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Depot Medroxyprogesterone Acetate Use and Blood Lead Levels in a Cohort of Young Women

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Background: Injectable contraceptive use is common, with 74 million users worldwide. Use of the injectable contraceptive depot medroxyprogesterone acetate (DMPA) is associated with bone mineral density loss. We hypothesize that increased bone resorption with DMPA use allows for mobilization of the toxic metal lead stored in bone to blood, presenting users with increased systemic exposure to lead.

Objective: The objective of our study was to investigate the association between current DMPA use and blood lead concentrations.

Methods: We conducted a cross-sectional analysis using enrollment data from the Study of Environment, Lifestyle & Fibroids (SELF), a cohort of 1,693 African-American women who were 23–35 years of age. Data on DMPA use were collected by computer-assisted telephone interview. Blood lead concentrations were measured in whole blood samples among 1,548 participants (91% of cohort). We estimated the adjusted percent difference in blood lead concentrations and 95% confidence intervals (CI) between current DMPA users and nonusers using multivariable linear regression.

Results: Geometric mean blood lead concentration was 0.69 μg/dL (95% CI: 0.67, 0.71). After adjustment, current DMPA users (7% of cohort) had blood lead concentrations that were 18% higher than those of nonusers (95% CI: 8%, 29%). Similar associations were observed with additional analyses to assess for potential bias from smoking, DMPA-induced amenorrhea, use of estrogen-containing contraceptives, having given birth in the prior year, and history of medical conditions or current medication use associated with bone loss.

Discussion: Our results indicate that current DMPA use is associated with increased blood lead concentrations. Further research, particularly in populations highly exposed to lead, is warranted to consider tradeoffs between the adverse effects of lead on human health and the importance of DMPA as a contraceptive option to prevent unintended pregnancy. https://doi.org/10.1289/EHP7017

Introduction

Depot medroxyprogesterone acetate (DMPA) is an injectable progestin-only contraceptive that is used in more than 90 countries worldwide (Black et al. 2006). DMPA is an important contraceptive option to prevent unintended pregnancy; a single injection provides 3 months of effective contraceptive coverage, with a convenient dosing schedule and privacy (ACOG 2014). Since its approval by the U.S. Food and Drug Administration (FDA) in 1992, DMPA has been used by one in five sexually active U.S. women, with more frequent use reported among African-American women (Daniels and Mosher 2013). Worldwide, the use of injectable contraceptives is increasing, from 17 million users in 1994 to 74 million users in 2019 (United Nations 2019). However, unlike other progestin-only contraceptives, the inhibition of pituitary gonadotropin secretion by DMPA results in the substantial reduction of ovarian estrogen production (Bahamondes et al. 2000, 2014; Clark et al. 2001; Miller et al. 2000), with one study reporting a mean weekly estradiol level among DMPA users similar to that observed in postmenopausal women (Clark et al. 2001; Randolph et al. 2011). Just as estrogen deficiency after menopause increases bone resorption and bone loss (Lobo 2014), lower bone mineral density has been observed during DMPA use (Nappi et al. 2012). The recovery of bone mineral density after discontinuation of DMPA has minimized some of the concerns posed by the FDA black box warning on the potential loss of bone mineral density with prolonged use (ACOG 2014; Vondracek et al. 2009). However, ramifications other than bone health from increased bone resorption may exist.

Increased bone resorption during DMPA use may present users with increased systemic exposure to the toxic metal lead. More than 90% of lead that enters the body from exogenous exposure is stored in the skeleton (Barry 1975). Although lead has a long elimination time from bone (1–2 decades) in comparison with blood (1 month) (Abadin et al. 2007), lead can transfer between bone and other tissue compartments and blood; it is estimated that bone lead contributes 45%–70% of lead in blood (Gulson et al. 1995), providing an endogenous source of blood lead. Increased blood lead concentrations have been associated with other hypoestrogenic states during which increased bone resorption occurs, such as menopause and lactation (Gulson et al. 1998, 2003; Hernandez-Avila et al. 2000; Nash et al. 2004; Silbergeld et al. 1988; Symanski and Hertz-Picciotto 1995). The potential for increased mobilization of lead from bone to systemic circulation during DMPA use is of public health concern. There is widespread scientific consensus that there are no safe levels of lead in blood. Lead can adversely affect

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all organ systems, even in adulthood, with neurological, renal, cardiovascular, hematological, immunological, and reproductive effects being well-documented (Abadin et al. 2007; ATSDR 2019).

