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# The associations of exposure to combined hormonal contraceptive use on bone mineral content and areal bone mineral density accrual from adolescence to young adulthood: A longitudinal study

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ABSTRACT

*Background:* The association of long term combined hormone based contraceptives (CHC) use on bone mineral content (BMC) and areal bone mineral density (aBMD) development remains controversial, as it appears that the relationship may be age-dependent. The purpose of this study was to investigate the long-term associations of CHC exposure on the accrual of bone parameters from adolescence into young-adulthood.
*Methods:* 110 women (67 exposed to CHC) were drawn from the Pediatric Bone Mineral Accrual Study (PBMAS). Serial measures of total body (TB), lumbar spine (LS) and femoral neck (FN) BMC and aBMD were assessed by DXA (a total of 950 scans) and aligned by biological age (BA, years from peak height velocity [PHV]). Multilevel random effects models were constructed to assess the time dependent associations between annual CHC exposure and the development of bone parameters.
*Results:* After BA, height, lean tissue mass, fat mass, calcium and vitamin D intake, and physical activity were controlled, it was observed that those individuals exposed to CHC 6-years post PHV developed significantly less ($-0.00986 \pm 0.00422$ g/cm$^2$) TB aBMD than their non CHC exposed peers. Additionally, there were significant BA by CHC exposure interactions, where CHC exposure 6-years or more post PHV resulted in developing less TB BMC ($-4.94 \pm 2.41$ g), LS BMC ($-0.29 \pm 0.11$ g) and LS aBMD ($-0.00307 \pm 0.00109$ g/cm$^2$). One year after the attainment of PHV, CHC users were predicted to have 1.2% more TB BMC, 3.8% more LS BMC and 1.7% more LS aBMD than non-users. At 9-years post PHV the predicted differences showed that CHC users had 0.9% less TB BMC and 2.7% less LS BMC and 1.6% less LS BMD than those not exposed to CHC.
*Conclusions:* CHC may not hinder the development of BMC or aBMD during adolescence; however, exposure 6-years or more after PHV may be detrimental.


## 1. Introduction

Osteoporosis is a skeletal disease that affects millions of individuals worldwide and is characterized by low areal bone mineral density (aBMD) and microarchitecture deterioration, leading to increased bone fragility. Although osteoporosis is a disease associated with fractures in old age, its antecedents are found in adolescence, with the accrual of adolescent bone mass proposed to influence fracture risk in adulthood (Bonjour et al., 2009; Baxter-Jones et al., 2011). Estrogen is a major regulator of bone growth, influencing the sexual dimorphism of the skeleton and the maintenance of bone mineral homeostasis, which in turn alters both the development of bone strength and the acquisition of peak bone mass (Berger et al., 2010). Estrogens act on bone by regulating bone tissue metabolism, primarily through associations with the promotion of osteoblastic activity and the suppression of osteoclastic resorption (Dempster, 2006; Almeida, 2010; Chen et al., 2009; Zallone, 2006; Tremollieres, 2013). In women, the effects of estrogen on the skeleton appear most notably during adolescence and after menopause. During adolescence there is a surge in estrogen levels associated with adolescent growth and sexual development, and during menopause, estrogen levels rapidly decline, exposing women to a hypoestrogenic state (Tremollieres, 2013). Thus, the exposure to estrogen during these key periods may dramatically influence a woman's bone health.

Combined hormonal contraceptives (CHC) are one of the most commonly used methods of contraception (Black et al., 2009). In addition to contraception though, 88% of CHC users report taking CHC for non-contraceptive purposes, such as menstrual regulation, menstrual pain and treating acne (Jones, 2011) thus, it is not unusual to see CHC use beginning as early as 10 years of age and continuing well into adulthood.

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In Canada alone, nearly 67% of adolescents between 15–19 years of age report using CHCs (Black et al., 2009). The associations between CHC use and bone health remains controversial, with recent evidence suggesting that the association of CHCs may be age dependent (Tremollieres, 2013; Nappi et al., 2012; Ziglar and Hunter, 2012; Martins et al., 2006). Prospective observations show that compared with non-using age similar adolescent or young adult controls, CHC use is associated with negative changes in areal bone mineral density (BMD) and content (BMC) (Polatti et al., 1995; Scholes et al., 2010, 2011; Berenson et al., 2008). Other prospective studies show no BMD differences with CHC use (Bonny et al., 2011; Rome et al., 2004). The observed negative effects during adolescence are thought to be the result of CHCs reducing the physiological levels of systemic estrodial, inhibiting the development of peak bone mass (Ziglar and Hunter, 2012; Martins et al., 2006). In adulthood, CHCs appear to provide no benefit to total body, lumbar spine or femoral neck aBMD in premenopausal women. Associations during the third and fourth decades of life are unknown. These conflicting results from adolescence to adulthood, highlight the potential age dependent associations that the exposure to CHCs may have on bone health throughout life; however previous studies results are often limited to 1 to 3 years in duration, with a limited number exceeding 5 years of follow-up (Beksinska et al., 2009; Lloyd et al., 2000), and often fail to control for the duration of CHC use, which may mediate the relationship between CHCs and bone health (Scholes et al., 2010, 2011). Additionally, bone undergoes vast changes during the adolescent period, and has been previously identified as a critical window for bone mineral accrual, with nearly 50% of adult bone mineral mass accrued during the 4 years around peak linear growth (Bailey, 1997; Baxter-Jones et al., 2003, 2010a). Therefore, the initiation of CHC use may have dramatically different effects on the bone if consumed during this key period of bone development. However, there remains a paucity of longitudinal studies that span the entire adolescent growth period into adulthood that address whether the exposure to CHCs is associated with the accrual of bone mass.

