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REVIEW

Factors influencing peak bone mass gain

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Abstract **Bone mass is a key determinant of osteoporosis and fragility fractures. Epidemiologic studies have shown that a 10% increase in peak bone mass (PBM) at the population level reduces the risk of fracture later in life by 50%. Low PBM is possibly due to the bone loss caused by various conditions or processes that occur during adolescence and young adulthood. Race, gender, and family history (genetics) are responsible for the majority of PBM, but other factors, such as physical activity, calcium and vitamin D intake, weight, smoking and alcohol consumption, socioeconomic status, age at menarche, and other secondary causes (diseases and medications), play important roles in PBM gain during childhood and adolescence. Hence, the optimization of lifestyle factors that affect PBM and bone strength is an important strategy to maximize PBM among adolescents and young people, and thus to reduce the low bone mass or osteoporosis risk in later life. This review aims to summarize the available evidence for the common but important factors that influence bone mass gain during growth and development and discuss the advances of developing high PBM.**

Keywords peak bone mass; children; adolescents; genetic; risk factors

Introduction

Osteoporosis is a systemic osteopathy characterized by a decrease in bone density and quality, the destruction of bone microstructure, and an increase in bone brittleness caused by genetic and environmental factors [1]. Bone mineral density (BMD) is recognized as the most important predictor of osteoporosis, and fracture is the ultimate manifestation. Currently, approximately 200 million people worldwide suffer from osteoporosis [2], and 83.9 million of which are in China [3]. As reported, the burden of treatment for osteoporosis and osteoporotic fractures has been rising rapidly. Approximately 2.33 million osteoporotic fractures are estimated in 2010 in China, which cost $9.45 billion [4].

BMD is the bone mineral content (BMC) in the bone tissue and a measurable indicator related to bone mass, reflecting bone strength [5]. Various factors can affect the accumulation and loss of BMD in bone tissue, and the perniciousness of bone loss are well recognized in adults, especially among the elderly. However, the attention to bone health during childhood and adolescence is not sufficient as a 10% increase in peak bone mass (PBM) gain can delay the onset of osteoporosis by 13 years [6], and a 6.4% decrease in bone mass in children period has been associated with a twofold risk of fracture in adulthood [7].

The process of gaining PBM is influenced by a number of factors, including genetics and ethnicity, nutrition (calcium and vitamin D), physical activity, exposure to risk factors (such as smoking and alcohol intake), and some diseases and medications. Osteoporosis is the most common cause of low BMD, but other diseases, such as osteogenesis imperfecta (OI), can be characterized by low BMD. Besides osteoporosis, other diseases, such as OI and osteomalacia, are common causes of low BMD.

OI is a rare connective tissue disorder characterized by the increased frequency of fractures [8]. About 85% of patients with OI have an autosomal dominant mutation in the type 1 collagen coding genes (*COL1A1* and *COL1A2*), and patients with mild OI may remain undiagnosed until adulthood and present early-onset or accelerated osteoporosis [9]. In addition, osteomalacia, a disorder in which a newly formed osteoid at the site of bone turnover is not properly mineralized, can be characterized by reduced BMD [9]. Therefore, understanding the determinants of

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bone acquisition from adolescence to young adulthood and the strategies to optimize PBM are critical. The main purpose of this paper is to summarize the available factors, such as genetic factors, dietary factors, chronic diseases and medications, and other environmental factors (including weight, smoking and alcohol consumption, vitamin D, calcium, and physical activity), that influence bone mass gain in children, adolescents, and young adults.

Peak bone mass

BMD measurement

According to the World Health Organization (WHO), the dual energy X-ray absorptiometry (DXA) screening can be applied to diagnose osteoporosis among postmenopausal women and men (age $>$ 50 years). The individuals with T-score at lumbar spine (LS) or hip below -2.5 can be diagnosed with osteoporosis, and individuals with T-score of -1 to -2.5 can be diagnosed with osteopenia or low bone mass [10]. For children and young adults, the International Society for Clinical Densitometry has advocated the use of Z-score, which describes standard deviations from healthy age- and sex-matched individuals' BMD, rather than T-score, and the wording "low bone mass" is for Z-scores less than or equal to -2.0 standard deviation [11]. Although radiographic examination is more frequently applied in the clinical diagnosis of vertebral fractures, DXA scan can be used to do this assessment. A study of vertebral fracture assessment (VFA) has used the DXA scan in 20 children and adolescents and reported a sensitivity of 83% and specificity of 100% for VFA compared with the VFA of subjects with lateral spine radiographs as the gold standard [12]. A more recent study by Adiotomre *et al.* reported that the mean sensitivity values of radiographs and DXA in diagnosing vertebral fracture are 74% and 70%, respectively, with specificity of up to 96% and 97%, respectively, in 250 children aged 5–15 years [13].

Quantitative computed tomography (QCT) can also assess bone mass but is not as widely utilized as DXA. QCT can measure cortical and trabecular BMD separately. The volumetric BMD (as opposed to "areal" DXA-BMD) and geometric/structural parameters, which contribute to bone strength, can also be obtained [14]. A limitation is that the WHO definition of osteoporosis in terms of bone densitometry (T-score of -2.5 or below using DXA) is not applicable. An alternative method of estimating BMD is derived from quantitative ultrasound (QUS), which usually consists of two different ultrasound measurement techniques, namely, the broadband ultrasound attenuation and the velocity of sound, typically at the heel calcaneus [15]. QUS is safe, rapid, and relatively cheap. Thus, QUS may be used in very large samples, such as approximately 500 000 samples in the UK Biobank.

