**Differential relationships between parent-child DXA and pQCT bone measures: Results from the Southampton Women’s Survey**

Holroyd CR1,2\*, Carter S1\*, Crozier SR1, D’Angelo S1, Curtis EM1,2, Moon RJ1,3, Davies JH3, Ward KA1, Dennison EM1,4, Inskip HM1, Godfrey KM1,4, Cooper C1,4,5+, Harvey NC1,4+

1MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK

2Rheumatology Department, University Hospital Southampton NHS Foundation Trust, Southampton, UK

3Paediatric Endocrinology, University Hospital Southampton NHS Foundation Trust, Southampton, UK

4NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

5NIHR Biomedical Research Centre, University of Oxford, Oxford, UK

SC and CRH are joint first authors; CC and NCH are joint senior authors.

**Corresponding author**

Professor Nicholas Harvey

MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, SO16 6YD, UK

Email: nch@mrc.soton.ac.uk

**Keywords:** osteoporosis; epidemiology; mother-offspring; BMD; developmental origins

**Abstract**

*Aim*: To investigate the associations between indices of bone health in childhood and corresponding parental measures.

*Methods*: The Southampton Women’s Survey characterised 12,583 non-pregnant women aged 20-34 years; 3,158 subsequently had singleton live births. In a subset, dual-energy x-ray absorptiometry (DXA) measurements of bone area(BA), bone mineral content(BMC) and areal bone mineral density(aBMD) lumbar spine and total hip were obtained in the parent/offspring (aged 8-9 years) trios. Another subset of children (aged 6-7 years) and their parents, had peripheral quantitative computed tomography (pQCT; 4% and 38% tibia) measures. Using multivariable linear regression we examined relationships between mother/father and offspring, adjusting for parental age, habitual walking speed and education; offspring age and sex; and the corresponding bone measure in the other parent (β-coefficients (95%CI) unit/unit for each bone measure).

*Results*: Data were available for 260 trios with DXA and 99 with pQCT. There were positive associations for BA, BMC and aBMD between either parent and offspring. Mother-child associations were of greater magnitude than father-child; for example, mother-child aBMD (β=0.26g.cm-2/g.cm-2 (0.21,0.32)) and father-child aBMD (β=0.16g.cm-2/g.cm-2 (0.11,0.21)), P-difference in β=0.007. In the subset with pQCT there was a positive association for mother-offspring 4% tibial total area (β=0.33mm2/mm2 (0.17,0.48)), but little evidence of a father-offspring association (β=-0.06mm2/mm2 (-0.17,0.06)). In contrast offspring 38% cortical density was more strongly associated with this measure in fathers (β=0.48mg.cm-3/mg.cm-3 (0.15,0.82)) than mothers (β=0.27mg.cm-3/mg.cm-3 (-0.03,0.56)). In general mother-father differences were attenuated by adjustment for height.

*Conclusions*: Whilst offspring bone measures are independently associated with those of either parent, the magnitude of the association is often greater for maternal than paternal relationships. These findings are consistent with an in utero influence on offspring growth but might also reflect genetic and epigenetic parent of origin effects.

*Summary:* In an established parent-offspring cohort, associations between parent and offspring bone indices were generally greater in magnitude for mother-offspring than father-offspring relationships.

**Introduction**

Osteoporosis is an increasingly important public health problem worldwide, which has substantial impacts both at an individual level and on society as a whole, due to its association with low trauma fractures[1]. Bone strength in later life is dependent upon the peak bone mass achieved in early adult life and the rate of bone loss with advancing age[2]. Peak bone mass has been shown to be a major contributor to the risk of osteoporosis and fracture in later life, and so potential strategies to optimise peak bone mass are likely to be important in reducing the burden of osteoporosis in older age[3].

There is increasing evidence that poor height and weight growth early in life leads to reduced peak bone mass attained in early adulthood and an increased risk of fracture in older age[3]. Whilst a consistently demonstrated component of the variance in adult areal bone mineral density (aBMD) is explained by fixed genetic variation[4], there is clearly scope for environmental factors, both pre- and post-natally, to affect bone development to peak. Indeed we have demonstrated associations between bone mass and childhood physical activity and body composition, together with maternal factors such as diet, physical activity, lifestyle and 25-hydroxyvitamin D concentrations during pregnancy[3, 5, 6]. Parent-offspring studies of aBMD associations have generally been of mothers to daughters, and there is scant evidence to inform differential patterns of association by parent or by offspring sex despite the growing evidence for paternal effects in infant and child outcomes [7]. Given that the offspring have spent typically nine months receiving maternal nutrition in utero, parent-offspring aBMD relationships which differ by parent might point to a role for the early environment in utero as much as specific parent of origin gene inheritance[8].

We therefore aimed to investigate parent-offspring associations, by parent and by offspring sex, in measures of bone derived from dual-energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) in the Southampton Women’s Survey, a large, well-established population-based parent-offspring cohort.

**Methods**

*The Southampton Women’s Survey (SWS)*

The Southampton Women’s Survey (SWS) is a large, unique prospective parent-offspring cohort that recruited 12,583 non-pregnant women aged 20-34 years living in the city of Southampton[9]. Participants were visited at home by a trained research nurse. At the initial visit a questionnaire was administered to assess physical activity, general health, smoking history, menstrual and obstetric history, education, ethnicity, housing, benefits, social class and own and partner’s occupation[10, 11]. Anthropometric assessments included height (measured by stadiometer; Seca, Birmingham, UK), weight (measured by digital scales; Seca, Birmingham, UK). Women enrolled in the study were asked to immediately inform the study team if they became pregnant, and gave consent for their GP or hospital clinician to also communicate this information. Pregnant women were invited to attend research clinics for interviews at 11 weeks (early pregnancy) and 34 weeks (late pregnancy). At these visits, a lifestyle questionnaire was again completed along with repeat anthropometric measurements (as described for the initial visit). The 3158 liveborn singleton children born in the SWS cohort have been followed-up through childhood.

