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Long-term childhood body mass index and adult bone mass are linked through concurrent body mass index and body composition

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ABSTRACT

Body mass plays a crucial role in the bone growth and development, but few studies have examined the association of long-term cumulative impact and trajectory patterns of childhood body mass index (BMI) with adult bone mass, and the mediation effect of adult BMI and body composition on these associations. A total of 397 Chinese adults (54.4%) who had been examined for BMI 4–8 times during childhood (6–19 years) and bone mass in adulthood (29–37 years), were included for analysis. Adult bone mineral content (BMC), areal bone mineral density (aBMD) and body composition were assessed via dual-energy x-ray absorptiometry. Childhood BMI growth curves were constructed using a random-effects mixed model. The area under the curve (AUC) was calculated to represent the long-term impact of childhood BMI. At baseline, 24.4%, 66.2%, 7.6% and 1.8% of the participants were underweight, normal weight, overweight and obese, respectively. Quadratic curve parameters of childhood BMI differed significantly between groups of adult whole body (WB) BMC, lumbar spine (LS) aBMD and femoral neck (FN) aBMD, with low BMC/aBMD groups having lower childhood BMI than the normal groups. AUC of childhood BMI was significantly and positively related to adult WB BMC and aBMD at each site, irrespective of sex. Significant mediation effects of adult BMI were shown on the association of childhood BMI AUC with adult WB BMC in males (52.0%) and FN aBMD in both sexes (males: 65.4%; females: 64.3%). Additionally, mediation effect of fat mass index was only noted on the association of childhood BMI AUC with adult WB BMC (41.3%), with a positive total indirect effect estimated at 0.118. The adult lean mass index, by contrast, mediated the childhood BMI-adult BMC/aBMD association positively at all sites in males (71.5%~89.2%) and at WB BMC in females (45.0%). These findings suggest that the impact of body weight on adult bones originates from childhood, which is mediated by concurrent BMI and body composition.

1. Introduction

Osteoporotic fracture affects millions of people worldwide, resulting in enormous medical, social, and economic burdens [1,2]. Bone mass, as a proxy measure of bone strength, has been frequently used in the assessment of individual's subsequent fracture risk [3,4]. Extensive studies have demonstrated a strong and positive association between body weight and bone mass, indicating that body weight is a vital determinant in bone mineral accrual [5–7].

Childhood and adolescence are critical periods in the development of lifelong bone health [8]. During these growth periods, weight status may influence skeletal health via sustained mechanical loading and potential hormonal changes. Longitudinal studies have demonstrated the associations of childhood body mass index (BMI) with adult bone mineral content (BMC) and bone mineral density (BMD) [9–14]. However, few pediatric cohorts have examined the impact of longitudinal changes in BMI and its cumulative influence during childhood on adult bone mass. In addition, BMI tracks from childhood to adulthood [15], suggesting that childhood BMI might affect bone health in later life through adulthood BMI (the mediation effect). Moreover, body mass can be decomposed into fat mass and lean mass. It has been suggested that fat mass and lean mass exert divergent effects on bone strength [16–18], thus the association of childhood BMI and adult bone mass may be mediated by adult FMI and LMI differently. To date, the

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degree of mediation effects of adult BMI and body composition on the childhood BMI-adult bone relation has been largely unknown [19].

In present study, utilizing data from a longitudinal cohort followed up since childhood, we aimed to estimate the impact of growth patterns and cumulative impact of BMI during childhood on adult BMC and BMD, and explore quantitatively the potential roles of adult BMI and body composition on these associations.

2. Methods

2.1. Study population

The Beijing Blood Pressure study is a longitudinal cohort study of hypertension and risk factors beginning from childhood in 1987 [20]. At baseline, 2442 children and adolescents aged 6–18 years were recruited using a random cluster sampling method from twelve schools located in urban Beijing, China. After the baseline survey, 807 children aged 6–12 years were invited to participate in examinations every year from 1988 to 1994. In this longitudinal cohort, 397 individuals (54.4% males; age range = 29–37 years; mean age = 31.7 years at follow-up) who had been examined for BMI 4–8 times (7.6 visits per person on average) in childhood and bone mass in the last adult survey in 2010–2011 formed the current study cohort. The average follow-up duration was 22.9 years. There was no significant difference in characteristics at baseline between included and excluded children (Supplemental Table 1).

At each examination, written informed consent was obtained from study participants or from a parent/guardian in those under 18 years of age. Study protocols were approved by the institutional review board and Ethics Committee of Capital Institute of Pediatrics, Beijing, China.

2.2. General examination

All measurements were obtained by trained study staff according to standardized protocols. At each study visit during childhood and adulthood, weight and height were measured twice with lightweight clothing and no shoes using an automatic measurement instrument (BSM330, Biospace Co., Ltd., Korea), and the mean value was used to calculate BMI as weight in kilograms divided by the square of height in meters. Participants were stratified into four BMI categories as underweight, normal, overweight and obesity based on the sex and age-specific international BMI centiles in childhood, and BMI cut-offs (18.5, 25 and 30 kg/m^2) in adulthood [21]. Information on adult lifestyles (smoking, alcohol drinking, and physical activity) was obtained by means of a staff administered standardized questionnaire in the last survey in 2010–2011. Smokers and drinkers were defined as current cigarette smoking and frequent alcohol consuming (daily or most days of the week) in the past 12 months, respectively. Physical activity was measured based on questions about intensity, frequency and duration of leisure physical activities, as well as that for each commuting method per week, and quantified by metabolic rate (MET) [22].

