

REVIEW ARTICLE

Adolescent use of combined hormonal contraception and peak bone mineral density accrual: A meta-analysis of international prospective controlled studies

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Summary

Objective: Many women use combined hormonal contraceptives (CHC) during adolescence during which they are accruing peak areal bone mineral density (BMD) that relates to lifetime fracture risk. To build BMD requires formation with which CHC-related exogenous oestrogen may interfere. We compared peak BMD accrual in adolescents using and not using CHC.

Design/Participants: We performed literature searches for prospective published peer-reviewed articles providing 12- to 24-month BMD change in adolescent (12- to 19-year-old) women using CHC vs CHC-unexposed control women.

Methods: Meta-analyses used random-effects models to assess BMD change rate at lumbar spine (LS) and other sites in adolescent CHC users vs CHC nonusers.

Results: Literature searches yielded 84 publications of which nine were eligible. Adolescent-only data were sought from cohorts with wider age inclusions. The 12-month LS meta-analysis with eight paired comparisons in 1535 adolescents showed a weighted mean BMD difference of -0.02 (95% confidence interval [CI]: -0.05 to 0.00) g/cm^2 in CHC-exposed adolescents ($P = 0.04$). The 24-month LS meta-analysis with five paired comparisons in 885 adolescents showed a highly significant weighted mean BMD difference of -0.02 (95% CI: -0.03 to -0.01) g/cm^2 in CHC-exposed adolescents ($P = 0.0006$). Heterogeneities by I^2 were 96% and 85%, respectively. Insufficient data for other bone sites precluded quantitative analysis.

Conclusion: Given that adolescent exposure to CHC appears to be increasing, this evidence for potential impairment of peak spinal BMD accrual is of concern and suggests a potential public health problem. Randomized controlled trial data are needed to determine CHC effects on adolescent bone health.

KEYWORDS

adolescence, combined hormonal contraception, lumbar spine, meta-analysis, osteoporosis, peak bone mineral density, prospective

1 | INTRODUCTION

Combined hormonal contraceptives (CHC) are the most common birth control method used worldwide and are increasingly used by adolescent women.¹⁻³ CHC are proven effective for contraception and generally safe.⁴ Because menopausal oestrogen treatment is positive for bone health, it has been assumed that CHC use would also be bone-protective. The association of CHC use with areal bone mineral density (BMD) change has only been documented since the mid-1990s.⁵

Adolescence is a key time in women's life cycle for bone accrual, for decreasing later life osteoporosis and lifetime fragility fracture risk.^{6,7} Premenopausal BMD values are related to prevalent fractures in a cross-sectional evaluation of the adult population-based Canada-wide Canadian Multicentre Osteoporosis Study (CaMos).⁸ Peak BMD at both the femoral neck and the total hip is gained in women between ages 16 and 19 years and lumbar spine peak BMD is achieved between ages 33 and 40 in prospective population-based data from the Youth and Adult CaMos Cohorts.⁹ Those who achieve a lower peak BMD are widely believed to be at increased risk of later life fractures,^{6,7} although prospective BMD and incident fragility fracture data are scarce.

Genetics accounts for more than 50% of peak bone mass; as well, a family history of fragility fracture has recently been shown to increase premenopausal BMD loss.¹⁰ However, factors such as adequate calcium and other nutrition,¹¹ menstrual cycle/ovulatory disturbances¹² and physical activity¹³ also influence peak BMD acquisition.

Increasingly, adolescent women are prescribed CHC for *non-contraceptive* indications such as cramps, acne and irregular cycles²; there is thus a need to understand the potential relationship of CHC use with adolescent women's peak BMD acquisition. CHC use may be a concern in adolescence because, to accrue peak BMD, active bone growth through *modelling* is necessary, and this requires bone formation. CHC has long been known to suppress bone remodelling.¹⁴ Since oestrogen decreases bone turnover and suppresses bone resorption, it is positive for the adult skeleton that is generally in a state of bone loss. The dynamic bone state in adolescence is different. Supraphysiological ethinyl oestradiol (EE) doses are needed for effective contraception; therefore, use of CHC in adolescence may suppress bone growth as it suppresses bone resorption since the two processes are coupled.^{2,3} Suppression of bone biomarker levels has been documented even with CHC EE doses as low as 20 µg which is considered "low dose" compared with earlier CHC products.^{5,15,16}

We carried out a meta-analysis of published data reporting prospective BMD changes in healthy adolescent women with first use of CHC and in nonusing controls. Our hypothesis was that CHC use would impair adolescent BMD accrual.

