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Long-term effects of maternal calcium supplementation on childhood growth differ between males and females in a population accustomed to a low calcium intake

Kate Anna Ward [a,b,*], Landing Jarjou [c], Ann Prentice [a,c]

[a] Nutrition and Bone Health, Medical Research Council Elsie Widdowson Laboratory, Cambridge, UK
[b] MRC Lifecourse Epidemiology, University of Southampton, Southampton, UK
[c] Calcium, Vitamin D and Bone Health, MRC Keneba, MRC Unit The Gambia, Gambia

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ABSTRACT

The importance of adequate calcium intakes for healthy growth and bone development has long been recognised. Recent evidence suggests that calcium supplementation may have sex-specific effects on bone growth in childhood. The aim was to describe the long-term effects of calcium supplementation in pregnant Gambian women with a low calcium intake (ISCRTN96502494) on offspring height, weight, bone and body composition in childhood, and whether the effects differ by sex.

Children of mothers who participated in the original calcium supplementation trial were measured at age 8–12 years using dual-energy X-ray absorptiometry and peripheral quantitative computed tomography. Linear models tested for sex*supplement interactions before and after adjusting for current age and size in early life. 447 children, aged 9.2(SD 0.9) years, were measured. Significant sex*supplement interactions ($p < 0.05$) were observed for many of the anthropometric and bone outcomes, Females whose mothers received calcium (F-Ca) were shorter, lighter with smaller bones and less bone mineral than those whose mothers received placebo (F-P), differences (SE) ranged from height = −1.0 (0.5)% to hip BMC −5.5 (2.3)%. Males from mothers in the calcium group (M-Ca) had greater mid-upper arm circumference (MUAC) (+2.0 (1.0)%, $p = 0.05$) and fat mass (+11.6 (5.1)%, $p = 0.02$) and tended towards greater BMC and size than those whose mothers were in the placebo group (M-P). The differences in anthropometry and body composition were robust to adjustment for current height and weight, whereas all bone differences became non-significant. F-P were taller with more BMC than M-P, whereas F-Ca had similar sized bones and mineral content to M-Ca.

Calcium supplementation of pregnant women with low calcium intakes altered the childhood trajectories of growth and bone and body composition development of their offspring in a sex-specific manner, resulting in slower growth among females compared to placebo and accelerated growth among males by age 8–12 years.

1. Introduction

Childhood growth encompasses linear growth (stature), bone accrual (both in width and mineral accumulation) and growth of the tissue compartments and organs (somatic growth). The importance of adequate dietary calcium (Ca) intakes for healthy skeletal growth has long been recognised. Despite this, many trials have not shown significant effects of Ca supplementation on bone growth and mineralisation [1] and those that have shown effects often do not have a sufficient follow-up period to determine whether the effects are sustained. One reason for this may be that the trials are mostly conducted in countries where intakes are, on average, in alignment with dietary recommendations [2]. Less is known from populations where habitual Ca intakes are low. Also, it is not known whether changes in Ca intake at different stages of childhood and adolescence have differential effects on longitudinal and appositional skeletal and somatic growth, and whether the response to intervention differs between males and females [3–5].

Evidence from our studies in rural Gambia, where dietary Ca intakes are very low, have suggested that Ca supplementation may have unexpected effects depending on the stage of life and in a sex-specific manner. In a Ca supplementation trial (ISRCTN28836000) of pre-pubertal children with low habitual dietary Ca intakes of around 300 mg/day, we showed that the timing of the pubertal growth spurt was brought forward in males who had received a Ca carbonate supplement for 12 months at age 8–12 years, such that their height and bone development were greater in mid-adolescence than males in the placebo group

* Corresponding author at: K. Ward, MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Tremona Road, SO16 6YD, UK.
E-mail address: kw@mrc.soton.ac.uk (K.A. Ward).

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[6,7], whereas no such effects were observed in the females [6]. Continued follow-up of the males showed that those who had received the calcium supplement pre-puberty stopped growing earlier, and were significantly shorter (3.5 (SE 1.1) cm) at the end of growth than those who had been in the placebo group [6]. In addition, the short-term increases in bone mineral content (BMC) and bone area (BA) in these males due to Ca supplementation were attenuated [6–9].

In a second study, a trial of maternal Ca supplementation during pregnancy (ISCRTN96502494), we reported that, contrary to expectations, mothers who received a daily Ca carbonate supplement from 20 weeks gestation to term mobilised more bone mineral during lactation than those who received placebo [10,11], resulting in lower BMD that was still evident 5 years post supplementation [11]. There were no supplement effects observed on the size of their offspring at birth or during 12 months post-partum [12,13]. There were also no effects seen on infant whole body and radial BMC measured in a sub-set, although a weakly significant group effect was observed whereby the whole body BMC and BA of the infants of mothers who had received Ca supplement had increased more slowly by 12 months than those of the infants of mothers in the placebo group [10,12,13]. Males were significantly heavier at 2 weeks and longer at 52 weeks than females. At age 8–12 years, there were no significant differences between males and females in the cohort in height, weight or body mass index. Girls had greater fat mass, whole body and spine BMC than the boys but lower lean mass, bone area and BMC at the hip [14]. Because males were heavier at 2 weeks and longer at 52 weeks, and that there were no differences in height and weight at age 8–12 years, the data demonstrate different rates of growth in males and females.