2.3. Bone mass and body composition measurements

BMC of the whole body (WB), and areal BMD (aBMD) of the lumbar spine (LS) from L1–L4, and the femoral neck (FN) were assessed using dual-energy X-ray absorptiometry (DXA) (Hologic Explorer, Hologic Inc., Bedford, MA, USA) by a trained technician according to a standardized protocol. The phantom was verified every morning before scanning the participants. The precision (CV%) was 0.536% for both BMC and aBMD measurements and passed the precision quality control required by the International Society for Clinical Densitometry (ISCD). All DXA values were analyzed using Apex version 4.0 software following the manufacturer's guidelines. BMC and aBMD status for separate site was classified into low and normal groups, defined as below and above the age-, sex-specific median derived from the present study.

Table 1
Characteristics of study participants by sex.

	Male (n = 216)	Female (n = 181)
Childhood		
Initial examination		
Age, year	9.5 (2.4)	9.0 (2.4)
Weight, kg	30.6 (11.4)	27.9 (10.4)
Height, cm	134.4 (15.2)	131.6 (15.3)
BMI, kg/m^2	16.4 (2.6)	15.6 (2.7)
BMI category[a]		
Underweight	36 (16.7)	61 (33.7)
Normal	158 (73.2)	105 (58.0)
Overweight	18 (8.3)	12 (6.6)
Obesity	4 (1.9)	3 (1.7)
Last examination		
Age, year	16.1 (2.4)	15.9 (2.4)
Weight, kg	58.2 (15.0)	54.4 (13.5)
Height, cm	167.4 (9.8)	159.3 (5.8)
BMI, kg/m^2	20.6 (4.2)	20.1 (3.8)
BMI category[a]		
Underweight	21 (9.7)	39 (21.5)
Normal	157 (72.7)	123 (68.0)
Overweight	27 (12.5)	14 (7.7)
Obesity	11 (5.1)	5 (2.8)
AUC measures		
Average age, year	13.0 (2.4)	12.4 (2.5)
Total AUC of BMI	18.3 (3.2)	17.5 (3.0)
Incremental AUC of BMI	2.2 (1.2)	2.0 (1.0)
Adulthood (last exam)		
Age, year	32.4 (2.3)	31.9 (2.4)
Weight, kg	78.1 (14.4)	59.0 (9.9)
Height, cm	173.4 (6.7)	161.7 (5.5)
BMI, kg/m^2	25.9 (4.3)	22.6 (3.9)
BMI category[a]		
Underweight	5 (2.3)	20 (11.5)
Normal	91 (42.1)	117 (64.6)
Overweight	86 (39.8)	32 (17.7)
Obesity	34 (15.7)	12 (6.6)
FMI, kg/m^2	7.5 (2.5)	8.0 (2.5)
LMI, kg/m^2	18.0 (2.1)	14.2 (1.5)
WB BMC, g	2480.5 (18.0)	2028.6 (19.6)
LS aBMD, g/cm^2	0.984 (0.128)	0.996 (0.104)
FN aBMD, g/cm^2	0.832 (0.133)	0.760 (0.098)
Smokers, n (%)	105 (53.8)	10 (6.7)
Drinkers, n (%)	50 (26.2)	14 (10.0)
Physical activity, Met*hour/week	12.1 (21.8)	4.6 (10.5)

Data are presented in mean (SD) or %. AUC, area under the curve; FMI, fat mass index; LMI, lean mass index WB, whole body; LS, lumbar spine; FN, femoral neck

[a] BMI categories were defined based on the sex and age-specific international BMI centiles for thinness, overweight and obesity in childhood, and BMI cut-off points of 18.5, 25 and 30, respectively, in adulthood.

Body composition, including fat mass (FM) and lean mass (LM) was also measured by DXA. LM was obtained by subtracting bone mineral content and FM from body mass. LM and FM were converted to lean mass index (LMI) and fat mass index (LMI), by dividing them by the square of height (m^2), respectively.

2.4. Statistical analyses

Nonlinear growth curve parameters of childhood BMI repeatedly measured 4–8 times were estimated by sex groups using a random-effects mixed model by SAS proc. MIXED (SAS Institute Inc., Cary, North Carolina, USA) as previously reported [23,24]. The mixed model incorporates fixed and random effects and allows the intercept, linear and nonlinear parameters to vary from individual to individual. The random effect coefficients represent the difference between the fixed effect parameters and the observed BMI values for each individual. This model allows for repeated measurements and different numbers of unequally spaced observations across individuals. The mixed linear

