Osteoporos Int
DOI 10.1007/s00198-015-3440-3

POSITION PAPER

The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations

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Received: 20 October 2015 / Accepted: 10 November 2015

Abstract Lifestyle choices influence 20–40 % of adult peak bone mass. Therefore, optimization of lifestyle factors known to influence peak bone mass and strength is an important strategy aimed at reducing risk of osteoporosis or low bone mass later in life. The National Osteoporosis Foundation has issued this scientific statement to provide evidence-based guidance and a national implementation strategy for the purpose of helping individuals achieve maximal peak bone mass early in life. In this scientific statement, we (1) report the results of an evidence-based review of the literature since 2000 on factors that influence achieving the full genetic potential for skeletal mass; (2) recommend lifestyle choices that promote maximal bone health throughout the lifespan; (3) outline a research agenda to address current gaps; and (4) identify implementation strategies. We conducted a systematic review of the role of individual nutrients, food patterns, special issues, contraceptives, and physical activity on bone mass and strength development in youth. An evidence grading system was applied to describe the strength of available evidence on these individual modifiable lifestyle factors that may (or may not) influence the development of peak bone mass (Table 1). A summary of the grades for each of these factors is given below. We describe the underpinning biology of these relationships as well as other factors for which a systematic

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Published online: 08 February 2016

review approach was not possible. Articles published since 2000, all of which followed the report by Heaney et al. [1] published in that year, were considered for this scientific statement. This current review is a systematic update of the previous review conducted by the National Osteoporosis Foundation [1].

Lifestyle Factor	Grade
Macronutrients	
Fat	D
Protein	C
Micronutrients	
Calcium	A
Vitamin D	B
Micronutrients other than calcium and vitamin D	D
Food Patterns	
Dairy	B
Fiber	C
Fruits and vegetables	C
Detriment of cola and caffeinated beverages	C
Infant Nutrition	
Duration of breastfeeding	D
Breastfeeding versus formula feeding	D
Enriched formula feeding	D
Adolescent Special Issues	
Detriment of oral contraceptives	D
Detriment of DMPA injections	B
Detriment of alcohol	D
Detriment of smoking	C
Physical Activity and Exercise	
Effect on bone mass and density	A
Effect on bone structural outcomes	B

Considering the evidence-based literature review, we recommend lifestyle choices that promote maximal bone health from childhood through young to late adolescence and outline a research agenda to address current gaps in knowledge. The best evidence (grade A) is available for positive effects of calcium intake and physical activity, especially during the late childhood and peripubertal years—a critical period for bone accretion. Good evidence is also available for a role of vitamin D and dairy consumption and a detriment of DMPA injections. However, more rigorous trial data on many other lifestyle choices are needed and this need is outlined in our research agenda. Implementation strategies for lifestyle modifications to promote development of peak bone mass and strength within one's genetic potential require a multisectored (i.e., family, schools, healthcare systems) approach.

Keywords Bone mineral content · Diet · Nutrition · Peak bone mass · Physical activity

Abbreviations

%ucOC	Percentage of undercarboxylated osteocalcin
95 % CI	95 % Confidence interval
aBMD	Areal bone mineral density
BMC	Bone mineral content
CDC	US Centers for Disease Control and Prevention
CSA	Cross-sectional area
CSMI	Cross-sectional moment of inertia
CT	Computed tomography
DEQAS	Vitamin D External Quality Assessment Scheme
DMPA	Depot medroxyprogesterone acetate
DONALD	Dortmund Nutritional and Anthropometric Longitudinally Designed
DXA	Dual-energy x-ray absorptiometry
HHS	US Department of Health and Human Services
HRpQCT	High-resolution peripheral quantitative computed tomography
HSA	Hip structural analysis
IGF	Insulin-like growth factor
IOM	Institute of Medicine
NHANES	National Health and Nutrition Examination Survey
OC	Oral contraceptive
OR	Odds ratio
pQCT	Peripheral quantitative computed tomography
PRAL	Potential renal acid load
QCT	Quantitative computed tomography
RCT	Randomized controlled trial
RDA	Recommended dietary allowance
SSI	Stress–strain index
UHT	Ultra-heat-treated
uN	Urinary nitrogen
USDA	US Department of Agriculture
vBMD	Volumetric bone mineral density

Introduction

Bone accretion

During growth and development, skeletal growth proceeds through the coordinated action of bone deposition and resorption to allow bones to expand (periosteal apposition of cortical bone) and lengthen (endochondral ossification) into their adult form [2]. This process of bone modeling begins during fetal growth and continues until epiphyseal fusion, usually by the end of the second decade of life [1]. Bone modeling is sensitive to mechanical loading, emphasizing the importance of physical activity throughout growth [2]. Some skeletal characteristics, such as cortical density and structural strength, determined by bone dimensions and thickness, continue to increase after epiphyseal fusion and into the third decade of life. Quantitatively, the amount of bone mineral acquired from

Table 1 Evidence grading system

Level of evidence[a]	Description
A: Strong	Clear evidence from at least one large, well-conducted, generalizable RCT that is adequately powered with a large effect size and is free of bias or other concerns
	OR
	Clear evidence from multiple RCTs or many controlled trials that may have few limitations related to bias,measurement imprecision, inconsistent results, or other concerns
B: Moderate	Evidence obtained from multiple, well-designed, conducted, and controlled prospective cohort studies that have used adequate and relevant measurements and that gave similar results from different populations
	OR
	Evidence obtained from a well-conducted meta-analysis of prospective cohort studies from different populations
C: Limited	Evidence obtained from multiple prospective cohort studies from diverse populations that have limitations related to bias, measurement imprecision, or inconsistent results or have other concerns
	OR
	Evidence from only one well-designed prospective study with few limitations
	OR
	Evidence from multiple well-designed and conducted cross-sectional or case-controlled studies that have very few limitations that could invalidate the results from diverse populations
	OR
	Evidence from a meta-analysis that has design limitations
D: Inadequate	Evidence from studies that have one or more major methodological flaws or many minor methodological flaws that result in low confidence in the effect estimate
	OR
	Insufficient data to support a hypothesis
	OR
	Evidence derived from clinical experience, historical studies (before and after), or uncontrolled descriptive studies or case reports

RCT randomized controlled trial

[a] Refers to the body of evidence

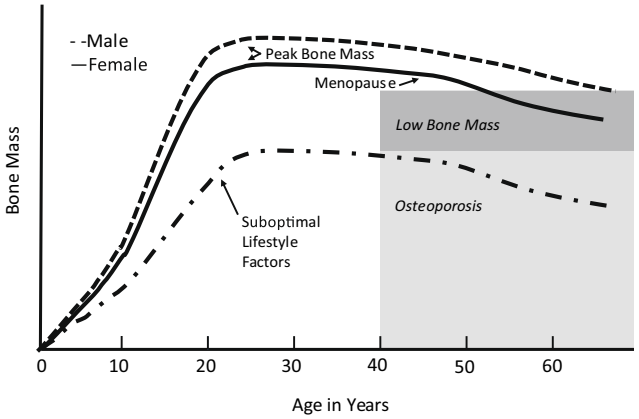

Fig. 1 Bone mass across the lifespan with optimal and suboptimal lifestyle choices

birth to adulthood follows distinct age- and sex-specific patterns (Fig. 1). Bone mass is acquired relatively slowly throughout childhood. With the onset of puberty and the adolescent growth spurt in height, bone mineral accretion is rapid, reaching a peak shortly after peak height gain (Fig. 2). For total body bone mineral, the peak bone mineral accretion rate occurs at 12.5 ± 0.90 years in girls and 14.1 ± 0.95 years in boys of European ancestry [3]. During the 4 years surrounding the peak in bone accretion, 39 % of total body bone mineral is acquired; by 4 years following the peak, 95 % of adult bone mass has been achieved [4]. Within a population, the distribution of bone mass becomes more variable, in part due to differences in height and other skeletal dimensions as adult size is attained, the timing and magnitude of peak bone mineral accrual, the cessation of bone accretion, and lifestyle factors. This period of rapid accretion may be a time of both opportunity and vulnerability for optimizing peak bone mass.

Changes in the structure (size and shape) and composition (amount of cartilage, cortical, and trabecular bone) of bone also occur with progression through puberty and thereby influence bone strength (Fig. 3). Cortical bone is the compact bone that forms the outer shell protecting bone marrow and trabecular bone. Trabecular bone is composed of rods and plates in a sponge-like structure, adding to the structural strength of bone. Cortical and trabecular bone differ in their responsiveness to disease effects, medications, muscle-loading and impact-loading physical activity, and hormonal changes. The relative importance of cortical versus trabecular bone in optimizing peak bone mass and strength and in minimizing fracture risk has not been firmly established in either childhood or adulthood. Distinct increases in trabecular bone of the spine and long bones occur between sexual maturity stages 3 and 4 [5–7]. The density of cortical bone is lower among children and adolescents than among adults, and it may even go through a transient period of increased porosity, particularly for boys [7, 8]. The density of cortical bone increases more rapidly as epiphyseal fusion occurs and continues into the third decade of life [9]. Both the inner and outer dimensions of long bones increase as growth proceeds, providing greater structural strength. The accumulation of bone mineral and changes in density and structural strength of bone may also continue into the third decade of life, depending on the bone compartment and skeletal site under consideration (Fig. 1).

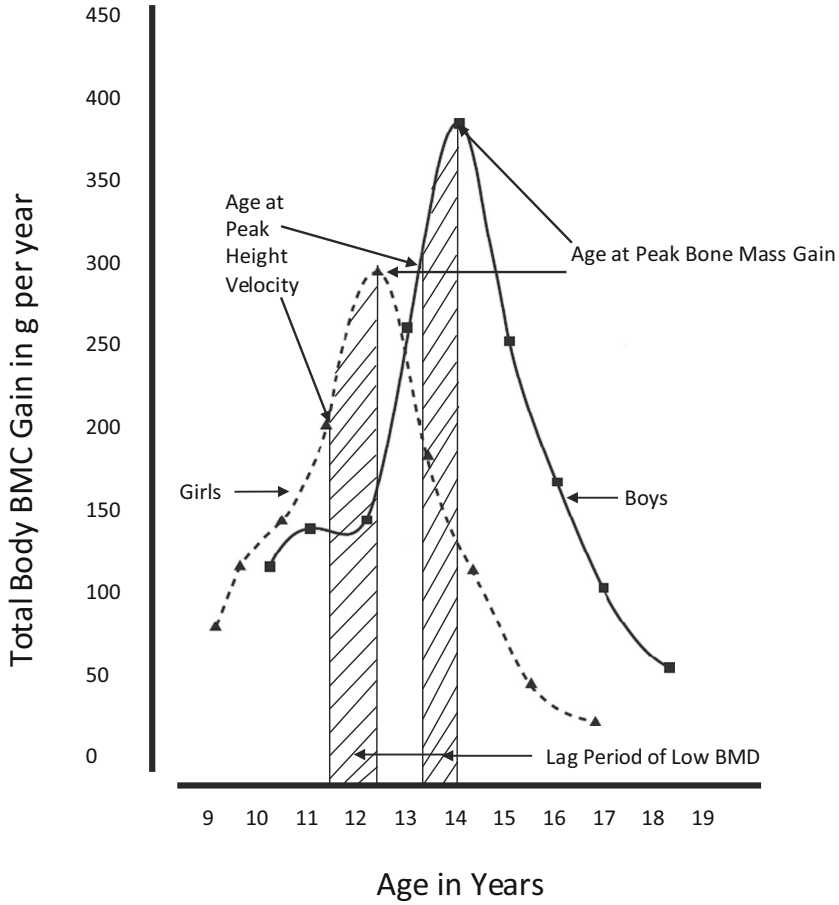

Fig. 2 Peak BMC gain and peak height velocity in boys and girls from longitudinal DXA analysis. Adapted from Bailey et al. [3]

Definition of peak bone mass

Peak bone mass is generally thought of as the amount of bone gained by the time a stable skeletal state has been attained during young adulthood. The concept of peak bone mass more broadly captures *peak bone strength*, which is characterized by mass, density, microarchitecture, microrepair mechanisms, and the geometric properties that provide structural strength.

There are several nuances to this concept that deserve recognition. The concept of peak bone mass is different when applied to an individual as opposed to a population. For an individual, peak bone mass may refer to the maximum amount of bone accrued during young adulthood. Alternatively, the concept of peak bone mass may refer to an individual's maximal or genetic potential for bone strength (i.e., bone mineral content (BMC), areal bone mineral density (aBMD), or other measures of bone strength). At the population level, peak bone mass is attained when age-related changes in a bone outcome are no longer positive and have attained a plateau or maximum value [10].

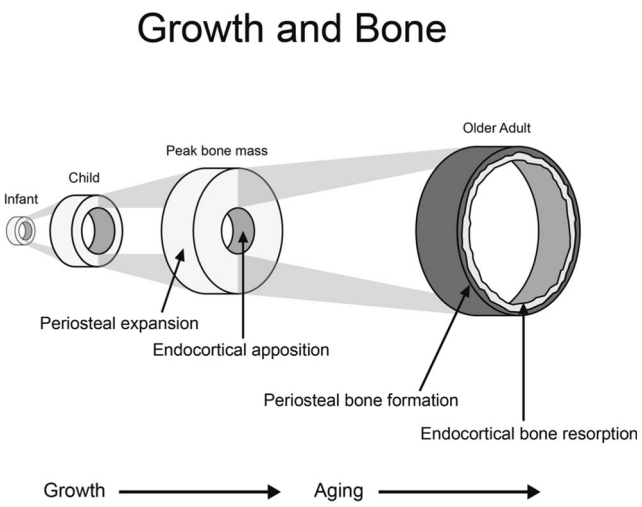

Fig. 3 Changes in structural composition of bone throughout the lifespan

Importance of peak bone mass

Fracture

Optimizing bone accrual during growth may be of greatest significance in preventing current or future fractures, as measures of bone mass, density, and structural strength are associated with fracture in children and adults [11–13]. The frequency of fractures is higher among children compared to

young and middle-aged adults [14], reflecting the vulnerability of the growing skeleton prior to peak bone mass. Among healthy children, as many as one half of boys and one third of girls will sustain a fracture by age 18 years, with one fifth sustaining two or more fractures [15, 16]. Children who sustain a fracture before age 4 years are especially vulnerable to a subsequent fracture [17]. Thirty to 50 % of childhood fractures involve the forearm [14, 15, 18–20] and result from falls to an outstretched arm. There is a positive relationship between fracture frequency and level of physical activity due to the increased risk of falls during physical activity [21]. Thus, although physical activity is critical for bone modeling, children with higher levels of physical activity are more likely to have fractures [3, 22–28].

There is a developmental period during the rapid growth of late childhood and early adolescence when the skeleton is particularly vulnerable to fracture (Fig. 4) [29]. Recently, high-resolution peripheral quantitative computed tomography (HRpQCT) has been used to explain the microarchitectural basis for the observation of increased fracture frequency among young adolescents [7]. The combination of thinner cortical bone, lower total volumetric bone mineral density (vBMD), and increased cortical porosity, particularly in boys, suggests that linear bone growth outpaces bone mineralization, resulting in transient bone fragility.

Understanding factors that affect bone strength early in life is important because low bone strength is associated with fracture risk in later life, independent of fall incidence and physical activity [30]. Childhood bone mass is predictive of fracture risk during childhood, with an 89 % increase in fracture risk per SD decrease in size-adjusted bone mass [31]. Moreover, among children who experience similar forearm injuries, those with greater bone density have been shown to be less likely to fracture [32]. Preterm children have low bone mass during late childhood [33], and birth weight is related to bone mass in later adult life (age ≥60 years) [34].

Recent work using HRpQCT suggests that microarchitectural changes underlie increased bone fragility in children who sustain a distal forearm fracture following mild trauma compared to nonfracture controls [35]. Differences such as cortical thinning are seen at both the distal radius and distal tibia in children presenting with a forearm fracture in which the degree of trauma is mild (e.g., fall from standing height), but not in those where the trauma is moderate (e.g., fall while riding a bicycle). Further analysis, including microfinite element analysis of HRpQCT data, showed that the mild trauma distal forearm fracture cases had reduced bone strength (i.e., failure load) compared to children without a fracture history. Moderate trauma is sufficient to break healthy bones that are not otherwise inherently at increased risk of fracture. Clark et al. [21] have shown that, irrespective of bone mass, fracture risk rises as the amount of vigorous activity increases. Additional studies have shown that a forearm fracture in a child is associated with lower areal and vBMD, cortical area, and bone strength using peripheral quantitative computed tomography (pQCT) and dual-energy x-ray absorptiometry (DXA) [11]. Cohort studies in the USA and South Africa show that boys and girls of European descent have a greater fracture risk than children of African descent [36, 37], a finding that parallels patterns of osteoporosis and hip fracture in elderly adults [38, 39].

In childhood and adolescence, stress fractures exhibit a different pattern from typical long bone fractures. The lifetime prevalence of stress fracture among the general population is below 4 % [40], and stress fractures are more common among women than among men [41]. In studies of military populations, where stress fractures are most common, the rate ratio

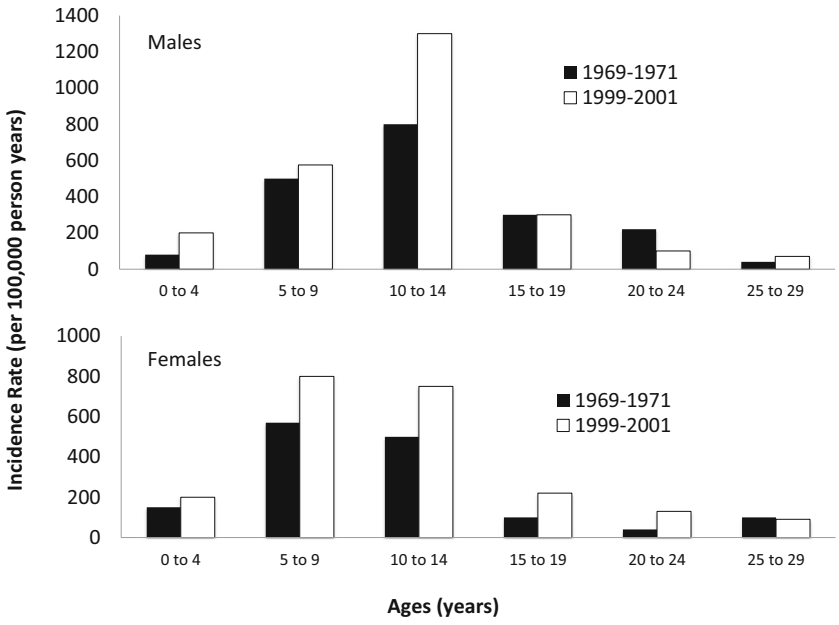

Fig. 4 Incidence of fractures of the distal forearm from birth through young adulthood. Adapted from Khosla et al. [29]

may be 10:1 [42–47], with up to 20 % of female recruits in basic training reported to have sustained a stress fracture [44–48] (note: military studies include young adults aged ≥18 years). Risk factors for stress fractures among recruits include low quantitative ultrasound values, smoking, history of being sedentary [49], and volume of training [40, 44, 50]. White race and a reported family history of osteoporosis or osteopenia may also represent significant risk factors [51, 52].

Tracking

Tracking refers to the stability of a trait over time. The degree to which indicators of bone strength track from childhood to peak bone mass and beyond is of paramount importance to optimizing peak bone mass for lifelong skeletal health. If bone "status" (i.e., bone mass, density, or structural strength relative to one's peers of the same age and sex) at any given time point were not associated with its future status, then concerns would only be relevant to prevention of childhood fractures, not osteoporosis later in life. In fact, numerous prospective studies have demonstrated that measures of bone density track quite strongly from childhood through adolescence, with tracking correlations ranging from 0.5 to 0.9 depending on the skeletal site, trait, and duration of follow-up, with most estimates falling in the range of 0.6 to 0.7 [32, 53–57]. Tracking correlations decline during adolescence and then rebound, a phenomenon that is likely due to variability in the timing of puberty and peak bone accrual. Adjustment for height status largely eliminates this transient decline in tracking [32, 57]. One study of children aged 8–16 years ($n = 183$) examined the factors associated with tracking deviation. Positive deviation (i.e., improvement in spine and hip aBMD tertile) was associated with having been breast-fed, gains in lean mass, aerobic fitness, and sports participation. Gains in adiposity were associated with negative deviations in tracking [55]. These findings provide strong evidence that bone status during childhood, when peak bone mass is accumulated, is indicative of bone status in young adulthood. However, the fact that tracking correlations are far from unity suggests that lifestyle factors can alter bone status in both positive and negative directions.

Timing of peak bone mass

If the magnitude of peak bone mass attained in young adulthood is an important predictor of osteoporosis later in life, then the timing of peak bone mass is also important because it defines the lifecycle phase during which peak bone mass can be optimized. Regardless of whether one is referring to peak bone mass of an individual or a population, the timing of peak bone mass varies by skeletal site. Estimates based on longitudinal studies are preferred over cross-sectional population studies for identifying the timing of peak bone mass because they capture the process of bone accretion. For example, using longitudinal observations and the plateau method, the Canadian Multicentre Osteoporosis Study identified the ages of peak bone mass for women; for lumbar spine aBMD, it was between the ages of 33 and 40 years, whereas ages of peak bone mass for total hip BMD were between 16 and 19 years [10].

Estimates of the timing of peak bone mass further depend on the parameters of bone (i.e., mass, density, geometry, microarchitecture) under consideration. Using quantitative computed tomography (QCT), Riggs et al. [9] showed that women aged 20–29 years ($n = 15$) were losing trabecular bone at a rate of 1–1.75 % per year at the distal radius and lumbar spine, but they were gaining cortical bone at a rate of 0.25 % per year in the tibia. By contrast, men ($n = 8$) in this age range did not exhibit significant changes in these outcomes [9]. Cross-sectional data on >1000 men, aged 18.0–20.9 years, in the Gothenburg Osteoporosis and Obesity Determinants Study suggest that aBMD of the lumbar spine, femoral neck, and total body did not increase with age, but positive age-related associations were observed for aBMD of the radius, cortical, and trabecular vBMD, and cortical thickness of the radius and tibia as measured by DXA and pQCT [58]. The positive association with cortical thickness was attributed to a smaller medullary diameter, and not to periosteal expansion.

Because the timing of peak bone mass and strength varies by skeletal site and bone compartment, it is important to establish and retain behaviors that contribute to skeletal health, including region-specific changes (e.g., hip, spine). Moreover, until the lifelong importance of peak bone mass is fully understood [52], it is prudent to assume that these behaviors are needed to sustain skeletal health through the life cycle.

Methods for measuring peak bone mass

Insights into the development of peak bone mass are based on studies using DXA and QCT. These measurement techniques characterize different aspects of bone strength; DXA primarily measures bone mass (or bone mineral content [BMC]) and aBMD, which are integrated measures of cortical and trabecular bone.QCT can provide distinct measures of cortical and trabecular vBMD, bone geometry (e.g., periosteal and endosteal circumference and structural strength) and, in some cases, microarchitecture.

Dual-energy x-ray absorptiometry

The vast majority of studies on peak bone mass have utilized DXA, a low-dose x-ray technology that measures the attenuation of x-ray beams as they pass through tissues of varying density. DXA is a two-dimensional imaging technique that uses a planar image to estimate bone area. This technology is ideal for use in children because it is rapid, safe, widely available, and precise, with effective dose ranges from 0.03

to 15.2 μSV [59]. Because of the smaller bone size and lower density of bones in growing children, special software has been developed by the major DXA manufacturers to measure aBMD and BMC in children. DXA does not measure vBMD but instead provides what is referred to as aBMD. Since DXA does not capture the depth of bone, it systematically underestimates vBMD in children with poor growth. For this reason, adjusting DXA measures of BMC and aBMD for stature is recommended [60, 61]. This adjustment serves to distinguish between gains in BMC or aBMD that are independent of gains in stature. In addition, cortical and trabecular bone are superimposed in the DXA image, thus providing a composite estimate of the mass and density of these two bone compartments.

Lack of agreement exists regarding whether BMC or aBMD should be the outcome of interest in bone accretion studies in children. BMC is determined, in large part, by bone size because it reflects the mineral content of one region or the entire skeleton; aBMD only partly adjusts for bone size and a size-related artifact remains [61]. Using spine QCT measures as a reference method, Wren and colleagues have shown that DXA BMC was a better measure to use in children (ages 6–17 years), particularly in prepubertal children, than aBMD [62]. We agree with those who argue that, to account for size in studies of children, it is best to use BMC adjusted for bone area [63, 64], height-for-age Z-score [61], lean mass [65, 66], or other combinations of anthropometric variables [64, 67, 68] or to use calculated bone mineral apparent density [69], because these provide a more accurate reflection of a child's bone health.

DXA measures have also been used to estimate structural strength of the proximal femur using the hip structural analysis (HSA) algorithm [70]. HSA estimates subperiosteal width, cross-sectional area (CSA), and section modulus in the narrow neck, intertrochanteric region, and shaft of the proximal femur. These outcomes are associated with treatment effects in adults as well as disease and exercise effects in children and adolescents [71–73].

Peripheral quantitative computed tomography

DXA only partly describes bone strength, which is the broader concern for understanding peak bone mass. Other modalities are used to more directly measure vBMD, microarchitecture, and geometry. Many of these characteristics can easily be measured in children with relatively low radiation exposure (0.59–1.09 mSv) [74]. QCT and pQCT are three-dimensional techniques that also use attenuation of x-ray beams to construct bone images. Cortical and trabecular bone compartments vary in density, and the differential attenuation of x-ray beams in the three-dimensional reconstruction allows for separate determination of trabecular and cortical vBMD, as well as numerous other measures of bone geometry (e.g., total bone area, periosteal and endosteal circumference) and structural strength in compression, bending, and torsion (e.g., section modulus, strain–strength index). Full-sized computed tomography (CT) scanners are used to measure the spine and other sites, and dedicated pQCT scanners measure the radius, tibia, or distal femur. Newer HRpQCT scanners achieve sufficient resolution for building microstructural finite element models of whole bone failure load, a surrogate measure of bone's resistance to fracture, as well as cortical porosity, and trabecular plate and rod microstructure [74].

Mechanical loading

Physical activity comprises any body movement produced by muscle contraction resulting in energy expenditure above a resting level [75]. Exercise is a more restrictive concept and is defined by planned, organized, and repetitive physical activity aimed at maintaining or enhancing one or more components of physical fitness or a specific health outcome, such as bone strength [68]. The randomized controlled trials (RCTs) reviewed in this scientific statement used targeted exercise as an intervention to improve bone strength, whereas most of the longitudinal studies measured physical activity, including active transportation and activities of everyday life [76]. Physical activity has long been regarded as behavior likely to influence bone health [77, 78]. Epidemiological and clinical trial research dating back more than two decades confirms the positive impact of regular physical activity on bone [3, 27, 78–81]. However, we are only beginning to quantify the specific dimensions, dose, and timing of physical activity needed for maximal bone strength. What is known, primarily from animal studies, is that increased mechanical loads placed on bone through both impact and muscle forces cause deformation (strains) of whole bone [82, 83]. These strains activate mechanosensitive cells (i.e., osteocytes), embedded within the bone, which signal molecules to activate osteoblasts and osteoclasts. The signaling begins the process of bone adaptation to *changes* in physical activity, as well as other mechanical loads (e.g., an increase in body weight). To initiate an osteogenic response, bone must be subjected to a strain magnitude that surpasses a threshold determined by the habitual strain range in the predominant loading direction. The threshold varies between individuals (and also bone sites) according to physical activity habits and other factors (e.g., maturity status). Thus, children and adolescents may respond differently to similar mechanical loading conditions. Inactive children may respond to low-impact loading and improve bone mass or structure, while more active children will need a higher mechanical load to promote a skeletal response [84].

The skeleton needs to be strong for load bearing and light for mobility. A manner of minimizing the amount of bone mass needed in a cross-section without decreasing strength is to modify the distribution of bone mass and therefore

changing bone structure. Throughout life, but mainly during growth, periosteal apposition increases the diameter of long bones and endocortical resorption enlarges the marrow cavity. Cortical thickness is determined by the net changes occurring at the periosteal and endosteal surface of bone. However, even without an increase in cortical thickness, the displacement of the cortex increases bending strength because resistance to bending is proportional to the fourth power of the distance from the neutral axis. In addition to the independent effect of physical activity on mass and density, increased mechanical loading via physical activity may influence structural changes in bone to increase strength in response to the new loading condition [25, 73, 85].

Bone is most responsive to physical activities that are dynamic, moderate to high in load magnitude, short in load duration, odd or nonrepetitive in load direction, and applied quickly [84]. The load magnitude is produced by impact with the ground (e.g., tumbling or jumping), impact with an object (racquet sports), or muscle power moves such as the lift phase in jumping and vaulting. On the other hand, due to desensitization of the osteocytes, static loads and repetitive low-magnitude loads are not osteogenic [86–88]. Although physical activity is a modifiable factor that contributes to peak bone mass and strength, our understanding of how to quantify the dimensions of physical activity that are osteogenic (including frequency, intensity, time, and type) is incomplete.

Body composition

It is widely recognized that lean body mass is among the strongest correlates of bone mass, density, and structural strength during childhood [89–92]. During adolescence, the peak in total body lean mass accretion occurs just prior to peak bone mineral accretion [2, 93], although at specific sites, peak increases in lean mass and bone strength may be coordinated [94]. In the latter phase of the adolescent growth spurt, following the peak, continued gains in lean mass are strong predictors of increases in BMC [95].

A major challenge in understanding the relationship between lean mass and bone is that both lean mass and bone mass have a strong heritable component. A study of young adult twins (aged 23–31 years) found that additive genetic factors accounted for 87 % of the variation in total body BMD, 81 % of the variation in lean mass, and 69–88 % of the covariance between lean mass and BMD depending on the skeletal site. Population differences also provide evidence of genetic determinants of lean and bone mass. Cardel et al. [96] compared groups of African or European ancestry ($n = 301$, aged 7–12 years) using ancestry informative DNA markers and found that a greater amount of African admixture was associated with greater lean mass and BMC after adjusting for socioeconomic status, sex, age, height, race/ethnicity, and pubertal status.

The effect of fat mass on bone mineral accretion and attainment of peak bone mass is far more controversial. Generally, greater body weight increases the effects of weight-bearing activity on bone. As children grow and increase in weight, both lean and fat mass increase. To reduce the likelihood of confounding from the bone loading effects of lean mass, it is important to first account for the effect of lean mass on bone in order to determine the effects of fat mass.

The source of adipose tissue may be important in considering the effects of body composition on bone outcomes. Visceral adipose tissue has different metabolic effects compared to subcutaneous fat, and it may be deleterious to bone by reducing bone quality. Adipose infiltrations of muscle and bone marrow associated with excess adiposity also have adverse effects on bone. Muscle density measured by pQCT is lower when the fat content within muscle is increased.

Nonmodifiable factors

Genetics

An estimated 60–80 % of the variability in bone mass and osteoporosis risk is explained by heritable factors. aBMD is lower among daughters of women with osteoporosis [97] and in men and women with first-degree relatives who have osteoporosis [98]. The familial resemblance of BMC is expressed prior to puberty [99, 100]. Genome-wide association studies have identified more than 70 loci associated with adult bone density or fractures [101, 102]. However, only a few such studies have been conducted in children [1, 103–106]. Twin studies also suggest that genetic predisposition determines up to 80 % of peak bone mass; the remaining 20 % is modulated by environmental factors and sex hormone levels during puberty [107].

Population ancestry

In North America, ethnic differences in vBMD and aBMD have been reported in children [5, 108, 109]. Among individuals aged 9–25 years, aBMD was consistently greater at all sites for African Americans compared to other groups, whereas Caucasians had greater values than Asians and Hispanics. In studies comparing children of Asian, European, and Hispanic ancestry, group differences in BMC were attributable to differences in bone size [110–112]. Ethnic differences in the rate of BMD gain have also been observed [109]. Differences between Caucasians, Asians, and Hispanics are smaller than between blacks and other groups; thus, pediatric reference ranges for BMC and aBMD are presented for African Americans and non-African Americans, and the International Society for Clinical Densitometry recommends using race-specific reference ranges in childhood because they reflect genetic potential for bone accretion [60, 111]. Studies

using QCT provide insights into the population ancestry differences in DXA measures by describing cortical bone dimensions and trabecular density [5, 113–115]. As noted earlier, trabecular density increases during puberty. The magnitude of the pubertal increase in trabecular density is greater in African-American individuals than in Caucasians, and African-American children have greater total femoral bone in cross-sectional analyses [5, 6, 115].

Sex

Among children and adolescents, males have greater BMC and aBMD than females. These differences become more pronounced with the onset and progression through puberty or at the ages that correspond to these maturational changes [108, 109, 116–118]. The exact age at which these differences emerge is unclear. Earlier studies of infants (aged ≤12 months) did not find sex differences in total body BMD [119, 120] or spine BMC and aBMD [121, 122]; however, males (aged 1–18 months) had greater total body BMC than females [123]. A recent study of infants and toddlers aged 1–36 months confirmed the absence of sex differences in aBMD in very young children but found greater BMC in males than in females. Sex differences in the body size of infants and toddlers may account for BMC differences and the absence of aBMD differences. By about 5 years of age, girls have lower values for spine and hip aBMD than boys, a finding that persists when adjusted for age, height, and weight [124].

Studies of bone strength by pQCT reveal a more complex pattern of sex differences. In a study of 665 healthy individuals aged 5–35 years, cortical BMC, periosteal circumference, and section modulus were lower in the 38 % site of the tibia for females compared with males across all stages of puberty. However, cortical vBMD was greater and endosteal circumference was lower in peripubertal and postpubertal females compared to males. These differences were not attributable to differences in muscle mass or bone size [115]. In a 20-month longitudinal study of 128 children across puberty, boys exhibited a 10 % greater increase in total area and cortical area compared to girls, but the increase in the size of the marrow cavity was significantly less for girls than for boys [125]. Further evaluation showed that sex differences in bone strength are primarily due to the 4–6 % greater bone area in boys, which is evident in prepubertal children [126]. HRpQCT studies of the radius show that girls have higher cortical vBMD in midpuberty and postpuberty (9.4 and 7.4 %, respectively) and lower cortical porosity than boys (−118 and −56 %, respectively) [127].

Maturation

Advancement through puberty is associated with increases in BMC and aBMD, as well as cortical and trabecular vBMD. Moreover, several studies suggest that the timing of maturation may affect peak bone mass, particularly in girls. For example, Gilsanz et al. [128] showed that earlier age of pubertal onset was associated with greater DXA BMC and aBMD at skeletal maturity in both boys and girls, independent of prepubertal BMC and aBMD values and duration of puberty. Chevalley et al. [129] found that girls who attained menarche earlier had higher aBMD at multiple skeletal sites prior to, during, and after puberty. A Canadian longitudinal study (depicted in Fig. 2) found that girls who mature early had 3–4 % more total body BMC at age 20 years than girls who matured at an average age. However, maturational effects were only observed at the total body and not at other sites; no maturational timing effects were observed in males [130]. The absence of a maturation timing effect on aBMD and BMC of the lumbar spine, femoral neck, and total body was confirmed in a study of Swedish military recruits in which young men were followed until age 24 years. However, as with girls, later puberty in boys was associated with lower radius aBMD (−4.2 %, by DXA), as well as lower cortical (−0.7 %) and trabecular vBMD (−4.8 %, by pQCT) [131]. The long-term consequences of the effect of pubertal timing on peak bone mass remain to be determined.

Modifiable factors

Diet and physical activity are the primary modifiable factors associated with bone health, although other lifestyle and environmental factors may also be at play. Here, we review these factors and their contribution to peak bone mass.

Although we separately address the contribution of physical activity to peak bone mass and strength, we address nutrient interactions with physical activity and their effects on bone in the respective nutrient discussions. Several narrative and meta-analysis review articles were recently published that also address the strength of the evidence for physical activity and bone development [132–137].

Scientific statement aims

In this scientific statement, we (1) report the results of an evidence-based review of the literature since 2000 on factors that influence achieving the full genetic potential for skeletal mass, (2) recommend lifestyle choices that promote maximal bone health throughout the lifespan, (3) outline a research agenda to address current gaps, and (4) identify implementation strategies.

Methods

We performed a comprehensive PubMed (http://www.ncbi.nlm.nih.gov/pubmed) search of the scientific literature for

articles published from January 2000 through December 2014. For all search terms, the following search strategy was used: ((((search term[Title/Abstract]) AND bone[Title/Abstract]) AND child*[Title/Abstract]) AND adolescen*[Title/Abstract]) NOT review[Publication Type]. Language, date, and species filters were then applied to the list of search results to eliminate articles not in English, articles published outside the 2000–2014 window, and animal studies. Searches for some of the topics required less restrictive searching in order to yield viable results, such as removal of the terms "child*" and/or "adolescen*," or by expanding searches to scan terms found in "All Fields" rather than just "Title/Abstract." MeSH terms were also utilized in some instances. Studies that contained subjects aged ≤21 years were included, except in the alcohol and smoking literature, in which studies that contained subjects aged ≤22 years were accepted due to lack of data in younger populations. Figure 5 represents the flow diagram of the systematic review for peak bone mass that includes search topics and the number of search returns.

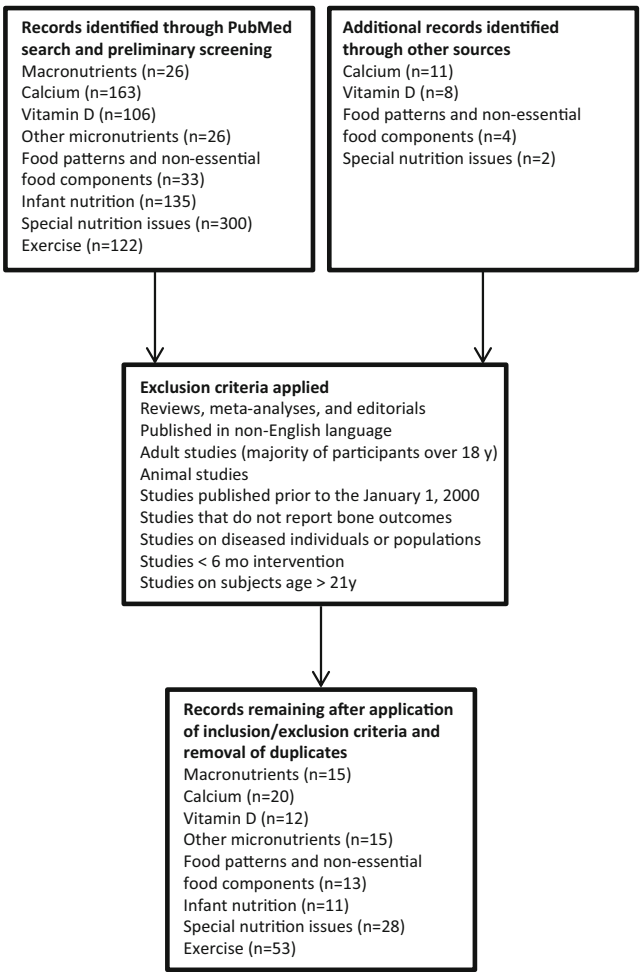

Fig. 5 Flow diagram of the systematic review on peak bone mass

To further narrow the search results for the broader topics (e.g., calcium, vitamin D, physical activity), we assigned authors to subcommittees based on their expertise and these subcommittees then reviewed the resultant abstracts. We excluded any articles that were not describing RCTs or observational studies, any studies that did not examine bone outcomes, and any interventions that were <6 months in duration. Studies and drug trials addressing disease states, with the exceptions of eating disorders and obesity, were likewise excluded. The articles that remained after the applications of these criteria were then rated based on the extent of scientific evidence as outlined in Table 1. This evidence grading system has previously been utilized by prominent organizations such as American Society for Nutrition [138] and the American Diabetes Association [139] and is recommended by other experts [140]. The assigned grade reflects the strength of available evidence on individual modifiable lifestyle factors that may (or may not) influence the development of peak bone mass. We assigned evidence grades after we achieved consensus among the writing group.

