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Lifecourse relationship between maternal smoking during pregnancy, birth weight, contemporaneous anthropometric measurements and bone mass at 18 years old. The 1993 Pelotas Birth Cohort

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ABSTRACT

Background: Maternal smoking during pregnancy is associated with short-term and also long-term harmful effects on offspring.
Objective: The aim of this study is to evaluate the associations of maternal smoking during pregnancy with offspring bone health at 18 years old, and the role of birth weight and contemporaneous height, weight and body mass index (BMI) in this association.
Data from the 1993 Pelotas Birth Cohort were analyzed using path analysis stratified by sex.
Adolescents at 18 years old ($N = 1512$ males, 1563 females).
DXA-determined total body bone mineral density (BMD) and bone mineral content (BMC) were assessed at 18 years old.
Results: Each additional cigarette smoked during pregnancy was associated with a lower BMC by −4.20 g in males (95% CI −8.37; −0.05), but not in females [−2.22 g (95% CI −5.49; 1.04)]; weaker inverse associations were observed for BMD. This inverse association was explained by the influence of maternal smoking on birth weight and contemporaneous anthropometry, particularly height. A 1 kg higher birth weight was associated with a higher BMC by around 144 g in males and by around 186 g in females, and also with a higher BMD by around 0.019 g/cm^2 in males and by around 0.018 g/cm^2 in females, respectively.
Conclusions: Lifecourse analysis using path models has enabled to evaluate the role of mediators in the associations of maternal smoking during pregnancy and birth weight with bone mass in the offspring, thus generating improved understanding of the etiology of bone health and the importance of early life experiences.

1. Introduction

Evidence has shown that smoking during pregnancy is harmful to the newborn (1–4), especially affecting birth weight (2,3,5). In recent years there has been growing interest in the impact of early life events including smoking during pregnancy (6), and birth weight (7,8) on height during childhood and adolescence (9) and on bone health as an attempt at better understanding how these exposures contribute to the pathophysiology of osteoporosis (10,11).

Maternal smoking, diet and physical activities levels are thought to contribute to the in-utero modulation of bone mineral acquisition (11). Osteoporosis is a medical condition of global public health concern because of the consequences of low-energy fractures in individuals with this disease (12). Those who have low accumulation of calcium in the bones have a high risk of osteoporotic fractures during their adult life (12) because of high rates of bone loss in adulthood (10,13). It is thus important to understand the potentially-modifiable factors which promote or inhibit the gain of bone mass during childhood and adolescence.

Few studies have examined the association between maternal smoking during pregnancy and bone mass in offspring. Jones et al. described an inverse association with spine and femur BMD at 8 years old (14); however this effect was not seen in a second follow-up visit

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when the offspring were 16 years old (15). Macdonald-Wallis et al. reported that maternal smoking during pregnancy was associated with higher BMC in girls aged 10 (6), but given the similar associations of maternal and paternal smoking in pregnancy, the authors concluded that the association was not likely to be causal.

In light of the scant existing evidence on this topic, especially among adolescents, the aim of this study was to evaluate the association of maternal smoking during pregnancy with BMD and BMC in participants from the 1993 Pelotas Birth Cohort at age 18, as well as to assess the potential role of birth weight, and height, weight and body mass index (BMI) at 18 years old as mediators in this association.

2. Methods

All live born infants born in 1993 to mothers who were residents of the urban area of Pelotas, a city located at southern Brazil, were eligible to participate in the birth cohort study. A total of 5249 newborns were included in the study (16 refusals). More detailed information about methodology and follow-up of the cohort study have been published previously (16). The analyses shown here are based on the perinatal study and on the follow-up at age 18 years.

At the perinatal survey the mothers or caretakers answered a questionnaire on health, smoking during pregnancy and socioeconomic conditions. Mothers reported the number of cigarettes smoked per day during the pregnancy in a questionnaire and it was analyzed as a continuous variable in order to allow for a potential dose–response; coefficients can thus be interpreted as the change in outcome/mediator for each additional cigarette smoked during pregnancy. Birth weight was measured by hospital staff with 10-g precision pediatric scales calibrated regularly by the research team. In the current analysis birth weight was evaluated in kilograms and analyzed as a continuous variable.