1214 children attending the SWS 8-9-year follow-up completed a lifestyle questionnaire and underwent dual-energy X-ray absorptiometry (DXA) assessment of their whole body, hip, and spine using a Hologic Discovery A machine (Hologic Inc., Bedford, MA, USA; Software V12.7.3). The child’s parents were also invited to attend for DXA assessment, during which bone area (BA), bone mineral content (BMC), and areal bone mineral density (aBMD) measurements were made at the lumbar spine, and hip sites. The manufacturer’s coefficient of variation for this instrument for whole body aBMD was 0.75%. A subset of 653 children underwent pQCT assessment of their non-dominant lower leg at 6-7 years old. Parents of these children underwent the same pQCT assessment when attending the 8-9 year parental visit (4% and 38% tibia sites), using a Stratec XCT-2000 instrument (Stratec Inc., Pforzheim, Germany). DXA and pQCT scans were reviewed and those with excessive movement or clothing artefacts were omitted from the analysis.

*Statistical analysis*

All baseline characteristics were checked for normality of distribution. T-tests and Mann-Whitney U tests were used to compare normally distributed and non-normally distributed maternal pre-pregnancy characteristics respectively against the larger SWS cohort.

Multivariable linear regression was used to examine parent-child relationships for both offspring 8-9-year DXA scans and 6-7-year pQCT scans. The Hausman test was used to compare the magnitude of regression coefficients. DXA measurements included in this study were BA, BMC and aBMD for the participant’s lumbar spine and non-dominant hip. We analysed pQCT variables from the 4% tibial site (total area, trabecular volumetric bone mineral density (vBMD)) and the 38% tibial site (total area, cortical area, and cortical vBMD).

The covariates considered were informed by prior literature and biological plausibility to account for true confounders and measures potentially on the causal pathway (parental and child height). Thus models were initially adjusted for the equivalent bone measure of the opposite parent, maternal late pregnancy walking speed, maternal and paternal age at DXA scan, maternal pre-pregnancy educational level and the age of the child (Model 1). In previous work we observed that late pregnancy walking speed was associated inversely with offspring bone mass, independent of fat mass[12]. Further models added adjustment for maternal and paternal height at DXA scan (Model 2), and additionally child’s height at DXA scan (Model 3). While Models 1-3 were undertaken for both the whole sample and the sample stratified by offspring sex for DXA outcome measures, sample size restrictions made stratification by offspring sex untenable for pQCT measurements. Whole sample analyses were additionally adjusted for offspring sex. All data were analysed using Stata 14.0 (StataCorp, Texas, USA).

**Results**

*Baseline demographics*

Baseline characteristics of the children at DXA are shown in Table 1a. Mean (SD) age was 9.2 (0.2) years, and 51% of the children were male. Girls and boys had similar BMI [Girls: median 17.0 kg/m2 (IQR 15.7, 18.9); Boys: 16.2 kg/m2 (15.2, 17.8)]. Boys had higher birthweights [mean 3468 (SD 565) g] than girls [3404 (536) g]. Mean lumbar spine BA, and hip aBMD and BMC, were higher in boys. Conversely, girls had higher mean lumbar spine aBMD. Baseline characteristics of the parents are presented in Table 1b. Mean (SD) age of the mothers [41.2 (3.4) years] was lower than that for the fathers [43.8 (5.1) years)]. On average, fathers were taller and heavier than mothers, and were more likely to have smoked regularly in the past. Fathers also consumed more alcohol and milk per week than did mothers and had higher rates of previous fracture. 97.0% of mothers and 96.6% of fathers reported being of White ethnicity. Compared with the wider SWS cohort, mothers included in this sample were somewhat older, taller and had a lower BMI than those who did not attend 8-9-year DXA offspring follow-up clinics (Supplementary Table 1).

*Parent and offspring bone measures are positively associated, partly independent of body size*

Strong positive associations were observed between maternal or paternal lumbar spine DXA measurements (BA, BMC and aBMD), and the corresponding indices in the offspring (Table 2). Mother-child BA and BMC associations were somewhat attenuated by incorporation of parental and child height in the models, but mother-child aBMD and father-child associations in general were little changed by this adjustment. Parent-offspring associations at the hip site followed a similar pattern to the lumbar spine relationships (Table 3).

*Mother-offspring of greater magnitude than father-offspring DXA associations*

Mother-child lumbar spine associations were consistently of greater magnitude than father-child associations (Table 2, Figure 1); for example, offspring lumbar spine aBMD was more strongly associated with maternal lumbar spine aBMD (Model 1: β = 0.29g.cm-2/g.cm-2 (95%CI 0.20, 0.38), P<0.001) than with paternal lumbar spine aBMD (Model 1: β = 0.16g.cm-2/g.cm-2 (0.11, 0.21), P<0.001). At the hip, mother-child associations were of greater magnitude than father-child associations for BA, but not BMC or aBMD (Table 3, Figure 1): Model 1 for maternal hip BA: β = 0.33cm2/cm2 (0.23, 0.44), P=0.001); paternal hip BA (β = 0.14cm2/cm2 (0.07, 0.21), P=0.11). These by-parent differences were more apparent for boys than girls for the lumbar spine sites and for hip bone area (Figure 1). Adjustment for parental and child’s height tended to reduce the by-parent differences [Model 2 (parental height) and Model 3 (parental and child’s height); Supplementary Figure 1], predominantly by reducing the effect size for mother-child associations. The models stratified by sex of the child are presented in Supplementary Tables 2 and 3, showing similar findings in that generally maternal associations were stronger than the paternal ones. No evidence was observed for maternal or paternal associations being stronger for one sex than the other.