2 | MATERIALS AND METHODS

The Cochrane handbook for systematic reviews and MOOSE checklist criteria were applied in designing, conducting and reporting this systemic review and meta-analysis. A standardized (unpublished) protocol defined types of studies and outcomes related to our

research question: *Is there a difference in the rate of areal bone mineral density (BMD) change in healthy adolescent women first using combined hormonal contraception (CHC) compared with those who are similar but not using CHC?*

2.1 | Search strategy

Our literature search strategy is summarized in Table S1. We began our literature search in 2014 seeking open-label clinical trials and observational longitudinal studies of CHC vs placebo/no intervention in 12- to 19-year-old adolescent women. Electronic systematic searches (1970-2018) of PubMed, Web of Science, Cochrane Library, EMBASE and Google Scholar were conducted. MeSH terms of "Bone Mineral Density," "Combined Oral Contraceptives," "Adolescent" and "Prospective" and synonyms of these terms were used. Abstracts from obstetrics and gynaecology, endocrinology and American Society for Bone and Mineral Research annual scientific meetings were screened. Reference lists of relevant publications and reviews were assessed for additional publications. Authors of several publications that included adolescent with young adult women were contacted and requested to provide the adolescent-only data and the standard deviation of the rate of BMD change; this value is needed for meta-analysis.

2.2 | Inclusion/exclusion criteria

We sought peer-reviewed published papers on prospective observational data and clinical trials that reported absolute BMD change (as measured by dual-energy X-ray absorptiometry [DXA]) over one and 2 years (or percentage change with absolute baseline BMD data thus allowing us to compute actual BMD change). These values were available in at least one CHC group and one control group per eligible publication; CHC-using women in each study were reported *new* CHC users. Prospective observational studies and randomized comparative trials (RCT) of two CHC agents with a *nonrandomized control* group were also included. Participants were recruited through health care facilities/services or randomly sampled from the general population. Participants were healthy adolescent women aged 12-19 years for whom there was a clear record of taking or not taking CHC. Any CHC formulations including both an oestrogen and a progestin (synthetic progesterone-like steroid) were eligible (including oral, patch and vaginal ring preparations). The aim of all methods of delivery is to achieve a "supraphysiological" dose equivalent oestrogen value with a near-"physiological" progestin concentration. However, no full study used these other CHC delivery methods and there was only one person in the large Brajic study who reported use of the vaginal ring.

We excluded cross-sectional designs, progestin-only contraceptive use, depot-medroxyprogesterone or progestin-releasing IUD use, or continuous or long-cycle CHC use. We excluded studies that did not measure BMD using dual-energy X-ray absorptiometry (DXA). We also excluded studies of adolescent women with known bone-affecting conditions such as amenorrhoea, anorexia nervosa or

osteogenesis imperfecta. All languages were included; all retrieved, eligible studies, however, were in English. Finally, we excluded studies that did not measure and report BMD at standard intervals of baseline, 12 months and/or 24 months.

2.3 | Data extraction

Primary searches of databases and screening of abstracts were iteratively performed independently by two authors (TSB and AG) between 2014 and 2017. After eliminating noneligible studies, data from full texts were extracted using a customized table. JCP reviewed and compared the extracted with the primary data. The final eligible studies were decided by consensus (TSB, AG and JCP). When the same study population was reported in multiple publications, only the report with the most statistical power was included.

Risk of bias was assessed by the Newcastle-Ottawa Quality Assessment Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) for Cohort Studies based on selection of participant groups, their comparability and outcome ascertainment in each group.¹⁷ Final evaluation was performed independently by JCP and AG who, if there were disagreements, came to agreement by consensus (Table S2).

Two manuscripts were published and added after primary searches with the last search being in January 2018. In studies that compared CHC agents having different EE doses with non-using controls, following Cochrane guidelines, different dose formulations were statistically combined into a single group.¹⁸ We included the published data from the population-based, country-wide CaMos Youth Cohort.³

The following data were extracted for each study: study design, participant age, sample size, follow-up length, CHC preparation(s), BMD at the baseline and at 12- and 24-month follow-up periods (as relevant) and, if available, any reported adjustment for confounding variables such as body mass index (BMI), calcium intakes, racial origin and cigarette smoking history.

