HHS Public Access

Author manuscript

Bone. Author manuscript; available in PMC 2018 December 18.

Published in final edited form as:

Bone. 2018 November ; 116: 301–306. doi:10.1016/j.bone.2018.08.021.

Assessing the genetic correlations between early growth parameters and bone mineral density: A polygenic risk score analysis

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Abstract

Objective: The relationships between early growth parameters and bone mineral density (BMD) remain elusive now. In this study, we performed a large scale polygenic risk score (PRS) analysis to evaluate the potential impact of early growth parameters on the variations of BMD.

Methods: We used 2286 Caucasian subjects as cohort 1 and 3404 Framingham Heart Study (FHS) subjects as cohort 2 in this study. BMD at ulna & radius, hip and spine were measured using dual energy X-ray absorptiometry. BMD values were adjusted for age, sex, height and weight as covariates. Genome-wide single-nucleotide polymorphism (SNP) genotyping of the 2286 Caucasian subjects was performed using Affymetrix Human SNP Array 6.0. The GWAS datasets of early growth parameters were driven from the Early Growth Genetics Consortium, including birth weight (BW), birth head circumference (BHC), childhood body mass index (CBMI), pubertal height growth related indexes and tanner stage. Polygenic Risk Score (PRSice) and linkage disequilibrium (LD) score regression analysis were conducted to assess the genetic correlation between early growth parameters and BMD.

Results: We detected significant genetic correlations in cohort 1, such as total spine BMD vs. CBMI (p value = 1.51×10^{-4}, $rg = 0.4525$), right ulna and radius BMD vs. CBMI (p value = 1.51×10^{-4}, $rg = 0.4399$) and total body BMD vs. tanner stage (p value = 7.00×10^{-4}, $rg = -0.0721$). For cohort 2, significant correlations were observed for total spine BMD vs. height change

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Conflicts of interest

None.

standard deviation score (SDS) between 8 years and adult (denoted as PGF + PGM) (p value = 3.97×10^{-4}, rg = −0.1425), femoral neck BMD vs. the timing of peak height velocity by looking at the height change SDS between age 14 years and adult (denoted as PTF + PTM) (p value = 7.04×10^{-4}, rg = −0.2185), and total spine BMD vs. PTF + PTM (p value = 6.86×10^{-4}, rg = −0.2180).

Conclusion: Our study results suggest that some early growth parameters could affect the variations of BMD.

Keywords

Osteoporosis; Early growth parameters; Polygenic risk score

1. Introduction

Osteoporosis is a metabolic bone disease characterized by decreased bone mineral density (BMD) and increased risk of fragility fractures. With the increase of elderly people, osteoporosis has become a serious public health problem worldwide, which leads to heavy burden on the health care system and society. Previous studies reported that osteoporosis affected up to 75 million individuals in Europe, Japan and the United States [1]. It was estimated that genetic factors accounted for approximately 50% to 85% of the variance of the BMD [2]. Extensive genetic studies of osteoporosis have identified a group of genetic loci associated with the variations of BMD [2–4]. However, the genetic mechanism of BMD still remains elusive.

Previous studies have observed significant correlations between early growth parameters and the BMD. For instance, multiple studies found that birth weight (BW) was significantly associated with BMD [5–8]. In addition, the BMD at lumbar spine and femoral neck was positively correlated to body mass index (BMI) [9]. Pubertal height also had a significant relationship with the variation of the BMD of lumbar spine in boys [10]. However, the biological mechanism of the observed effects of the early growth parameters on the variations of BMD is not well understood. To the best of our knowledge, limited efforts have been paid to evaluate the potential genetic relationships between early growth parameters and BMD.

Extensive genetic studies of the early growth parameters have been conducted [11–15]. Genetic factors appear to play important roles in the development of early growth parameters [13]. For instance, it has been demonstrated that the heritability of height and BMI were maintained at approximately 30% after puberty [13]. Recent genome wide association studies (GWAS) identified multiple genetic loci associated with birth weight [11,12]. BMI increases progressively from adolescence to young adulthood. It has been found that adolescent BMI is highly heritable (70–90%) [14]. The BMI transition from adolescence to young adulthood was best described by a quadratic trajectory that was highly accounted (61.7–86.5%) by additive genetic influences [14]. Additionally, twin studies have shown that breast size is about 56% heritable [15].