*Differences by parent in mother-offspring and father-offspring pQCT bone relationships*

Parent-offspring pQCT associations are summarised in Table 4. Mother-offspring, but not father-offspring, associations were apparent at 4% total area, robust to adjustment for parental and offspring heights (Model 3: β=0.30mm2/mm2 (0.15, 0.46), p<0.001). Father-offspring associations were observed for 38% cortical area (Model 3: β=0.10mm2/mm2 (0.02, 0.18), P=0.01) and 38% cortical density (Model 3: β=0.64mg.cm-3/mg.cm-3 (0.27, 1.00), P=0.001), with associations that were either robust for, or strengthened by, adjustment for parental and offspring height (Figure 2 and Supplementary Figure 2).

**Discussion**

In this study within the Southampton Women’s Survey parent-offspring cohort, we observed associations between parent and offspring bone indices at the lumbar spine and hip, which generally persisted after adjustment for parent and/or offspring body size. Furthermore, many of the associations were of greater magnitude for mother-offspring than father-offspring suggesting a potential parent of origin effect.

There is a paucity of studies using techniques other than DXA to assess the genetic influence on bone mass, and few published have focused on parent-child pairs[13-15]. A recent Australian study used HRpQCT at the distal radius and tibia to measure volumetric bone mineral density in 177 mother-offspring pairs from the T-Bone cohort; the mean offspring age in this cohort was 25 years[13]. Strong positive relationships were observed across all the parameters measured, and heritability estimates ranged from 42%-74% at the tibia and 24%-67% at the radius. Whilst estimates of genetic heritability vary widely depending upon the study design and setting, there is clearly a direct genetic component to the variance in aBMD within a population. GWAS studies explain a component of this variation on the basis of identified loci, and the largest GWAS to date, in we which identified more than 300 conditionally independent SNPs linked with aBMD, genotype accounted for at most 20% of the variance in adult aBMD (in this case estimated from quantitative heel ultrasound)[16]. It is likely that a large number of SNPs either identified but not meeting the threshold for genome-wide significance, or yet to be discovered, will explain more of the variance, but there is clearly scope for environmental factors to influence peak aBMD obtained by young adulthood[3]. Importantly, it must be remembered that genetic heritability simply refers to the proportion of the variance in the aBMD distribution within a population which is explained by genetics[17]. The overall mean of the distribution can therefore be moved, for example by population-wide secular changes in diet quality and socioeconomics, without changing the spread of the distribution. The secular changes in height in several populations over recent decades provides a case in point[18-27]. The same genetic effect in a population with a low prevalence of a key environmental factor, compared with a population with a high prevalence of that factor will lead to different estimates of genetic heritability. These considerations should be borne in mind in considering the potential underlying mechanisms here.

The association between parent and offspring bone mass can therefore be potentially explained in terms of inherited genotype, inherited environment (for example exposure to second-hand smoking in childhood and dietary/socio-economic factors), and in terms of early life in utero effects. These latter mechanisms are of course mother-specific and might be an explanation for the differences observed in the magnitude of mother-offspring compared with father-offspring relationships. A further complication is that an apparently environmental maternal in utero effect could be direct, for example due to placental nutritional transfer, or reflect an indirect genetic influence, for example on height. Thus, with greater body size, maternal BMC is likely to be higher due to her larger pelvis[28]. Last trimester fetal growth is necessarily constrained by the size of the pelvis in order to permit delivery of the baby[3, 29, 30]. A larger pelvis therefore is likely to be able accommodate greater offspring growth, without constraint[31], and may result in a larger child at birth, with larger BA and BMC as a result[32]. We observed that size-dependent measures of offspring bone from DXA and pQCT appeared to have a stronger maternal association, and consequently this difference was attenuated by adjustment for height. The associations at the lumbar spine were more marked for mother than father across BA, BMC and aBMD. Such considerations, and differential relationships between bone indices and height by site[33], may well be relevant to observation of greater effect size in mother-offspring compared with father-offspring associations for lumbar spine compared with hip bone mineral density. However, strong relationships remained even after adjustment for maternal height (a surrogate for maternal size), suggesting the potential importance of other mechanisms. In addition, in the subset of those with pQCT measures, at the 38% tibia, cortical BMD association was of greater magnitude for father-child compared with mother-child, suggesting possible sex-specific differences by trabecular/cortical sites.

A further explanation for the parent-child bone mass relationships is that of inherited environmental factors. A study in the Bristol ALSPAC cohort demonstrated that maternal socioeconomic status has opposing influences on offspring bone mass through opposite associations with offspring height and weight[34]. It has been well documented that certain parental activities are highly correlated with those of their offspring, such as physical activity and diet, which may in turn confound parent-offspring bone comparisons. Finally, parent of origin genetic effects, termed “imprinting”, whereby epigenetic phenomena result in only the gene inherited from a specific parent being expressed, might be relevant here[35]. There are around eighty known imprinted genes, but growth-related genes, such as *IGF2*, tend to be paternally expressed[36], which would be expected to lead to greater father-offspring than mother-offspring associations rather than the dominant mother-offspring relationships observed in the present study. However, such epigenetic processes are the subject of intense ongoing investigation and an imprinting effect, or indeed other parent-specific mechanisms such as micro-RNA in seminal fluid or sperm histone changes, could all play a role in differential parental associations[37-39].