At the follow-up when participants were 18 years old, a total of 4106 adolescents were assessed (follow-up rate of 81.4%). At this time, tests were performed to assess body composition including bone densitometry by dual-ray absorptiometry (DXA) using a Lunar Prodigy Advance Bone Densitometer (GE, Germany) by two trained technicians. A total of 3855 participants (94% of those attending the follow-up) had their entire body scanned. DXA is currently the gold standard for estimating bone mass (17).

The outcomes were whole body BMD (grams per square centimeter, g/cm^2) and BMC (grams, g). Both measures were analyzed as continuous variables. Contemporaneous anthropometric measures collected at 18 years included body weight (kilograms), height (centimeters) and BMI (kg/m^2).

The correlations between our exposures and outcomes were assessed using Pearson correlation test. To understand the relationships between maternal smoking during pregnancy, offspring birth weight, offspring concurrent anthropometric condition at age 18 and offspring bone mass, a path analysis using the structural equation modeling command in Stata (sem) was performed, with Fig. 1 depicting our hypothesized relationships between the variables. In this model one can notice that we wished to test whether maternal smoking during pregnancy had a direct effect (i.e. not mediated by any other variable in our analysis model) on BMD/BMC (dotted line) in addition to the indirect effects (i.e. the association mediated through birth weight and contemporaneous anthropometric measures) (solid line). Mediation by height, weight and BMI were each considered separately. Also, the total effect (entire association, comprising both the 'direct' and 'indirect' effects) of maternal smoking and the total effect of birth weight were calculated (total effect = indirect + direct).

We made the a priori decision to stratify all analyses by gender based on the evidence from literature about sexual differences in bone acquisition (10,18). Variables from the perinatal survey used as confounders (group 1) in the adjusted analysis were: partner smoking during pregnancy as a dichotomous variable (smoker/non-smoker); family income (wages); maternal education (years of schooling); maternal skin color (white/non-white); maternal age (years); maternal height (cm); and gestational age (weeks) estimated from the last menstrual period or using the Dubowitz score (19) when information on the last menstrual period was not available. Variables from the 18 year old follow-up (group 2) included in the model as confounders were: smoking (no/yes if the adolescent use to smoke at least one time per week), alcohol consumption (frequency of alcohol consumption per month), physical activity (score of minutes per day during leisure time measured by the International Physical Activity Questionarie short version), and calcium intake (adjusted by total calories consumption) (see Fig. 1). Confounders from group 1 remained in all the models. Confounders from group 2 were added to the model when contemporaneous mediators were evaluated.

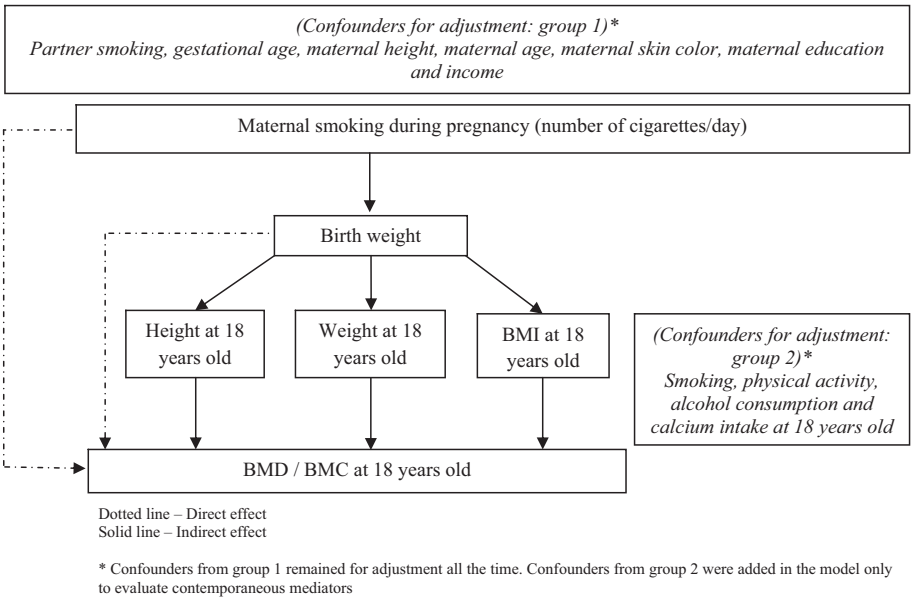


Fig. 1. Analytical model to evaluate the association between number of cigarettes/day smoked by the mother during pregnancy and total body bone mass density (BMD) and bone mineral content (BMC) at 18 years old, and assessing how much of this relationship is mediated by birth weight and current height, weight and body mass index (BMI) at 18 years.

