Contraception: *Original Research*

Depot Medroxyprogesterone Acetate, Oral Contraceptive, Intrauterine Device Use, and Fracture Risk

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OBJECTIVE: To assess fracture risk among women with depot medroxyprogesterone acetate (DMPA), oral contraceptive pill (OCP), and intrauterine device (IUD) use.

METHODS: A retrospective cohort study of 308,876 women age 12–45 years who initiated DMPA, combined or progestin-only OCPs, and copper and levonorgestrel IUDs from 2005 to 2015. Cumulative DMPA, OCP, and IUD use was assessed. Time since last DMPA injection was quantified as recent (within 2 years) and past (more than 2 years ago). Crude fracture rate was estimated using a Poisson distribution. Unadjusted and adjusted hazard ratios (HRs) were estimated using cox proportional hazards models.

RESULTS: Thirteen percent of women used DMPA, 78.6% combined OCPs, 17.4% progestin-only OCPs, and 26.2% IUDs; 29.5% used more than one method. There were 7,659 fractures in 1,391,251 person-years (5.5/1,000 person-years [95% CI 5.4–5.6]). The fracture rate for women with any DMPA use was 6.6 (95% CI 6.1–7.2) and 7.8 (95% CI 6.0–10.0) for women with recent use and more than 2 years of cumulative use. Women who had recent use with 2 years or less, or more than 2 years of cumulative use had higher fracture risk compared with women who had no DMPA use and used other methods (adjusted HR 1.15 [95% CI 1.01–1.31] and 1.42 [95% CI 1.10–1.83], respectively). Fracture risk was not increased in women with past DMPA use. Women who had more than 2 years cumulative use of combined OCPs and women with any progestin-only OCP use had lower fracture risk compared with women who did not use OCPs and used other methods (adjusted HR 0.85 [95% CI 0.76–0.96] and 0.88 [95% CI 0.80–0.97], respectively).

CONCLUSION: Use of DMPA beyond 2 years should not be considered an absolute contraindication. Although DMPA use was associated with slightly increased fracture risk compared with other methods, the absolute risk of fracture was small and was not observed after discontinuation.

(Obstet Gynecol 2019;134:581–9)
DOI: 10.1097/AOG.0000000000003414

Depot medroxyprogesterone acetate (DMPA) is an effective injectable contraceptive that has been used by approximately 20% of sexually active U.S. women.[1,2] Because of its 3-month duration of action and lack of requirement of an office procedure for initiation or supplies to keep at home, it offers advantages over oral contraceptive pills (OCPs) and intrauterine devices (IUDs), particularly for adolescents. However, DMPA inhibits the secretion of pituitary gonadotropins, resulting in anovulation and decreased production of estrogen and has been associated with decreased bone mineral density (BMD) over time.[3,4] In contrast, OCPs and IUDs appear to have little effect on BMD.[5,6]

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Supported by the Kaiser Permanente Northern California Community Benefits Internal Grant.

The authors thank Fiona Sinclair for her contributions to data acquisition and study conduct.

Each author has confirmed compliance with the journal's requirements for authorship.

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Financial Disclosure
Tina Raine-Bennett has served as a consultant for Teva Pharmaceutical Industry for work unrelated to the current study. Tina Raine-Bennett, Malini Chandra, Mary Anne Armstrong, and Stacey Alexeeff have received grant funding for work unrelated to the current study from Bayer A.G. Joan Lo has received grant funding for work unrelated to the current study from Sanofi and Amgen. Money was paid to their institution from Teva Pharmaceutical Industry, Bayer A.G., Sanofi, and Amgen.