To our knowledge, the association between current DMPA use and blood lead concentrations has been examined in only one study. In a cross-sectional study of 174 adolescent clinic patients, higher mean blood lead concentrations were reported among DMPA users compared with concentrations among oral contraceptive users and nonhormonal contraceptive users (Iglesias et al. 2008). However, that study included only 28 current DMPA users, and analyses were not adjusted for potential confounders, such as smoking, that substantially contribute to the concentration of lead in blood (Abadin et al. 2007). Hence, the purpose of the present study was to investigate the association between current DMPA use and blood lead concentrations using data from a large cohort of young African-American women for whom extensive covariate data were available.

Methods

Study Population

We conducted a cross-sectional analysis using enrollment data from the Study of Environment, Lifestyle & Fibroids (SELF). SELF is an ongoing prospective cohort study of 1,693 African-American women designed to identify risk factors for fibroid incidence and growth as previously described (Baird et al. 2015). Briefly, African-American women ages 23–35 y residing in the Detroit, Michigan, area were enrolled in SELF from 2010 to 2012. To reach a diverse sample of African-American women from the area, broad recruitment strategies were employed, including the use of a study website, fliers, brochures at health care clinics, local radio, television, newspaper advertisements, information booths at community events, and letters describing the study to African-American women who had been seen at the Henry Ford Health System, a collaborating institution in Detroit. The primary eligibility criteria included having an intact uterus and having no prior clinical diagnosis of fibroids, cancer that required radiation or chemotherapy, or the autoimmune diseases lupus, Grave's disease, Sjogren's, scleroderma, or multiple sclerosis requiring medication. The parent SELF study was approved by institutional review boards at the National Institute of Environmental Health Sciences and Henry Ford Health System. The present analyses used deidentified SELF data and was deemed not to involve human subjects by the Human Research Protection Program at Michigan State University.

At enrollment, participants attended a clinic visit in which trained study personnel measured each participant's height and weight and collected biological samples, including blood samples that were analyzed for hemoglobin (g/dL) (Baird et al. 2015) and serum 25-hydroxyvitamin D (25(OH)D) (Jukic et al. 2016); the annual mean 25(OH)D was estimated using a cosinor model to account for seasonal changes (Jukic et al. 2016). Participants also completed computer-assisted telephone and web-based interviews and self-administered questionnaires, including the Block 2005 Food Frequency Questionnaire (Baird et al. 2015). These study activities were used to ascertain information on demographics, lifestyle behaviors, and diet, as well as reproductive, medical, and contraceptive history.

DMPA Use

During the computer-assisted telephone interview at enrollment, hormonal contraceptive data were collected, including whether the participant had ever used "hormone shots like Depo-Provera." If the participant responded yes, then she was asked whether she was currently using hormone shots like Depo-Provera®. DMPA injectable contraceptives (150 mg/1.0 mL intramuscular or 104 mg/0.65 mL subcutaneous) were the only FDA-approved injectable contraceptives in the United States at the time of the SELF enrollment, and both formulations are associated with similar changes in bone mineral density (Kaunitz et al. 2009). However, the intramuscular formulation is primarily used in the United States (Upadhyay et al. 2016). Each participant was also asked about the total duration of DMPA use over her lifetime, because DMPA use can be episodic; data were not collected on the duration of the current episode of DMPA use. If a participant had discontinued DMPA use, she was asked about the age at last use. In the present analyses, the exposure of interest was current DMPA use. Women not currently using DMPA were defined as nonusers, and this comparison group included both past DMPA users and never users. This comparison group was used to avoid selection bias that may transpire with the use of never users. Only 57% of participants reported never using DMPA, and these participants tend to have higher socioeconomic status, which is associated with lower blood lead concentrations, in comparison with current and past DMPA users.