All analysis was performed using Stata 12 software (StataCorp, College Station, Texas). The study was approved by the Research Ethics Committee of the Federal University of Pelotas Medical School. All participants signed an informed consent form.

3. Results

Originally, the 1993 Pelotas Birth Cohort comprised 5249 newborns (49.5% males). Whole body DXA data was obtained for 3855 participants at age 18. Of these, 1906 (49.4%) were males and 1949 (50.6%) females. For the path analysis model 1512 males and 1563 females had data on all necessary variables. Table 1 shows a comparison by gender between the study participants and those who were lost to follow-up (n = 1593 losses/exclusions + 169 deaths + 412 with incomplete data). It can be seen in Table 1 that participants included in our analyses had higher birth weight, lower weight and BMI at 18 years, higher gestational age at birth and older mothers than those not included in the analysis.

BMD, BMC, height, weight, BMI and birth weight were normally distributed. In both sexes there was a correlation between maternal smoking during pregnancy, birth weight, current height, weight and BMI, BMD and BMC. This correlation was higher among males than among females (data not shown in tables and figures).

Table 2 shows the overall association between maternal smoking and BMC/BMD, and also, the association remained after accounting by mediation. Maternal smoking was associated with lower BMC at age 18 by −4.20 g in males (95% CI −8.37; −0.05) for each additional cigarette smoked by the mother during pregnancy, but not in females [−2.22 g (95% CI −5.49; 1.04)]. Although there was a suggestion that maternal smoking during pregnancy was associated with lower BMD, coefficients were small and the confidence intervals included the null value (Table 2).

Table 1
Characteristics of participants with complete data compared with participants with missing data or losses of follow-up, stratified by gender. The 1993 Pelotas Birth Cohort. Brazil.