2.4 | Statistical analysis

The standard deviation (SD) of mean absolute BMD change was often not reported. If not available from authors, we used values from the CaMos Youth Cohort adolescent data.³ For the 24-month analysis, we used the SD of absolute lumbar spine BMD change in CHC-using and nonusing women from CaMos after 24 months to impute the SD for other 24-month duration studies. We included data from lumbar spine levels L1-4; actual segmental levels, however, were rarely noted in these publications. The pooled estimate of absolute change (its mean and 95% confidence interval [CI]) at the lumbar spine BMD site after 12 or 24 months of CHC use or for a similar duration in controls was computed using the Cochrane analysis tool Review Manager (RevMan; Computer program). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. (<http://tech.cochrane.org/revman>). Statistical heterogeneity was measured by the I^2 statistic. Random-effects

models were used; a sensitivity analysis repeated each meta-analysis using a fixed-effect model; for further sensitivity evaluation of the 12- and 24-month meta-analyses, we systematically removed each of the individual studies in turn while re-analysing the meta-analysis.

There were limited numbers of eligible studies providing the necessary primary data. Studies including femoral neck and total hip BMD changes after 24 months (2 years), given that 12 months (1 year) is often too short a time interval to measure the slower changes at femoral sites, were numerically described; too few data at these sites prevented quantitative synthesis. Where the original data included adolescents in combination with young adults, we contacted the authors for the adolescent-only data. We were able to obtain and include in this meta-analysis adolescent-only data for studies from Seattle, USA,¹⁹ Botucatu, Brazil,²⁰ and Galveston, USA.¹⁶

3 | RESULTS

The PRISMA diagram (Figure 1) describes the process of inclusion of eligible studies. The initial systematic database search retrieved 88 papers; an additional 16 papers were identified from other sources through January 2018. After removing duplicates, the abstracts of 84 papers were screened. Full texts of 22 papers were examined and 13 papers were excluded because they were, respectively, lacking BMD change data at 12 or 24 months, original data, a CHC arm, a placebo or control arm, a prospective design and because the study duration was less than 12 months. Nine publications were included in the final analysis; eight are in the 12-month and five in the 24-month meta-analyses.

Table 1 summarizes the included studies. Studies were performed in the United States,^{15,16,19,21-23} Brazil,²⁰ China²⁴ and Canada.³ One of these studies was a random sample of a residential population within 50 km of nine study centres across a country,³ two others were within health maintenance organizations with a random or other sampling,^{16,19} and two were RCTs with open-label controls^{23,24}; the rest were convenience samples. Various adjustments for age and/or race, BMI and baseline BMD were performed in four of nine studies^{3,15,16,19}; many also described smoking, calcium intakes, alcohol consumption and exercise levels. The available BMD change data were inconsistently adjusted for these variables. The main reported outcomes were BMD changes at various skeletal sites.

Quality assessment results (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) are presented in the Table S2. All studies scored a low risk of bias and received 8 or 9 stars (of a possible 9) in two discrete assessments. CHC users and nonusers were clearly defined in all studies; the reported study designs and statistical analyses were replicable and valid; assessment for dropout or nonresponse rates and ascertainment methods was similar between users and non-users.

Twelve-month prospective spinal BMD analysis included pooled meta-analysis of eight studies with 1535 participants. It showed a significant random-effects weighted mean difference in absolute