Timing of PBM accumulation

PBM, the largest amount of bone accumulated at the end of growth, is a very important predictor of osteoporosis and fracture risk in the future. Generally, bone mass is believed to considerably increase during the first 20 years and reaches a plateau in the late adolescence or young adulthood in males and females [16,17] (Fig. 1). A longitudinal data have shown that in women and men,

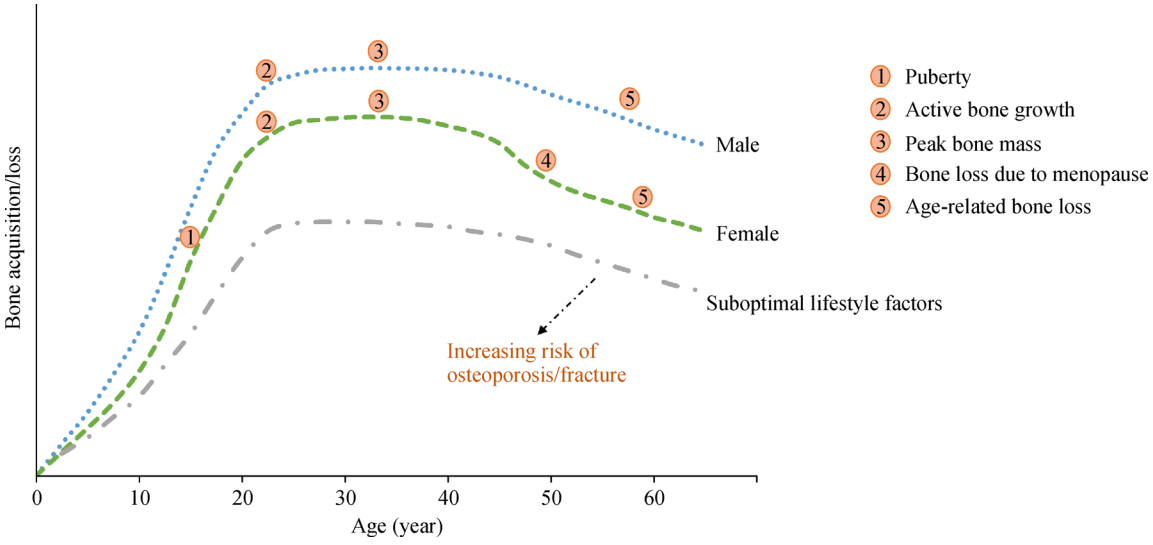

Fig. 1 Bone mass throughout the life span.

more than 94% of BMD is acquired at the age of 16 [18]. Puberty is an important period for bone acquisition and contributes largely to the PBM value [19]. However, the timing of PBM is still disputed. Other data have suggested that the bone mineral is still being accumulated until the third decade of life [20,21].

PBM and fracture risk

Population-based studies have shown that roughly half of the boys and one-third of the girls would undergo a fracture by age of 18 and 1/5 would have two or more fractures [22,23]. Epidemiologic studies have shown that a 10% increase in PBM at the population level reduces the risk of fracture later in life by 50% [24]. A large cohort study including 6213 children with mean age of 9.9 years followed for two years has shown that the risk of fracture is related to BMD and BMC. Moreover, a weak inverse relationship exists between BMD and subsequent fracture risk (odds ratio (OR) per standard deviation (SD) decrease = 1.12; 95% CI: 1.02–1.25), and fracture risk is inversely related to BMC adjusted for bone area, height, and weight (OR = 1.89; 95% CI: 1.18–3.04) [25]. Additional studies using DXA and pQCT have also suggested a significant association between the forearm fracture in children and the lower areal and among vBMD, cortical area, and bone strength [26]. A low PBM may lead to higher risk of osteoporosis and fracture, whereas a high PBM may reduce or delay the onset of osteoporosis, which provides great reserves for adults and elderly. Therefore, achieving a high bone density and bone strength accrual during childhood and adolescence is more conducive for the prevention of fractures. In addition, understanding the factors that influence bone mass and bone microarchitecture early in life is important because poor bone health is associated with fracture risk in later life.

Factors influencing PBM gain

Bone health in adulthood is largely dependent on bone density acquired during childhood and adolescence. The bone mass gain during childhood and adolescence is influenced by multiple factors, including gender, genetic factors, ethnicity, and other environmental factors, such as physical activity, diet (calcium and protein intake), endocrine status (sex hormones, growth hormone, insulin-like growth factor 1, and vitamin D), and other risk factors, such as alcohol intake and cigarette smoking (including passive smoking) [5,24,27–29]. As environmental and behavioral factors account for 20% to 40% of adult PBM [30,31], the early identification of the factors associated with poor bone health and the provision of reliable counseling may help children and teenagers take action to maximize BMD before their PBM is completed.