The advantage of using longitudinally gathered data is that it is possible to determine an individual's bone parameter accrual trajectories, while adjusting for the associations associated with other known confounders. The uniqueness of this longitudinal approach to data analysis is that it accounts for the wide variation shown among women's growth parameters at any given age, and in the velocity of these parameters from one age to the next. Growth curves for bone mineral accrual can be constructed by aligning all subjects on a comparable biological age index (age from peak height velocity [PHV]) to account for the known maturational impact on bone growth (Baxter-Jones et al., 2003). The introduction of multilevel statistical models (Goldstein et al., 2002) has assisted researchers in fitting growth curves to longitudinal measurements over time. In the multilevel framework each individual has their own straight line growth trajectory, with intercepts and slope coefficients varying between individuals. Using this technique the independent time dependent effects of growth, maturation, environmental effects, and CHC usage on BMC and aBMD accrual can be identified. Therefore, the purpose of this longitudinal study was to investigate the time dependent associations of exposure to CHCs on the accrual of bone mass from adolescence to young adulthood.

## 2. Methods

### 2.1. Participants

Women participants were drawn from the University of Saskatchewan's mixed-longitudinal designed Pediatric Bone Mineral Accrual Study (PBMAS). The PBMAS has been described in detail elsewhere (Bailey et al., 1999; Baxter-Jones et al., 2008). In brief, the PBMAS cohort consists of 259 individuals (aged 8 to 15 years) recruited from two elementary schools in the city of Saskatoon between 1991 and 1993. The PBMAS began with eight chronological age clusters (8 to 15 years) in 1991, with additional recruitment of 8 and 9 year olds in 1992 and 1993. In the initial study phase, data were collected annually until 1997; after a five-year break data collection resumed and were collected annually between 2002 and 2011. In 1991 a total of 228 students (115 girls; 8 to 15 years of age) provided written informed consent to participate, and 220 children (113 girls) were DXA scanned. By 1997, 197 individuals (aged 12 to 21 years) had been assessed on more than one occasion (median 6 occasions). From 2003 to 2007 data were collected on 169 returning participants (84 women aged 18 to 31 years) (median 4 occasions). From 2009 to 2011, 107 participants returned for another follow-up measurement (65 women aged 23 to 33 years of age; Table 1). This mixed-longitudinal study design allowed for the assessment of a 26 year developmental pattern between the ages of 8–33 years, within a 20 year data collection period. At each measurement occasion the same anthropometric, body composition, physical activity, dietary intakes and bone measures were recorded using the same instruments. From 2003 onwards CHC usages was recorded as an additional measure both retrospectively (1991–2001) and prospectively (2002–2011). To be included in the present study participants were required to be: (i) women; (ii) have a valid assessment of peak height velocity (PHV); (iii) have at least two DXA assessments (one during childhood/adolescence and one in young adulthood); (iv) have a record of CHC use; and (v) have no history of diseases known to affect growth or bone development. This resulted in the inclusion of 110 young women, with 67 women reporting to have used a CHC at least once between 1991 and 2011. Table 1 shows the number of women scanned each year by age group and CHC exposure; note that not all individuals were assessed at all measurement occasions hence the change in numbers from year to year within age groups. From 1991 to 2011 the medium number of scans was 10 (range 1 to 14). A total of 950 scans were performed over a 20 year period, of these 205 scans were of women exposed to CHC in the previous 12 months. Written informed consent was obtained from all participants (parental assent for minors). All procedures were approved by the University of Saskatchewan's biomedical review committee.

### 2.2. Anthropometry

Anthropometric measures included height and weight, assessed following the anthropometric standards outlined by Ross and Marfell-Jones (Ross and Marfell-Jones, 1991). Stretch stature was recorded without shoes to the nearest 0.1 cm against a wall mounted stadiometer (Holtain Limited, Crymych, UK). Weight was measured on a calibrated digital scale to the nearest 0.5 kg (Model 1631, Tanita Corp, Tokyo, Japan).

### 2.3. Chronological age

A decimal chronologic age (CA, years) was determined by identifying the numbers of days between an individual's date of birth and the date at the assessment occasion.

### 2.4. Biological age (peak height velocity) assessments

Biological age (BA, years), a measure of somatic maturation, was defined by identifying the CA of attainment of peak linear growth during adolescence (peak height velocity [PHV]). To determine the CA at PHV, whole year height velocities were calculated for each participant. A cubic spline fitting procedure was applied to each individual's whole year velocity values and the CA at the highest point was estimated (GraphPad Prism 5, GraphPad Software, San Diego, CA, USA). A BA was then calculated by subtracting the CA at PHV from the CA at time of measurement for each individual (e.g. CA at time of measurement = 10.5 years, CA of PHV = 13.4 years, BA at measurement = 10.5 − 13.4 = −2.9 years).

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