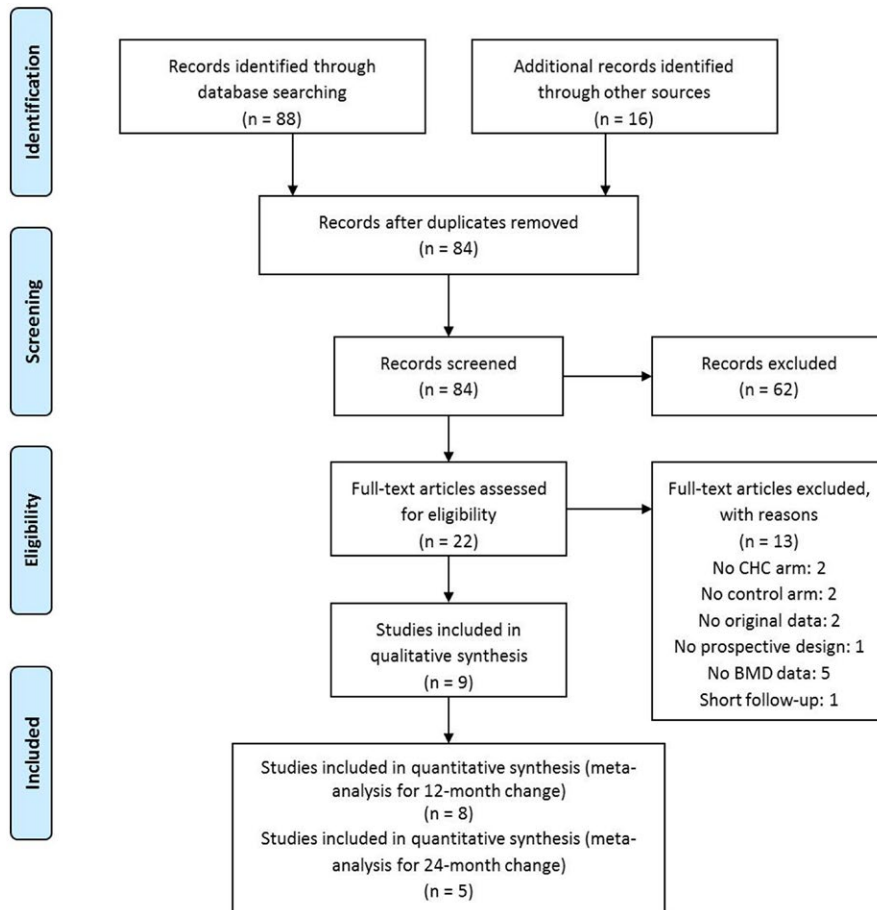


FIGURE 1 This PRISMA flow diagram outlines the process of selection of publications to be included in this meta-analysis of adolescent areal bone mineral density (BMD) change over time by use of combined hormonal contraceptives (CHC) or not [Colour figure can be viewed at wileyonlinelibrary.com]

spinal BMD change of -0.02 (95% CI: -0.05 to -0.00) $\text{g}/\text{cm}^2/\text{y}$ ($P = 0.04$) for CHC users compared to nonusers (Figure 2). However, heterogeneity (I^2) was high at 96%.

Twenty-four-month spinal BMD prospective data included pooled meta-analysis of five studies in 885 adolescents. Results showed a random-effects weighted mean difference of -0.02 (95% C: -0.04 to -0.01) $\text{g}/\text{cm}^2/2$ y between CHC users and nonusers (Figure 3). This was a highly statistically significant result with $P < 0.0006$. There was also an important degree of heterogeneity in this comparison ($I^2 = 85\%$).

To analyse whether the negative effects of the CHC on BMD change were continuing to increase at 24 months in the same proportion as the 12-month results for the four studies which had data for both 12 and 24 months, we performed a different meta-analysis. We found that in four studies with both 12- and 24-month data, the standardized mean difference went from -0.333 (-0.675 to 0.009) after 12 months of CHC use to -0.832 (-1.422 to -0.242) after 24 months of CHC use suggesting ongoing bone loss.

In description of changes at the femoral neck BMD site, Cromer,¹⁵ Berenson,¹⁶ Gai²⁴ and Brajic,³ all reported 24-month percentage (or absolute for Brajic) changes for nonusing controls and CHC-using women. Cromer reported 24-month changes of $+3.8\%$ in nonusers and $+3.0\%$ in CHC-using adolescents.¹⁵ Berenson¹⁶ reported a 24-month mean gain of $+0.54\%$ for nonusers but a loss of -0.76%

in CHC-using adolescents. Gai²⁴ reported femoral neck change of $+0.98\%$ in nonusers vs -0.61% and $+0.49\%$ in the two CHC user groups, respectively. Finally, Brajic reported that adolescents who never used CHC had greater adjusted femoral neck BMD gain than CHC users: mean difference $+0.009$ g/cm^2 (95% CI: -0.002 to 0.021).³ Thus, there was a trend for the CHC-using women to have less positive femoral neck BMD change than adolescent women controls.

Data for the total hip BMD change by CHC use were only available in two eligible 24-month studies. Change of $+0.67\%$ at the total hip site for Scholes et al¹⁹ among nonusers was nearly identical to the changes in CHC users. CaMos total hip data showed never-CHC-using adolescents gained significantly more unadjusted total hip BMD $+0.012$ $\text{g}/\text{cm}^2/2$ y (95% CI: 0.001 to 0.023) than CHC users.³

Whole body data comparisons by CHC-using vs nonusing adolescents were over 24 months by Scholes¹⁹ and over 12 months by Biason.²⁰ Scholes documented that those on CHC with >30 micrograms of oestrogen gained significantly less WB BMD than nonusing women (-0.58 , 95% CI of diff; -1.29% to -0.13%)¹⁹; Biason showed that WB BMD change was a loss in those on CHC (-0.30%) compared with an important gain in nonusing adolescents ($+3.89\%$).²⁰ Thus, the whole body comparisons showed more positive BMD change in the nonusing CHC controls.

