on bone loss in perimenopausal women. *J Bone Miner Res* **9**, 963–970.
25. Dawson-Hughes B, Dallal GE, Krall EA *et al.* (1990) A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N Engl J Med* **323**, 878–883.
26. Nordin BEC (1997) Calcium and osteoporosis. *Nutrition* **13**, 664–686.
27. Ho SC, Chen YM, Woo JL *et al.* (2004) High habitual calcium intake attenuates bone loss in early postmenopausal Chinese women: and 18 month follow up study. *J Clin Endocrinol Metab* **89**, 2166–2170.
28. Cooper C, Westlake S, Harvey N *et al.* (2005) Review: developmental origins of osteoporotic fracture. *Osteoporosis Int* **17**, 337–347.
29. Hui SL, Slemenda CW & Johnston CC Jr (1990) The contribution of bone loss to postmenopausal osteoporosis. *Osteoporosis Int* **1**, 30–34.
30. Hernandez CJ, Beaupre GS & Carter DR (2003) A theoretical analysis of the relative influences of peak BMD, age-related bone loss and menopause on the development of osteoporosis. *Osteoporosis Int* **14**, 843–847.
31. Cooper C, Eriksson JG, Forsen T *et al.* (2001) Maternal height, childhood growth and risk of hip fracture later in life: a longitudinal study. *Osteoporosis Int* **12**, 623–629.
32. Ferrari SL, Chevalley T, Bonjour JP *et al.* (2006) Childhood fragility fractures are associated with decreased bone mass gain during puberty: an early marker of persistent bone fragility? *J Bone Miner Res* **21**, 501–507.
33. Manias K, McCabe D & Bishop N (2006) Fractures and recurrent fractures in children; varying effects of environmental factors as well as bone size and mass. *Bone* **39**, 652–657.
34. Matkovic V, Kostial K, Simonovic I *et al.* (1979) Bone status and fracture rates in two regions of Yugoslavia. *Am J Clin Nutr* **32**, 540–549.
35. Heaney RP (1992) Calcium in the prevention and treatment of osteoporosis. *J Intern Med* **231**, 169–180.
36. Specker B (2004) Nutrition influences bone development from infancy through toddler years. *J Nutr* **134**, 691S–695S.
37. Bishop NJ, King FJ & Lucas A (1993) Increased bone mineral content of preterm infants fed with a nutrient enriched formula after discharge from hospital. *Arch Dis Child* **68** (5 Spec no.), 573–578.
38. Fewtrell MS, Prentice A, Jones SC *et al.* (1999) Bone mineralisation and turnover in preterm infants at 8–12 years of age: the effect of early diet. *J Bone Miner Res* **14**, 810–820.
39. Specker BL, Beck A, Kalkwarf H *et al.* (1997) Randomized trial of varying mineral intake on total body bone mineral accretion during the first year of life. *Pediatrics* **99**, E12.
40. Harvey NC, Robinson SM, Crozier SR *et al.* (2009) Breastfeeding and adherence to infant feeding guidelines do not influence bone mass at age 4 years. *Br J Nutr* **102**, 915–920.
41. Bonjour JP, Carrie AL, Ferrari S *et al.* (1997) Calcium-enriched foods and bone mass growth in prepubertal girls: a randomized, double-blind, placebo-controlled trial. *J Clin Invest* **99**, 1287–1294.
42. Matkovic V, Landoll JD, Badenhop-Stevens NE *et al.* (2004) Nutrition influences skeletal development from childhood to adulthood: a study of hip, spine, and forearm in adolescent females. *J Nutr* **134**, 701S–705S.
43. Zhu K, Du X, Cowell CT *et al.* (2005) Effects of school milk intervention on cortical bone accretion and indicators relevant to bone metabolism in Chinese girls aged 10–12 y in Beijing. *Am J Clin Nutr* **81**, 1168–1175.
44. Cheng S, Lyytikainen A, Kroger H *et al.* (2005) Effects of calcium, dairy product, and vitamin D supplementation on bone mass accrual and body composition in 10–12-y-old girls: a 2-y randomized trial. *Am J Clin Nutr* **82**, 1115–1126.