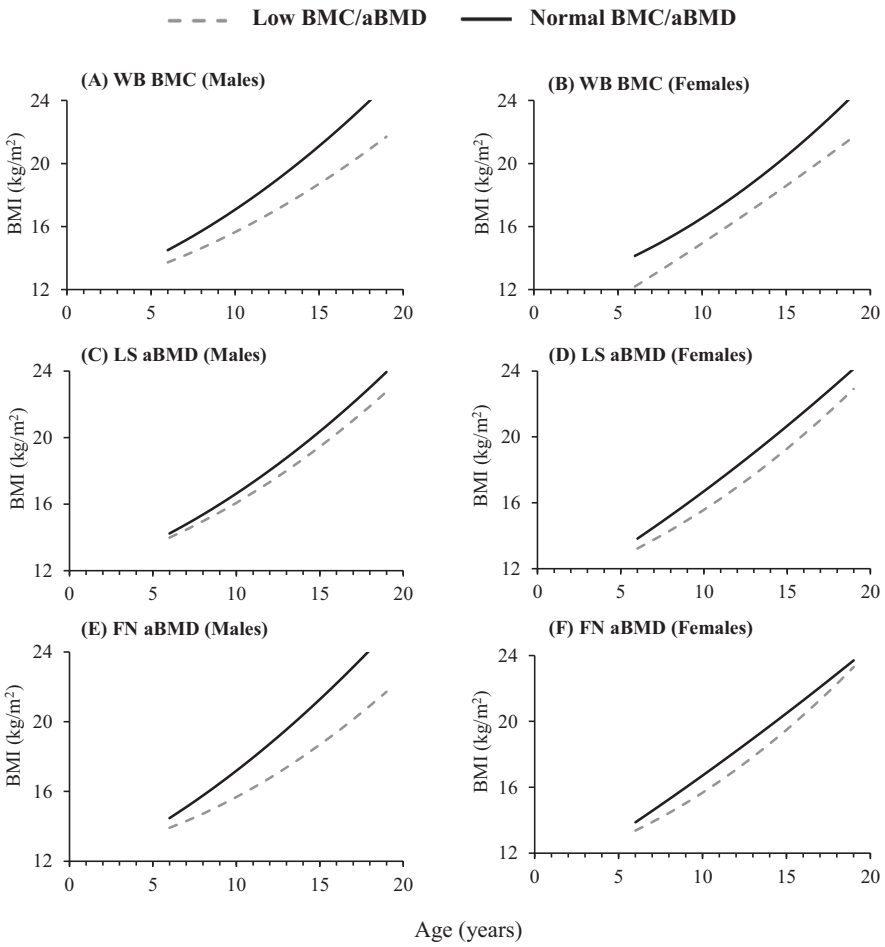

Fig. 1. Growth curve of childhood BMI by adult BMC/aBMD groups.
WB, whole body; LS, lumbar spine; FN, femoral neck.
Adult WB BMC and aBMD for separate skeletal site were classified into low and normal groups, defined as below and above the age-, sex-specific median derived from the present study. Black solid line indicated normal adult BMC/aBMD group, grey dash line indicated low adult BMC/aBMD group. The equation of each curve was listed as below after adjustment of adult covariates (age, height, physical activity, smoking and drinking). The detailed comparison of curve parameters between low and normal BMC/aBMD groups was presented in Supplemental Table 2.
(A) WB BMC (Males)
Low: BMI = 17.4 + 0.628 age + 0.148 age^2
Normal: BMI = 19.3 + 0.823 age + 0.185 age^2
(B) WB BMC (Females)
Low: BMI = 17.1 + 0.735 age + 0.050 age^2
Normal: BMI = 18.7 + 0.801 age + 0.204 age^2
(C) LS aBMD (Males)
Low: BMI = 18.0+ 0.691 age + 0.169 age^2
Normal: BMI = 18.7 + 0.760 age + 0.164 age^2
(D) LS aBMD (Females)
Low: BMI = 17.4+ 0.748 age + 0.177 age^2
Normal: BMI = 18.4 + 0.788 age + 0.082 age^2
(E) FN aBMD (Males)
Low: BMI = 17.5 + 0.626 age + 0.177 age^2
Normal: BMI = 19.3 + 0.825 age + 0.156 age^2
(F) FN aBMD (Females)
Low: BMI = 17.4 + 0.755 age + 0.208 age^2
Normal: BMI = 18.5 + 0.781 age + 0.051 age^2

model computes maximum likelihood estimates of curve parameters, generating 397 different sets of curve parameters for all children. The model selection was based on the Akaike's information criterion. Quadratic curves were fitted for BMI in sex groups.

$$BMI_i = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})\,age + (\beta_2 + b_{2i})\,age^2 + \varepsilon$$

where $\beta = (\beta_0, \beta_1, \beta_2)'$ is a vector of fixed effect parameters, $b = (b_0, b_1, b_2)'$ is a vector of random effect parameters, and ε is an unknown error term. Age was centered to the mean age (12.7 years) to remove the collinearity of age with its higher-order terms. The term age^2 was divided by 10 to improve the model fitting. The area under the curve (AUC) was calculated as integral of the curve parameters for each subject (Supplemental Fig. 1). To compare AUC values among children with different follow-up years, the AUC values were divided by the number of follow-up years. Total AUC represents the long-term cumulative impact; incremental AUC represents a combination of linear and nonlinear longitudinal trends during childhood.

