

Change in Bone Mineral Density Among Adolescent Women Using and Discontinuing Depot Medroxyprogesterone Acetate Contraception

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Background: Several studies report an association between depot medroxyprogesterone acetate (DMPA) injectable contraception and decreased bone mineral density. Adolescents, who are still gaining bone, may be particularly affected, but there has been little study of the association in adolescent users and none following discontinuation.

Objective: To evaluate bone mineral density changes in adolescents using and discontinuing use of DMPA contraception.

Design: A population-based prospective cohort study.

Participants: One hundred seventy adolescent women, aged 14 to 18 years; 80 baseline DMPA users and 90 age-similar, unexposed comparison women. Sixty-one participants discontinued DMPA use during follow-up.

Main Outcome Measure: Bone mineral density, measured every 6 months for 24 to 36 months at the hip, spine, and whole body, comparing mean bone mineral density changes in DMPA users and discontinuers with nonusers.

Results: Among DMPA users, bone mineral density declined significantly relative to nonusers at the hip and spine but not the whole body. Annualized mean percentage changes, adjusted for covariates, were hip, -1.81% vs -0.19% ; $P < .001$; spine, -0.97% vs 1.32% ; $P < .001$, and whole body, 0.73% vs 0.88% ; $P = .78$ for DMPA users vs nonusers, respectively. New users lost bone mineral density more rapidly than prevalent users. Discontinuers experienced significantly increased bone mineral density relative to nonusers at all anatomical sites; annualized mean percentage changes were hip, 1.34% vs -0.19% ; $P = .004$; spine, 2.86% vs 1.32% ; $P = .004$; and whole body, 3.56% vs 0.88% ; $P < .001$.

Conclusions: Use of DMPA contraception in adolescents was associated with significant continuous losses of bone mineral density at the hip and spine. However, significant gains postdiscontinuation provide evidence that the loss of bone mass is apparently reversed.

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ATTAINMENT OF PEAK BONE mass during adolescence and early adulthood has lifelong implications for fracture risk. A number of studies now provide evidence that use of the progestin-based injectable contraceptive depot medroxyprogesterone acetate (DMPA) (Depo-Provera; Pfizer US Pharmaceutical Group, New York, NY) may adversely affect bone mineral density (BMD).¹⁻¹⁵ Depot medroxyprogesterone acetate is a popular contraceptive worldwide and is currently the only injectable contraceptive available in the United States. Adolescents disproportionately rely on this method, with 10% of US women aged 15 to 19 years using this method vs 3% of US women overall.¹⁶ Adolescents are also still attaining peak BMD and thus may be particularly vulnerable

to any hormonal effects on BMD accompanying this method.^{17,18}

Relatively few studies have focused on the possible effects of DMPA on BMD in adolescent users. One study reported decreased spine BMD in DMPA users relative to controls.³ Our earlier evaluation of a reproductive-age cohort found that the youngest age group (aged 18-21 years) had the greatest BMD difference from age-similar comparison women at baseline¹⁰ but also showed the greatest gains after DMPA use was discontinued.¹⁴ To our knowledge, there has been no evaluation of changes in BMD in younger teen users after DMPA discontinuation.

We report the results of a 3-year prospective study of changes in BMD during DMPA use and after discontinuation in a population-based cohort of 170 adolescent women, aged 14 to 18 years at enrollment.

STUDY PARTICIPANTS

This study was conducted at Group Health Cooperative, a mixed-model managed health care system located in Seattle, Wash, with approximately 15000 enrollees aged 14 to 18 years. All study procedures were reviewed and approved by the Group Health Human Subjects Committee. We obtained written informed consent from participants (or from parents, with assent from minors).

The study sampling and recruitment methods are detailed in an earlier report.¹⁹ Briefly, recruitment occurred from June 1999 to December 2000. Potential participants were selected from a population-based sampling frame derived from the health plan's computerized data files. We selected monthly samples that included all 14- to 18-year-old women who were receiving DMPA injections and a random sample of age-similar comparison women who were not using DMPA.

Once selected, participants who were aged 18 years were contacted directly via letter and subsequent telephone recruitment. If potential participants were younger than 18 years, we sent a letter to the parent(s) describing the study and inviting their daughter's participation. Although use of hormonal contraception was noted as 1 factor of interest, the contraceptive status of potential participants was not included in order to protect confidentiality. Subsequently, study staff telephoned parents to discuss the study, and if we received permission and the teen was interested, we spoke directly to the potential participant.