TABLE 1 Descriptive characteristics of studies included in the primary pooled analyses of prospective studies of adolescent women and areal bone mineral density (BMD) change by use of combined hormonal contraceptives (CHC) or not

First author, reference [#]	Region and year	Study design	Age range (y)	BMD site measurement (s)	Number of participants		Total duration (mo)
					CHC	Control	
Cromer ²¹	USA 1996	Prospective comparative study	12-21	Spine	9	17	12
Lara-Torre ²²	USA 2004	Non-randomized prospective study	11-21	Spine	16	10	12
Berenson ^{16,a}	USA 2008	Prospective controlled study	Subgroup: 16-19 (total: 16-33)	Spine	36	14	12
				Femoral neck Total hip	29	8	24
Cromer ^{15,a}	USA 2008	Prospective controlled study	12-18	Spine	62	95	12
				Femoral neck	62	95	24
Scholes ^{19,a}	USA 2011	Prospective controlled study	Subgroup: 14-18 (total: 14-30)	Spine	115	75	12
				Total hip	93	55	24
				Whole body			
Gai ^{24,a,b}	China 2012	Open-label randomized comparative trial of two CHC agents with non-randomized controls ^c	16-18	Spine	277	136	12
				Femoral neck	261	115	24
Biason ²⁰	Brazil 2015	Prospective controlled study	12-19	Spine Whole body	26	35	12
Gersten ^{23,b}	USA 2016	Open-label randomized, comparative trial of two CHC agents with non-randomized controls ^c	12-18	Spine Total hip	240	372	12
Brajic ^{3,a}	2017 Canada	Prospective, population-based cohort	Subgroup: 16-19 (total: 16-24)	Spine Femoral neck Total hip	113	54	24

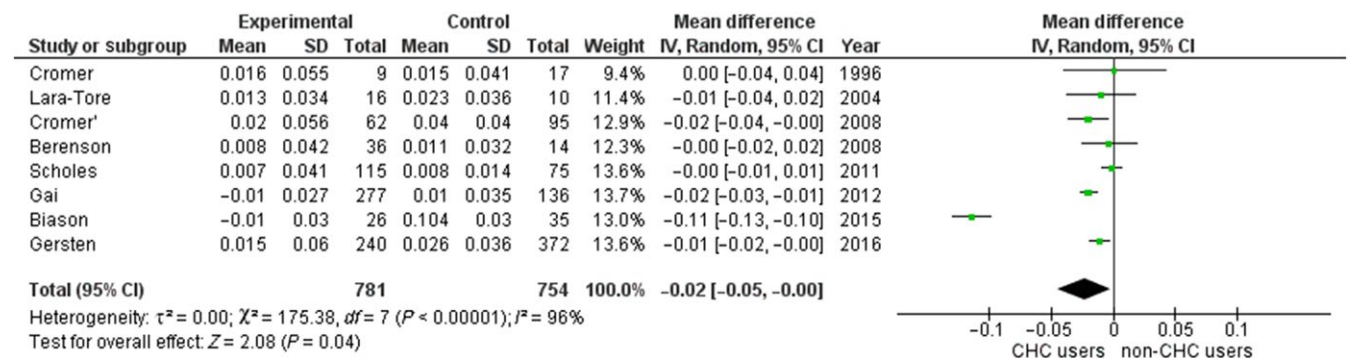
^aIncluded in 24-mo comparison.

^bThe two CHC arms in these studies were randomized and blinded, but the controls were open-label and nonrandomized.

^cThis randomized controlled trial compared the two CHC groups but had a nonrandomized control group thus it became a prospective observational study

Sensitivity analyses for the 12- and 24-month random-effects meta-analyses with fixed-effect models showed similar results as the primary analysis. Sensitivity analysis after removing one or more of the 12-month studies caused the pooled result to become nonsignificant ($P > 0.05$). However, the result of the pooled effect for the 24-month lumbar spine BMD change comparison did not alter from the primary analysis after successive omission of each individual study. Removing the 24-month

Cromer data,¹⁵ however, reduced the heterogeneity; I^2 changed from 85% to 74%. There was no study that had no overlap with the effect size in the 24-month analysis. In 12-month analysis, however, Biason et al could be considered an outlier, but we could not find any characteristics that made it different from other studies in terms of sample size, inclusion criteria, CHC dosing or other demographic features. Removing it from the meta-analysis also made no difference to the outcome.