Polygenic risk score (PRS) is a sum of risk alleles, typically weighted by their effect sizes estimated from GWAS [16]. By utilizing identified disease loci, PRS analysis can explore

the genetic relationships among various complex diseases and traits [16]. It has been successfully applied to multiple complex diseases, such as sporadic early-onset Alzheimer's disease [17] and breast cancer [18]. Recently, multiple GWAS of the early growth parameters have identified a group of genetic loci associated with the early growth parameters [19–28]. These study results provide an opportunity to systematically evaluate the relationships between early growth parameters and BMD by utilizing PRS approach.

In this study, we conducted a PRS analysis to evaluate the potential genetic correlations between BMD and early growth parameters in 2286 Caucasian subjects as cohort 1, followed by a repeated analysis in 3404 Framingham Heart Study (FHS) subjects as cohort 2. Our study results provided novel clues for understanding the mechanism of the early growth parameters affecting the variation of BMD.

2. Materials and methods

2.1. Caucasian subject samples for osteoporosis

A total of 2286 unrelated Caucasian subjects living in Kansas City and its surrounding areas were used here, including 558 males and 1728 females [29]. Comprehensive exclusion criteria were applied to control potential confounding effects on the variation of bone mass. We excluded the subjects with chronic disorders involving vital organs (heart, lung, liver, kidney and brain), serious metabolic diseases and nutritional diseases. BMD at total body, hip, spine and ulna & radius were measured using Hologic 4500W dual energy X-ray absorptiometry (Hologic Inc., Bedford, MA, USA). Single nucleotide polymorphism (SNP) genotyping was performed using Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA, USA). The arrays were scanned using GeneChip Scanner 3000 7G. The Institutional Review Board of University of Missouri-Kansas City approved this study Inform-consent documents were signed by all participants before participating this study [29].

2.2. FHS study samples of osteoporosis

The PRS analysis of the BMD and the early growth parameters was further repeated in the FHS samples, which consisted of 3404 Caucasian subjects. The genotype and phenotype data of FHS samples were downloaded from the dbGaP database (http://view.ncbi.nlm.nih.gov/dbgap). Briefly, the BMD values of hip and spine were measured by dual X-ray absorptiometry machine (Lunar DPX-L). Genome-wide genotyping were performed using Affymetrix500K mapping array plus Affymetrix 50 K supplementary array. Two genotype sets were merged together to form a single dataset of ~550,000 SNPs in order to maximize the genotype coverage. Detailed information of the study design and sample recruitments has been described in a previous study [30].

2.3. GWAS summary dataset of birth weight (GWAS-BW)

Data of BW, available in three large-scale GWAS meta-analyses, were downloaded from http://www.egg-consortium.org/ [19–21], including 153,781 individuals in total. Briefly, BWs were self-reported in adulthood or collected from medical records. Genome-wide SNP genotyping was carried out using high-density SNP arrays, such as Affymetrix Genome-

wide Human SNP Array 6.0, Illumina 550 K Infinium, Illumina 317 and Affymetrix 500 K. Inverse variance fixed-effects metaanalyses were undertaken using METAL (2009-10-10 release) [31] and GWAMA (version 2.0.6) [32] tools. Finally, 16,245,523 SNPs were used for the genetic correlation analysis in this study. Detailed description of sample characteristics, experimental design, statistical analysis and quality control can be found in the previous studies [19–21].

2.4. GWAS summary dataset of birth head circumference (GWAS-BHC)

Data of birth head circumference (BHC) of a large GWAS metaanalysis was used in this study [22,23]. Briefly, this study included 10,768 individuals of European ancestry, enrolled in pregnancy and/or birth cohort (median age range of 11–18 months). The BHC was measured manually in infancy. Genome-wide SNP genotype data were obtained using high-density SNP arrays, such as Illumina 317 and 610 K, Ilumina 610 Quad array, Illumina 660 Quad array and Affymetrix Human SNP Array 5.0. Meta-analysis was performed using the inverse-variance method under fixed-effect model. Finally, 2,449,806 SNPs were used for the genetic correlation analysis in this study. Detailed description of sample characteristics, experimental design, statistical analysis and quality control can be found in the previous studies [22,23].