Genetics of PBM

Family and twin studies suggest that BMD has a high heritability, and the estimates range from 50% to 85% [32,33]. Before the genome-wide association study (GWAS) is widely carried out, the *LRP5* [34] and *ESR1* [35] genes have been identified to be associated with BMD in children and adolescents. Although the GWAS for osteoporosis and related traits are mostly conducted in the adult population, some have also been performed among younger individuals, including children [36–38], teenagers [39], and premenopausal women [40,41]. The Avon Longitudinal Study of Parents and Children (ALSPAC) study has confirmed that the SP7 (Sp7 transcription factor) [36], nuclear factor κB receptor activating factor (RANK) [42], and osteoporogeterin (OPG) [42] are associated with BMD in children. In 2012, a large-scale GWAS has been conducted in a children cohort (Generation R) in the Netherlands [37] and determined that WNT16 rs917727_T is associated with systemic and head BMD in 2660 children. This site is also associated with BMD in adults. The study by Kemp *et al*. [43] determined that a subset of the loci associated with adult BMD are also associated with BMD in children. The rare variants near EN1, which are first identified in adults [44], are confirmed to be associated with high bone mass in children [45]. Recently, Chesi *et al*. [38] reported two loci associated with BMD achieving a genome-wide significant level. These loci are rs7797976 within CPED1 in girls and rs7035284 on 9p21.3 in boys. The association between CPED1–WNT16–FAM3C and BMD has been previously reported for other skeletal sites (skull and total body aBMD) in children of European ancestry [37]. Importantly, this locus is also associated with wrist BMD, bone strength, cortical bone thickness, and fracture risk of forearm in adults [46], PBM in premenopausal women [41], and bone mass and fracture risk of European elderly [47,48]. The loci associated with BMD in childhood are sometimes associated with BMD in adults (some with sex- and puberty-specific effects) [38,49], suggesting that the effect of genetic variants on BMD may act over the whole lifetime. Until now, several GWAS have successfully identified many variants and genes in children and young adults (Table 1 and Fig. 2).

Obesity/overweight and bone health

To date, little agreement exists on the effect of overweight and adiposity on the skeletal development and the mechanisms underpinning these changes [52]. Understanding how the body composition influences the bone health and development of children and young adults is critical because childhood and adolescence are important stages for bone growth. Recently, a systematic review and meta-analysis of 27 studies, including 5958 subjects aged 2–18 years, have shown that overweight and obese

Table 1 The bone-related loci identified by GWAS in children and/or young populations to date

Site	Population	Chromosome	Loci	Samples	References
LL-BMD	Children	1p36.12	WNT4	8007 European; 1177 Other; 232 Greater Middle Eastern	[43]
		7q31.31	WNT16		
		9q34.11	FUBP3		
		12p11.22	KLHDC5/PTHLH		
		14q32.12	RIN3		
SK-BMD	Children	1p36.12	WNT4	8007 European; 1177 Other; 232 Greater Middle Eastern	[43]
		6q22.32	CENPW		
		6q23.2	EYA4		
		7q31.31	CPED1		
		8q24.12	TNFRSF11B (OPG)		
		11p14.1	LGR4		
		11q13.2	LRP5		
		18q21.33	TNFRSF11A (RANK)		
TB-BMD	Children	1p36.12	WNT4	8007 European; 1177 Other; 232 Greater Middle Eastern	[43]
		2q24.3	GALNT3		
		7q31.31	CPED1-WNT16-FAM3C	2660 children; 12 066 individuals	[37]
		9q34.11	FUBP3	8007 European; 1177 Other; 232 Greater Middle Eastern	[43]
		12p11.22	KLHDC5/PTHLH		
		13q14.11	TNFSF11 (RANKL)		
		14q32.12	RIN3		
		12Q13	SP7	1518 European	[36]
UL-BMD	Children	1p36.12	WNT4	8007 European; 1177 Other; 232 Greater Middle Eastern	[43]
		2q24.3	GALNT3		
		6q22.32	CENPW		
		7q31.31	CPED1-WNT16-FAM3C	8007 European; 1177 Other; 232 Greater Middle Eastern	[43]
				337 African American or Afro-Caribbean, 908 European, 126 Hispanic or Latin American, Other; 481 European	[38]
				933 European American; 486 European	[50]
		13q14.11	TNFSF11 (RANKL)	8007 European; 1177 Other; 232 Greater Middle Eastern	[43]
		14q23.3	SPTB	933 European American; 486 European	[50]
C-vBMD	Children and young adult	6q25.1	CCDC170	5878 European; followed by replication in 1052 European	[51]
		6q25.1	ESR1		
		8q24.12	TNFRSF11B (OPG)		
	Adolescent and young adult	13q14.11	TNFSF11 (RANKL)	1934 European; replication in 3835 European	[39]
	Children and young adult			5878 European; replication in 1052 European	[51]
T-vBMD	Children and young adult	1q43	FMN2/GREM2	2500 European; replication in 1022 European	[51]
Hip-BMD	Children	3p14.1	MAGI1	933 European American; 486 European	[50]
FN-BMD	Children	14q22.3	TBPL2	933 European American; 486 European	[50]
LS-BMD	Children	9p21.3	IZUMO3	933 European American; 486 European	[50]

LL, lower limbs; SK, skull; TB, total-body less head; UL, upper limbs; C-vBMD, cortical volumetric BMD; T-vBMD, trabecular volumetric BMD; FN, femoral neck; LS, lumbar spine.