Variables	Males			Females		
	N Percentage/mean (s.e.)			*N* Percentage/mean (s.e.)		
	Participants included in analyses	Participants excluded from analyses due to losses of follow-up or missing data	*p*-value	Participants included in analyses	Participants excluded from analyses due to losses of follow-up or missing data	*p*-value
Perinatal (parents)						
Maternal smoking (cigarettes/day) during pregnancy	N = 1512 2.5 (0.14)	N = 1089 2.9 (0.18)	0.063[a]	N = 1563 2.7 (0.15)	N = 1081 3.1 (0.19)	0.087[a]
Partner smoking during pregnancy	N = 1512	N = 862		N = 1563	N = 866	
No	51.4%	50.7%	0.722[b]	49.0%	51.0%	0.511[b]
Yes	48.6%	49.3%		50.3%	49.7%	
Family income (minimal wages)	N = 1512 4.5 (0.16)	N = 1033 4.0 (0.16)	0.012[a]	N = 1563 4.4 (0.15)	N = 1025 4.0 (0.17)	0.090[a]
Maternal skin color	N = 1512	N = 1089		N = 1563	N = 1079	
White	76.6%	79.0%	0.148[a]	78.4%	74.6%	0.024[a]
Non-white	23.4%	21.0%		21.6%	25.4%	
Maternal education (years)	N = 1512 7.0 (0.09)	N = 1085 6.6 (0.11)	0.003[a]	N = 1563 7.0 (0.09)	N = 1078 6.2 (0.11)	<0.001[a]
Maternal height (cm)	N = 1512 159.8 (0.17)	N = 1062 159.8 (0.21)	0.982[a]	N = 1563 160.0 (0.17)	N = 1063 159.5 (0.21)	0.079[a]
Maternal age (years)	N = 1512 26.5 (0.17)	N = 1088 25.3 (0.19)	<0.001[a]	N = 1563 26.5 (0.15)	N = 1081 25.2 (0.20)	<0.001[a]
Perinatal (participants)						
Birth weight (kg)	N = 1512 3.26 (0.01)	N = 1081 3.16 (0.02)	<0.001[a]	N = 1563 3.14 (0.01)	N = 1073 3.03 (0.01)	<0.001[a]
Gestational age (weeks)	N = 1512 39.5 (0.06)	N = 893 39.1 (0.08)	<0.0001[a]	N = 1563 39.5 (0.06)	N = 1067 39.3 (0.07)	0.022[a]
At 18 *years old (participants)*						
Calcium intake (adjusted by total calories)	N = 1512 722.1 (8.7)	N = 425 722.1 (8.7)	0.014[a]	N = 1563 701.6 (8.9)	N = 459 659.1 (16.5)	0.024[a]
Physical activity score (leisure)	N = 1512 545.4 (16.6)	N = 494 578.6 (31.5)	0.330[a]	N = 1563 230.7 (9.5)	N = 523 202.1 (15.5)	0.127[a]
Alcohol consumption (times per months)	N = 1512 2.1 (0.04)	N = 333 2.0 (0.08)	0.173[a]	1563 1.7 (0.03)	354 1.7 (0.07)	0.625[a]
Smoking (use to smoke at least one time per week)	N = 1512	N = 502	0.547[b]	N = 1563	N = 528	0.579[b]
No	76.8%	78.1%		78.0%	76.9%	
Yes	23.2%	21.9%		21.9%	23.1%	
Height (cm)	N = 1512 173.8 (0.17)	N = 463 173.7 (0.36)	0.746[a]	N = 1563 161.3 (0.16)	N = 434 160.0 (0.32)	<0.001[a]
Weight (kg)	N = 1512 70.1 (0.33)	N = 463 72.7 (0.83)	<0.001[a]	N = 1563 60.9 (0.31)	N = 434 61.3 (0.73)	0.618[a]
Body mass index (kg/m^2)	N = 1512 23.2 (0.10)	N = 463 24.0 (0.25)	<0.001[a]	N = 1563 23.4 (0.11)	N = 434 23.9 (0.27)	0.062[a]
Bone mineral density (g/cm^2)	N = 1512 1.227 (0.002)	N = 391 1.215 (0.005)	0.031[a]	N = 1563 1.135 (0.002)	N = 389 1.130 (0.004)	0.347[a]
Bone mineral content (g)	N = 1512 2966.7 (11.8)	N = 391 2921.6 (23.9)	0.085[a]	N = 1563 2415.8 (9.9)	N = 389 2390.8 (20.4)	0.263[a]

N—number of observations.
[a] *t*-test testing the null hypothesis that the mean is the same in those included in analysis and those excluded due to losses of follow-up or missing data.
[b] Chi-square test for heterogeneity testing the null hypothesis that the prevalence is the same in those included in analysis and those excluded due to loss to follow-up or missing data.

Table 2
Associations between maternal smoking in pregnancy and bone mineral content and density mediated by birth weight and concurrent anthropometry. $N = 1512$ males and 1563 females. The 1993 Pelotas Birth Cohort, Brazil.