2.5. GWAS summary dataset of childhood BMI (GWAS-CBMI)

Values of childhood BMI from a large GWAS meta-analysis was used here [24]. Briefly, this GWAS study included 35,668 children from 20 studies. In some studies, weight and height, as well as age at measurement time, were collected retrospectively from participants' medical records during recruitment. The BMI was calculated as weight (kg)/height (m^2). In others studies, the weight and the height were measured without shoes and in light clothing at research center, or data were obtained from health clinic registers. All the included children were of European ethnic origin. Genotyping was conducted using high-density Illumina or Affymetrix SNP arrays. Fixed-effects inverse variance meta-analysis was conducted. Finally, 2,499,691 SNPs were used for the genetic correlation analysis in this study. Detailed description of sample characteristics, experimental design, statistical analysis and quality control can be found in the previous study [24].

2.6. GWAS summary dataset of pubertal growth (GWAS-PG)

A large scale GWAS meta-analysis results of pubertal height and growth was used in this study [25], which consisted of 18,737 European subjects. Briefly, the study analyzed three primary phenotypes, defined as follows. First, they targeted the take-off phase of the growth spurt [height standard deviation score (SDS) at 10 years in girls and 12 years in boys, denoted as 10F + 12 M]. Second, they assessed the overall contribution of growth across puberty to adult height (height change SDS between 8 years and adult, denoted as PGF + PGM) that reflects the total magnitude of growth during the pubertal growth spurt. Finally, they approximated the timing of peak height velocity by looking at the height change SDS between age 14 years and adult (denoted as PTF + PTM). The study subjects were driven from the cohorts participating in the Early Growth Genetics Consortium [21]. Commercial platforms were used for genome-wide SNP genotyping, such as high-density SNP arrays on Illumina and Affymetrix platforms. A fixed effects inverse-variance meta-analysis model

was used to test the effect of each variant on pubertal growth. Finally, 2,479,699 SNPs were used for the genetic correlation analysis of 10F + 12 M, 2,384,831 SNPs for PGF + PGM, and 2,401,289 SNPs for PTF + PTM in this study. Detailed description of sample characteristics, experimental design, statistical analysis and quality control can be found in the previous study [25].

2.7. GWAS summary dataset for Tanner stage (GWAS-TS)

A large scale GWAS meta-analysis results of Tanner stage (early pubertal traits, male genital and female breast development) was used in this study [26]. Briefly, this study comprised of over 11,000 European samples. Tanner stage was assessed by a clinician researcher, or it was based on self-reports using pictures or schematic drawings. Tanner stage was measured by self-assessment in the Avon Longitudinal Study of Parents and Children (ALSPAC), the Western Australian Pregnancy cohort (Raine) and TEENAGE studies. Genotyping was conducted using high-density Illumina or Affymetrix SNP arrays. Meta-analysis of individual cohort results was performed using GWAMA version 2.0.5 [32]. Finally, 2,183,192 SNPs were used for the genetic correlation analysis in this study. Detailed description of sample characteristics, experimental design, statistical analysis and quality control can be found in the previous study [26].

2.8. GWAS summary dataset for adult BMI (ABMI)

Data of the adult BMI (ABMI) from GWAS was used here [27], which consisted of 1,339,224 individuals. Briefly, the BMI, measured or self-reported weight in kg per height in meters squared was adjusted for age, age squared, and any necessary study-specific covariates in a linear regression model. The resulting residuals were transformed to approximate normality using inverse normal scores. Genotyping was conducted using Metabochip, a custom genotyping array for genetic studies of metabolic, cardiovascular, and anthropometric studies [33]. Fixed effects meta-analyses were conducted using the inverse variance-weighted method implemented in METAL [31]. Finally, 2,554,637 SNPs were used for the genetic correlation analysis in this study. Detailed description of sample characteristics, experimental design, statistical analysis and quality control can be found in the previous study [27].

2.9. GWAS summary dataset for adult height

Data of adult height from a large scale GWAS meta-analysis was used [28]. Briefly, this study consisted of 253,288 individuals of European ancestry. Commercial platforms were used for genome-wide SNP genotyping, such as Metabochip array [33] and Illumina's Metabochip array. A total of 2,550,858 SNPs were meta-analyzed using inverse variance fixed effects method. Meta-analysis was performed as described for the standard GWAS. Finally, 2,471,733 SNPs were used for the genetic correlation analysis in this study. Detailed description of sample characteristics, experimental design, statistical analysis and quality control can be found in the previous study [28].