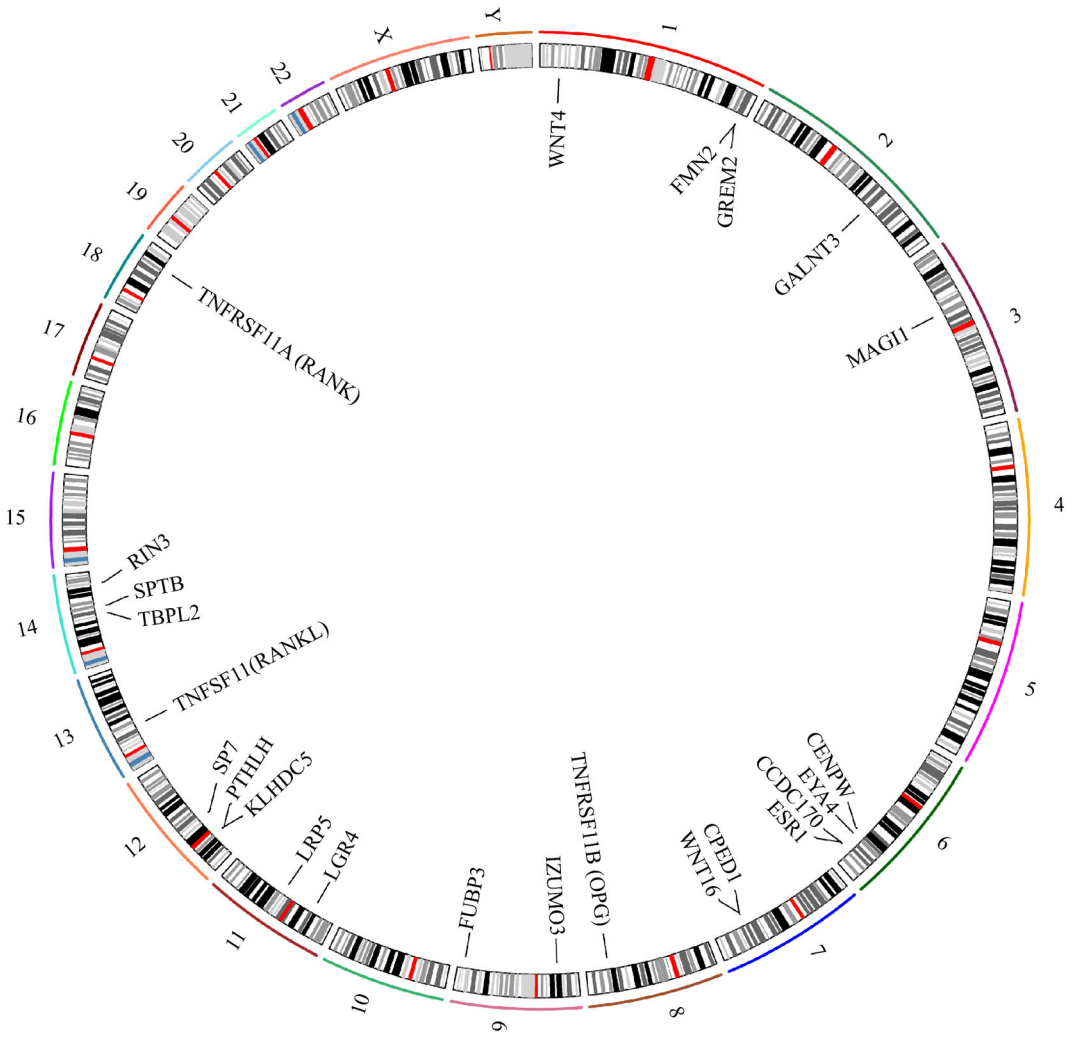

Fig. 2 Genes identified in GWAS studies using BMD in children and young population.

children have significantly higher BMD compared with normal-weight children ($P < 0.05$) [53]. These studies in children have suggested a positive relationship between adiposity and BMD, which started to weaken in later childhood, reversed during adolescence [54,55], and potentially maintained until early adulthood [56].

A longitudinal study [57] has followed 71 young females (aged 17–22 years) for six years and found that weight gainers have higher BMD and greater cortical thickness at the proximal femur shaft than individuals with stable weight. Wetzsteon and colleagues [58] followed up 445 children (aged 9–11 years) for 16 months and identified that absolute bone strength is greater in overweight children, but the increase in bone strength is because of the lean mass change and not fat mass. Another study [59] has also suggested that overweight males have higher bone quality (total BMD, total area, trabecular bone volume fraction (BV/TV), and trabecular number at the radius) compared with normal-weight young males, but the bone quality of overweight adolescents seems to have adapted to lean mass and not fat mass. More recent studies have also supported that lean mass is more important for optimizing bone strength during growth, whereas fat mass may negatively affect bone strength in weight-bearing sites in children and adolescents [60,61].

Leptin, as a multifunctional important cytokine derived from fat tissue, has an important role in bone metabolism and development [62]. First, leptin can promote the differentiation of bone marrow stromal cells (BMSC) into osteoblastic lineage and inhibit differentiation into fat [63]. Second, leptin can directly act on osteoblasts, enhance differentiation and maturation of osteoblasts, and finally improve bone formation [64]. Third, leptin can also inhibit osteoclast development, which may be through the immune system to affect the secretion of cytokines, stimulate the expression of OPG in peripheral

blood monocytes, reducing the expression level of RANK ligand (RANKL) via the RANKL/RANK/OPG system to inhibit the generation of osteoclasts and bone absorption [63]. Alternatively, leptin can act on the central hypothalamic pathway and the sympathetic nervous system to inhibit osteoblast proliferation. In this central pathway, leptin binds to hypothalamic receptors, inducing an increase in the sympathetic activity that signals to osteoblasts via the β2 adrenergic receptors (Adrβ2) [62]. Subsequently, two different downstream pathways, namely, the c-myc and the PKA-ATF4 pathways, are activated. In the c-myc pathway, the expression of c-myc is inhibited, thereby regulating the expression of cyclin D1, which finally leads to the suppression of osteoblast proliferation [62]. The RANKL expression is upregulated via the PKA–ATF4 pathway, which consequently enhances the bone resorption of osteoclasts [62]. By contrast, in the arcuate nuclei, leptin signal transduction upregulates CART expression, which suppresses the synthesis of RANKL in osteoblasts via an unknown mechanism.

The effect of physical activity in optimizing PBM

Throughout life, the bone is a living tissue that can respond to strains produced by muscular activity and mechanical load [5]. Adolescence is generally considered the best time to strengthen bones. During this period, the rate of bone modeling and remodeling is high, and the periosteal surface is growing rapidly. Physical activity during puberty increases the bone mass on the bone surface and enhances bone strength. The effects of physical activity on bone mass mainly come from the mechanical load from the direct stimulation of femur and muscle contraction. A high-magnitude, rapidly applied, and novel loading is most effective, and the duration is less important when the threshold number of cycles is reached [65]. In addition, physical activity can increase the absorption of nutrients, such as vitamin D and calcium [66]. Most studies have shown that physical activity is one of the main non-pharmacological methods to increase and maintain BMD and geometry [65]. Conversely, skeletal unloading due to cast immobilization or prolonged bedrest leads to bone loss [67].