We excluded potential participants who were pregnant, lactating, or planning to become pregnant; who were using DMPA for noncontraceptive indications; or who had any conditions or medication use known to affect BMD. We also excluded potential comparison women who were premenarcheal or who reported previous DMPA use.

Following their baseline enrollment visit, study participants were asked to make follow-up clinic visits every 6 months. The study design incorporated a minimum of 24 months' follow-up on all participants but allowed up to 36 months of follow-up for participants who entered the study early in the recruitment period.

We originally enrolled 174 participants, 81 of whom were using DMPA contraception and 93 who were not.¹⁹ During evaluation of the more detailed data from follow-up, 4 were found to be ineligible and were excluded (1 DMPA-exposed participant with prior steroid use and 3 comparison participants with prior DMPA use). Thus, the final study group consisted of 80 women using DMPA contraception and 90 nonusing, unexposed women. At 6, 12, 18, and 24 months, we completed follow-up visits for 90%, 84%, 82%, and 78% of the cohort, respectively. Less than 24 months of follow-up data were obtained for 34 women, principally because of being unable to contact the participant (n=11) or the participant becoming pregnant or seeking pregnancy (n=10). Additional 30- and 36-month visits were obtained from 110 and 77 participants, respectively. Ninety-one percent of participants made at least 2 follow-up visits.

DATA COLLECTION

At baseline and follow-up visits, participants completed questionnaires covering health history, contraception, pregnancy history, smoking, physical activity, caffeine intake, alcohol use, and demographics; a food frequency questionnaire of dietary consumption in the past 30 days²⁰; height and weight measurements; and BMD measurements of the hip, spine, and whole

body. We assessed BMD using dual-energy x-ray absorptiometry. Initially, we used a Hologic QDR 4500 (Hologic, Waltham, Mass) at clinic 1 and a Hologic QDR 2000 at clinic 2. In May 2002, clinic 1 upgraded to a Hologic Delphi model and the QDR 4500 was moved to clinic 2. We evaluated the possible shift in *in vivo* BMD readings in a volunteer sample of 20 women at each clinic site who were measured on both the original and replacement machines. The standard errors of the estimate for the linear regression equations (root mean square residual) were 0.013 to 0.022 g/cm², which are similar to those reported in the literature²¹ and to our own precision studies.¹⁴ Based on these cross-calibration assessments, each BMD measurement after the densitometer change was adjusted using a linear regression model for each woman's values at each anatomical site, standardizing to the original machine.

STATISTICAL ANALYSES

The primary study outcome was change in BMD for the hip, spine, and whole body for continuous DMPA use and DMPA discontinuation relative to nonuse. Analyses required that participants make at least 2 study visits to contribute BMD-change data to a given exposure category. We evaluated BMD change in 2 ways: (1) Using a general linear regression model, we evaluated adjusted mean percentage change from baseline at 12, 18, and 24 months. (2) We examined adjusted mean change in BMD (in grams per centimeter squared) for each 6-month interval in the 3 exposure groups using a marginal generalized estimating equations approach. This included additional comparison of BMD change with varying cumulative duration of exposure. These repeated measures models used all available data and accounted for differential follow-up and participants' changing exposure status during the course of the study. The exposure of interest, DMPA use, was entered as a time-dependent covariate, and each participant was classified as to her status at the beginning of every 6-month interval. Women who missed a visit reentered analyses at the next visit they completed. An independent working correlation structure was assumed since both time-dependent and fixed baseline covariates were included. Covariates that were associated with either BMD or DMPA exposure were evaluated for inclusion in the models either to increase precision or to control for possible confounding. Analyses were adjusted for baseline covariates (BMD, ethnicity [white], prior pregnancy, age at menarche) and time-dependent covariates (age, smoking status, calcium intake, and percentage body fat). For participants wearing non-removable navel jewelry, the underlying vertebral BMD was calculated using the *z* scores from the uninvolved vertebrae.