**FIGURE 2** This random-effects forest plot assessed the 12-mo weighted mean difference in mean absolute change from baseline in g/cm for spinal areal bone mineral density (BMD) in adolescent-combined hormonal contraceptives (CHC) users and nonusers/controls [Colour figure can be viewed at wileyonlinelibrary.com]

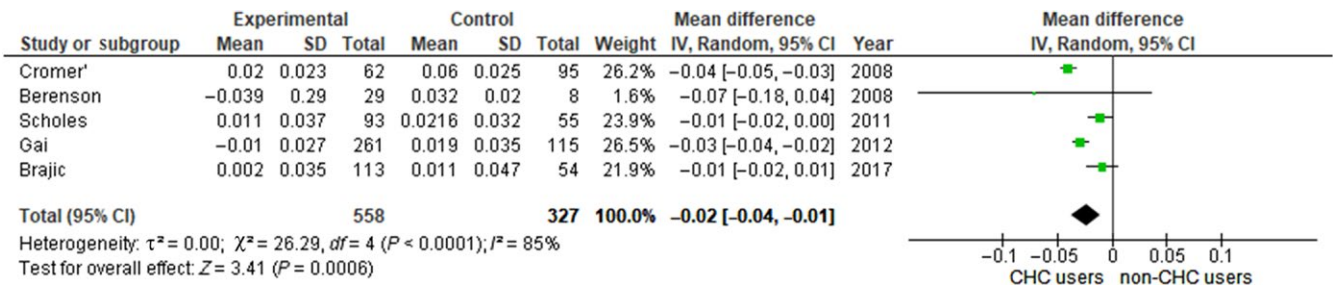


FIGURE 3 This random-effects forest plot assessed the 24-mo weighted mean difference in mean absolute change from baseline in g/cm^2 for spinal areal bone mineral density (BMD) in adolescent-combined hormonal contraceptives (CHC) users and nonusers/controls [Colour figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

This first meta-analysis of prospective changes in spinal bone mineral density in healthy adolescents, comparing those first using oestrogen-progestin CHC agents with similar CHC nonusers, showed significantly less lumbar spine 24-month BMD accrual in those on CHC. These results are of public health relevance because today a higher percentage of women are starting CHC in adolescence rather than in early adulthood as was true in the past.²⁵

Individually, the examined studies of BMD change in adolescents by CHC use may⁵ or may not²⁴ show significant results. However, quantitatively pooled data show that CHC use is associated with significant negative BMD changes over 24 months. Although BMD loss during use of depot-medroxyprogesterone is recovered after stopping,²⁶ the only available data suggest that, when stopping CHC, recovery does not occur.¹⁹

There are several strengths of this study including that it is the first quantitative synthesis of studies of change in spinal BMD in adolescent women using and not using CHC. In addition, we reported absolute change in g/cm^2 to avoid the biasing influence of the baseline value on percentage change.²⁷ Finally, it is a strength that the authors of publications with wider age ranges of participants have provided their adolescent-only data.^{16,19,20}

A limitation is that there are no randomized, placebo-controlled trials of BMD change on CHC vs CHC nonusing adolescent women. We were able to find sufficient quantitative data from observational prospective studies and from two randomized trials of different CHC agents compared with open-label controls. We were unable to obtain sufficient data for quantitative analysis of all the publications that have relevant primary research data. Few studies have reported whole body BMD change, a usual adolescent clinical BMD measurement site. We also could not uniformly adjust these BMD change data for BMI, race and cigarette smoking, important variables in adolescent bone acquisition. Although the 24-month weighted mean spinal BMD change difference between CHC users and nonusers was small ($-0.02 \text{ g}/\text{cm}^2$ per 2 years), this difference is 60% of a SD of the 2-year BMD change in CaMos population-based CHC nonusing controls.³ In randomized placebo-controlled therapy trials in menopausal women, as small a difference in BMD change as 1% per year was associated with an 8% decrease in subsequent fracture risk.²⁸

Perhaps the major limitation of this study is high heterogeneity of the included studies. Several measures are recommended for dealing with high heterogeneity in meta-analysis: carrying out a meta-regression and/or conducting a subgroup analysis to name a few; however, the small number of eligible studies in the analysis did not allow any further adjustment in our case. However, our 24-month results were robust to sensitivity analyses especially since a random-effects model does not assume homogeneity of effects. We had insufficient power to assess oestrogen doses or to differentiate the potential BMD effects of the various progestins that are commonly part of CHC. We were also unable, due to few eligible publications, to accurately evaluate publication bias.

