Developmental Origins of Osteoporotic Fracture: the Role of Maternal Vitamin D Insufficiency

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ABSTRACT Osteoporosis is a major cause of morbidity and mortality through its association with age-related fractures. Although most efforts in fracture prevention have been directed at retarding the rate of age-related bone loss and reducing the frequency and the severity of trauma among elderly people, evidence is growing that peak bone mass is an important contributor to bone strength during later life. The normal patterns of skeletal growth have been well characterized in cross-sectional and longitudinal studies. It has been confirmed that boys have higher bone-mineral content, but not volumetric bone density, than girls. Furthermore, there is a disassociation between the peak velocities for height gain and bone mineral accrual in both genders. Puberty is the period during which volumetric density appears to increase in both axial and appendicular sites. Many factors influence the accumulation of bone mineral during childhood and adolescence, including heredity, gender, diet, physical activity, endocrine status, and sporadic risk factors (e.g., cigarette smoking). In addition to these modifiable factors during childhood, evidence has also accrued that fracture risk might be programmed during intrauterine life. Epidemiological studies have demonstrated a relationship between birth-weight, weight in infancy, and adult bone mass. This appears to be mediated through modulation of the set-point for basal activity of endocrine systems such as the GH/IGF-1 and parathyroid hormone/vitamin D axes. Maternal vitamin D insufficiency is associated with reduced bone mineral acquisition during intrauterine and early postnatal life. Furthermore, both low birth size and poor childhood growth are directly linked to the later risk of hip fracture. The optimization of maternal nutrition and intrauterine growth should also be included within preventive strategies against osteoporotic fracture, albeit for future generations. J. Nutr. 135: 2728S–2734S, 2005.

KEY WORDS: osteoporosis • epidemiology • growth • programming

Osteoporosis is a skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, which predisposes to fracture (1). These fractures typically occur at the hip, the spine, and the wrist. It has been estimated that the remaining lifetime risk of fracture at one of these three sites at age 50 y is 50% among women and 20% among men. In the United Kingdom, the annual cost to the National Health Service of managing osteoporotic fractures is £1.7 billion, with about 80% of this figure attributable to hip fracture. The risk of osteoporotic fracture ultimately depends on two factors: the mechanical strength of bone and the forces applied to it. Bone mass (a composite measure, including contributions from bone size and from its volumetric mineral density) is an established determinant of bone strength, and the bone mass of an individual in later life depends upon the peak attained during skeletal growth and the subsequent rate of bone loss. Several longitudinal studies attest to the tracking of bone mass through childhood and adolescence, and mathematical models suggest that modifying peak bone mass will have biologically relevant effects on skeletal fragility in old age. There is evidence to suggest that peak bone mass is inherited, but current genetic markers are able to explain only a small proportion of the variation in individual bone mass or fracture risk (2).

Environmental influences during childhood and puberty have been shown to benefit bone-mineral accrual, but the relatively rapid rate of mineral gain during intrauterine and early postnatal life, coupled with the plasticity of skeletal...
development in utero, offer the possibility of profound interactions between the genome and the early environment at this stage in the life course. There is a strong biological basis for such a model of disease pathogenesis. Experimentalists have repeatedly demonstrated that minor alterations to the diet of pregnant animals can produce lasting changes in the body build, the physiology, and the metabolism of the offspring (3). This is one example of a ubiquitous phenomenon (phenotypic or developmental plasticity), which enables one genotype to give rise to a range of different physiological or morphological states in response to different prevailing environmental conditions during development. Its essence lies in the critical period during which a system is plastic and sensitive to the environment, followed by a loss of that plasticity and a fixed functional capacity. The evolutionary benefit of the phenomenon is that in a changing environment, it maximizes phenotypic diversity and enables the production of phenotypes that are better matched to their environment than would be possible with the production of the same phenotype in all environments. This review will address the role played by influences during intrauterine or early postnatal life in establishing the risk of osteoporosis in later years. In particular, the role of maternal vitamin D insufficiency as a risk factor for intrauterine and early postnatal bone mineral accrual will be discussed.