Tables 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13 summarize the articles that were chosen for inclusion in the current review, and these include additional articles located via review articles, meta-analyses, and expert knowledge of the literature.

Results

Nutrition and peak bone mass

Macronutrients

Fat (Table 2) The search for fat identified no RCTs, 1 prospective study, and 1 cross-sectional study published since 2000, encompassing 163 individuals (Table 2). Data from the prospective study demonstrated that changes in aBMD of the spine in males between ages 16 and 22 years were positively associated with serum levels of arachidonic acid and all omega-3 fatty acids, including DHA [141]. The cross-sectional study by Eriksson et al. [142] showed positive correlations between total body BMC and serum nervonic acid and arachidonic acid as well as negative associations with α-linolenic acid.

Our evidence grade for fat was based on findings from one prospective study with methodological limitations and one cross-sectional study.

Grade: Level of evidence D was assigned for evidence for the benefit of fat on bone.

Table 2 Fat and bone health in children and adolescents

Macronutrient	Reference	Study description	Population description	Number of subjects	End points	Results					
Prospective studies											
Fat	Hogstrom et al. 2007 [141]	The objective of this study was to investigate the role of fatty acids in bone accumulation and the attainment of peak bone mass in young men	Sex: male Age: 16.7 years at baseline Race: white Location: Sweden Year(s): 1994 (baseline), first follow-up was at a mean of 6 years (age 22 years)	78	Data are shown for the overall group ($N = 78$)	Total body		Hip		Spine	
						r	*P*	*r*	*P*	*r*	*P*
					Palmitic acid	−0.04	NS	01	NS	0.01	NS
					Palmitoleic acid	0.04	NS	0.03	NS	0.02	NS
					Stearic acid	0.07	NS	0.02	NS	0.04	NS
					Oleic acid	−0.19	NS	−0.10	NS	−0.22	NS
					Linoleic acid	0.00	NS	−0.06	NS	−0.15	NS
					Eicosatrienoic acid	−0.09	NS	−0.04	NS	−0.08	NS
					Arachidonic acid	0.12	NS	0.15	NS	0.25	<0.05
					Eicosapentaenoic acid	0.04	NS	0.02	NS	0.16	NS
					Docosapentaenoic acid	0.02	NS	−0.07	NS	0.05	NS
					DHA	0.10	NS	0.07	NS	0.26	<0.05
					PUFA	0.14	NS	0.07	NS	0.16	NS
					MUFA	−0.18	NS	−0.09	NS	−0.21	NS
					SFA	0.04	NS	0.03	NS	0.05	NS
					n-6	0.04	NS	0.00	NS	0.07	NS
					n-3	0.10	NS	0.07	NS	0.26	<0.05
					n-6:*n*-3	−0.12	NS	−0.13	NS	−0.26	<0.05
					Data presented above include Pearson's correlations between fatty acids measured in the phospholipid fraction for changes in aBMD from 16 to 22 years						
Cross-sectional studies											
Fat	Eriksson et al. 2009 [142]	Serum phospholipid fatty acid pattern was studied in relation to bone parameters in healthy children	Sex: male and female Mean age: 8.2 years Race: Caucasian Location: Gothenburg, Sweden Year(s): not specified	85	Data are shown for the overall group ($N = 85$)	Total body BMC (g)					
						Correlation (*r*)		*P*			
					Palmitic acid (16:0)	0.17		NS			
					Stearic acid (18:0)	−0.15		NS			
					Arachidic acid (20:0)	0.20		NS			
					Nervonic acid (24:1*n*-9)	0.27		<0.05			
					Linoleic acid (18:2*n*-6)	−0.17		NS			
					Arachidonic acid (20:4*n*-6)	0.23		<0.05			
					α-Linolenic acid (18:3*n*-3)	−0.22		<0.05			
					DHA (22:6*n*-3)	0.03		NS			
					∑ *n*-6	−0.07		NS			
					∑ *n*-3	0.03		NS			
					n-6:*n*-3	−0.06		NS			
					Data presented above are from Pearson's correlations						

25(OH)D 25-hydroxyvitamin D, *aBMD* areal bone mineral density, *ANCOVA* analysis of covariance, *BMC* bone mineral content, *IGF* insulin-like growth factor, *NS* not significant

Table 3 Protein and bone health in children and adolescents

Macronutrient	Reference	Study description	Population description	Number of subjects	End points	Results			
RCTs									
Protein	Ballard et al. 2006 [143]	This study investigated whether 6 months of protein supplementation in conjunction with a strength and conditioning training program improves vBMD, bone geometry, and total body BMC.	Sex: male and female Age: 18–25 years Race: not specified Location: South Dakota, USA Year(s): not specified	68	Data are shown for the protein supplemented group ($n = 36$)	Mean change, protein group ($n = 36$)	P		
					4 % site				
					Total vBMD (mg/cm^3)	0.20	NS		
					Trabecular vBMD (mg/cm^3)	−0.50	NS		
					Total area (cm^2)	5.0	NS		
					20 % site				
					Cortical vBMD (mg/cm^3)	2.4	NS		
					Cortical area (cm^2)	1.7	NS		
					Cortical thickness (mm)	0.05	NS		
					Periosteal circumference (mm)	−0.20	NS		
					Endosteal circumference (mm)	−0.50	NS		
					Polar SSI (mm^3)	57	NS		
					Total body				
					BMC (g)	−3.5	NS		
					Bone area (cm^2)	−3.9	NS		
					Leg				
					BMC (g)	1.3	NS		
					Arm				
					BMC (g)	5.7	NS		
					Data presented above are least-squares means determined by ANCOVA while controlling for initial height and weight and baseline bone value.				
Prospective studies									
Protein	Alexy et al. 2005 [144]	This study examined whether the long-term dietary protein intake and diet net acid load are associated with bone status in children. In a prospective study design, long-term dietary intakes were calculated from 3-day weighed dietary records that were collected yearly over the 4-year period before a one-time bone analysis using pQCT.	Sex: male and female Age: 6–18 years Race: white Location: Dortmund, Germany Year(s): 1998–1999 subcohort of the DONALD study	229	Data are shown for the overall group ($N = 229$)	Protein (g/day)			
						ß	$ß_{stand}$	r^2	P
					Forearm				
					Periosteal circumference (mm^2)	0.07	0.17	0.03	<0.01
					Cortical area (mm^2)	0.42	0.27	0.04	<0.01
					BMC (mg/mm)	0.46	0.26	0.03	<0.01
					Polar SSI (mm^3)	1.83	0.29	0.06	<0.01
					• Data presented above are results from stepwise multiple regression and after adjustment for age, sex, and energy intake. • $ß_{stand}$ is the standardized parameter estimate. • Children with a higher dietary PRAL had significantly less cortical area ($P < 0.05$) and BMC ($P < 0.01$). • Long-term calcium intake had no significant effect on any bone variable.				
Protein	Bounds et al. 2005 [146]	This study aimed to identify factors related to children's bone	Sex: male and female	52	Data are shown for the overall group ($N = 229$)	Protein intake (g) over ages 2–8 years			

Table 3 (continued)

Macronutrient	Reference	Study description	Population description	Number of subjects	End points	Results		
		mineral indexes at age 8 years, and to assess bone mineral indexes in the same children at ages 6 and 8 years. Children's dietary intake and BMC were assessed as part of a longitudinal study from ages 2 months to 8 years.	Age: 6 years (baseline) and 8 years (follow-up) Race: white Location: Knoxville, TN Year(s): not specified			*r*	*P*	
					Total body			
					BMC at age 8 years	0.37	≤0.05	
						ß	Partial R^2	*P*
					BMC model 1	(+) 2.40	0.08	<0.01
					Data presented above show the Pearson's correlation coefficient (*r*) relating protein intake over ages 2–8 years, representing 27 days of dietary data. BMC model 1 ($R^2 = 0.69$, $F = 20.7$, $P < 0.01$)			
Protein	Vatanparast et al. 2007 [147]	This mixed-longitudinal study investigated the influence of protein intake on bone mass measures in young adults, considering the influence of calcium intake through adolescence. Dietary intake was assessed via serial 24-h recalls carried out at least once yearly.	Sex: male and female Age: 8–21 years during phase I of the study; 17–29 years for phase II Race: majority Caucasian Location: Saskatoon, Saskatchewan, Canada Year(s): 1991–1997 (phase I); 2003–2006 (phase II); participating in the University of Saskatchewan Pediatric Bone Mineral Accrual Study	133	Data are shown for the overall group ($N = 133$) and a subgroup ($n = 44$)	Protein intake (g)		
						Regression coefficient	Partial R^2	*P*
					Total body ($N = 133$)			
					BMC	NS	—	NS
					BMC net gain	0.11	0.21	0.02
					Total body ($n = 44$)			
					BMC	0.21	0.33	0.04
					BMC net gain	0.21	0.37	0.02
					The net gain of total body BMC and the net gains of height and weight from age of peak height velocity to early adulthood were entered into the model. Variables in the multiple regression model (stepwise) were sex, current height, weight, physical activity level, protein intake, vegetable and fruit intake, and periadolescence intakes of vegetables and fruit, protein, and physical activity. Protein intake predicted total body BMC net gain in all subjects. In females at periadolescence or early adulthood with adequate calcium intake(>1000 mg/day) ($n = 44$), protein intake positively predicted total body BMC and BMC net gain.			
Protein	Zhang et al. 2010 [148]	This study assessed the association between protein intakes and bone mass accrual in girls who participated in a 5-year study including 2 years of milk supplementation (intervention groups only) and 3 years of follow-up study.	Sex: female Mean age: 10.1 years Race: Chinese Location: Beijing Year(s): 1999–2004	757	Data are shown for the overall group ($N = 757$)	Average protein intake		
						ß	*P* value	
					Total body			
					Bone area	–	NS	
					BMC	−1.92	0.02	
					Proximal forearm			
					Bone area	−9.11	<0.01	
					BMC	−10.2	<0.01	
					Distal forearm			
					Bone area	–	NS	
					BMC	−4.82	<0.01	
					• Data presented above (ß) represent the percentage change in the dependent variable associated with intake of protein after controlling for baseline bone mass and pubertal development, age and physical activity, survey time, group, and clustering by			

Table 3 (continued)

Macronutrient	Reference	Study description	Population description	Number of subjects	End points	Results
					schools. Protein, among other nutrients, was included in an initial model and flowed by backward elimination with $P < 0.01$ as the standard for retention, exclusion by the regression model. • When protein intake was considered according to animal or plant food sources, protein from animal foods, particularly meat, had significant negative effects on BMC accrual at the proximal and distal forearm ($P < 0.05$).	
Protein	Remer et al. 2011 [145]	The aim of the study was to examine whether the association of long-term dietary acid load and protein intake with children's bone status can be confirmed using approved urinary biomarkers and whether these diet influences may be independent of potential bone-anabolic sex steroids. Data were collected in 197 healthy children during the 4 years preceding proximal forearm bone analyses by pQCT.	Sex: male and female Age: 6–18 years Race: white Location: Dortmund, Germany Year(s): 1998–1999 subcohort of the DONALD study	197	Data are shown for the overall group ($N = 197$)	Urinary uN: ß / *P*; Urinary PRAL: ß / *P*
					Forearm	
					BMC (mg/mm) [log 10]	0.03 / <0.01 / −0.02 / 0.03
					Cortical area (mm^2) [log 10]	0.02 / <0.01 / −0.02 / 0.03
					Polar SSI (mm^3) [log 10]	0.02 / <0.01 / −0.01 / NS
					Periosteal circumference (mm)	0.50 / 0.03 / 0.02 / NS
					BMD (mg/cm^3)	5.40 / NS / −8.70 / NS
					• Data presented above are from multivariate regression models showing independent associations of both long-term protein intake (as uN) and PRAL as explanatory variables with forearm bone variables. Data are adjusted for age, sex, pubertal stage, forearm muscle area, forearm length, and urinary calcium. • Data show that 1 Z-score variation in uN leads to an average 7.2 % increase in BMC and a 4.7 % increase in cortical area as well as SSI. A 1 Z-score uN corresponds to 0.28-g protein intake/kg body wt, implying that an additional 1-g protein intake/kg body wt may lead to an average increase of 26 % in BMC and 17 % in cortical area and SSI. A 1-g protein intake/kg body wt is associated with an average increase of 1.8-mm periosteal circumference.	
Cross-sectional studies						
Protein	Hoppe et al. 2000 [149]	The objective of the study was to identify associations between dietary factors and total body bone measurements in a random sample of healthy Danish children.	Sex: male and female Age: 10 years Race: Danish, otherwise unspecified Location: Hvidovre, Denmark Year(s): 1997–1998, from the Copenhagen Cohort Study on Infant Nutrition and Growth	105	Data are shown for the overall group ($N = 105$)	Protein (g/day): Pearson's *r* / *P*
					Total body	
					Bone area (cm^2)	0.31 / <0.01
					BMC (g)	0.33 / <0.01
					• The data above are unadjusted. • In the multiple linear regression analysis including height, weight, sex, energy intake, and bone-related nutrients in the model, dietary protein was not significantly associated with bone area or BMC. After backward elimination, in which height, weight, and sex were forced to stay in the model, dietary protein was positively associated with bone area ($P < 0.05$). • Inclusion of pubertal stages in the analyses did not alter the bone area or BMC outcomes.	
Protein	Iuliano-Burns et al. 2005 [150]	This cross-sectional study assessed monozygotic and dizygotic male twin pairs to test the following hypotheses: (1) associations between bone mass and dimensions and exercise are greater than between bone mass and dimensions and protein or	Sex: male Age: 7–20 years Race: not specified Location: Melbourne, Australia Year(s): 1997–2001	112 (56 twin pairs)	Data are shown for the overall group ($N = 112$)	Differences in protein: Univariate ß / *P*; Size adjusted ß / *P*; All lifestyle and size adjusted ß / *P*
					Differences in BMC (g)	
					Total body	3.5 / NS / 1.3 / NS / 1.3 / NS

Table 3 (continued)

Macronutrient	Reference	Study description	Population description	Number of subjects	End points	Results					
		calcium intakes; and (2) exercise or nutrient intake are associated with appendicular bone mass before puberty and axial bone mass during and after puberty.			Arms	0.8	<0.05	0.7	<0.05	0.8	<0.05
					Legs	1.6	NS	0.3	NS	0.3	NS
					Lumbar spine	0.0	NS	0.0	NS	0.0	NS
					Differences in BMC (%)						
					Total body	0.3	<0.05	0.2	<0.05	0.1	NS
					Arms	0.4	<0.05	0.4	<0.01	0.4	<0.05
					Legs	0.3	NS	0.1	NS	0.1	NS
					Lumbar spine	0.1	NS	0.1	NS	0.2	NS
					Differences in bone dimensions (mm)						
					Cortical thickness	0.0	NS	0.0	NS	0.0	NS
					Periosteal diameter	0.0	NS	0.0	NS	0.0	NS
					Endosteal diameter	0.0	NS	0.0	NS	−0.0	NS
					Differences in bone dimensions (%)						
					Cortical thickness	0.2	NS	0.1	NS	0.4	NS
					Periosteal diameter	0.1	NS	0.0	NS	0.0	NS
					Endosteal diameter	−0.0	NS	−0.1	NS	−0.3	NS
					• Data presented above are ß coefficients for within-pair differences in protein versus (1) within-pair differences in BMC and bone dimensions, (2) within-pair differences in size-adjusted BMC and bone dimensions, and (3) when all within-pair differences in protein, calcium, exercise duration, and size are included in the regression equation. • A 1-g difference in protein intake was associated with a 0.8-g (0.4 %) difference in arm BMC ($P < 0.05$). These relationships were present in peripubertal and postpubertal pairs but not in prepubertal pairs. Exercise during growth appears to have greater skeletal benefits than variations in protein or calcium intakes, with the site-specific effects evident in more mature twins.						
Protein	Chevalley et al. 2008 [151]	This study analyzed the relationship between physical activity levels and protein compared with calcium intake on BMC in healthy prepubertal boys.	Sex: male Age: 6.5–8.5 years Race: white Location: Geneva, Switzerland Year(s): recruitment period 1999–2000, otherwise unspecified	232	Data are shown for the overall group ($N = 232$)	Correlation with protein intake (g/day)					
						r	P		$ß_{Adjusted}$		P
					BMC (g)						
					Radial metaphysis	0.26	<0.01		0.20		0.01
					Radial diaphysis	0.21	<0.01		0.12		NS
					Total radius	0.27	<0.01		0.20		0.01
					Femoral neck	0.20	<0.01		0.19		0.03
					Total hip	0.18	<0.01		0.12		NS
					Femoral diaphysis	0.23	<0.01		0.19		0.03
					Lumbar spine	0.24	<0.01		0.22		<0.01
					Data presented above are from univariate (r) and multivariate ($ß_{Adjusted}$) analyses; the latter takes into account the respective contribution of physical activity, protein, and calcium intakes.						
Protein	Esterle et al. 2009 [152]	This study explored dietary calcium sources and	Sex: female Age: 12–22 years	192	Data are shown for the postmenarchal group only ($n = 142$)	Protein from milk			Protein from other foods		

Table 3 (continued)

Macronutrient	Reference	Study description	Population description	Number of subjects	End points	Results
		nutrients possibly associated with lumbar bone mineralization and calcium metabolism in adolescent girls and evaluated the possible influence of a genetic polymorphic trait associated with adult-type hypolactasia.	Race: Caucasian Location: France Year(s): not specified			Adj R^2 / ß$_{stand}$ / P / Adj R^2 / ß$_{stand}$ / P
					Lumbar spine BMC (g)	
					Absolute	0.61 / 0.14 / <0.01 / 0.61 / <0.01 / NS
					Adjusted	0.60 / 0.13 / 0.02 / 0.60 / <0.01 / NS
					• Data presented above are from multivariate linear analyses. • Absolute protein intake is expressed in g/days. • Adjusted protein intake for weight, years after menarche, and vertebral area is expressed in g/kg/days. • Girls with milk intakes <55 mL/day had significantly lower BMC compared to girls consuming >260 mL/day. • Neither BMC nor milk consumption was associated with −13,910 LCT polymorphism.	
Protein	Ekbote et al. 2011 [153]	The aim of this study was to examine lifestyle factors as determinants of total body BMC and bone area in Indian preschool children.	Sex: male and female Age: 2–3 years Race: Indian Location: Pune, India Year(s): 2009	71	Data are shown for the overall group ($N = 71$)	Protein (g/days) Normal / Malnourished / All r / P / r / P / r / P
					Total body	
					Bone area	0.65 / <0.01 / 0.57 / <0.01 / 0.58 / <0.05
					BMC	0.62 / <0.01 / 0.44 / <0.05 / 0.55 / <0.01
					Data presented above are from Pearson's correlation coefficients correlating protein intake and bone among normal children, malnourished children, and all (normal and malnourished children combined).	
Protein	Libuda et al. 2011 [154]	This study examined relevant nutrients that are supposed to have an impact on bone parameters and compared their effect sizes with those of known predictors of bone development.	Sex: male and female Median age: 8.1 years Race: white Location: Dortmund, Germany Year(s): 1998–1999 subcohort of the DONALD study	107	Data are shown for the overall group ($N = 107$)	Protein (g/MJ) ß / ß$_{stand}$ / R^2 / P
					Forearm	
					Polar SSI (mm^3)	– / – / – / NS
					Periosteal circumference (mm)	– / – / – / NS
					BMC (mg/mm)	1.49 / 0.11 / 0.01 / NS
					Cortical area (mm^2)	1.37 / 0.11 / 0.01 / NS
					• Data presented above are from stepwise linear regression analyses, considering muscle area, BMI standard deviation scores, body fat %, age, sex, and rostenediol, as well as intakes of protein, calcium, vitamin D, and PRAL. • Of all nutrients considered, only protein showed a trend for an association with BMC ($P = 0.073$) and cortical area ($P = 0.056$) in stepwise linear regression models. • None of the other dietary variables were associated with bone parameters. • The protein effect did not differ between sexes.	

Adj adjusted, *ANCOVA* analysis of covariance, *BMC* bone mineral content, *BMD* bone mineral density, *DONALD* Dortmund Nutritional and Anthropometric Longitudinally Designed Study, *NS* not significant, *pQCT* peripheral quantitative computed tomography, *PRAL* potential renal acid load, *RCT* randomized controlled trial, *SSI* stress–strain index, *uN* urinary nitrogen, *vBMD* volumetric bone mineral density

Table 4 Calcium and bone health in children and adolescents

Nutrient	Reference	Study description	Population description	Number of subjects	End points	Results	
RCTs							
Supplements							
Calcium carbonate, 1000 mg/day	Dibba et al. 2000 [160]	12-month randomized, double-blind, placebo-controlled study Supplementation increased calcium intake from 342 to 1056 mg/day By young adulthood, there was no difference in the amount of bone accrued (mineral or size) or the rate of bone growth between supplemented and placebo.	Sex: 80 boys, 80 girls Age: 8.3–11.9 year Race: Gambian, otherwise unspecified Location: rural Gambia, West Africa	160		Difference in % gain between groups	
					Midshaft arm BMC	4.6 ± 0.9[a]	
					Distal radius BMC	5.5 ± 2.7[a]	
					Adjusted for bone width, weight, and height		
Calcium carbonate, 800 mg + 400 IU vitamin 3/day	Moyer-Mileur et al. 2003 [163]	1-year double-blind RCT Baseline calcium: not reported Average intake during study: supplement, 1524 (353); placebo, 906 (345); 30 % dropout Trabecular vBMD values were significantly greater in the supplemented group at baseline.	Sex: female Age: 12 years; Tanner stage 2 Race: white Location: USA	100	Tibial pQCT measurements	Calcium and D	Placebo
					Trabecular vBMD % increase[a]	1.0	−2.0
					Trabecular BMC % increase[a]	4.1	1.6
					Adjusted for baseline values		
Elemental calcium, 1000 mg/day	Rozen et al. 2003 [330]; Dodiuk-Gad et al. 2005 [331]	12-month double-blind, placebo-controlled Habitual calcium intakes <800 mg/day Compliance dropped from 71 ± 26 % during the initial 6 months to 56 ± 34 % for the remaining study period ($P = 0.0001$) In follow-up study by Dodiuk-Gad et al., girls who have had compliance of ≥75 % on supplementation had significantly higher total body BMD after 3.5 years after supplementation than controls.	Sex: female; >1 year postmenarchal Age: 12–17 years Race: 85 Jewish girls and 27 Arab girls Location: Haifa, Israel	112		Calcium supplement	Placebo
					Lumbar spine BMC	4.52 ± 0.48	3.95 ± 0.58
					Total body BMC	4.63 ± 0.42	4.65 ± 0.54
					Femoral neck BMC	4.30 ± 0.86	3.00 ± 0.81
					Lumbar spine BMD	3.66 ± 0.35[a]	3.00 ± 0.43
					Total body BMD	3.80 ± 0.30[a]	3.07 ± 0.29
					Femoral neck BMD	2.00 ± 0.51	1.39 ± 0.42
					Not adjusted		
Calcium carbonate (Caltrate) supplement, 1200 mg/day	Cameron et al. 2004 [161]	24-month RCT of twins Baseline calcium intake: 786, trt; 772, control in those who completed 24 months All were premenarchal at baseline	Sex: female Age: 8–13 years Race: not specified Location: Australia	103 (50 twin pairs + 1 set of triplets)	End of 24-month intention to treat	Difference in % gain between groups	
					Total body BMC	3.69[a]	
					Hip BMD	−0.39[a]	
					Spine BMD	1.40[a]	

Table 4 (continued)

Nutrient	Reference	Study description	Population description	Number of subjects	End points	Results	
		24 (38 %) of pairs completed 24 months Compliance was 76 % for both groups			Femoral neck BMD End of 12 months Total body BMC Hip BMD Spine BMD Femoral neck BMD Adjusted for age, height, and weight	−0.57 2.47[a] 1.64[a] 1.64[a] 1.13	
Calcium carbonate, 500 mg/day	Molgaard et al. 2004 [332]	12-month randomized, double-blind, placebo-controlled intervention Subjects stratified at randomization according to baseline calcium intake Group A ($n = 60$) habitually consumed 1000–1307 mg/day (40th–60th percentile), and group B ($n = 53$) habitually consumed <713 mg/day (<20th percentile)	Sex: female Age: 12 years ± 6 months Race: white Location: Denmark	113	No significant interaction between habitual calcium intake (groups A and B) and the intervention (Calcium carbonate–Placebo) in the analyses of height, weight, BMC, size-adjusted BMC, bone area, or BMD (all $P > 0.15$). When groups A and B were analyzed together, there was a significant effect of the intervention on BMD (0.8 %; 95 % CI, 0.01 %, 1.54 %; $P = 0.049$).		
Calcium citrate malate, 1000 mg/day	Matkovic et al. 2005 [333]	4-year randomized clinical trial and optionally extended for an additional 3 years Baseline calcium: 830 ± 236 mg/day 51 % of the subjects completed the 7-year trial.	Sex: female Age: 11 years; Tanner 2 Race: white Location: USA	354		Calcium supplement	Placebo
					End of 4-year gain		
					Total body BMD (g/cm^2)	0.215 ± 0.037[a]	0.204 ± 0.0353
					Proximal radius BMD (g/cm^2)	0.167 ± 0.088	0.171 ± 0.079
					Distal radius BMD (g/cm^2)	0.106 ± 0.047[a]	0.092 ± 0.046
					Cortical area/total area	0.079 ± 0.021	0.072 ± 0.0213
					End of 7-year gain		
					Total body BMD (g/cm^2)	0.268 ± 0.049	0.263 ± 0.044
					Proximal radius BMD (g/cm^2)	0.162 ± 0.038	0.156 ± 0.036
					Distal radius BMD (g/cm^2)	0.171 ± 0.047	0.165 ± 0.040
					Cortical area/total area	0.095 ± 0.025[a]	0.085 ± 0.024*2*
					By young adulthood, significant effects remained at metacarpals and at the forearm of tall persons.		
Calcichew, 1000 mg/day	Prentice et al. 2005 [162]	13-month randomized, double-blind, placebo-controlled study	Sex: male Age: 16–18 years	143		Difference in % gain between groups	
					Total body BMC	0.33 ± 0.34	

Table 4 (continued)

Nutrient	Reference	Study description	Population description	Number of subjects	End points	Results
		Subjects were stratified by high or low exercise at baseline. Those in the low group were randomized to exercise intervention or none. Compliance with exercise was poor and no statistically significant differences were found between groups. For final analysis, all exercise intervention groups were combined. Subjects were told to not take the supplement with meals. Baseline calcium: 1197, supplement; 1199, placebo Total calcium intake during study: supplement, 1858 ± 629; placebo, 1283 ± 586 Latter factored in compliance	Race: 90 % white; 10 % from various ethnic groups Location: Cambridge, UK		Lumbar spine BMC	0.18 ± 0.54
					Total hip BMC	1.09 ± 0.54[a]
					Femoral neck BMC	1.21 ± 0.65
					Intertrochanter BMC	0.99 ± 0.56
					Trochanter BMC	0.29 ± 0.80
					Ultradistal radius BMC	0.36 ± 0.86
					Adjusted for bone area, weight, and height	
Calcium carbonate, 800 mg/day and vitamin D_3 400 IU/day	Greene and Naughton 2011 [164]	6-month randomized placebo-controlled trial Baseline calcium: 763–786 mg/day	Sex: female; identical twins Age: 9–13 years Race: not indicated Location: Australia	40 (20 pairs)	pQCT	Tibial difference in % gain between groups
					4 % location	
					Trabecular vBMD (mg/mm^3)	5.2 ± 1.96[a]
					Trabecular area (mm^2)	5.4 ± 1.33[a]
					Subcort density (mg/mm^3)	3.4 ± 0.82
					Subcortical area (mm^2)	0.8 ± 0.07
					SSI (mm^3)	6.6 ± 1.26[a]
					14 %	
					Cortical BMD (mg/mm^3)	0.1 ± 0.04
					Cortical area (mm^2)	1.3 ± 0.35
					Total bone area (mm^2)	0.3 ± 0.02
					Medullary CSA (mm^2)	−0.4 ± 0.02
					SSI (mm^3)	1.7 ± 0.22
					38 %	
					Cortical BMD (mg/mm^3)	0.8 ± 0.03
					Cortical area (mm^2)	5.8 ± 0.8[a]

Table 4 (continued)

Nutrient	Reference	Study description	Population description	Number of subjects	End points	Results		
					Total bone area (mm^2)	0.5 ± 0.03		
					Medullary CSA (mm^2)	−6.2 ± 1.6[a]		
					SSI (mm^3)	0.7 ± 0.06		
					66 %			
					Cortical BMD (mg/mm^3)	0.1 ± 0.02		
					Cortical area (mm^2)	5.7 ± 0.39[a]		
					Total bone area (mm^2)	−0.7 ± 0.03		
					Medullary CSA (mm^2)	−8.1 ± 1.82[a]		
					Muscle CSA (mm^2)	0.6 ± 0.02		
						Radial difference in % gain between groups		
					4 % location			
					Trabecular vBMD (mg/mm^3)	3.3 ± 0.28[a]		
					Trabecular area (mm^2)	2.8 ± 0.36[a]		
					Subcortical density (mg/mm^3)	0.1 ± 0.03		
					Subcortical area (mm^2)	0.3 ± 0.01		
					SSI (mm^3)	5.7 ± 0.51[a]		
Calcium carbonate pills	Khadilkar et al. 2012 [334]	1-year double-blind RCT of calcium, multivitamin with zinc, and vitamin D_3	Sex: female Age: 8–12 years Race: Indian Location: Pune, India	214	Total body BMC increase	Percent gain by group		
						Calcium + multivitamin	Calcium	Control
						21.5 ± 5.7[a]	23.1 ± 6.1[a]	19.4 ± 4.2
					Adjusted for Tanner stage and lean body mass			
Calcium, 1000 mg/day by pill or cheese Vitamin D, 800 IU/day	Cheng et al. 2005 [159]	2-year RCT; randomized to 1 of 4 groups: calcium 1000 mg/day + vitamin D 200 IU/day; calcium 1000 mg/day; cheese (1000 mg/day); placebo Baseline calcium 664–680 mg/day	Sex: female Age: 10–12 years Race: not indicated Location: Finland	195		Calcium + vitamin D	Calcium	Placebo
					DXA			
					Total body BMC (%)	34.7	35.0	35.0
					Femoral neck BMC (%)	24.0	23.3	22.4
					Total femur BMC (%)	33.6	36.4	33.6
					pQCT			
					Radius CSA	23.0	26.0	21.3
					Radius BMC	22.6	24.4	22.2
					Tibial CSA	15.6	15.8	14.8
					Tibial BMC	23.0	24.3	22.7
					No significant differences			
Fortified foods								
Calcium citrate-malate, 792 mg/day dissolved in a fruit drink	Lambert et al. 2008 [165]	18-month randomized trial with follow-up 2 years after supplement withdrawal	Sex: 96 girls Age: 11–12 years Race: white	96		Calcium supplement	Placebo	
					Total body BMC (g)	1698 ± 14[a]	1667 ± 14	
					Lumbar spine BMC	43.0 ± 0.6[a]	41.1 ± 0.6	

Table 4 (continued)

Nutrient	Reference	Study description	Population description	Number of subjects	End points	Results	
		Low calcium intake at baseline (mean 636 mg/day) Differences in gain no longer apparent 2 years after supplement withdrawal	Location: Sheffield, UK		Total hip BMC Adjusted for baseline values, age at menarche, and age at menarche × visit interaction	27.7 ± 0.3	27.2 ± 0.4
Calcium-enriched beverage, 1200 mg/day	Gibbons et al. 2004 [166]	18-month placebo-controlled, double-blind RCT of a high-calcium beverage. Controls received 400 mg/day Baseline calcium intake: 934, supplement; 985, placebo 12-month additional follow-up after end of intervention	Sex: male and female Age: 8–10 years Race: NZ European or Pakeha Location: New Zealand	154		Treatment	Control
					Total body BMD	4.4 %	3.3 % (NS)
					Hip BMD	4.8 %	3.9 % (NS)
					Spine BMD	5.9 %	5.8 % (NS)
					Trochanter BMD	6.2 %	5.1 % (NS)
					Femoral neck BMD	6.7 %	7.0 % (NS)
Calcium-fortified foods, 850 mg/day	Chevalley et al. 2005 [168]	1-year double-blind RCT of calcium-fortified foods (850 mg/day) compared to an isocaloric control	Sex: male Age: 6.5–8.5 years Race: white Location: Switzerland	235	Spine BMD (L2–4) Femoral diaphysis BMD Femoral neck BMD Trochanter BMD Radius BMD	No difference in gain 19 % greater increase in trt ($P < 0.006$) 3 % lesser increase (NS) 22 % greater (NS) 15 % greater (NS)	
600 mg calcium in 375 mL soymilk	Ho et al. 2005 [167]	1-year follow-up study between 104 adolescent girls receiving the fortified food and 95 girls in the control group	Sex: female Age: 14–16 years Race: Chinese Location: Hong Kong, China	210		Mean % change treatment ± SD	Mean % change, control
					Neck of the femur BMD	2.7 ± 2.94	1.8 ± 3.49
					Trochanter BMD	3.3 ± 3.27[a]	1.6 ± 2.94
					Intertrochanter BMD	3.6 ± 3.05[a]	2.32 ± 2.95
					Total hip BMD	3.1 ± 2.39[a]	2.05 ± 2.22
					Total hip BMC	3.8 ± 3.05[a]	2.6 ± 2.96
Dairy foods							
Dairy foods, 1000 mg/day	Merrilees et al. 2000 [169]	2-year RCT of dairy foods Baseline calcium: 744, s upplement; 765, control 1 year after end of supplementation, differences no longer seen	Sex: female Age: 15–17 years Race: unspecified NZ Location: New Zealand	91	Spine BMD Trochanter BMD Femoral neck BMD	1.5 % greater increase in trt ($P < 0.05$) 4.6 % greater increase in trt 4.8 % greater increase in trt	
330 mL UHT milk (560 mg calcium), 330 mL UHT milk + 200 or 320 IU vitamin D_3, or control	Du et al. 2004 [170]	2-year school-based randomized trial	Sex: female Age: 10–12 years Race: Chinese Location: Beijing, China	757	Total body BMC Bone area	35.9 % ($P = 0.03$) 31.3 % greater increase in trt ($P = 0.2$)	

95 % CI 95 % confidence interval, *BMC* bone mineral content, *BMD* bone mineral density, *CSA* cross-sectional area, *NS* not significant, *pQCT* peripheral quantitative computed tomography, *RCT* randomized controlled trial, *SSI* stress–strain index, *trt* treatment, *UHT* ultra-heat-treated, *vBMD* volumetric bone mineral density

[a] Significantly greater than the control

Table 5 Calcium and exercise and bone health in children and adolescents

Reference	Study description	Population description	Number of subjects	End points	Results	
Molgaard et al. 2001 [245]	1-year prospective observational study to determine effects of dietary calcium and physical activity on bone changes.	Sex: 140 boys, 192 girls Age: 5–19 years at baseline Race: Caucasian Location: Copenhagen, Denmark	332		Correlation with calcium intake, *r*	Correlation with physical activity, *r*
				Whole bone area gain adjusted for height and weight	0.03, girls	0.28
					−0.34, boys	0.28
				Total body BMC gain adjusted for bone area, height, and weight	0.21, girls	−0.06
					0.34, boys	−0.04
Carter et al. 2001 [171]	Cross-sectional study to investigate the relationship between calcium intake and BMC.	Sex: 108 boys and 119 girls Mean age: 13 years Race: Primarily Caucasian Location: Saskatoon Canada	227	Total body BMC	No association	
				Lumbar spine BMC	No association	
Lloyd et al. 2000 [174]	6-year prospective study to determine effects of dietary calcium and physical activity on bone changes	Sex: girls Age: 12–18 years at baseline Race: Caucasian Location: Pennsylvania	81	Total body BMC gain	NS	
				Total body BMD gain	NS	
				Femoral neck BMD[a]	$r = 0.42$ with exercise	
Lappe et al. 2014 [172]	6-year prospective study of calcium intake and physical activity on bone accrual	Sex: boys and girls Age: 5–16 years at baseline Race: white, black, Asian, Hispanic, and non-Hispanic Location: 5 sites in the USA	1743		Mixed-model analyses	
				Total body BMC gain[a]	Associated with physical activity in nonblacks	
				Spine BMC gain[a]	Associated with physical activity in blacks and nonblack males	
				Total hip BMC gain[a]	Associated with calcium in nonblack females	
				Adjusted for changes in height, age, and baseline BMC	Associated with physical activity in nonblacks and black males	

BMC bone mineral content, *BMD* bone mineral density, *NS* not significant

[a] Significantly greater than the control

Table 6 Vitamin D and bone health in children and adolescents

Reference	Study description	Population description	Number of subjects	Primary end points	Results				
RCTs									
Du et al. 2004 [170]	This study was a 2-year milk intervention trial in girls from nine primary schools in Beijing. Schools were randomized into three groups: (1) a carton of 330-mL milk fortified with calcium per school day, (2) a carton of 330-mL milk fortified with 200 or 320 IU 8 mg vitamin D_3, and (3) control	Sex: female Age: 10–12 years Race: Asian (Chinese) Location: Beijing, China Year(s): 1999–2001 Baseline 25(OH)D as mean (SD) in nmol/L: Control: 19.1 (7.4) Calcium only: 17.7 (8.7) Calcium + vitamin D: 20.6 (8.8)	757	Data are shown for a subsample with bone measures ($N = 346$)	Percent change Milk with calcium ($n = 111$)	Milk with calcium + vitamin D ($n = 113$)	Control ($n = 122$)	P	
				Total body					
				Bone area	29.5	28.5	31.3	NS	
				BMC	38.4	39.7	35.9	<0.01	
					Percent change, calcium + vitamin D, minus calcium	P	Percent change, calcium + vitamin D, minus control	P	
				Total body					
				Bone area	0.8	NS	−1.8	0.04	
				BMC	−0.8	NS	2.6	<0.01	
				Size-adjusted BMC	1.3	<0.01	2.4	<0.01	
				• Mean percent change values in the calcium + vitamin D group were significantly different from controls. • Adjusted percentage difference in change values are adjusted for baseline. • Size-adjusted BMC is adjusted for baseline BMC, bone area, height, weight, and menstrual status.					
Cheng et al. 2005 [159]	The purpose of this study was to examine the effects of both food-based and pill supplements of calcium and vitamin D_3 on bone mass and body composition. Children were randomized into four groups: (1) 1000 mg calcium + 200 IU vitamin D_3, (2) 1000 mg calcium + vitamin D_3 placebo, (3) 1000 mg calcium from dairy products, and (4) calcium + vitamin D_3 placebo for 2 years	Sex: female Age: 10–12 years Race: Finnish, otherwise unspecified Location: Jyvaskyla and surrounding cities in Central Finland Year(s): Unspecified Baseline 25(OH)D as mean (95 % CI): 45.9 (43.8, 48.0) nmol/L	195	Data are shown for the overall group who started the intervention ($N = 181$)	Percent change Calcium ($n = 41$)	Calcium + vitamin D_3 ($n = 46$)	Cheese ($n = 39$)	Placebo ($n = 39$)	P
				Lumbar spine					
				Bone area	28.4	23.0	25.3	23.4	NS
				BMC	24.0	46.9	52.4	47.0	NS
				Total hip					
				Bone area	24.1	17.0	18.1	17.3	NS
				BMC	20.3	33.6	36.9	33.6	NS
				Femoral neck					
				Bone area	3.8	12.6	13.1	15.0	NS
				BMC	3.3	24.0	26.5	22.4	NS
				Radius					
				CSA	26.0	23.0	26.2	21.3	NS
				BMC	24.4	22.6	25.9	22.2	NS
				vBMD	2.6	3.4	3.1	2.0	NS
				Polar moment of inertia	62.0	53.3	61.8	51.8	NS
				Tibia					
				CSA	15.8	15.6	15.9	14.8	NS
				BMC	24.3	23.0	25.2	22.7	NS
				vBMD	7.5	6.9	8.3	7.8	NS
				Cortical bone thickness	29.8	31.7	37.1	31.1	NS
				Polar moment of inertia	41.5	41.3	42.6	39.7	NS
				• Data presented above show no interaction between the groups with the intent-to-treat analysis.					