2.10. Statistical analysis

For the cohort 1 and cohort 2, the SNPs with Hardy-Weinberg equilibrium (HWE) testing p values < 0.0001, minor allele frequencies (MAF) < 0.01 and genotyping call rate < 95% were excluded. Finally, 753,382 SNPs were used for the 2286 Caucasian subjects and 443,430 SNPs were used for the FHS samples. Using linear regression model, the raw BMD values were first adjusted for age, sex, height and weight as covariates [34–36]. The residues from linear regression were then used as the phenotypic values of BMD for genetic correlation analysis [34]. Genetic correlation analysis of BMD with BW, BHC, CBMI, 10F + 12 M, PGF + PGM, PTF + PTM and TS were conducted by the Polygenic Risk Score (PRSice) software [16] (https://github.com/choishingwan/PRSice), respectively. All the SNPs in the GWAS were included in the genetic correlation analysis. There are totally 63 statistical tests (9 BMD traits × 7 early growth parameters) in this study. After Bonferroni correction, the significant genetic correlations were identified at p value < 7.9×10^{-4} (0.05/63). In addition, linkage disequilibrium (LD) score regressions [37] were used to estimate the genetic correlation coefficients between early growth parameters and BMD. Using the LD score regression, we also evaluated the genetic correlation of ABMI vs. CBMI, adult height vs. 10F + 12 M, adult height vs. PGF + PGM and adult height vs. PTF + PTM.

3. Results

After strict Bonferroni correction, we detected several genetic correlations between early growth parameters and BMD. For cohort 1, we observed genetic correlations between total body BMD and TS (p value = 7.00×10^{-4}, $rg = -0.0721$). For right ulna and radius BMD, the genetic correlations were observed for CBMI (p value = 1.51×10^{-4}, $rg = 0.4399$). For total spine BMD, they were observed for CBMI (p value = 1.51×10^{-4}, $rg = 0.4525$). We also detected several suggestive correlations, such as femoral neck BMD vs. CBMI (p value = 3.81×10^{-3}, $rg = 0.298$), total spine BMD vs. TS (p value = 3.86×10^{-3}, $rg = 0.746$) and total body BMD vs. PGF + PGM (p value = 4.66×10^{-2}, $rg = -0.5308$). The significant SNPs and the corresponding genes in the GWAS of cohort 1 are presented in Supplementary Table S1.

For cohort 2, we observed the genetic correlation between femoral neck BMD and PTF + PTM (p value = 7.04×10^{-4}, $rg = -0.2185$). For total spine BMD, the genetic correlations were observed for PTF + PTM (p value = 6.86×10^{-4}, $rg = -0.2180$) and PGF + PGM (p value = 3.97×10^{-4}, $rg = -0.1425$). Several suggestive correlations were also detected, such as total femur BMD vs. BHC (p value = 1.17×10^{-2}, $rg = 0.3074$) and femural trochanter BMD vs. PGF + PGM (p value = 2.26×10^{-3}, $rg = -0.2595$) (Tables 1 and 2). The LD score regression analysis results of ABMI vs. CBMI, adult height vs. 10F + 12M, adult height vs. PGF + PGM and adult height vs. PTF + PTM are summarized in Table 3.

4. Discussion

To reveal the potential genetic effects related to the early growth parameters on the development of osteoporosis, we conducted a PRS analysis using two independent cohorts. We observed several genetic correlations between early growth parameters and BMD,

mainly including BMD vs. pubertal growth factors and BMD vs. CBMI. Considering that adult BMD values have been adjusted for adult height and adult weight, the correlation analysis results generally represent the relationships between BMD and early growth parameters. Our study results may provide novel insight into the genetic architecture of BMD.

One important finding of this study is the disclosure of the pubertal growth parameters, which showed correlation evidence with the BMD. Puberty is a particularly crucial period, when the amount of bone mineral accrued is equal to the amount of bone mineral typically lost throughout later life [38]. The pubertal development plays a key role in bone acquisition [39]. The substantial impact of puberty on the BMD has been observed in both boys and girls [40]. The maximal BMD accrual occurs in the years surrounding the puberty. At least 90% of peak bone mass is acquired by age 18 [38]. Particularly the early puberty is a period of increased bone adaptation to mechanical loading due to the speed of bone growth and endocrine changes at this time [41]. It has been observed that the greatest difference in humerus bone mineral mass developed between mid and late puberty [38]. Based on previous and our study results, we suggest the important impact of the puberty on the development of the BMD. Further studies are warranted to confirm our findings and reveal the biological mechanism of the puberty-related factors affecting the variation of the BMD.