There has been ongoing and legitimate skepticism that CHC-related negative cross-sectional BMD data even, if it is in a population-based cohort,²⁵ and adolescent BMD loss data as in this meta-analysis, are simply surrogate markers that may or may not reflect the principal medical outcome of fractures. However, the literature includes three large prospective cohort studies of CHC-using women showing incident fracture risks of 7-30% higher than in controls who never used CHC.²⁹⁻³¹

In summary, significantly less spinal bone mineral density accrual occurs in adolescent women who were first taking combined hormonal contraceptives compared with those not using them. This suggests that CHC, even though now including much lower oestrogen doses than in the past, still has sufficiently high doses to decrease bone turnover and thus to likely suppress the bone formation necessary for optimal adolescent bone growth to peak BMD. Since CHC use is now commonly started during adolescence and is recommended for treatment of mild symptomatic, non-contraceptive reasons such as acne and cramps,² there may be a negative public health impact from this current practice. These analysed data can only show associations; therefore, randomized placebo-controlled trial data directly comparing CHC and CHC nonusers' BMD changes are needed.

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only in abstract but now published online in *J. of Musculoskeletal Neuronal Interactions*, July 2017. We appreciate the assistance of Wan Ki Wong, Centre for Clinical Evaluation and Epidemiology of the Vancouver Coastal Health Research Institute, for his aid in quantitative issues related to this meta-analysis. We appreciate the Centre for Menstrual Cycle and Ovulation Research's Dharani Kalidasan, MSc, for coordinating our work in creating and submitting this manuscript.

CONFLICT OF INTEREST

Scholes reports a grant from Bayer AG that is unrelated to the submitted work. All other authors have no competing interests.

AUTHOR'S CONTRIBUTIONS

This study was designed by AG and JCP. TSB, AG and JCP acquired the data. Statistical analysis was performed by AG. It was written by AG and JCP. DS, TBLG and AB have each provided the adolescent data from their respective publications on BMD change over 12 and/or 24 months. All authors have critically reviewed this manuscript, and it has been revised in response to their suggestions; all approved it for submission for publication.