Table 6 (continued)

Reference	Study description	Population description	Number of subjects	Primary end points	Results			
				• There was a significant interaction with cortical thickness of the tibia between the groups ($P < 0.05$) where this measure increased more in the cheese group with a compliance >50 % versus placebo ($P = 0.01$), calcium + vitamin D ($P < 0.01$), or calcium ($P = 0.04$). • Bonferroni correction for multiple comparisons was applied to these analyses.				
El-Hajj Fuleihan et al. 2006 [175]	Musculoskeletal responses were determined in response to weekly doses of vitamin D_3 (1400 and 14,000 IU) over 1 year	Sex: female Age: 10–17 years Race: Lebanese, otherwise unspecified Location: greater Beirut, Lebanon area Year(s): 2001–2003 Baseline 25(OH)D as mean (SD): 14 (8) ng/ml	179	Data are shown for the overall group ($N = 168$)	Percent change High-dose treatment, 14,000 IU/week ($n = 55$)	Low-dose treatment, 1400 IU/week ($n = 58$)	Placebo ($n = 55$)	P
				Lumbar spine				
				Bone area	4.3	5.0	4.0	NS
				BMC	12.9	14.5	10.8	NS
				Total hip				
				Bone area	5.7	4.0	2.4	<0.01
				BMC	12.8	11.2	7.8	0.02
				Femoral neck				
				Bone area	0.8	0.0	0.7	NS
				BMC	5.2	4.4	3.9	NS
				Trochanter				
				Bone area	7.8	6.8	4.7	NS
				BMC	14.2	13.6	9.4	NS
				Total body				
				Bone area	6.2	6.1	5.0	NS
				BMC	12.0	11.3	8.7	NS
				Lean mass	9.0	8.7	5.7	0.05
				• In premenarchal girls, trochanter BMC and lean mass reached significance. • Postmenarchal girls did not exhibit significant changes in any parameters of interest.				
Viljakainen et al. 2006 [177]	This study sought to determine the effect of vitamin D_3 supplementation (200 or 400 IU/day) for 1 year on bone mineral augmentation in adolescent girls with adequate dietary calcium intake.	Sex: female Age: 11.4 ± 0.4 years Race: white Location: Helsinki, Finland Year(s): 2001–2003 Baseline 25(OH)D as mean (SD) in nM: Placebo: 47.8 (18.2) 5 μg/day: 46.3 (17.4) 10 μg/day: 46.7 (16.2)	228	Data are shown for the overall group ($N = 212$)	Mean change High-dose treatment, 400 IU/day ($n = 74$)	Low-dose treatment, 200 IU/day ($n = 65$)	Placebo ($n = 73$)	P
				Lumbar spine				
				Bone area (cm^2)	3.8	4.1	3.5	NS
				BMC (g)	6.2	5.9	5.1	NS
				Femur				
				Bone area (cm^2)	2.0	2.2	2.4	NS
				BMC (g)	3.3	3.4	3.2	NS
				• Data presented above are for the intent-to-treat analysis. • In the compliance-based analysis only in the entire sample, vitamin D supplementation vs placebo increased femoral BMC augmentation by 14.3 % with 200-IU doses and by 17.2 % with 400-IU doses ($P = 0.012$) • In the compliance-based analysis only in the entire sample, a dose–response effect was observed at the lumbar spine with the 400-IU ($P = 0.039$), but not the 200-IU dose. • In a subanalysis based on puberty ($n = 111$) and using a compliance-based analysis only, adjusted for Tanner stage, increase in bone area, and weight gain, there was a dose-dependent and significant difference in the lumbar spine BMC augmentation at midpuberty ($P = 0.01$), but not at early puberty.				
Andersen et al. 2008 [180]	The aim of this study was to assess the effect of	Sex: male and female Age: 10–63 years	247	Data are shown for the girls group only ($n = 26$)	Median value			P

Table 6 (continued)

Reference	Study description	Population description	Number of subjects	Primary end points	Results			
	supplemental vitamin D on bone status in Pakistani immigrants. This 1-year intervention with vitamin D_3 (10 and 20 μg /day) included girls (10.1–14.7 years), women (18.1–52.7 years), and men (17.9–63.5 years) of Pakistani origin living in Denmark	Race: of Pakistani origin Location: Copenhagen area, Denmark Year(s): 2002–2003 Baseline 25(OH)D as median (25th, 75th percentiles) in nmol/L: Placebo: 7.3 (5.3, 23.6) 10 μg/day: 16.9 (12.1, 21.1) 20 μg/day: 8.8 (5.2, 17.1)			20 μg/day ($n = 9$)	10 μg/day ($n = 9$)	Placebo ($n = 8$)	
				Baseline				
				Total body				
				Bone area (cm^2)	1633	1497	1760	NS
				BMC (g)	1473	1308	1666	NS
				Lumbar spine				
				Bone area (cm^2)	39.9	41.2	43.2	NS
				BMC (g)	30.0	28.3	33.9	NS
				1 year				
				Total body				
				Bone area (cm^2)	1784	1669	1906	NS
				BMC (g)	1625	1595	1923	NS
				Lumbar spine				
				Bone area (cm^2)	42.7	42.7	46.5	NS
				BMC (g)	39.5	35.6	41.9	NS
				Data presented above indicate no significant differences between groups at baseline (nonparametric ANOVA) and no effect of the intervention on bone indices.				
Khadilkar et al. 2010 [178]	This study investigated the effect of quarterly doses of vitamin D_2 supplementation (300,000 IU or 7.5 mg) on BMC in underprivileged adolescent girls over 1 year	Sex: female Age: 14–15 years Race: Indian Location: Pune, India Year(s): 2006–2007 Baseline 25(OH)D as median (25th percentile–75th percentile): Vitamin D + calcium group: 24.5 (12.7–33.2) nmol/L Placebo + calcium group: 20.8 (12.7–30.4) nmol/L	50	Data are shown for the overall group ($N = 50$)	Percent change Vitamin D + calcium ($n = 25$)		Placebo + calcium ($n = 25$)	*P*
				Total body				
				Bone area	5.1		3.6	NS
				BMC	10.1		8.2	NS
				Lumbar spine				
				Bone area	3.3		3.9	NS
				BMC	10.5		11.3	NS
				• Data presented above are unadjusted median percent change values. • After adjusting for age (current), height, weight, lean body mass, initial dietary calcium, and calcium compliance, there was a significant increase in the size and compliance adjusted total BMC and bone area change in subjects who were within 2 years of menarche versus those less than 2 years since menarche (both $P \leq 0.04$).				
Molgaard et al. 2010 [173]	This study investigated the effect of vitamin D_3 supplementation (5 or 10 μg/day) for 1 year on bone mass and bone turnover, as well as the possible influence of VDR and ER genotype on the effect of the supplementation	Sex: female Age: 10–11 years Race: Danish-born citizens, otherwise unspecified Location: Copenhagen and Frederiksberg, Denmark Year(s): 2001–2003 Baseline 25(OH)D as mean (SD) in nmol/L: Placebo: 43.4 (17.1) 5 μg/day: 41.9 (17.6) 10 μg/day: 44.4 (16.6)	225	Data are shown for the overall group ($N = 225$)	Mean change High-dose treatment, 400 IU/day ($n = 75$)	Low-dose treatment, 200 IU/day ($n = 75$)	Placebo ($n = 75$)	*P*
				Total body				
				Bone area (cm^2)	195	189	188	NS
				BMC (g)	249	245	241	NS
				Lumbar spine				
				Bone area (cm^2)	4.9	5.5	5.6	0.04
				BMC (g)	7.4	8.1	8.2	NS
				• Lumbar spine bone area in the high-dose group differed significantly from placebo. • Vitamin D supplementation increased total body BMC ($P = 0.048$) in the FF VDR genotype but not in the Ff or ff VDR genotypes.				

Table 6 (continued)

Reference	Study description	Population description	Number of subjects	Primary end points	Results			
Ward et al. 2010 [179]	This study aimed to determine the effect of vitamin D_2 supplementation (4 doses of 150,000 IU given over 1 year) on the adolescent musculoskeletal system determined by DXA and peripheral quantitative computed tomography.	Sex: female Age: 12–14 years Race: multiethnic, primarily South Asian Location: Manchester, UK Year(s): 2006–2007 Baseline 25(OH)D as mean (SD) in nmol/L: Placebo: 17.9 (7.4) Vitamin D: 18.1 (8.0)	73	Data are shown for the overall group ($N = 72$)	Mean change Vitamin D		Placebo	*P*
				Lumbar spine				
				Bone area (cm^2)	0.20		0.15	NS
				BMC (g)	0.52		0.57	NS
				Radius 4 %				
				Total BMD (mg/cm^3)	21.3		13.01	NS
				Trab BMD (mg/cm^3)	3.07		3.23	NS
				CSA_4 (mm^2)	6.19		9.27	NS
				Radius 50 %				
				CSMA (mm^2)	−29.4		47.1	NS
				CSA_50 (mm^2)	−0.67		−1.91	NS
				Ct BMC (mg/mm)	2.73		3.12	NS
				Ct BMD (mg/cm^3)	17.4		23.9	NS
				Ct area (mm^2)	1.26		1.28	NS
				Cort thk (mm)	0.10		0.12	NS
				SSI (mm^3)	3.02		6.91	NS
				Tibia 4 %				
				Total BMD (mg/cm^3)	10.5		9.79	NS
				Trab BMD (mg/cm^3)	9.31		7.00	NS
				CSA_4 (mm^2)	−1.19		−3.28	NS
				Tibia 66 %				
				CSMA (mm^2)	161.2		197.6	NS
				CSA_66 (mm^2)	17.09		7.70	NS
				Ct BMC (mg/mm)	7.68		9.66	NS
				Ct BMD (mg/cm^3)	14.26		13.98	NS
				Ct area (mm^2)	3.98		5.85	
				Cort thk (mm)	−0.02		0.09	
				SSI (mm^3)	116.3		85.15	
				• *P* values presented above are adjusted for baseline and follow-up weight, follow-up height, and baseline bone measurement. • There were no effects of vitamin D supplementation on bone.				
Al-Shaar et al. 2013 [176]	This study investigated the impact of weekly vitamin D_3 (1400 and 14,000 IU) on hip geometric dimensions over 1 year. The images were acquired from DXA-derived hip structural analyses	Sex: male and female Age: 10–17 years Race: Lebanese, otherwise unspecified Location: greater Beirut, Lebanon area Year(s): 2001–2003 Baseline 25(OH)D as medians [interquartile range]:	338	Data are shown for females only ($n = 167$)	Percent change High-dose treatment, 14,000 IU/week ($n = 54$)	Low-dose treatment, 1400 IU/week ($n = 58$)	Placebo ($n = 55$)	*P*
				Narrow neck				
				CSA	8.1	8.3	8.2	NS
				Outer diameter	2.0	0.8	2.8	0.02
				Section modulus	11.4	11.3	11.7	NS
				Buckling ratio	−4.2	−6.5	−2.0	0.05
				Shaft				

Table 6 (continued)

Reference	Study description	Population description	Number of subjects	Primary end points	Results			
		Overall, girls: 11.9 [9.1–16.6] ng/ml Overall, boys: 15.5 [6.0–44.9] ng/ml		CSA	10.4	11.6	9.9	NS
				Outer diameter	2.1	2.3	1.4	NS
				Section modulus	12.5	13.5	11.0	NS
				Buckling ratio	−7.2	−8.4	−8.9	NS
				Intertrochanter				
				CSA	8.5	9.5	7.1	NS
				Outer diameter	2.5	1.3	1.9	NS
				Section modulus	12.7	13.1	10.1	NS
				Buckling ratio	−3.0	−5.6	−3.6	NS
				• Data presented above were adjusted for baseline height, change in lean mass and height, sun exposure, physical activity, calcium intake, and menarchal status. • Boys did not exhibit significant changes in any parameters of interest. • A dose effect was not detected and no beneficial effect of vitamin D was observed by pubertal stage.				
Prospective studies								
Breen et al. 2011 [181]	This study sought to determine relationships among 25(OH)D, IGF-I, and bone in prepubertal females over a period of up to 9 years (median of 5 years)	Sex: female Age: 4–8 years Race: white and black Location: Georgia, USA Year(s): 1997–2008	76	Data are shown for the overall group ($N = 76$)	Combined 25(OH)D + IGF-I	25(OH)D		IGF-I
				BMC				
				Total body	0.84	0.81		0.87
				Lumbar spine	0.72	0.70		0.76
				Proximal femur	0.81	0.77		0.85
				Forearm	0.78	0.76		0.81
				• Data are presented above as R^2 and the linear mixed models regressed BMC on age, IGF-I, 25(OH)D, season, and race, and interactions among these variables and show that IGF-I was more strongly associated with BMC accrual than 25(OH)D at all sites • The rate of BMC accrual was negatively associated with 25(OH)D. When IGF-I and 25(OH)D were included in the same regression equation, 25(OH)D did not have a significant predictive effect on BMC accrual above and beyond that of IGF-I.				
Cross-sectional studies								
Cheng et al. 2003 [182]	Associations of serum 25(OH)D with BMC at different bone sites were measured by DXA and pQCT.	Sex: female Age: 10–12 years Race: Finnish, otherwise unspecified Location: Jyvaskyla, Finland Year(s): 1999–2000	193	Data are shown for the overall group ($N = 193$)	Deficient, ≤25 nmol/L ($n = 61$)	Insufficient, 26–40 nmol/L ($n = 89$)	Sufficient, >40 nmol/L ($n = 43$)	P
				Total body				
				Bone area (cm^2)	1468	1475	1436	NS
				BMC (g)	1380	1414	1347	NS
				Femur				
				Bone area (cm^2)	23.9	23.7	23.1	NS
				BMC (g)	19.7	20.4	18.9	0.05
				Femoral neck				
				Bone area (cm^2)	3.837	3.84	3.67	NS
				BMC (g)	3.21	3.30	3.13	NS
				Lumbar spine				
				Bone area (cm^2)	27.5	28.1	27.3	NS
				BMC (g)	22.6	23.9	21.9	NS
				Distal radius				

Table 6 (continued)

Reference	Study description	Population description	Number of subjects	Primary end points	Results			
				Whole bone CSA (mm^2)	241	226	209	<0.01
				Whole bone vBMD (mg/cm^3)	273	292	298	<0.01
				Trabecular vBMD (mg/cm^3)	221	229	231	NS
				Tibia shaft				
				Whole bone CSA (mm^2)	368	372	363	NS
				Whole bone vBMD (mg/cm^3)	848	865	853	0.02
				Trabecular vBMD (mg/cm^3)	525	534	524	NS
				• Data are adjusted for Tanner stage and BMI. • *P* value is shown with Bonferroni adjustment in the ANOVA for multiple comparisons. • Sufficient is different from the insufficient group in BMC of the femur ($P = 0.04$). • Sufficient is different from the deficient group in whole bone CSA and vBMD of the radius ($P < 0.01$). • Insufficient is different from the deficient group in whole bone CSA ($P = 0.05$) and vBMD ($P < 0.01$) of the radius and whole bone vBMD ($P < 0.02$) of the tibia.				
Foo et al. 2009 [183]	This cross-sectional study investigated the influence of low vitamin D status on bone mass, bone turnover, and muscle strength.	Sex: female Age: 15 years Race: Chinese, otherwise unspecified Location: Beijing, China Year(s): 2004	301	Data are shown for the overall group ($N = 301$)	Severe deficiency, <25 nmol/L ($n = 94$)	Deficiency, ≤50 nmol/L ($n = 174$)	Sufficient, >50 nmol/L ($n = 33$)	*P* trend
				Size-adjusted BMC (g)				
				Total body	2230	2291	2417	<0.01
				Proximal forearm	1.44	1.47	1.53	<0.01
				Distal forearm	1.10	1.52	1.86	<0.01
				Data are presented as means adjusted for pubertal breast stage, handgrip muscle strength, organized sports participation, physical activity level, dietary vitamin D, and calcium.				
Lee et al. 2013 [184]	Risk factors were evaluated for low 25(OH)D status and its relationships with bone health	Sex: male and female Age: 9.3 ± 1.9 years Race: Korean, otherwise unspecified Location: Seoul and Gyeonggi-do, South Korea Year(s): unspecified	100	Data are shown for the overall group ($N = 100$)	Total body BMC			*P*
				Unadjusted	0.028			0.08
				Adjusted model 1	0.02			0.07
				Adjusted model 2	0.02			0.04
				• Data presented above are β scores correlating 25(OH)D with BMC and corresponding *P* values using multiple linear regression analyses • Model 1 is adjusted for sex, puberty, fat mass, and lean mass • Model 2 is adjusted for model 1 variables + physical activity and calcium intake				

25(OH)D 25-hydroxyvitamin D, *95 % CI* 95 % confidence interval, *ANOVA* analysis of variance, *BMC* bone mineral content, *Cort thk* cortical thickness, *CSA* cross-sectional area, *CSMA* cross-sectional moment of inertia, *Ct* cortical, *DXA* dual-energy x-ray absorptiometry, *IGF* insulin-like growth factor, *NS* not significant, *RCT* randomized controlled trial, *SSI* stress–strain index, *Trab* trabecular, *vBMD* volumetric bone mineral density, *VDR* vitamin D receptor

Table 7 Other micronutrients and bone health in children and adolescents

Micronutrient	Reference	Study description	Population description	Number of subjects	End points	Results
RCTs						
Magnesium	Carpenter et al. 2006 [185]	1-year placebo-controlled, double-blind RCT of 300 mg/day supplementation of MgO	Sex: female Age: 8–14 years Race: white Location: New Haven, CT	44	BMC of total hip, femoral neck, Ward's area, and lumbar spine	Combined overall hip Treatment: 1.05 % Placebo: 0.97 %, $P = 0.0534$
Prospective studies						
Fluoride	Levy et al. 2009 [187]	Lifetime associations of average daily fluoride intake and DXA bone outcomes at age 11 years	Sex: male and female Age: birth to 11 years for fluoride assessments; mean age 11.2 years for DXA assessment Race: 97 % white Location: Iowa Year(s): recruitment took place from 1992 to 1995 (fluoride study) and from 1998 to 2000 (bone development study)	481	BMC	Hip / Spine / Total body less head
					Girls	
					0–11 years	0.07, NS / 0.17, NS / 0.10, NS
					0–8.5 years	0.04, NS / 0.13, NS / 0.08, NS
					0–3 years	0.03, NS / 0.06, NS / 0.05, NS
					3–6 years	−0.01, NS / 0.05, NS / 0.02, NS
					6–8.5 years	0.11, NS / 0.19, 0.01 / 0.16, NS
					85.5–11 years	0.18, 0.01 / 0.24, <0.01 / 0.19, NS
					Boys	
					0–11 years	0.21, 0.01 / 0.23, 0.01 / 0.23, 0.01
					0–8.5 years	0.21, 0.01 / 0.23, 0.01 / 0.24, 0.01
					0–3 years	0.22, 0.01 / 0.22, 0.01 / 0.23, 0.01
					3–6 years	0.14, NS / 0.18, NS / 0.19, 0.01
					6–8.5 years	0.09, NS / 0.12, NS / 0.10, NS
					85.5–11 years	0.14, NS / 0.14, NS / 0.15, NS
					• Data are from unadjusted bivariate associations (r) with fluoride intake and bone outcomes and corresponding P value. • No statistically significant relationships between daily fluoride intake and bone measures were found in adjusted models (for age, height, weight, and Tanner stage).	
Fluoride	Levy et al. 2014 [188]	Lifetime associations of average daily fluoride intake and DXA bone outcomes at age 15 years	Sex: male and female Age: birth to 15 years for fluoride assessments; mean age 15.3 years for DXA assessments Race: 98 % white Location: Iowa Year(s): recruitment took place from 1992 to 1995 (fluoride study) and from 1998 to 2000	358	BMC	Females: ß / R^2 / Partial R^2; Males: ß / R^2 / Partial R^2
					Total body less head	234, 0.02 / 0.03 / 0.03 — 182, NS / 0.02 / 0.02
					Spine	7.32, 0.04 / 0.03 / 0.03 — 5.24, NS / 0.02 / 0.02
					Hip	2.92, NS / 0.01 / 0.01 — 1.79, NS / <0.01 / <0.01
					• Data are from unadjusted bivariate associations (β) with fluoride intake and bone outcomes and corresponding P value. • With adjustment for height, weight, time since PHV, Tanner stage, calcium intake, and physical activity, none of the associations remained statistically significant.	

Table 7 (continued)

Micronutrient	Reference	Study description	Population description	Number of subjects	End points	Results	
			(bone development study)		• No significant differences were observed between fluoride intake and bone measures across tertiles of fluoride intake from birth to 15 years.		
Observational studies							
Vitamin K	O'Connor et al. 2007 [191]	Cross-sectional associations of undercarboxylated osteocalcin (%ucOC) as an index of vitamin K status and BMC	Sex: female Age: 11–12 years Race: presumed white Location: Denmark	223	Serum %ucOC and total body BMC	$\beta = -0.045$, $P = 0.016$	
					Lumbar BMC	$\beta = -0.055$, $P = 0.037$	
Sodium	Hoppe et al. 2000 [149]	Cross-sectional analysis of nutrient intakes determined by 7-day diet records and bone	Sex: half were female, half were male Age: 10 years Race: presumed white Location: Denmark Year(s): 1997–1998	105	Total body BMC	$r = -0.206$, $P < 0.05$	
					Anterior–posterior projected bone area (cm^2)	$r = -0.215$, $P < 0.05$	
Phosphorous	Hoppe et al. 2000 [149]	Cross-sectional analysis of nutrient intakes determined by 7-day diet records and bone	Sex: half were female and half were male Age: 10 years Race: presumed white Location: Denmark Year(s): 1997–1998	105	Total body BMC	$r = -0.297$, $P < 0.01$	
					Anterior–posterior projected bone area (cm^2)	$r = -0.284$, $P < 0.01$	
Vitamin C	Prynne et al. 2006 [189]	Cross-sectional Cambridge Bone Studies to relate fruit and vegetable and nutrient intake from 7-day food diaries in 5 age and sex cohorts	Sex: female and male, nearly half of each Age: 16–19 years Race: presumed white Location: UK	257		Percent change with doubling in vitamin C intake from univariate analysis, in 4th-grade girls only	
						Boys	Girls
					Total body BMC	5.5, $P < 0.01$	1.4, NS
					Spine BMC	5.6, $P < 0.05$	2.1, NS
					Total hip BMC	5.7, $P < 0.05$	−0.05, NS
					Femoral neck BMC	5.4, $P < 0.01$	5.2, NS
					Trochanter BMC	5.8, $P < 0.05$	2.5, NS
Vitamin C, zinc, and iron	Laudermilk et al. 2012 [190]	Cross-sectional analysis of nutrient intakes determined by the Harvard Youth/Adolescent Food frequency Questionnaire	Sex: female Age: 8–12 years, 4th- and 6th-grade students Race: ~87 % white, 7 % Asian, 3 % black, 2 % Latino and 1 % Native Hawaiian Location: Tucson, Arizona	453 ($n = 184$ 4th graders, $n = 179$ 6th graders)	pQCT	Vitamin C	Zinc
					Femur 20 % site		
					Cortical density	NS	0.16, $P < 0.05$
					Periosteal circumference	0.17, $P < 0.05$	NS
					Endosteal circumference	0.17, $P < 0.05$	NS
					SSI	0.18, $P < 0.05$	NS
					Tibia 4 % site		
					Trabecular area	0.18, $P < 0.05$	NS
					Periosteal circumference	0.19, $P < 0.01$	NS
					Tibia 66 % site		
					Cortical density	NS	0.15, $P < 0.05$

Table 7 (continued)

Micronutrient	Reference	Study description	Population description	Number of subjects	End points	Results				
					Cortical area	0.15, $P < 0.05$			NS	
					SSI	0.18, $P < 0.05$			NS	
					In regression modeling, iron was negatively associated with femoral cortical area and tibia SSI.					
Fluoride	Grobler 2009 [186]	This field study included the whole population of children aged 10–15 years living in areas of high and low fluoride in the drinking water.	Sex: male and female Age: 10–15 years Race: not specified, but of mixed ethnicity (i.e., from Khoi, Caucasian, and Negroid roots that developed into a homogenous ethnic group over many years) Location: South Africa Year(s): not specified	166 ($n = 77$ from a 0.19 mg/L F area; $n = 89$ from a 3.00 mg/L F area)		High fluoride		Low fluoride		P
						Girls	Boys	Girls	Boys	
					Radius BMC (g)					
					10–11 years	1.29	1.29	1.26	1.32	NS
					12–13 years	1.56	1.41	1.33	1.29	<0.05[a]
					14–15 years	1.80	1.80	1.18	1.52	<0.05[a]
					Radius bone width (cm)					
					10–11 years	0.97	0.98	0.98	1.01	NS
					12–13 years	1.09	1.08	1.04	1.15	NS
					14–15 years	1.10	1.14	1.18	1.21	NS

%ucOC percentage of undercarboxylated osteocalcin, *BMC* bone mineral content, *DXA* dual-energy x-ray absorptiometry, *NS* not significant, *PHV* peak height velocity, *pQCT* peripheral quantitative computed tomography, *RCT* randomized controlled trial, *SSI* stress–strain index

[a] Significant differences in BMC in the 12- to 13-year-olds and the 14- to 15-year-olds were found among boys from the high fluoride area and girls from the low fluoride area

Protein (Table 3) The search for protein identified 1 RCT, 5 prospective studies, and 6 cross-sectional studies published since 2000, encompassing 2255 individuals (Table 3). In the one RCT, there was no effect of supplementing 42 g protein over 6 months on changes in tibia trabecular or cortical bone measures at the 4 or 20 % sites, respectively, measured from the distal tibia metaphysis, or on changes in total body BMC [143]. Alexy et al. [144] demonstrated in a cohort of German children that protein intakes over 4 years were positively associated with, and were predictors of, forearm periosteal circumference, cortical area, BMC, and stress–strain index (SSI). The investigators also showed that long-term dietary potential renal acid load (PRAL) was negatively associated with forearm BMC and cortical area. PRAL is increased by sulfur amino acid content of the diet and is decreased by alkaline salts as occurs in plant foods. In the same cohort studied over 4 years, Remer et al. [145] reported that urinary nitrogen (uN) was positively associated with forearm periosteal circumference, cortical area, BMC, and SSI, and urinary PRAL was negatively associated with forearm BMC and cortical area. Protein intakes in males and females between the ages of 2 months and 8 years were positively associated with total body BMC [146]. Using a mixed-longitudinal design, protein intakes were shown to positively predict total body BMC net gain in males and females between ages 8 and 21 years [147]. Moreover, protein intakes in periadolescent females were positively associated with total body BMC and total body BMC net gains, but only in those with calcium intakes >1000 mg/day. Over a period of 5 years, protein intakes in children with low calcium intakes were negatively associated with distal and proximal forearm BMC and total body BMC [148].

Hoppe et al. [149] reported that protein intakes among Danish children were positively related to total body bone area, but not BMC, when adjusted for height, weight, and sex. Differences in arm BMC between twins were partially explained by protein intakes, such that a 1-g difference in protein intake resulted in a 0.4 % difference in arm BMC [150]. Chevalley et al. [151] reported that protein intakes in prepubertal males were positively related to BMC of the radial metaphysis, total radius, femoral neck, femoral diaphysis, and the lumbar spine when controlling for physical activity and calcium intakes. Absolute or adjusted (for body weight, years after menarche, and vertebral area) protein intake from milk, but not from other foods, was positively associated with lumbar spine BMC [152]. In a group of healthy and malnourished Indian children aged 2–3 years, protein intake was positively related to total body BMC and bone area [153]. However, energy-adjusted protein intakes were not significantly associated with forearm geometrical measures in another group of children [154].

Our evidence grade for protein was based on findings from four prospective studies indicating positive findings and one null RCT.

Grade: Level of evidence C was assigned for the benefit of protein on bone.

Micronutrients

Calcium (Tables 4 and 5) The search for calcium identified 16 RCTs published since 2000, encompassing 3077 individuals (Table 4). In addition, five studies that used both calcium and physical activity interventions were evaluated for main and interaction effects [81, 155–158]. Four observational studies published since 2000, encompassing 2383 individuals, looked at calcium and physical activity interactions on bone (Table 5). When categorized according to the type of calcium intervention, nine studies included supplementation with pills/chews, four used calcium-fortified foods, two used dairy foods, and one used a combination of dairy and pills. Most of the studies included primarily white subjects. A variety of skeletal variables were used as study outcomes. Most studies evaluated the effects of calcium intake on DXA outcomes, including BMC, aBMD, and bone area of the total body, lumbar spine, total hip, femoral neck, intertrochanteric and trochanteric areas of the hip, and distal and ultradistal areas of the forearm. Very few studies reported all possible DXA outcomes, and specific outcomes varied among studies. Three RCTs assessed bone mass and structure using pQCT.

All but one [159] of the nine RCTs using supplement pills found a small, but consistent, positive effect on aBMD and/or BMC accrual as measured by DXA. The benefit to the supplemented group compared to the placebo group ranged from 0.57 to 5.80 %. None of the studies found a significant effect at all (i.e., hip, spine, and radius) of the usual DXA skeletal sites, and the specific sites that benefited varied among the studies. Only three of the RCTs with DXA reported adjusting for body size [160–162], which is important because longitudinal growth confounds interpretation of changes in aBMD and BMC. The difference in height-adjusted BMC accrual between supplemented and placebo groups in these four studies ranged from 0.80 to 4.60 %.

One of the best-designed studies was a single-blind co-twin study of girls aged 8–13 years given calcium carbonate 1200 mg/day or placebo for 24 months [161]. Baseline calcium intake was 786 mg/day (calcium) and 772 mg/day (control; not significant), values considerably lower than the recommended dietary allowance (RDA) (1000 mg/day for ages 4–8 years and 1300 mg/day for ages 9–18 years). Of 64 twin pairs enrolled, 24 pairs completed the study. Compliance with supplementation was 76 % for both groups (calcium and placebo). At the end of study, the calcium group had gained 3.69 % more total body BMC (adjusted for age, height, and weight) than the control group. There were no significant differences in change in BMD at the total hip, spine, or femoral neck. In post hoc analyses, significant differences in gain were

Table 8 Food patterns and bone health in children and adolescents

Food	Source	Study description	Population description	Number of subjects	End points		Results		
RCTs									
Dairy	Du et al. 2004 [170]	2-year school-based randomized trial of 330 mL milk, 330 mL milk + 5 or 8 μg vitamin D_3, or control	Sex: female Age: 10–12 years Race: Chinese Location: Beijing, China	757			Group mean increase Treatment	Placebo/control	*P*
					Height		0.95 %	0.087 %	<0.0005
					Total body BMC		38.4 %	35.9 %	0.03
					Bone area		29.5 %	31.3 %	0.2
Dairy	Courteix et al. 2005 [158]	12-month randomized, double-blind, placebo-controlled study Baseline calcium: supplement = 1008 (398); placebo = 988 (345) Was combined with an exercise intervention that found a combined effect not reported here. After randomization, fewer subjects were in the dairy group than in the placebo group (34 vs 79, respectively, at the baseline). It was expected that 240 subjects would be recruited, but because of the publicity surrounding Mad Cow disease, many parents were afraid of dairy products.	Sex: premenarchal female Age: 8–13 years Race: Caucasian Location: France	113			Calcium supplement	Placebo	
					Total body	BMC	155 ± 79	166 ± 66	
					Lumbar spine	BMC	3.429 ± 2.388	3.228 ± 2.642	
					Femoral neck	BMC	0.248 ± 0.187	0.185 ± 0.103	
					Trochanter	BMC	0.941 ± 0.525	0.796 ± 0.582	
					Wards	BMC	0.001 ± 0.054	0.047 ± 0.086	
					Ultradistal radius	BMC	0.104 ± 0.091	0.111 ± 0.107	
					Mid radius	BMC	0.305 ± 0.230	0.355 ± 0.322	
					1/3 distal	BMC	0.072 ± 0.078	0.093 ± 0.077	
					Adjusted for lean tissue mass. All NS				
Dairy	Cheng et al. 2005 [159]	2 year double-blind, placebo-controlled RCT of calcium (1000 mg) + vitamin D_3 (200 IU), calcium (1000 mg), cheese (1000 mg calcium), and placebo	Sex: female Age: 10–12 years Race: presumed white Location: Finland	195			Cheese		*P*
					Total body	BMD (%)	10.4	8.9 (compliance >50)	0.044
					Femoral neck	BMC (%)	26.5	22.4	NS
					Total femur	BMC (%)	36.9	33.6	NS
					Spine	BMC (%)	52.4	47.0	NS
					Tibia cortical thickness	pQCT (%)	37.1	31.1 (compliance 50)	0.01
Dairy	Merrilees et al. 2000 [169]	2-year RCT of dairy food supplementation and 1-year follow-up after cessation of intervention	Sex: female Age: 15–17 years Race: presumed white Location: New Zealand	91	Total body	BMC (g)	168.9	167.4	NS
					Lumbar spine	BMC (g)	3.83	2.58	NS
					Femoral neck	BMC (g)	0.12	0.06	NS
					Trochanter	BMC (g)	0.75	0.25	<0.05

Table 8 (continued)

Food	Source	Study description	Population description	Number of subjects	End points	Results			
			Stratified by forearm BMD at baseline		Difference disappeared 1 year after cessation				
Fiber	Abrams et al. 2005 [193]	1-year placebo-controlled RCT of 8 g/day mixed short and long inulin-type fructans	Sex: half were male and half were female Age: 9–13 years Tanner stage 2 or 3 Race: 53 % white, 14 % black, 22 % Hispanic, 10 % Asian Location: Houston, TX Between 5th and 95th percentile BMI	100	Total body	BMC, %	18.3	16.7	0.03
Observational studies									
Total diet	Wosje et al. 2010 [335]	Prospective study with cross-sectional analysis by age to relate 3-day diet records to fat and bone mass in children during the age period of 3.8–7.8 years, using reduced-rank regression	Sex: male and female (167/158) Age: 3.8–7.8 years Race: 75 % white, 25 % black Location: Cincinnati, OH Year(s): 2000–2004	325	Fat mass (kg) Bone mass (g)	Diets high in dark-green and deep-yellow vegetables and processed meats and low in fried foods were associated with lower fat mass ($P<0.001$) and higher bone mass ($P=0.03$ for year 1, $P=0.2$ for year 2, and $P<0.01$ for years 3 and 4)			
Fruits and Vegetables	Prynne et al. 2006 [189]	Cross-sectional Cambridge Bone Studies to relate fruit and vegetable and nutrient intake from 7-day food diaries in 5 age and sex cohorts	Sex: female and male, nearly half of each Age: 16–19 years Race: presumed white Location: UK	257		Percent change with doubling in fruit and vegetable intake from univariate analysis			
						Boys	*P*	Girls	*P*
					Total body BMC	9.2	<0.001	5.2	0.02
					Spine BMC	7.8	0.002	8.8	0.001
					Total hip BMC	6.6	0.008	5.0	0.04
					Femoral neck BMC	10.3	<0.001	6.5	0.07
					Trochanter BMC	7.9	0.01	5.2	NS
Fruits and vegetables	McGartland et al. 2004 [195]	Cross-sectional study on effect of fruit and vegetable intake on BMD	Sex: male and female Age: 12 and 15 years Race: presumed white Location: Northern Ireland	1345	Forearm BMD Heel BMD	12-year-old girls consuming high amounts of fruit had significantly higher heel BMD ($\beta=0.037$; 95 % CI, 0.017, 0.056). No other associations were observed.			
Fruits and vegetables	Tylavsky et al. 2004 [196]	Cross-sectional study on the effect of low (<3 servings) versus high (≥3 servings) fruit and vegetable intake on urinary calcium excretion and bone mass	Sex: female Age: 8–13 years Race: white Location: Tennessee, USA	56	Total body bone area Wrist bone area	Compared with the low-consumption group, the high fruit and vegetable consumption group had 6 and 8.3 % larger total body ($P<0.03$) and wrist bone area ($P<0.03$).			
					Total body BMC Wrist BMC	Whole body and wrist BMC was 7.4 ($P=0.07$) and 7.0 % ($P=0.09$) larger in the high-consumption group ($P>0.05$).			

