

# Childhood Bone Mass Acquisition and Peak Bone Mass May Not Be Important Determinants of Bone Mass in Late Adulthood

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## ABSTRACT

During childhood and adolescence, bone mass acquisition occurs primarily through skeletal growth. It is widely assumed that bone mass acquisition throughout childhood is an important determinant of the risk of osteoporosis in late adulthood; bone mass is thought to resemble a bank account in which deposits persist indefinitely. However, several well-controlled clinical studies suggest that increasing bone mass acquisition during childhood will have only transient effects. A likely explanation is that bone mass is governed by a homeostatic system that tends to return to a set point after any perturbation and, therefore, bone mass depends primarily on recent conditions, not those in the distant past. Indeed, in an animal model, we have shown evidence that bone mass acquisition in early life has no effect on bone mass in adulthood, in part because many areas of the juvenile skeleton are replaced in toto through skeletal growth. Therefore, it should not be assumed that alterations in childhood bone mass acquisition will affect bone mass many decades later in late adulthood. This issue remains open and the solution may depend on the type of childhood condition (for example calcium intake versus exercise) and its magnitude, timing, and duration. To date, both animal studies and clinical studies suggest that much of the effect of early bone mass acquisition does not persist.

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### Key Words

bone mass acquisition, childhood, adolescence, peak bone mass

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**B**ONE MASS INCREASES dramatically during childhood and adolescence, peaking in young adulthood (Fig 1A). Bone mass then plateaus and finally declines, sometimes eventuating in osteoporosis, a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.<sup>1</sup> It is often assumed that bone mass acquisition throughout childhood is an important determinant of bone density and fracture risk late in life.<sup>2,3</sup> Thus, for example, it is generally thought that optimizing calcium intake in a young child will lead to a greater peak bone mass in young adulthood and that this increment in bone mass will have a persistent effect decades later (Fig 1B). An analogy is sometimes made between bone mass and a bank account: we make deposits to our account during childhood and adolescence and withdrawals during adulthood. According to this model, greater deposits in childhood will produce a greater peak balance. Assuming that withdrawals in adulthood occur at the usual pace, the greater peak balance should delay the eventual decline into the bankruptcy of osteoporosis.

The assumption that childhood bone mass acquisition affects bone mass in the latter part of the life span is frequently repeated in review articles. For example, Heaney et al state that “achieving a high adult peak bone mass is protective against late-life fragility fractures. . . .

There has been a nearly universal consensus that early-life experiences are important. . . .”<sup>2</sup> This same concept is asserted in the 2000 National Institutes of Health consensus statement on osteoporosis,<sup>1</sup> and the assumption seems to affect public policy. The recent Surgeon General’s report on bone health states that “failure to achieve an optimized bone mass at the end of adolescence leaves an individual with much less reserve to withstand the normal losses during later life.”<sup>3</sup> Educational literature produced by the Department of Health and Human Services states that “[b]etween the ages 10 to 18 is when you make the bone that must last a lifetime—this bone is known as peak bone mass. To reach the best possible peak bone mass means getting enough exercise and calcium. Bones are like a bank account—if you deposit lots of exercise and calcium now, when you are young, you will have strong bones for later in life”<sup>4</sup> and, therefore, “osteoporosis is a pediatric preventable disease.”<sup>5</sup>

In this article we explore the biological mechanisms responsible for bone mass acquisition during childhood that determine peak bone mass, and then we critically examine the assumption that bone mass acquisition early in life is an important determinant of bone mass in later life.