Blood Lead Concentrations

Nonfasting whole blood samples were collected at enrollment in a manner that was in accord with recommendations by the U.S. Centers for Disease Control and Prevention (CDC) to limit metal contamination and promote specimen stability (CDC 2016). Specifically, venipuncture was performed using a stainless-steel needle, and the whole blood sample was collected in a vacutainer that was prescreened for metal contamination. In addition, the whole blood sample used for the laboratory analysis of blood lead concentrations was the first blood specimen collected. After collection, the sample was not further processed and was permanently stored at the National Institute of Environmental Health Sciences Repository, Experimental Pathology Laboratories, Inc. at -20°C (Baird et al. 2015). Whole blood samples were available for 1,664 participants (98% of the original cohort of 1,693 participants). Lead was quantified by inductively coupled dynamic reaction cell plasma mass spectrometry (ICP-DRC-MS) (CDC 2016) by the Inorganic and Radiation Analytical Toxicology Branch Laboratory, Division of Laboratory Science, National Center for Environmental Health at the CDC. Of the 1,664 participants, samples for 116 participants could not be analyzed due to sample clotting, resulting in a sample size of 1,548 women for the present analyses. Only one participant had a blood lead concentration below the limit of detection (LOD; 0.07 μg/dL); for that participant, we used the value of the LOD divided by the square root of 2 (0.05 μg/dL) (Hornung and Reed 1990).

Statistical Analyses

For descriptive purposes, we compared participant characteristics at enrollment between current DMPA users and nonusers. We also estimated the geometric mean blood lead concentration, adjusted for age and smoking, and accompanying 95% confidence interval across categories of participant characteristics among nonusers of DMPA.

To evaluate the association between current DMPA use and blood lead concentrations, we conducted multivariable linear regression and estimated the percent difference in blood lead concentrations and accompanying 95% confidence intervals, comparing current DMPA users with nonusers. Specifically, we modeled the natural log of the blood lead concentrations and estimated the percent difference using the formula $[\exp(\text{beta}) - 1] \times 100$. Informed by prior studies reporting factors associated with DMPA

use and exposure sources of lead (Abadin et al. 2007; ATSDR 2019; Scholes et al. 1999, 2002), we identified variables for adjustment in the regression model. We adjusted for participant age (continuous), education (≤HS/GED, some college/Associate's degree, Bachelor's/Master's/doctoral degree), current smoking (yes, no), and alcohol use in the last year (none, moderate, heavy) (see Model 1 in Table 2). We repeated the analyses, additionally adjusting for factors associated with bone health, including having given birth in the previous year (yes, no), $\log_2$-transformed estimated annual mean 25(OH)D concentrations (continuous), estimated total calcium intake (<800, ≥800 mg/d), and a composite variable (yes, no) for history of medical conditions or current medication use associated with bone loss (thyroid condition, anorexia nervosa, irritable bowel syndrome, anticonvulsant, thyroid hormone replacement, heparin, glucocorticoid medication use) (see Model 2 in Table 2) (Vondracek et al. 2009; U.S. Department of Health and Human Services 2004). Current medication use was informed by the prescription medications participants brought to the clinic visit and used in the prior 24 h.