45. Cadogan J, Eastell R, Jones N *et al.* (1997) Milk intake and bone mineral acquisition in adolescent girls: randomised, controlled intervention trial. *Br Med J* **315**, 1255–1260.
46. Zhu K, Zhang Q, Foo LH *et al.* (2006) Growth, bone mass, and vitamin D status of Chinese adolescent girls 3 y after withdrawal of milk supplementation. *Am J Clin Nutr* **83**, 714–721.
47. Winzenberg T, Shaw K, Fryer J *et al.* (2006) Effects of calcium supplementation on bone density in healthy children: meta-analysis of randomised controlled trials. *Br Med J* **333**, 775.
48. Bonjour JP, Chevalley T, Ammann P *et al.* (2001) Gain in bone mineral mass in prepubertal girls 3·5 years after discontinuation of calcium supplementation: a follow-up study. *Lancet* **358**, 1208–1212.
49. Javaid MK, Crozier SR, Harvey NC *et al.* (2006) Maternal vitamin D status during pregnancy and childhood bone mass at 9 years: a longitudinal study. *Lancet* **367**, 36–43.
50. Greer FR, Searcy JE, Levin RS *et al.* (1982) Bone mineral content and serum 25-hydroxyvitamin D concentrations in breast-fed infants with or without supplemental vitamin D: one year follow-up. *J Pediatr* **100**, 919–922.
51. Greer FR & Marshall S (1989) Bone mineral content, serum vitamin D metabolite concentrations, and ultraviolet B light exposure in infants fed human milk and without vitamin D_2 supplements. *J Pediatr* **114**, 204–212.

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52. Greer FR (2008) 25-Hydroxyvitamin D: functional outcomes in infants and young children. *Am J Clin Nutr* **88**, Suppl., 529S–533S.
53. Cheng S, Tylavsky F, Kruger H *et al.* (2003) Association of low 25-hydroxyvitamin D concentrations with elevated parathyroid hormone concentrations and low cortical bone density in early pubertal and prepubertal Finnish girls. *Am J Clin Nutr* **78**, 485–492.
54. Zamora SA, Rizzoli R, Belli DC *et al.* (1999) Vitamin D supplementation during infancy is associated with higher bone mass in prepubertal girls. *J Clin Endocrinol Metab* **84**, 4541–4544.
55. Viljakainen HT, Natri A, Karkkainen M *et al.* (2006) A positive dose-response effect of vitamin D supplementation on site-specific bone mineral augmentation in adolescent girls: a double-blinded randomised placebo-controlled 1-year intervention. *J Bone Miner Res* **21**, 836–844.
56. El-Hajj Fuleihan, Nabulsi M, Tamin H *et al.* (2006) Effect of vitamin D replacement on musculoskeletal parameters in school children: a randomised controlled trial. *J Clin Endocrinol Metab* **91**, 405–412.
57. Jones G, Riley MD, Whiting S (2001) Association between urinary potassium, urinary sodium, current diet, and bone density in prepubertal children. *Am J Clin Nutr* **73**, 839–844.
58. Tylavsky FA, Holliday K, Danish R *et al.* (2004) Fruit and vegetable intakes are an independent predictor of bone size in early pubertal children. *Am J Clin Nutr* **79**, 311–317.
59. Vatanparast H, Baxter-Jones A, Faulkner RA *et al.* (2005) Positive effects of vegetable and fruit consumption and calcium intake on bone mineral accrual in boys during growth from childhood to adolescence: the University of Saskatchewan Pediatric Bone Mineral Accrual Study. *Am J Clin Nutr* **82**, 700–706.
60. Tucker KL, Chen H, Hannan MT *et al.* (2002) Bone mineral density and dietary patterns in older adults: the Framingham Osteoporosis Study. *Am J Clin Nutr* **76**, 245–252.
61. Feskanich D, Weber P, Willett WC *et al.* (1999) Vitamin K intake and hip fractures in women: a prospective study. *Am J Clin Nutr* **69**, 74–79.