ISSN: 0029-7844/19

In 2004, the U.S. Food and Drug Administration (FDA) issued a "black box" warning on DMPA owing to concerns over the effect of DMPA use on BMD and cautions that use of DMPA beyond 2 years should be considered only if other contraceptive methods are inadequate. Providers may limit DMPA use to 2 years or not initiate DMPA owing to concerns about adverse effects on bone health. Currently, the evidence addressing the important clinical question of whether DMPA use is associated with fracture risk provides mixed results and does not provide conclusive evidence of elevated fracture risk. Existing U.S. studies have been conducted in select populations and may not be generalizable.[7,8] European studies suggest that DMPA users have increased fracture risk; however, study design shortcomings limit interpretation.[9–11] In a review of studies that have examined fracture risk associated with OCP use, results were mixed and an overall difference in fracture risk was not found.[12]

The goal of this study was to assess incident fracture risk among adolescents and premenopausal women who used DMPA, OCPs, or IUDs at Kaiser Permanente Northern California, a large, integrated health care delivery system that serves more than 1 million women of reproductive age annually. We focused on risk associated with DMPA use and hypothesized that fracture risk is increased with DMPA use when compared with OCP and IUD use, whereas there is no increased risk for OCP use and IUD use compared with other methods.

METHODS

This was a retrospective cohort study of women from Kaiser Permanente Northern California who were age 12–45 years and initiated DMPA, combined or progestin-only OCPs, or a copper or levonorgestrel IUD, between January 1, 2005, and December 31, 2015. Data for the study were abstracted by the second author (M.C.) from Kaiser Permanente's comprehensive electronic health record. Kaiser Permanente Northern California's Division of Research maintains a research database that serves as a repository for the clinical and administrative databases from the Epic-based electronic medical record system called HealthConnect®, as well as legacy data sources that predate the implementation of the Epic system, which occurred in 2008. The records included health plan enrollment data, demographic information, ambulatory prescriptions from pharmacy records, hospitalization and outpatient visit data with diagnoses from health plan records or claims, and internal, state, and social security mortality data. This study was approved by the Institutional Review Board of the Kaiser Foundation Research Institute with waiver of consent.

The date of the first DMPA injection, OCP prescription dispensed, or IUD insertion during the study period was considered the index date. Women were required to have continuous health plan membership for 12 months (no more than a 1-month gap) before the index date to assess prior contraceptive use as well as risk factors for fractures. Women were considered to have initiated one of these methods if they had no evidence of use of the method in the 12 months before the index date. To minimize potential bias associated with use of other hormonal methods, we excluded the relatively small number of women who used implants, transdermal patches, or vaginal rings in the 12 months before the index date or during the study period. We also excluded women with evidence of history of oophorectomy, osteoporosis or osteomalacia diagnosis, or who had osteoporosis medications dispensed (bisphosphonates, teriparatide, calcitonin, raloxifene) documented in the 12 months before the index date.

Start and end dates of contraceptive use were determined using a combination of diagnostic and procedure codes (International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification), Current Procedural Terminology codes, and medication codes (National Drug Codes and Kaiser specific codes) identified in the pharmacy databases. Over time, an individual woman may have used more than one contraceptive method and had many episodes of use, so we created time-updated variables to capture these changes. Each DMPA injection was assigned 90 days of exposure. For OCPs, each dispensed pack was assigned 28 days of exposure. Because pharmacy databases provide information only about the date OCPs were dispensed, we made assumptions about initiation of dispensed drugs to approximate the patients' actual use.[13] We allowed a 14-day gap between prescriptions to adjust for initiation after the dispense date. If a second prescription for the same type of OCP (combined compared with progestin-only) was filled before the exposure end date, the end date of the second prescription was adjusted to account for early pick-up. Intrauterine device exposure was determined by the interval between insertion and removal dates. To account for potential undocumented IUD removals, if a DMPA injection was given or more than three packs of OCPs were dispensed during IUD use, an IUD end date was imputed.

Depot medroxyprogesterone acetate exposure was quantified into categories using a 2-year

cumulative use cutoff to correspond with the FDA boxed warning, which cautions against use of DMPA for more than 2 years. We also assessed the potential of waning of effect due to BMD recovery after discontinuation and examined time since last injection. Depot medroxyprogesterone acetate exposure was categorized as: 1) no use; 2) recent use (last injection 2 or fewer years ago), 2 or fewer years of cumulative exposure; 3) recent use, more than 2 years of cumulative exposure; 4) past use (last injection more than 2 years ago), 2 or fewer years cumulative exposure; 5) past use, more than 2 years of cumulative exposure; and 6) any use. To quantify IUD, combined and progestin-only OCP exposure, we also used a 2-year cutoff and defined categories of cumulative exposure: 1) no use, 2) 2 or fewer years, 3) more than 2 years, and 4) any use.