To investigate the relationship between trajectory patterns of childhood BMI and adult bone mass, we used analysis of covariance (ANCOVA) to test the differences in growth curve parameters between low and normal BMC/aBMD groups. Multivariable linear regression was performed to examine the long-term burden and trend of childhood BMI on adult bone mass. Prior to regression analyses, total and incremental AUC values of BMI were adjusted for average childhood age by regression residual analyses and then standardized with *Z*-transformation (mean = 0, SD = 1) by sex groups. Adult height, BMI, FMI and LMI were adjusted for adult age in the same manner. In addition, for analyses of incremental AUC, baseline values of childhood BMI were included in the model for adjustment to control the regression-to-the-mean bias. Sex, adult age, height, physical activity, smoking and drinking were included as covariates in the regression models.

To quantify the mediation effect of adult BMI and body composition on the association of childhood BMI with adult bone mass, general causal mediation analyses were performed using linear regression models as previously proposed by MacKinnon [25]. Two mediation models were used and depicted in Supplemental Fig. 2. In single mediator model, the predictor variable (X) was total/incremental AUC of childhood BMI; the mediator variable (M) was adult BMI measured in the last survey; the outcome variables (Y) were adult WB BMC, LS aBMD and FN aBMD in separate models. In general, there were 4 steps involved in the mediating effect calculation: [1] showing that the predictor variable determines the outcome (Model Y = C*X) (C = total effect); [2] showing that the predictor variable affects the mediator (Model M = A*X) (A = indirect effect 1); [3] showing that the mediator determines the outcome controlling for the predictor (Model Y = B*M + C′*X) (B = indirect effect 2, C′ = direct effect); [4] calculating the proportion of mediation as mediation effect (%) = (A*B/C) *100%. In the parallel two mediator model, the single mediator M (adult BMI) was extended to two mediators, M_1 (adult FMI) and M_2 (adult LMI), and their own specific effects were computed as follows: [1] showing the relations between predictor variable and mediators, separately (Model $M_1 = A_1X$; Model $M_2 = A_2X$) (A_1 = indirect effect 1 of M_1; A_2 = indirect effect 1 of M_2); [2] showing the relation between predictor and the outcome after controlling for mediators (Model $Y = B_1M_1 + B_2M_2 + C'X$) ($B_1$ = indirect effect 2 of M_1, B_2 = indirect effect 2 of M_2, C′ = direct effect); [3] estimating the mediated effect of M_1 as (A_1*B_1/C) *100%, and the mediated effect of M_2 as (A_2*B_2/C) *100%. Sobel test was used to test the significance of the mediation effect [26]. Covariates included in the regression models for adjustment were adult age, height, physical activity, smoking and drinking.

Table 2
Linear regression analyses of childhood BMI, adult BMI and body composition measures on adult WB BMC (g) and aBMD (g/cm^2) at different sites.

	WB BMC	LS aBMD	FN aBMD
Male			
Childhood measures (No adjustment)			
Total AUC	0.484 (0.060) ***	0.194 (0.068) **	0.381 (0.064) ***
Incremental AUC[a]	0.220 (0.068) **	0.043 (0.071)	0.199 (0.069) **
Childhood measures (Adjustment for adult BMI)			
Total AUC	0.233 (0.086) **	0.061 (0.106)	0.140 (0.103)
Incremental AUC[a]	0.007 (0.066)	−0.080 (0.079)	0.009 (0.076)
Childhood measures (Adjustment for adult FMI and LMI)			
Total AUC	0.208 (0.085) *	0.054 (0.102)	0.107 (0.091)
Incremental AUC[a]	0.011 (0.064)	−0.058 (0.076)	0.024 (0.068)
Adulthood measures			
BMI	0.511 (0.058) ***	0.245 (0.072) *	0.479 (0.069) ***
FMI[b]	−0.048 (0.085)	−0.029 (0.101)	−0.054 (0.091)
LMI[c]	0.586 (0.085) ***	0.262 (0.101) *	0.510 (0.091) ***
Female			
Childhood measures (No adjustment)			
Total AUC	0.393 (0.073) ***	0.178 (0.077) *	0.285 (0.076) ***
Incremental AUC[a]	0.110 (0.076)	0.103 (0.075)	0.123 (0.075)
Childhood measures (Adjustment for adult BMI)			
Total AUC	0.302 (0.091) **	0.183 (0.086) *	0.091 (0.077)
Incremental AUC[a]	−0.029 (0.079)	0.053 (0.073)	−0.026 (0.066)
Childhood measures (Adjustment for adult FMI and LMI)			
Total AUC	0.283 (0.091) **	0.186 (0.098)	0.115 (0.094)
Incremental AUC[a]	−0.032 (0.079)	0.089 (0.083)	−0.022 (0.080)
Adulthood measures			
BMI	0.329 (0.074) ***	0.099 (0.077)	0.303 (0.060) ***
FMI[b]	−0.045 (0.103)	−0.023 (0.109)	0.242 (0.104) *
LMI[c]	0.408 (0.103) ***	0.133 (0.109)	0.137 (0.104)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
AUC, area under the curve; FMI, fat mass index; LMI, lean mass index; WB, whole body; LS, lumbar spine; FN, femoral neck. BMC and aBMD measures were adjusted for adult age and height, BMI measures were adjusted for corresponding age, and FMI and LMI were adjusted by adult age by regression residual analyses in each sex and then standardized with *Z*-transformation (mean = 0, SD = 1). Covariates in all models included adult age, height, physical activity, smoking and drinking.
[a] First measure of BMI in childhood was *Z*-transformed and included in the model.
[b] Additional adjustment of adulthood LMI.
[c] Additional adjustment of adulthood FMI.