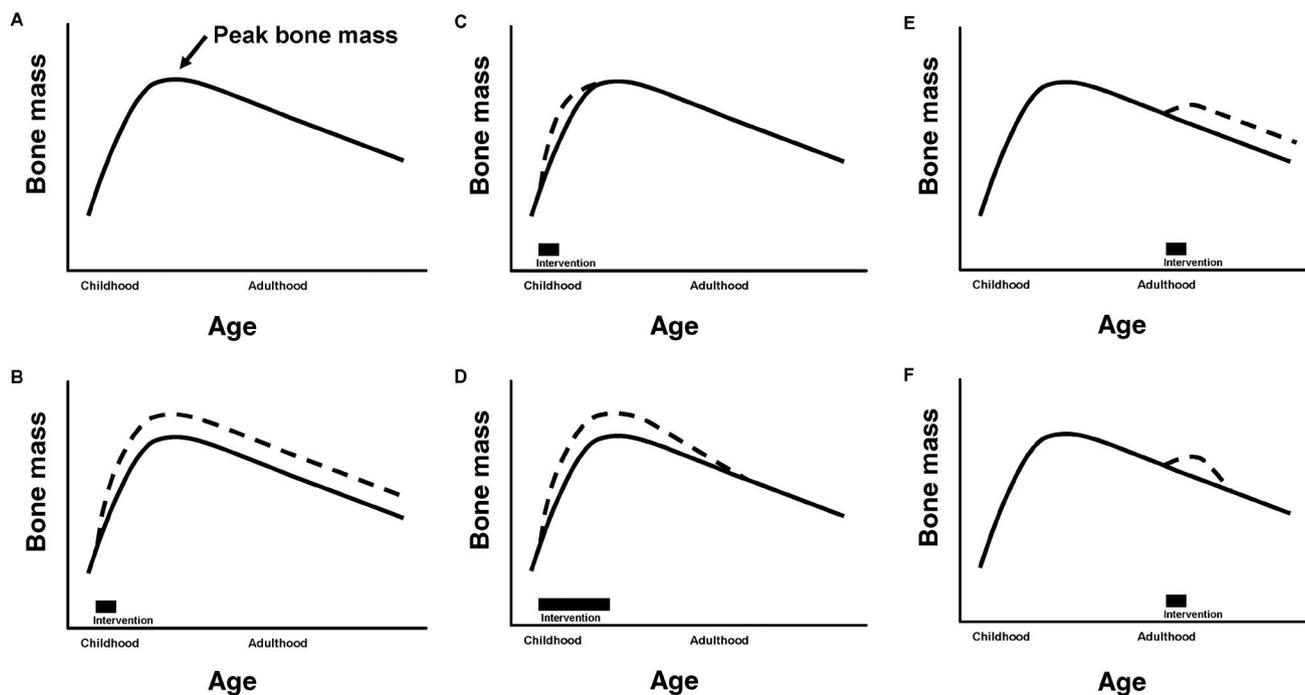


FIGURE 1

Conceptual graphs of bone mass as a function of age. A, In normal individuals, bone mass increases during childhood and adolescence, peaks in young adulthood, and then decreases in later adulthood. B, It is often assumed that an intervention (solid box) during childhood to increase bone mass acquisition will have a persistent effect on bone mass throughout life. C, However, several studies suggest that increased bone mass acquisition in childhood does not necessarily increase peak bone mass. D, Similarly, increasing peak bone mass does not necessarily result in an increased bone mass in late adulthood. Even interventions in later adulthood to increase bone mass do not necessarily have persistent effects (E); the effects may disappear with time as homeostatic mechanisms bring bone mass back toward a set point (F). Thus, bone mass may be determined primarily by recent conditions, not those in the distant past. The dashed curves represent the bone mass resulting from the intervention; the solid curves represent bone mass in the absence of intervention.

## ACQUISITION OF BONE MASS IN CHILDHOOD

In adults, changes in bone mass occur primarily through remodeling, a process in which osteoclastic bone resorption is coupled with local osteoblastic bone formation. In children, bone mass is affected not only by remodeling but also by skeletal growth or modeling, a process in which bone formation and resorption are uncoupled and occur at different sites, resulting in an increase in overall bone size. The enormous increase in bone mass seen during childhood and adolescence is primarily because of this increase in bone size. Skeletal growth occurs by several different mechanisms that allow for both longitudinal and cross-sectional growth.

Longitudinal growth of long bones and vertebrae occurs through endochondral ossification. In this process, new trabecular bone is formed using a cartilaginous template generated by the growth plate. As a tubular bone elongates, older trabeculae near the center of the bone are resorbed to make room for the marrow cavity (Fig 2).<sup>6</sup> More peripherally located trabeculae coalesce to form cortical bone, which causes elongation of the metaphyseal cortex.<sup>7</sup> In the diaphysis, periosteal cortical bone formation coupled with endosteal cortical bone resorption lead to cross-sectional bone growth. Later in adolescence, bone formation also occurs at the endosteal surface, which further increases cortical thickness.<sup>8</sup>

Skeletal growth slows with age and eventually ceases. For longitudinal bone growth, this decline seems to be attributable to a mechanism that is intrinsic to the growth plate; recent evidence suggests that growth-plate chondrocytes may have a finite proliferative capacity that is gradually exhausted.<sup>9</sup> Growth-inhibiting conditions in childhood slow down proliferation and, thus, seem to conserve the proliferative capacity of the growth plate. If the growth-inhibiting condition resolves, the growth-plate chondrocytes will have retained more of their proliferative capacity than normal and, thus, will grow more rapidly than normal, resulting in catch-up growth.<sup>10,11</sup> Whether analogous mechanisms govern periosteal bone growth is not known.