The aim of the current study was to determine whether there were lasting effects of the maternal Ca supplementation in this trial on the growth, bone development and body composition of the offspring when the children were aged 8–12 years, prior to the adolescent growth spurt. This was assessed using anthropometry, dual-energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT). The hypothesis was that the children of mothers who received Ca supplementation would be taller and have higher BMC and bone mineral density (BMD) than those whose mothers had been in the placebo group, and that these differences would differ by sex. Our secondary aims were to determine the effects of maternal Ca supplementation on the tibial cortical and trabecular bone compartments and on body composition (fat and lean masses, mid-upper arm circumference and triceps skinfold thickness).

2. Subjects and methods

2.1. Subjects

This study was conducted at MRC Keneba, West Kiang, The Gambia. All children, whose mothers had taken part in the supplementation trial of Ca in pregnancy (ISCRTN96502494) and had delivered a healthy baby, were invited to participate when aged 7.8 to 11.9 years. Details of the trial have been previously published [12,13]. Briefly, recruitment was in three ante-natal clinics serving 16 villages. Randomisation was stratified by antenatal clinic in blocks of four to minimise bias and potential confounding by season. Pregnant mothers in the supplement group received 1500 mg Ca as Ca carbonate (3 tablets of Calcichew ™, Calcichew; Nycomed Pharma AS, Asker, Norway; distributed in the United Kingdom by Shire Pharmaceutical Development Ltd., Andover, UK), or a matching placebo, daily from 20 weeks of pregnancy until term. Mean (SD) maternal dietary Ca intakes during the trial were 1831 (177) mg/day in the calcium group and 356 (159) mg/day in the placebo group [13].

Measurement visits were scheduled to ensure equal distribution of children across the age-range and study period, and took place during the dry season, a time of year when food shortages, malaria and infectious illnesses are less prevalent. The study was approved by the Joint MRC/Gambian Government Ethics Committee and informed written consent was obtained from the parent or guardian of each child.

2.2. Anthropometry

Standing height was measured to the nearest 0.1 cm using a stadiometer (SECA 225, Birmingham, UK). Height-for-age z-scores (HAZ) as an indicator of maturity were calculated using WHO growth references [15]. Weight was measured on electronic scales (Tanita HD310, Amsterdam, The Netherlands) to the nearest 0.1 kg, with the subject wearing light clothing and no shoes. Mid-upper arm circumference (MUAC) and triceps skinfold thickness (TST) were measured at the mid-point of the upper left arm using a non-stretchable tape measure and a skinfold calliper (Holtain Ltd., UK) respectively. Data were available from the original trial on length, weight and head circumference at birth and during infancy [12].

2.3. Dual energy X-ray absorptiometry (DXA)

Bone and body composition measurements were obtained using a GE Lunar Prodigy DXA scanner, software version 10.51.006 (GE Medical Systems, GE Lunar Corporation, Madison, USA). Outcome measures were whole body less head (WB) [16], lumbar spine (LS), total hip BMC (g) and BA (cm^2). Lean and fat mass (g) measurements were obtained from the whole body scan. At MRC Keneba, the precision of repeated measurements of aBMD at different skeletal sites in 35 adults, measured twice with repositioning, was: whole body 0.6%, lumbar spine 0.8% and total hip 0.7%.

2.4. Peripheral quantitative computed tomography (pQCT)

A Stratec XCT-2000 scanner (Stratec Medizintechnik, Pforzheim, Germany), was used to obtain measurements of the metaphyseal (8%) and diaphyseal (50%) tibia. Measurements were taken using a voxel size 0.5 mm, slice thickness 2 mm and scan location was determined by placing the reference line on the distal border of the tibia endplate. Outcome measures were at the 8% site; total volumetric BMD (mg/cm^3) and total cross-sectional area (mm^2), and at the 50% site; tibia cross-sectional area (mm^2), cortical BMC (mg/mm) and cortical area (mm^2). Metaphyseal scans were analysed using CALCBD, contour mode 1, peel mode 1, threshold 180 mg/cm^3, and at the diaphysis, separation mode 1, threshold 710 for cortical content and area and 280 mg/cm^3 for total area. The precision of repeated measures in adults ($n = 35$, measured twice with repositioning) at our centre was <1% for all outcomes.

2.5. Statistical analysis

Statistical analysis was performed using the Linear Model facility in Data Desk 6.1.1 (Data Description, Ithaca, NY). Summary data are presented as mean (SD) or median (interquartile range). Sex differences in the early life variables of participants in the current study were tested for using one-way ANOVA except for maternal parity at the time of the trial and season of birth of the offspring, where the Chi-square test was used. There was no evidence of a supplement effect or a sex*supplement interaction in any of the early life variables.

Sex-specific supplement effects on each outcome variable were tested for using multiple regression and analysis of covariance, by including a sex*supplement interaction term in all models. Variables were converted to natural logarithms prior to statistical modelling, whereby, for discrete variables, difference × 100 corresponds closely to percentage difference [(difference/mean) × 100] [17]. Scheffé post-hoc tests were used to adjust for multiple testing and to report differences between sex*supplement groups. The four sex*supplement groups were: males whose mothers had been in the calcium supplement group in pregnancy (M-Ca); females of mothers in the calcium group (F-Ca); males whose