We also calculated an estimated volumetric BMD (in grams per centimeter cubed) for the spine, since during periods of growth, the volume at the spine increases at a faster rate than the area. Thus, the areal density (in grams per centimeter squared) as measured by dual-energy x-ray absorptiometry will increase with bone growth even when the volumetric BMD remains unchanged. For each vertebra, the volumetric BMD was calculated as the areal BMD divided by the square root of the area. The overall volumetric BMD was the average of the volumetric BMDs of the 4 lumbar vertebrae.²²

RESULTS

STUDY SAMPLE

Baseline characteristics of the cohort, by DMPA exposure status, are shown in **Table 1**. Thirty percent of participants were 16 years or younger, and 30% were non-

white. The DMPA-exposed teens were significantly more likely than DMPA-unexposed participants to currently smoke, have been pregnant, and have navel jewelry, an earlier age at menarche, lower calcium intake, and higher body mass index, body fat, and percentage body fat.

All women using DMPA were receiving the standard contraceptive dose (150 mg every 3 months). At baseline, DMPA use ranged from 1 to 13 injections (approximately 1-39 months). About 30% of the group had received only 1 injection (defined as *new users*), 31% had received 2 to 3 injections, 21% had 4 to 7, and 18% had 8 or more (Table 1). Median duration of use among prevalent users at baseline was 4 injections (approximately 12 months). Among the 90 women in the comparison group, 19% reported oral contraceptive use at baseline. This group had lower baseline BMD than other comparison women (data not shown). However, as these differences were not significant for any anatomical site, the entire DMPA-unexposed group comprised the comparator.

Baseline BMD was lower at all anatomical sites for DMPA-exposed as compared with unexposed participants, but differences were not statistically significant (Table 1).²² Of the teens who were receiving DMPA injections, 61 (71%) discontinued DMPA injections at some point during follow-up; 21% discontinued within the first 6 months of enrollment. Following discontinuation, we were able to follow up participants for a mean of 14 months (range, 0.4 to 36.0 months). The range of DMPA use prior to discontinuation was 3 to 62 months (60 of 61 discontinuers had at least 2 injections at discontinuation). In the comparison group, 6 participants initiated DMPA use and subsequently contributed time as new DMPA users.

CHANGES IN BMD WITH CONTINUOUS DMPA USE

For study participants who continued to use DMPA, mean BMD declined during follow-up at the hip and spine. Whole body BMD increased slightly (**Figure 2**). Among comparison women, there were small mean BMD decreases at the hip, with increased BMD at the spine and whole body.

After adjusting for baseline and time-dependent covariates, the mean percentage change in BMD from baseline (at 12-, 18-, and 24-month follow-ups) differed significantly for the hip and spine for DMPA users relative to comparison women (Figure). Changes at these 2 sites were greater for new users of this method than for prevalent users; for example, after 24 months, new users showed a -6.09% change at the hip while change for prevalent users was -2.04%. Change for nonusers was -0.92%.

Results were similar in the repeated measures models, which evaluated mean BMD change, in grams per centimeter squared, at 6-month intervals (Table 2). Adjusted BMD change at the hip was -0.0088 g/cm² for continuous DMPA users compared with -0.0010 g/cm² in nonusers for each 6-month interval; at the spine, the adjusted mean change was -0.0050 vs 0.0062 g/cm² for users and nonusers, respectively; and at whole body adjusted mean change was 0.0039 vs 0.0046 g/cm², respectively. Differences between users and nonusers were sig-

Table 1. Participant Characteristics at Baseline by DMPA Exposure Status*

Characteristic	DMPA User (n = 80)	DMPA Nonuser (n = 90)
Age, y		
14-16	27.5	32.2
17-18	72.5	67.8
Mean (SE)	17.1 (0.1)	16.9 (0.1)
Ethnicity		
White	63.8	75.6
African American	15.0	4.4
Asian	3.8	4.4
Hispanic	3.8	2.2
Other	13.8	13.3
Education ≥ high school	38.8	31.1
Current smoker	36.3	10.0
Personal history of fracture	39.7	36.8
Relative with hip/spine fracture†	20.0	30.0
Ever pregnant	24.1	4.4
Navel jewelry	17.5	5.6
Current oral contraceptive use‡	NA	18.9
No. of DMPA injections		NA
1	30.0	
2-3	31.3	
4-7	21.3	
≥8	17.5	
Age at menarche, y, mean (SE)	12.0 (0.2)	12.5 (0.1)
Weight-bearing physical activity, mean (SE)§	59.3 (1.7)	62.4 (1.4)
Calcium intake, mg/d, mean (SE)	973 (74)	1174 (64)
Alcohol intake, g/d, mean (SE)	2.0 (0.7)	0.7 (0.2)
Caffeine intake, mg/d, mean (SE)	60.3 (10.0)	45.3 (8.7)
Weight, kg, mean (SE)	65.7 (1.5)	63.5 (1.3)
Height, cm, mean (SE)	163.5 (0.7)	165.3 (0.7)
Body mass index, kg/m ² , mean (SE)	24.6 (0.5)	23.2 (0.4)
Fat tissue, g, mean (SE)	22 920 (916)	19 725 (781)
Lean tissue, g, mean (SE)	40 838 (636)	42 424 (646)
Fat tissue, %, mean (SE)	35.1 (0.7)	31.0 (0.7)
Total hip BMD, g/cm ² , mean (SE)	0.941 (0.013)	0.969 (0.014)
Spine BMD, g/cm ² , mean (SE)	0.969 (0.012)	0.990 (0.013)
Whole body BMD, g/cm ² , mean (SE)	1.078 (0.011)	1.085 (0.011)