We conducted several sensitivity analyses. First, we restricted the study population to never smokers ($n = 1{,}139$) to evaluate the adequacy of adjusting for smoking in the main analyses. Second, we repeated the analyses, adjusting for hemoglobin (continuous) because blood lead is stored in red blood cells (Abadin et al. 2007) and current DMPA users are less likely to be anemic due to DMPA-induced amenorrhea (Hubacher et al. 2009; Schwallie and Assenzo 1973). Third, we compared current DMPA users to those who had used DMPA in the past but were not currently using this contraceptive method. We conducted this sensitivity analysis to address the concern that an observed association may be due to unmeasured risk factors for lead exposure that might be more common among current DMPA users than nonusers. For this sensitivity analysis, we restricted past DMPA users to those who had discontinued use 3 or more years prior to the enrollment visit to correspond with the recovery of bone mass after discontinuation (Scholes et al. 2002). Fourth, we repeated the analyses, restricting the study population to those not currently using estrogen-containing contraception ($n = 1{,}332$) because prior studies of combined hormonal contraception and bone mineral density have reported mixed results (Liu and Lebrun 2006; Martins et al. 2006). Fifth, we restricted the study population to those who had not given birth in the previous year. This sensitivity analysis was conducted to exclude women who may have increased blood lead concentrations from bone resorption during the later stages of pregnancy or lactation (Abadin et al. 2007). Last, we conducted an analysis excluding study participants with a history of medical conditions or current medication use associated with bone loss.

We also conducted an exploratory analysis to evaluate the dose–response relationship between current DMPA use and blood lead. In this analysis, we compared current DMPA users with a lifetime duration of DMPA use of greater than 1 y, current DMPA users with a lifetime use of DMPA ≤1 y, and women not currently using DMPA. Although total lifetime duration of DMPA use is not a proxy for duration of current use because women may start, stop, and restart DMPA use, it is likely that current DMPA users with a lifetime use of DMPA ≤1 y have only used DMPA for a short while. However, some current users with >1 y of lifetime use may have re-started DMPA use only recently.

Results

At enrollment, 7% of participants ($n = 102$) reported current DMPA use. Among current DMPA users, the median duration of lifetime use was 5 y [interquartile range (IQR): 2–9], with a maximum of 15 y of lifetime use reported. Current DMPA users tended to be younger and had lower educational attainment, household income, alcohol consumption, and body mass index in comparison with nonusers (Table 1). Current DMPA users were more likely to report greater total intake of calcium and having given birth in the past year and had higher hemoglobin levels than nonusers.

The geometric mean blood lead concentration in the overall cohort was 0.69 μg/dL [95% confidence interval (CI): 0.67, 0.71], and two participants had blood lead concentrations ≥5 μg/dL. The geometric mean blood lead concentrations in the SELF was higher than that of non-Hispanic black (0.60 μg/dL, 95% CI: 0.53, 0.68) and white women (0.53 μg/dL, 95% CI: 0.48, 0.59) of the same age in the National Health and Nutrition Examination Survey for years 2011–2012 (Table S1) (https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/overview.aspx?BeginYear=2011). Among participants not currently using DMPA, those with higher blood lead concentrations tended to be older and have lower educational attainment and household income. They were also more likely to smoke, consume alcohol, have given birth in the past year and be currently lactating, and to have had a history of high blood lead concentrations as an infant or child (Table 1).

The geometric mean and distribution of blood lead concentrations was higher for current DMPA users (0.83 μg/dL, 95% CI: 0.75, 0.93) than nonusers (0.68 μg/dL, 95% CI: 0.66, 0.70) (Table 2, Table S2, Figure S1). After multivariable adjustment, current users of DMPA at enrollment had blood lead concentrations that were 18% higher than those of nonusers (95% CI: 8%, 29%) (Table 2). A post hoc analysis using total annual household income (<$20,000, $20,000 − $50,000, >$50,000) instead of education yielded nearly identical results (Table S3). We also observed a similar percent difference in blood lead concentrations in each of our sensitivity analyses in which we: *a*) restricted the study population to never smokers (19% higher, 95% CI: 8%, 32%); *b*) additionally adjusted for hemoglobin (17% higher, 95% CI: 7%, 28%); *c*) compared current DMPA users with past DMPA users who had discontinued ≥3 y prior to enrollment (15% higher, 95% CI: 4%, 28%); *d*) restricted the study population to those not currently using estrogen-containing contraception (16% higher, 95% CI: 6%, 27%); *e*) restricted the study population to women who had not given birth in the previous year (16% higher, 95% CI: 5%, 28%); and *f*) excluded participants with a history of medical conditions or current medication use associated with bone loss (20% higher, 95% CI: 9%, 32%).