A longitudinal study has shown that physically active adolescents (aged 8–15 years) have 8%–10% greater hip BMC at age 23–30 years than less active individuals [68]. A 4-year exercise program in children determined that girls and boys who added various intensities of physical activity (40 min/day and 5 days/week) have gained higher lumbar spine BMC by 7.0% and 3.3%, respectively, and higher femoral neck width by 1.7% and 0.6%, respectively, than the control subjects who only have normal physical education curriculum and duration within normal limits [69]. Another longitudinal trial study has shown that children who engaged in school-based exercise interventions for nine months have higher whole body (6.2%), total hip (7.7%), and femoral neck (8.1%) BMC compared with the controls [70]. After three years of discontinuation of the intervention, these benefits persisted with a sustained 7%–8% increment of BMC in the total hip and femoral neck of conditioned individuals [70]. A controlled cross-sectional study conducted among professional baseball players has shown that the effect of physical activity during youth on bone strength and bone size is kept throughout life [71]. Janz *et al*. [72] conducted a 10-year prospective study on 530 participants starting at age 5, with five measurements at ages 8, 11, 13, 15, and 17 years, and tried to address how moderate-and-vigorous intensity physical activity (MVPA) affects bone mass and geometric properties. This study determined that individuals who experienced the most MVPA have higher bone mass and better geometry at age 17 years.

The effect of physical activity on BMD or BMC has also been proven in randomized controlled trials (RCTs) [73–76]. Fuchs *et al*. [73] investigated the effect of high-intensity jumping on the lumbar spine and the hip bone mass in prepubertal 5.9–9.8 year-old children. The jumping and control groups have participated in exercise intervention three times per week during school days. After seven months, the BMC at lumbar spine ($P < 0.05$) and the femoral neck ($P < 0.001$) and the BMD at the lumbar spine ($P < 0.01$) and bone area at femoral neck ($P < 0.001$) have significantly increased in the jumping group [73]. In another RCT [76], a 10 min jumping activity twice a week for eight months during adolescence seems to improve bone accrual in a sex-specific manner. The bone mass of the whole body has increased in boys, whereas the bone mass at the lumbar spine and hip has improved in girls.

The effect of socioeconomic status on BMD

Bone mass depends on the acquisition in childhood and decline in adulthood and can be influenced by socio-economic conditions throughout life [77]. Socioeconomic status (SES) is suggested to be associated with a variety of acute and chronic diseases, including osteoporosis [78,79]. However, the currently available literature has remained controversial [80–82]. Low SES has a strong and well-documented association with various adverse health outcomes and increases the risk of hip fracture in the elderly [83,84]. However, the association between low SES and femoral neck BMD, which is the main indicator of hip fracture risk, is not observed [85,86].

Overall, the findings are more consistent among Indian, Korean, and Australian women, in which women who have lower education and/or income usually have lower BMD [81,82,87]. For men, the results are relatively inconsistent [81,82,88]. An early study reported that

osteoporosis is a disease of men with higher SES in New Zealand [88], whereas another study in Australia has suggested no association between SES and BMD in men [82]. In Korean men, an association between low education and household income and low BMD is observed [81]. In 2013, Karlamangla *et al*. reported that socioeconomic advantage in childhood, which is independent of adult SES, is associated with great bone strength at the femoral neck [89]. Crandall *et al*. also reported that socioeconomic advantage in childhood, not current financial advantage, and higher adult education level are associated with higher adult lumbar spine BMD in 729 midlife adults in the United States [77].

The influence of age at menarche on bone mass

Menarche refers to the first menstrual period of women, which is the beginning of the female sexual cycle. Menarche is an important indicator of female puberty and a sensitive indicator for evaluating female growth and maturity. The early and delayed age of menarche may affect the health of adult women. For example, the early onset of menarche may increase the risk of type 2 diabetes [90] and breast [91] and endometrial [92] cancers. Studies have reported that menarche is an important sign of the rapid increase in BMD [93]. Early adolescence is an important period of female BMD growth, and women with early menarche have higher bone mass [93]. However, another study has shown that late menarche may be beneficial for adult bone strength when controlling prepubertal bone strength [94]. Therefore, from a clinical perspective, the relationship between menarche age and PBM should be studied.

Late menarche is regarded as a risk factor for osteoporosis as it possibly alters PBM achievement. Most studies have reported that late menarche is associated with lower BMD at several skeletal sites [94–96] and higher fracture risk for different skeletal sites [97–99]. Also, epidemiological studies have indicated that for the same reduced lifetime exposure to estrogen, individuals with late menarche have higher risk of fracture at spine, proximal femur, and forearm than individuals with early menopause [97–99]. Chevalley *et al*. [95] reported that subjects with later menarche age (14.0 years (0.7 sd)) has lower aBMD than those with earlier menarche age (12.1 years (0.7 sd)) in total radius, diaphysis, and metaphysis in 124 healthy women aged 20.4 years (0.6 sd), and LATER vs. EARLIER has shown lower total and cortical volumetric BMD and cortical thickness (CTh). Interestingly, Šešelj *et al*. [94] analyzed the data derived from serial hand-wrist radiographs of female participants and indicated that late menarche may lead to great bone diameter and strong bone strength, which may even result in lower BMC or BMD. The age of menarche also affects the occurrence of osteoporosis in postmenopausal women. A study including 243 postmenopausal women has found that 18% of the participants have osteoporosis, and individuals with menarche greater than 13 years tended to have osteoporosis (OR = 4.46; P = 0.035) [100].