3. Results

Table 1 summarizes the study variables with respect to long-term level and trend of childhood BMI and adulthood characteristics by sex. At baseline, 24.4%, 66.2%, 7.6% and 1.8% of the participants were underweight, normal weight, overweight and obese, respectively. The rates for overweight and obesity increased to 4.0% and 10.3% at the last examination in childhood, and to 29.7% and 11.6% in adulthood. Most overweight/obese children stayed on the same track to adulthood. Only three (5.0%) males and four (11.8%) females who were overweight/obese during childhood were under-/normal weight in adulthood. On the other hand, 49.2% and 18.0% under-/normal weight boys and girls in childhood had become overweight/obese adults.

Fig. 1 provides childhood BMI growth curve patterns by adult WB BMC and aBMD groups at two sites. The curve parameters were adjusted for covariates and presented in Supplemental Table 2. In both sexes, those with low adult BMC/aBMD demonstrated sustained lower BMI levels across childhood compared with the normal groups. The differences were especially greater in curve parameters of WB BMC in both sexes and FN aBMD in males, with lower intercept ($\beta_0 + b_0$) of BMI at age of 12.7 (the mean age centered to) and the linear slope ($\beta_1 + b_1$) of BMI (the tangent lines at age of 12.7) in the low BMC/aBMD group than the normal group ($p < 0.01$). For LS aBMD, similar curve patterns were displayed, but no significant differences in cure parameters were observed between low and normal aBMD groups in males (all $p > 0.05$).

Table 2 presents the association of BMI measures and adult body composition (FMI and LMI) with adult WB BMC and aBMD at two sites in linear regressions, adjusting for adult covariates (age, height, physical activity, smoking and drinking). In both males and females, higher total AUC of childhood BMI associated with higher adult WB BMC, LS aBMD and FN aBMD. No significant associations were observed between incremental AUC of childhood BMI and adult bone mass, except for those with WB BMC ($\beta = 0.220$, $p = 0.001$) and FN aBMD ($\beta = 0.199$, $p = 0.004$) in males. When adult BMI or adult body composition was included for additional adjustment, most associations between childhood BMI and adult BMC/aBMD became nonsignificant. Only the association between total AUC of childhood BMI and WB BMC remained to be statistically significant in both sexes ($p < 0.05$). Meanwhile, unlike the consistent associations between adult BMI and BMC/aBMD, the relations of adult FMI and LMI to aBMD differed by sex and skeletal sites. The regression coefficients of adult FMI and BMC/aBMD were not statistically significant across sites in males, yet a positive coefficient was found for FN aBMD in females ($\beta = 0.242$, $p = 0.021$). In contrast to FMI, adult LMI was positively associated with all three bone mass indicators in males (all $p < 0.05$) and with WB BMC in females ($\beta = 0.408$, $p < 0.001$).

The standardized regression coefficients (A, B, C and C′) and mediation effect of adult BMI and body composition on the total AUC of childhood BMI-adult BMC/aBMD associations, adjusting for covariates are illustrated in Figs. 2 and 3, respectively. For the childhood BMI-adult WB BMC association, the mediation effect of adult BMI was estimated at 52.0% in males, with both significant total indirect effect of 0.252 and direct effect of 0.232 (Fig. 2, panel A). Similar effect was not observed in females, except for the significant direct effect of childhood BMI on adult WB BMC estimated at 0.202 (Fig. 2, panel B). For the associations of childhood BMI with aBMD at two skeletal sites, marked mediation effect of adult BMI was noted in both sexes at FN aBMD (males: 65.4%; females: 64.3%), but not for that at LS aBMD. After the decomposition of BMI into FMI and LMI, sex- and site-specific indirect