Abbreviations: BMD, bone mineral density; DMPA, depot medroxyprogesterone acetate.

*Values are expressed as percentages unless otherwise indicated.

†An answer of "unknown" was considered no (34 exposed, 30 unexposed).

‡Health plan pharmacy records show that 5% of total oral contraceptive prescriptions in this age group were for lower-dose formulations (containing 20 µg of estrogen).

§Physical activity calculated by assessing frequency of 21 activities, multiplying by level of weight bearing (0-2), and summing the results to arrive at a total score for each participant.

nificant at the hip and spine ($P < .001$ at hip and spine; $P = .78$ for whole body). Based on these models, the calculated annualized mean percentage change in BMD among DMPA continuous users, after adjustment, was -1.81%, -0.97%, and 0.73% at the hip, spine, and whole body, respectively, compared with -0.19%, 1.32%, and 0.88% for comparison women.

In evaluating BMD change with varying cumulative durations of use, the adjusted mean change in BMD for each 6-month interval decreased with increasing DMPA cumulative use (P value for grouped linear trend = .003, .004, and .07 for the hip, spine, and whole body, respectively) (data not shown). Change was greatest for those

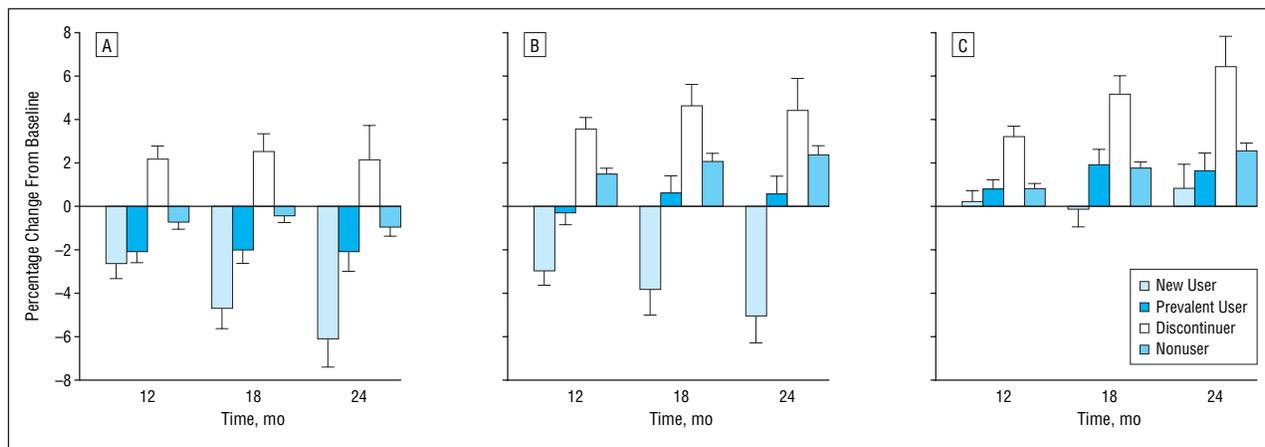


Figure. Mean percentage change in bone mineral density (BMD) from baseline by depot medroxyprogesterone acetate (DMPA) exposure status, adjusted for baseline covariates (BMD, ethnicity, pregnancy, age at menarche) and time-dependent covariates (age, smoking status, calcium intake, percentage body fat). Error bars represent 1 SE from the mean. New users (n=17, 9, and 8 at 12, 18, and 24 months, respectively) received 1 DMPA injection; prevalent users (n=26, 18, and 14 at 12, 18, and 24 months, respectively) received more than 1 DMPA injection. For DMPA discontinuers (n=26, 14, and 5 at 12, 18, and 24 months, respectively), the intervals refer to the length of time participants were followed up after becoming discontinuers. The number of nonusers at 12, 18, and 24 months was 69, 69, and 59, respectively. A, Total hip BMD. B, Spine BMD. C, Whole body BMD.