In our exploratory analysis of the dose–response relationship, current users of DMPA who have used DMPA for more than 1 y in their lifetime had blood lead concentrations that were 20% higher than those of nonusers (95% CI: 9%, 33%), whereas current DMPA users who have used DMPA for 1 y or less in their lifetime had blood lead concentrations that were 8% higher, although accompanied by a wide confidence interval (95% CI: −11%, 31%) (Table S4).

Discussion

In our study sample, current DMPA use was associated with increased blood lead concentrations. This association is biologically plausible. DMPA acts centrally at the level of the hypothalamus and pituitary to inhibit gonadotropin secretion, resulting in the suppression of ovarian estradiol production. Substantially lower serum estradiol concentrations have been reported after the initiation of DMPA use (Miller et al. 2000) and when comparing DMPA users with nonusers (Bahamondes et al. 2000, 2014). One study, in which serum estradiol concentrations were measured weekly during a 13-wk DMPA contraceptive coverage period, reported a mean serum estradiol concentration of 18.9 pg/mL (Clark et al. 2001), a concentration similar to that observed

Table 1. Participant characteristics at enrollment by current depot medroxyprogesterone acetate use and blood lead concentrations, Study of Environment, Lifestyle & Fibroids, 2010–2012 ($n = 1{,}548$).

Characteristic	Current DMPA use[a]		Blood lead (μg/dL)
	Yes $n = 102$ *n* (%)	No $n = 1{,}446$ *n* (%)	Among women not currently using DMPA ($n = 1{,}446$) Adjusted GM (95% CI)[b]
Age at enrollment visit (y)[c]			
23–25	31 (30)	319 (22)	0.65 (0.62, 0.69)
26–28	26 (25)	367 (25)	0.68 (0.65, 0.72)
29–31	24 (24)	385 (27)	0.68 (0.65, 0.71)
32–35	21 (21)	375 (26)	0.71 (0.68, 0.74)
Education[d]			
≤HS or GED	36 (35)	296 (20)	0.80 (0.76, 0.84)
Some college or Associate's/technical degree	50 (49)	723 (50)	0.69 (0.66, 0.71)
Bachelor's, Master's, or doctoral degree	16 (16)	426 (29)	0.60 (0.58, 0.63)
Total annual household income (USD$)[d]			
<20,000	66 (65)	632 (44)	0.75 (0.73, 0.78)
20,000–50,000	27 (26)	545 (38)	0.64 (0.62, 0.67)
>50,000	9 (9)	258 (18)	0.61 (0.58, 0.64)
Smoking status[e]			
Never	76 (75)	1,063 (74)	0.60 (0.59, 0.62)
Former	6 (6)	107 (7)	0.73 (0.67, 0.79)
Current <10 cigarettes/d	14 (14)	203 (14)	1.03 (0.97, 1.09)
Current ≥10 cigarettes/d	6 (6)	73 (5)	1.18 (1.07, 1.31)
Alcohol consumption last year			
None	41 (40)	414 (29)	0.64 (0.62, 0.67)
Moderate	44 (43)	740 (51)	0.67 (0.65, 0.69)
Heavy	17 (17)	292 (20)	0.77 (0.73, 0.82)
Body mass index (kg/m^2)			
<25.0	39 (38)	278 (19)	0.69 (0.65, 0.73)
25.0 to <30.0	22 (22)	308 (21)	0.70 (0.67, 0.74)
30.0 to <35.0	13 (13)	282 (20)	0.67 (0.63, 0.71)
35.0 to <40.0	6 (6)	247 (17)	0.69 (0.65, 0.73)
≥40.0	22 (22)	331 (23)	0.66 (0.63, 0.69)
Exercise in past 12 months[d]			
Low	11 (11)	227 (16)	0.64 (0.61, 0.68)
Low to moderate	29 (29)	329 (23)	0.68 (0.65, 0.72)
Moderate	30 (30)	386 (27)	0.71 (0.68, 0.74)
High	17 (17)	282 (20)	0.66 (0.63, 0.70)
Very high	14 (14)	218 (15)	0.70 (0.66, 0.75)
Daily total calcium intake (mg/d) during prior year[f]			
Low (<800 mg/d)	44 (43)	771 (53)	0.68 (0.65, 0.70)
High (≥800 mg/d)	58 (57)	675 (47)	0.69 (0.66, 0.71)
Estimated annual mean 25(OH)D concentration			
<Median (15.31 ng/mL)	52 (51)	719 (50)	0.70 (0.68, 0.72)
≥Median (15.31 ng/mL)	50 (49)	722 (50)	0.67 (0.64, 0.69)
Conditions or medication use associated with bone loss[g]			
No	89 (87)	1,319 (91)	0.68 (0.67, 0.70)
Yes	13 (13)	127 (9)	0.65 (0.60, 0.71)
Birth in last year			
No	85 (83)	1,362 (94)	0.68 (0.66, 0.69)
Yes, not currently lactating	14 (14)	74 (5)	0.77 (0.70, 0.86)
Yes, currently lactating	3 (3)	10 (1)	0.86 (0.65, 1.14)
Low hemoglobin (<12 g/dL)[d]			
No	89 (87)	1,003 (70)	0.69 (0.67, 0.71)
Yes	13 (13)	421 (30)	0.66 (0.63, 0.69)
Told by doctor had high lead levels when infant or child[d]			
No	99 (100)	1,343 (98)	0.68 (0.66, 0.69)
Yes	0 (0)	28 (2)	0.79 (0.67, 0.94)