This study used a well-characterised prospective mother-offspring cohort study, with “gold-standard” measures bone mass. However, several limitations should be considered in the interpretation of our results. Firstly, our sample was a subset of the larger SWS cohort, and both mothers and offspring differed in several ways from the overall study population. There was little ethnic diversity within the participating mothers, with 97% of mothers of white ethnicity. This reflects the local population from which the women were recruited and gives more homogeneity to the study population, but needs to be considered in the generalisability of the findings to the wider population. As the results are based on internal comparisons within the cohort, there is little reason to expect that this would have erroneously led to the observed associations. Secondly, DXA scanning of children is subject to several limitations, due to their lower BMD when compared with adults and the propensity of younger participants to move during scanning. Appropriate software was used, but the developing growth plate at the hip means that the precision at this site in children is somewhat lower than in adults[40]. Thirdly, there are also limitations with the use of pQCT analysis in growing children. Although standard protocols were used, the possibility of relative differences in the scan position dependent upon tibial length, and operator variability, remain. Fourthly, we were not able to account for every factor that might influence the parent-child relationship such as 25-hydroxyvitamin D concentrations and chronic illnesses. However, in this predominantly healthy, population-based cohort of mainly white ethnicity, the frequency of symptomatic vitamin D deficiency or severe chronic illness is likely to be extremely low.

In conclusion, parent and offspring bone indices are positively associated, with a greater magnitude of relationship in many cases observed for the mother-offspring compared with father-offspring associations. These relationships appeared partly independent of maternal and/or offspring body size, and independent of other potentially confounding factors. Whilst parent of origin genetic effects are potential explanations, these marked mother-offspring associations may suggest in-utero environmental influences on childhood bone development.

**Acknowledgements**

We thank the administrative staff, research nurses and participants of the SWS for their contributions. CRH and SC are joint first author. CC and NCH are joint senior author. This work was supported by grants from Medical Research Council (MRC) [4050502589 (MRC LEU)], Bupa Foundation, British Heart Foundation, National Institute for Health Research (NIHR) Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, NIHR Oxford Biomedical Research Centre, University of Oxford and the UK Royal Osteoporosis Society Osteoporosis and Bone Research Academy. EMC has been supported by the Wellcome Trust (201268/Z/16/Z) and an NIHR Clinical Lectureship. KMG is supported by the National Institute for Health Research (NIHR Senior Investigator (NF-SI-0515-10042), the European Union (Erasmus+ Programme ImpENSA 598488-EPP-1-2018-1-DE-EPPKA2-CBHE-JP) the British Heart Foundation (RG/15/17/3174) and the US National Institute On Aging of the National Institutes of Health (Award No. U24AG047867). The work leading to these results was supported by the European Union’s Seventh Framework Programme (FP7/2007–2013), projects EarlyNutrition, ODIN and LifeCycle under grant agreements numbers 289346, 613977 and 733206, and by the BBSRC (HDHL-Biomarkers, BB/P028179/1), as part of the ALPHABET project, supported by an award made through the ERA-Net on Biomarkers for Nutrition and Health (ERA HDHL), Horizon 2020 grant agreement number 696295.

**Conflicts of interest**

CR Holroyd, S Carter, SR Crozier, S D’Angelo, EM Curtis, RJ Moon, JH Davies, KA Ward, EM Dennison, HM Inskip, KM Godfrey, C Cooper, NC Harvey declare that they have no conflicts of interest in relation to this work.

**References**

[1] N. Harvey, E. Dennison, C. Cooper, Osteoporosis: impact on health and economics, Nat.Rev.Rheumatol. 6(2) (2010) 99-105.

[2] C.J. Hernandez, G.S. Beaupre, D.R. Carter, A theoretical analysis of the relative influences of peak BMD, age-related bone loss and menopause on the development of osteoporosis, Osteoporos Int 14(10) (2003) 843-847.

[3] N. Harvey, E. Dennison, C. Cooper, Osteoporosis: a lifecourse approach, J Bone Miner Res 29(9) (2014) 1917-25.

[4] J.P. Kemp, J.A. Morris, C. Medina-Gomez, V. Forgetta, N.M. Warrington, S.E. Youlten, J. Zheng, C.L. Gregson, E. Grundberg, K. Trajanoska, J.G. Logan, A.S. Pollard, P.C. Sparkes, E.J. Ghirardello, R. Allen, V.D. Leitch, N.C. Butterfield, D. Komla-Ebri, A.T. Adoum, K.F. Curry, J.K. White, F. Kussy, K.M. Greenlaw, C. Xu, N.C. Harvey, C. Cooper, D.J. Adams, C.M.T. Greenwood, M.T. Maurano, S. Kaptoge, F. Rivadeneira, J.H. Tobias, P.I. Croucher, C.L. Ackert-Bicknell, J.H.D. Bassett, G.R. Williams, J.B. Richards, D.M. Evans, Identification of 153 new loci associated with heel bone mineral density and functional involvement of GPC6 in osteoporosis, Nat Genet 49(10) (2017) 1468-1475.

[5] M.K. Javaid, S.R. Crozier, N.C. Harvey, C.R. Gale, E.M. Dennison, B.J. Boucher, N.K. Arden, K.M. Godfrey, C. Cooper, Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study, Lancet 367(9504) (2006) 36-43.

[6] C. Cooper, N.C. Harvey, N.J. Bishop, S. Kennedy, A.T. Papageorghiou, I. Schoenmakers, R. Fraser, S.V. Gandhi, A. Carr, S. D'Angelo, S.R. Crozier, R.J. Moon, N.K. Arden, E.M. Dennison, K.M. Godfrey, H.M. Inskip, A. Prentice, M.Z. Mughal, R. Eastell, D.M. Reid, M.K. Javaid, Maternal gestational vitamin D supplementation and offspring bone health (MAVIDOS): a multicentre, double-blind, randomised placebo-controlled trial, The lancet. Diabetes & endocrinology 4(5) (2016) 393-402.

[7] H.S. Choi, J.H. Park, S.H. Kim, S. Shin, M.J. Park, Strong familial association of bone mineral density between parents and offspring: KNHANES 2008-2011, Osteoporos Int 28(3) (2017) 955-964.

[8] N.C. Harvey, M.K. Javaid, J.R. Poole, P. Taylor, S.M. Robinson, H.M. Inskip, K.M. Godfrey, C. Cooper, E.M. Dennison, Paternal skeletal size predicts intrauterine bone mineral accrual, J Clin Endocrinol.Metab 93(5) (2008) 1676-1681.

