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Birth weight is positively related to bone size in adolescents but inversely related to cortical bone mineral density: Findings from a large prospective cohort study

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ABSTRACT

To examine the influence of intrauterine environment on subsequent bone development, we investigated the relationship between birth weight and cortical bone parameters, and the role of puberty, bone resorption and insulin as possible mediators. Bone outcomes were obtained from mid-tibial pQCT scans performed at age 15.5 years in 1960 males and 2192 females from the ALSPAC birth cohort. Birth weight was positively related to periosteal circumference (PC) [beta = 0.40 (0.34, 0.46)], which was largely but not completely attenuated after adjustment for height and weight [beta = 0.07 (0.02, 0.12)] (SD change in outcome per 1 kg increase in birth weight with 95% CI). Based on our height and weight adjusted model, the association was stronger in females compared to males (P = 0.02 for gender interaction), and persisted in 2842 participants with equivalent results at age 17.7 years. Conversely, birth weight was inversely related to cortical bone mineral density (BMD_C) at age 15.5 years after adjusting for height and weight [beta = −0.18 (−0.23, −0.13)], with a stronger association in males compared to females (P = 0.01 for gender interaction), but an equivalent association was not seen at 17.7 years. In further analyses performed on data from age 15.5 years, the association between birth weight and PC was unaffected by adjustment for puberty (Tanner stage at age 13.5 years), bone resorption (fasting beta-carboxyterminal cross linking telopeptide (βCTX) at age 15.5 years) or insulin (fasting insulin at age 15.5 years). In contrast, the association with BMD_C was attenuated by approximately 30% after adjustment for puberty or bone resorption, and by 50% after adjustment for both factors combined. We conclude that the inverse relationship between birth weight and BMD_C is in part mediated by effects of puberty and bone resorption, which may help to explain the transitory nature of this association, in contrast to the more persisting relationship with PC.

Introduction

Nutritional deprivation during pregnancy may increase the risk of developing a range of chronic diseases in later life, including osteoporosis, as a result of programming [1]. Adverse environmental conditions in utero are proposed to affect the trajectory of subsequent skeletal growth and development, resulting in suboptimal bone structure and an increased risk of osteoporotic fracture in later life. Birth weight has been widely used as a proxy measure for nutritional status during pregnancy, in studies examining relationships between adverse exposures in utero and bone outcomes in later life [2,3]. For example, in studies based on pQCT scans, positive relationships between birth weight and cross sectional area were reported in 631 participants mean age 79 years at the radius and tibia [4], in 120 young adults from the Gambia at the radius and tibia [5], and in 1350 participants age 60–64 years at the distal radius from the 1946 birth cohort [6]. In a further study, birth weight was found to be positively related to femoral neck cross sectional area as measured by QCT, in 1831 men mean age 73 years [7].

Whereas birth weight appears to be positively related to subsequent bone size, it is less clear how other skeletal characteristics are affected. In DXA-based studies, no associations were seen between birth weight and bone mineral density (BMD), following adjustment for height and weight [8–12]. However in our previous study based on ALSPAC, we found an inverse relationship between birth weight and total body BMC adjusted for BA [12]. In previous pQCT studies, birth weight was unrelated to cortical or trabecular BMD [4,6,7], but an inverse

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association was seen between birth weight and BMD at the radius in men from the 1946 birth cohort [6],

In terms of biological pathways involved in mediating these relationships, conceivably, birth weight and bone size may be regulated by common mechanisms involved in growth such as the GH/IGF1 axis, but in a previous study this was not found to contribute to these relationships [9]. Bone turnover markers may provide information on another potential pathway, but in the twin study described above, no difference in bone turnover markers was observed according to birth weight [8]. To the extent that birth weight is inversely related to cortical BMD (BMD_C), a further potential pathway is insulin, which is positively related to BMI but inversely related to BMD_C [13]. In the present study, we aimed to examine relationships between birth weight and subsequent bone size and BMD_C as measured by pQCT of the mid tibia in adolescents from the ALSPAC cohort. We also studied the role of possible causal pathways contributing to these relationships, including age of puberty onset, a measure of bone resorption and insulin.

Methods

ALSPAC is a geographically based UK cohort that recruited pregnant women residing in Avon (South-west England) with an expected date of delivery between April 1st 1991 and December 31st 1992 [14,15]. 14,541 is the initial number of pregnancies for which the mother enrolled in the ALSPAC study and had either returned at least one questionnaire or attended a "Children in Focus" clinic by 19/07/99. Of these initial pregnancies, there were a total of 14,676 foetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above. The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently represented on the built files and reflecting enrolment status at the age of 18 is 706 (452 and 254 recruited during Phases II and III respectively), resulting in an additional 713 children being enrolled. The phases of enrolment are described in more detail in the cohort profile paper: <http://ije.oxfordjournals.org/content/early/2012/04/14/ije.dys064.full.pdf+html>. The total sample size for analyses using any data collected after the age of seven is therefore 15,247 pregnancies, resulting in 15,458 foetuses. Of this total sample of 15,458 fetuses, 14,775 were live births and 14,701 were alive at 1 year of age. The study website contains details of all the data that is available through a fully searchable data dictionary: http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/.