The positive effect of ABMI on the variation of the BMD has been reported in previous studies [9,42]. In this study, we also observed positive genetic correlation between the BMD and CBMI in the cohort 1 of this study. Childhood is crucial period for bone growth, accounting for about half of the bone mass achieved in adulthood [43]. Thus, CBMI can be used as a determinant for adult bone mass and the BMD values [44–46]. Obesity during childhood was associated with increased vertebral bone density and increased whole body bone mass [45]. Moreover, CBMI can predict bone mineral accrual and bone size positively and independently [44]. Additionally, we also observed the positive genetic correlation between ABMI and CBMI. In a previous study, the BMI levels among children and adolescents were variable [47]. The adult BMI predictor can explain a fraction of the genetic variations of CBMI [48]. There is evidence suggesting that CBMI and ABMI contribute to the development of osteoporosis independently. For instance, in a 20-year prospective study, researchers observed that increased skeletal loading by body weight in childhood led to an increase in peak bone mass independent of current ABMI [46].

Notably, for BW, suggestive correlations were observed for total hip BMD and total body BMD in cohort 1 and for femoral neck BMD in cohort 2. In a large national cohort of female twins, intra-pair differences in BW were significantly associated with BMD at the spine, total hip and femoral neck [5]. It also has been demonstrated that young adults born prematurely at very low BW (< 1500 g) would have lower femoral neck and total body BMD than do their term-born peers with normal BW in Finland [8]. Further studies are needed to confirm our study results.

We observed that TS were associated with total body BMD, similarly to a previous study [49]. Another study observed that BMD values were significantly associated with different Tanner's pubertal stage [50]. In addition, we observed suggestive genetic correlations

between BHC and total hip BMD in cohort 1, and between BHC and total femur BMD in cohort 2. Interestingly, among Turkish infants it has been identified that the BMD can be affected by BHC [51].

There are three limitations of this study that should be noted. First, the early growth parameters associated with SNPs sets were driven from previous GWAS [19–28]. The accuracy of our correlation analysis may be affected by the power of previous GWAS of the early growth parameters. Second, all study subjects were Caucasian subjects in this study. Due to different genetic background, our study results should be interpreted with caution when applied to other populations. Last, lack of a replication cohort is an important limitation of this study. Further studies with other independent samples and biological studies are needed to confirm our findings.

In summary, utilizing PRS analysis, we evaluated the impact of the early growth parameters on the variations of the BMD in 2286 Caucasians subjects and 3404 FHS subjects. We observed genetic correlations between the early growth parameters and the variations of BMD. We hope that our study results could provide novel clues for the pathogenic and therapic studies of osteoporosis.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2018.08.021.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

This study was partially supported by the National Natural Scientific Foundation of China (81472925, 81673112), and the Technology Research and Development Program of in Shaanxi Province of China (2013KJXX-51), and the Fundamental Research Funds for the Central Universities. QT, HS and HWD were partially supported by grants from the National Institutes of Health (R01AR057049, R01AR059781, D43TW009107, P20 GM109036, R01MH107354, R01MH104680, R01GM109068), the Edward G. Schlieder Endowment fund and the Tsai and Kung endowment fund to Tulane University. The Framingham Heart Study and the Framingham SHARe project were conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the Boston University. The Framingham SHARe data used for the analyses described in this manuscript were obtained through dbGaP (accession numberphs000007.v3.p2). This manuscript was not prepared in collaboration with investigators of the Framingham Heart Study and does not necessarily reflect the opinions or views of the Framingham Heart Study, Boston University, or the NHLBI.

Formatting of funding sources

This work was partially supported by the National Natural Scientific Foundation of China [grant numbers 81472925, 81673112]; and the Technology Research and Development Program of in Shaanxi Province of China [grant numbers 2013KJXX-51] and the Fundamental Research Funds for the Central Universities. QT, HS and HWD were partially supported by grants from the National Institutes of Health [grant numbers R01AR057049, R01AR059781, D43TW009107, P20 GM109036, R01MH107354, R01MH104680, R01GM19068], the Edward G. Schlieder Endowment fund and the Tsai and Kung endowment fund to Tulane University.

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Table 1

The genetic correlation analysis *p* values between early growth parameters and bone mineral density.