Table 2. Multivariable Repeated Measures Model: Mean BMD Change per 6-Month Interval by DMPA Exposure Status*

DMPA Use	Sample Size	No. of 6-mo Intervals†	Mean BMD Change (g/cm ²)‡ (95% CI)		
			Hip	Spine	Whole Body
Continuous users	63	171	-0.0088 (-0.0116 to -0.0061)§	-0.0050 (-0.0077 to -0.0023)§	0.0039 (-0.0002 to 0.0080)
New	22	62	-0.0101 (-0.0138 to -0.0065)§	-0.0091 (-0.0136 to 0.0046)§	0.0021 (-0.0018 to 0.0059)
Prevalent	41	109	-0.0078 (-0.0112 to -0.0043)§	-0.0025 (-0.0054 to -0.0003)§	0.0055 (-0.0003 to 0.0113)
Discontinuers	38	82	0.0058 (0.0014 to 0.0102)	0.0133 (0.0088 to 0.0177)	0.0186 (0.0125 to 0.0246)§
Nonusers	84	367	-0.0010 (-0.0028 to 0.0009)	0.0062 (0.0046 to 0.0078)	0.0046 (0.0029 to 0.0063)

Abbreviation: BMD, bone mineral density; CI, confidence interval; DMPA, depot medroxyprogesterone acetate.

*Analyses are of participants who made a minimum of 2 visits within a given exposure category and who had complete covariate information. For discontinuers, 61 discontinued DMPA use but 20 did so at their last visit and 3 participants were missing covariate data.

†Each participant contributed at least 1 and up to 6 6-month intervals to the models.

‡Adjusted for baseline covariates (BMD, ethnicity, pregnancy, age at menarche) and time-dependent covariates (age, smoking status, calcium intake, percentage body fat).

§ $P \leq .001$ for difference from nonusers.

|| $P = .004$ for difference from nonusers.

with the least cumulative use, but DMPA users continued to lose BMD at the hip and spine well beyond 24 months of use.

Changes in the volumetric BMD at the spine (in grams per centimeter cubed) were smaller, but differences between DMPA users and nonusers continued to be highly significant ($P < .001$) (data not shown).

CHANGES IN BMD FOLLOWING DISCONTINUATION DMPA USE

The 61 participants who discontinued DMPA use at some time during the study had bone loss patterns during DMPA use that were similar to participants who continued use. After discontinuation, BMD increased.

Eighteen months postdiscontinuation, the adjusted mean percentage changes from baseline were significantly higher for DMPA discontinuers than for nonusers at all anatomical sites ($P = .005, .023, \text{ and } .001$ at the hip, spine, and whole body for discontinuers compared

with nonusers), with the greatest changes occurring at the whole body (Figure).

In our examination of changes in BMD (in grams per centimeter squared), the adjusted mean gains among DMPA discontinuers for each 6-month interval were 0.0058, 0.0133, and 0.0186 g/cm² for the hip, spine, and whole body, respectively; for nonusers, changes were -0.0010, 0.0062, and 0.0046 g/cm² (Table 2). The annualized adjusted mean percentage change in BMD was 1.34%, 2.86%, and 3.56% for the hip, spine, and whole body for DMPA discontinuers compared with -0.19%, 1.32%, and 0.88% for nonusers. Differences between DMPA discontinuers and nonusers were statistically significant at all anatomical sites ($P = .004, .004, \text{ and } < .001$ for the hip, spine, and whole body, respectively).

Women who discontinued DMPA use gained BMD during all of the available follow-up time, and we noted no differences in gain by the duration of DMPA use at discontinuation (data not shown). Adjusted mean BMD values for discontinuers were at least as high as those of

nonusers for all anatomical sites at 12 months and at all subsequent follow-up intervals.

Gains in volumetric BMD at the spine were also significant for discontinuers relative to nonusers ($P < .05$) (data not shown).

COMMENT

There is increasing evidence that DMPA use may adversely affect skeletal health, plausibly because of the estrogen depletion accompanying use of this progestin-based agent.^{23,24} The DMPA-associated changes may be particularly important for adolescent women, who are in the process of attaining peak bone mass. This prospective evaluation in a cohort of adolescents addressed the related questions of BMD changes that accompany both DMPA use and DMPA discontinuation.