Developmental origins of osteoporosis and fracture

Epidemiological studies of coronary heart disease performed over a decade ago demonstrated strong geographic associations between death rate from the disorder in 1968–1978, and infant mortality in 1901–1910 (4). Subsequent research, based on individuals whose birth records had been preserved for seven decades, revealed that men and women who were undernourished during intrauterine life and therefore had low birthweight or were thin at birth, had an increased risk for coronary heart disease, hypertension, noninsulin dependent diabetes, and hypercholesterolemia (5). These associations are explained by a phenomenon known as programming (6); this term describes persisting changes in structure and function caused by environmental stimuli acting at critical periods during early development. It is not in question that the human skeleton can be programmed by undernutrition. Rickets has served as a long-standing example of undernutrition at a critical stage of early life, leading to persisting changes in structure and function caused by environmental stimuli affecting at critical periods during early development. What is new is the realization that some of the body’s “memories” of early undernutrition become translated into pathology and thereby determine disease in later life (7). Evidence has now accumulated that such intrauterine programming contributes to the risk of osteoporosis in later life. Evidence that the risk of osteoporosis might be modified by environmental influences during early life stems from three groups of studies: a) bone mineral measurements undertaken in cohorts of adults whose detailed birth and/or childhood records have been preserved; b) studies characterizing the nutrition, the body build, and the lifestyle of pregnant women and relating these to the bone mass of their newborn offspring; and c) studies relating childhood growth rates to the later risk of hip fracture.

Epidemiological studies

The first epidemiological evidence that osteoporosis risk might be programmed came from a study of 153 women born in Bath during 1968–1969 who were traced and studied at age 21 y (8). Data on childhood growth were obtained from linked birth and school health records. There were statistically significant (P < 0.05) associations between weight at 1 y and bone mineral content (BMC),6 but not density, at the lumbar spine and the femoral neck; these relationships were independent of adult weight and body mass index. The data suggested a discordance between the processes that govern skeletal growth and those that influence mineralization. They also provided direct evidence that the trajectory of bone growth might be modified in utero, an assertion previously only supported by inference from measurements of body height. The association between weight in infancy and adult bone mass was replicated in subsequent cohort studies of men and women ages 60–75 y, who were born and still lived in Hertfordshire (9–11). These studies showed highly significant relationships between weight at 1 y and adult bone area at the spine and hip (P < 0.005); the relationships with BMC at these two sites were weaker but remained statistically significant (P < 0.02) (Fig. 1). They also remained after adjustment for known genetic markers of osteoporosis risk, such as polymorphisms in the gene for the vitamin D receptor (VDR) (12), and after adjustment for lifestyle characteristics in adulthood that might have influenced bone mass (physical activity, dietary calcium intake, cigarette smoking, and alcohol consumption). More detailed analyses of the interactions between polymorphism in the gene for the VDR (Bsm 1 polymorphism), birthweight, and bone mineral density (BMD) have recently been published from the same cohort study (13). In the cohort as a whole, there were no significant associations between either birthweight or VDR genotype and BMC. However, the relationship between lumbar spine BMC and VDR genotype varied according to birthweight (Fig. 2). Among individuals in the lowest third of birthweight, spine BMC was higher (P = 0.01) among individuals of genotype “BB” (the homozygous genotype generally associated with higher bone density) after adjustment for age, sex, and weight at baseline. In contrast, spine BMC was reduced (P = 0.04) in individuals of the same genotype who were in the highest third of the birthweight distribution. A statistically significant (P = 0.02) interaction was also found between VDR genotype and birthweight as determinants of BMD. These results suggest that genetic influences on adult bone size and mineral density may be modified by undernutrition in utero. Subsequent studies from the United States, Australia, and Scandinavia have replicated these relationships between weight in infancy and adult bone mass (Table 1). Finally, a recent twin study (14) evaluated the relationship between birthweight and bone mass among twins with a mean age of 47.5 y. Statistically significant relationships were found between the intrapair differences in birthweight and in BMC after adjustment for height and weight, even among monzygous twin pairs. These data suggest that even in genetically identical subjects, a relationship can be detected between birthweight and adult bone mass.