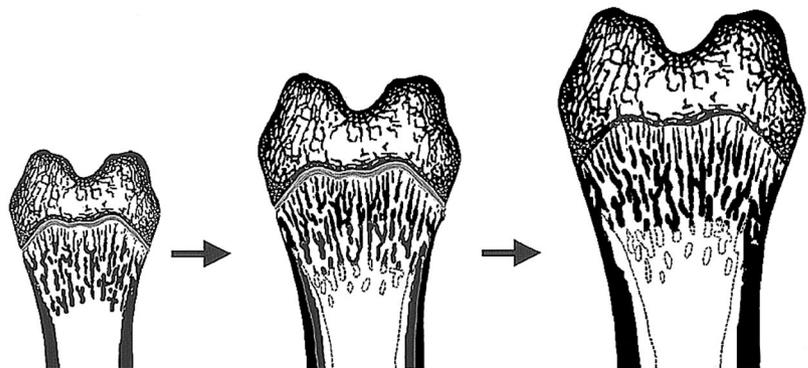
## DOES EARLY BONE MASS ACQUISITION AFFECT PEAK BONE MASS?

Genetic factors account for ~50% to 85% of the variance in adult bone mineral density, depending on the site examined.<sup>12,13</sup> Because heredity does not determine all of the variance, environmental modifications might make a substantial impact on peak bone mass. In an effort to maximize peak bone mass, public health efforts have targeted childhood as a critical time for maximizing calcium intake, weight-bearing exercises, and other bone-promoting regimens.<sup>3</sup> Likewise, medical interventions that decrease bone mass are often avoided because of the concern that peak bone mass will be compromised. But, do these interventions in childhood truly affect adult bone mass?

We recently explored this question using an animal model.<sup>6</sup> Young rabbits were treated between 5 and 10 weeks of age with high doses of glucocorticoid, which induced osteoporosis. The rabbits were then followed off glucocorticoid until 26 weeks of age, at which time their skeletal growth was nearing completion. Under the common assumption that bone mass is similar to a bank account, we would predict that this severe failure of bone mass acquisition during growth would have a long-lasting effect and lead to a diminished peak bone mass. However, after the glucocorticoid treatment was stopped, bone size, density, and strength recovered completely to match the values of untreated controls. Thus, early bone mass acquisition had no effect on peak bone mass. Fluorescent labeling of newly formed bone with oxytetracycline demonstrated that the recovery from osteoporosis did not occur through remodeling of osteoporotic bone. Rather, the osteoporotic bone was resorbed and replaced in toto with new healthy bone through the processes of normal longitudinal and cross-sectional skeletal growth. In the long-bone metaphysis, the osteoporotic trabecular bone formed during dexamethasone treatment was resorbed as the medullary cavity enlarged and was replaced by new bone formed by endochondral ossification at the growth plate. In the long-bone diaphysis, the periosteal bone formation rate

FIGURE 2

Schematic diagram representing the replacement of juvenile bone through skeletal growth. As the bone enlarges, new bone (black) is created by endochondral bone formation at the growth plate and periosteal bone formation at the cortex. As the marrow cavity expands, the juvenile bone (gray) is largely resorbed. Areas surrounded by dotted lines represent juvenile bone that has been resorbed.



was decreased during dexamethasone treatment but afterward rebounded above controls, normalizing cortical width. The mechanism responsible for this catch-up growth in the cortex is not known; it might be analogous to the catch-up growth that occurs at the growth plate, or it could be a result of increased mechanical load. These data in an animal model suggest that early bone mass acquisition has little effect on adult bone mass.