Table 8 (continued)

Food	Source	Study description	Population description	Number of subjects	End points	Results
					Total body BMD Wrist BMD	Whole body and wrist BMD did not differ significantly between the low- and high-consumption groups ($P > 0.05$).
					Urinary calcium	Those reporting high fruit and vegetable intake had lower concentrations of urinary calcium/kg body weight ($P < 0.02$).
Fruits and vegetables	Whiting et al. 2004 [197]	Cross-sectional study of bone growth in children	Sex: male and female Age: 8–14 years Race: presumed white Location: Saskatoon, Canada Year(s): 1991–1997	131	BMC	Fruit and vegetable intake appears to influence BMC in adolescent girls but not boys.
Fruits and vegetables	Vatanparast et al. 2005 [198]	Cross-sectional study on the effect of milk products, vegetables, and fruit on total body BMC	Sex: male and female Age: 8–20 years Race: presumed white Location: Saskatoon, Canada Year(s): 1991–1997	150	Total body BMC	Fruit and vegetable intake was a significant independent predictor of total body BMC in boys but not girls.
Caffeine	Conlisk and Galuska 2000 [204]	Cross-sectional study on effect of caffeine on BMD in healthy women	Sex: 177 women Age: 19–26 years Race: presumed white Location: Midwestern USA Year(s): 1991	177	Caffeine consumption for past 12 weeks by self-report BMD at the lumbar spine and femoral neck by DXA	Caffeine was not significantly associated with BMD.
Carbonated beverages	Wyshak 2000 [200]	Cross-sectional study of carbonated beverage consumption and bone fractures	Sex: girls Age: 9th and 10th graders (mean age 15.8 years) Race: unspecified, American high school students Location: "urban high school," USA	460	Self-reported physical activity, carbonated beverage consumption, and bone fractures	Carbonated beverage consumption and bone fractures were associated (OR, 3.14; 95 % confidence limit, 1.45, 6.78; $P = 0.004$).
Carbonated beverages	McGartland et al. 2003 [194]	Cross-sectional observational study of the association between CSDs and BMD in postprimary schools in Northern Ireland	Sex: 744 girls, 591 boys Age: 12 years (323 boys, 376 girls); 15 years (268 boys, 368 girls) Race: presumed white Location: Belfast, Northern Ireland Year(s): 2000	1335	CSD consumption via RD-administered dietary history method BMD of the nondominant forearm (distal radius) and dominant heel (os calcis) by DXA	A significant inverse relationship between total CSD intake and BMD was observed in girls at the dominant heel (β, −0.099; 95 % CI, −0.173 to −0.025). Non-cola consumption was inversely associated with dominant heel BMD in girls (β, −0.121; 95 % CI, −0.194 to −0.048), and diet drinks were also inversely associated with heel BMD in girls (β, −0.087; 95 % CI, −0.158 to −0.016). No consistent relationships were observed between CSD intake and BMD in boys.
Carbonated beverages	Ma and Jones 2004 [199]	Population-based case–control study to investigate the association between soft drink and milk consumption, physical	Sex: half male and half female Age: 9–16 years Race: presumed white Location: Tasmania, Australia	206 fractures 206 controls	Bone mass using DXA at the total body, lumbar spine, right femoral neck: BMC aBMD	None of the drink types (milk, cola, and carbonated drinks) was significantly different between cases and controls for total fracture. For wrist and forearm fractures, there was a positive association between cola drink consumption and fracture risk (OR, 1.39/unit; 95 % CI, 1.01, 1.91).

Table 8 (continued)

Food	Source	Study description	Population description	Number of subjects	End points	Results
		activity, bone mass, and upper limb fractures in children aged 9–16 years	Year(s): 1998–2002		BMAD Soft drink and dairy drink consumption (in-person interview)	
Carbonated beverages	Manias et al. 2006 [201]	Cross-sectional study of recurrent fracture, diet, and physical activity	Sex: 78 girls, 72 boys Age: 4–16 years Race: presumed white Location: Sheffield, UK	150	Bone area, BMC, BMD of spine, lower body, and upper body by DXA Fracture history and trauma severity Diet (including beverage consumption), physical activity, and other lifestyle factors via questionnaires	Children with recurrent fractures had a significantly lower milk intake, lower levels of physical activity, a higher BMI, and a higher consumption of carbonated beverages than controls.
Carbonated beverages	Libuda et al. 2008 [202]	Prospective (DONALD) study of diet from 3-day diet records for 4 years prior to a single forearm pQCT measure	Sex: 113 girls, 115 boys Age: 6–18 years Race: presumed white Location: Germany	228	Forearm pQCT	Carbonated beverage consumption was inversely associated with BMC ($P < 0.05$), cortical area ($P < 0.05$), and polar strength strain index ($P < 0.05$), polar strength strain index ($P < 0.01$), and periosteal circumference ($P < 0.05$) of the radius assessed by pQCT, after adjustment for age, sex, total energy intake, muscle area, BMI SD scores, and growth velocity.

95 % CI 95 % confidence interval, *aBMD* areal bone mineral density, *BMAD* bone mineral apparent density, *BMC* bone mineral content, *BMD* bone mineral density, *CSD* carbonated soft drink, *DONALD* Dortmund Nutritional and Anthropometric Longitudinally Designed, *DXA* dual-energy x-ray absorptiometry, *NS* not significant, *OR* odds ratio, *pQCT* peripheral quantitative computed tomography, *RCT* randomized controlled trial, *RD* registered dietician, *SSI* stress–strain index

Table 9 Infant nutrition and bone health in children and adolescents

Source	Study description	Population description	Number of subjects	End points	Results		
Koo et al. 2003 [211]	6-month randomized, double-blind, parallel study assessing changes in bone mineral accretion by DXA in healthy infants fed a milk-based formula with or without palm olein	Sex: 57 males, 71 females Age: Infants >2 weeks at baseline Race:72 African American, 48 Caucasian, 8 Hispanic/Asian/other Location: USA and Canada	128	Total body BMC (%)	Group mean increase		
					Breast-fed	Control formula (milk-based formula)	Treatment (milk-based formula with palm olein)
				3 months		62.1	76.2*
				6 months		134.3	149.6*
Observational studies							
Butte et al. 2000 [216]	Prospective cohort study of breast-fed and formula-fed infants over 24 months	Sex: 33 males, 43 females Age: >2 weeks at baseline Race: 55 Caucasian, 7 African American, 11 Hispanic, 3 Asian Location: USA	76	Total body BMC (g)	Breast-fed (<12 months)	Breast-fed (>12 months)	Formula-fed
				12 months	Data not reported	Lower[a]	Higher[a,**]
				24 months	310 ($P=0.05$)	289 ($P=0.05$)	Data not reported
Jones et al. 2000 [217]	Prospective cohort study to determine whether breastfeeding in early life is associated with bone mass in prepubertal children	Sex: 215 males, 115 females Age: 8 years at follow-up Race: predominantly Caucasian Location: Tasmania	330		Breast-fed	Bottle fed	
				Total body BMD at 8 years (g/cm^2)	0.642 ± 0.082	0.627 ± 0.073*	
				Femoral neck BMD at 8 years (g/cm^2)	0.608 ± 0.072	0.590 ± 0.068	
				Lumbar spine BMD at 8 years, g/cm^2	0.781 ± 0.047	0.766 ± 0.047**	
Ma and Jones 2003 [219]	Population-based case-controlled study to examine the association between bone mass and upper limb fractures in children	Sex: 206 males, 124 females Age: 8 years at follow-up Race: predominantly Caucasian Location: Tasmania	324		Breast-fed		
				Multivariate OR (95 % CI)	0.43 (0.19–0.94)[a]		

Table 9 (continued)

Source	Study description	Population description	Number of subjects	End points	Results		
Young et al. 2005 [221]	BMD was assessed in healthy 4-year-old children after confirming the type of infant feeding by history. All children had exclusively consumed human milk, infant formula without palm olein oil, or an infant formula with palm olein oil.	Sex: 58 % male Mean age: 4.5 years Race: 85 % Caucasian Location: USA	178		Human milk	Formula without palm olein oil	Formula with palm olein oil
				Total body BMC at 4 years (g)	566 ± 12	583 ± 10[c]	570 ± 7
Harvey et al. 2009 [213]	Prospective cohort study examining associations between duration of breastfeeding and compliance with infant dietary guidelines and later bone size and density at age 4 years	Sex: 158 males, 149 females Age: 6 months at baseline Race: not reported Location: UK	599		Breast milk (<1 month)	Breast milk (2–6 months)	
					No difference[a]	No difference[a]	
Molgaard et al. 2011 [212]	Random sample of infants from the Copenhagen Cohort Study of Infant Growth and Nutrition were investigated to determine if early nutrition and early growth are associated with later bone mass in adolescence.	Sex: 44 males, 65 females Age: birth to 12 weeks. Examination at 17 years Race: Danish origin; otherwise not reported Location: Denmark Years: 1987–2005	109	Lumbar spine BMC	The duration of exclusive breastfeeding was positively correlated with the sex-adjusted lumbar spine BMC[a,**].		
Pirila et al. 2011 [214]	Prospective study of infants divided into three equal-sized groups according to the total duration of breastfeeding (short = 3 months, intermediate = >3 to <7 months, and prolonged = >7 months) followed-up after 32 years	Sex: 76 males, 82 females Age: 2 weeks to 12 months in original cohort; 31.7–34.0 years at follow-up Race: not reported Location: Finland Year(s): 2007–2009	158	Total body BMC	In males, short breastfeeding was associated with higher bone area, BMC, and BMD compared to longer breastfeeding. Males in the short breastfeeding group had on average 4.7 % higher total body BMD than males in the prolonged breastfeeding group[a,**].		
Fewtrell et al. 2013 [220]	To compare total body and lumbar spine bone in children aged 10 years that as infants participated in a randomized trial and either were breast-fed or randomly received a control formula or an *sn*-2 palmitate-enriched formula using a double-blind permuted block allocation. The study was completed at 12 weeks and follow-up measurements were taken at 10 years.	Sex: 52 % male, 48 % female Age: birth to 12 weeks; follow-up at 10 years Race: not reported Location: Cambridge, UK	91		Breast-fed	Formula with standard fat blend	Formula with high *sn*-2 fat blend
				Lumbar spine BMC (g)	23.12 ± 4.46	22.54 ± 4.52	24.38 ± 5.15

Table 9 (continued)

Source	Study description	Population description	Number of subjects	End points	Results		
				Total body BMC (g)	1062 ± 213	1049 ± 264	1097 ± 231
Jones et al. 2013 [218]	Birth cohort study to determine if early life factors (e.g., breastfeeding) were associated with bone mass and fractures in 16-year-old adolescents	Sex: 265 males, 150 females Age: 16 years at follow-up Race: predominantly Caucasian Location: Tasmania	415	OR (95 % CI)	Any fracture	Upper limb fracture	Lower limb fracture
				Intention to breastfeed	0.71 (0.55–0.94)[c]	0.80 (0.55–1.66)	0.63 (0.36–1.13)
				Breastfeeding at 1 month	0.65 (0.48–0.87)[c]	0.84 (0.54–1.73)	0.49 (0.26–0.93)[c]
				Breastfeeding at 3 months	0.80 (0.60–1.09)	0.87 (0.58–1.31)	0.82 (0.45–1.48)
				Maternal recall of breastfeeding	0.69 (0.54–0.89)[c]	0.73 (0.51–1.39)	0.75 (0.42–1.34)
Kalkwarf et al. 2013 [215]	A cross-sectional study to describe age, sex, race, growth, and human milk feeding effects on bone	Sex: 158 males, 149 females Age: 1–36 months Race: 225 Caucasian, 63 African American, 15 mixed Caucasian and African American, and 4 Asian Location: USA	307		Human milk	No human milk	
				Overall BMD Z-score	−0.05	0.21**	

95 % CI confidence interval, *BMC* bone mineral content, *BMD* bone mineral density, *DXA* dual-energy x-ray absorptiometry, *OR* odds ratio, *RCT* randomized controlled trial

[a] Values were reported in a figure and via text

*$P < 0.01$; **$P < 0.05$

Table 10 DMPA injections and oral contraceptive use on bone health in adolescents

Source	Study description	Population description	Number of subjects	End points	Results		
Observational studies							
Lloyd et al. 2000 [223]	An 8-year longitudinal study of white females in the Penn State Young Women's Health Study. OC users were those individuals who had used low-dose monophasic OCs for a minimum of 6 months at age ~12 and were still using them at age 20 years.	Sex: 62 females Age: 11.9 ± 0.5 years at baseline Race: Caucasian Location: USA	62	Total body BMC (g) at 12 years	OC users	Nonusers	
					1463.0 ± 64.0	1402.5 ± 45.5	
				Total body BMC (g) at 20 years	2272.2 ± 55.9	2214.2 ± 45.1	
				Total body BMD (g/cm^2) at 12 years	0.92 ± 0.01	0.91 ± 0.01	
				Total body BMD (g/cm^2) at 20 years	1.13 ± 0.01	1.12 ± 0.01	
				Hip BMD (g/cm^2) at 20 years	1.01 ± 0.02	0.99 ± 0.02	
				The OC users did not differ in anthropometric, body, or total bone measurements at baseline or at age 20 years (no differences in age at menarche or exercise at age 20 years). OC pill use by healthy white teenage females did not affect acquisition of peak bone mass.			
Lara-Torre et al. 2004 [225]	Nonrandomized prospective study to examine BMD in control adolescent subjects vs those receiving DMPA injections or OCs over a 2-year period	Sex: 71 females Age: 11–19 years Race: Caucasian and black Location: USA	148		OC users[b]	DMPA injection[b]	Nonuser[b]
				% change in lumbar BMD at 6 months	1.170 (−0.14, 2.48)	−0.249 (−1.25, −0.75)*	2.768 (0.48, 5.05)
				% change in lumbar BMD at 12 months	2.35 (0.16, 3.78)	−1.59 (−2.53, 0.59)*	2.45 (−2.01, 5.99)
				% change in lumbar BMD at 18 months	3.82 (−0.62, 6.41)	−2.91 (−3.64, −2.23)*	0.73 (−1.01, 1.54)
				% change in lumbar BMD at 24 months	−1.01 (−1.23, 5.33)	−1.85 (−4.15, −0.23)*	5.89 (5.37, 6.85)
				There was a statistically significant difference in BMD between DMPA users and the control at 6, 12, 18, and 24 months. There was no statistical difference between OC pill users and the control at any time point.			
Lloyd et al. 2004 [224]	A 10-year longitudinal study of white females in the Penn State Young Women's Health Study. OC users were those individuals who had used low-dose monophasic OCs for a minimum of 6 months at age ~12 years and were still using them at age 22 years.	Sex: 80 females Age: 21.7 ± 0.1 years Race: Caucasian Location: USA	80		OC users	Nonusers	
				Total body BMC (g) at 22 years	2260 ± 55	2316 ± 66	

Table 10 (continued)

Source	Study description	Population description	Number of subjects	End points	Results		
				Total body BMD (g/cm^2) at 22 years	1.14 ± 0.01	1.15 ± 0.02	
				Hip BMD (g/cm^2) at 22 years	1.0 ± 0.02	1.0 ± 0.02	
				Femoral neck section modulus (cm^3) at 22 years	1.29 ± 0.05	1.32 ± 0.05	
				Femoral neck section modulus (cm^3) at 22 years	1.70 ± 0.06	1.74 ± 0.07	
				OC pill use among adolescents was not correlated with bone or body composition measurements.			
Rome et al. 2004 [227]	Prospective, observational design study to examine the effects of DMPA injections or OC (20 μg ethinyl estradiol/100 μg levonorgestrel) use on bone biochemical markers over 12 months	Sex: 165 females Age: 11–18 years Race: Caucasian and black Location: USA	370	Spine and femoral neck BMD	No significant differences reported between spine and femoral neck BMD for each group at each time point. Spine BMD was lower in the DMPA injection group vs the OC group. Exact values not reported		
Cromer et al. 2008 [226]	Observational prospective cohort study to examine the effects of DMPA injections or OC (20 μg ethinyl estradiol/100 μg levonorgestrel) use on BMD over 24 months	Sex: 375 females Age: 12–18 years Race: Caucasian and black Location: USA	433		OC users	DMPA injection	Nonuser
				Spine BMD (g/cm^2)	1.03 ± 0.11	0.98 ± 0.09*	0.98 ± 0.11
				Femoral neck BMD (g/cm^3)	0.97 ± 0.14	0.92 ± 0.14*	0.92 ± 0.15
				Over 24 months, mean percent change in spine BMD was −1.5 % (DMPA injection), 4.2 % (OC use), and 6.3 % (control).			
				Over 24 months, mean percent change in femoral neck BMD was −5.2 % (DMPA injection), 3.0 % (OC use), and 3.8 % (control).			
				Adolescent girls receiving DMPA injections had significant loss of BMD. Clinical significance of this loss may be mitigated by the slowed loss after the first year of DMPA use.			
Pikkarainen et al. 2008 [228]	4-year follow-up study examining the effects of estrogen-progestin OC use	Sex: 122 females Age: 12–19 years Race: Assumed predominantly Caucasian Location: Finland	122		OC user (1–2 years)	OC user (>2 years)	Nonuser
				Lumbar spine area (cm^2) at baseline	56.1 ± 6.1	56.7 ± 5.9	55.1 ± 5.9
				Lumbar spine area (cm^2) at 4 years	58.6 ± 6.1	58.7 ± 0.7	59.5 ± 6.3
				Femoral neck area (cm^2) at baseline	4.79 ± 4.33	4.64 ± 0.37	4.66 ± 0.40
				Femoral neck area (cm^2) at 4 years	4.80 ± 0.3	4.7 ± 0.4	4.7 ± 0.40
				Lumbar spine BMC (g) at baseline	54.3 ± 11.8	57.5 ± 11.9	51.2 ± 10.2
				Lumbar spine BMC (g) at 4 years	59.10 ± 11.7	60.2 ± 12.3	59.2 ± 10.0
				Femoral neck BMC (g) at baseline	4.3 ± 0.8	4.4 ± 0.8	4.1 ± 0.6
				Femoral neck BMC (g) at 4 years	4.5 ± 0.8	4.4 ± 0.7	4.3 ± 0.6

Table 10 (continued)

Source	Study description	Population description	Number of subjects	End points	Results		
				There was a significant trend of a lesser increase of BMC in lumbar spine in the OC users (>2 years) than in the other two groups ($P < 0.0046$).			
				The development of the femoral neck was significantly different between the OC users (1–2 years) and OC users (>2 years). The longer duration of OC use seemed to suppress normal BMC development (P for linearity = 0.038)			
Walsh et al. 2008 [230]	A case-controlled matched study aiming to examine whether the effects of DMPA injections are age-specific and to determine the effects of DMPA on hormones and bone turnover	Sex: 100 females (50 pairs) Age: 12–18 years Race: Caucasian and black Location: USA	100		DMPA injection[a]	Nonusers[a]	
				Lumbar spine BMD (g/cm^2)	1.003 (0.972–1.035)*	0.947 (0.950–0.977)	
				Total hip BMD (g/cm^2)	0.983 (0.950–1.016)*	0.931 (0.897–0.966)	
				Distal forearm BMD (g/cm^2)	0.465 (0.446–0.483)	0.474 (0.457–0.491)	
				DMPA injections are associated with a bone density deficit at the spine and hip when used before peak bone mass.			
Bonny et al. 2011 [222]	Prospective longitudinal study examining the relationship between weight and BMD and the correlation between weight change and BMD in premenarcheal girls reporting DMPA use or OC (20 μg ethinyl estradiol/100 μg levonorgestrel) use	Sex: 433 females Age: 12–18 years Race: Caucasian and black Location: USA	433		User	DMPA injection	Nonuser
				Correlation between absolute change in weight (kg) and absolute change in femoral neck BMD at 12 months	1.000	1.000	1.000
				Correlation between absolute change in weight (kg) and absolute change in femoral neck BMD at 24 months	1.000	1.000	1.000
				Correlation between absolute change in weight (kg) and absolute change in spine BMD at 12 months	−0.82	−0.101	0.10
				Correlation between absolute change in weight (kg) and absolute change in spine BMD at 24 months	−0.12	0.098	0.48
				Body weight was significantly positively associated with femoral neck BMD and spine BMD regardless of the contraceptive method ($P < 0.05$).			

Table 10 (continued)

Source	Study description	Population description	Number of subjects	End points	Results	
				Change in body weight at 12 and 24 months was highly correlated with change in femoral neck BMD ($P < 0.0001$) for all treatment groups.		
				No statistically significant correlation between change in weight and change in spine BMD was seen in the DMPA, OC, or control subjects at 12 or 24 months.		
Biason et al. 2015 [229]	Nonrandomized parallel-control study with 1-year follow-up assessing the effect of OC (20 μg ethinyl estradiol/150 μg desogestrel) users on bone density	Sex: 67 females Age: 12–19 years Race: Assumed Brazilian Location: Brazil	67		OC user	Nonuser
				% variation lumbar BMD (g/cm^2)	2.07	12.16
				% variation lumbar BMC (g)	1.57*	16.84
				% variation subtotal BMD (g/cm^2)	0.56*	5.28
				% variation subtotal BMC (g)	1.18*	16.04
				% variation whole body BMD (g/cm^2)	0.84	5.28
				% variation whole body BMC (g)	1.22*	11.34
				Use of low-dose OCs was associated with lower bone mass acquisition in adolescents over a 1-year period.		
				OC users showed low bone mass acquisition in the lumbar spine and had BMD and BMC median variations of 2.07 and 1.57 %, respectively, between the measurements at baseline and 12 months.		
				Nonusers showed median variations of 12.16 and 16.84 % for BMD and BMC, respectively, over the same period.		

95 % CI confidence interval, *BMC*, bone mineral content, *BMD* bone mineral density, *RCT* randomized controlled trial

[a] Mean (95 % CI)

[b] Median (25 %, 75 %)

*$P < 0.05$ compared with control

Table 11 Alcohol consumption and bone health in children and adolescents

Reference	Study description	Population description	Number of subjects	End points	Results			
Prospective studies								
Korkor et al. 2009 [231]	This 4-year prospective study assessed the relationship between smoking and alcohol intake and bone mass. Students in 9th grade were recruited. Number of alcoholic beverages in the last week was reported in the 9th through 12th grades. Subjects classified as any alcohol over 4 years vs not	Sex: 37 males, 72 females Age: 14–19 years at enrollment Race: white 83 %, Asian 1 %, Hispanic 4 %, unknown 12 % Location: Wisconsin, USA Year(s): 2000–2003	109	Peripheral DXA	Simple model, any alcohol intake	Adjusted model, any alcohol, or smoking		
				Heel aBMD in 12th grade (g/cm^2)	−0.042, $P = 0.047$ *(−7.2 %)*	−0.028, $P = 0.05$ *(−4.8 %)*		
				The simple model includes any alcohol over the 4-year study (yes, $n = 13$; no, $n = 96$). The adjusted model was adjusted for sex baseline aBMD dairy intake. Large overlap in smoking and alcohol use. Any smoking or alcohol combined ($N = 14$) was associated with a −0.028-g/cm^2 lower aBMD.				
Lucas et al. 2012 [235]	This prospective study quantified the association between early initiation of smoking and alcohol intake and forearm BMD in early and late adolescence. Alcohol intake reported at age 13 and 17 years and classified as never, tried but not currently drinking, <1 drink/week, or ≥1 drink/week	Sex: female Age: 13 and 17 years Race: not specified Location: Portugal Year(s): 2003–2007	716	Peripheral DXA	Drinking at age 13 years vs never ($n = 298$)			
				Distal radius aBMD	Tried, not currently drinking ($n = 380$)	Drinks < 1/week ($n = 26$)	Drinks ≥ 1/week ($n = 8$)	*P* value
				At age 13 years	0.3 %	−2.0 %	−1.1 %	0.826
				At age 17 years	−1.1 %	2.3 %	−4.8 %	0.282
					Drinking at age 17 years vs never ($n = 120$)			
					Tried, not currently ($n = 273$)	Drinks, not daily ($n = 266$)	Drinks, daily ($n = 54$)	*P* value
				At age 17 years	1.1 %	0.0 %	−2.3 %	0.471
					Ever drank in adolescence vs never ($n = 84$)			
					Tried 13 years but before 17 years ($n = 213$)	Tried before 13 years ($n = 419$)		*P* value
					−0.9 %	−2.0 %		0.216
					Means are adjusted for menarche age, alcohol intake, sports, and BMI.			
Dorn et al. 2013 [233]	This 3-year prospective study of girls examined bone accrual according to smoking, alcohol intake, depression,	Sex: female Age: 11–17 years	262	DXA Total body BMC (g) Spine aBMD (g/cm^2)	There was no significant association between alcohol use and any bone outcome measure.			

Table 11 (continued)

Reference	Study description	Population description	Number of subjects	End points	Results
	and anxiety. Alcohol use was coded as 0–5 drinks or ≥6 drinks in lifetime.	Race: 62 % white, 33 % black, 5 % other Location: Ohio, USA Year(s): 2003–2010		Hip aBMD (g/cm^2)	Regression models were adjusted for race, puberty stage, weight, height, age at menarche, contraceptive use, calcium intake, vitamin D status, and physical activity.
Cross-sectional studies					
Elgan et al. 2002 [237]	This cross-sectional study conducted in nursing students measured lifestyle and physiologic factors. Alcohol intake was measured by questionnaire.	Sex: female Age: 16–24 years Race: not reported Location: Lund, Sweden Year(s): 1999	218	Peripheral DXA Heel aBMD (g/cm^2)	Correlation with alcohol intake, $r = -0.05$ (P = NS) Alcohol intake not significant ($P = 0.84$) in regression models adjusting for age, weight, physical activity, and hormonal age Average alcohol intake 16.6 g/month; 79 % reported some alcohol intake
Kyriazopoulos et al. 2006 [236]	This cross-sectional study evaluated the influence of current dietary factors (calcium, proteins, alcohol, coffee, and tea intake), exercise, smoking, and sunlight on forearm bone mass in young Greek men. Alcohol intake reported as consumption per week	Sex: male Age: 18–30 years, mean 22 years Race: *not reported* Location: Greece Year(s): *not reported*	300	Peripheral DXA Distal radius BMC (g) Distal radius aBMD (g/cm^2) Ultradistal radius aBMD (g/cm^2)	Mean alcohol intake 3.78 ± 1.35 times/week. No association between alcohol intake (times/week) and bone measures with and without adjustment for height, weight, calcium intake, sunlight exposure, exercise, and work
Dorn et al. 2011 [232]	This cross-sectional analysis of baseline data examined how bone mass and density varied according to smoking, alcohol intake, depression, and anxiety. Alcohol intake reported as no drinks ($n = 135$), 1–5 drinks ($n = 59$), ≥6 drinks ($n = 67$) in the past year	Sex: female Age: 11–17 years Race: 62 % white, 33 % black, 5 % other Location: Ohio, USA Year(s): 2003–2007	261	DXA Total body BMC (g) Spine aBMD (g/cm^2) Total hip aBMD (g/cm^2) Femoral neck aBMD (g/cm^2)	No significant main effect of alcohol group and any outcome measure ($P > 0.10$). Analyses were adjusted for age, weight, height, race, and maturational stage. Significant interactions between alcohol, smoking, and depression symptoms on bone outcomes. Stronger negative association between depressive symptoms and total body BMC among individuals who smoked and used alcohol
Eleftheriou et al. 2013 [238]	A cross-sectional study evaluating the association of smoking, alcohol consumption, and prior exercise with lower limb bone volume, composition, and structure by MRI and DXA in a large cohort of healthy Caucasian males. Alcohol intake was coded as none, low (1–9 U/week), moderate (12–21 U/week), or high (>21 U/week)	Sex: male Age: mean 19.9 years Race: Caucasian Location: UK Year(s): not reported	651	DXA	Difference between Alcohol intake group vs none
					Low 1–9 U/week / Moderate 12–24 U/week / High > 24 U/week / *P* value
				Total hip aBMD	1.5 % / 2.3 % / −0.6 % / 0.017
				Femoral neck aBMD	−1.1 % / 2.8 % / −0.7 % / 0.015
				Proximal femur geometry by MRI	
				Periosteal volume	NS, data not shown
				Endosteal volume	NS, data not shown
				Cortical volume	NS, data not shown
				Adjusted for height, weight, smoking, and weight-bearing activity	
Winther et al. 2014 [234]	This cross-sectional, population-based study compared BMD levels of Norwegian adolescents with lifestyle	Sex: male and female Age: 15–17 years Race: not reported	835		Difference between alcohol users vs not

Table 11 (continued)

Reference	Study description	Population description	Number of subjects	End points	Results			
	factors. Alcohol intake reported as never, ≤1 per month, or ≥2 per month. Alcohol use recoded for analysis as yes vs no	Location: Norway Year(s): 2010–2011						
					Age adjusted		Multivariable adjusted	
				DXA	β	*P* value	β	*P* value
				Males ($n = 492$)				
				Total hip aBMD (g/cm^2)	0.027	0.057	0.035	0.006
				Femoral neck aBMD (g/cm^2)	0.030	0.037	0.028	0.021
				Females ($n = 469$)				
				Total hip aBMD (g/cm^2)	−0.014	0.297	–	–
				Femoral neck aBMD (g/cm^2)	−0.013	0.330	–	–
				Alcohol uses include intakes of up to 1/month (44.7 % of girls, 36.4 % of boys) and ≥2 times/month (30.3 % of girls, 30.9 % of boys) vs never (23.4 % of girls, 30.4 % of boys).				
				Multivariable analyses were adjusted for age, BMI, height, sexual maturation, physical activity, smoking, diseases, and medications known to affect bone hormonal contraceptives.				

aBMD areal bone mineral density, *BMC* bone mineral content, *BMD* bone mineral density, *DXA* dual-energy x-ray absorptiometry, *NS* not significant

Table 12 Smoking and bone health in children and adolescents

Reference	Study description	Population description	Number of subjects	End points	Results
Prospective studies					
Lappe et al. 2001 [42]	This prospective study of female army recruits examined risk factors for developing stress fractures during 8 weeks of basic training.	Sex: female Age: 21.1 ± 3.7 years Race: 31 % black, 53 % white, 16 % other Location: USA Years: 1995–1996	3758	Stress fracture	Odds ratios (95 % CI) History of smoking 1.34 (1.05–1.71) Years smoked 1.05 (1.02–1.08) •Adjusted for age, race and bone speed of sound
Elgan et al. 2003 [240]	This prospective study is a 2-year follow-up of the cohort reported in 2002 and investigated the joint effects of OC use and smoking. Smoking reported as monthly average. Twenty-eight subjects smoked as follows: $n = 1$, >25 cig/day; $n = 6$, 15–24 cig/day; $n = 16$, 5–14 cig/day;, $n = 4$, ≤4 cig/day.	Sex: female Age: 18–26 Race: not reported Location: Lund, Sweden Year(s): 2001	118	Peripheral DXA Heel aBMD T2 aBMD (g/cm^2) Unadjusted Adjusted[a] 2-year change in aBMD (g/cm^2) Unadjusted Adjusted[a]	Difference from reference group, nonsmoker/no OC use ($n = 35$) Smoker/no OC use ($n = 9$) / Nonsmoker/OC use ($n = 57$) / Smoker/OC use ($n = 17$) 0.0013 / 0.014 / −0.012 −0.032* / −0.014 / −0.017* −0.035* / −0.013 / −0.016 −0.06 / −0.010 / −0.021 [a]Adjusted for age, physical activity baseline BMD, body weight *$P < 0.05$
Lappe et al. 2008 [241]	Secondary analyses of this randomized calcium and vitamin D supplementation trial examined other risk factors for developing stress fractures during basic training.	Sex: female Age: 19 years (17–35 years) Race: not specified Location: USA Years 2001–2006	5201	Stress fracture	Risk of fracture was 41 % higher in women with history of smoking when adjusted for treatment group, $P = 0.0075$ Odds ratio for fracture was 1.32 (0.99–1.75) in women with history of smoking when adjusted for treatment, amenorrhea, high exercise, Depo Provera use, age, and running speed.
Korkor et al. 2009 [231]	This 4-year prospective study assessed the relationship between smoking and alcohol intake and bone mass. Students in 9th grade were recruited. Number of cig smoked per day reported in the 9th, 10th, 11th, and 12th grades. Subjects classified as any smoking over 4 years vs not	Sex: 37 males, 72 females Age: 14–19 years at enrollment Race: white 83 %, Asian 1 %, Hispanic 4 %, unknown 12 % Location: Wisconsin, USA Year(s): 2000–2003	109	Peripheral DXA Heel aBMD in 12th grade (g/cm^2)	Simple model, any smoking[a] / Adjusted model, any alcohol or smoking[b] −0.0249, $P = 0.29$ / −0.0281, $P = 0.05$ −4.3 % / −4.8 % [a]Any smoking over the 4-year study (yes, $n = 8$; no, $n = 101$) [b]Adjusted for sex baseline aBMD dairy intake Large overlap in smoking and alcohol use. Any smoking or alcohol combined ($N = 14$) was associated with a −0.028-g/cm^2 lower aBMD.
Lucas et al. 2012 [235]	This prospective study quantified the association between early initiation of smoking and alcohol intake and forearm BMD in early and late adolescence. Smoking reported at age 13 and 17 years and classified as:	Sex: female Age: 13 years and 17 years Race: *not specified* Location: Portugal Year(s): 2003–2007	713	Peripheral DXA Distal radius aBMD At age 13 years At age 17 years	Smoking at age 13 years vs never smoked ($n = 523$) Tried, not currently smoking ($n = 165$) / Smokes ($n = 24$) / P value 1.1 % / −0.6 % / 0.410 −2.3 % / −0.7 % / 0.068 Smoking at age 17 years vs never ($n = 390$)

Table 12 (continued)

Reference	Study description	Population description	Number of subjects	End points	Results			
	tried but not currently smoking, smokes but not daily or smokes daily				Tried, not currently ($n=224$)	Smokes, not daily ($n=33$)	Smokes, daily ($n=72$)	P value
				At age 17 years	−2.3 %	−3.2 %	−0.7 %	0.438
					Ever smoked in adolescence vs never smoked ($n=353$)			
				At age 17 years	Tried 13 years but before 17 years ($n=167$)	Tried before 13 years ($n=192$)	P value	
					0.4 %	−1.8 %	0.103	
				Adjusted for menarche age, alcohol intake, sports, and BMI				
Dorn et al. 2013 [233]	This 3-year prospective study of girls examined bone accrual according to smoking, alcohol intake, depression, and anxiety. Smoking measured every 3 months and coded as cigarettes smoked in last 30 days: 0, 1–2 days, 3–5 days, 6–9, 10–19 days, 20–29 days, or 30 day	Sex: female Age: 11–17 years Race: 62 % white, 33 % black, 5 % other Location: Ohio, USA Year(s): 2003–2010	262	DXA Total body BMC (g) Spine aBMD (g/cm^2) Hip aBMD (g/cm^2)	No significant main effect or age × smoking interaction on total body Significant age × smoking interaction for spine and hip aBMD. As smoking increased, the rate of bone accrual decreased as girls got older. Regression models adjusted for race, puberty stage, weight, height, and contraceptive use			
Cross-sectional studies								
Elgan et al. 2002 [237]	This cross-sectional study conducted in nursing students measured lifestyle and physiologic factors. Smoking was measured by questionnaire and dichotomized as yes/no. 23 % smoked on a daily basis, 22 % were party smokers, and 55 % were nonsmokers.	Sex: female Age: 16–24 years Race: not reported Location: Lund, Sweden Year(s): 1999	218	Peripheral DXA Heel aBMD (g/cm^2)	Smoking status not significantly associated with aBMD in bivariate analyses. Data not shown Smoking not significant ($P=0.48$) in regression models adjusting for age, weight, physical activity, and hormonal age			
Afghani et al. 2003 [336]	A cross-sectional analysis of baseline data from a smoking cessation trial. Analyses investigated the role of body composition, physical activity, menarche, smoking, and second-hand smoke on regional bone mass among Asian adolescents living in Wuhan, China. Smoking questions assessed if subjects "smoked at least 100 cigarettes in their life?" and "have smoked in last 30 day." Smoking was reclassified for analyses as smoking yes/no.	Sex: male and female Age: 12–16 years, 14.5 ± 0.5 Race: Asian Location: Wuhan, China Year(s): *not reported*	466	Peripheral DXA	Correlation with smoking (yes/no)[a]	P value	Multivariable models[b]	
				Boys ($n=300$)				
				Forearm BMC	0.05	NS	NS	
				Forearm aBMD	0.04	NS	–	
				Heel BMC	0.05	NS	NS	
				Heel aBMD	0.00	NS	–	
				Girls ($n=166$)				
				Forearm BMC	0.15	<0.05	NS	
				Forearm aBMD	0.04	NS	–	
				Heel BMC	0.08	NS	NS	
				Heel aBMD	0.09	NS	–	

[a] Unclear how correlation derived given that smoking was a dichotomous variable

[b] Adjusting for age, height, lean mass, fat mass, team sports participation, menarche, and passive smoking

Table 12 (continued)

Reference	Study description	Population description	Number of subjects	End points	Results			
				Low level of smoking and inconsistent report of smoking in the sample limits conclusions. 38 % of girls and 14 % of boys inconsistently answered smoking questions. Among smokers, 58 % of girls and 51 % of boys smoked ≤1 cigarette in last 30 days.				
Kyriazopoulos et al. 2006 [236]	This cross-sectional study evaluated the influence of current dietary factors (calcium, proteins, alcohol, coffee, and tea intake), exercise, smoking, and sunlight on forearm bone mass in young Greek men. Smoking coded as daily smoking (58.6 %) or no	Sex: male Age: 18–30 years, mean 22 years Race: *not reported* Location: Greece Year(s): *not reported*	300	Peripheral DXA Distal Radius BMC Distal radius aBMD Ultradistal radius aBMD	There was no association between daily smoking (58.6 % of sample) and bone measures with and without adjustment for height, weight, calcium intake, sunlight exposure, exercise, and work. Data not shown			
Lorentzon et al. 2007 [239]	The GOOD study is a cross-sectional study involving a random selection of males in Gothenburg. Bone mass, density, and geometry measured by DXA and pQCT. Smoking quantified as cigarettes/day and duration. For analyses, subjects were classified as smokers ≥1 cig/day vs not.	Sex: male Age: 18–20 years Race: *not reported* Location: Gothenburg, Sweden Year(s): *not reported*	1063		Difference between smoked ≥1 cigarette/day[a] vs not			
					Unadjusted	*P* value	Adjusted[b]	*P* value
				DXA				
				Total body aBMD	−2.1 %	<0.01	−1.8 %	0.01
				Spine aBMD	−4.3 %	<0.001	−3.3 %	<0.01
				Femoral neck aBMD	−5.3 %	<0.001	−3.9 %	<0.01
				Trochanter aBMD	−6.6 %	<0.001	−5.0 %	<0.01
				pQCT				
				Tibia				
				Cortical vBMD	0.0 %	0.91	–	NS
				Cortical thickness	−4.5 %	<0.001	−4.0 %	<0.001
				Periosteal circumference	0.0 %	0.97	–	NS
				Endosteal circumference	2.5 %	<0.05	2.7 %	0.01
				Trabecular vBMD	−4.2 %	<0.01	−3.8 %	<0.01
				Radius				
				Cortical vBMD	−0.1 %	0.55	–	NS
				Cortical thickness	−2.8 %	<0.01	−2.9 %	<0.01
				Periosteal circumference	0.7 %	0.32	–	NS
				Endosteal circumference	3.3 %	0.02	4.5 %	<0.01
				Trabecular vBMD	−2.7 %	0.16	–	NS
				[a]Smokers consumed 9.3 ± 6.3 cig/day. Mean duration of smoking 4.1 ± 2.1 years. Smokers less active than nonsmokers [b]Adjusted for calcium intake, physical activity, age, height, and weight. Smokers had reduced BMD due to smaller cortical thickness greater endosteal circumference			
Dorn et al. 2011 [232]	This cross-sectional analysis of data examined how bone mass and density varied according to smoking, alcohol intake, depression, and anxiety. Smoking ever in their life coded as never ($n = 104$), 1 puff to	Sex: female Age: 11–17 years Race: 62 % white 33 % black, 5 % other Location: Ohio, USA Year(s): 2003–2007	261	DXA				
				Total body BMC (g)	No significant differences among smoking groups			
				Spine aBMD (g/cm^2)	No significant differences among smoking groups			
				Total hip aBMD (g/cm^2)	1 puff to 2 cig group 6.5 % greater than >100 cig group, $P < 0.05$			
				Femoral neck aBMD (g/cm^2)	1 puff to 2 cig group 6.0 % greater than >100 cig group, $P < 0.05$			