The outcome of interest was incident fracture defined as the first nontraumatic (fragility) fracture occurring after the index date through the end of follow-up December 31, 2017. We selected fracture sites and encounters in specific departments to increase the likelihood of identifying incident and fragility fractures. Fractures were identified using International Classification of Diseases, Ninth Revision (ICD-9) codes (805.x, 807.0x, 808.x-814.x, 820.x-824.x, 825.0x, and 825.2x). We identified fractures in patients with an inpatient admission, emergency and urgent care department, or outpatient surgery clinic (eg, general, orthopedics, podiatry, and spine) visit. Humerus and wrist fractures were included only in patients with an inpatient admission, emergency department, or outpatient orthopedic or urgent care visit, and hip fractures only in patients with an inpatient admission. Open fractures and those associated with major transport trauma such as motor vehicle accidents (ICD-9 E800-848) were excluded. Fractures in multiple or undefined sites or fractures of the head, fingers, and toes were also excluded. For women with a fracture in the 12 months before the index date, the fracture was required to be in a different site than the prior fracture to be considered an incident fracture. Owing to the large number of fractures, we did not perform clinical adjudication for each fracture to confirm nontraumatic fractures. Chart review was conducted on a random sample of 2.5% of fractures (n=200) in our dataset to validate the approach for identifying incident nontraumatic fractures; electronically abstracted data were consistent with chart review data in 95% of cases (95% CI 92.1–97.9).

Potential confounders assessed included age, race–ethnicity, and clinical risk factors identified in the 12 months before the index date that might affect bone health based on risk factors identified in the literature, including history of epilepsy (based on diagnostic codes and at least one antiepileptic drug dispensed), alcohol use disorder (based on diagnostic codes assigned on two different days), oral corticosteroid medications dispensed (greater than or equal to 1,825 mg prednisone equivalent), and prior fracture.[3,14–16] History of smoking (current or former, never, or missing) and body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) (normal or underweight [25 or less], overweight or obese [greater than 25], and missing) at the closest visit within 12 months before or after the index date. Chart review was conducted on a random sample of 0.1% of the study population (n=300) to validate electronically abstracted data revealing accuracy of 95% (95% CI 92.5–97.5).

Variables were summarized with frequencies and percentages for categorical variables or with means and SDs for continuous variables. Missing data is noted in the tables and included in the analyses. Comparisons between the excluded women and the study population were examined using chi-square tests. Contraceptive exposure periods were calculated from the index date to the date of first fracture, end of health plan membership, death, or December 31, 2017. Women were censored after the first fracture. We estimated crude fracture rate with 95% CIs per 1,000 person-years for demographic and clinical risk factors and contraceptive exposures using a Poisson distribution.

To explore the relationship between contraceptive method exposure and fracture risk, we estimated risks using Cox proportional hazards models while controlling for potential confounders. Unadjusted and adjusted hazard ratios (HRs) with 95% CI were estimated. Contraceptive exposure variables were treated as time-dependent variables updated every 30 days to account for changes in contraceptive methods used and nonuse over the duration of the study for each woman. Because some women changed contraceptives over time, the reference category (no use) for a particular method includes the women who did not use the method but used one or more of the other methods during the study period. We controlled for age group, race–ethnicity, BMI, smoking status, and clinical risk factors in the year before the index date including glucocorticoid use, epilepsy, alcohol use disorder, and history of fracture. Sensitivity analyses to compare fully adjusted results with simpler models without the covariates epilepsy, corticosteroid use, or prior fracture individually and in combination