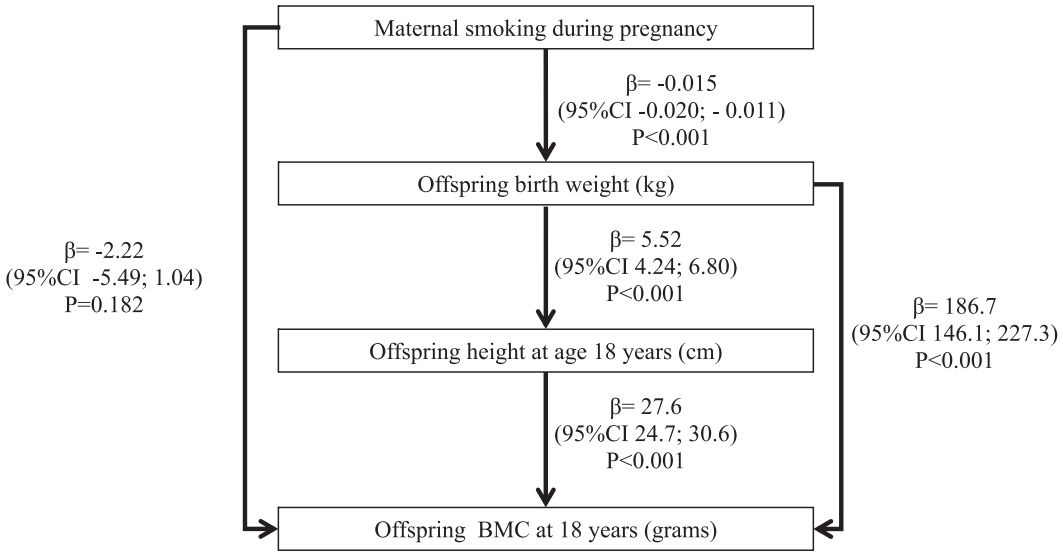
Association	BMC		BMD	
	Males	Females	Males	Females
	β (95%CI) *p*-value	β (95%CI) *p*-value	β (95%CI) *p*-value	β (95%CI) *p*-value
Overall association	−4.20 (−8.37; −0.05) $P = 0.048$	−2.22 (−5.49; 1.04) $P = 0.182$	−0.0006 (−0.0014;0.0003) $P = 0.188$	−0.00002 (−0.0007;0.0006) $P = 0.943$
Association after accounting for mediation by birth weight (kg) and concurrent height (cm)	−1.15 (−3.78; 3.48) $P = 0.936$	1.16 (−1.76; 4.08) $P = 0.437$	−0.0002 (−0.001; 0.001) $P = 0.657$	0.0003 (−0.0004; 0.0009) $P = 0.404$
Association after accounting for mediation by birth weight (kg) and concurrent weight (kg)	−0.053 (−2.88; 2.77) $P = 0.971$	−0.727 (−2.99; 1.54) $P = 0.529$	−0.0001 (−0.0009; 0.0007) $P = 0.767$	−0.0002 (−0.0073; 0.0069) $P = 0.769$
Association after accounting for mediation by birth weight (kg) and concurrent BMI (kg/m^2)	−0.676 (−4.02; 2.67) $P = 0.692$	−1.17 (−3.81; 1.47) $P = 0.384$	−0.0002 (−0.0010; 0.0006) $P = 0.631$	−0.00001 (−0.006; 0.006) $P = 0.991$

β—linear regression coefficient per each additional cigarette smoked during pregnancy; 95%CI—95% confidence interval; *p*-value—from Wald's test.
kg—kilograms.
cm—centimeters.
BMI—body mass index.
Adjusted by partner smoking, gestational age, maternal height, maternal age, maternal skin color, maternal education, income, and adolescent smoking, physical activity status, alcohol consumption and calcium intake (adjusted by total calories consumption).

Each additional cigarette smoked by the mother during pregnancy was associated with lower birth weight, and higher birth weight (each additional kg) was associated with greater height, weight and BMI at age 18 (Figs. 2 and 3 and supplementary Figs. 4–13). Greater height, weight and BMI at age 18 were all associated with greater BMC and BMD. For example, a 1 cm greater height at age 18 was associated with a 34.7 g greater BMC at age 18 in females (95% CI 31.5; 38.0).