DOES BMD DECREASE DURING DMPA USE?

In this group of teens, those who continued use of DMPA experienced continuous and significant declines in adjusted BMD at both the hip and spine relative to comparison women. Our findings accord with those of other longitudinal studies of this association in older premenopausal women.^{2,5,12,14,15,25} A clinic-based study of adolescents by Cromer et al³ (15 new DMPA users and 17 controls; mean age, 15.5 years) also noted 12-month spine BMD losses similar in magnitude to those seen in the 24 new DMPA users in this study. Our inclusion of prevalent users allowed us to document that changes in BMD were greatest during the first 1 to 2 years of use but continued beyond this time frame; our range of DMPA exposure extended from 1 to 24 injections (approximately 1 to 72 months) by the study's conclusion. We also observed similar between-group differences at multiple anatomical sites. In comparing these results with our recent cohort study among reproductive-age women from this same defined population,¹⁴ annualized mean percentage change was slightly higher at the hip and spine in the adolescents.

If not reversed, changes of the magnitude reported here could, potentially, have clinical consequences. Prospective studies relating BMD to the risk of fractures in postmenopausal women²⁶ have shown that each standard deviation decrease in BMD approximately doubles the risk of fracture. The limited data available indicate that this relationship may apply to younger women as well.²⁷ The population standard deviation for white women is about 13%.²⁸ In our data, BMD at the hip decreased approximately 0.05 g/cm² after 24 months, about 5% loss.

IS BMD REGAINED FOLLOWING DMPA DISCONTINUATION?

Given the efficacy and acceptability of this method and the growing evidence of DMPA-associated BMD losses, it is of great interest to know if any effects on BMD are reversible. Our findings suggest that, on discontinuation, BMD begins to undergo rapid recovery, particularly at the spine and whole body (Table 2). The process

of recovery may be somewhat slower at the hip. To our knowledge, no other studies have evaluated bone recovery following DMPA discontinuation specifically in adolescents. However, our results generally accord with those reported for older premenopausal women² and for our reproductive-age cohort.¹⁴ In the current study, mean annualized gains following discontinuation were greater than those seen in our reproductive-age cohort (1.34% vs 1.04% per year for the hip, and 2.86% vs 1.41% for the spine).

The increases in BMD after DMPA discontinuation show similarities to BMD changes after normal lactation, which appears to exert substantial but largely transient effects on BMD.²⁹⁻³¹ It would be difficult to determine whether DMPA-exposed women achieved the BMD that they would have in the absence of DMPA use. We did find, however, that adjusted mean BMD values for women 12 months or more after discontinuation were at least as high as those of comparison women at all of the anatomical sites.

In evaluating the possible association between DMPA and BMD, this study offers a number of strengths. To our knowledge, this is the most sizeable study to date in adolescents and the first population-based study, and it is the only evaluation of BMD changes following discontinuation of DMPA use. By using a prospective cohort design that enrolled both new and prevalent users of DMPA, we were able to evaluate durations of exposure well beyond the study's follow-up length to assess both short- and long-term changes (a range of 1-24 injections by the end of the study). Of particular importance, we could assess BMD changes following DMPA cessation after short- and long-term use. We also used a population-based sampling strategy. This allowed us to enroll exposed and unexposed participants from the same defined population, minimizing comparability issues. We evaluated the consistency of our results by measuring BMD at multiple anatomical sites and by calculating volumetric BMD in this group of growing teens. Finally, we measured and controlled for the potentially confounding roles of numerous covariates of interest.

The main limitation of these data was attrition to the cohort, due primarily to the need to censor participants who became pregnant or began seeking pregnancy. We evaluated our BMD change in a number of ways, and in the repeated measures models of BMD change, we included all available data from each participant. Our study design also did not allow for assessment of BMD prior to DMPA exposure. However, in the 30% of exposed participants who had received only 1 injection at baseline, mean BMD very closely approximated that of unexposed comparison women at all anatomical sites.

Given the increasing public health importance of osteoporosis,³² factors that may affect peak bone mass attainment and maintenance have received deservedly greater emphasis. This study provides evidence that DMPA use by adolescents adversely impacts BMD at key anatomical sites. However, these results in teens and those from our previous cohort provide reassurance that bone loss is regained, even in younger users.

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