The present study is based on research clinics to which the whole cohort was invited, held when participants were mean ages of 15.5 years. Ethical approval was obtained from the ALSPAC Law and Ethics committee, and the Local Research Ethics Committees. Parental consent and child's assent were obtained for all measurements made. Birth weight was abstracted from obstetric records.

Tibial pQCT

BMD_C and bone mineral content (BMC_C) of the mid (50% from the distal endplate) right tibia were obtained using a Stratec XCT2000L (Stratec, Pforzheim, Germany) during the age 15.5 year research clinic to which all ALSPAC participants were invited as part of a study investigating the effects of physical activity on cortical bone as previously published [16]. Further analyses were also performed based on equivalent pQCT measures obtained at age 17.7 years [17]. Periosteal circumference (PC), endosteal circumference (EC) and cortical thickness (CT) were derived using a circular ring model. Cortical bone was defined using a threshold above 650 mg/cm^3 [16], and cortical bone mineral density (BMD_C) subsequently derived. Strength strain index (SSI) for a circular ring model was calculated according to the formula published by the manufacturer.

Plasma insulin and beta-carboxyterminal cross linking telopeptide (βCTX)

Participants were asked to fast overnight (for those attending in the morning) or for a minimum of six hours for those attending after lunch. Blood plasma samples (EDTA) were immediately spun and frozen at −80 °C. Measurements were assayed shortly (3–9 months) after samples were taken with no previous freeze-thaw cycles. Insulin was measured by an ultrasensitive ELISA (Mercodia, Uppsala, Sweden) automated microparticle enzyme immunoassay that does not cross-react with pro-insulin. Its sensitivity was 0.07 mu/L and inter and intra-assay CVs were <6%. Electrochemiluminescence immunoassays (ECLIA) (Roche Diagnostics, Lewes, UK) were used to measure plasma concentrations of βCTX (detection limit 0.01 ng/mL). Inter- and intra-assay coefficients of variation (CVs) were <6% across the working range.

Other variables

Gestational age was calculated from the last menstrual period (from medical records) and the actual date of delivery. Height at clinic attendance was measured using a Harpenden stadiometer (Holtain Ltd., Crymych, UK) and weight was measured to the nearest 50 g using Tanita weighing scales (Tanita UK Ltd, Uxbridge). Data on lean mass and fat mass were obtained from total body DXA scans performed at the age 15.5 year clinic, using a Lunar Prodigy scanner (Lunar Radiation Corp, Madison, WI) with paediatric scanning software (GE Healthcare Bio-Sciences Corp., Piscataway, NJ). Puberty was assessed using a Tanner stage questionnaire at age 13.5 years (pubic hair domain) (range from 13.1 to 14.4 years), as previously found to be related to hip development as assessed by DXA [16]. To take account of any residual effect due to the actual age of completion, this age was also included in the model. Maternal education and paternal social class, assessed by questionnaire completed by the mother during the third trimester of pregnancy, were used as indicators of socio-economic status.

Statistical analyses

Linear regression was used to explore the linear effects of birth weight on pQCT outcomes. Adjustment was initially made for gender, gestation and age at scan. To examine whether birth weight also influenced pQCT parameters via a pathway that was independent of body size, further analyses adjusted for height and weight. Since relationships between many of these measures and pQCT outcomes varied by gender [16], interaction terms were also fitted in combined analyses. Sensitivity analyses were also performed to assess the effects of fat mass, lean mass and socio-economic status. Subgroup analyses by gender and formal interaction tests were used to investigate any modifying effects of gender. The mediating effects of puberty, blood insulin and βCTX were also investigated. These analyses were also adjusted by a time of day indicator to take account of possible diurnal variation (am/pm). Blood insulin and βCTX levels were normalised by log (base e) transformation.

Results

Participant characteristics

4152 participants mean age 15.5 years were identified with data for birth weight, pQCT and the main confounders. Compared with the rest of the cohort, these participants had a higher socio economic status as reflected by greater maternal education and higher paternal social class, and birth weight was also slightly higher (Supplementary Table 1). BMD_C was higher in girls, whereas measures of cortical bone size (PC, CT) and strength (SSI) were greater in boys (Table 1). Birth