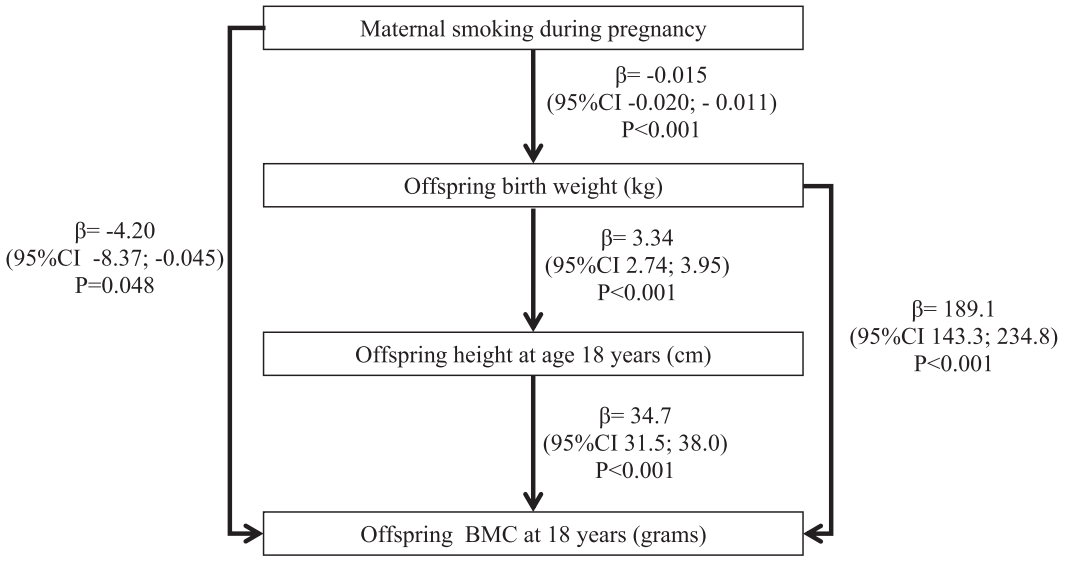
Birth weight and concurrent height, weight and BMI all mediated the relationship between maternal smoking during pregnancy and offspring bone health to some extent; in each case, the inverse association between smoking during pregnancy and bone health was reduced to non-significance after taking these pathways into account (Table 2). Mediation by concurrent height was the most important; after taking into account birth weight and concurrent height, smoking during pregnancy was no longer associated with lower BMC or BMD. Weight and BMI at age 18 were weaker mediators for the association smoking during pregnancy—and offspring bone health; for example before taking into account mediation, the overall association between each additional cigarette smoked by the mother during pregnancy and BMC pointed to a BMC reduction by −4.20 g (95% CI −8.37; −0.05); after accounting for mediation by birth weight and height at age 18, this association was reduced to non-significance −1.15 g (95% CI −3.78; 3.48).

The overall association between each additional birth weight kg and BMC pointed to a BMC increment by 144 g in males and 186 g in females, respectively, and with BMD was 0.019 g/cm^2 in males and 0.018 g/cm^2 in females, respectively (Figs. 2, 3 and supplementary Figs. 4–13); after accounting for mediation by concurrent height,



β-linear regression coefficient; 95%CI-95% confidence interval; P-p-value from Wald's test; BMC-bone mineral content in grams
Adjusted by confounders from group 1 (partner smoking, gestational age, maternal height, maternal age, maternal skin color, maternal education and income) and group 2 (smoking, physical activity, alcohol consumption and calcium intake at 18 years old). Confounders from group 1 remained for adjustment all the time. Confounders from group 2 were added in the model only to evaluate contemporaneous mediators.

Fig. 2. Overall association between maternal smoking during pregnancy, offspring birth weight, offspring height and bone mineral content at age 18 in females ($N = 1563$). The 1993 Pelotas Birth Cohort.



β-linear regression coefficient; 95%CI-95% confidence interval; P-p-value from Wald's test; BMC-bone mineral content in grams
Adjusted by confounders from group 1 (partner smoking, gestational age, maternal height, maternal age, maternal skin color, maternal education and income) and group 2 (smoking, physical activity, alcohol consumption and calcium intake at 18 years old). Confounders from group 1 remained for adjustment all the time. Confounders from group 2 were added in the model only to evaluate contemporaneous mediators

Fig. 3. Overall association between maternal smoking during pregnancy, offspring birth weight, offspring height and bone mineral content at age 18 in males ($N = 1512$). The 1993 Pelotas Birth Cohort.

weight and BMI at 18, the association was reduced to non-significance.

4. Discussion

Our findings point to an inverse association of maternal smoking during pregnancy with bone health. This inverse association is stronger in males, but no evident in females, and appears to be almost completely mediated through birth weight and contemporaneous anthropometric measures. Height seems to be the most important contemporaneous mediator. In addition, birth weight showed a positive association with BMD/BMC at 18 years in both sexes. To the best of our knowledge, this is the first study to assess the associations of maternal smoking during pregnancy and birth weight with bone mass in late adolescence in a large prospective birth cohort study using path analysis models to consider several potential mediators. Maternal smoking during pregnancy evaluated by the number of cigarettes smoked per day, allows us to demonstrate a dose–response effect.