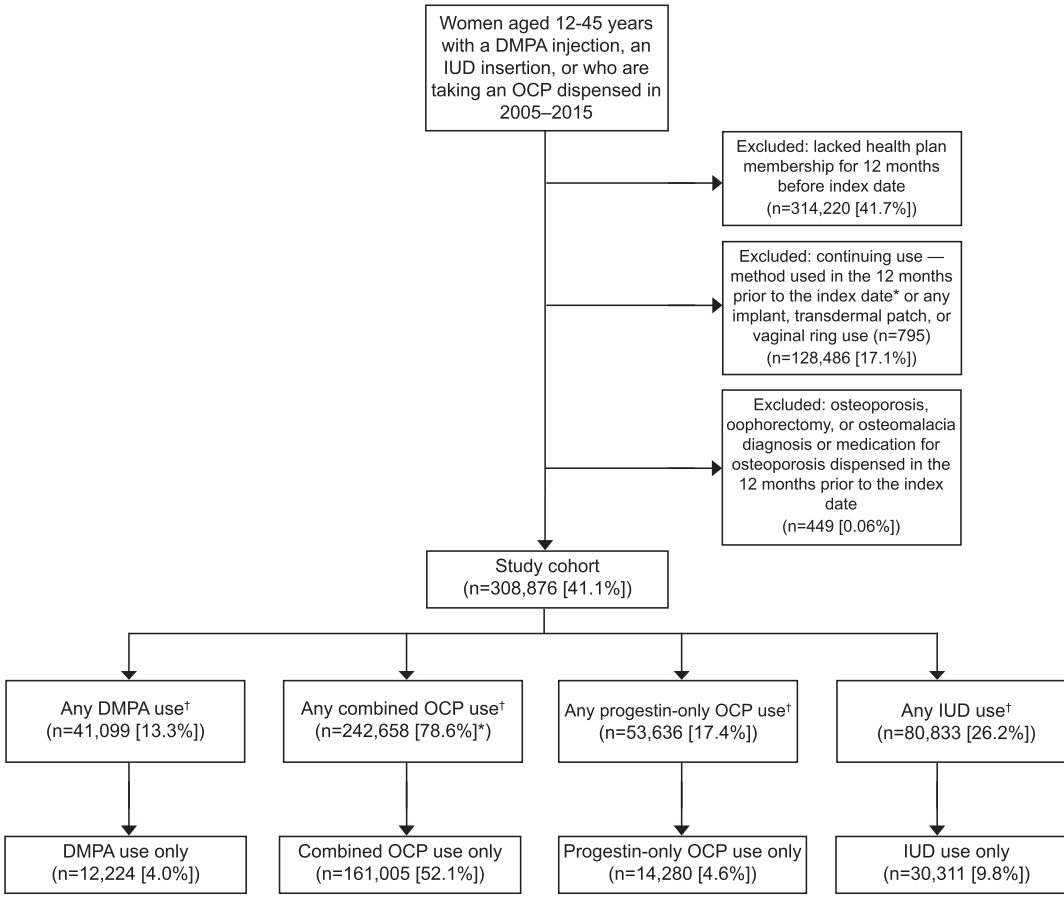

Fig. 1. Study population. *Women were considered to have initiated a method if they had no evidence of use of the method in the 12 months before the index date. †Women may have used one or more methods; categories overlap and add to more than 100%. DMPA, depomedroxyprogesterone acetate; OCP, oral contraceptive pills; IUD, intrauterine device.

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were conducted. Data were analyzed using SAS 9.3 and 9.4; $P<.05$ was considered statistically significant.

RESULTS

There were 752,031 women with a DMPA injection, OCPs dispensed, or copper or levonorgestrel IUD insertion during the study period. After exclusions for insufficient length of health plan membership before the index date and prior method use, the final study population included 308,876 women (Fig. 1). We found that the study population was slightly younger than women who were excluded mean 26.3 years compared with 27.7, ($P<.001$). White women (59.4%) were slightly more likely to be excluded than African American (53.8%) and Hispanic women (57.8%) ($P<.001$). A larger portion of women with DMPA (62%) and combined OCP use (61%) were excluded than women with IUD use (49%) and progestin-only OCP use (49%) ($P<.001$).