[9] H.M. Inskip, K.M. Godfrey, S.M. Robinson, C.M. Law, D.J. Barker, C. Cooper, Cohort profile: The Southampton Women's Survey, Int J Epidemiol. (2005).

[10] H.M. Inskip, K.M. Godfrey, S.M. Robinson, C.M. Law, D.J. Barker, C. Cooper, S.W.S.S. Group, Cohort profile: The Southampton Women's Survey, Int J Epidemiol 35(1) (2006) 42-8.

[11] S.E. Borland, S.M. Robinson, S.R. Crozier, H.M. Inskip, Stability of dietary patterns in young women over a 2-year period, Eur.J.Clin Nutr. (2007).

[12] N.C. Harvey, M.K. Javaid, N.K. Arden, J.R. Poole, S.R. Crozier, S.M. Robinson, H.M. Inskip, K.M. Godfrey, E.M. Dennison, C. Cooper, Maternal predictors of neonatal bone size and geometry: the Southampton Women's Survey, Journal of Developmental Origins of Health and Disease 1(1) (2010) 35-41.

[13] Y. Yang, F. Pan, F. Wu, K. Squibb, R. Thomson, T. Winzenberg, G. Jones, Familial resemblance in trabecular and cortical volumetric bone mineral density and bone microarchitecture as measured by HRpQCT, Bone 110 (2018) 76-83.

[14] H. Nagy, R. Chapurlat, E. Sornay-Rendu, S. Boutroy, P. Szulc, Family resemblance of bone turnover rate in mothers and daughters--the MODAM study, Osteoporos Int 26(3) (2015) 921-30.

[15] K.L. Popp, J.M. Hughes, A. Martinez-Betancourt, M. Scott, V. Turkington, S. Caksa, K.I. Guerriere, K.E. Ackerman, C. Xu, G. Unnikrishnan, J. Reifman, M.L. Bouxsein, Bone mass, microarchitecture and strength are influenced by race/ethnicity in young adult men and women, Bone 103 (2017) 200-208.

[16] J.A. Morris, J.P. Kemp, S.E. Youlten, L. Laurent, J.G. Logan, R.C. Chai, N.A. Vulpescu, V. Forgetta, A. Kleinman, S.T. Mohanty, C.M. Sergio, J. Quinn, L. Nguyen-Yamamoto, A.L. Luco, J. Vijay, M.M. Simon, A. Pramatarova, C. Medina-Gomez, K. Trajanoska, E.J. Ghirardello, N.C. Butterfield, K.F. Curry, V.D. Leitch, P.C. Sparkes, A.T. Adoum, N.S. Mannan, D.S.K. Komla-Ebri, A.S. Pollard, H.F. Dewhurst, T.A.D. Hassall, M.G. Beltejar, D.J. Adams, S.M. Vaillancourt, S. Kaptoge, P. Baldock, C. Cooper, J. Reeve, E.E. Ntzani, E. Evangelou, C. Ohlsson, D. Karasik, F. Rivadeneira, D.P. Kiel, J.H. Tobias, C.L. Gregson, N.C. Harvey, E. Grundberg, D. Goltzman, D.J. Adams, C.J. Lelliott, D.A. Hinds, C.L. Ackert-Bicknell, Y.H. Hsu, M.T. Maurano, P.I. Croucher, G.R. Williams, J.H.D. Bassett, D.M. Evans, J.B. Richards, An atlas of genetic influences on osteoporosis in humans and mice, Nat Genet 51(2) (2019) 258-266.

[17] C.W. Slemenda, J.C. Christian, C.J. Williams, J.A. Norton, C.C. Johnston, Jr., Genetic determinants of bone mass in adult women: a reevaluation of the twin model and the potential importance of gene interaction on heritability estimates, J Bone Miner Res JID - 8610640 6(6) (1991) 561-567.

[18] S. Bartkowiak, J.M. Konarski, R. Strzelczyk, J. Janowski, R.M. Malina, Secular change in height and weight of rural school children and youth in west-central Poland: 1986 to 2016, Am J Hum Biol (2020) e23461.

[19] A. Gomula, N. Nowak-Szczepanska, S. Koziel, Secular trend and social variation in height of Polish schoolchildren between 1966 and 2012, Acta Paediatr (2020).

[20] A. Holmgren, A. Niklasson, A.S. Aronson, A. Sjöberg, L. Lissner, K. Albertsson-Wikland, Nordic populations are still getting taller - secular changes in height from the 20th to 21st century, Acta Paediatr 108(7) (2019) 1311-1320.

[21] E. Kalka, A. Pastuszak, K. Buśko, Secular trends in body height, body weight, BMI and fat percentage in Polish university students in a period of 50 years, PloS one 14(8) (2019) e0220514.

[22] N. Koepke, J. Floris, C. Pfister, F.J. Rühli, K. Staub, Ladies first: Female and male adult height in Switzerland, 1770-1930, Econ Hum Biol 29 (2018) 76-87.

[23] Ł. Kryst, M. Żegleń, A. Woronkowicz, R. Das, R. Saha, S. Das, P. Dasgupta, Long-term changes in body proportions since 1952 to 2011 in children and adolescents from Kolkata (India), Anthropol Anz 75(3) (2018) 201-213.

[24] M. Lopuszanska-Dawid, H. Kołodziej, A. Lipowicz, A. Szklarska, A. Kopiczko, T. Bielicki, Social class-specific secular trends in height among 19-year old Polish men: 6th national surveys from 1965 till 2010, Econ Hum Biol 37 (2020) 100832.

[25] T.M. Pavlica, R.S. Rakić, B.K. Popović, V.P. Puškaš, Secular trend in growth and nutritional status in a sample of girls aged 7-9 years from Serbia, Homo 69(5) (2018) 280-286.