Table 12 (continued)

Reference	Study description	Population description	Number of subjects	End points	Results			
	2 cig ($n=54$), and 3–99 cig ($n=51$), >100 cig/day ($n=52$)			Analyses adjusted for age, weight, height, race, and maturational stage. Significant interactions between alcohol and tobacco use, and depression symptoms on bone outcomes. Stronger negative association between depressive symptoms and total body BMC among individuals who smoked and used alcohol.				
Eleftheriou et al. 2013 [238]	A cross-sectional study evaluating the association of smoking, alcohol consumption, and prior exercise with lower limb bone volume, composition, and structure by MRI and DXA in a large cohort of healthy Caucasian males. Smoking status coded as nonsmoker, ex-smoker (>6 months), recent ex-smoker (≤6 months), or current smoker	Sex: male Age: mean 19.9 years Race: Caucasian Location: UK Year(s): not reported	651		Difference[a] between smoking status vs nonsmoker ($n=329$)			
					Ex-smoker >6 months ($n=41$)	Recent ex-smoker ≤6 months ($n=35$)	Current smoker ($n=244$)	*P* value
				DXA				
				Total hip aBMD	−5.0 %	−6.0 %	−4.7 %	0.0001
				Femoral neck aBMD	−5.9 %	−5.3 %	−4.0 %	0.001
				MRI				
				Periosteal volume	−5.0 %	−4.3 %	−0.4 %	0.004
				Endosteal volume	NS, data not shown			
				Cortical volume	NS, data not shown			
				[a]Adjusted for height weight, alcohol intake, and weight-bearing activity				
Winther et al. 2014 [234]	This cross-sectional population-based study compared BMD levels of Norwegian adolescents with lifestyle factors. Smoking was classified as daily smoking, sometimes smokes, or never smokes.	Sex: male and female Age: 15–17 years Race: Location: Norway Year(s): 2010–2011	835		Difference between smoking[a] vs not			
					Age adjusted		Multivariable adjusted[a]	
				DXA	Beta	*P* value	Beta	*P* value
				Males ($n=492$)				
				Total hip aBMD (g/cm^2)	−0.039	0.012	0.029	0.037
				Femoral neck aBMD (g/cm^2)	−0.025	0.116	–	–
				Females: ($n=469$)				
				Total hip aBMD (g/cm^2)	−0.026	0.074	–	–
				Femoral neck aBMD (g/cm^2)	−0.031	0.031	–	–
				[a]Includes daily smoking (5.5 % of girls and 3.8 % of boys) and sometimes smokes (15.9 % girls, 20.2 % of boys) vs never smokes (76.6 % of girls and 74.2 % of boys)				
				[b]Adjusted for age, BMI, height, sexual maturation, physical activity, alcohol intake, diseases, and medications known to affect bone and hormonal contraceptives				

aBMD areal bone mineral density, *BMC* bone mineral content, *BMD* bone mineral density, *cig* cigarette, *DXA* dual-energy x-ray absorptiometry, *GOOD* Gothenburg osteoporosis and obesity determinants, *OC* oral contraceptive, *pQCT* peripheral quantitative computed tomography

Table 13 Physical activity and exercise on bone mass and density in children and adolescents

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
RCTs						
Witzke and Snow 2000 [337]	9-month jumping intervention Recruited for exercise group No randomization	Sex: female Age: 13–15 years Race: not listed Location: Corvallis, OR	53	Frequency: 3×/week Intensity: varied Time: 30–45 min/session Type: resistance training: squats, lunges, toe/heel raises, bench stepping, and jumping. Plyometric training: two-footed, in-place jumps to stair jumping, bounding, depth jumps Control: regular PE	DXA *Significant* TR BMC *NS* TB, FN, LS, FS BMC	Percent change, mean ± SD EX: 3.13 ± 6.44* CON: 1.96 ± 6.69 Both groups experienced a significant increase in percent change in bone mass compared to zero for TB, FN, LS, and FS, but only EX improved BMC of the TR (3.1 vs 1.9 %).
McKay et al. 2000 [338]	8-month loading intervention Randomized by school	Sex: male and female Age: 6.9–10.2 years Race: 34 % Asian, 66 % white Location: Richmond, British Columbia	144	Frequency: 3×/week (2× PE, 1× classroom) Intensity: progressive Time: 10–30 min (minimum 10 min loading) Type: variety: games, circuit training, dances. Ten tuck jumps required at beginning of each session Control: regular PE	DXA *Significant* TR aBMD *NS* TB, LS, PF, FN aBMD	Percent change, mean ± SEM EX: 4.4 ± 0.5* CON: 3.2 ± 0.3 EX group showed significantly greater change in TR aBMD than CON group (4.4 vs 3.2 %). No group differences at other sites.
Heinonen et al. 2000 [244]	9-month step aerobics/jumping intervention Randomized by school	Sex: female Age: 10–15 years Race: not specified Location: Tampere, Finland	126	Frequency: 2×/week Intensity: progressive Time: 50 min (10-min warm-up, 15-min nonimpact aerobic exercises, 20-min high-impact/jump training, 5-min cool down) Type: both-leg jumps at floor level, both-leg box jumps, one-leg box jumps Control: normal PA	DXA *Significant* LS BMC FN BMC TR BMC	Difference (g), mean (95 % CI) Premenarchal EX vs CON: 1.01 (0.23, 1.78)* Postmenarchal EX vs CON: 0.09 (0.02, 0.15)* *P* value Effect of EX (pre vs post): * * In the premenarchal girls, BMC increased significantly more in the EX than in CON at LS (8.6 vs 5.3 %) and FN (9.3 vs 5.3 %). The postmenarchal girls showed no significant posttraining intergroup differences at any site.
Fuchs et al. 2001 [306]	7-month jumping intervention Randomized by gender	Sex: male and female Age: 7.5 years ± 0.17 Race: 87 white, 1 Asian, 1 white-Hispanic Location: Corvallis, OR	89	Frequency: 3×/week, opposite PE Intensity: progressed from 50 to 80 jumps/day over 12 sessions; 100 jumps/day were performed for the remaining sessions Time: 20 min/session (5-min warm-up, 10-min jumping or	DXA *Significant* FN BMC FN BA LS BMC LS aBMD *NS* FN aBMD, LS BA	Postintervention values EX: 2.00 ± 0.07***; CON: 1.89 ± 0.06 EX: 3.13 ± 0.08***; CON: 2.96 ± 0.07 EX: 22.06 ± 0.57*; CON: 21.64 ± 0.58 EX: 0.571 ± 0.008**; CON: 0.553 ± 0.008 EX group had significantly greater changes in FN and LS BMC than CON group (4.5 and 3.1 %, respectively). EX group also had significantly greater changes in FN BA (2.9 %) and LS aBMD (2.0 %) than CON group.

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
				stretching, 5-min cool down) Type: jumps off 61-cm box Control: nonimpact stretching		
Nichols et al. 2001 [243]	15-month resistance training intervention Randomized	Sex: female Age: 14–17 years Race: not specified Location: Texas Woman's University, TX	16	Frequency: 3×/week Intensity: progressive Time: not specified Type: 15 exercises all major muscle groups, combination free weights and machines Control: not specified	DXA *Significant* FN aBMD *NS* TB, LS, WA, TR aBMD TB, LS, FN, WA, TR BMC LS, FN BMAD	Percent change, mean EX: 3.67**; CON: 1.35 FN aBMD increased significantly in EX group (40 %), but not in CON group. No significant changes seen at other sites
Mackelvie et al. 2001 [26]	9-month jumping intervention Randomized by school	Sex: female Age: 9–12 years Race: multiethnic population of city (45 % white, 34 % Asian, and 21 % mixed ethnicities) reflected in cohort Location: Richmond, British Columbia	177	Frequency: 3×/week (2x PE, 1 classroom) Intensity: progressed over school year by increasing number of jumps per station (from 10 to 20) and height (from 10 to 50 cm) Time: 10–12 min (5 circuits, ~1.5–2 min each) Type: jumping exercises—jumping jacks, lunge jumps, hopping, jumping over various obstacles, drop jumps from platform Control: stretching	DXA *Significant* LS BMC LS aBMD FN BMC FN aBMD FN vBMD *NS* TB, PF, TR BMC TB, PF, TR aBMD	Change, mean (95 % CI) Prepubertal EX; Prepubertal CON; Early Pubertal EX; Early Pubertal CON LS BMC: 4.70 (4.38, 5.02)*; 4.18 (3.92, 4.44) LS aBMD: 0.057 (0.050, 0.064)**; 0.044 (0.038, 0.049) FN BMC: 0.31 (0.28, 0.34)*; 0.26 (0.24, 0.29) FN aBMD: 0.043 (0.036, 0.050)*; 0.034 (0.028, 0.039) FN vBMD: 0.010 (0.004, 0.015)*; 0.002(−0.003, 0.006) There were no significant differences between prepubertal EX and CON groups. Early pubertal girls in EX group gained 1.5 to 3.1 % more bone at FN and LS than CON girls; gain at other sites did not differ
Mackelvie et al. 2002 [339]	7-month jumping intervention Randomized by school	Sex: male Age: 8.8–11.7 years Race: multiethnic population of city (45 % white, 34 % Asian, and 21 % mixed ethnicities) reflected in cohort Location: Richmond, British Columbia	121	Frequency: 3×/week (2× PE, 1 classroom) Intensity: progressed over school year by increasing number of jumps per station (from 10 to 20) and height (from 10 to 50 cm) Time: 10–12 min (5 circuits, ~1.5–2 min each) Type: jumping exercises—jumping jacks, lunge jumps, hopping, jumping over various obstacles, drop jumps from platform Control: stretching	DXA *Significant* TB BMC PF aBMD *NS* LS, PF, FN, TR BMC LS, FN, TR aBMD	Change, mean (95 % CI) EX; CON TB BMC: 105.8 (97.7, 113.9)**; 90.0 (81.9, 98.2) PF aBMD: 0.025 (0.020, 0.030)*; 0.017 (0.013, 0.022) The EX group gained more TB BMC (1.6 %) and PF aBMD (1 %) than CON group did after adjusting for age, baseline weight, change in height, and loaded PA.
Kontulainen et al. 2005 [125]	20-month follow-up to 9-month step aerobics/jumping intervention Randomized by school	Sex: female Age: 10–15 years Race: not specified Location: Tampere, Finland	99	Frequency: 2×/week Intensity: 100 both-leg jumps at floor level, increased to 200 box jumps (30 cm) using both legs and one leg Time: 50 min (10-min warm-up, 15-min nonimpact aerobic exercises, 20-min	DXA *Significant* LS BMC *NS* FN, TR BMC	Percent difference, mean (95 % CI) LS BMC: 4.9 (0.9, 8.8)* EX group had 4.9 % greater BMC accrual at the LS than the CON group during the 20-month follow-up. No other sites showed significant differences.

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
				high-impact/jump training, 5-min cool down) Type: both-leg jumps at floor level, both-leg box jumps, one-leg box jumps Control: normal PA		
Petit et al. 2002 [73]	7-month jumping intervention Randomized by school	Sex: female Baseline age: 9–12 years Race: multiethnic population of city (~34 % Hong Kong Chinese and 57 % white) reflected in cohort Location: Richmond, British Columbia	177	Frequency: 3×/week (2× PE, 1 classroom) Intensity: progressed over school year by increasing number of jumps per station (from 10 to 20) and height (from 10 to 50 cm) Time: 10–12 min (5 circuits, ~1.5–2 min each) Type: jumping exercises—jumping jacks, lung jumps, hopping, jumping over various obstacles, drop jumps from platform Control: stretching	DXA *Significant* None *NS* NN, IT, FS aBMD	No significant differences seen between EX and CON groups
Laing et al. 2002 [340]	36-month gymnastics participation Recruited due to enrollment in gymnastics	Sex: female Age: 8–13 years at baseline Race: all Caucasian (except one Hispanic control) Location: Athens, Georgia	17	Frequency: not specified Intensity: not specified Time: 9–24 h/week Type: regionally competitive gymnastics: vault, uneven bars, balance beam, floor routine Control: no gymnastics	DXA *Significant* TB aBMD LS aBMD PF aBMD TB BMC LS BMC TB BA LS BA FN BA PF BA *NS* FN, TR, Rad aBMD PF, FN, TR, Rad BMC FN, Rad BA	At year 3, significant differences between EX and CON were noted at TB, LS, and PF for aBMD. Significant differences were noted for TB and LS for BMC. Both the EX group and CON groups had significant increases in BA at the TB, LS, FN, and PF.
MacKelvie et al. 2003 [341]	20-month jumping intervention Randomized by school	Sex: female Age: 8.8–11.7 years at baseline Race: multiethnic population of city (57 % white, 34 % Hong Kong Chinese, 5 % East Indian, 4 % other ethnic origin or mixed ethnicity) reflected in the cohort	75	Frequency: 3×/week (2× PE, 1 classroom) Intensity: *year 1*: progressed over school year by increasing number of jumps per station (from 10 to 20) and height (from 10 to 50 cm); *year 2*: higher proportion of high-impact jumps. Height increased every 8–10 weeks	DXA *Significant* LS BMC FN BMC *NS* TB, PF, TR BMC LS, PF, FN, TR BA	Change, mean (95 % CI) EX: 10.9 (9.9, 11.9)* CON: 9.3 (8.4, 10.1) EX: 0.66 (0.58, 0.73)* CON: 0.55 (0.48, 0.61) There were substantially greater gains in LS (41.7 vs 38.0 %) and FN (24.8 vs 20.2 %) BMC in EX group than in CON group. No significant differences between groups at other sites.

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
		Location: Richmond, British Columbia		Time: 10–12 min (5 circuits, ~1.5–2 min each) Type: *year 1*: jumping exercises such as jumping jacks, lung jumps, hopping, jumping over various obstacles, and drop jumps from platform; *year 2*: plyometric jumps, alternating-foot jumps, and 2-ft obstacle jumps Control: stretching		
Van Langendonck et al. 2003 [342]	9-month impact intervention on twins Twins randomized to exercise or control, keeping birth order equal between groups	Sex: female (21 twin pairs) Age: 8.7 years (SD = 0.7) Race: not specified Location: Belgium	42	Frequency: 3×/week Intensity: after the first trimester, participants went barefoot or wore very thin gym shoes to enhance mechanical loading Time: 10 min/session Type: 3 impact exercises- rope skipping 50 times; hopping 20 times as far as possible with the left and right leg; jumping from a wooden box of 40 cm high landing on both feet 30 times. 2 nonimpact exercises- moving 3.5 m sideways in a push-up position six times and six times moving 3.5 m backward on hands and feet like a crab Control: asked not to perform the exercises at school or home	DXA *Significant* None *NS* LS, FN, PF, RA, TB BMC LS, FN, PF, RA, TB aBMD LS, FN, PF, RA, TB BA	None of the bone indices differed significantly between the EX and CON groups after the 9-month intervention.
Iuliano-Burns et al. 2003 [155]	8.5-month randomized intervention trials with two factors (exercise and calcium) that each had two levels	Sex: female Age: 7–11 years Race: 15 % Asian descent Location: Melbourne, Australia	66	Frequency: 3×/week (PE) Intensity: moderate (2–4× body wt GRF) Time: 20 min/session Type: hopping-, jumping-, and skipping-based activities Control: stretching and low-impact dance routines (1× body wt)	DXA *Significant* Leg BMC Femur BMC T-F BMC Arm BMC Hum BMC U-R BMC *NS* TB, LS BMC	Change, mean ± SEM EX: Calcium: 58.9 ± 7.1[b]; 29.9 ± 4.1[b]; 15.5 ± 1.9[a,c]; 7.3 ± 0.9[c]; 4.4 ± 0.5[a,c] EX: Placebo: 21.1 ± 1.8[d,f]; 10.3 ± 1.3[c,d]; 3.1 ± 0.4[c,d] CON: Calcium: 50.1 ± 3.3[b]; 24.1 ± 2.0[b]; 17.1 ± 1.3[d]; 13.1 ± 0.91[d]; 4.7 ± 0.4[d,e] CON: Placebo: 18.3 ± 2.2[f]; 10.8 ± 1.3[a]; 3.3 ± 0.4[a,c] Like letters denote significant difference between groups ($P < 0.05$). An exercise-calcium interaction was detected at the femur (7.1 %). By contrast, there was no exercise–calcium interaction detected at the T-F; however, there was a main effect of exercise: BMC increased 2–4 % more in the calcium-supplemented groups than in the nonsupplemented groups at the humerus (12.0 vs 9.8 %) and R-U (12.6 vs 8.6 %).
Specker and Binkley 2003 [81]	1-year randomized, placebo-controlled, partially blinded trial of PA and	Sex: male and female Age: 3–5 years Race: 94 % white, 6 % other Location: South Dakota	178	Frequency: 5×/wk Intensity: not specified	DXA Significant	Change, mean ± SEM EX: Calcium EX: Placebo CON: Calcium CON: Placebo

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
	calcium supplementation			Time: 30 min/day (5-min warm-up, 20-min activity, 5-min cool down) Type: hopping, jumping, skipping activities (17 different weekly programs) Control: 30 min/day of activities to keep them sitting quietly	Leg BMC *NS* TB, arm BMC TB, arm, leg BA	40.9 ± 1.3 38.2 ± 1.2 37.3 ± 1.4 38.5 ± 1.3 There was a significant interaction ($P < 0.05$) between the activity and supplement groups in leg BMC gain; the difference in BMC gain between EX and CON groups was more pronounced in children receiving calcium vs placebo. Among children receiving the placebo, leg BMC gain was similar in the EX and CON groups. However, among children receiving calcium, those in EX group has 9.7 % greater increase in leg BMC than those in CON group.
Stear et al. 2003 [156]	15.5-month randomized, double-blind trial of PA and calcium supplementation	Sex: female Age: 17.3 ± 0.4 years Race: not listed Location: UK	131	Frequency: 3×/wk Intensity: moderate-to-vigorous intensity, moderate-to-high impact Time: 45 min/session (7- to 10-min warm-up, 30-min workout, 5- to 8-min warm-down and stretch) Type: exercise-to-music aerobics class Control: not invited to exercise sessions	DXA *Significant* None *NS* TB, LS, Rad, R-Ul, R-Dis BMC TB, LS, Rad, R-Ul, R-Dis SA-BMC	No significant differences seen between EX and CON groups
MacKelvie et al. 2004 [295]	20-month jumping intervention Randomized by school	Sex: male Age: 8.8–12.1 years Race: multiethnic population of city (~34 % Hong Kong Chinese and 57 % North American/Western European Caucasian, 5 % Southeast Asian, and 4 % other or mixed ethnicity) reflected in cohort Location: Richmond, British Columbia	64	Frequency: 3×/wk (2× PE, 1 classroom) Intensity: progressed over 2 years by increasing number of jumps per station (from 10 to 20) and height (from 10 to 50 cm Time: 10–12 min (5 circuits, ~1.5–2 min each) Type: jumping exercises such as jumping jacks, lung jumps, hopping, jumping over various obstacles, drop jumps from platform Control: stretching	DXA *Significant* FN BMC TB, LS, PF, FN, TR BA *NS* TB, LS, PF, TR BMC	Change, mean (95 % CI) EX: 0.50 (0.45, 0.55)** CON: 0.39 (0.34, 0.43) FN BMC changes were significantly greater in EX boys (4.3 %); changes in bone area and BMC for other regions were not significantly different between groups.
McKay et al. 2005 [297]	8-month jumping intervention Control group used from previous study	Sex: male and female Age: 8.9 to 11.0 years Race: 38 % Caucasian, 48 % Asian, 15 % other (including mixed ethnic, black, and South Asian) Location: Richmond, British Columbia	124	Frequency: 3×/days Intensity: 5× body wt, maximum rate of force was >400 body wt/s (independent sample of 70 boys and girls) Time: 3 min/day Type: 10 counter movement jumps (two-foot take off, clutch knees, two-foot landing)	DXA *Significant* TB BMC TB BA PF BMC IT BMC *NS* LS, PF, IT, GT, FN BA LS, GT, FN BMC	Change, mean (95 % CI) EX / CON 92.7 (83, 102)* / 106 (98, 114) 76.7 (66.9, 86.5)* / 95.6 (87.6, 103.6) 2.3 (2.1, 2.6)* / 1.9 (1.7, 2.1) 1.5 (1.3, 1.7)* / 1.2 (1.0, 1.3) CON group had greater increase in adjusted TB BMC (1.4 %). EX group gained significantly more BMC at the PF (2 %) and at the IT region (27 %).

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results	
				Control: not specified, from previous study			
Laing et al. 2005 [343]	24-month quasi-experimental prospective gymnastics study Recruited due to enrollment in gymnastics	Sex: female Age: 4–8 years Race: 64 % white, 27 % black, 3 % Asian, 2 % Hispanic, 1 % Indian, and 3 % other Location: Athens, Georgia	143	Frequency: 1×/week Intensity: not specified Time: 1 h/session Type: recreational gymnastics class Control: participating in nongymnastic activities or no activities	DXA	Postintervention values, mean ± SD	
					Significant	EX	CON
					TB BA	1392 ± 247*	1545 ± 314
					TB BMC	997 ± 255*	1151 ± 323
					TB aBMD	0.708 ± 0.06*	0.736 ± 0.07
					LS BA	34.1 ± 50.5*	36.6 ± 6.17
					LS BMC	20.5 ± 5.47*	22.6 ± 6.24
					PF BA	18.8 ± 4.04*	20.4 ± 4.53
					PF BMC	12.5 ± 4.07*	14.1 ± 4.56
					FA BA	7.39 ± 1.58*	8.05 ± 1.80
					FA BMC	2.85 ± 0.85*	3.19 ± 0.97
					NS LS, PF, FA aBMD	Values suggest that EX remained lower in bone mineral measures after 2 years; however, after adjusting for initial differences, it was determined that EX had greater BA, BMC, and aBMD responses compared with CON at some skeletal sites.	
Yu et al. 2005 [242]	36-week strength training intervention Randomized	Sex: male and female Age: 9–11 years Race: not specified Location: Hong Kong	63	Frequency: *phase 1*: 3×/week; *phase 2*: 1×/week Intensity: *phase 1*: 75 % 10 RM, increased to 100 % over time. 1 set, 20 reps; *phase 2*: weight adjusted according to ability. 2–3 sets of 10–20 reps Time: *phase 1*: 75 min/session (10-min warm-up, 30-min strength training, 10-min agility training, 5-min cool down); *phase 2*: 60 min/session (5-min warm-up, 10-min stretching, 40-min strength training, 5-min cool down) Type: *phase 1*: circuits (9 stations for strength training, 1 station for agility, 1 aerobic station); *phase 2*: similar to phase 1 Control: hypocaloric diet, no strength training	DXA *Significant* None NS: TB, TH, LS BMC	No significant differences in BMC were observed between the EX and CON groups at 36 weeks.	
Valdimarsson et al. 2006 [344]	1-year expanded PE intervention Randomized by school	Sex: female Age: 6.5–8.9 years Race: Caucasian Location: Malmö, Sweden	103	Frequency: 5 days/week Intensity: varied Time: 40 min/day Type: normal PE curriculum (running, jumping, climbing ropes, variety of ball games). Activities	DXA	Change, mean (SD)	

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results	
				varied to reduce boredom. No specific osteogenic training program was added. Control: normal PE curriculum, duration within normal limits (1–2 sessions/week, in total 60 min/week)			
					Significant	EX	CON
					L2-L4 BMC	2.4 (1.1)**	1.8 (0.7)
					L3 BMC	0.94 (0.63)***	0.53 (0.30)
					L2-L4 aBMD	0.044 (0.03)***	0.026 (0.01)
					L3 aBMD	0.047 (0.03)***	0.025 (0.02)
					L3 width	0.17 (0.12)***	0.09 (0.06)
					NS	The annual gain in BMC was 4.7 % higher in the LS and 9.5 % higher in L3 in the EX group than in the CON group. The annual gain in aBMD was 2.8 % higher in the LS and 3.1 % higher in L3 in the EX group than in the CON group. The annual gain in L3 width was 2.9 % higher in the EX group than in the CON group.	
					TB, FN, leg BMC		
					TB, FN, leg aBMD		
					L3, FN vBMD		
					FN width		
Linden et al. 2006 [345]	2-year expanded PE intervention Randomized by school	Sex: female Age: 6.5–8.9 years Race: white Location: Malmö, Sweden	99	Frequency: 5 days/week Intensity: varied Time: 40 min/day Type: normal PE curriculum (running, jumping, climbing ropes, variety of ball games). Activities varied to reduce boredom. No specific osteogenic training program was added. Control: normal PE curriculum, duration within normal limits (1–2 sessions/week, in total 60 min/week)	DXA	Change, mean	
					Significant	EX	CONZ
					L2-L4 BMC	2.2*	1.8
					L3 BMC	0.8***	0.6
					L2-L4 aBMD	0.034*	0.026
					FN vBMD	−0.004**	0.006
					L3 width	0.136**	0.092
					NS	The annual gain in BMC was greater in the EX group than in the CON group: L2-L4 3.8 %, L3 7.2 %. The EX group had greater annual gain in aBMD at L2-L4 (1.2 %). There was also a greater mean annual gain in bone size in the L3 vertebra (1.8 %).	
					TB, FN, leg BMC		
					TB, L3, FN, leg aBMD		
					L3 vBMD		
					FN width		

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results			
Bass et al. 2007 [157]	8.5-month randomized intervention trials with two factors (exercise and calcium) that each had two levels	Sex: male Age: 7–11 years Race: 22 % Asian descent Location: Melbourne, Australia	88	Frequency: 3×/week (PE) Intensity: moderate (2–8× body wt GRF) Time: 20 min/session Type: hopping-, jumping-, and skipping-based activities Control: stretching and low-impact dance routines (1× body wt)	DXA	Change, mean (SD)			
						EX		CON	
					Significant	Calcium	Placebo	Calcium	Placebo
					Leg BMC	64.4 (4.2)[abc]	54.0 (4.7)[a]	47.7 (4.2)[b]	43.3 (3.2)[c]
					Femur BMC	30.1 (1.8)[abc]	24.9 (1.9)[a]	24.8 (1.4)[b]	23.1 (1.3)[c]
					T-F	23.4 (2.1)[a]			16.8 (1.5)[a]
					NS TB, LS, arm, Hum, U-R BMC	Like letters denote significant difference between groups ($P < 0.05$). The increase in femur BMC in the EX + calcium group was ~2 % greater than the increase in the EX + placebo, no-EX + calcium, or no-EX + placebo groups. At the T-F, the increase in BMC in the EX + calcium group was ~3 % greater than in the no-EX + placebo group			
Linden et al. 2007 [298]	1-year expanded PE intervention Randomized by school	Sex: male Age: 6.7–9.0 years Race: Caucasian (except 1 boy adopted from Colombia) Location: Malmö, Sweden	138	Frequency: 5 days/week Intensity: varied Time: 40 min/day Type: normal PE curriculum (running, jumping, climbing ropes, variety of ball games). Activities varied to reduce boredom. No specific osteogenic training program was added. Control: normal PE curriculum, duration within normal limits (1–2 sessions/week, in total 60 min/week)	DXA	Change, mean (SD)			
					Significant	EX		CON	
					L3 BMC	0.87 (0.55)***		0.58 (0.26)	
					L3 aBMD	0.041 (0.04)**		0.027 (0.02)	
					L3 width	0.14 (0.14)***		0.07 (0.07)	
					NS TB, FN BMC TB FN aBMD L3, FN vBMD FN width	The mean annual gain in L3 BMC was 5.9 % higher, L3 aBMD a mean 2.1 % higher, and L3 width a mean 2.3 % higher in the EX group than in the CON group.			
Barbeau et al. 2007 [346]	10-month MVPA intervention Randomized	Sex: female Age: 8–12 years Race: black	201	Frequency: every day school in session	DXA	Difference, mean (95 % CI)			

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
		Location: Georgia		during school year; during summer Intensity: HR > 150 bpm during MVPA activity (HR monitor) Time: 110-min after-school program (80 min of PA) Type: 25-min skills development (dribbling basketball), 35-min MVPA, 20-min toning and stretching Control: no intervention		
					Significant	
					BMC	0.044 (0.024, 0.064)***
					aBMD	0.020 (0.012, 0.027)***
						Compared to the CON group, the EX group had a greater increase in BMC and aBMD.
Schneider et al. 2007 [347]	1-year MVPA intervention Randomized by school	Sex: female Age: 15.04 years (SD = 0.79) Race: 57 % non-Hispanic white, 20 % Hispanic, 17 % Asian, 6 % other Location: 2 public high schools, location not specified	122	Frequency: 5 days/week Intensity: varied Time: 60 min/day Type: supervised activities included variety of aerobic (3×/week, including aerobic dance, kickboxing, and brisk walking) and strength-building (1×/week, including weightlifting and yoga) activities Control: no intervention	DXA	Percent change, mean
					Significant	EX CON
					TS BMC	6.3** 1.4
					NS TB, LS, FN, TH, TR BMC TB, LS, FN, TH, TS, TR aBMD	The effect of EX on BMC for the TS was significant and increased 6.3 % as opposed to 1.4 % in the CON group. None of the other sites for BMC or any aBMD measures were significant.
Gunter et al. 2008 [24]	7-month jumping intervention Randomized by school	Sex: male and female Age: 7–10 years Race: not specified Location: Corvallis, OR	56	Frequency: 3×/week, during PE Intensity: Progressed to reach 90–100 jumps per session Time: 30 min/session (warm-up, fitness development (jumping), lesson focus, closing activity)	DXA	Postintervention values, mean (SD)

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results			
				Type: jumping Control: similar class structure, no jumping during fitness development					
						Male		Female	
					Significant	EX	CON	EX	CON
					TH BMC	28.5 (9.2)[a]	25.7 (7.56)[a]	24.6 (6.2)[a]	24.3 (6.1)[a]
					FN BMC	3.8 (0.96)[b]	3.6 (0.77)[b]	3.3 (0.74)[b]	3.3 (0.71)[b]
					Other variables	[a]Males greater than females ($P < 0.05$); [b]males greater than females ($P < 0.01$)			
					TB, LS, TR BMC	Three years after the intervention had concluded, the EX group had 2.3, 3.2, 4.4, and 2.9 % greater BMC than controls at the LS, TH, FN, and TB, respectively.			
Gunter et al. 2008 [24]	7-month jumping intervention Randomized by school	Sex: male and female Age: 7–10 years Race: 47 white, 2 Asian Location: Corvallis, OR	49	Frequency: 3×/week, opposite PE Intensity: progressed to reach 100 jumps/session by the 5th wk of the program Time: 20 min/session (5-min warm-up, 10-min jumping or stretching, 5-min cool down) Type: jumps off 24 in box Control: nonimpact stretching	DXA	Postintervention values, mean (SD)			
					Significant	Males		Females	
						EX	CON	EX	CON
					TH BMC	39.93 (9.56)[a]	39.31 (9.93)	31.26 (5.40)[a]	30.15 (3.38)
					FN BMC	4.92 (0.88)[a]	4.73 (0.93)	4.18 (0.53)[a]	4.21 (0.69)
					TR BMC	11.11 (2.62)[a]	10.91 (2.54)	8.31 (1.42)[a]	7.49 (1.05)
						[a]Males significantly greater than females for all values ($P < 0.01$). Participants in the EX group had 1.4 % more TH BMC than those in the CON group after 8 years			
Weeks et al. 2008 [296]	8-month jumping intervention Randomized	Sex: male and female Age: boys 13.8 years (0.4); girls 13.7 years (0.5) Race: not specified Location: Gold Coast, Australia	81	Frequency: 2×/week Intensity: 1–3 Hz at a height of 0.2–0.4 m Time: 10 min (~300 jumps) Type: varied, but included jumps, hops, tuck jumps, jump squats, stride jumps, star jumps, lunges, side lunges, and skipping. Occasionally supplemented with upper body strengthening activities, including push-ups and exercises with resistive latex bands	DXA	Girls in the EX group improved FN BMC (13.9 %) more than those in the CON group. Between-group comparisons of change showed EX group effects only for TB BMC (10.6 %) for boys. Boys in the EX group gained more TR BMC, LS BMC, and TB BMC than girls in the EX group.			

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results	
				Control: usual PE warm-up and stretching			
					Significant		
					FN BMC		
					TR BMC		
					TB BMC		
					NS		
					FN, LS BA		
					LS BMC		
Macdonald et al. 2008 [299]	11-month PA and jumping intervention Randomized by school	Sex: male and female Age: 9–11 years Race: 53 % Asian (both parents or all four grandparents born in Hong Kong or China, India, Philippines, Vietnam, Korea, or Taiwan. 35 % Caucasian (parents born in North America or Europe). 12 % children mixed ethnicity or other ethnic origins Location: Vancouver and Richmond, British Columbia	410	Frequency: *Classroom Action*: 5 days/week; *Bounce at the Bell*: 5 days/week PA + 3×/day, 4 days/week jumping Intensity: not specified Time: *Classroom Action*: 15 min PA; *Bounce at the Bell*: 15 min PA + short bouts high-impact jumping Type: *Classroom Action*: skipping, dancing, playground circuits, simple resistance exercises with bands; *Bounce at the Bell*: Classroom Action + short bouts high-impact jumping. Phase I included 5 two-foot landing jumps (or 10 one-foot landing jumps) at each session. Phase II jumps were increased each month of the school year until a maximum of 36 jumps/day was reached. Control: usual PE	DXA	Percent difference, mean (95 % CI)	
					Significant	Males	Females
					FN BMC	0.96 (−0.003, 1.93)*	0.09 (0.005, 0.172)**
					LS BMC	30.8 (7.2, 54.4)**	
					TB BMC		
					NS PF BMC	Boys in EX group had greater gains in BMC at the LS (2.7 %) and TB (1.7 %) than the controls did. Girls in the EX group had greater gains in FN BMC (3.5 %) than in controls.	
Alwis et al. 2008 [300]	1-year expanded PE intervention	Sex: female Age: 6.5–8.9 years	103	Frequency: 5 days/week Intensity: varied	DXA	No between-group differences were found during the 12-month study period for changes in FN variables.	

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results	
	Randomized by school	Race: Caucasian Location: Malmö, Sweden		Time: 40 min/day Type: normal PE curriculum (running, jumping, climbing ropes, variety of ball games). Activities varied to reduce boredom. No specific osteogenic training program was added. Control: normal PE curriculum, duration within normal limits (1–2 sessions/week, in total 60 min/week)	*Significant* None *NS* FN BMC, aBMD, vBMD		
Alwis et al. 2008 [300]	2-year expanded PE intervention Randomized by school	Sex: male Age: 6.7–9.0 years Race: Caucasian Location: Malmö, Sweden	137	Frequency: 5 days/week Intensity: varied Time: 40 min/day Type: normal PE curriculum (running, jumping, climbing ropes, variety of ball games). Activities varied to reduce boredom. No specific osteogenic training program was added. Control: normal PE curriculum, duration within normal limits (1–2 sessions/week, in total 60 min/week)	DXA	Change, mean (SD)	
					Significant	EX	CON
					L3 BMC	0.72 (0.30)**	0.58 (0.26)
					L3 width	0.11 (0.07)**	0.07 (0.07)
					NS TB, FN BMC FN width	The mean annual gain in L3 BMC (3 %) and L3 width (1.3 %) were greater in the EX group than in the CON group .	
Alwis et al. 2008 [300]	2-year expanded PE intervention Randomized by school	Sex: female Age: 6.8–8.9 years Race: Caucasian Location: Malmö, Sweden	83	Frequency: 5 days/week Intensity: varied Time: 40 min/day Type: normal PE curriculum (running, jumping, climbing ropes, variety of ball games). Activities varied to reduce boredom. No specific	DXA	No between-group differences were observed for annual changes in the FN variables.	