Human studies also suggest that alterations in bone mass acquisition during childhood may not have persistent effects. In a study by Johnston et al,<sup>14</sup> identical twin pairs were randomly assigned to receive either calcium supplementation or placebo in a double-blind fashion for 3 years during childhood and adolescence. In the prepubertal children, calcium supplementation increased the gain in bone density. However, after 3 years of follow-up, the effect disappeared.<sup>15</sup> Similarly, Bonjour et al,<sup>16</sup> randomly assigned prepubertal girls to receive either calcium-enriched foods or placebo for 1 year. The intervention group showed a significantly greater increase in bone mass and density (average of 6 anatomic sites by dual-energy x-ray absorptiometry) at the end of treatment period<sup>17</sup> and at follow-up 3 to 5 years after discontinuation.<sup>18</sup> A recent report described the follow-up results at 8 years. The report focused on a posthoc division of the subjects according to menarcheal age, but in the overall subject population, the average bone density at the 6 sites was no longer significantly different between the groups.<sup>18</sup>

Surprisingly, even if the calcium supplementation is not discontinued, there still may not be much effect on peak bone mass. In a recently reported study, calcium supplementation was given to girls beginning in early puberty. At the end of 4 years, a significant effect on bone mineral density was observed, but by 7 years the effect was largely lost.<sup>19</sup>

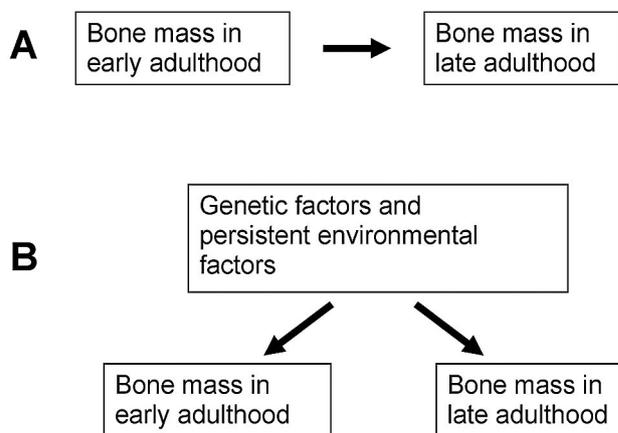
Thus, clinical studies suggest that interventions to increase bone mass acquisition in childhood do not necessarily increase peak bone mass (Fig 1C). However, the persistence of effects may depend on the nature of the intervention; although calcium supplementation seems to have little long-term effect, a persistent increase in mechanical load may have a more lasting effect.<sup>20,21</sup>

### DOES PEAK BONE MASS AFFECT BONE MASS IN LATE ADULTHOOD?

Suppose that one could identify and implement an effective method to increase peak bone mass. Does it necessarily follow that this alteration in peak bone mass will have a persistent effect decades later (Fig 1B), as is commonly assumed? The veracity of this assumption seems obvious on the basis of simple mathematical reasoning.<sup>2</sup> After all, bone mass at 70 years of age is the mathematical sum of peak bone mass at 30 years of age, plus all the bone that was formed between ages 30 and 70, minus all the bone that was resorbed in those years.

Therefore, it would seem self-evident that increasing the peak bone mass would cause an increase in bone mass at age 70. However, this reasoning is only valid if the 3 variables in the equation (peak bone mass, subsequent bone formation, and subsequent bone resorption) are independent, which is not the case. Bone mass is governed by a homeostatic system with the set point of the system determined by genetics, mechanical load, and other environmental factors.<sup>22</sup> Therefore, any perturbation in the system tends to be corrected over time. As a result, the rate of bone loss in adulthood may depend on the peak bone mass; consequently, it is not mathematically certain that increasing bone mass acquisition during childhood will necessarily lead to a greater bone mass at age 70.

If we cannot prove the importance of peak bone mass theoretically, can we prove it empirically? Several lines of evidence have been cited in support of this concept. For example, bone density tends to track along a percentile, at least in the short-term. So, if an individual has a low bone density at one point in life, he or she tends to have a low bone density later in life.<sup>23</sup> If this tendency were to extend from the time of peak bone mass in early adulthood to the time of osteoporosis in late adulthood, this might suggest that peak bone mass affects later bone mass. However, association does not imply causality. The association between early bone mass and later bone mass could arise from a direct causal link between the two (Fig 3A), but it could also arise if both early bone mass and later mass are influenced by the same factors (Fig 3B). Indeed, bone mass and density throughout life are probably influenced by genetic factors and, perhaps, persistent lifestyle factors. Thus, the concordance between early bone mass and later bone mass could reflect the fact that both are influenced by a person's genetic makeup rather than a direct causal link.



**FIGURE 3** Possible explanations for the association between bone mass in early adulthood and bone mass in late adulthood. A, One possible explanation is a direct causal link; bone mass in early adulthood affects bone mass in late adulthood. B, Another possibility is that genetic factors and persistent environmental factors affect bone mass throughout life. Arrows indicate a cause-and-effect relationship.