The effect of calcium and vitamin D on bone growth

Calcium accounts for 1%–2% of adult human body weight, and more than 99% of the total body calcium can be found in bones and teeth [101]. The transepithelial calcium absorption is initiated with calcium entry into the epithelial cells from the intestinal luminal through the calcium-permeable channels, and this process is strongly supported by vitamin D action [102]. The vitamin D endocrine system plays an important role in maintaining the extracellular fluid calcium concentration and bone homeostasis [103]. Usually, the vitamin D status is assessed by measuring the serum 25-hydroxyvitamin D (25-OHD) concentration, and vitamin D deficiency is diagnosed by measuring the serum 25-OHD [104]. Calcium and vitamin D are the main nutritional interventions to prevent and treat osteoporosis [105]. However, vitamin D deficiency is a global health problem and considered as common in elderly, children, and adults [106]. For example, severe vitamin D deficiency (serum level of 25-OHD below 15 nmol/L or 6 ng/mL) leads to rickets in children and osteomalacia in adults.

In a 12-month randomized double-blind study, Dibba *et al*. assessed the effect of calcium supplementation on forearm BMC in 80 girls and 80 boys (aged 8.3–11.9 years) who are adjusted for height, weight, and bone width and determined that the group with calcium supplementation has higher BMC and BMD at the distal radius and midshaft compared with the control group [107]. Another randomized study lasting 13 months identified that the intervention in boys aged 16–18 years with calcium carbonate supplementation (1000 mg calcium/day) has resulted in greater BMC in different sites, including the whole body, lumbar spine, hip, and intertrochanter, compared with the control group with placebo [108]. Ho *et al*. undertook a 1-year follow-up study among 104 Chinese girls receiving 600 mg calcium/day in 375 mL soymilk and 95 girls aged 14–16 years as control and found a percentage increase (45%–113%) in intertrochanter BMD, trochanter BMD, total hip BMD, and total hip BMC in the supplementation group compared with the control group [109]. However, another trial in 96 girls, with mean age of 12 years supplied with 792 mg calcium/day for 18 months, is observed with gains in BMD and BMC in total body, lumbar spine, and total hip, but gains in BMC and BMD do not exist after 42 months, suggesting a short-term effect [110]. In a 2-year trial of milk intervention with and without 5 or 8 mg vitamin D_3 (cholecalciferol) among 757 Chinese girls, Du *et al*. reported that individuals receiving additional vitamin D_3 has greater increase in the

change in total body BMD and BMC compared with those only receiving milk [111].

In a meta-analysis [112] including six studies with 541 individuals receiving vitamin D and 343 receiving placebo aged 1 month to 20 years, Winzenberg *et al*. reported that vitamin D supplementation affects the BMD increase at the lumbar spine, but not at the total hip and the forearm. Individuals with vitamin D deficiency can benefit from vitamin D supplementation, particularly in lumbar spine BMD and total body BMC, but the benefit no longer exists in children and adolescents with normal vitamin D levels [112]. In a 1-year trial, 179 girls (aged 10–17 years) are randomly assigned into three groups (oral vitamin D doses of 200 IU/day or 2000 IU/day and oral placebo). Results show that hip BMC and bone area have increased in the high-dose group, and the BMD and/or the BMC at several skeletal sites have increased significantly in both supplementation groups in premenarcheal girls ($P < 0.05$), but no significant change in BMD or BMC in postmenarcheal girls is observed [113]. Another study performed among 50 Indian underprivileged adolescent girls (aged 14–15 years) has shown that vitamin D supplementation (7.5 mg ergocalciferol, 4 times/year) can increase the total BMD and bone area in individuals who are within 2 years of menarche, but not in those who are $\geqslant$ 2 years postmenarche [114]. Al-Shaar *et al*. [115] investigated the effect of weekly vitamin D_3 supplementation (1400 and 14 000 IU) on the hip geometric dimensions in 338 boys and girls (mean age at approximately 13 years) for over one year and found that vitamin D supplementation increases aBMD (7.9% for low doses, 6.8% for high doses, and 4.2% for placebo) and reduces the buckling ratio of the narrow neck (6.1% for low doses, 2.4% for high doses, and 1.9% for placebo). Conversely, no significant change in any parameter of interest in boys has been observed [115].

The effect of smoking and alcohol on BMD

Tobacco contains a variety of compounds. Most of these compounds are harmful to humans, and nicotine is the most abundant and most toxic substance. Nicotine changes the permeability of the blood vessel wall, hinders the exchange of substances inside and outside the blood vessels, leading to ineffective absorption and utilization of nutrients, such as protein and calcium. Other toxic substances in tobacco also increase the acidity of the blood and promote the dissolution of bones [116]. The pathogenesis of alcohol-induced osteoporosis is not completely clear, and the effect of alcohol on the bone is believed to be through direct and indirect actions [117]. The direct effect of alcohol on the activity of bone cells is the inhibition of the growth of marrow mesenchymal stem cells and its transformation into osteoblasts [118]. Nevertheless, elucidating the mechanism of the influence of alcohol on bone metabolism is complicated because the effects of alcohol on different organs (including bone) depend on the time profile and the extent of alcohol exposure.