Maternal nutrition, lifestyle, and neonatal bone mineral

The second piece of epidemiological evidence that osteoporosis might arise, in part through developmental maladaptation, stems from investigation of a series of mothers through pregnancy; anthropometric and lifestyle maternal characteristics were related to the bone mineral of their newborn offspring (15). After adjusting for sex and gestational age, neonatal bone mass was strongly, positively associated with birthweight, birth length, and placental weight. Other deter-

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6 Abbreviations used: BMC, bone mineral content; BMD, bone mineral density; IGF, insulin-like growth factor; VDR, vitamin D receptor.
minants included maternal and paternal birthweight and maternal triceps skin-fold thickness at 28 wk (Fig. 3). Maternal smoking and maternal energy intake at 18 wk gestation were negatively associated with neonatal BMC at both the spine and the whole body (Fig. 4). The independent effects of maternal and paternal birthweight on fetal skeletal development support the notion that paternal influences, for example, through the imprinting of growth-promoting genes such as insulin-like growth factor 2 (IGF-2), contribute strongly to the establishment of the early skeletal growth trajectory, while maternal nutrition and body build modify fetal nutrient supply and subsequent bone accretion, predominantly through influences on placentation.

In the most recent data from mother/offspring cohorts, body composition has been assessed by dual energy X-ray absorptiometry in 216 children at age 9 y (16). They and their parents had previously been included in a population-based study of maternal nutrition and fetal growth. The nutrition, body build, and lifestyle of the mothers had been characterized during early and late pregnancy, and samples of umbilical venous blood had been obtained at birth. Reduced maternal height, lower preconceptional maternal weight, reduced maternal fat stores during late pregnancy, a history of maternal smoking and lower maternal social class were all associated with reduced whole body BMC of the child at age 9 y. Lower ionized calcium concentration in umbilical venous serum also predicted reduced childhood bone mass ($r = 0.19, P = 0.02$) (Fig. 5); this association appeared to mediate the effect of maternal fat stores, smoking and socioeconomic status on the bone mass of the children at age 9 y. About 25% of the mothers had suboptimal vitamin D status as assessed by serum 25-hydroxyvitamin D concentration (Fig. 6). The children born to these mothers had significantly ($P < 0.01$) reduced whole-body bone mineral content at age 9 y. This deficit in skeletal growth remained significant even after adjustment for childhood weight and bone area (16). These data suggest that the placental capacity to maintain the maternal-fetal calcium gradient is important in optimizing the trajectory of postnatal skeletal growth.

### Maternal vitamin D status and bone-mineral accrual in the offspring

Significant changes in maternal vitamin D and calcium metabolism occur during pregnancy to provide the calcium

<table>
<thead>
<tr>
<th>Site</th>
<th>Birthweight</th>
<th>Weight at 1 y</th>
<th>correlation coefficients (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.15 (0.10–0.20)</td>
<td>0.25 (0.19–0.32)</td>
<td></td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.12 (0.07–0.18)</td>
<td>0.20 (0.14–0.27)</td>
<td></td>
</tr>
<tr>
<td>Whole body</td>
<td>0.19 (0.10–0.28)</td>
<td>0.44 (0.35–0.52)</td>
<td></td>
</tr>
<tr>
<td>BMD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.12 (0.07–0.16)</td>
<td>0.11 (0.04–0.18)</td>
<td></td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.12 (0.07–0.16)</td>
<td>0.05 (−0.02–0.12)</td>
<td></td>
</tr>
<tr>
<td>Whole body</td>
<td>0.24 (0.17–0.30)</td>
<td>0.25 (0.15–0.35)</td>
<td></td>
</tr>
</tbody>
</table>