Note: CI, confidence interval; DMPA, depot medroxyprogesterone acetate; GED, general equivalency diploma; GM, geometric mean; HS, high school; 25(OH)D, 25-hydroxyvitamin D.
[a]At enrollment visit.
[b]Geometric mean blood lead concentration adjusted for age (continuous) and current smoking (yes, no).
[c]Geometric mean blood lead concentration adjusted only for current smoking (yes, no).
[d]Missing data on education ($n = 0$ exposed, $n = 1$ unexposed); annual household income ($n = 0$ exposed, $n = 11$ unexposed), exercise ($n = 1$ exposed, $n = 4$ unexposed); estimated annual mean 25(OH)D concentration ($n = 0$ exposed, $n = 5$ unexposed); hemoglobin ($n = 0$ exposed, $n = 22$ unexposed); told by doctor had high lead levels when infant or child ($n = 3$ exposed, $n = 75$ unexposed).
[e]Geometric mean blood lead concentration adjusted only for age (continuous).
[f]Total calcium intake includes intake from both dietary and supplement sources.
[g]Self-reported history of medical conditions (thyroid condition, anorexia, irritable bowel syndrome) or current medication use (anticonvulsant, thyroid hormone replacement, heparin, or glucocorticoid) associated with bone health.

among postmenopausal women (Randolph et al. 2011). The reduction in estrogen contributes to the well-documented association between DMPA use and lower bone mineral density (Lobo 2014; Nappi et al. 2012). Bone is the primary storage site for lead (Silbergeld et al. 1993), and increased bone resorption during DMPA use allows for the mobilization of lead from bone stores to blood. Increased blood lead levels have been observed during other periods of increased bone resorption, including lactation

Table 2. Percent difference (95% CI) in geometric mean of blood lead concentrations between current depot medroxyprogesterone acetate (DMPA) users and nonusers, Study of Environment, Lifestyle & Fibroids, 2010–2012.