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REFERENCES

- Skouby S. Contraceptive use and behavior in the 21st century: a comprehensive study across five European countries. *Eur J Contracept Reprod Health Care*. 2004;9(2):57-68.
- Prior J. Adolescents' use of combined hormonal contraceptives for treatment and contraception: evidence of potential lifelong negative reproductive and bone effects. *Women's Reproductive Health*. 2016;3:73-93.
- Brajic T, Schlammerl K, Macdonald H, et al. Combined hormonal contraceptive use and bone mineral density changes in adolescent and young women in a population-based Canada-wide cohort. *J Musculoskelet Neuronal Interact*. 2017;18:227-236.
- Beral V, Hermon C, Kay C, Hannaford P, Darby S, Reeves G. Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study. *BMJ*. 1999;318(7176):96-100.
- Polatti F, Perotti F, Filippa N, Gallina D, Nappi RE. Bone mass and long-term monophasic oral contraceptive treatment in young women. *Contraception*. 1995;51(4):221-224.
- Weaver C, Gordon C, Janz K, et al. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. *Osteoporos Int*. 2016;27(4):1281-1386.
- Boot AM, de Ridder MA, van der Sluis IM, van Slobbe I, Krenning EP, de Muinck Keizer-Schrama SM. Peak bone mineral density, lean body mass and fractures. *Bone*. 2010;46(2):336-341.
- Goshtasebi A, Berger C, Barr SI, et al. Adult premenopausal bone health related to reproductive characteristics—population-based data from the Canadian multicentre osteoporosis study (CaMos). *Int J Environ Res Public Health*. 2018;15(5):1023.
- Berger C, Goltzman D, Langsetmo L, et al. Peak bone mass from longitudinal data: implications for the prevalence, pathophysiology, and diagnosis of osteoporosis. *J Bone Miner Res*. 2010;25(9):1948-1957.
- Prior J, Hitchcock C, Vigna Y, Seifert-Klaus V. Premenopausal trabecular bone loss is associated with a family history of fragility fracture. *Geburtshilfe Frauenheilkunde*. 2016;76(08):895-901.
- Barr SI, Petit MA, Vigna YM, Prior JC. Eating attitudes and habitual calcium intake in peripubertal girls are associated with initial bone mineral content and its change over 2 years. *J Bone Miner Res*. 2001;16(5):940-947.
- Bedford JL, Prior JC, Barr SI. A prospective exploration of cognitive dietary restraint, subclinical ovulatory disturbances, cortisol, and change in bone density over two years in healthy young women. *J Clin Endocrinol Metab*. 2010;95(7):3291-3299.
- Welten D, Kemper H, Post G, et al. Weight-bearing activity during youth is a more important factor for peak bone mass than calcium intake. *J Bone Miner Res*. 1994;9(7):1089-1096.
- Ott SM, Scholes D, LaCroix AZ, Ichikawa LE, Yoshida CK, Barlow WE. Effects of contraceptive use on Bone Biochemical markers in young women. *J Clin Endocrinol Metab*. 2001;86(1):179-185.
- Cromer BA, Bonny AE, Stager M, et al. Bone mineral density in adolescent females using injectable or oral contraceptives: a 24-month prospective study. *Fertil Steril*. 2008;90(6):2060-2067.
- Berenson AB, Rahman M, Breitkopf CR, Bi LX. Effects of depot medroxyprogesterone acetate and 20 µg oral contraceptives on bone mineral density. *Obstet Gynecol*. 2008;112(4):788.
- Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Accessed March 20, 2013].
- Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*, vol. 4. Hoboken, NJ: John Wiley & Sons; 2011.
- Scholes D, Hubbard RA, Ichikawa LE, et al. Oral contraceptive use and bone density change in adolescent and young adult women: a prospective study of age, hormone dose, and discontinuation. *J Clin Endocrinol Metab*. 2011;96(9):E1380-E1387.
- Biason TP, Goldberg T, Kurokawa CS, Moretto MR, Teixeira AS, de Carvalho Nunes HR. Low-dose combined oral contraceptive use is associated with lower bone mineral content variation in adolescents over a 1-year period. *BMC Endocr Disord*. 2015;15(1):15.
- Cromer BA, Blair JM, Mahan JD, Zibners L, Naumovski Z. A prospective comparison of bone density in adolescent girls receiving depot medroxyprogesterone acetate (Depo-Provera), levonorgestrel (Norplant), or oral contraceptives. *J Pediatr*. 1996;129(5):671-676.
- Lara-Torre E, Edwards CP, Perlman S, Hertweck SP. Bone mineral density in adolescent females using depot medroxyprogesterone acetate. *J Pediatr Adolesc Gynecol*. 2004;17(1):17-21.
- Gersten J, Hsieh J, Weiss H, Ricciotti NA. Effect of extended 30 µg ethinyl estradiol with continuous low-dose ethinyl estradiol and cyclic 20 µg ethinyl estradiol oral contraception on adolescent bone density: a randomized trial. *J Pediatr Adolesc Gynecol*. 2016;29(6):635-642.
- Gai L, Jia Y, Zhang M, et al. Effect of two kinds of different combined oral contraceptives use on bone mineral density in adolescent women. *Contraception*. 2012;86(4):332-336.
- Prior JC, Kirkland SA, Joseph L, et al. Oral contraceptive use and bone mineral density in premenopausal women: cross-sectional, population-based data from the Canadian Multicentre Osteoporosis Study. *Can Med Assoc J*. 2001;165(8):1023-1029.
- Cromer BA, Scholes D, Berenson A, Cundy T, Clark MK, Kaunitz AM. Depot medroxyprogesterone acetate and bone mineral density in adolescents—the Black Box Warning: a Position Paper of the Society for Adolescent Medicine. *J Adolesc Health*. 2006;39(2):296-301.

27. Vickers AJ. The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: a simulation study. *BMC Med Res Methodol*. 2001;1(1):6.
28. Hochberg MC, Greenspan S, Wasnich RD, Miller P, Thompson DE, Ross PD. Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. *J Clin Endocrinol Metab*. 2002;87(4):1586-1592.
29. Vessey M, Mant J, Painter R. Oral contraception and other factors in relation to hospital referral for fracture - findings in a large cohort study. *Contraception*. 1998;57:231-235.
30. Cooper C, Hannaford P, Croft P, Kay CR. Oral contraceptive pill use and fractures in women: a prospective study. *Bone*. 1993;14:41-45.
31. Barad D, Kooperberg C, Wactawski-Wende J, Liu J, Hendrix SL, Watts NB. Prior oral contraception and postmenopausal fracture: a Women's Health Initiative observational cohort study. *Fertility and Sterility*. 2005;84(2):374-383.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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