	Traits	BW	BHC	CBMI	10F + 12M	PGF + PGM	PTF + PTM	TS
Cohort 1	Total body BMD	2.73×10^{-2}	-	9.18×10^{-4}	-	4.66×10^{-2}	6.79×10^{-3}	7.00×10^{-4}
	Total hip BMD	4.87×10^{-2}	9.09×10^{-3}	4.43×10^{-2}	-	-	-	-
	Femoral neck BMD	-	4.49×10^{-2}	3.81×10^{-3}	3.51×10^{-3}	-	-	2.52×10^{-2}
	Right ulna and radius BMD	-	-	1.51×10^{-4}	-	1.08×10^{-2}	1.91×10^{-2}	1.51×10^{-2}
	Total spine BMD	-	-	1.51×10^{-4}	2.13×10^{-2}	4.35×10^{-2}	3.87×10^{-3}	3.86×10^{-3}
Cohort 2	Total femur BMD	3.50×10^{-2}	1.17×10^{-2}	-	-	4.20×10^{-3}	6.17×10^{-3}	-
	Femoral neck BMD	3.59×10^{-2}	-	-	4.78×10^{-2}	4.66×10^{-3}	7.04×10^{-4}	-
	Femural trochanter BMD	3.80×10^{-2}	-	-	3.22×10^{-2}	2.26×10^{-3}	-	-
	Total spine BMD	-	-	-	1.43×10^{-2}	3.97×10^{-4}	6.86×10^{-4}	-

Note. BMD, bone mineral density. BW, Birth weight. BHC, Birth Head Circumference. CBMI, Childhood body mass index. 10F + 12M, the take-off phase of the growth spurt height standard deviation score SDS at 10 years in girls and 12 years in boys. PGF + PGM, the overall contribution of growth across puberty to adult height change SDS between 8 years and adult. PTF + PTM, the timing of peak height velocity by looking at the height change SDS between age 14 years and adult. TS, Tanner stage. ABMI, Adult body mass index. A-Height, Adult Height. The *p* values were calculated by PRSice. Only the *p* values < 0.05 were included in this table.

Table 2

The genetic correlation coefficients between early growth parameters and bone mineral density.

	Traits	BW	BHC	CBMI	10F + 12 M	PGF + PGM	PTF + PTM	TS
Cohort 1	Total body BMD	0.0913	-	0.3876	-	−0.5308	−0.4067	−0.0721
	Total hip BMD	−0.028	−0.0241	0.0801	-	-	-	-
	Femoral neck BMD	-	−0.1065	0.2980	0.1736	-	-	0.0681
	Right ulna and radius BMD	-	-	0.4399	-	−0.5462	−0.2309	0.0901
	Total spine BMD	-	-	0.4525	0.0810	−0.2178	−0.3106	0.7460
Cohort 2	Total femur BMD	−0.0803	0.3074	-	-	−0.1899	−0.2003	-
	Femoral neck BMD	−0.0153	-	-	0.1194	−0.1518	−0.2185	-
	Femural trochanter BMD	−0.1680	-	-	0.1863	−0.2595	-	-
	Total spine BMD	-	-	-	0.2068	−0.1425	−0.2180	-

Note. BMD, bone mineral density. BW, Birth weight. BHC, Birth Head Circumference. CBMI, Childhood body mass index. 10F + 12M, the take-off phase of the growth spurt height standard deviation score SDS at 10 years in girls and 12 years in boys. PGF + PGM, the overall contribution of growth across puberty to adult height change SDS between 8 years and adult. PTF + PTM, the timing of peak height velocity by looking at the height change SDS between age 14 years and adult. TS, Tanner stage. The genetic correlation coefficients with p values < 0.05 were included in this table.

Table 3

The LD score regression analysis results of early growth parameters and corresponding adult traits.

	Coefficients	*p* value
ABMI vs. CBMI	0.7435	2.48×10^{-99}
Adult height vs. 10F + 12M	0.7274	6.62×10^{-67}
Adult height vs. PGF + PGM	0.5303	4.31×10^{-23}
Adult height vs. PTF + PTM	0.2088	0.0008

Note: 10F + 12M, the take-off phase of the growth spurt height standard deviation score SDS at 10 years in girls and 12 years in boys; PGF + PGM, the overall contribution of growth across puberty to adult height change SDS between 8 years and adult; PTF + PTM, the timing of peak height velocity by looking at the height change SDS between age 14 years and adult; ABMI, adult body mass index; CBMI, childhood body mass index.