Analyses	Current DMPA use	*n* (%)	Crude blood lead (μg/dL) GM (95% CI)	Model 1[a] % difference (95% CI)	Model 2[b] % difference (95% CI)
Main analysis ($n = 1{,}548$)	No	1,446 (93)	0.68 (0.66, 0.70)	Ref	Ref
	Yes	102 (7)	0.83 (0.75, 0.93)	19 (9, 30)	18 (8, 29)
Restricted to never smokers ($n = 1{,}139$)	No	1,063 (93)	0.60 (0.59, 0.62)	Ref	Ref
	Yes	76 (7)	0.76 (0.67, 0.86)	21 (9, 34)	19 (8, 32)
Additional hemoglobin adjustment ($n = 1{,}526$)[c]	No	1,424 (93)	0.68 (0.67, 0.70)	Ref	Ref
	Yes	102 (7)	0.83 (0.75, 0.93)	18 (8, 29)	17 (7, 28)
Past DMPA users as unexposed group ($n = 546$)[d,e]	Past use	444 (81)	0.75 (0.71, 0.78)	Ref	Ref
	Current use	102 (19)	0.83 (0.75, 0.93)	17 (5, 29)	15 (4, 28)
Excluding current users of estrogen-containing contraception ($n = 1{,}332$)	No	1,233 (93)	0.70 (0.68, 0.72)	Ref	Ref
	Yes	99 (7)	0.84 (0.75, 0.94)	17 (7, 29)	16 (6, 27)
Restricted to women who had not given birth in prior year ($n = 1{,}447$)	No	1,362 (94)	0.68 (0.66, 0.70)	Ref	Ref
	Yes	85 (6)	0.81 (0.71, 0.92)	16 (5, 27)	16 (5, 28)[f]
Restricted to women without a history of medical conditions or current medication use associated with bone loss ($n = 1{,}408$)	No	1,319 (94)	0.68 (0.67, 0.70)	Ref	Ref
	Yes	89 (6)	0.85 (0.76, 0.96)	22 (11, 34)	20 (9, 32)[g]

Note: CI, confidence interval; DMPA, depot medroxyprogesterone acetate; GM, geometric mean; Ref, reference.
[a]Adjusted for age (continuous), education (≤HS/GED, some college/Associate's degree, Bachelor's/Master's/doctoral degree), current smoking (yes, no), and alcohol use in last year (none, moderate, heavy).
[b]Adjusted for age (continuous), education (≤HS/GED, some college/Associate's degree, Bachelor's/Master's/doctoral degree), current smoking (yes, no), alcohol use in last year (none, moderate, heavy), birth in last year (yes, no), $\log_2$-transformed estimated annual mean 25(OH)D concentrations (continuous), total calcium intake (<800, ≥800 mg/d) and self-reported history of medical conditions (thyroid condition, anorexia, irritable bowel syndrome) or current medication use (anticonvulsant, thyroid hormone replacement, heparin, or glucocorticoid) associated with bone health (yes, no).
[c]Hemoglobin data missing for 22 women not currently using DMPA.
[d]Past DMPA users who discontinued ≥3 y prior to enrollment. Median time since discontinuing DMPA use was 8 y (interquartile range: 5–11 y).
[e]Total lifetime months of use for past DMPA users was median 12 months (interquartile range: 6–36 months) and for current DMPA users was median 60 months (interquartile range: 24–108 months).
[f]Variable birth in last year (yes, no) not included in multivariable model.
[g]Variable self-reported history of medical conditions or current medication use associated with bone health (yes, not) not included in multivariable model.

and menopause (Gulson et al. 1998, 2003; Hernandez-Avila et al. 2000; Nash et al. 2004; Silbergeld et al. 1988; Symanski and Hertz-Picciotto 1995).

Our finding is consistent with the prior study that examined this association. A small cross-sectional study was conducted among adolescent clinic patients ages 13–21 y seeking care at a medical center in the Bronx, New York (Iglesias et al. 2008). Iglesias et al. (2008) reported higher mean blood lead concentrations among current DMPA users ($n = 28$) compared with current oral contraceptive pill users ($n = 25$), and nonhormonal contraceptive users ($n = 121$). However, the analyses were not adjusted for factors that may confound the association.

The present study benefited from the rich data available for the adjustment of confounding factors, including age, smoking, education, alcohol use, and recent birth, and the pursuit of detailed sensitivity analyses. We were able to thoroughly investigate potential sources of bias and demonstrate robust results across the sensitivity analyses. It is substantially larger than the prior study, and it is the first study among African-American women in their 20s and 30s for whom DMPA has been available as a contraceptive for most of their reproductive lives. In addition, the misclassification of current DMPA use is likely minimal because the administration of DMPA in the United States requires a health care visit and an intramuscular injection, and this visit would have transpired in the 3 months before the enrollment visit.