In a study with 1068 young men (mean age = 18.9 years), Lorentzon *et al*. [119] reported that smoking for an average of four years is significantly associated with lower aBMD (between -1.8% and -5.0%) and lower cortical thickness (–2.9% to –4.0%) depending on skeletal sites. In another prospective study of females aged 11–19 years, Dorn *et al*. reported that individuals who smoke frequently have lower rate of BMD accrual at the lumbar spine and the total hip [120]. A 5-year longitudinal study including 833 young men aged 18–20 years has shown that the individuals who started to smoke since baseline have substantially smaller increases in aBMD at the total body ($P < 0.01$) and lumbar spine ($P = 0.04$) and considerably greater decreases in aBMD at the total hip ($P < 0.01$) and femoral neck ($P < 0.01$) than individuals who did not smoke at baseline and follow-up stage [121]. Some studies have investigated the relationship between alcohol intake and PBM in the late adolescence and young adulthood stages, and the results are inconsistent. Some studies suggest that alcohol intake has a significant negative association with BMD [121,122], whereas others suggested that alcohol intake has a significant positive association with BMD [123]. Some studies found no association between alcohol intake and bone outcomes [120,124]. Lucas *et al*. observed a significant association between low BMD (Z-score < -1) in late adolescence and having ever smoking and drinking by age of 13 years (OR = 2.33) after adjusting for menarche age and sports practice [125]. However, a study among 723 healthy young male soldiers has shown that soldiers who had moderate alcohol consumption have high BMD ($P \leqslant 0.015$) [126].

Secondary causes of bone loss

Many clinical conditions affecting young people (Table 2) can be associated with the loss of bone mass and quality, leading to an increased risk of fracture throughout life. In this review, some common conditions that can lead to bone loss and their underlying mechanisms are summarized.

Endocrine states

Endocrine states, such as glucocorticoid osteoporosis, growth hormone deficiency, diabetes, and primary hyperparathyroidism, are common secondary causes of osteoporosis and low BMD. The main feature in the pathogenesis of glucocorticoids on bone loss is that glucocorticoids decrease the number and function of osteoblasts, leading to the suppression of bone formation and enhancement of the activity of osteoclasts [127]. During the period of initial exposure to glucocorticoids,

Table 2 Main conditions potentially causing an altered bone density in childhood and young people

Chronic and inflammatory	Malabsorption syndromes	**Iatrogenic causes**	**Medications**	**Neuromuscular and metabolic**
Inflammatory bowel disease	**Endocrine**	Corticosteroids	Glucocorticoids	Duchenne
Celiac disease	Diabetes type I	Anticonvulsants	PPIs (chronic use)	Gaucher's disease
Nephropathies	Hypovitaminosis D	Gonadotropin-releasing hormone analogue	Anticonvulsants	Hemochromatosis
Cystic fibrosis	Hypogonadism (amenorrhea, Turner, anorexia nervosa)	L-thyroxine (high dose)	Aromatase inhibitors, depot MPA	Galactosemia
(Juvenile) rheumatoid arthritis	Cushing's syndrome	Antiretroviral drugs	High-dose thyroxine	Glycogen storage disease
Systemic mastocytosis	Primary hyperparathyroidism	Anticoagulants	Cytotoxic chemotherapy	Marfan syndrome
Malabsorption	Primary hypoparathyroidism	Chemotherapeutic drugs	Glitazones	**Others**
HIV	Panhypopituitarism; GH deficiency	Aromatase inhibitor	Cyclosporine (tacrolimus)	Immobilization/little use
Organ transplant	McCune Albright syndrome	**Nutritional problems**	GnRH inhibitors	Intense physical activity
Connective tissue diseases	**Hormonal causes**	Nervous anorexia	Heparin (long-term)	Post-transplant
Thalassemia	Premature menopause or premature ovarian insufficiency	Lactose intolerance	HAART	Paget's disease of youth
Leukemia	Athletic amenorrhea	Deficiency of calcium and copper	**Malignancies**	Juvenile idiopathic osteoporosis
Alcohol-related liver diseases	Pregnancy	Vegetarian diets	Leukemia	Prematurity
Pancreatic insufficiency	Estrogen deficiency	Malnutrition	Lymphoma	
Gastrectomy	Insensitivity syndrome of estrogen	Total parenteral nutrition	Solid tumors	

glucocorticoids can enhance the expression of RANKL and the macrophage colony stimulating factor, which are the necessary factors for osteoclast formation, leading to an increase in bone resorption [127]. In addition, other indirect actions mediating the increase in bone resorption and decrease in bone formation are reported. For example, glucocorticoids decrease the expression of insulin-like growth factor 1 (IGF-1) and sex steroids, leading to suppression of bone formation and enhancement of bone resorption, respectively. Meanwhile, glucocorticoids reduce calcium absorption from the intestines by inhibiting vitamin D actions and inhibit renal tubular calcium reabsorption to enhance bone resorption [127].

The optimal levels of growth hormone, IGF-1, thyroid hormone, and gonadal sex steroids are essential for the completion of normal skeletal growth, puberty, and bone mineral accrual. Growth hormone deficiency is associated with delayed skeletal maturation and low BMD mainly through reduced bone formation [128]. Another example of the endocrine causes of low BMD on the young individuals is type 1 diabetes mellitus, which is one of the common endocrine pediatric diseases. The pathogenesis of diabetes-related osteoporosis is complicated and mainly includes calcium, vitamin D metabolism, and insulin abnormalities, resulting in low blood calcium and low blood phosphorus, which cause the loss of basic materials for bone formation. At the same time, hyperglycemia may stimulate the formation of excessive cytokines, such as IL-1 and IL-6, reduce the OPG/RANKL ratio, further promote the formation and activity of osteoclasts, and inhibit the differentiation and mineralization of osteoblasts [129]. Primary hyperparathyroidism is associated with an increase in the expression of RANKL by cells of the osteoblast lineage and an increase in osteoclast-mediated bone resorption [130].