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
				osteogenic training program was added. Control: normal PE curriculum, duration within normal limits (1–2 sessions/week, in total 60 min/week)		
					Significant	
					None	
					NS	
					FN BMC, aBMD	
Meyer et al. 2011 [348]	9-month additional PE session intervention Randomized by class	Sex: male and female Age: prepubertal = 6–7 years; early pubertal = 11–12 years Race: not specified Location: Aargau and Baselland, Switzerland	291	Frequency: 2×/week (PE); 3×/day (activity breaks); 1×/day (home activity) Intensity: not specified Time: 45 min/session (PE); 2–5 min/session (activity breaks); 10 min/day (home activity) Type: Two PE lessons (plus 3 regular PE classes) taught mostly outdoors by PE teachers. All five sessions included jumping activities like hopping, jumping up and down stairs, rope skipping, etc. During academic lessons, 3–5 activity breaks comprised motor skill tasks such as jumping around on one leg, balancing on one leg, power games, or coordinative tasks were introduced every day. Daily home activity included aerobic, strength, or motor skill tasks like tooth brushing while standing on one leg, jumping up and down the stairs, and rope jumping. Control: participated in regular PE classes 3×/week	DXA	Difference, Z-score (95 % CI)
					Significant	EX
					TB BMC	0.138 (0.06, 0.216)***
					FN BMC	0.136 (0.008, 0.264)*
					LS BMC	0.118 (0.028, 0.2017)**

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
					TB aBMD	0.212 (0.088, 0.337)***
					LS aBMD	0.184 (0.083, 0.285)***
					NS FN aBMD	Compared to CON group, children in EX group showed statistically significant increases in BMC of TB (5.5 %), FN (5.4 %), and LS (4.7 %) and aBMD of TB (8.4 %) and LS (7.3 %)
Silva et al. 2011 [349]	Sports study Recruited based on sport participation	Sex: male Age: 10–18 years Race: not specified Location: Brazil	46	Inclusion criteria: 3 year experience in sport, training at least 10 h/week in previous 6 months, only PA associated with sport, high competitive level Control: normal PE	DXA	aBMD, mean (SD)
					Significant	Tennis / Soccer / Swimming / Controls
					PF aBMD	1.02 (0.18)* / 1.08 (0.16)*
					NS LS, TB aBMD	Results showed higher mean values in the PF region of tennis and soccer players than of swimmers and controls. In relation to the impact of sporting activities based on bone age determination, a significant difference in aBMD was observed at all evaluated sites at the end of puberty (16–18 years) compared with 10–12 years, with increases of 78 % at the LS, 37 % at the PF, and 38 % TB.
Lofgren et al. 2012 [28]	4-year expanded PE intervention Randomized by school	Sex: male and female Age: 6.5–8.7 years Race: Caucasian Location: Malmö, Sweden	221	Frequency: 5 days/week Intensity: varied Time: 40 min/day Type: normal PE curriculum (running, jumping, climbing ropes, variety of ball games). Activities varied to reduce boredom. No specific osteogenic training program was added Control: normal PE curriculum, duration within normal limits (1–2 sessions/week, in total 60 min/week)	DXA	Change, mean (95 % CI)
					Significant	Male / Female
						EX / CON / EX / CON
					TB BMC	179.6 (160.5, 198.7)* / 166.4 (149.4, 183.4)
					LS BMC	7.0 (6.5, 7.6)* / 6.2 (5.8, 6.6) / 9.1 (7.9, 10.3)** / 7.1 (6.1, 8.0)
					FN BMC	0.29 (0.26, 0.31) / 0.27 (0.24, 0.31) / 0.39 (0.33, 0.45)** / 0.28 (0.23, 0.33)
					TR BMC	0.92 (0.82, 1.02)** / 0.72 (0.62, 0.83)
					L3 width	0.13 (0.11, 0.14)** / 0.11 (0.09, 0.12)
					FN width	0.12 (0.11, 0.13)* / 0.11 (0.09, 0.12) / 0.15 (0.12, 0.17)** / 0.10 (0.08, 0.13)

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results	
						The mean annual gain in LS BMC was 7.0 % higher in girls and 3.3 % higher in boys, and in FN width 1.7 % higher in girls and 0.6 % higher in boys in the EX group than in the CON group.	
Detter et al. 2014 [303]	6-year expanded PE intervention Randomized by school	Sex: male and female Age: 6–8 years Race: Caucasian Location: Malmö, Sweden	295	Frequency: 5 days/week Intensity: varied Time: 40 min/day Type: normal PE curriculum (running, jumping, climbing ropes, variety of ball games). Activities varied to reduce boredom. No specific osteogenic training program was added, Control: normal PE curriculum, duration within normal limits (1–2 sessions/week, in total 60 min/week)	DXA	Difference, mean (95 % CI)	
					Significant	Male	Female
					LS aBMD	0.006 (0.002, 0.01)**	0.01 (0.003, 0.02)*
					FN BMC		0.07 (0.01, 0.12)*
					NS	Girls in the EX group, compared with girls in the CON group, had 0.009 g/cm^2 larger gain annually in LS aBMD and 0.07 g larger gain in FN BMC. Boys in the EX group has 0.006 g/cm^2 larger gain annually in LS aBMD than CON boys,	
					TB, FN aBMD		
					TB, LS BMC		
					FN, LS BA		
Observational studies							
Reference	Study description	Population description	*N*	Exposure	End points	Results	
Lehtonen-Veromaa et al. 2000 [350]	1-year prospective case comparison	Sex: 155 females Baseline age: 9–15 years Race: white Location: Turku, Finland	51 gymnasts, 50 runners, 54 controls	Method: self-report questionnaire (2×) Variable: leisure-time PA met (h/week)	Follow-up TH (and subregions), LS aBMD, and BA	The 1-year increase in adjusted aBMD at the FN of the gymnasts was 115 % larger than that of the controls and 125 % larger than that of the runners. The 1-year increase in adjusted aBMD at the TR of the gymnasts was 49 % larger than that of controls.	
Molgaard et al. 2001 [245]	1-year prospective follow-up	Sex: 140 males, 192 females Baseline age: 5–19 years Race: white Location: Copenhagen, Denmark	332	Method: 24-h recall questionnaire (3×) (I, supine; II, sitting; III, walking; IV, breathless PA) Variable: breathless PA (h/day)	Follow-up TB BMC, BA	Breathless PA not associated with BMC or BA	
Gustavsson et al. 2003 [351]	2.5-year and 6-year prospective case comparison	Sex: 68 males Baseline age: 16 years Race: white Location: Umea, Sweden	22 hockey, 21 retired hockey, 25 controls	Method: reported participation in ice hockey Variable: group membership: hockey, retired hockey, no hockey	Follow-up at 30 months (~2.5 years) and follow-up at 70 months (~6 years) TB, FN, LS aBMD	At 30 months, hockey players had greater gains in aBMD FN than controls (0.07 vs 0.03 g/cm^2). Hockey players had significantly higher aBMD at FN and TB than controls. At 70 months, hockey players had greater aBMD at the FN, TB, and LS compared to nonplayers. Retired hockey players still had 4 % higher aBMD of FN than nonplayers after 70 months	
Nurmi-Lawton et al. 2004 [352]	3-year prospective case comparison	Sex: 97 females Baseline age: 7.9–17.2 years Race: primarily white Location: England	45 gymnasts, 52 controls	Method: reported participation in gymnastics Variable: group membership	Multilevel model comparing differences in TB, LS, arm, and leg BMC, as well as aBMD each year	Gymnasts had 24–51 % greater BMC and 13–28 % greater aBMD than controls.	

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
				gymnastics, no gymnastics		
Laing et al. 2005 [343]	2-year quasi-experimental	Sex: 143 females Baseline age: 4–8 years Race: 64 % white, 27 % Black, 3 % Asian, 2 % Hispanic, 4 % other Location: Athens, Georgia	65 gymnasts, 78 controls	Method: reported participation in gymnastics Variables: group membership gymnastics, no gymnastics, and h gymnastics participation per week	Follow-up TB, LS, PF, forearm BMC, aBMD, and BA	LS aBMD and forearm BA increased at a greater rate in gymnasts than in controls. Forearm BA increased at a greater rate in high-hours-per-week gymnastics over low-hours-per-week gymnastics
Janz et al. 2006 [353]	3-year prospective follow-up	Sex: 171 males, 199 females Baseline age: 5 years Race: primarily white Location: Iowa, USA	370	Method: ActiGraph accelerometer Variables: total PA ct/min, active min/day (≥3000 ct/min)	Follow-up TB, TH, TR, and LS BMC	PA was significantly associated with TB, TH, TR, and LS BMC in males. In females, PA was associated with TB and TR BMC. PA explained 1–2 % of variance in BMC.
Nordstrom et al. 2006 [354]	~8-year prospective case comparison	Sex: 90 males Baseline age: 15–19 years Race: Caucasian Location: Umea, Sweden	63 athletes, 27 controls	Method: reported participation in ice hockey or badminton Variables: weight-bearing PA (h/week)	Follow-up and sustained effects TB, FN, TH, and Hum BMD; FN BA, TH BA	Active athletes had significantly higher BMD at all measured sites vs controls ($P < 0.05$). Former athletes still had higher BMD of the FN, TH, and Hum than did controls ($P < 0.05$).
Baxter-Jones et al. 2008 [22]	~15-year prospective follow-up	Sex: 72 males, 82 females Baseline age: 8–15 years Race: not specified Location: Saskatoon, Saskatchewan, Canada	154	Method: self-report questionnaire (3×/year for 3 years, 2×/year after) Variable: general level of PA for year (1–5)	Follow-up (age 23–30 years) TB, LS, TH, and FN BMC	In young adulthood, males who were physically active as adolescents had 8–9 % greater BMC at TB, TH, and FN compared to inactive adolescent males. In young adulthood, females who were active adolescents had 9 % greater TH and 10 % greater FN compared to inactive adolescent females
Cheng et al. 2009 [54]	7-year prospective follow-up	Sex: 396 females Baseline age: 10–13 years Race: not specified Location: Jyvaskyla, Finland	396	Method: self-report leisure-time PA questionnaire with parent help Variables: leisure-time PA score	Follow-up TB BMC	PA did not contribute to variability in BMC.
Janz et al. 2010 [355]	3-year and 6-year prospective follow-up	Sex: 148 males, 185 females Baseline age: 5 years Race: primarily white Location: Iowa, USA	333	Method: ActiGraph accelerometer Variables: MVPA min/day (>3000 ct/min)	Follow-up at age 8 and age 11 TB, TH, and LS BMC	After adjustment for concurrent (age 8 or 11) age, height, weight, somatic maturity, and MVPA, age 5 MVPA was significant predictor of ages 8 and 11 BMC in boys and girls at TB, TH, and LS.
Tervo et al. 2010 [356]	~12-year case comparison	Sex: 85 males Baseline age: 15–19 years Race: not specified Location: Umea, Sweden	18 badminton, 44 ice hockey, 23 controls	Method: reported participation in badminton or ice hockey Variables: weight-bearing PA (h/week)	Follow-up and sustained effects of TB, Hum, LS, FN, and leg aBMD	After adjusting for confounders, badminton players gained significantly more aBMD at all sites compared to both ice hockey players and controls. Ice hockey players gained significantly more aBMD at FN and Hum than at controls. After the end of the active career, ice hockey players and badminton players lost aBMD at a similar rate resulting in still significantly higher aBMD at all sites in badminton players compared to both ice hockey players and controls
Erlandson et al. 2011 [357]	4 year prospective case comparison	Sex: 163 males and females Baseline age: 4–7 years	163 gymnasts, ex-gymnasts, nongymnasts	Method: parental-report questionnaire	Multilevel model comparing TB, FN, and LS BMC	By year 4, recreational and precompetitive gymnasts had 3 % more TB and 7 % more FN BMC than those in other sports when body size, PA, and diet were considered

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
		Race: 95 % white, 2 % Asian, 3 % other (biracial) Location: Saskatoon, Saskatchewan, Canada		Variables: current PA score		
Scerpella et al. 2011 [358]	~12-year prospective case comparison	Sex: 20 females Baseline age: 8–12 years Race: not specified Location: Syracuse, New York, USA	6 ex-gymnasts, 14 nongymnasts	Method: self-report questionnaire Variables: activity (h/week)	Follow-up and sustained effect of skull aBMD and BMC; R-UD and 1/3 radius BA, BMC, and aBMD	All R-UD parameters were higher in ex-gymnasts than in nongymnasts ($P < 0.02$). In contrast, skull aBMD was not associated with gymnastic status. Gymnastic cessation was associated with an abrupt, temporary decrease in 1/3 aBMD, R-UD BMC, and R-UD aBMD. No significant gymnast cessation effects were observed for 1/3 BMC, 1/3 BA, R-UD BA, or skull aBMD
Erlandson et al. 2012 [359]	14-year prospective case comparison	Sex: 47 females Baseline age: 8–15 years Race: not specified Location: Saskatoon, Saskatchewan, Canada	25 gymnasts, 22 controls	Method: self-report questionnaire Variables: past-week PA score	Follow-up TB, FN, LS BMC, and aBMD	Gymnasts had significantly greater size-adjusted BMC and aBMD compared to nongymnasts at all sites, with the exception of FN aBMD in adulthood. Retired gymnasts had greater size-adjusted TB (13 %), LS (19 %), and FN (13 %) BMC and TB (8 %) and LS (13 %) aBMD compared to nongymnasts.
Farr et al. 2013 [360]	2-year prospective follow-up	Sex: 248 females Baseline age: 9–12 years Race: 90 % white, 6 % Asian, 2 % black or African American, 1 % Native American or Alaska Native, 1 % Native Hawaiian or Pacific Islander, and 0.5 % other Location: Tucson, Arizona, USA	248	Method: self-report questionnaire Variables: past-year PA score	Follow-up tibia and femur cortical and trabecular vBMD	PA associated with increases in trabecular vBMD at metaphyseal femur
Francis et al. 2014 [361]	10-year prospective follow-up	Sex: 156 males, 170 females Baseline age: 5 years Race: primarily white Location: Iowa, USA	326	Method: ActiGraph accelerometer Variables: MVPA min/day (> 2296 ct/min) VPA min/day (> 4011 ct/min)	Follow-up at ages 13 and 15 LS and TH BMC	Ages 13 and 15 male LS BMC adjusted for baseline LS BMC predicted by age 5 MVPA and VPA
Janz et al. 2014 [248]	10-year prospective follow-up	Sex: 217 males, 235 females Baseline age: 5 years Race: primarily white Location: Iowa, USA	452	Method: ActiGraph accelerometer Variables: MVPA min/day (>2296 ct/min) VPA min/day (> 4011 ct/min)	TH and LS BMC at five measurement cycles (age 5, 8, 11, 13, and 15 years). Multilevel model included individual growth curves for each participant	MVPA and VPA added to prediction BMC at all assessed cycles except MVPA LS BMC in females age 5, and males in the 90th percentile for VPA had 8.5 % more hip BMC than males in the 10th percentile for VPA. At age 15, this difference was 2.0 %. Females at age 5 in the 90th percentile for VPA had 6.1 % more hip BMC than those in the 10th percentile for VPA. Age 15 difference was 1.8 %.
Janz et al. 2014 [248]	12-year prospective follow-up	Sex: 160 males, 189 females Baseline age: 5 years Race: primarily white Location: Iowa, USA	349	Method: ActiGraph accelerometer Variables: MVPA min/day (>2296 ct/min)	Follow-up (age 17) TB and TH BMC and aBMD	At age 17, girls in high trajectory for MVPA had greater TB BMC, TH BMC, and TH aBMD than in the other trajectories. Boys in the high trajectory for MVPA had greater TB BMC, TH BMC, and TH aBMD than in the other trajectories.
Cardadeiro et al. 2014 [362]	1-year prospective follow-up	Sex: 81 males, 96 females Baseline age: 10–12 years Race: primarily white Location: Lisbon area, Portugal	177	Method: bone-specific administered questionnaire ActiGraph accelerometer Variables: PA score Sedentary min/day (≤100 ct/min)	Follow-up aBMD PF and subregions	PA measured with questionnaire and accelerometer measured MVPA significant in TR aBMD males. Questionnaire significant in superolateral FN aBMD, inferomedial FN aBMD, and FN aBMD in females

Table 13 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
				Light min/day (101–2295 ct/min) Moderate min/day (2296–4011 ct/min) Vigorous min/day (>4012 ct/min)		
Lappe et al. 2014 [172]	6-year prospective follow-up	Sex: 910 males, 833 females Baseline age: 5–19 years Race: nonblack, black Location: Los Angeles, CA; Cincinnati, OH; Omaha, NE; Philadelphia, PA; New York, NY	1743	Method: self/parental-report questionnaire (1×/year) Variable: weight-bearing PA (h/week)	Follow-up and mixed-model analysis %chgBMC for TB, LS, and TH at each TS of maturity	The greatest BMC accrual at all skeletal sites occurred at TS4, with the exception that the greatest % accrual in hip BMC in females was at TS3. Significant PA × TS interactions were only observed in nonblack males and only for TB BMC. All other PA × TS interaction effects were nonsignificant. PA was a significant predictor of chgBMC at all skeletal sites after adjustment for calcium in nonblack males, LS and TH in black males, TB and TH in nonblack females, and at LS in black females.

%chgBMC percent accrual of BMC, *95 % CI* 95 % confidence interval, *aBMD* areal bone mineral density (g/cm^2), *BA* bone area (cm^2), *BMAD* bone mineral apparent density (g/cm^2), *BMC* bone mineral content (g), *CON* control group, *DXA* dual-energy x-ray absorptiometry, *EX* exercise group, *FA* forearm, *FN* femoral neck, *FS* femoral shaft, *GRF* ground reaction force, *GT* greater trochanter, *Hum* humerus, *IT* intertrochanter, *LS* lumbar spine, *MVPA* moderate-through-vigorous-intensity physical activity, *NN* narrow neck, *NS* not significant, *PA* physical activity, *PE* physical education, *PF* proximal femur, *RA* right arm, *Rad* radius, *RCT* randomized controlled trial, *R-Dis* radius, distal, *R-Ul* radius, ultradistal, *SA-BMC* size-adjusted bone mineral content, *TB* total body, *T-F* tibia–fibula, *TH* total hip, *TR* trochanter, *TS* Tanner stage, *U-R* ulna-radius, *vBMD* volumetric bone mineral density (g/cm^3), *VPA* vigorous physical activity, *WA* Ward's area

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

seen in total body BMC (2.47 %), hip BMD (1.64 %), and spine BMD (1.64 %) in the calcium group after 12 months of supplementation. Confidence in the findings at 24 months is lessened due to the high rate of attrition (63 %). Another confounder is that the girls studied were peripubertal and thus varied in their estrogen status. At baseline, all subjects were premenarchal, whereas by the end of the study, 13 of the 48 subjects were postmenarchal (five concordant and three discordant pairs.)

Dibba et al. [160] tested the effects of calcium carbonate 1000 mg/day on radius BMC and BMD accrual in a 12-month RCT of prepubertal Gambian children who had low baseline calcium intake (342 mg/day). Supplementation resulted in a higher size-adjusted BMC in the midshaft radius (4.6 ± 0.9 %; $P < 0.0001$) and in the distal radius (5.5 ± 2.7 %; $P = 0.042$). This study showed a greater difference in gain between groups than the study by Cameron et al. [161], which supports the premise that children more deficient in a nutrient are likely to have greater benefit from supplementation. Prentice et al. [162] conducted a 13-month RCT of calcium carbonate 1000 mg/day in older adolescent males in Great Britain. Baseline and study calcium intakes were high, even in the placebo group, which was meeting the RDA. Nonetheless, calcium supplementation resulted in an approximately 1 % greater increase in total hip BMC after adjustment for bone area, weight, and height. The calcium intervention also resulted in greater height.

Three RCTs evaluated the effect of both calcium and vitamin D supplement pills on gain in tibial trabecular vBMD as measured by pQCT measurement on the distal tibia. Moyer-Mileur et al. [163] found a significant difference in gain at the 10 % skeletal measurement site on the distal tibia, whereas Greene and Naughton [164] found a significant 5.2 % difference in gain at the 4 % distal tibia site. Both the 10 and 4 % tibia sites represent primarily trabecular bone. Cheng et al. [159] found no effects. Only Greene and Naughton [164] reported adjusting for body size (limb length). However, the vitamin D doses (200 and 400 IU/day) were below the RDA of 600 IU/day, which raises doubt as to whether vitamin D status was optimized in these subjects.

Of the four RCTs using calcium fortification of food or beverages [165–168], all but one [166] found a significant supplement effect on skeletal gain, which ranged from 3.2 to 19.0 %. In the study showing no effect [166], the average dietary calcium intake of the placebo group was 1395 mg/day, which was above the threshold and likely accounts for the lack of effect of a calcium supplement.

Two RCTs were identified that supplemented with dairy foods. One study [169] found that 1000 mg of dairy resulted in a 1.5 % greater gain in spine BMD compared to controls. In the study by Du et al. [170], 10-year-old girls were randomized to one of three groups: group 1 consumed 330 mL/day of ultra-heat-treated (UHT) milk fortified with a calcium salt containing 560-mg calcium, group 2 consumed 330 mL/day of UHT and 200–320 μg of vitamin D, and a control group followed their usual diet. The calcium salt also contained phosphorus and protein, both of which affect bone. Baseline calcium intake was about one third of the RDA among the three groups. After 24 months, groups 1 and 2 gained significantly greater size-adjusted total body BMC than the controls, and group 2 with vitamin D supplementation gained more than group 1 ($P = 0.006$). Cheng et al. [159] supplemented with both pills and cheese, and the authors found an effect with cheese only.

Three of the four RCTs of calcium and exercise combined [81, 155, 157] found that the combined intervention had a significantly greater effect on bone accrual as assessed by DXA than either exercise or calcium alone. Specker and Binkley [81] also found an interaction effect on cortical thickness and area as measured by pQCT.

Only four observational studies of calcium intake and bone accrual were found [171–174]. Three found no association between calcium intake and accrual, whereas one prospective study [172] found a significant association between calcium intake and spine BMC adjusted for height change only in nonblack girls.

Our evidence grade for calcium was based on positive findings from 90 % of the RCTs using supplement pills, which found a small, biologically, and statistically significant positive effect on aBMD and/or BMC accrual. The bone accrual in the supplemented group compared to the placebo group was largest in children who had the lowest intakes at baseline. This supports the premise of a threshold nutrient such as calcium (i.e., if usual intake of calcium exceeds requirements, then it is unlikely that any benefit of the intervention will be detected). Thus, on the basis of this review, we conclude that dietary intake guidelines for calcium are not being met by all children and adolescents.

Grade: Level of evidence A was assigned for the benefit of calcium on bone.

Vitamin D (Table 6) The search for vitamin D identified nine publications from 8 RCTs, 1 prospective study, and 3 cross-sectional studies published since 2000, encompassing 2962 individuals (Table 6). Four of the eight RCTs provide evidence for a beneficial effect of vitamin D supplementation on bone accrual. El-Hajj Fuleihan et al. [175] found that Lebanese children receiving weekly doses of 14,000 IU vitamin D_3 over 1 year had improved hip BMC and bone area (using conventional DXA) and narrow neck outer diameter and buckling ratio (using the HSA program) [176]. Furthermore, trochanter BMC improved in premenarchal, but not postmenarchal, females [175]. There were no significant effects of supplementation observed in boys. Viljakainen

et al. [177] showed that Finnish females assigned to placebo or 200 or 400 IU vitamin D_3 over 1 year exhibited no differences in BMC gains at the lumbar spine or femur. A compliance-based analysis was conducted, which included only those subjects with >80 % compliance. After adjusting for bone area, weight gain, and changes in maturation, greater increases in lumbar spine BMC were observed with 400 IU vitamin D_3 and in femur BMC with either 200 or 400 IU D_3 [177]. The increase in lumbar spine BMC in this study was identified in perimenarchal, but not premenarchal, females. Du et al. [170] demonstrated that the addition of 200–320 IU of vitamin D_3 to calcium-fortified milk significantly increased size-adjusted total body BMC over 2 years compared to controls. When analyzing the data by menarchal status, the significant increase in size-adjusted total body BMC was observed only in females that had experienced menarche versus premenarche. Khadilkar et al. [178] found that supplementing vitamin D-deficient girls (girls with mean baseline serum 25(OH)D concentrations 20–25 nmol/L) with quarterly doses of 300,000 IU vitamin D_2 along with daily supplementation of 250 mg elemental calcium over 1 year improved adjusted total body BMC and bone area more compared with girls who were supplemented with calcium alone. These positive findings were observed in the compliance-based analyses only and in females within 2 years of starting their menstrual cycle, adjusting for multiple factors including fat-free mass.

Four of the eight RCTs showed no effect of vitamin D supplementation on bone. Ward et al. [179] reported that quarterly supplementation with 150,000 IU vitamin D_2 versus placebo in vitamin D-deficient adolescent females did not improve DXA- and pQCT-derived bone outcomes over 1 year, including measures of tibia and radius trabecular or cortical bone. Molgaard et al. [173] reported that supplementation with 200 or 400 IU vitamin D in 10- to 11-year-old females over 1 year had no effect on changes in total body or lumbar spine BMC or in bone area. Similarly, supplementation with either 400 or 800 IU to vitamin D-deficient females over 1 year had no effect on unadjusted total body BMC gains compared to placebo [180]. Finally, supplements containing 200 IU with 1000-mg calcium had no effect on total body, lumbar spine, femoral neck, or total femur BMC gains over 2 years compared to placebo, calcium alone (1000 mg), or a cheese-supplemented group [159].

A prospective study in prepubertal girls conducted over a 5-year period found that as serum 25(OH)D concentrations declined with age, there were significant increases in BMC at multiple skeletal sites [181]. This study showed that serum 25(OH)D did not have a predictive effect on BMC accrual above and beyond that of insulin-like growth factor (IGF)-I [181]. In a cross-sectional study of females aged 10–12 years, those with deficient serum 25(OH)D ≤25 nmol/L had lower cortical vBMD at the distal radius than those with values ≥26 nmol/L, and they also had lower cortical vBMD at the tibial shaft compared to subjects with values between 26 and 40 nmol/L [182]. Moreover, Foo et al. [183] found that 15-year-old Chinese females with vitamin D deficiency (i.e., <25 nmol/L) had lower size-adjusted total body and forearm BMC than females with sufficient values (>50 nmol/L). In a study of 9-year-old Korean children, serum 25(OH)D was positively associated with total body BMC after adjusting for multiple variables, which included physical activity and calcium intake [184].

The evidence grade for vitamin D was based on the point that four of eight RCTs showed improvements in BMC accrual. Furthermore, one of the positive RCTs was well designed, used an intent-to-treat analysis, was adequately powered, and employed a wide range of supplement doses. The evidence grade B reflects the lack of generalizability across the RCTs, which included primarily female subjects with little diversity in population ancestry.

Grade: Level of evidence B was assigned for the benefit of vitamin D on bone.

Micronutrients other than calcium and vitamin D (Table 7) The search for other micronutrients identified 1 RCT, 2 prospective studies, and 6 cross-sectional studies published since 2000, encompassing 2192 individuals (Table 7). Only one RCT was identified and that was for magnesium [185]. Magnesium supplementation at 300 mg/day for 1 year was significantly associated with a ~3 % increase in overall hip measures of BMC and a borderline significant increase in lumbar spine BMC among white girls. In prospective studies, fluoride was not related to BMC in adjusted models [186–188]. Cross-sectional studies report that a positive association of vitamin C intake and BMC was observed only in boys [189], and positive associations of vitamin C and zinc intakes with bone size and strength were observed in fourth-grade, but not sixth-grade, girls [190]. By contrast, negative associations between high intakes of sodium and phosphorus and total body BMC and bone area in white boys and girls were observed [149]. Iron intake was negatively associated with femoral cortical area [190].

Cross-sectional studies also showed advantages of a biomarker of vitamin K status only in white females [191]. In their study of 245 healthy girls in the USA aged 3–16 years, Kalkwarf et al. [192] reported that better vitamin K status (assessed by plasma phylloquinone and serum percentage of undercarboxylated osteocalcin [%ucOC]) was associated with decreased bone turnover, but it was not associated with baseline BMC. Serum %ucOC was not associated with changes in BMC of the hip, total body, or total body minus the head, but it was surprisingly associated with positive changes in lumbar spine BMC [192]. In contrast with this study, a more recent association study of 223 healthy peripubertal Danish girls

found that better vitamin K status was associated with increased total body and lumbar spine BMC, but not with bone turnover [191].

Our evidence grade for other micronutrients was based on one RCT of magnesium supplementation, two prospective studies of fluoride intake, two cross-sectional studies assessing vitamin C and vitamin K intake, and one cross-sectional study assessing intakes of zinc, iron sodium, and phosphorus.

> *Grade*: Level of evidence D was assigned for the benefit of micronutrients other than calcium and vitamin D on bone.

Food patterns (Table 8)

The search for food patterns identified 5 RCTs and 12 observational studies published since 2000, encompassing 6282 individuals (Table 8).

Dairy

Three 2-year RCTs showed increased gains in some bone sites with dairy food consumption [159, 169, 170]. The study by Cheng et al. [159] found an increase with cheese consumption in bone quality assessed by tibia cortical thickness using pQCT in addition to total body BMD, but only in those participants who were at least 50 % compliant. The advantage of trochanter BMC in the study with dairy supplementation disappeared 1 year after cessation [169]. These RCTs were not generalizable because they were conducted only in presumably white girls, except for the study by Du et al. [170] conducted in Asians.

Fiber

One RCT was found and the authors reported a benefit of prebiotic fibers on total body BMC gains in boys and girls over 1 year [193]. One cross-sectional study [194] showed dietary patterns that favored higher bone mass and lower fat mass including higher amounts of dark-green and deep-yellow vegetables and lower amounts of fried foods.

Fruits and vegetables

The five cross-sectional studies identified consistently found some type of benefit to bone with increased and/or high intake of fruits and vegetables [189, 195–198].

Detriment of cola and caffeinated beverages

We identified six studies that examined the effects of carbonated beverages or caffeine-containing beverages and bone accrual during childhood and peak bone mass. Several cross-sectional studies have shown inverse associations between cola or carbonated beverages and bone outcomes in children or young adults. In a population-based, case–control study of children who had experienced upper limb fractures, Ma and Jones [199] found that wrist and forearm fractures were significantly associated with cola drink consumption (odds ratio (OR), 1.39 per unit; 95 % confidence interval (95 % CI), 1.01, 1.91), but not after adjustment for sedentary activities (e.g., television, computer, and video watching). Wyshak [200] found that carbonated beverage consumption was associated with a history of fracture (OR, 3.14; 95 % CI, 1.45, 6.78). The association was strongest for girls reporting higher levels of physical activity (OR, 7.00; 95 % CI, 2.00, 24.45). Similarly, Manias et al. [201] evaluated children with a first-time fracture ($n = 50$), those who had recurrent fractures ($n = 50$), and a fracture-free group ($n = 50$). The recurrent fracture group had lower levels of milk intake and physical activity and higher BMI and carbonated beverage intake than controls; those with one or more fractures had significantly lower total body and lumbar spine BMC and aBMD. A 4-year prospective study of 228 children showed that carbonated beverage consumption increased as milk intake declined, and carbonated beverage intake was negatively associated with strength of the radius (polar SSI) even after adjusting for milk intake [202].

Lower aBMD has been found in children with higher carbonated beverage intakes [194, 201]. McGartland et al. [194] found a significant inverse relationship between total carbonated beverage intake and heel (but not forearm) BMD among girls after adjusting for age, height, weight, pubertal status, social status, alcohol intake, smoking habits, physical activity, liquid milk consumption, and calcium obtained from sources other than liquid milk. These findings suggest that aBMD in girls may be more sensitive to the effects of carbonated beverages compared with boys. McGartland et al. [194] also observed a significant inverse association between carbonated beverage intake and milk intake in both boys and girls.

Remarkably few studies have considered the potential effects of caffeinated beverages on peak bone mass. Caffeine consumption is of concern because it is associated with increased urinary excretion of calcium [203]. In a cross-sectional study of young white women, aged 19–26 years ($n = 177$), Conlisk and Galuska [204] examined the association of caffeine consumption and femoral neck BMD. Caffeine intake was estimated by self-reported consumption of coffee, decaffeinated coffee, tea, colas, chocolate products, and select medications. After adjustment for potential confounders (height, BMI, age at menarche, calcium intake, protein consumption, alcohol consumption, and tobacco use),

caffeine consumption was not significantly associated with aBMD. These findings do not provide support for negative effects of caffeine intake in this age range.

Fruits and vegetables

To our knowledge, there are no long-term prospective studies of vegetarian children with bone outcomes. Few studies have examined the influences of vegetarian dietary patterns on bone, but there is some evidence in adults that adhering to vegan diets is associated with lower bone mass [205] and fractures [206]. It has been hypothesized that following a diet composed primarily of fruits and vegetables would provide a nutrient profile, specifically higher potassium and plant-based proteins, which would favorably influence acid–base balance and bone mass [207]. Alternatively, following a vegetarian diet may exclude certain food groups that contain essential bone-related nutrients such as calcium [208], although a recent large US study using National Health and Nutrition Examination Survey (NHANES) data found no differences in calcium intakes between strict vegetarians and nonvegetarians [209]. In an editorial, Lanham-New [210] takes the position that vegetarianism is not a serious risk factor for osteoporosis. She recognizes that the study of vegetarian dietary patterns and bone is complex because specific patterns of vegetarian diets include or exclude bone-related nutrients and lifestyle factors, serum hormone concentrations, and dietary assessment methods could confound the findings.

Our evidence grade for food patterns was based on 3 RCTs showing a positive benefit of dairy consumption to bone accrual, 1 RCT using mixed chain length fermentable fibers, and 12 observational studies, respectively.

> *Grade*: Level of evidence B was assigned for the benefit of dairy consumption on bone. Level of evidence C was assigned for the benefit of certain types of fiber and fruit and vegetable intake on bone, as well as for a detrimental effect of cola and caffeinated beverages on bone.

Infant nutrition (Table 9)

The search for infant nutrition identified 1 RCT and 10 observational studies published since 2000, encompassing 2715 individuals (Table 9). In the identified RCT, Koo et al. [211] found a positive effect of infant formula enriched with palm olein on bone mineral accretion in healthy term infants compared to the control formula. Of the ten observational studies identified in the search, three compared the effects of duration of breastfeeding [212–214], three assessed later bone outcomes in breast-fed versus formula-fed infants [215–217], two assessed later bone outcomes of breast-fed infants only [218, 219], and two compared breast-fed versus formula-fed versus enriched formula-fed infants [220, 221].

Formula-fed infants had better BMC and BMD in the first 6 months of life compared to breast-fed infants in two of the observational studies [215, 216]; however, breastfeeding was shown to be advantageous in two observational studies assessing later bone outcomes in 8-year-old children [217, 219] and 16-year-old adolescents [218]. Mixed results were obtained for studies testing the duration of breastfeeding in infants who were exclusively breast-fed [212–214]. The addition of palm olein and *sn*-2 palmitate to infant formula was not shown to be beneficial on later total body BMC outcomes in 4.5- and 10-year-old children [220, 221]. This is contrary to the RCT by Koo et al. [211].

Our evidence grade for infant nutrition was based on the lack of RCTs, inconsistent length of follow-up observational studies, and lack of consistent results across studies.

> *Grade*: Level of evidence D was assigned for the benefit of duration of breastfeeding on bone. Level of evidence D was assigned for the benefit of breastfeeding versus formula feeding on bone. Level of evidence D was assigned for the benefit of enriched formula feeding on bone.

Adolescent special issues

Detriment of DMPA injections and oral contraceptives (Table 10) The search for contraception identified no RCTs, 8 observational studies, and no cross-sectional studies since 2000, encompassing 1815 individuals (Table 10). Six studies reported null effects of oral contraceptives (OCs) versus a control on bone [222–227] and two studies reported suppression of bone mineral accrual and bone mass acquisition in adolescents [228, 229]. Injections of depot medroxyprogesterone acetate (DMPA) showed a consistent detrimental effect to bone in three studies [225, 226, 230], while one study found null effects [227]. An additional study suggested that the change in body weight due to DMPA injection may override the potential detrimental effect to bone [222].

> *Grade*: Level of evidence B was assigned for the detriment of DMPA injections on bone. Level of evidence D was assigned for the detriment of OCs on bone.

Detriment of alcohol (Table 11) The search for alcohol identified no RCTs, 3 prospective studies, and 5 cross-sectional studies published since 2000, encompassing 3352 individuals (Table 11). Four studies used peripheral DXA measurements only. There was large variability among studies in the amount of alcohol consumed by study participants and the classification of alcohol intake from ever tried to number of drinks per

day. Overall, the reported alcohol consumption by adolescents studied was relatively low. In some studies, adolescents who consumed alcohol were more likely to smoke [231–235], necessitating statistical adjustment for smoking to investigate the independent effects of alcohol intake on bone. The majority of studies found no association between alcohol intake and bone outcomes [232, 233, 235–237]. Among studies reporting a statistically significant association, the direction of the association was inconsistent. Some reported that alcohol intake was associated with lower bone density [231], whereas others reported that alcohol intake was associated with higher bone density [234, 238].

Our evidence grade for alcohol consumption was based on insufficient data to support a hypothesis, owing to no RCTs, low alcohol exposure, and multiple methodological differences among the few studies performed.

> *Grade*: Level of evidence D was assigned for the detriment of alcohol on bone.

Detriment of smoking (Table 12) The search for smoking identified no RCTs, 6 prospective studies, and 7 cross-sectional studies published since 2000, encompassing 13, 955 individuals (Table 12). Six of the studies used peripheral DXA, and two studies examined stress fractures as the bone outcome. There was large variability among studies with respect to extent of smoking in the study participants, both in terms of the proportion who had ever smoked as well as frequency of smoking (e.g., cigarettes per day). Smoking exposure was lowest in young adolescents and increased with age up to young adulthood. Classification of smoking exposure for statistical analyses was also variable across studies (e.g., 1 puff in lifetime versus daily smoking). Some studies reported that adolescents who smoked were more likely than their non-smoking peers to engage in behaviors that also could negatively impact bone health, namely lower physical activity levels [238, 239], lower dietary calcium intake [239], and greater alcohol use [231–235], making statistical adjustment for these behaviors critical to enable the interpretation of study findings.

Results from studies examining the association between bone density and smoking during adolescence are mixed. Some find significant deficits in bone mass or aBMD at one or more skeletal sites, ranging from −1.8 (not available for all studies) to −6.5 % [232–234, 239, 240], whereas others found no difference in bone according to smoking exposure [231, 235–237]. In the prospective study of adolescent females (aged 13–19 years) by Dorn et al. [233], the effect of smoking on bone accrual became more pronounced as girls got older. Compelling data demonstrating the deleterious effects of smoking on bone come from studies of military recruits. Among male military recruits (aged 18–22 years), Lorentzon et al. [239] found that smoking ≥1 cigarette/day (average 9/day) for an average of 4 years was associated with lower aBMD ranging from −1.8 to 5.0 % depending on the skeletal site. Cortical thickness measured by pQCT was −2.9 to −4.0 % lower in smokers owing to greater endosteal circumference. Eleftheriou et al. [238] found that aBMD at the hip was −4.7 % lower among current smokers compared to never smokers. By contrast, the authors found that ex-smokers had a smaller (−4.3 to −5.0 %) periosteal circumference measured by MRI compared to never smokers, but there were no differences in bone dimensions between current smokers and never smokers. In a study of female military recruits, Lappe et al. [42] found that a history of smoking was associated with an increased risk (OR, 1.34; 95 % CI, 1.05, 1.71) of stress fracture during 8 weeks of basic training. However, years of exercise, which was associated with a reduced risk of stress fracture, was not accounted for in these analyses and effects of smoking may have been overestimated. In a second study of female military recruits, history of smoking was similarly associated (OR, 1.32; 95 % CI, 0.99, 1.75) with risk of stress fracture even when accounting for fitness (running speed) and years of prior exercise [241].

Our evidence grade for smoking was based on multiple well-designed cross-sectional studies.

> *Grade*: Level of evidence C was assigned for the detriment of smoking on bone.

Physical activity and exercise

Effect on bone mass and density (Table 13) The search for the effects of physical activity on BMC identified 36 RCTs and 20 observational studies published since 2000, encompassing 9942 individuals (Table 13). Eighty-three percent ($n = 30$) of the RCT studies reported statistically significant ($P < 0.05$), and many were likely clinically significant (~3 % difference), differences between exercise and control groups at the completion of the intervention. With one exception [242], interventions finding no statistically significant difference between exercise and control groups used similar exercise volume, type, and length as those studies reporting significant effects. Most of the exercise intervention studies of prepubertal, early pubertal, and midpubertal children found increases (~1–6 % difference over 6 months) in the bone mineral of the total body, hip, or lumbar spine. The type of interventions varied but typically ranged from 7 to 24 months in duration, 2–5 sessions per week, 10–60 min per session, and they included sports, games, dance, or high-impact exercises (jumping, hopping). Fewer studies existed for late-pubertal and postpubertal adolescents, and the effects were less dramatic (0.3–1.9 % difference over 6 months), despite a similar intervention dose compared to interventions that focused on

younger participants [156, 243]. For example, within the same intervention, one study found skeletal effects in premenarchal but not in postmenarchal females [244].

We reviewed 20 prospective longitudinal studies, with 90 % of these studies ($n = 18$) reporting statistical differences in bone mass or density between the most physically active children and adolescents in their cohorts and those who were less active. The range in percent difference was wide, although studies that examined youth engaged in organized sports consistently reported greater differences than other study populations. Two studies [54, 245] reported no differences in mass or density between the most active and less active participants. However, these studies used specific self-report measures of physical activity known to have considerable measurement error [246, 247]. By contrast, when using an objective measure of physical activity, the Iowa Bone Development Study demonstrated 10–16 % greater hip BMC and 8 % greater hip aBMD in participants who accumulated the greatest amount of activity from childhood through adolescence (12-year follow-up) [248]. One of the most important of the prospective observational studies, the University of Saskatchewan Paediatric Bone Mineral Accrual Study [3], used a mixed-longitudinal design to evaluate relationships between self-reported general level of physical activity and BMC in a group of healthy Canadian adolescents. The investigators reported that children and adolescents who were physically active at ages 8–15 years had 8–10 % more hip BMC as young adults (aged 23–30 years) compared to less active peers (after controlling for their adult physical activity levels and baseline bone outcomes). This study suggested the possibility of long-term sustained benefits of childhood physical activity on adult BMC [22]. In conclusion, long-term prospective observational studies of heterogeneous cohorts of youth have examined self-selected, everyday physical activity levels and BMC, aBMD, or vBMD. These studies have convincingly and repeatedly shown that participation in high levels of physical activity is associated with greater bone mass accrual compared to less active peers.