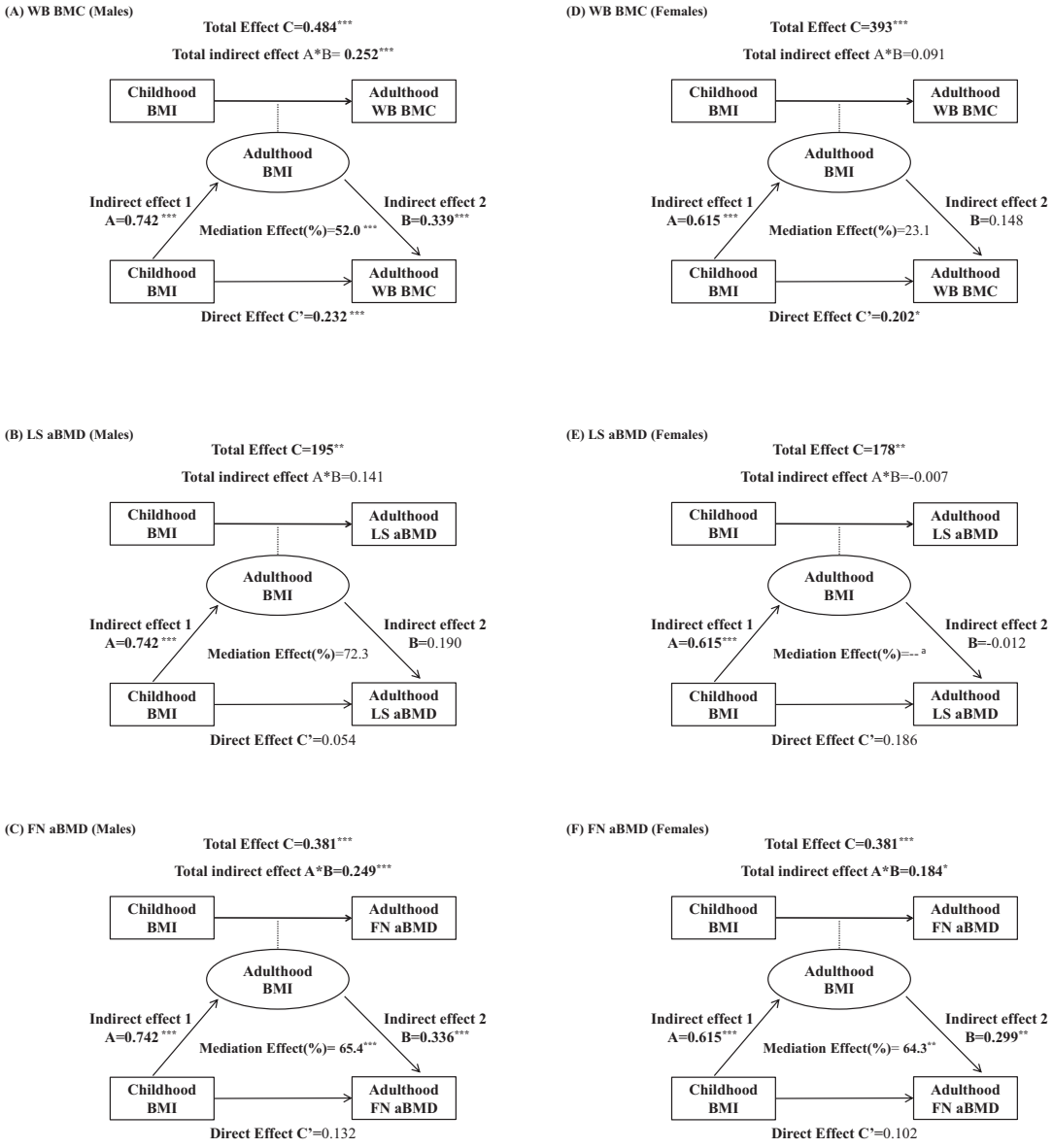

Fig. 2. Mediation effect of adult BMI on the total AUC of childhood BMI-adult BMC/aBMD associations.
WB, whole body; LS, lumbar spine; FN, femoral neck;
A, B, C and C′ were standardized regression coefficients;
C = total effect (i.e. the impact of childhood BMI on adult BMC/aBMD without considering mediation);
A = indirect effect 1 (i.e. the effect of childhood BMI on adult BMI);
B = indirect effect 2 (i.e. the influence of adult BMI on adult BMC/aBMD through the path from childhood BMI to adult BMC/aBMD);
C′ = direct effect (i.e. the independent effect of childhood BMI on adult BMC/aBMD with controlling for adult BMI);
A*B = total indirect effect (i.e. the total amount of mediation of adult BMI in the childhood BMI-adult BMC/aBMD pathway);
Mediation effect (%) = (A*B/C) *100% (i.e. the proportion of mediation on adult BMC/aBMD explained by adult BMI).

effects of body composition indicators were demonstrated. In males, the childhood BMI-adult BMC/aBMD associations were mostly mediated by adult LMI (71.5%~89.2%) at each skeletal site, with significant total indirect effect of LMI and nonsignificant total indirect of FMI (Fig. 3, panel A–C). In females, by contrast, the mediation effect of LMI was only presented on the association of total AUC of childhood BMI with adult bone mass at WB BMC (45.0%). Meanwhile adult FMI was found to have a significant total indirect effect on FN aBMD (Fig. 3, panel F). The mediation effects of adult BMI and body composition on the incremental AUC of childhood BMI-adult BMC/aBMD association were only estimated at WB BMC and FN aBMD in males because of the nonsignificant relationship between childhood BMI incremental AUC and adult BMC/aBMD at other sites. In Supplemental Table 3, the mediation parameters were substantially similar to those with total AUC of childhood BMI as the predictor.

4. Discussion

Higher body mass has long been recognized as a protective factor of bone loss and fracture [5–7,27]. A meta-analysis of 60,000 men and women from 12 prospective population-based cohorts clearly indicated that high BMI was protective against osteoporotic fractures equally in men and women [27]. Increased mechanical load on the skeleton is probably the most dominant factor account for the higher bone mass in heavier individuals [28,29]. Despite the well-known developmental origins of osteoporosis, data are still inadequate regarding the impact of