1 Data are derived from published studies ($n = 10$) relating weight in infancy and adult bone mass.
needed for fetal bone mineral accretion (17). Approximately 25–30 g of calcium are transferred to the fetal skeleton by the end of pregnancy, most of which is transferred during the last trimester. It has been estimated that the fetus accumulates up to 250 mg calcium daily during the third trimester. Increased intestinal calcium absorption is the primary mechanism for obtaining extra calcium during this phase of pregnancy. Fractional calcium absorption increases from about 35% in the nonpregnant state to 60% during the third trimester. Serum concentrations of 1,25-dihydroxyvitamin D increase about 50% over the nonpregnant state during the second trimester and by 100% during the third trimester.

Evidence that maternal vitamin D status influences neonatal calcium homeostasis arises principally from studies of immigrant mothers to the United Kingdom. Thus, parathyroid hormone concentrations among Asian mothers in the United Kingdom were inversely associated with serum 25-hydroxyvitamin D concentrations. Reduced serum 25-hydroxyvitamin D concentrations were reported in as many as 50% of women from ethnic minority groups in the United Kingdom. This finding has been replicated among healthy Swiss mothers and their term infants at delivery. Several randomized trials of vitamin D supplementation during pregnancy have also been conducted (Table 2). Although not all studies have been included in the table, those performed in larger numbers of subjects with adequate controls have generally demonstrated an elevation in maternal 25-hydroxyvitamin D levels and improvements in neonatal calcium homeostasis. Thus, a quasi-randomized trial of 1139 Scottish women attending different obstetric wards evaluated the response to 400 IU vitamin D daily from approximately the 12th week of gestation, compared with a placebo containing no vitamin D. Plasma 25-hydroxyvitamin D, calcium, and phosphorous concentrations were measured at wk 24 and wk 34 of gestation, as well as in samples obtained from cord plasma and from the neonate on day 6. Plasma 25-hydroxyvitamin D concentrations were higher among the mothers who received vitamin D, compared with those who received placebo, at 24 wk, 34 wk, and delivery; as well as on day 6 for the infants (18).

About the same time, a double-blind, randomized trial of vitamin D supplementation was performed with 126 pregnant Asian women in the United Kingdom. Fifty-nine of these women received 1000 IU vitamin D daily, beginning at 28–32 weeks gestation, compared with a placebo containing no vitamin D. Plasma 25-hydroxyvitamin D concentrations were measured at wk 24 and wk 34 of gestation, as well as in samples obtained from cord plasma and from the neonate on day 6. Plasma 25-hydroxyvitamin D concentrations were higher among the mothers who received vitamin D, compared with those who received placebo, at 24 wk, 34 wk, and delivery; as well as on day 6 for the infants (18).
later osteoporosis stems from studies using noninvasive assessment of bone mineral. The clinically important consequence of reduced bone mass is fracture, and data are now available that directly link growth rates in childhood with the risk of later hip fracture (23). Studies of a unique Finnish cohort in whom birth and childhood growth data were linked to hospital discharge records for hip fracture have permitted follow-up of around 7000 men and women who were born in Helsinki University Central Hospital from 1924–1933. Body size at birth was recorded, and about 10 measurements were obtained of height and weight throughout childhood. Hip-fracture incidence was assessed in this cohort using the Finnish hospital discharge registration system. After adjustment for age and sex, there were two major determinants of hip-fracture risk: tall maternal height (P = 0.001), and low rate of childhood growth (height, P = 0.006; weight, P = 0.01). The effects of maternal height and childhood growth rate were statistically independent of each other and remained after adjusting for socioeconomic status. More important, hip-fracture risk was also elevated (P = 0.05) among babies born short. These data are compatible with endocrine programming influencing the risk of hip fracture. In addition, the observation that fracture subjects were shorter at birth, but of average height by age 7 y, suggests that hip-fracture risk might be particularly elevated among children in whom growth of the skeletal envelope is forced ahead of the capacity to mineralize, a phenomenon that is accelerated during pubertal growth.