[26] W.M. Wilson, J. Bulkan, B.A. Piperata, K. Hicks, Secular trends in adult stature among the Makushi of Guyana in the 20th Century, Am J Hum Biol 31(5) (2019) e23285.

[27] Y.Q. Zhang, H. Li, H.H. Wu, X.N. Zong, Secular trends in weight, height and weight for height among children under 7 years in nine cities of China, 1975-2015: results from five repeated cross-sectional surveys, BMJ open 9(10) (2019) e029201.

[28] B. Fischer, P. Mitteroecker, Covariation between human pelvis shape, stature, and head size alleviates the obstetric dilemma, Proc Natl Acad Sci U S A 112(18) (2015) 5655-60.

[29] R.A. McCance, E.M. Widdowson, The determinants of growth and form, Proc R Soc Lond B Biol Sci JID - 7505889 185(78) (1974) 1-17.

[30] J.M. Tanner, The interaction of heredity and environment in the control of growth, Foetus into Man: Physical growth from conception to maturity, Castlemead Publications, Ware, 1989, pp. 119-164.

[31] M.A. Hanson, K.M. Godfrey, Commentary: Maternal constraint is a pre-eminent regulator of fetal growth, Int.J.Epidemiol. 37(2) (2008) 252-254.

[32] J.C.K. Wells, J.N. Figueiroa, J.G. Alves, Maternal pelvic dimensions and neonatal size: Implications for growth plasticity in early life as adaptation, Evol Med Public Health 2017(1) (2017) 191-200.

[33] E. Seeman, Structural basis of growth-related gain and age-related loss of bone strength, Rheumatology (Oxford) 47 Suppl 4 (2008) iv2-8.

[34] E.M. Clark, A. Ness, J.H. Tobias, Social position affects bone mass in childhood through opposing actions on height and weight, J.Bone Miner.Res. 20(12) (2005) 2082-2089.

[35] A. Kong, V. Steinthorsdottir, G. Masson, G. Thorleifsson, P. Sulem, S. Besenbacher, A. Jonasdottir, A. Sigurdsson, K.T. Kristinsson, A. Jonasdottir, M.L. Frigge, A. Gylfason, P.I. Olason, S.A. Gudjonsson, S. Sverrisson, S.N. Stacey, B. Sigurgeirsson, K.R. Benediktsdottir, H. Sigurdsson, T. Jonsson, R. Benediktsson, J.H. Olafsson, O.T. Johannsson, A.B. Hreidarsson, G. Sigurdsson, A.C. Ferguson-Smith, D.F. Gudbjartsson, U. Thorsteinsdottir, K. Stefansson, Parental origin of sequence variants associated with complex diseases, Nature 462(7275) (2009) 868-74.

[36] W. Reik, K. Davies, W. Dean, G. Kelsey, M. Constancia, Imprinted genes and the coordination of fetal and postnatal growth in mammals, Novartis Found Symp JID - 9807767 237 (2001) 19-31.

[37] L.K. Klastrup, S.T. Bak, A.L. Nielsen, The influence of paternal diet on sncRNA-mediated epigenetic inheritance, Molecular genetics and genomics : MGG 294(1) (2019) 1-11.

[38] M. Kumar, K. Kumar, S. Jain, T. Hassan, R. Dada, Novel insights into the genetic and epigenetic paternal contribution to the human embryo, Clinics (Sao Paulo, Brazil) 68 Suppl 1(Suppl 1) (2013) 5-14.

[39] Y. Zhang, J. Shi, M. Rassoulzadegan, F. Tuorto, Q. Chen, Sperm RNA code programmes the metabolic health of offspring, Nature reviews. Endocrinology 15(8) (2019) 489-498.

[40] N.J. Crabtree, A. Arabi, L.K. Bachrach, M. Fewtrell, G. El-Hajj Fuleihan, H.H. Kecskemethy, M. Jaworski, C.M. Gordon, Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD Pediatric Official Positions, J Clin Densitom 17(2) (2014) 225-42.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Overall** | **Boys** | **Girls** |
|  | n | Mean/ Median | SD | n | Mean/ Median | SD | n | Mean/Median | SD |
| **Age (yrs)** | 279 | 9.2 | 0.2 | 146 | 9.2 | 0.2 | 133 | 9.2 | 0.2 |
| **Height (cm)** | 278 | 135.6 | 5.8 | 145 | 135.0 | 5.2 | 133 | 136.2 | 6.4 |
| **Weight (kg)\*** | 263 | 30.7 | 27.5, 34.6 | 133 | 30.0 | 27.2, 33.4 | 130 | 31.8 | 28.1, 36.4 |
| **BMI \*(kg/m2)** | 272 | 16.6 | 15.5, 17.8 | 132 | 16.2 | 15.2, 17.8 | 130 | 17.0 | 15.7, 18.9 |
| **Birthweight (g)** | 277 | 3437 | 551 | 144 | 3468 | 565 | 133 | 3404 | 536 |
|  |  |  |  |  |  |  |  |  |  |
| **Lumbar spine BA (cm2)** | 279 | 39.2 | 4.2 | 146 | 39.9 | 4.2 | 133 | 38.4 | 4.1 |
| **Lumbar spine BMC (g)** | 279 | 23.2 | 3.9 | 146 | 23.2 | 3.9 | 133 | 23.3 | 3.8 |
| **Lumbar spine aBMD (g/cm2)** | 279 | 0.6 | 0.1 | 146 | 0.6 | 0.1 | 133 | 0.6 | 0.1 |
| **Hip BA (cm2)** | 279 | 21.1 | 2.8 | 146 | 20.6 | 2.7 | 133 | 21.5 | 2.8 |
| **Hip BMC (g)** | 279 | 14.9 | 2.7 | 146 | 15.0 | 2.8 | 133 | 14.7 | 2.6 |
| **Hip aBMD (g/cm2)** | 279 | 0.7 | 0.1 | 146 | 0.7 | 0.1 | 133 | 0.7 | 0.1 |

**Table 1a:** Offspring baseline characteristics

\*Summary statistics median (IQR); BA= bone area; BMC=bone mineral content; aBMD=areal bone mineral density.