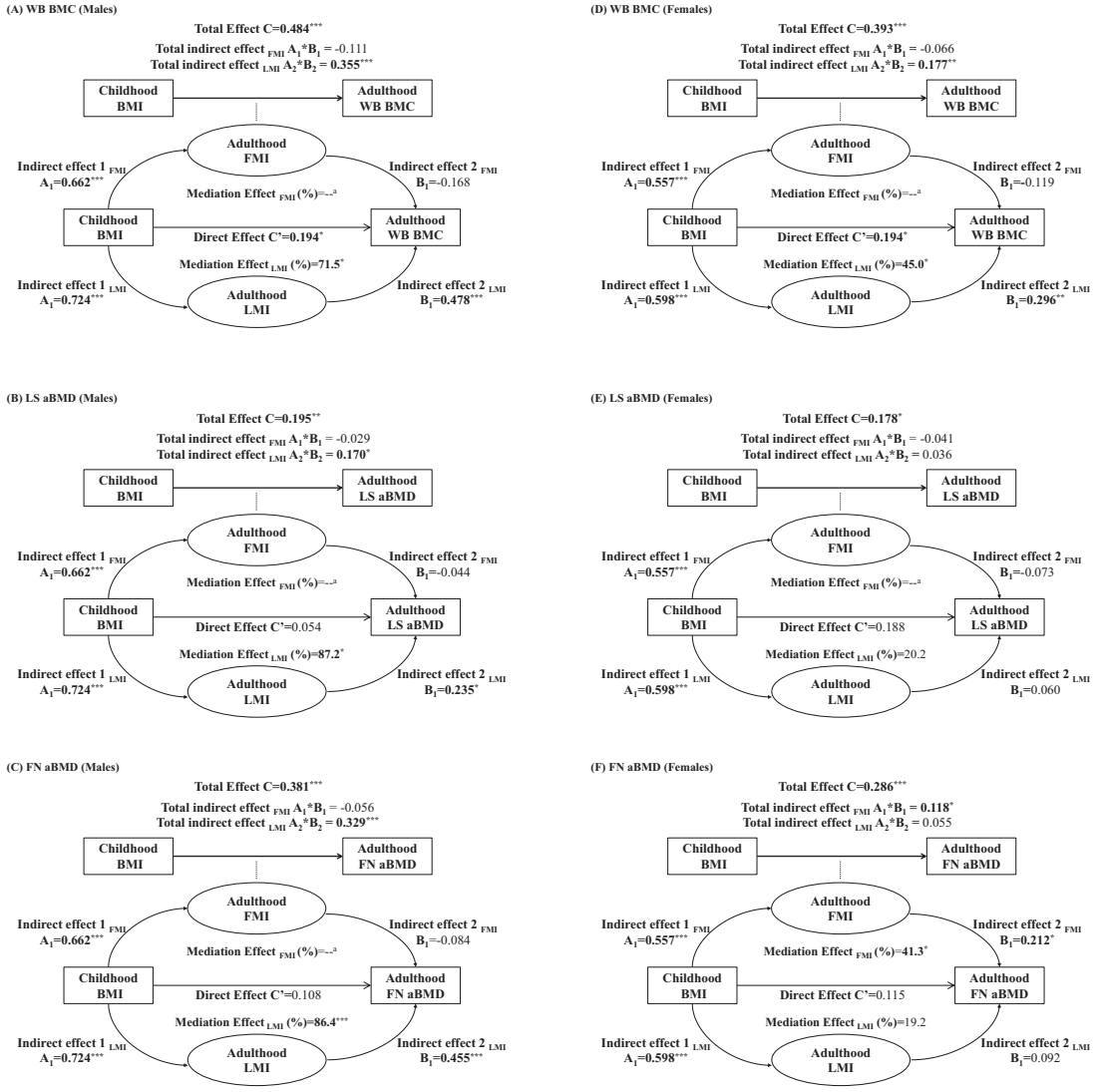

Fig. 3. Mediation effect of adult FMI and LMI on the total AUC of childhood BMI-adult BMC/aBMD associations.
WB, whole body; LS, lumbar spine; FN, femoral neck; FMI, fat mass index; LMI, lean mass index;
A_i, B_i, C and C′ were standardized regression coefficients;
C = total effect (i.e. the impact of childhood BMI on adult BMC/aBMD without considering mediation);
A_1 = indirect effect 1 of FMI (i.e. the effect of childhood BMI on adult FMI);
A_2 = indirect effect 1 of LMI (i.e. the effect of childhood BMI on adult LMI);
B_1 = indirect effect 2 of FMI (i.e. the independent influence of adult FMI on adult BMC/aBMD through the path from childhood BMI to adult BMC/aBMD, with consideration of the childhood BMI-adult LMI-adult BMC/aBMD pathway);
B_2 = indirect effect 2 of LMI (i.e. the independent influence of adult LMI on adult BMC/aBMD through the path from childhood BMI to adult BMC/aBMD, with consideration of the childhood BMI-adult FMI-adult BMC/aBMD pathway);
C′ = direct effect (i.e. the independent effect of childhood BMI on adult BMC/aBMD with controlling for adult FMI and LMI);
A_1*B_1 = total indirect effect of FMI (i.e. the total amount of mediation of adult FMI in the childhood BMI-adult BMC/aBMD pathway);
A_2*B_2 = total indirect effect of LMI (i.e. the total amount of mediation of adult LMI in the childhood BMI-adult BMC/aBMD pathway);
Mediation effect $_{FMI}$ (%) = (A_1*B_1/C)*100% (i.e. the proportion of mediation on adult BMC/aBMD explained by adult FMI);
Mediation effect $_{LMI}$ (%) = (A_2*B_2/C) *100% (i.e. the proportion of mediation on adult BMC/aBMD explained by adult LMI).