Developmental origins of osteoporosis

The observed relationship between osteoporosis risk and size at birth or during infancy does not imply a causal role of being born small but reflects the sensitivity of fetal growth to adverse intrauterine influences. The term "maternal constraint" encapsulates those environmental factors that influence birth size even in healthy pregnancies, for example, maternal size, age, parity, and multiple pregnancy. Among

**TABLE 2**

**Trials of vitamin D supplementation during pregnancy**

<table>
<thead>
<tr>
<th>Trial</th>
<th>No.</th>
<th>Location</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockburn (1980)</td>
<td>1139</td>
<td>Scotland</td>
<td>400 IU/d or placebo</td>
<td>25(OH)D maternal↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cord↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infant↑</td>
</tr>
<tr>
<td>Brooke (1980)</td>
<td>126</td>
<td>UK</td>
<td>1000 IU/d or placebo</td>
<td>Ca maternal↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asian</td>
<td></td>
<td>Cord↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neonatal↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Maternal weight↑</td>
</tr>
<tr>
<td>Marya (1981)</td>
<td>120</td>
<td>Asian</td>
<td>600,000 IU (×2); 1200 IU/d or placebo</td>
<td>Ca maternal↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indian</td>
<td></td>
<td>Cord↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ALP maternal↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cord↑</td>
</tr>
<tr>
<td>Marya (1988)</td>
<td>200</td>
<td>Asian</td>
<td>600,000 IU (×2); or placebo</td>
<td>Ca/P maternal↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indian</td>
<td></td>
<td>Cord↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ALP maternal↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cord↑</td>
</tr>
<tr>
<td>Delvin (1986)</td>
<td>34</td>
<td>France</td>
<td>1000 IU/day; or no vitamin D</td>
<td>25(OH)D cord↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neonatal↑</td>
</tr>
<tr>
<td>Mallet (1986)</td>
<td>68</td>
<td>France</td>
<td>200,000 IU (×1); 1000 IU/d; or no vitamin D</td>
<td>25(OH)D maternal↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>with both regimes</td>
</tr>
</tbody>
</table>

↑, elevation; →, no change; ↓, decrease; ALP, alkaline phosphatase.

wk of gestation, whereas 67 women received placebo. Maternal calcium concentrations, but not cord calcium concentrations, were higher for the vitamin D supplemented group at delivery, compared with the placebo treated group. Infant plasma calcium concentrations on days 3 and 6 were also significantly higher in the vitamin D supplemented group compared with the control group. Five cases of symptomatic hypocalcemia occurred in the control group, whereas no cases occurred in the treated group (19). Although there was no difference in birthweight between the two groups, a greater proportion of small-for-gestational-age infants were born in the placebo-treated arm (29%) compared with the vitamin D arm (15%).

Marya et al. (20) performed a randomized study of high-dose oral vitamin D in pregnancy. They randomized 120 women to receive either 600,000 IU vitamin D orally during the seventh and eighth months of their pregnancy or 1200 IU daily during the entire third trimester. A third group was randomized to no therapy. The mothers receiving high-dose therapy exhibited greater serum calcium and lower serum alkaline phosphatase concentrations compared with those not receiving vitamin D or those receiving 1200 IU daily. Similar findings have been observed in trials conducted in France (21,22).

In summary, observational studies and vitamin D supplementation trials among pregnant women at high risk of vitamin D deficiency have shown improved neonatal handling of calcium with improved maternal vitamin D status. What currently remains uncertain is the extent to which maternal vitamin D supplementation might also retard the frequency of osteopenia within the normal range of fetal growth and neonatal size.

**Childhood growth and hip fracture**

Most evidence relating the intrauterine environment to later osteoporosis stems from studies using noninvasive assessment.
modifiable mechanisms limiting nutrient supply to the fetus, maternal nutrition has received the most attention, but other early environmental factors such as smoking, infectious exposure, and season of birth may have long-term effects.