**Table 1b:** Baseline parental characteristics

|  |  |  |
| --- | --- | --- |
|  | **Mothers (n=279)** | **Fathers (n=279)** |
|  | n | Mean/Median/% | SD/IQR |  | n | Mean/Median/% | SD/IQR |  |
| **Age (years)** | 266 | 40.9 | 3.5 |  | 270 | 43.7 | 5.3 |  |
| **Height (cm)** | 279 | 164.8 | 6.2 |  | 279 | 176.9 | 6.7 |  |
| **Weight (kg)\*** | 279 | 68.1 | (61.1, 79.4) |  | 279 | 85.5 | (76.4, 96.2) |  |
| **Parity at birth of index child** | 279 |  |  |  |  |  |  |  |
|  Primiparous | 144 | 51.6% |  |  |  |  |  |  |
|  Multiparous | 135 | 48.4% |  |  |  |  |  |  |
| **Current smoking** | 22/248 | 8.9% |  |  | 30/254 | 11.8% |  |  |
| **Ever smoked regularly** | 86/262 | 32.8% |  |  | 116/265 | 43.8% |  |  |
| **Smoked in EP** | 19/276 | 6.9% |  |  |  |  |  |  |
| **Smoked in LP** | 17/268 | 6.3% |  |  |  |  |  |  |
| **Alcohol consumption (units per week)\*** | 263 | 3.0 | (1.0, 7.5) |  | 270 | 7.0 | (2.2, 16.0) |  |
| **Pre-menopausal** | 272/279 | 97.5% |  |  |  |  |  |  |
| **Previous fracture** | 101/263 | 38.4% |  |  | 157/265 | 59.3% |  |  |
| **≥ 0.5 pints of milk/day** | 136/262 | 51.9% |  |  | 174/261 | 66.7% |  |  |
| **Ethnicity** | 263 |  |  |  | 265 |  |  |  |
|  White | 255 | 97.0% |  |  | 256 | 96.6% |  |  |
|  BAME | 8 | 3.0% |  |  | 9 | 3.4% |  |  |

\*Summary statistics median (IQR); EP = Early pregnancy; LP = Late pregnancy;

**Table 2:** Relationships between DXA derived parent and offspring lumbar spine in boys and girls combined.

|  |  |
| --- | --- |
| **Lumbar spine DXA** | Whole sample |
| β | 95% CI | P | n |
| **Maternal** |  |  |  |  |
| **BA (cm2)** |  |  |  |  |
| Model 1 | 0.29 | 0.20, 0.38 | < 0.001 | 236 |
| Model 2 | 0.21 | 0.10, 0.32 | < 0.001 | 236 |
| Model 3 | 0.17 | 0.08, 0.26 | < 0.001 | 235 |
| **BMC (g)** |  |  |  |  |
| Model 1 | 0.15 | 0.12, 0.19 | < 0.001 | 236 |
| Model 2 | 0.14 | 0.10, 0.18 | < 0.001 | 236 |
| Model 3 | 0.12 | 0.08, 0.15 | < 0.001 | 235 |
| **aBMD (g/cm2)** |  |  |  |  |
| Model 1 | 0.26 | 0.21, 0.32 | < 0.001 | 236 |
| Model 2 | 0.26 | 0.21, 0.32 | < 0.001 | 236 |
| Model 3 | 0.25 | 0.20, 0.31 | < 0.001 | 235 |
|  |  |  |  |  |
| **Paternal** |  |  |  |  |
| **BA (cm2)** |  |  |  |  |
| Model 1 | 0.09 | 0.02, 0.16 | 0.01 | 236 |
| Model 2 | 0.07 | -0.01, 0.16 | 0.08 | 236 |
| Model 3 | 0.10 | 0.03, 0.16 | 0.005 | 235 |
| **BMC (g)** |  |  |  |  |
| Model 1 | 0.08 | 0.05, 0.11 | < 0.001 | 236 |
| Model 2 | 0.08 | 0.04, 0.11 | < 0.001 | 236 |
| Model 3 | 0.07 | 0.05, 0.10 | < 0.001 | 235 |
| **aBMD (g/cm2)** |  |  |  |  |
| Model 1 | 0.16 | 0.11, 0.21 | < 0.001 | 236 |
| Model 2 | 0.15 | 0.10, 0.20 | < 0.001 | 236 |
| Model 3 | 0.14 | 0.09, 0.19 | < 0.001 | 235 |

Model 1: Adjusted for equivalent bone measure of the opposite parent, maternal late pregnancy walking speed, maternal and paternal age at DXA scan, maternal pre-pregnancy educational level and the sex and age of the child; Model 2: Model 1 + maternal and paternal height at DXA scan; Model 3: Model 2 + child’s height at DXA scan.