62. Wangen KE, Duncan AM, Merz-Demlow BE *et al.* (2000) Effects of soy isoflavones on markers of bone turnover in premenopausal and postmenopausal women. *J Clin Endocrinol Metab* **85**, 3043–3048.
63. Barker DJ (1990) The fetal and infant origins of adult disease. *Br Med J* **301**, 1111.
64. Barker DJ (1995) The fetal and infant origins of disease. *Eur J Clin Invest* **25**, 457–463.
65. Cooper C, Westlake S, Harvey N *et al.* (2006) Review: developmental origins of osteoporotic fracture. *Osteoporosis Int* **17**, 337–347.
66. Godfrey K, Walker-Bone K, Robinson S *et al.* (2001) Neonatal bone mass: influence of parental birthweight, maternal smoking, body composition, and activity during pregnancy. *J Bone Miner Res* **16**, 1694–1703.
67. Namgung R & Tsang RC (2003) Bone in the pregnant mother and newborn at birth. *Clin Chim Acta* **333**, 1–11.
68. Ganpule A, Yajnik CS, Fall CHD *et al.* (2005) Bone mass in Indian children – relationships to maternal nutritional status and diet during pregnancy: the Pune Maternal Nutrition Study. *J Clin Endocr Metab* **91**, 2994–3001.
69. Raman L, Rajalakshmi K, Krishnamachari KA *et al.* (1978) Effect of calcium supplementation to undernourished mothers during pregnancy on the bone density of the neonates. *Am J Clin Nutr* **31**, 466–469.
70. Koo WW, Walters JC, Esterlitz J *et al.* (1999) Maternal calcium supplementation and fetal bone mineralisation. *Obstet Gynecol* **94**, 577–582.
71. Tobias JH, Steer CD, Emmett PM *et al.* (2005) Bone mass in childhood is related to maternal diet in pregnancy. *Osteoporos Int* **16**, 1731–1741.
72. Tobias JH & Cooper C (2004) PTH/PTHrP activity and the programming of skeletal development in utero. *J Bone Miner Res* **19**, 177–182.
73. McLarnon SJ & Riccardi D (2002) Physiological and pharmacological agonists of the extracellular calcium sensing receptor. *Eur J Pharmacol* **447**, 271–278.
74. Kovacs CS & Kronenberg HM (1997) Maternal-fetal calcium and bone metabolism during pregnancy, puerperium, and lactation. *Endocr Rev* **18**, 832–872.
75. Lanske B, Karaplis AC, Lee K *et al.* (1996) PTH/PTHrP receptor in early development and Indian hedgehog-regulated bone growth. *Science* **273**, 663–666.
76. Javaid MK, Crozier SR & Harvey NC (2006) Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. *Lancet* **367**, 36–43.
77. Purvis RJ, Barrie WJ, MacKay GS *et al.* (1973) Enamel hypoplasia of the teeth associated with neonatal tetany: a manifestation of maternal vitamin D deficiency. *Lancet* **ii**, 811–814.
78. Reif S, Katzir Y, Eisenberg Z *et al.* (1988) Serum 25-hydroxyvitamin D levels in congenital craniotabes. *Acta Paediatr Scand* **77**, 167–168.
79. Harvey NC, Javaid MK, Poole JR *et al.* (2008) Paternal skeletal size predicts intrauterine bone mineral accrual. *J Clin Endocr Metab* **93**, 1676–1681.
80. Congdon P, Horsman A, Kirby PA *et al.* (1983) Mineral content of the forearms of babies born to Asian and white mothers. *Br Med J* **286**, 1233–1235.
81. Martin R, Harvey NC, Crozier SR *et al.* (2007) Placental calcium transporter (PMCA3) gene expression predicts intrauterine bone mineral accrual. *Bone* **40**, 1203–1208.
82. Cole Z, Gale C, Javaid M *et al.* (2009) Maternal dietary patterns during pregnancy and childhood bone mass: A longitudinal study. *J Bone Miner Res* **24**, 663–668; Epublication 2 December 2008.

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