There is evidence in the literature demonstrating that maternal smoking during pregnancy affects birth weight negatively leading to high rates of low birth weight (2,20,21). In fact, this association has also been published previously using data from the 1993 Pelotas Birth Cohort (5). Our findings corroborated the inverse correlation between maternal smoking during pregnancy and birth weight. The biological mechanism for explaining the effect of maternal smoking during pregnancy on low birth weight appears to be mediated by conditions such as fetal chronic hypoxia resulting from increased placental vascular resistance (22). For this reason, we hypothesized *a priori* that some long-term effects of maternal smoking on offspring bone health could be mediated by birth weight.

The effect of birth weight on BMD/BMC at different ages had been previously described as positive in several reviews (7,8,23). Cooper et al. have postulated that the hypothalamic–pituitary axis plays a major role in this association, and enhance birth weight as a predictor of basal levels of growth hormone (GH) and cortisol, two skeletally active hormones that influence not only bone mass acquisition in young people, but also late bone loss rates in older people (10). Our findings also show a positive effect of birth weight on BMD/BMC at 18 years old in both sexes. According to our findings, birth weight played a mediator role in the long-term inverse indirect effect of maternal smoking during pregnancy and offspring's BMD/BMC at 18.

The long-term effect of maternal smoking during pregnancy on bone health has been poorly evaluated in the literature. Jones et al. (14), in 1999, published the first population-based longitudinal study that evaluated the inverse effects of maternal smoking on spine and femur BMD in 330 children under 8 years of age. At a follow-up visit of this cohort (16 years old), Jones et al. (15) showed no association between smoking intra uterus with BMD or fracture. Our findings agree with these reported by Jones et al. at 16 years because no direct effects on BMD/BMC at 18 were found. In addition, indirect effect passing through birth weight and contemporaneous anthropometric variables were evident in our results. Publications evaluating the long-term effects of maternal smoking during pregnancy on bone health offspring are sparse. In 2011, the ALSPAC cohort study assessed the effects of maternal and partner smoking during pregnancy on offspring bone mass in 7121 children aged 9.9 years. They found higher mean BMC in girls of smoking mothers, although they also saw similar associations for paternal smoking, and hence concluded that the associations could be confounded by familial characteristics rather than due to an intrauterine mechanism (6).

In our study, height at 18 years is the concurrent anthropometric measure that most completely mediates the association between smoking during pregnancy and offspring bone health. After accounting for birth weight and concurrent height, there was no longer an association between smoking during pregnancy and lower BMC or BMD. Weight and BMI explained some of the association between maternal smoking during pregnancy and offspring BMC/BMD, but the mediation was not as complete as was seen with height. A previous report from the 1993 Pelotas Birth Cohort showed that maternal smoking during pregnancy negatively influences offspring's height at different ages including adolescence (9). This inverse association was also described using data from ALSPAC (24). In our analysis inverse correlation between maternal smoking and offspring's height at 18 years reaffirms this association.

Some limitations in the present study should be highlighted. First, maternal smoking information was self-reported retrospectively, immediately after birth. People in general, particularly mothers, are

known to report lower rates of smoking during pregnancy (25), as they are aware that smoking is a harmful habit for their own health and their children's health as well. However, this limitation would affect the results in a conservative way. Second, there was no information on the number of cigarettes smoked by the partner, and lastly, adolescents with extreme body weight and height were not evaluated with DXA due to the limitations of the equipment. In addition, data on vitamin D and calcium consumption during pregnancy by the mother and on adolescent vitamin D and calcium status were unavailable, so their role in the observed associations could not be assessed.

There are strong features about the 1993 Pelotas Birth Cohort. Its longitudinal design with a high follow-up rate at age 18 (81.4%) ensured the representativeness of the sample despite some statistically significant differences between study participants and those lost to follow-up.

Our detailed longitudinal data and life course analysis using path models has enabled us to evaluate the role of mediators in the associations of maternal smoking during pregnancy and birth weight with bone mass in the offspring, thus generating improved understanding of the etiology of bone health and the important of early life experiences.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.earlhumdev.2014.08.024.

Conflict of interest statement

There are no potential conflicts of interest, real or perceived.

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