Experimental evidence that the prenatal or the perinatal environment can influence adult postnatal physiology is available in several mammalian species (7,24). These studies demonstrate that manipulation of the periconceptual, embryonic, fetal, or neonatal environment can lead to altered postnatal cardiovascular and/or metabolic function. Although the environmental triggering cues are not yet fully understood, most manipulations have been dietary and include general maternal undernutrition (25,26), low-protein diet (27), or high-fat diet (28,29). Animal models for the developmental origins of osteoporosis replicate the observations made in humans. In the first such model, the feeding of a low-protein diet to pregnant rats produced offspring that exhibited a reduction in bone area and BMC, with altered growth plate morphology in adulthood (30). Maternal protein restriction also downregulated the proliferation and differentiation of bone-marrow stromal cells (31), as assessed by fibroblast colony formation at 4 and 8 wk.

There have been several models proposed to explain the changing demography of chronic diseases of affluence, such as osteoporosis, cardiovascular disease, and type 2 diabetes mellitus. Exclusively genetic models (thrifty genotype) cannot explain the steep temporal trends and observed birth cohort effects on the incidence of osteoporotic fracture. The alternative thrifty phenotype model suggests that the fetus becomes growth retarded in response to adverse environmental conditions in utero, and the associated adaptations induce a phenotype better suited to a deprived postnatal food/energy environment. However, this model does not easily account for the graded effect on disease risk seen across the normal birth-weight range, or the way in which the disparity between the prenatal and postnatal environment determines the level of risk.

These models have recently been brought together (7). Developmental responses to environmental stimuli need not provide immediate advantages but may alter the sensitivity of the organism to an anticipated future environment. Such predictive adaptive responses are made during the phase of developmental plasticity to optimize the phenotype for the probable environment of the mature organism, and epigenetic change is likely to be the mechanistic basis.

SUMMARY

Undernutrition and other adverse influences arising in fetal life or immediately after birth have a permanent effect on body structure, physiology, and metabolism. The specific effects of undernutrition depend on the time and the development at which it occurs; rapidly growing fetuses and neonates are more vulnerable. Its effects include altered gene expression, reduced cell numbers, imbalance between cell types, altered organ structure, and changes in the pattern of hormonal release and tissue sensitivity to these hormones. Evidence is now accumulating from human studies that programming of bone growth might be an important contributor to the later risk of osteoporotic fracture. Body weight in infancy is a determinant of adult BMC, as well as of the basal levels of activity of the growth hormone/IGF-1 and hypothalamic-pituitary-adrenocortical axes. Epidemiological studies have suggested that maternal smoking and vitamin D status during pregnancy influence intrauterine skeletal mineralization. Finally, childhood growth rates have been directly linked to the risk of hip fracture many decades later. Further studies of this phenomenon are required in order that effective preventive strategies against osteoporosis throughout the life course may be delineated and more effectively applied.

CONCLUSIONS

Several modifiable factors influence the growing skeleton and permit it to achieve its full genetic potential. These may act during intrauterine or early postnatal life, childhood, or adolescence. While many important research questions need to be addressed in this area, concerted action in health policy should be directed at 1) optimizing maternal nutrition and intrauterine growth; 2) improving the calcium intake and the general nutritional levels of all children (consumption of dairy products with supplementation as necessary should ensure adequate dietary calcium and protein, as well as other important nutrients, such as phosphorus, magnesium, and potassium during childhood and during pregnancy among women); 3) increasing the general exercise level of prepubertal and pubertal children; and 4) ensuring adequate vitamin D status, not just during infancy but throughout the period of growth. Further research into the interaction between the genome and the early environmental risk factors for osteoporotic fracture is urgently required so that environmental modification can be targeted to those at the greatest risk. Finally, intervention studies exploring the role of maternal lifestyle and nutrition, particularly maternal vitamin D status, on bone mineral accrual among the offspring of these mothers, will provide much-needed evidence on this approach to the reduction in fracture risk of future generations.

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LITERATURE CITED