Our evidence grade for physical activity and exercise on bone mass and density was based on consistent evidence from many RCTs and observational studies.

> *Grade*: Level of evidence A was assigned for the benefit of physical activity and exercise on bone mass and density.

Effect on bone structural outcomes (Table 14)

The search for the effects of physical activity on bone structure/geometry identified 17 RCTs and 8 observational studies published since 2000, encompassing 4722 individuals (Table 14). Slightly more than one third ($n = 6$) reported statistically significant effects of exercise on bone structural outcomes. However, of the 11 studies that reported no statistical differences between exercisers and controls, six reports were from the same study (the Malmö Pediatric Osteoporosis Prevention Study). This study was designed to evaluate whether increasing time in physical activity in a cohort could be used as a population-based prevention strategy to improve bone outcomes. Prepubertal children were randomized by schools into a 5-day/week, 40-min/day physical education curriculum or a 1- to 2-day/week, 60-min/week curriculum. The content of the physical education curricula did not differ and specific osteogenic exercise was not prescribed. By contrast, in a 1-year RCT in young children (aged 3–5 years) randomized at the individual level, Specker and Binkley [81] used research staff to deliver (presumably) osteogenic exercise (gross motor skills such as hopping, jumping, and skipping) and reported that gross motor skill exercise increased periosteal and endosteal circumferences at the 20 % site of the distal tibia compared to fine motor skill exercise. The effect of gross motor exercise (2 % difference) persisted 1 year after follow-up; however, the intervention group was also more physically active at least 6 months after the intervention (raising the possibility that the sustained effect was due to continued high levels of physical activity) [249]. Using a 7-month, 3-day/week, ~12-min/day jumping protocol, researchers with the University of British Columbia Centre for Hip Health and Mobility [73] reported structural changes at the hip in early pubertal girls (but not prepubertal girls) compared to controls who stretched. The difference in section modulus, a measure of the strength of bone during bending, was 4 %. A similar University of British Columbia project by Macdonald et al. [250] used a 16-month, 5-day/wk, ~15-min/day jumping protocol and compared this intervention to usual physical education (which the intervention participants also received). A significant difference of 3 % greater tibia midshaft tibia cross-sectional moment of inertia (CSMI) in boys was reported. Changes in CSMI suggest a change in cross-sectional geometry due to increased periosteal apposition in one of the planes. However, other structural differences were not statistically significant in the study by Macdonald et al. [250].

We identified eight prospective observational studies that examined associations between physical activity and whole bone structure. All studies (100 %) found statistically significant, and likely clinically significant, differences between the most active and less active cohort members. The University of Saskatchewan Pediatric Bone Mineral Accrual Study found an 8–12 % greater CSA and section modulus of the proximal femur in young adults who were active as adolescents (compared to peers who were less active as adolescents) [251]. In the same cohort, Duckham et al. [252] reported 13 % greater polar SSI and 10 % total bone CSA of the tibia in young adults who were active as adolescents compared to less active peers during adolescence. In females, differences of 10 % greater cortical CSA and 12 % cortical content of the tibia were found.

Table 14 Physical activity and exercise on bone structure in children and adolescents

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
RCTs						
Heinonen et al. 2000 [244]	9-month step aerobics/ jumping intervention Randomized by school	Sex: female Age: 10–15 years Race: not specified Location: Tampere, Finland	126	Frequency: 2×/week Intensity: progressive Time: 50 min (10-min warm-up, 15-min nonimpact aerobic exercises, 20-min high-impact/jump training, 5-min cool down) Type: both-leg jumps at floor level, both-leg box jumps, one-leg box jumps Control: normal PA	pQCT *Significant* None *NS* Tibia CoD, CoA, BSI	At the tibial midshaft, the intergroup differences (CoD, CoA, and BSI) were not significant
Petit et al. 2002 [73]	7-month jumping intervention Randomized by school	Sex: female Age: 9–12 years Race: multiethnic population of city (~34 % Hong Kong Chinese and 57 % white) reflected in cohort Location: Richmond, British Columbia	177	Frequency: 3×/week (2× PE, 1 classroom) Intensity: progressed over school year by increasing number of jumps per station (from 10 to 20) and height (from 10 to 50 cm) Time: 10–12 min (5 circuits, ~1.5–2 min each) Type: jumping exercises—jumping jacks, lung jumps, hopping, jumping over various obstacles, drop jumps from platform Control: stretching	pQCT *Significant* NN CSA NN Z NN CT IT ED *NS* NN length, SPW, ED IT CSA, SPW, Z FS CSA, SPW, Z, ED, CT	Change in early pubertal girls, mean (95 % CI) EX / CON 0.060 (0.043, 0.077)* / 0.035 (0.021, 0.049) 0.145 (0.118, 0.0172)* / 0.106 (0.084, 0.129) 0.012 (0.008, 0.016)* / 0.007 (0.004, 0.010) 0.092 (0.064, 0.120)* / 0.138 (0.114, 0.161) There was no difference in change for bone structure in the PRE girls. The more mature girls (EARLY) in the EX group showed significantly greater gains in CSA and reduced endosteal expansion. Changes in SPW did not differ. Structural changes improved Z at the NN (4.0 %), but not at the IT region. There were no differences at the primarily cortical FS.
Specker and Binkley 2003 [81]	1-year randomized, placebo-controlled, partially blinded trial of PA and calcium supplementation	Sex: male and female Age: 3–5 years Race: 94 % white, 6 % other Location: South Dakota	178	Frequency: 5 days/week Intensity: not specified Time: 30 min/day (5-min warm-up, 20-min activity, 5-min cool down) Type: hopping, jumping, skipping activities (17 different weekly programs) Control: 30 min/day of activities to keep them sitting quietly	pQCT *Significant* PCirc ECirc *NS* CA, CT	Exercise group had greater PCirc and ECirc than control group ($P < 0.05$).
MacKelvie et al. 2004 [295]	20 month jumping intervention Randomized by school	Sex: male Age: 8.8–12.1 years Race: multiethnic population of city	64	Frequency: 3×/week (2× PE, 1 classroom) Intensity: progressed over school year by increasing	HSA *Significant* NN CSMI	Change, mean (95 % CI) EX / CON 0.23 (0.20, 0.27)* / 0.17 (0.14, 0.20)

Table 14 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
		(~34 % Hong Kong Chinese and 57 % North American/Western European Caucasian, 5 % Southeast Asian, and 4 % other or mixed ethnicity) reflected in cohort Location: Richmond, British Columbia		number of jumps per station (from 10 to 20) and height (from 10 to 50 cm Time: 10–12 min (5 circuits, ~1.5–2 min each) Type: jumping exercises-jumping jacks, lung jumps, hopping, jumping over various obstacles, drop jumps from platform Control: stretching	NN Z *NS* NN length, CSA, PW, EW, CT IT CSMI, CSA, PW, Z, ED, CT FS CSA, PW, CSMI, Z, EW, CT	0.13 (0.11, 0.15)* 0.09 (0.072, 0.11) At the NN region, EX boys had significantly greater changes in Z (7.5 %). Changes at the IT and FS regions were not significantly different between groups.
McKay et al. 2005 [297]	8-month jumping intervention Control group used from previous study	Sex: male and female Age: 8.9 to 11.0 years Race: 38 % Caucasian, 48 % Asian, 15 % other (including mixed ethnic, black, and South Asian) Location: Richmond, British Columbia	124	Frequency: 3×/day Intensity: 5× body wt, maximum rate of force was > 400 body wt/s (independent sample of 70 boys and girls) Time: 3 min/day Type: 10 counter movement jumps (two-foot take off, clutch knees, two-foot landing) Control: not specified, from previous study	HSA *Significant* None *NS* NN and FS BMD, CSA, SW, Z, ED, CT	Change in bone structural parameters did not differ between groups.
Macdonald et al. 2007 [25]	16-month PA and jumping intervention Randomized by school	Sex: male and female Age: 10.2 ± 0.6 years Race: 53 % Asian (Hong Kong or China, India Philippines, Vietnam, Korea, or Taiwan), 35 % Caucasian (North America or Europe), 12 % mixed or other ethnic origins Location: Richmond and Vancouver, British Columbia	410	Frequency: *Classroom Action*: 5 days/week; *Bounce at the Bell*: 5 days/week PA + 3×/day, 4 days/week jumping Intensity: not specified Time: *Classroom Action*: 15 min of PA; *Bounce at the Bell*: 15 min of PA + short bouts of high-impact jumping Type: *Classroom Action*: skipping, dancing, playground circuits and simple resistance exercises with bands; *Bounce at the Bell*: Classroom Action + short bouts high-impact jumping Control: regular PE	pQCT *Significant* None *NS* Distal and midshaft BSI, ToA, ToD	Change in bone structural parameters did not differ between groups.
		Sex: Male	138	Frequency: 5 days/week	HSA	

Table 14 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
Linden et al. 2007 [298]	1 year expanded PE intervention Randomized by school	Age: 6.7–9.0 years Race: Caucasian (except 1 boy adopted from Colombia) Location: Malmö, Sweden		Intensity: varied Time: 40 min/day Type: normal PE curriculum (running, jumping, climbing ropes, variety of ball games). Activities varied to reduce boredom. No specific osteogenic training program was added. Control: normal PE curriculum, duration within normal limits (1–2 sessions/week, in total 60 min/week)	*Significant* None *NS* FN CSMI, Z, CSA	Change in bone structural parameters did not differ between groups.
Macdonald et al. 2008 [299]	8-month PA and jumping intervention Randomized	Sex: male and female Age: 9–11 years Race: 53 % Asian (both parents or all four grandparents born in Hong Kong or China, India, Philippines, Vietnam, Korea, or Taiwan. 35 % Caucasian (parents born in North America or Europe). 12 % children mixed ethnicity or other ethnic origins Location: Vancouver and Richmond, British Columbia	410	Frequency: *Classroom Action*: 5 days/week; *Bounce at the Bell*: 5 days/week PA + 3×/day, 4 days/week jumping Intensity: not specified Time: *Classroom Action*: 15 min PA; *Bounce at the Bell*: 15 min PA + short bouts high-impact jumping Type: *Classroom Action*: skipping, dancing, playground circuits, simple resistance exercises with bands; *Bounce at the Bell*: Classroom Action + short bouts high-impact jumping. Phase I included 5 two-foot landing jumps (or 10 one-foot landing jumps) at each session. Phase II jumps were increased each month of the school year until a maximum of 36 jumps/day was reached. Control: Usual PE	HSA *Significant* None *NS* NN Z, CSA, SPW	Change in bone structural parameters did not differ between groups.
Alwis et al. 2008 [300]	1-year expanded PE intervention Randomized by school	Sex: female Age: 6.5–8.9 years Race: Caucasian Location: Malmö, Sweden	103	Frequency: 5 days/week Intensity: varied Time: 40 min/day Type: normal PE curriculum (running, jumping, climbing ropes, variety of ball games). Activities varied to reduce boredom. No specific osteogenic training program was added. Control: normal PE curriculum, duration within normal limits	HSA *Significant* None *NS* FN length, PW, CSA, Z, CSMI, EW, CT	Change in bone structural parameters did not differ between groups.

Table 14 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
				(1–2 sessions/week, in total 60 min/week)		
Alwis et al. 2008 [300]	2-year expanded PE intervention Randomized by school	Sex: male Age: 6.7–9.0 years Race: Caucasian Location: Malmö, Sweden	137	Frequency: 5 days/week Intensity: varied Time: 40 min/day Type: normal PE curriculum (running, jumping, climbing ropes, variety of ball games). Activities varied to reduce boredom. No specific osteogenic training program was added. Control: normal PE curriculum, duration within normal limits (1–2 sessions/week, in total 60 min/week)	HSA *Significant* None *NS* FN CSA, Z, CSMI	Change in bone structural parameters did not differ between groups.
Alwis et al. 2008 [300]	2-year expanded PE intervention Randomized by school	Sex: female Age: 6.8–8.9 years Race: Caucasian Location: Malmö, Sweden	291	Frequency: 2×/week (PE); 3×/day (activity breaks); 1×/day (home activity) Intensity: not specified Time: 45 min/session (PE); 2–5 min/session (activity breaks); 10 min/day (home activity) Type: 2 PE lessons (plus 3 regular PE classes) taught mostly outdoors by PE teachers. All five sessions included jumping activities such as hopping, jumping up and down stairs, rope skipping, etc. During academic lessons, 3–5 activity breaks comprised motor skill tasks such as jumping around on one leg, balancing on one leg, power games, or coordinative tasks were introduced every day. Daily home activity included aerobic, strength, or motor skill tasks such as tooth brushing while standing on one leg, jumping up and down the stairs, and rope jumping. Control: participated in regular PE classes 3×/week	HSA *Significant* None *NS* FN CSA, PW, Z, CSMI	Change in bone structural parameters did not differ between groups.
Weeks et al. 2008 [296]	8-month jumping intervention Randomized	Sex: male and female Age: boys 13.8 years (0.4); girls 13.7 years (0.5)	81	Frequency: 2×/week Intensity: 1–3 Hz at a height of 0.2–0.4 m	DXA *Significant* LS IBS	Percent change, mean EX: 17.9* CON: 14.4

Table 14 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
		Race: not specified Location: Gold Coast, Australia		Time: 10 min (~300 jumps) Type: varied, but included- jumps, hops, tuck jumps, jump squats, stride jumps, star jumps, lunges, side lunges, and skipping. Occasionally supplemented with upper body strengthening activities, including push-ups and exercises with resistive latex bands Control: usual PE warm-up and stretching	*NS* FN, LS BMAD FN CSMI	LS IBS improved more for EX participants than for CON. No other differences in 8-month change in parameters of bone strength reached significance.
Greene et al. 2009 [301]	28-week drop-landing intervention Randomized	Sex: female Age: 6–10 years Race: not listed Location: Sydney, Australia	39	Frequency: 3×/week Intensity: 14-cm height drop for low drop, 28-cm height drop for high drop (GRF 2–4× body wt); 10 sets of 5 steps per set; 50 steps per session Time: 15 min/day Type: single leg drop-landing exercises with nondominant leg serving as the training leg (dominant leg served as within-participant untrained control) Control: normal activity	pQCT *Significant* None *NS* Cort, Medullary, and Total BA at Proximal, Mid, Distal	Change in bone structural parameters did not differ between groups.
Macdonald et al. 2009 [250]	16-month PA and jumping intervention Randomized	Sex: male Age: 10.2 ± 0.6 years Race: 52 % Asian (Hong Kong or China, India, Philippines, Vietnam, Korea, or Taiwan), 35 % Caucasian (North America or Europe), 12 % mixed or other ethnic origins Location: Richmond and Vancouver, British Columbia	205	Frequency: *Classroom Action*: 5 days/week; *Bounce at the Bell*: 5 days/week PA + 3×/day, 4 days/week jumping Intensity: not specified Time: *Classroom Action*: 15 min PA; *Bounce at the Bell*: 15 min PA + short bouts high-impact jumping Type: *Classroom Action*: skipping, dancing, playground circuits, simple resistance exercises with bands; *Bounce at the Bell*: Classroom Action + short bouts high-impact jumping. Phase I included 5 two-foot landing jumps (or 10 one-foot landing jumps) at each session. Phase II jumps were increased each month of the school year until a maximum of 36 jumps/day was reached. Control: Usual PE	pQCT *Significant* I_{max} *NS* I_{min}, I_{max}/I_{min}, CoA- Ant, CoA- Med, CoA- Post, CoA- Lat, CTh- Ant, CTh- Med, CTh- Post, CTh- Lat	Difference, mean (95 % CI) 338.6 (16.4, 660.9)* The EX boys had a 3 % greater gain in I_{max} than CON boys. No other bone structural parameters differed between groups.
		Sex: male and female	221	Frequency: 5 days/week	HSA	Change, mean (95 % CI)

Table 14 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
Lofgren et al. 2012 [28]	4-year expanded PE intervention Randomized by school	Age: 6.5–8.7 years Race: Caucasian Location: Malmö, Sweden		Intensity: varied Time: 40 min/day Type: normal PE curriculum (running, jumping, climbing ropes, variety of ball games). Activities varied to reduce boredom. No specific osteogenic training program was added Control: normal PE curriculum, duration within normal limits (1–2 sessions/week, in total 60 min/week)	FN CSA FN Z FN CSMI	Male Female EX CON 0.11 (0.10, 0.13)* 0.09 (0.07, 0.11) 0.06 (0.05, 0.06)* 0.05 (0.04, 0.06) 0.10 (0.08, 0.11)* 0.08 (0.07, 0.09) The EX girls had significantly greater gain in all HSA outcomes than CON girls. No differences were seen for boys.
Anliker et al. 2012 [302]	9-month jumping intervention Randomized by school	Sex: male and female Age: 8–12 years Race: not listed Location: Lucerne, Switzerland	45	Frequency: 2×/week Intensity: intensity increased weekly. Number of jumps increased over time from ~60 to ~150 per session Time: 10 min Type: Jumping and sprinting exercises, including two- and one-legged hopping, drop jumps, side to side jumps, jumping jacks, jumps and landings from a podium, jumps over barriers and short multidirectional sprints Control: not specified	pQCT *Significant* None *NS* Tibia 4 % vBMC, vBMDtr, vBMDtot, BAtb, BAtot	Change in bone structural parameters did not differ between groups.
Detter et al. 2014 [303]	6-year expanded PE intervention Randomized by school	Sex: male and female Age: 6–8 years Race: Caucasian Location: Malmö, Sweden	133	Frequency: 5 days/week Intensity: varied Time: 40 min/day Type: normal PE curriculum (running, jumping, climbing ropes, variety of ball games). Activities varied to reduce boredom. No specific osteogenic training program was added Control: normal PE curriculum, duration within normal limits (1–2 sessions/week, in total 60 min/week)	Cross-sectional pQCT *Significant* None *NS* Tibia 4 %, Radius 4 % TR vBMD Tibia 38 %, Radius 66 % Cort vBMD Cort BMC Cort BA Cort Th CSA Polar SSI	Change in bone structural parameters did not differ between groups.

Observational studies

Reference	Study description	Population description	*N*	Exposure	End points	Results

Table 14 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
Forwood et al. 2006 [363]	7-year prospective follow-up	Sex: 109 males, 121 females Baseline age: 8–15 years Race: white Location: Saskatoon, Saskatchewan, Canada	230	Method: self-report questionnaire (3×/year for 3 years, 2×/year after) Variable: general level of PA for year (1–7)	Multilevel models for FN Z, CSA, and SPW (HSA)	MVPA positively associated with FN Z and FN CSA males and females. A male with PA score of 1 had 0.0972 cm^2 less CSA than a male with PA score of 5. Females with PA score of 1 had 0.0588 cm^2 less CSA than females with score of 5. Males with PA score of 1 had 0.0615 cm^2 less Z than males with PA score of 5. Females with PA score of 1 had 0.0355 cm^2 less Z than females with score of 5.
Janz et al. 2007 [364]	6-year prospective follow-up	Sex: 212 males, 233 females Baseline age: 5 years Race: primarily white Location: Iowa, USA	445	Method: ActiGraph accelerometer Variable: MVPA min/day (>3000 ct/min)	Multilevel models for FN Z and CSA (HSA)	MVPA positively associated with Z and CSA males and females. When adjusted, LM only significant males 40-min MVPA predicted 3–5 % greater CSA and Z compared to 10 min/day MVPA When CSA and Z adjusted for LM, associations attenuated in males but remain significant. Associations become insignificant in females.
Farr et al. 2013 [360]	2-year prospective follow-up	Sex: 248 females Baseline age: 9–12 years Race: 90 % white, 6 % Asian, 2 % black or African American, 0.5 % Native American or Alaska Native, 1 % Native Hawaiian or Pacific Islander, 0.5 % other Location: Tucson, Arizona, USA	248	Method: self-report questionnaire Variable: past-year PA score	Follow-up tibia and distal femur BSI	PA associated with increases in distal femur BSI
Gruodyte-Raciene et al. 2013 [365]	4-year prospective follow-up	Sex: 81 males, 84 females Baseline age: 4–10 years Race: 96 % white, 2 % Asian, 2 % other Locations: Saskatoon, Saskatchewan, Canada	165 92 gymnasts, 73 nongymnasts	Method: parental-report questionnaire Variable: PA score 1–2 h/week gymnastics exposure	Yearly trajectories of PF CSA and Z (HSA)	When compared to nongymnasts, gymnasts 6 % greater NN CSA, 7 % greater NN Z, 5 % greater IT CSA, 6 % greater IT Z, and 3 % S CSA
Janz et al. 2014 [248]	12-year prospective follow-up	Sex: 160 males, 189 females Baseline age: 5 years Race: primarily white Location: Iowa, USA	349	Method: ActiGraph accelerometer Variable: MVPA min/day (≥2296 ct/min)	Follow-up (age 17) FN Z and CSA Tibia BSI Tibia polar moment of inertia	Participants in high trajectory for MVPA had greater geometric outcome measures (Z: females 21.0 %, males 9.4 %; CSA: females 11.8 %, males 10.0 %; BSI: females 19.0 %, males 12.8 %; polar moment of inertia: females 38 %, males 8.4 %) at age 17 compared to other trajectories.
Jackowski et al. 2014 [251]	~15-year prospective follow-up	Sex: 55 males, 49 females Baseline age: 8–15 years Race: primarily white Location: Saskatoon, Saskatchewan, Canada	104	Method: self-report questionnaires Variable: average activity score	Follow-up (age 23–30) PF CSA and Z (HSA)	Around time of PHV, active adolescents had 8–12 % greater CSA and 9–12 % greater Z than inactive peers at PF. When adult CSA and Z were adjusted for height, weight, adolescent bone geometry, and sex, those active during adolescence maintained 5–7 % benefit in CSA and 6–8 % benefit in Z in adulthood compared to inactive. In young adulthood, males and

Table 14 (continued)

Reference	Study description	Population description	Number of subjects	Intervention	End points	Results
						females who were physically active as adolescents had greater bone geometric measures.
Duckham et al. 2014 [252]	~18-year prospective follow-up	Sex: 49 males, 73 females Baseline age: 8–15 years Race: primarily white Location: Saskatoon, Saskatchewan, Canada	122	Method: self-report questionnaire Variable: general PA score	Follow-up (age 24–34) tibia and radius BA, BSI, SSIp, CoC, CoA, CoD, ToA, ToD, TrC, TrD, and BSI_c (pQCT)	In young adulthood, males who were physically active as adolescents had 13 % greater SSIp and 10 % greater ToA at tibia. Females had 10 % larger CoA, 12 % larger CoC, and 3 % larger TrC at tibia.
Cardadeiro et al. 2014 [362]	1-year prospective follow-up	Sex: 81 males, 96 females Baseline age: 10–12 years Race: primarily white Location: Lisbon area, Portugal	177	Method: bone-specific administered questionnaire ActiGraph accelerometer Variables: PA score Sedentary min/day (≤100 ct/min) Light min/day (101–2295 ct/min) Moderate min/day (2296–4011 ct/min) Vigorous min/day (>4012 ct/min)	BMD distribution via three aBMD ratios: FN/PF, IM/SL, and TR/PF Geometric measures of the pelvis—IAD and PF ALA	Questionnaire significant in FN/PF ratio model in males

95 % CI 95 % confidence interval, *aBMD* areal bone mineral density (g/cm^2), *ALA* abductor lever arm, *Ant* anterior, *BA* bone area (cm^2), *BMAD* bone mineral apparent density (g/cm^2), *BMC* bone mineral content (g), *BMD* bone mineral density (g/cm^2), *BSI* bone strength index (mg^2/cm^4), BSI_c bone strength in compression, *CA* cortical area (mm^2), *CoA* cortical bone area (mm^2), *CoC* cortical content (mg/mm), *CoD* cortical density (mg/cm^3), *CON* control group, *Cort* cortical, *CSA* cross-sectional area (cm^2), *CSMI* cross-sectional moment of inertia, *CT* cortical thickness (mm), *ct* cortical, *ECirc (mm)* endosteal circumference, *ED* endosteal diameter (cm), *endo* endosteal, *EW* endosteal width, *EX* exercise group, *FN* femoral neck, *FS* femoral shaft, *HSA* hip structure analysis, *IAD* interacetabular distance, *IBS* index of bone structural strength, *IM* inferomedial, I_{max} maximum moment of area, I_{min} minimum moment of area, *IT* intertrochanter, *Lat* lateral, *LM* lean mass, *LS* lumbar spine, *Med* medial, *MVPA* moderate-through-vigorous-intensity physical activity, *NN* narrow neck, *NS* not significant, *PA* physical activity, *PCirc* periosteal circumference (mm), *PE* physical education, *peri* periosteal, *PF* proximal femur, *PHV* peak height velocity, *Post* posterior, *pQCT* peripheral quantitative computed tomography, *PW* periosteal width, *RCT* randomized controlled trial, *SL* superolateral, *SPW* shaft periosteal width (cm), *SSI* strength strain index, *SSIp* density-weighted polar section modulus (mm^3), *SW* subperiosteal width (cm), *tb* trabecular, *Th* thickness, *ToA* total area (mm^2), *ToD* total BMD (mg/cm^3), *tot* total, *TR* trabecular, *TrC* trabecular content, *vBMC* volumetric BMC (g/cm), *vBMD* volumetric bone mineral density (g/cm^3), *Z* section modulus (cm^3)

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

CSA and section modulus of the femoral neck as well as measures of tibial compressive and torsional strength have also been associated with physical activity in the Iowa Bone Development Study cohort. On average, the investigators reported a 14 % difference in various measures between cohort members who were most active during a 12-year follow-up compared to those who were less active [248].

Our evidence grade for physical activity and exercise on bone structure was based on semi-consistent evidence from many RCTs and observational studies.

Grade: Level of evidence B was assigned for the benefit of physical activity and exercise on bone structure.

Discussion

In this scientific statement, we updated a former effort published in 2000 to summarize the lifestyle choices that influence development of peak bone mass [1]. Unlike the earlier report, our review used a systematic approach to search predictors of bone mass from publications since 2000. We also considered our knowledge of physiological functions and biology of growth for areas for which a systematic review was not possible. Bone is a living tissue and as such requires all essential nutrients for growth and maintenance. The bony mineral tissue is composed of hydroxyapatite, a calcium-phosphate compound, with magnesium and trace amounts of other minerals. The connective tissue is composed primarily of the protein, collagen. The role of many micronutrients in bone is to assist in connective tissue synthesis and maturation. Iron, zinc, magnesium, copper, manganese, and vitamin K are cofactors in enzymes responsible for bone metabolism, collagen synthesis, and cross-linking. Vitamin D is metabolized to a steroid-like hormone that increases calcium absorption through a saturable, facilitated diffusion pathway. Mechanical loading from physical activity is essential to stimulate bone modeling to provide the stimulus necessary to develop a strong skeleton to support growth and development. In children and adolescents, the important focus is on bone accrual, with careful monitoring of growth parameters. Unfortunately, in contrast with adults, children and adolescents have not been the focus of research in many studies relating lifestyle factors to bone density or quality.

Grade A evidence

Both physical activity and calcium intake had strong and abundant evidence to be assigned a grade A level of evidence. This level of evidence is not often attained and merits priority action for public health efforts. Regrettably, calcium intake and physical activity are not achieved in recommended levels by our youth. A large difference in the nature of the evidence between physical activity and calcium intake is apparent. The evidence for physical activity and bone mass and geometry is a global approach, whereas the evidence for calcium intake and bone mass is a reductionist approach. The research available for physical activity does not examine the effects of specific types of exercise and few studies examine the dose loading effects of any one type of exercise. Therefore, we conclude that physical activity is important for growing bone, but we do not fully understand the characteristics of physical activity that impact bone such as mode, frequency, intensity, and duration. On the other hand, studies of the effects of diet on bone usually look at a single nutrient effect; there is much less evidence for the effects of diet quality as a whole. There is opportunity for researchers in both fields to consider the approaches of the other field.

Macronutrients

Fat

There was significant interest in dietary fat and bone metabolism in the decade preceding the 2000 review by Heaney et al. [1] that centered around ω-3 and ω-6 fatty acids and biomarkers of inflammation, primarily in animal models. Since 2000, the work has continued to examine the long-chain ω-3 fatty acids, DHA and eicosapentaenoic acid. The majority of studies have been conducted in adults, and the findings are equivocal with respect to improvements in bone mass [253]. Only one RCT was identified in children, but it was not included in this review due to the short 16-week duration of the intervention [254]. Prospective studies and RCTs in children and adolescents are lacking, and it is premature at this time to draw conclusions regarding the influences of dietary fat on bone during growth.

Protein

During pubertal growth, BMC accrual is markedly influenced by increasing IGF-I [181], and IGF-I is impacted by energy and protein intakes. We considered studies addressing both dietary protein intakes as well as PRAL. Prior to the 2000 review on peak bone mass by Heaney et al. [1], the interest in dietary protein and bone centered on calcium/protein ratios and calcium retention in adults, although the findings of several protein and bone cross-sectional studies in adults were mixed. Other dietary factors are also of interest including the effect of specific dietary proteins with higher sulfur-containing amino acids, which increase PRAL and may lead to lower bone quality. Much of what is known regarding dietary protein and bone quality emanates from adult studies, with limited work in children and adolescents. One short (6 months) RCT in adolescents [143] showed no benefits to

material or geometrical properties of bone and was not generalizable because it included only late adolescents and young adults aged 18–25 years. The majority of prospective [144–147] and cross-sectional [149–151, 153] studies support a positive relationship between protein intake and bone. The Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) Study [144, 145] demonstrated that protein intake was positively, and PRAL was negatively, associated with the geometrical properties of the forearm in a stepwise multiple regression model. Using biomarker data from that same cohort, long-term protein intake estimated by uN excretion and urinary PRAL were positively and negatively associated with forearm cortical BMC and area, respectively, when adjusting for age, sex, pubertal stage, forearm muscle area, forearm length, and urinary calcium. To further support a positive effect of dietary protein on bone growth, protein intake over approximately 8 years explained total body BMC net gain in the University of Saskatchewan Pediatric Bone Mineral Accrual Study [147]. In a multivariate regression model, long-term protein intake (over 2 years) positively predicted total body BMC. Collectively, the prospective studies lend support for a positive effect of protein on bone in growing children.

Only one prospective study showed negative relationships between dietary protein and bone [148]. The authors suggested that the negative relationships might have been due to low calcium intakes among the children. Consistent with this notion, Vatanparast et al. [147] reported that the positive effect of dietary protein on bone mass is most evident in those consuming adequate calcium (>1000 mg/day). Higher dietary protein accompanied by low calcium intakes (i.e., lower calcium/protein ratio) could lead to increased urinary calcium excretion [255] and lower bone mass; however, RCTs are needed to prove this assumption.

Micronutrients

Calcium

Storage of calcium in bone serves as a functional reserve to offset dietary shortages of calcium and is tapped when needed to maintain homeostasis. More than 99 % of the body's calcium is in the skeleton as a consistent proportion of bone mineral. The calcium reserve is very large relative to the cellular and extracellular metabolic pools of calcium; thus, dietary insufficiency rarely impairs calcium-dependent biochemical functions. However, long-term deficiency depletes the reserve and subsequently decreases bone mass and bone strength.

Because the human skeleton contains only about 2–3 % of the total adult body calcium at birth, the dietary requirements for calcium during the first 20–30 years of life are determined primarily by skeletal growth. Extreme calcium deficiency during growth can cause rickets [256, 257]. However, even moderate deficiency has deleterious effects on the skeleton, both short term and long term.

Balance studies are useful to show the effect of a nutrient in an otherwise controlled environment because the diet is strictly controlled. These studies have shown that calcium is a threshold nutrient, implying that calcium retention increases with calcium intake until a plateau is reached. Balance studies, rather than bone density or other skeletal measures, have been used to demonstrate this phenomenon because finding the threshold requires a range of intakes, which bracket the threshold intake. This is possible in balance studies that are sufficiently short to manage controlled diets until steady state is achieved. During peak bone mass accrual, there are racial and sex differences in the plateau calcium intake and the peak maximal retention in adolescents. Black girls have a higher maximal retention than white girls, and Chinese-American girls have the lowest maximal retention rates [258–260]. The intake at which the plateau occurs is not different between white and black girls, but it is lower in Chinese-American girls (1300 versus 970 mg/day). White boys have higher peak calcium retention rates than white girls, but the intake at which the plateau occurs is not different [261]. Chinese-American boys had both higher maximal calcium retention rates and intakes for maximal retention (1100 mg/day) than Chinese-American girls [260]. By contrast, Mexican-American boys and girls do not have different rates of calcium retention, and rates are similar to non-Hispanic white boys but are higher than for non-Hispanic white girls [262]. The intake for maximal retention for white adolescents has been established as the RDA for calcium for adolescents [263]. The recommended intakes for Chinese-American, and perhaps other Asian, adolescent girls could be lowered because maximal bone calcium accretion is achieved at lower calcium intakes than whites. However, actual calcium intakes for most Asian adolescent populations are considerably below this lower threshold intake [264]. Few balance studies have been conducted in children other than adolescents.

Numerous studies have been conducted to determine the amount/types of dietary calcium needed for development of maximal bone mass and strength and the ages/stages of development at which calcium intake might be more critical. Furthermore, efforts have been made to elucidate the relationship between calcium intake and physical activity in maximizing skeletal development.

Heaney [265] recently proposed guidelines for systematic reviews of clinical studies of nutrient effects. He proposed that all studies included in a systematic review of nutrient intake should have baseline nutrient status as an entry criterion and should start with subjects at similar baseline nutrient status values. Baseline nutrient status should be suboptimal, especially in the case of a threshold nutrient such as calcium. If subjects are calcium replete, an intervention to increase calcium intake will usually produce a null effect. Heaney also proposed that for inclusion, all studies should use similar

doses of the nutrient intervention and that co-nutrient status should be optimized to ensure that the test nutrient is the only nutrient-related factor in the response. However, in reality, few studies meet all of Heaney's proposed guidelines. The calcium doses of studies found for this review ranged from 500 to 1200 mg/day. Only three studies supplemented with vitamin D, which is an important co-nutrient for bone health. Importantly, all reported baseline calcium intakes were below the Institute of Medicine (IOM)—recommended levels, ranging from 181 to 1199 mg/day. Thus, in studies of children and adolescents whose average calcium intake is deficient, 90 % of the RCTs detected a statistically and biologically significant effect on bone accrual.

In our review of applicable RCTs, we found that designs of calcium supplement studies are inconsistent with regard to baseline calcium intake, supplement dose, optimization of vitamin D, outcome variables (skeletal site, BMD versus BMC versus area), and adjustment for confounders. Nonetheless, we find that calcium supplementation, whether with pills, fortified foods, or dairy, consistently increases gain in skeletal mass and density measures in children and adolescents, usually between 1.0 and 5.0 %. The skeletal sites showing a calcium effect were widely varied among the studies. Some studies did not adjust for body size, which confounds the outcomes because growing children will all have increases in BMC and BMD due to elongation of the skeleton. In addition, there is some evidence that calcium supplementation also increases gain in height [162].

Vitamin D

Prior to the peak bone mass review published in 2000 [1], no vitamin D RCTs in children or adolescents had been published. Eight RCTs have been conducted since then using vitamin D doses ranging from the equivalent of 200–2000 IU/day, and these RCTs have primarily targeted female subjects between the ages of 10 and 17 years [159, 170, 173, 175–178, 180]. Two publications [175, 176] originated from the same Lebanese RCT, the only RCT to include males. Four RCTs conducted in Lebanon, Finland, China, and the United Kingdom provide moderate evidence to support vitamin D supplementation effects on childhood and adolescent bone mineral accrual. Using an intent-to-treat analysis, supplementation was shown to improve hip BMC [175] and geometrical properties of the femoral neck [176] in females, but not males. In subgroup analyses, the vitamin D effect was more pronounced in prepubertal or early pubertal versus postpubertal girls, as well as in those with lower versus higher baseline 25(OH)D. Two RCTs that provided evidence demonstrating improvements in BMC gains after vitamin D supplementation only did so when analyzing results using a compliance-based analysis [177, 178]. Findings by Du et al. [170] and Khadilkar et al. [178] support the beneficial effects of vitamin D supplementation on total body BMC gains; however, unlike the other single-nutrient studies, vitamin D was combined with calcium. The remaining four RCTs [159, 173, 178, 180] did not show significant changes in BMC measures with supplementation, likely due to the use of small sample sizes or low vitamin D intervention doses, in some cases combined with baseline serum 25(OH)D concentrations above a threshold for demonstrating an effect.

Comparing the findings from the RCTs is complicated because of the different methodologies used to assess serum 25(OH)D, including radioimmunoassay (Diasorin), enzyme immunoassay (Immunodiagnostic Systems), and high-performance liquid chromatography. More confidence in the findings is generated because all laboratories participated in the Vitamin D External Quality Assessment Scheme (DEQAS) and met the standards. Moreover, various statistical approaches were employed among RCTs. The RCT that presented the most compelling evidence for a vitamin D effect on bone accrual presented intent-to-treat, unadjusted data [175]. In another study, positive findings were found only when taking into consideration compliance and statistically adjusting for changes in bone area, weight, and maturation [177]. The other RCTs adjusted for one or a combination of other potential confounders, including baseline bone values, bone area, age, maturation, height, weight, fat-free soft tissue, calcium intakes, sunlight exposure, and physical activity.

It is important to note that mean baseline serum 25(OH)D concentrations for all RCTs in our review were between 18 and 48 nmol/L, which are lower than the 50-nmol/L cutoff used to define vitamin D sufficiency [245]. Using changes in BMC as the primary outcome, even in study samples with deficient-to-low serum 25(OH)D, supplementation did not consistently promote gains. In a systematic review by Winzenberg et al. [266], the authors concluded that vitamin D supplementation is more likely to augment hip, forearm and lumbar spine aBMD in children with low serum 25(OH)D concentrations. To our knowledge, no RCTs with bone outcomes have been conducted in children and adolescents with serum 25(OH)D concentrations ≥50 nmol/L [263].

The osteogenic effects of calcitriol are attributed to its role in serum calcium homeostasis, partially through regulation of intestinal calcium absorption [267]. Calcium absorption was not assessed in the four RCTs in this review. One dose–response RCT in children entering the early stages of puberty with a mean baseline serum 25(OH)D of 70 nmol/L showed no effects of supplementation on fractional calcium absorption using vitamin D doses ranging from 400 to 4000 IU over 12 weeks [268]. These results are compatible with the aforementioned systematic review [266], which stated that the beneficial effects of vitamin D on bone may be less likely to occur in children with sufficient serum 25(OH)D.

Although we ranked the evidence for a positive effect of vitamin D supplementation on bone mineral accrual in children and adolescents as moderate, several unanswered questions remain. Only one study was conducted in males, and it is therefore premature to make conclusions regarding sexual dimorphism with respect to vitamin D supplementation and bone. Moreover, subgroup analyses were conducted in several studies in an attempt to identify critical times during childhood and adolescence during which supplementation may be most effective on bone. The results reported for premenarche, the early stages of puberty, or the postmenarche years, however, were inconsistent. These equivocal findings deserve further investigation.