Gastrointestinal and nutritional conditions

Multiple nutrients are needed in bone growth, development, and maintenance. Disorders resulting from nutrient deficiency, especially malnutrition calcium deficiency during childhood and adolescence, may affect the attainment of normal PBM. Celiac disease, in children, is associated with bone loss because of nutritional deficiency and malabsorption [131,132]. Decreased calcium absorption and an increase in the levels of inflammatory cytokines, including IL-1, IL-6, and TNF-α, may be responsible for the increase in bone resorption [133]. Inflammatory bowel diseases (IBDs), consisting of ulcerative colitis and Crohn's disease, are associated with bone loss. The mechanisms responsible for the bone loss in IBD include disease-related inflammatory activity and treatment-related side effects, including glucocorticoid therapy and nutritional deficiencies, leading to low body mass index and contributing to hypogonadism [134]. Anorexia nervosa is associated with weight loss, low BMD, and risk of fracture [135]. Also, the serum markers of bone formation are suppressed and the markers of bone resorption are increased, suggesting that bone formation is uncoupled from bone resorption [130].

Autoimmune disorders

The immune system and immune factors play an important role in the development of osteoporosis. For example, rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), and multiple sclerosis (MS) can lead to bone loss. RA is a common rheumatic disease, and the underlying disease activity and ongoing use of glucocorticoids can contribute to bone loss and risk for fractures. Cytokines, such as TNF-α and IL-1, can promote osteoclastic activity. Increased RANKL/OPG ratio and elevated bone turnover markers and sedimentation rate are predictors of rapid and persistent bone loss in patients with RA [136]. The mechanism of bone loss in AS is multifactorial. One factor is systemic inflammation, which increases the expression of RANKL. RANKL combines with the RANK receptor on the surface of osteoclast precursor cells, promoting osteoclast differentiation and maturation [137]. Mature osteoclasts secrete proteolytic enzymes and hydrochloric acid, which play a role in bone absorption that eventually leads to bone resorption and bone mass reduction, even osteoporosis [137]. Osteoclast-inducing inflammatory cytokines, such as IL-1, IL-6, soluble IL-6 receptor, and TNF-α, are elevated in patients with SLE and contribute to bone loss [130]. MS is a chronic inflammatory-demyelinating central nervous system disease that usually affects young adults [130,138] and reduces the physical inactivity and the mechanical load on the bones, which may be the major contributing factors for bone loss or osteoporosis [139].

Renal diseases

Hypercalciuria is related to low bone density and increased incidence of fracture and characterized by increased bone absorption, increased intestinal calcium absorption, and decreased renal tubular calcium reabsorption, which results in net calcium loss [140]. Individuals with chronic kidney disease (CKD) have a high prevalence of Klotho deficiency and low expression of Klotho, resulting in increased fibroblast growth factor (FGF23) levels [141]. Klotho deficiency enhances osteoblast activity while increasing the expression of FGF23 that suppresses osteoblast differentiation. Thus, the role of Klotho on the bone at different stages of CKD is still unknown [141]. Renal tubular acidosis is characterized by normal anion gap and hyperchloremic metabolic acidosis [142]. When

the hydrogen ion load is greater than the normal daily acid load, the bone buffers the hydrogen ions, which may result in a spectrum of metabolic bone disorders ranging from osteomalacia to osteoporosis and fractures [142]. Defective renal acidification may lead to an osteoblast-mediated activation of osteoclasts and a compensatory mobilization of alkali and calcium from the bone, resulting in bone loss [130]. In the cortical collecting tubule, calcium reabsorption is also reduced, resulting in renal calcium unbalance and bone loss [130].

Drug-induced bone loss

Drug-induced osteoporosis is a common type of secondary osteoporosis. Glucocorticoids are the most common cause of drug-induced osteoporosis (See the section of "Endocrine states"), and other drugs, such as proton pump inhibitors (PPIs), heparin, and anticonvulsants, also affect bone metabolism. PPIs are used for the disorders of the upper gastrointestinal tract. By increasing gastric pH, PPIs may decrease calcium absorption and induce negative effects on skeletal homeostasis [130]. As an effective drug for the treatment of thromboembolic disorders, heparin bound to OPG, the decoy receptor for RANKL, allows RANKL to induce osteoclastogenesis, which leads to enhanced bone resorption [130]. Anticonvulsants may cause bone loss, but the mechanisms are not clear. Anticonvulsants may accelerate vitamin D metabolism and can lead to low 25-OHD levels, high bone turnover, and secondary hyperparathyroidism, increasing the risk of bone loss [143].

Perspectives

PBM is obtained in early adulthood and affected by puberty developmental status. Genetics has a huge effect on BMD (especially PBM), but other factors also play very important roles. Factors, such as heredity, race, gender, age, and puberty development, are difficult to modify at present, but other factors, such as weight, nutrition, lifestyle (such as smoking and drinking), and physical activity, can be intervened. As environmental and behavioral factors account for 20%–40% of adult PBM, optimizing the factors associated with PBM and bone structure is a very important strategy for improving the bone accrual and strengthening the bone structure to decrease the risk of osteoporosis/fracture in later life. As the primary modifiable factors, diet and nutrition (e.g., calcium and vitamin D), physical activity, and exercise should be given more attention. More studies should be conducted to investigate the intensity, frequency, duration, and mode of physical activity in the future. Approximately 11 000 Chinese young individuals aged 15–25 years have been collected for follow-up to investigate the association of lifestyle and nutritional intake with bone mass gain.

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Compliance with ethics guidelines

Xiaowei Zhu and Houfeng Zheng declare that they have no conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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