body mass in early life on adult BMD. Both the New Delhi Birth Cohort study and the Cardiovascular Risk in Young Finns Study reported that childhood higher BMI with a single measurement was associated with higher adult BMD [12,13]. In the present study, we found significant and positive associations of childhood cumulative BMI (a measure of AUC during follow-up period) with adult WB BMC and aBMD at two sites. Additionally, it is observed in this study that intercepts ($\beta_0 + b_0$) of BMI at age of 12.7 were significantly lower in the low BMC/aBMD group than normal BMC/aBMD group at most skeleton sites; the linear slopes ($\beta_1 + b_1$) of BMI were significantly lower in the low WB BMC groups for both sexes and FN aBMD group for males compared with their normal BMC/aBMD counterparts. The findings on the growth curve parameters suggest that the influence of increased body mass on adult BMC/aBMD might originate from adolescence period.

Despite the consistently positive relationship of BMI and bone mass, lean mass and fat mass, two distinct parts of body mass showed divergent associations with bone strength. In line with previous studies [16,30], we demonstrated that lean mass exerted beneficial influence on bone mass in both sexes. Increased mechanical muscle force and altered levels of bone active factors (such as irisin) may contribute to the positive association between lean mass and BMC/aBMD [31]. However, incongruent results on FMI–BMC/aBMD relations were

presented in our study. Specifically, FMI was not significantly correlated with WB BMC or LS aBMD in either sex, but a positive association between FMI and FN aBMD was found in females not in males. Several underlying mechanisms are involved in this regard. It has been recognized that fat mass may influence bones via indirect (biomechanical) way and direct (biochemical) way [32,33]. As the mechanical loading is greater at weight-bearing locations than those at other part of the body [34], the biomechanical effect (beneficial) of fatness on hip bones may overweigh its biochemical effect (beneficial, dual or deleterious) [32], which may lead to site-specific fat-aBMD relationship. For the sex disparity demonstrated at FN aBMD, it may be related to differences in the estrogen and testosterone milieu between males and females [35,36].

The significant tracking correlation between childhood and adulthood BMI suggests that childhood BMI might affect adult BMD through adult BMI connection. In concordance with reports from the 1993 Pelotas (Brazil) birth cohort study and the Andhra Pradesh Children and Parents Study [14,19], we observed marked mediation effects of adult BMI on the childhood BMI-adult BMC/aBMD association. Furthermore, in regression models including concurrent body composition instead of BMI, we found discrepant mediation effects of FMI and LMI on the associations of childhood BMI and adult BMC/aBMD, with LMI as the dominant mediator in males but FMI in females. Other cohort studies have demonstrated that both fat mass and fat-free mass tracked from childhood to adulthood [37,38], and larger BMI gains in adulthood were caused by a greater increase of fat-free mass in men, but by greater increase of fat mass in females [39]. Thus, sex differences in mediation effects of FMI and LMI on the childhood BMI-adult BMC/aBMD association may partly reflect sex dimorphisms in the contribution of body composition on bone development during growth. Unfortunately, data on body composition in childhood were unavailable in present study. Further studies are needed to investigate the independent influences of childhood lean mass and fat mass on adult bone mass.

This school-based longitudinal cohort provides a unique opportunity to examine the impact of childhood cumulative BMI on adult WB BMC and aBMD at different sites and the mediation effects of adult BMI and body composition in such relationships. In addition, BMC and aBMD measures were determined by DXA, the gold standard of bone mineral densitometry [40]. There were, however, several limitations in this study. First, our analyses were limited to subjects with 4–8 times of childhood BMI measurements, and 50.8% of children in the total cohort were excluded based on this inclusion criterion. Although there was no significant difference in characteristics at baseline between included and excluded children, the limited sample size may relate to unstable mediation effect. Second, information on physical activity and nutritional intake in childhood was not collected, and the influence of these factors on adult aBMD could not be examined. Third, considering the low prevalence of childhood obesity in the studied population (1.8%, as shown in Table 1), current results should be generalized with caution for children with obesity. Recent observations on increased fracture in obese children have raised concerns about whether childhood excessive weight gain will lead to optimization of bone mass in later life [41,42].

In summary, childhood BMI had long-term positive cumulative impact on adult bone mass. Mediation effect of adult BMI and body composition on the association of childhood BMI with adult bones varied by skeletal sites and sexes; childhood BMI and adult FN aBMD were linked predominantly through adult BMI and LMI in males. These findings suggest that weight gain in early life and mid-adulthood coupled with improvement in lean mass is important for bone mass accrual and attenuate subsequent bone loss with aging.

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Author contributions

JM obtained funding, designed and conducted the study. HD, WC, YY, and SL performed the analysis, interpreted the data and drafted the manuscript. HD was also involved in obtaining funding (the China Scholarship Program and the Beijing Children's Hospital NSFC Incubation Fund). XZ, HC, DH, and JL were involved in data collection of and design of the study. All authors revised the manuscript for important intellectual content and approved the final version of the manuscript.

Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2019.01.027.

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