Micronutrients other than calcium and vitamin D

Few trials of any type have been conducted on micronutrients other than calcium and vitamin D relevant to bone health to guide recommendations. The studies on other micronutrients included in this review were not generalizable or were limited in sample size or other aspects of study design. Magnesium, phosphorus, vitamin K, vitamin C, zinc, and other nutrients play important structural and functional roles for bone. Only magnesium was tested in an RCT, but this benefit to BMC was only evaluated in a small group of white girls and only at one level of supplementation. Results of the two studies that found sex differences [189, 190] may be explained by the study group being in a period of active bone modeling. Boys experience peak bone mass accrual later than girls [3]. The benefits of vitamin C in the study by Prynne et al. [189] were not observed in girls of the same age, likely because the girls were more sexually mature. Benefits to younger girls were apparent in the study by Laudermilk et al. [190]. In cross-sectional analyses, inverse relations were observed between phosphorus and sodium intake and total body BMC and size-adjusted bone area [149]. Although phosphorus is an important component of bone mineral, it may be a marker for cola intake (see below under food patterns) or protein intake. The observed negative effect of sodium on bone mass and area may be explained by the negative effect of high dietary sodium intakes on calcium balance through greater urinary calcium excretion demonstrated in adolescent girls [269]. In that study, the negative effect of dietary sodium was more pronounced in white girls than in black girls. Calcium, magnesium, and potassium retention were all greater in black adolescent girls than in white adolescent girls [185, 269–271].

Vitamin K is a cofactor of vitamin K-dependent gamma-carboxylase, an enzyme required for the activation (gamma-carboxylation) of osteocalcin, a protein involved in bone formation and mineralization. Undercarboxylation of osteocalcin, a marker of vitamin K deficiency, was inversely associated with BMC [191]. Kalkwarf et al. [192] were the first to investigate the effects of vitamin K on bone mass and bone turnover in young girls and found little benefit to bone, except in the spine. It should be reemphasized that the girls in this study were aged 3–16 years, representing a broad span in terms of skeletal maturity. Even though experimental data suggest a stimulatory effect of vitamin K on bone formation [272], the relationship between vitamin K nutritional status and development of peak bone mass and strength in humans remains unclear.

Fluoride promotes osteoblast proliferation, increases aBMD in adults, and has been used as a therapeutic option for patients with osteoporosis [273]. The two prospective studies in children and adolescents [186, 274] suggest a possible osteogenic benefit of living in a specific location with higher fluoride concentrations in the water. Two US prospective reports from Iowa [187, 188], however, showed that lifetime fluoride intakes were not associated with BMC in 11- and 15-year-old adolescents. The public health benefits of water fluoridation for dental caries prevention in children are well documented, but the available limited evidence is insufficient to draw conclusions regarding fluoride and bone during growth.

Many of these micronutrients (i.e., calcium, vitamin D, potassium, and for some subgroups, magnesium and vitamins C and A) are shortfall nutrients compared to recommended intakes as determined by the 2015 Dietary Guidelines Advisory Committee [275].

Food patterns

The evidence since 2000 builds on earlier evidence, with additional RCTs showing a benefit to bone owing to the inclusion of dairy products in the diet. Dairy products contain colloidal calcium phosphate protein complexes in the form of casein micelles that have the minerals and nutrients needed for bone growth. Cross-sectional studies show a positive association between fruit and vegetable intake and higher bone mass. The explanation for the benefit of fruit and vegetable intake to bone is not clear. The benefit may be because of the nutrients that they provide, such as potassium, magnesium, and vitamin C [189, 276]; bioactive ingredients from specific fruits and vegetables, such as flavonoids [277]; or their alkaline ash-forming properties [189]. Studies in children on any of these hypotheses are limited. In a 4-year prospective study in German children aged 6–18 years, urinary net acid excretion, a good indicator of total body net endogenous acid load, was unrelated to bone measures [145].

Carbonated beverage and cola consumption was associated with reduced BMC, aBMD, or bone strength and higher fracture in several cross-sectional studies shown in Table 8, especially in girls. The negative effect of cola beverages and caffeine may be directly related to increased urinary calcium with caffeine or to excess phosphorus intake. To explore the potential mechanism by which carbonated beverages result in lower

bone accretion and fracture, Kristensen et al. [278] examined biomarkers of bone turnover in a controlled crossover intervention study with 11 men (aged 22–29 years). The authors compared 10 days on a low-calcium diet with cola versus milk added to the diet. The high cola intake was associated with increased bone turnover compared to the period of high milk intake. Alternatively, the negative effect of carbonated beverage consumption on bone may be explained by associated factors including low milk intake, reduced physical activity, and higher BMI [201]. The effect of diet on bone turnover in the study by Kristensen et al. [278] could be due to calcium in milk, rather than the cola, given that dietary calcium reduces bone resorption in adolescent girls [279]. Milk displacement by soft drinks is associated with reduced intakes of calcium and other nutrients found in milk. Regardless of the mechanism, the evidence suggests that cola consumption while on a low-calcium diet can have adverse effects on bone accretion and retention.

Bioactive food components may influence human gut microbial diversity, which in turn may offer a positive impact on skeletal health. The role of the gut microbiome in regulating bone mass was recently demonstrated using a germ-free mouse model [280]. Flavonoids, found ubiquitously in nature in many plant-derived foods, may also have the potential to positively affect bone health. Although our search did not identify any RCTs that assessed the effect of any flavonoid subclass (or polyphenols in general) in children or adolescents, several animal and/or in vitro analyses have shown a biological plausibility for these compounds to affect bone turnover and markers of bone health [277]. Because of their structural similarity to estrogen, soy isoflavones are currently the main class of flavonoids studied for their role in bone health.

Total dietary fiber does not appear to be related to bone accrual, but fibers that are fermentable to short-chain fatty acids in the lower gut by the gut microbiome are associated with increased calcium absorption [281–283]. In the only intervention study of sufficient duration to examine effects on BMC accrual, a combination of short- and long-chained fructooligosaccharides showed a significant benefit [193].

Infant nutrition

Breastfeeding during the first year of life has long been suggested to be optimal for infant nutrition; however, the available scientific literature is conflicting in terms of bone and fracture outcomes. Formula feeding may have the potential to increase short-term BMC and BMD outcomes [215, 216], possibly due to higher amounts of nutrients such as calcium and vitamin D in most infant formulas compared with breast milk (to note, infant formula contents likely vary between and within observational studies). An older landmark RCT [284] supports this hypothesis and reported that during the first 6 months of life, bone accretion is less in infants fed human or low-mineral formula but is greater in the second 6 months of life. Data from observational studies remain inconsistent since 2000. Additional studies addressing the impact of the duration of breastfeeding on peak bone mass development are also needed because current observational data have shown inconsistent results [212–214, 251]. It is important to note potential confounding bias because mothers who breastfeed have been shown to adopt other positive health behaviors for their children that could influence the development of peak bone mass. It is important to note that the American Academy of Pediatrics has recommended that infants who are breast-fed and children and adolescents who consume less than 1 L of vitamin D-fortified milk per day will likely need supplementation to reach 400 IU of vitamin D per day [285].

Data from the RCT assessing the effects of infant formula enriched with palm olein showed positive effects in relation to total body BMC at 3 and 6 months [211]. However, observational studies of children aged 4.5 and 10 years who consumed infant formula with either added palm olein or *sn*-2 palmitate during their infancy showed no significant differences in total body BMC [220, 221]. Overall, the data suggest that enrichment of infant formula with palm olein may be beneficial during the first 6 months of life.

Adolescent special issues

Detriment of DMPA injections and oral contraceptives

Data are conflicting regarding the effect of combined OCs on bone density among adolescent girls. OC pill use by healthy, white, teenage females did not affect acquisition of peak bone mass in one study [223]. However, studies that have examined the effect of low-dose estrogen OCs suggest otherwise. Some data suggest that long-term treatment with an oral monophasic contraceptive formulation (ethinylestradiol 20 μg + desogestrel 0.150 mg) raises concerns about suboptimal achievement of peak bone mass [286], especially when initiated during the teenage years. The skeletal effects of combined OCs are of greater concern in adolescents compared to their use in adult women [287, 288]. Initiation of combined OCs within the first 3 years after menarche is of particular concern [288]. OCs suppress endogenous estradiol production by suppressing the hypothalamic–pituitary–ovarian axis. There is growing consensus that OCs containing 20 μg of ethinylestradiol interfere with acquisition of peak BMD, although some studies have had inherent limitations including smoking status, small sample size, poor accounting for confounders, and so forth [289].

Contraception via injections of DMPA is associated with skeletal deficit at the spine and hip when used before peak bone mass. DMPA acts on the skeleton mainly through estrogen deficiency [230]. Pharmacological doses of DMPA may

also possess selective glucocorticoid activity and can alter the expression of glucocorticoid receptor-regulated genes. However, weight gain on DMPA may mitigate loss of BMD among adolescent users [222]. In addition, bone loss in female adolescents receiving DMPA for contraception is partly or fully reversible following discontinuation of DMPA, with faster recovery at the spine than at the hip [290]. DMPA is still used commonly in adolescents, but with caution given the potential skeletal implications.

Detriment of alcohol

Alcohol abuse is associated with lower aBMD and increased risk of fracture among adults. However, the association between low to moderate alcohol intake and bone density in adults is inconsistent, with low to moderate intakes associated with higher aBMD than that of abstainers in some studies [291]. Likewise, there is little evidence that alcohol intake at levels currently reported in studies among adolescents to date has any effect on attainment of peak bone mass. An important limitation of published studies is the ability to identify the effects of consuming large daily amounts alcohol (>3 servings/day) on bone due to its low reported prevalence in these studies.

There has been large variability among studies in the amount of alcohol consumed by study participants and the classification of alcohol intake from ever tried to number of drinks per day. Overall, the reported alcohol consumption by adolescents studied was relatively low. In some studies, adolescents who consumed alcohol were more likely to smoke [231–235], necessitating statistical adjustment for smoking to investigate the independent effects of alcohol intake on bone.

Binge drinking is an important consideration for adolescents, because about 90 % of the alcohol consumed by adolescents aged <21 years in the USA is in the form of binge drinking [292]. We did not identify any studies that examined the association between binge drinking on bone health in adolescents.

Detriment of smoking

Despite abundant evidence that smoking has many deleterious health effects, cigarette smoking continues to be common among adolescents and adults. In 2011, 18.1 % of high school students in the USA smoked ≥1 cigarettes in the last 30 days and 19.0 % of adults were current smokers [293].

The strength of evidence regarding the association between smoking and bone in adolescence has been limited by methodological challenges in quantifying smoke exposure and the need to disentangle the effects of smoking from other lifestyle factors such as physical activity, dietary calcium intake, and alcohol consumption. Differences in results across studies arise, in part, due to challenges in characterizing exposure and the low prevalence of regular smoking, limiting statistical power. Despite methodological challenges, results of the studies reviewed herein support the contention that smoking in adolescents may reduce peak bone mass. The large studies of young adult military recruits provide additional evidence that a history of smoking has deleterious effects on bone. Even if the effect of smoking during adolescence on bone mass is small, it may become important if the deleterious effects of smoking on aBMD compound over time. Adolescents who smoke often continue smoking in adulthood, possibly increasing their risk of osteoporosis and fracture later in life.

If the associations between active and passive smoke exposure and aBMD are causally related, curtailment of active and passive smoke exposure to children of all ages will likely facilitate maximal attainment of peak bone mass [294].

Physical activity and exercise

We judged the evidence of a positive effect of physical activity on mass and density as strong (Level A). The evidence is less clear in support of a positive effect of physical activity on structure; therefore, we judged the evidence to be moderate at this time (Level B). Similar bone structure RCT designs have resulted in positive effects [28, 81, 250, 295, 296], no effects [25, 244, 297–303], and different effects based on gender or maturity status [73]. However, despite the inconsistencies in RCT results, the evidence provided by well-designed RCTs [81] and prospective cohort studies [252] supports a positive effect on structure, including those using objective measures of physical activity [248]. Unlike RCTs with mass and density outcomes, the multitude of structural measures, sites for measurement (distal, proximal), and inconsistencies in adjustment for bone size present a unique challenge in evaluating the quality of studies examining and interpreting exercise effects on structure. A design limitation in most of the reviewed RCT studies (mass, density, and structure) was an inability to adequately assess the following: the physical activity levels of controls, the degree of effort in the exercisers, and the activity levels of the exercisers during periods of non-intervention. In short, issues of compliance were common threats to internal validity. In addition, physical activity interventions, in general, are susceptible to compensation effects (i.e., the intervention group does less physical activity outside of the intervention session to maintain a "normal" activity routine) [304].

There is a need to more precisely deliver the exercise dose and to understand the levels of physical activity in control and intervention groups. Laboratory-based work indicates an osteogenic effect at or above mechanical loads of 4.2 g-force [305], whereas RCTs suggest an osteogenic effect at or above 3.5 g-force [24, 306]. RCTs also suggest 3 days/week with 100 loads per session and approximately 7 months of

intervention are needed to detect change [24, 306, 307]. Due to the overlap in time and frequency in interventions that show change and those that do not, specific recommendations for these exercise dimensions (time and frequency) are equivocal [25, 73, 295, 301, 302]. At present, 100 loads per session and 3 days/week are reasonable time and frequency dimensions based on successful RCTs [24, 73, 306].

Almost all of the physical activity-related RCTs included in our review used jumping as the primary exercise type. This is a sound decision because jumping is the gross motor skill that mechanically loads the clinically important site of the hip via muscle loading during takeoff and via impact loading during landing. Animal and human studies have shown that jumping imposes a greater anabolic stimulus on bone than running or walking [306, 308], and the latter are activities commonly prescribed for metabolic health and obesity prevention. The known differences in types of physical activities for different targeted health outcomes suggest a need to promote physical activities that incorporate multiple motor skills (e.g., soccer, tumbling, tennis) or promote diverse physical activity patterns.

In addition to the RCTs and prospective longitudinal studies that we reviewed and graded, other types of research support physical activity as a causal factor for healthy bone mass, density, and structure [309]. Many of the mechanisms and pathways have been elucidated in laboratory studies [82, 308, 310] and the theoretical underpinning of why physical activity is expected to influence mass, density, and structure is clearly described in Frost's mechanostat model [77, 78], which is well respected in the greater scientific community [311–313].

Research gaps

We have identified many questions that will drive a future research agenda (Table 15). Trials should be designed to obtain at least B-level evidence. The following areas merit further investigation: differing effects of interventions depending on the life stage of growth; gene–environment interactions and how they may impact the development of peak bone mass; the need to identify and utilize biomarkers of exposure and effects; and the interaction of bone with other tissues throughout the body. It is important to recognize that the pediatric skeleton with open epiphyses differs from that of a fully grown adult who has reached his or her peak bone mass, and therefore, meaningful clinical targets and response to interventions will also differ. In addition, longitudinal studies are needed to document the relationship between growth and measures of bone fragility and fractures and to identify lifestyle interventions that may prevent fractures during this period of susceptibility.

Table 15 Future research agenda

Topic area	What we need to know
Life stages of growth for interventions	Are interventions more effective during different stages of growth (e.g., rapid or slow)? Can deficiencies in one stage be overcome subsequently?
	Is there an influence of fetal programming?
	What are the most effective diet and physical activity interventions at each stage?
	What is the influence of diet and physical activity patterns, in the short-term and over long periods?
	What are the determinants of bone acquisition and the impact of interventions in the understudied period of late adolescence to early adulthood?
	Does response to intervention vary by factors such as sex and population ancestry?
	Are there other understudied or unstudied lifestyle or environmental factors affect peak bone mass development (i.e., sleep, stress, etc.)?
Gene–environment interactions	Are there interactions that affect peak bone mass development?
Biomarkers of exposure and effect	How do we generate better markers of nutritional status, physical activity and bone loading, and other environmental exposures?
	Among adolescents, exposures to consider include lifestyle habits such as smoking (both nicotine and marijuana) and alcohol, among others.
	How do we generate better markers of stage of maturity, peak bone strength development, and associated intermediate mechanisms?
	Attention to the multiple factors involved in bone and mineral metabolism is needed in interpreting responses to dietary interventions, including a focus on interactions between vitamin D, phosphorus, calcium, and fibroblast growth factor 23.
Organ and tissue interactions	What are bone interactions with other tissues (i.e., brain, fat, muscle, gut, etc.) on development of peak bone mass?

Statistical guidelines

Analysis and interpretation of data from studies examining the effects of nutrition, dietary components, and physical activity on bone mass and/or strength requires thoughtful consideration (Table 16). Foremost is the baseline of the dietary or physical activity exposure in the study population. This is particularly important for threshold nutrients or dietary components that do not have a linear association with bone measures across a broad range of intakes. Animal studies also indicate that the effects of physical activity are likely to saturate [310]. In randomized trials, it is important to select participants who are likely to benefit from additional intake and/or exercise. For example, if usual intake of calcium exceeds requirements, then it is unlikely that any benefit of the intervention will be detected. The duration of the intervention is critical to consider in the design of intervention trials and

Table 16 Elements to consider in the analysis and interpretation of studies examining the effects of nutrition on bone mass or density

Element
Usual intake of nutrient or dietary component, nutritional status
Duration of intervention (randomized trials)
Age
Sex
Race
Maturational stage
Body size
Physical activity
Health status and medication use
Baseline bone values (prospective studies)

should be appropriate for the bone measure under study. Changes in calcium balance may be measureable within 3 weeks, whereas measureable changes in bone mass or strength due to a dietary and/or exercise intervention may not be evident for 6–12 months.

Subject characteristics, including age, sex, race, maturational stage, and skeletal or body size, should also be considered in the design and analysis of studies examining the association between nutrition or physical activity and bone outcomes because they are strongly associated with bone measures during growth. Statistical adjustment for these characteristics can dramatically reduce residual variability in regression models and improve statistical power to identify associations among dietary intake, physical activity, and bone. In addition, statistical adjustment may compensate for imbalances in these variables across ranges (observational studies) or among intervention groups (randomized trials). Several approaches have been used to account for skeletal size, the most common being height or bone area. Several chronic medical conditions (e.g., anorexia nervosa, cystic fibrosis, etc.) [314–318] and medications (e.g., glucocorticoids, anticonvulsants) [72, 319] are known to affect bone accrual during growth, and these should be accounted for in the study design or statistical analyses. Finally, prospective studies, both randomized trials and observation studies, should consider adjustment for baseline bone values and exposures to minimize the statistical phenomenon of regression toward the mean.

Implementation

Dietary intakes and physical activity levels of most US youth during the development of peak bone mass do not support maximal bone mass accretion for genetic potential. This increases risk for fracture both during childhood and later in life. Adherence to the US Department of Agriculture (USDA)/US Department of Health and Human Services (HHS) Dietary Guidelines for Americans and HHS Physical Activity Guidelines for Americans is an important and positive step toward ensuring healthy bone growth and/or maintenance throughout the lifecycle.

Diet

The recommended intakes of food groups and nutrients relevant to bone, their bone-related functions, and intake status are given in Tables 17 and 18. Shortfall food groups include dairy, fruits, and vegetables (Table 17). Consequently, intakes of nutrients provided by these food groups often do not meet national recommendations (Table 18). Dairy products provide most of the calcium and vitamin D in the diet as well as high-quality protein and significant amounts of magnesium, potassium, and other essential nutrients. Yet, approximately 66 % of boys and 83 % of girls during the time of peak height velocity do not meet the recommended intakes of milk [320]. Low intakes of fruits and vegetables can lead to insufficient intakes of vitamins A, C, E, and K and potassium. Potassium has only recently been associated with bone health [276]. Additional research is needed to confirm why higher fruit and vegetable intakes seem to contribute to pediatric bone health among cross-sectional studies. At present, continuing to advocate for children and adolescents to obtain recommended intakes of fruits and vegetables as described by the Dietary Guidelines for Americans has no downside, and may offer a potential benefit toward development of peak bone mass.

Recommended intakes of vitamin D are particularly difficult to achieve without fortified foods or supplements. Enriched and fortified foods provide almost 60 % of dietary vitamin D and 30 % of vitamin A as well as substantial amounts of B vitamins and iron [321]. Fortified foods provide most of the vitamin D in the US diet [263, 275]. Most US milk is fortified with 100 IU of vitamin D per cup [263]. Breakfast cereals often contain added vitamin D, as do some brands of orange juice, yogurt, margarine, and soy beverages. The USA requires infant formula to contain a minimum of 40 IU and a maximum of 100 IU of vitamin D per 100 kcal (21 CFR 107.100). Low-income, overweight/obese, and minority populations of children in the USA have been shown to have lower intakes of both vitamin D and calcium [209].

Very few foods naturally have vitamin D. Fatty fish (e.g., salmon, tuna, and mackerel) and fish liver oils are the best sources, whereas beef liver, cheese, and egg yolks contribute small amounts [263]. Some mushrooms naturally provide vitamin D, and mushrooms and yeast are available with enhanced levels of vitamin D from being exposed to ultraviolet light [322–324] but are scarce on the market.

There is recent growing interest in the possibility that intake of 25(OH)D, the metabolized form of vitamin D that is also present in animal foods such as meat, poultry, and eggs, may be contributing to vitamin D status in humans [325].

Table 17 Recommended and actual intakes and functions of food sources involved in development of peak bone mass

Food source	Bone-related function	Recommended servings[a]			Percentage of population with usual intakes below recommendations		
		Children	Males	Females	Children	Males	Females
Dairy (cups)[b]	Intakes correlated with linear growth, bone mass accrual, reduced fracture	2–3 years: 2 4–8 years: 2.5	9–13 years: 3 14–18 years: 3 19–30 years: 3	9–13 years: 3 14–18 years: 3 19–30 years: 3	2–3 years: 41 4–8 years: 42	9–13 years: 8 14–18 years: 68 19–30 years: 80	9–13 years: 84 14–18 years: 92 19–30 years: 94
Fruits (cups)[c]	Provide micronutrients for optimal bone growth, preserve bone and calcium economy through acid–base balance	2–3 years: 1 4–8 years: 1–1.5	9–13 years: 1.5 14–18 years: 2 19–30 years: 2	9–13 years: 1.5 14–18 years: 1.5 19–30 years: 2	2–3 years: 32 4–8 years: 63	9–13 years: 78 14–18 years: 87 19–30 years: 89	9–13 years: 81 14–18 years: 85 19–30 years: 93
Vegetables (cups)	Provide micronutrients for optimal bone growth, preserve bone and calcium economy through acid–base balance	2–3 years: 1 4–8 years: 1.5	9–13 years: 2.5 14–18 years: 3 19–30 years: 3	9–13 years: 2 14–18 years: 2.5 19–30 years: 2.5	2–3 years: 80 4–8 years: 92	9–13 years: 96 14–18 years: 97 19–30 years: 93	9–13 years: 95 14–18 years: 99 19–30 years: 94

[a] Based on the 2010 Dietary Guidelines for Americans, which may be accessed via http://www.health.gov/dietaryguidelines/dga2010/dietaryguidelines2010.pdf (modified from: http://www.choosemyplate.gov)

[b] Recommended servings of dairy are determined by age

[c] Recommended servings of fruits and vegetables are determined by age, sex, and level of physical activity

Amounts of 25(OH)D in foods currently are not included in the USDA food tables. Studies that have reported discrepancies between estimated vitamin D intakes and serum levels of 25(OH)D are driving the interest in determination of 25(OH)D in foods.

Physical activity

Regular physical activity in youth promotes healthier bones throughout childhood and adolescence. As part of the federally recommended ≥60 min of daily physical activity, children and adolescents should include bone-strengthening physical activity at least 3 days of the week. Bone-strengthening activities are those that are dynamic, moderate to high in load magnitude, short in load duration, odd or nonrepetitive in load direction, and applied quickly [84, 326].

Although complete data are lacking, the IOM estimates that only about one half of youth meet the current HHS Physical Activity Guidelines for Americans' recommendation for ≥60 min of daily moderate-to-vigorous intensity physical activity. The number of youth meeting this recommendation decreases with age [327] and precipitously declines in early adolescence, a time when bone appears most responsive to physical activity. Throughout childhood and adolescence, girls are less active than boys and are clearly missing opportunities to optimize bone health. The US Centers for Disease Control and Prevention (CDC) reports that as many as one third of youth report no physical activity in the preceding 5 days [328]. Regrettably, participation in bone-strengthening physical activities is not measured in the CDC Youth Risk Behavior Surveillance System. Daily opportunities for incidental physical activity have declined for both children and adolescents as a result of factors such as increased reliance on nonactive transportation, automation of activities for daily living, and greater opportunities for sedentary behavior. Disparities in opportunities for physical activity exist across racial, ethnic, and socioeconomic profiles [327].

Taking action

A multilayered approach must be applied to achieving the recommendations of the Dietary and Physical Activity Guidelines for Americans.

Families

Adults must model and participate in healthy behaviors and engage with family members during mealtime and exercise. Government resources such as MyPlate and the Youth Physical Activity Guidelines Toolkit are informative resources for parents.

Schools

Schools must continue to improve and implement optimal nutrition standards through programs such as the National School Lunch Program and the National School Breakfast Program. Specific strategies for creating an optimal

Table 18 Recommended and actual intakes and functions of nutrients involved in development of peak bone mass

Nutrients	Dietary sources	Bone-related function	RDA/AI			EAR[a,b]			Percentage of population with usual intakes < EAR[c,d] (%)		
			Children	Males	Females	Children	Males	Females	≥2 years	2–18 years	≥19 years
Macronutrients											
Protein (g/day)	Animal products, plants, legumes	Organic component of bone that also promotes bone mineral accrual	1–3 years: 13 4–8 years: 19	9–13 years: 34 14–18 years: 52 19–30 years: 56	9–13 years: 34 14–18 years: 46 19–30 years: 46	1–3 years: 0.87 4–8 years: 0.76	9–13 years: 0.76 14–18 years: 0.73 19–30 years: 0.66	9–13 years: 0.76 14–18 years: 0.71 19–30 years: 0.66	<3	<3	<3
Micronutrients											
Calcium (mg/day)	Dairy, dark leafy greens	Inorganic component of bone essential for rigidity, strength, and elasticity of bone tissue	1–3 years: 700 4–8 years: 1000	9–13 years: 1300 14–18 years: 1300 19–30 years: 1000	9–13 years: 1300 14–18 years: 1300 19–30 years: 1000	1–3 years: 500 4–8 years: 800	9–13 years: 1100 14–18 years: 1100 19–30 years: 800	9–13 years: 1100 14–18 years: 1100 19–30 years: 800	38	~47	~36
Phosphorus (mg/day)	Dairy, meat, processed foods, colas	Inorganic component of bone that also functions as an acid–base buffer	1–3 years: 460 4–8 years: 500	9–13 years: 1250 14–18 years: 1250 19–30 years: 700	9–13 years: 1250 14–18 years: 1250 19–30 years: 700	1–3 years: 380 4–8 years: 405	9–13 years: 1055 14–18 years: 1055 19–30 years: 580	9–13 years: 1055 14–18 years: 1055 19–30 years: 580	5	~16	~1
Magnesium (mg/day)	Dairy, dark leafy greens, nuts, whole grains	Regulates structural development of bone (i.e., hydroxyapatite)	1–3 years: 80 4–8 years: 130	9–13 years: 240 14–18 years: 410 19–30 years: 400	9–13 years: 240 14–18 years: 360 19–30 years: 310	1–3 years: 65 4–8 years: 110	9–13 years: 200 14–18 years: 340 19–30 years: 330	9–13 years: 200 14–18 years: 300 19–30 years: 255	45	~35	~48
Potassium (g/day)	Dairy, fruit (e.g., oranges), vegetables (e.g., potatoes)	Regulation of acid–base balance affecting bone metabolism	1–3 years: 3.0 4–8 years: 3.8	9–13 years: 4.5 14–18 years: 4.7 19–30 years: 4.7	9–13 years: 4.5 14–18 years: 4.7 19–30 years: 4.7	–	–	–	3 (<AI)	–	–
Zinc (mg/day)	Animal products, nuts, seeds	Required for collagen synthesis and bone formation	1–3 years: 3 4–8 years: 5	9–13 years: 8 14–18 years: 11 19–30 years: 11	9–13 years: 8 14–18 years: 9 19–30 years: 8	1–3 years: 2.5 4–8 years: 4.0	9–13 years: 7.0 14–18 years: 8.5 19–30 years: 9.4	9–13 years: 7.0 14–18 years: 7.3 19–30 years: 6.8	8	~5	~8
Iron (mg/day)	Animal products, fruits, vegetables, fortified grain products	Cofactor required for collagen synthesis and vitamin D activation	1–3 years: 7 4–8 years: 10	9–13 years: 8 14–18 years: 11 19–30 years: 8	9–13 years: 8 14–18 years: 15 19–30 years: 18	1–3 years: 3.0 4–8 years: 4.1	9–13 years: 5.9 14–18 years: 7.7 19–30 years: 6.0	9–13 years: 5.7 14–18 years: 7.9 19–30 years: 8.1	5	~2	~6
Manganese (mg/day)	Nuts, legumes, whole grains	Cofactor required for proteoglycan synthesis and bone formation	1–3 years: 1.2 4–8 years: 1.5	9–13 years: 1.9 14–18 years: 2.2 19–30 years: 2.3	9–13 years: 1.6 14–18 years: 1.6 19–30 years: 1.8	—	—	—	—	—	—
Vitamin K (μg/day)	Green vegetables, plant oils, margarine	Cofactor required for carboxylation of osteocalcin and bone formation	1–3 years: 30 4–8 years: 55	9–13 years: 60 14–18 years: 75 19–30 years: 120	9–13 years: 60 14–18 years: 75 19–30 years: 90	–	–	–	35 (<AI)	–	–
Vitamin C (mg/day)	Citrus fruits, dark leafy greens	Cofactor required for cross-linking of collagen fibers	1–3 years: 15 4–8 years: 25	9–13 years: 45 14–18 years: 75 19–30 years: 90	9–13 years: 45 14–18 years: 65 19–30 years: 75	1–3 years: 13 4–8 years: 22	9–13 years: 39 14–18 years: 63 19–30 years: 75	9–13 years: 39 14–18 years: 56 19–30 years: 60	25	~17	~28
Vitamin A (μg/day)			1–3 years: 300 4–8 years: 400	9–13 years: 600 14–18 years: 900	9–13 years: 600 14–18 years: 700	1–3 years: 210 4–8 years: 275	9–13 years: 445 14–18 years: 630	9–13 years: 420 14–18 years: 485	34	~28	~38

Table 18 (continued)

Nutrients	Dietary sources	Bone-related function	RDA/AI			EAR[a,b]			Percentage of population with usual intakes < EAR[c,d] (%)		
			Children	Males	Females	Children	Males	Females	≥2 years	2–18 years	≥19 years
	Dairy, darkly colored fruits and leafy vegetables	Implicated in bone formation and resorption		19–30 years: 900	19–30 years: 700		19–30 years: 625	19–30 years: 500			
Vitamin D (IU/day)	Fortified dairy, fatty fish	Regulates calcium homeostasis and bone metabolism	1–3 years: 600 4–8 years: 600	9–13 years: 600 14–18 years: 600 19–30 years: 600	9–13 years: 600 14–18 years: 600 19–30 years: 600	1–3 years: 400 4–8 years: 400	9–13 years: 400 14–18 years: 400 19–30 years: 400	9–13 years: 400 14–18 years: 400 19–30 years: 400	70	~75	~69

AI adequate intake, *EAR* estimated average requirement, *RDA* recommended dietary allowance

[a] RDA is the average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97–98 %) healthy individuals in a group. It is calculated from the EAR, which is the average daily nutrient intake level estimated to meet the requirements of half of the healthy individuals in a group. If sufficient scientific evidence is not available to establish an EAR, and thus calculate an RDA, an AI is usually developed. EARs have not been established for vitamin K, potassium, manganese, or other nutrients not yet evaluated via the DRI process

[b] Data are from the Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride (1997); Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline (1998); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001); Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (2002/2005); and Dietary Reference Intakes for Calcium and Vitamin D (2011). These reports may be accessed via www.nap.edu (modified from: http://www.iom.edu/Activities/Nutrition/SummaryDRIs/DRI-Tables.aspx)

[c] Data are from Fulgoni [366]

[d] Data are from Fulgoni et al. [321]

environment for inclusive physical education, extracurricular physical activities, and active classrooms are provided in the USA, most recently by the 2012 *Physical Activity Guidelines for American's Midcourse Report*: *Strategies to Increase Physical Activity Among Youth* [329] and the recent IOM report *Educating the Student Body*: *Taking Physical Activity and Physical Education to School* [327]. Early knowledge of nutrition and physical activity through consumer sciences and physical education courses should be mandatory in every K–12 school. Recess should be mandatory for every K–5 school.

Healthcare system

All allied healthcare providers should be required to be proficient in both counseling for nutrition and physical activity through their required curriculum and continuing education. Scientific groups such as the National Osteoporosis Foundation, the American Society for Nutrition, the Academy of Nutrition and Dietetics, the American College of Sports Medicine, and the Society for Health and Physical Educators among others should provide tool kits and educational materials with consistent messaging on nutrition and physical activity for bone health to allied healthcare providers.

Federal, state, and local policy

Government support for healthy growth and development should reach beyond obesity to antecedents of chronic disease, including osteoporosis. Subsidizing foods for bone health through programs such as Head Start, the National School Breakfast Program, the National School Lunch Program, the Supplemental Nutrition Assistance Program, and the Special Supplemental Nutrition Program for Women, Infants, and Children helps to ensure that all children meet their nutrition requirements. Examples of how physical activity requirements are supported include the Federal Safe Routes to Schools Program and the Let's Move program, as well as public–private sector collaborations such as the NFL Play 60 Challenge and the Partnership for a Healthier America. Through zoning, incentives, and innovative cooperative agreements with businesses, local governments can help to ensure access to fresh food as well as parks and youth recreation opportunities. Expanding successful federal, state, and local nutrition and physical activity programs as well as facilitating innovative collaboration between the public and private sectors are critical to creating a society in which bone health matters.

Conclusions

There is a critical need for more research focusing on bone health in youth. Future research should consider sex, population ancestry, and maturation. When possible, standardizing outcome measures would facilitate the pooling of data for evidence-based reviews.

The best evidence is available for positive effects of calcium intake and physical activity, especially during the late childhood and peripubertal years—a critical period for bone accretion. Good evidence is also available for a role of vitamin D and dairy consumption. However, more work is needed on physical activity dose response and the potential interaction between physical activity and diet quality. Weaker but physiologically plausible evidence is available and emerging for the effects of macronutrients and other micronutrients on bone among youth. It is important to address the factors most strongly linked to developing peak bone mass and strength from the current evidence through multilayered public health strategies. It is equally important to develop a research agenda to better understand other lifestyle factors that are less clearly understood for the purpose of building strong and healthy bones. Meanwhile, meeting federal guidelines for intakes of nutrients and physical activity while cautioning against harmful behaviors is a priority strategy.

Glossary

Terminology	Acronym	Definition
Areal bone mineral density	aBMD	DXA calculates BMD using area. This is not an accurate measurement of the true bone mineral density, which is mass divided by volume. It is a reasonable estimate of BMC.
Bone mineral content	BMC	DXA measures the BMC of the spine, hip, wrist, femur, or any other selected part of the skeleton. It does this by focusing an x-ray on a body site and measuring the proportion of light rays that pass through the tissue as opposed to being blocked by minerals in the bone. Using computer software, it then divides that number by the surface area of the bone being measured to create BMD.
Bone mineral density	BMD	BMD refers to the amount of mineral matter per square centimeter of bone. BMD is used as a predictor of osteoporosis and fracture risk.
Computed tomography	CT	CT is an imaging procedure that uses special x-ray equipment to create a series of detailed pictures, or scans, of areas inside the body. It is also called computerized tomography and computerized axial tomography (CAT) scanning.
Cross-sectional moment of inertia	CSMI	CSMI is a measure of the distribution of material around a given axis. It is used to calculate bending stress.
Dual-energy x-ray absorptiometry	DXA	DXA is a means of measuring BMD. It is the most widely used and most

		thoroughly studied bone density measurement technology. Two x-ray beams with different energy levels are aimed at the patient's bones. When soft tissue absorption is subtracted out, the BMD can be determined from the absorption of each beam by bone.
Hip structural analysis	HSA	HSA measures not only the BMD of the hip bone but also structural geometry of cross-sections traversing the proximal femur at specific locations. The bone mass image is used directly from the DXA scan, where pixel values are expressed in areal mass (g/cm^2). The method employs the principle that a line of pixel values across the bone axis corresponds to a cut plane traversing the bone at that location and contains some of the information about the cross-section.
Percentage of undercarboxylated osteocalcin	%ucOC	%ucOC is a measure of vitamin K status. Osteocalcin is a vitamin K-dependent protein produced by the bone. The ratio of undercarboxylated to carboxylated or total osteocalcin has been regarded as a marker of inadequate vitamin K status.
Peripheral quantitative computed tomography	pQCT	pQCT is a type of quantitative CT used for making measurements of the BMD in a peripheral part of the body, such as the forearms or legs, as opposed to CT that measures BMD at the hip and spine. pQCT is useful for measuring bone strength.
Potential renal acid load	PRAL	PRAL is a measure of the acidic or basic effects that a food has on the body.
Quantitative computed tomography	QCT	QCT measures BMD using a standard CT scanner with a calibration standard to convert Hounsfield units (HU) of the CT image to BMD values. QCT scans are primarily used to evaluate BMD at the lumbar spine and hip.
Stress–strain index	SSI	The SSI of a bone is a surrogate measure of bone strength determined from a cross-sectional scan by QCT or pQCT. The SSI is used to compare the structural parameters determined by analysis of QCT/pQCT cross-sectional scans to the results of a three-point bending test.
Volumetric bone mineral density	vBMD	In addition to aBMD using DXA, a projected posteroanterior lateral vertebral scan is added to measure vertebral width, height, and depth to estimate vBMD. This permits direct measurement of bone depth, rather than estimation of projected posteroanterior dimensions.

Compliance with ethical standards

Endorsing societies This scientific statement has been reviewed and endorsed by the following scientific societies:

American Bone Health
American College of Sports Medicine
Endocrine Society
National Osteoporosis Foundation
Society for Women's Health Research

Reviewers This scientific statement was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Osteoporosis Foundation in making this published report as sound as possible and to ensure that the report meets standards for both objectivity and evidence. We thank the following individuals for their peer review of this scientific statement:

Sue A. Shapses, PhD
Rutgers, The State University of New Jersey
Kimberly O'Brien, PhD
Cornell University
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This scientific statement was peer reviewed by the National Osteoporosis Foundation Research Committee and *Osteoporosis International*. This scientific statement was approved by the National Osteoporosis Foundation Board of Directors.

Sources of financial support Funding for the manuscript was provided by the Alliance for Potato Research and the Dairy Research Institute.

Conflicts of interest TCW is employed by the National Osteoporosis Foundation. CMW, CMG, KFJ, HJK, JML, RL, MO, and BSZ have no disclosures.

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