Our study had several limitations. Given the cross-sectional study design, it is possible that greater exogenous lead exposure among current DMPA users, compared with nonusers, may explain our results. In this study, data on well-established sources of lead exposure, including residence in older housing with deteriorating lead-based paint and consumption of contaminated drinking water, were not available (ATSDR 2019). Hence, sources of lead exposure that may be associated with DMPA use may not be fully accounted for by our adjustment factors, leading to the possibility of residual confounding. However, in our analyses using past DMPA users as the comparison group—a group that would be expected to be more similar to current DMPA users with regard to measured and unmeasured risk factors for lead exposure—current users had appreciably higher blood lead concentrations than past users. This finding suggests that unmeasured factors related to women choosing to use DMPA did not introduce bias in the present analysis. It is also possible that the observed increase in blood lead concentrations with DMPA use may partly be due to amenorrhea that accompanies DMPA use and the reduced loss of red blood cells where lead resides in blood (Abadin et al. 2007). However, an analysis with additional adjustment for hemoglobin yielded an estimate of association similar to that of the main analyses, minimizing this concern.

In this study we were also limited by the lack of data on duration of current DMPA use. These data would have provided insight into whether the release of lead from bone into blood mirrors the pattern of bone loss observed with DMPA use, with loss being greatest in the first 2 y after DMPA initiation and then continuing at a slower rate with longer use (d'Arcangues 2006). The results from our exploratory analyses suggest a dose–response relationship, although cautious interpretation of these results is warranted. Only 21 SELF participants were current DMPA users with 1 y or less lifetime use of DMPA. There is also the potential for misclassification because current users with more than 1 y of lifetime DMPA use could have recently restarted the method.

Further research is warranted to confirm our findings. Additionally, data are needed on the relationship between duration of DMPA use and blood lead concentrations, given that reproductive-age women may use DMPA for a substantial number of years between menarche and menopause. Information on consecutive months of DMPA use at the time of discontinuation would also allow for the investigation of the decline of blood lead levels with recovery of bone mineral density.

If our findings are replicated, an understanding of the public health impact of increased blood lead concentrations with DMPA use will be imperative from both the environmental and reproductive justice

perspectives. In the United States, the social and economic inequities that contribute to the disproportionate exposure to lead are also associated with DMPA use. There is widespread scientific consensus that no safe levels of blood lead exist and even low blood lead levels in adults have been linked to a range of adverse outcomes (Abadin et al. 2007). Yet, DMPA is an important contraceptive option for the prevention of pregnancy, management of menstrual pain, and treatment of pelvic pain associated with endometriosis (ACOG 2014, 2018; Barra et al. 2018; Buggio et al. 2017).

In addition, research is warranted to understand how our findings translate to communities and countries where the general population is exposed to higher environmental lead contamination. In the SELF, most participants had blood lead concentrations below the actionable level of 5 μg/dL set by the CDC. In contrast, mean blood lead concentrations markedly exceeding 5 μg/dL have been reported in studies of reproductive-age women in Kenya, Nigeria, and Ethiopia (Bede-Ojimadu et al. 2018). In these same countries, DMPA is the most commonly used hormonal contraceptive method (Tsui et al. 2017), playing a critical role in the prevention of unintended pregnancy. It is also important to understand the impact of postpartum DMPA use in breastfeeding women on infant lead exposure. DMPA can generally be administered early in the postpartum period in breastfeeding women, immediately after delivery in the United States (Curtis et al. 2016) or 6 wk postpartum in other countries (WHO 2015). Lead in breastmilk is transferred to infants, contributing to infant exposure to lead (Ettinger et al. 2014).

In conclusion, our data indicate an association between current DMPA use and increased blood lead concentrations. Further research, particularly in populations highly exposed to lead, is warranted to confirm our findings and to consider the tradeoffs between the adverse effects of lead on human health and the importance of DMPA as a contraceptive option to prevent unintended pregnancy.

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