To prove a direct causal link between peak bone mass and bone mass in later life (Fig 3A), we would need 2 groups that differed only in a behavior during childhood/adolescence that affects peak bone mass; behavior in adulthood would have to be similar. We would then look at the 2 groups in late adulthood to determine whether the difference in bone mass persisted. Some observational studies have tried to address this issue. For example, in young soccer players, athletic activity is associated with increased bone density, but cessation of the athletic activity leads to increased bone loss, exceeding that of controls.<sup>24</sup> This finding suggests that there is a tendency for gains not to persist but rather for the system to return toward a homeostatic set point after a perturbation (Fig 1D). In general, such studies suggest that the positive effects of physical activity on bone density may persist for years but not decades, although changes in bone size might be better preserved.<sup>21</sup> However, observational studies have obvious weaknesses such as the possibility that the 2 groups might have persisting lifestyle differences that would affect the rate of bone loss through adulthood. To be sure that the 2 groups differ only in peak bone mass, individuals would need to be randomly assigned during childhood to some intervention that affects peak bone mass. Once peak bone mass is achieved, the intervention would be stopped and the subjects followed for several decades to determine if the effect persists or if it fades away as bone mass returns to a homeostatic set point. The study should be placebo-controlled and double-blind. Obviously, a prospective study of this kind, lasting decades, would be very difficult to execute. In the absence of this ideal study, we are forced to rely on indirect and imperfect evidence; therefore, any conclusions must be considered tentative.

Similar to the interventional pediatric studies that have demonstrated lack of persistent effect on bone mass, the tendency of bone to revert to a homeostatic set point after an intervention has also been seen in later adulthood. Postmenopausal women who received estrogen and then stopped the treatment did not show a persistent effect from this deposition of bone mass but rather showed a loss of the beneficial effect with time.<sup>25</sup> These women demonstrated an increased rate of bone loss compared with untreated women after the intervention was stopped. In other words, the increased bone mass did not act like a deposit in a bank account (Fig 1E). Instead, the system seemed to return to its homeostatic set point (Fig 1F). Similar regression occurred after treatment with parathyroid hormone.<sup>26</sup> Thus, recent conditions, not conditions in the distant past, seem to be more important determinants of bone mass. If a deposit to the "bone bank" at age 60 does not persist until age 70, can we assume that deposits in childhood will last until age 70? Thus, bone mass in later adult life may depend more on genetic factors and conditions in the latter part of

adulthood, including nutritional, mechanical, pathologic, hormonal, and pharmacologic factors.

Perhaps if we began an intervention in childhood and continued it throughout life we could affect bone mass in late adulthood. However, we then must ask whether the resultant mass would be any greater than if we had started the intervention in adulthood. For example, if we are interested in optimizing bone mass at 70 years of age, would starting calcium supplementation at 3 years of age and continuing it for 67 years be any more effective than starting supplementation at 65 years of age and continuing it for 5 years? If bone mass depends primarily on recent conditions, the answer might well be no.

## CONCLUSIONS

During childhood and adolescence, bone mass acquisition occurs through skeletal growth or modeling, both longitudinal growth at the growth plate and cross-sectional growth at the periosteum. It is widely assumed that bone mass acquisition throughout childhood is an important determinant of the risk of osteoporosis in late adulthood; bone mass is thought to resemble a bank account in which deposits persist indefinitely. However, this assumption cannot be proven on theoretical grounds. It is equally conceivable that increasing bone mass acquisition during childhood will have only transient effects, because bone mass is governed by a homeostatic system that tends to return to a set point after any perturbation and, therefore, bone mass depends primarily on recent conditions, not those in the distant past. Indeed, several well-controlled clinical studies have suggested that the latter alternative is true, at least in part. In an animal model, we have shown evidence that bone mass acquisition in early life has no effect on bone mass in adulthood, in part because many areas of the juvenile skeleton are replaced in toto through skeletal growth. Thus, both modeling and remodeling may erase any early effects.

It should not be assumed that alterations in childhood bone mass acquisition will affect bone mass many decades later in late adulthood. This issue remains open, and its resolution may depend on the type of childhood condition (eg, calcium intake versus exercise) and its magnitude, timing, and duration. To date, both animal and clinical studies suggest that much of the effect of early bone mass acquisition does not persist.

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