**Table 3:** Relationships between DXA derived parent and offspring hip outcomes in boys and girls combined

|  |  |
| --- | --- |
| **Hip DXA** | Whole sample |
| β | 95% CI | P | n |
| **Maternal** |  |  |  |  |
| **BA (cm2)** |  |  |  |  |
| Model 1 | 0.33 | 0.23, 0.44 | < 0.001 | 239 |
| Model 2 | 0.25 | 0.11, 0.38 | < 0.001 | 239 |
| Model 3 | 0.22 | 0.12, 0.32 | < 0.001 | 238 |
| **BMC (g)** |  |  |  |  |
| Model 1 | 0.13 | 0.07, 0.19 | < 0.001 | 239 |
| Model 2 | 0.09 | 0.03, 0.15 | 0.005 | 239 |
| Model 3 | 0.08 | 0.04, 0.13 | 0.001 | 238 |
| **aBMD (g/cm2)** |  |  |  |  |
| Model 1 | 0.14 | 0.08, 0.21 | < 0.001 | 239 |
| Model 2 | 0.14 | 0.08, 0.21 | < 0.001 | 239 |
| Model 3 | 0.14 | 0.08, 0.21 | < 0.001 | 238 |
|  |  |  |  |  |
| **Paternal** |  |  |  |  |
| **BA (cm2)** |  |  |  |  |
| Model 1 | 0.14 | 0.07, 0.21 | < 0.001 | 239 |
| Model 2 | 0.12 | 0.03, 0.21 | 0.007 | 239 |
| Model 3 | 0.10 | 0.03, 0.16 | 0.003 | 238 |
| **BMC (g)** |  |  |  |  |
| Model 1 | 0.09 | 0.06, 0.13 | < 0.001 | 239 |
| Model 2 | 0.08 | 0.04, 0.12 | < 0.001 | 239 |
| Model 3 | 0.06 | 0.03, 0.10 | < 0.001 | 238 |
| **aBMD (g/cm2)** |  |  |  |  |
| Model 1 | 0.14 | 0.08, 0.20 | < 0.001 | 239 |
| Model 2 | 0.14 | 0.07, 0.20 | < 0.001 | 239 |
| Model 3 | 0.12 | 0.06, 0.18 | < 0.001 | 238 |

Model 1: Adjusted for equivalent bone measure of the opposite parent, maternal late pregnancy walking speed, maternal and paternal age at DXA scan, maternal pre-pregnancy educational level and the sex and age of the child; Model 2: Model 1 + maternal and paternal height at DXA scan; Model 3: Model 2 + child’s height at DXA scan.

**Table 4:** Relationships between pQCT derived parental and offspring bone health outcomes in boys and girls combined.

|  |  |  |
| --- | --- | --- |
| **pQCT at tibia** | Maternal | Paternal |
| β | 95% CI | P | n | β | 95% CI | P |  |
| **4% total area (mm2)** |  |  |  |  |  |  |  |  |
| Model 1 | 0.33 | 0.17, 0.48 | < 0.001 | 94 | -0.06 | -0.17, 0.06 | 0.33 | 94 |
| Model 2 | 0.34 | 0.17, 0.50 | < 0.001 | 94 | -0.09 | -0.21, 0.04 | 0.16 | 94 |
| Model 3 | 0.30 | 0.15, 0.46 | < 0.001 | 90 | 0.01 | -0.12, 0.13 | 0.93 | 90 |
| **4% trabecular density (mg/cm3)** |  |  |  |  |  |  |  |  |
| Model 1 | 0.11 | -0.20, 0.41 | 0.50 | 94 | -0.10 | -0.43, 0.24 | 0.56 | 94 |
| Model 2 | 0.11 | -0.21, 0.43 | 0.49 | 94 | 0.02 | -0.31, 0.35 | 0.90 | 94 |
| Model 3 | 0.12 | -0.19, 0.42 | 0.46 | 90 | 0.09 | 0.24, 0.43 | 0.58 | 90 |
| **38% total area (mm2)** |  |  |  |  |  |  |  |  |
| Model 1 | 0.15 | 0.00, 0.30 | 0.05 | 74 | 0.14 | 0.01, 0.27 | 0.03 | 74 |
| Model 2 | 0.11 | -0.04, 0.26 | 0.15 | 74 | 0.08 | -0.06, 0.22 | 0.24 | 74 |
| Model 3 | 0.06 | -0.09, 0.21 | 0.42 | 71 | 0.07 | -0.06, 0.20 | 0.30 | 71 |
| **38% cortical area (mm2)** |  |  |  |  |  |  |  |  |
| Model 1 | 0.10 | 0.00, 0.20 | 0.06 | 74 | 0.10 | 0.01, 0.19 | 0.04 | 74 |
| Model 2 | 0.06 | -0.04, 0.16 | 0.21 | 74 | 0.09 | 0.00, 0.18 | 0.04 | 74 |
| Model 3 | 0.06 | -0.02, 0.15 | 0.14 | 71 | 0.10 | 0.02, 0.18 | 0.01 | 71 |
| **38% cortical density (mg/cm3)** |  |  |  |  |  |  |  |  |
| Model 1 | 0.27 | -0.03, 0.56 | 0.07 | 74 | 0.48 | 0.15, 0.82 | 0.005 | 74 |
| Model 2 | 0.23 | -0.07, 0.54 | 0.13 | 74 | 0.53 | 0.19, 0.87 | 0.003 | 74 |
| Model 3 | 0.25 | -0.06, 0.57 | 0.12 | 71 | 0.64 | 0.27, 1.00 | 0.001 | 71 |

Model 1: Adjusted for equivalent bone measure of the opposite parent, maternal late pregnancy walking speed, maternal and paternal age at DXA scan, maternal pre-pregnancy educational level and the sex and age of the child; Model 2: Model 1 + maternal and paternal height at DXA scan; Model 3: Model 2 + child’s height at DXA scan.

**Figure 1:** Associations between offspring and parent DXA indices adjusted for equivalent bone measure of the opposite parent, maternal late pregnancy walking speed, maternal and paternal age at DXA scan, maternal pre-pregnancy educational level and the age of the child (and child’s sex for whole sample). P-values are for difference in beta-coefficient between mother-child and father-child associations by Hausman test.

**Figure 2:** Associations between exemplar offspring and parent pQCT bone indices adjusted for equivalent bone measure of the opposite parent, maternal late pregnancy walking speed, maternal and paternal age at DXA scan, maternal pre-pregnancy educational level and the age of the child (and child’s sex for whole sample). P-values are for difference in beta-coefficient between mother-child and father-child associations by Hausman test.