Most women (78.6%) used combined OCPs at some time over the study period, and half of the cohort (52.1%) had used a combined OCP only (Fig. 1). A much smaller proportion (13.3%) used DMPA at some time and 4% had used DMPA only. The demographic and clinical characteristics of the study population by contraceptive methods used are shown in Table 1. A third of women (29.5%) used more than one method over the study period. Mean follow-up time for the study population was 4.5 ± 3.5 years, with women who used more than one method and progestin-only OCPs having the longest mean follow-up (5.2 ± 3.7 and 5.2 ± 4.0 years, respectively). Use patterns were consistent with current prescribing patterns. Women who used progestin-only OCPs (mean age 28.9 ± 7.6 years) or IUDs (28.1 ± 8.7 years) were older than women who used combined OCPs (25.1 ± 8.9 years) or DMPA (23.0 ± 8.5 years). The method with the greatest proportion of adolescent users was DMPA with 37.1% of women who used

Table 1. Demographic and Clinical Characteristics of the Study Cohort by Contraceptive Methods Used Over the Study Period*

	All (N=308,876)	More than 1 Method (n=91,056 [29.5])	Any DMPA* (n=41,099 [13.3])	Any Combined OCP* (n=242,658 [78.6])	Any Progestin-Only OCP* (n=53,636 [17.4])	Any IUD* (n=80,833 [26.2])
Person-years of follow-up	1,391,251	471,766	97,733	905,333	159,794	337,464
Follow-up time (y)	4.5±3.5	5.2±3.7	4.3±3.3	4.5±3.5	5.2±4.0	4.8±3.6
Age at cohort entry (y)	26.3±9.0	25.2±8.3	23.0±8.5	25.1±8.9	28.9±7.6	28.1±8.7
12–17	65,381 (21.2)	21,672 (23.8)	15,252 (37.1)	60,275 (24.8)	4,242 (7.9)	12,055 (14.9)
18–29	130,393 (42.2)	40,539 (44.5)	16,160 (39.3)	107,383 (44.3)	23,702 (44.2)	32,558 (20.3)
30–39	79,527 (25.8)	23,253 (25.5)	7,142 (17.4)	52,506 (21.6)	20,729 (38.7)	26,467 (32.7)
40–45	33,575 (10.9)	5,592 (6.1)	2,545 (6.2)	22,494 (9.3)	4,963 (9.3)	9,753 (12.1)
Race–ethnicity						
White	130,196 (42.2)	38,336 (42.1)	14,197 (34.5)	107,420 (44.3)	22,018 (41.1)	34,975 (43.3)
African American	26,106 (8.5)	9,562 (10.5)	6,844 (16.7)	19,692 (8.1)	4,449 (8.3)	7,134 (8.8)
Asian or Pacific Islander	54,090 (17.5)	14,018 (15.4)	4,898 (11.9)	41,145 (17.0)	10,931 (20.4)	13,632 (16.9)
Hispanic	67,488 (21.8)	22,523 (24.7)	11,850 (28.8)	50,632 (20.9)	13,228 (24.7)	19,800 (24.5)
Other or unknown	31,036 (10.1)	6,617 (7.3)	3,310 (8.1)	23,769 (9.8)	3,010 (5.6)	5,292 (6.6)
Smoking status†						
Current or former	44,547 (14.4)	14,146 (15.5)	7,236 (17.6)	31,389 (12.9)	9,114 (17.0)	14,177 (17.5)
Never	208,888 (67.6)	58,444 (64.2)	26,116 (63.5)	164,548 (67.8)	33,596 (62.6)	53,913 (66.7)
Missing	55,441 (18.0)	18,466 (20.3)	7,747 (19.0)	46,721 (19.3)	10,926 (20.4)	12,743 (15.8)
Alcohol use disorder diagnosis‡	1,231 (0.4)	431 (0.5)	274 (0.7)	899 (0.4)	205 (0.4)	380 (0.5)
BMI (kg/m^2)†						
Normal or underweight (25 or less)	152,998 (49.5)	42,868 (47.1)	20,094 (48.9)	128,163 (52.8)	20,623 (38.5)	35,121 (43.5)
Overweight or obese (greater than 25)	140,185 (45.4)	43,367 (47.6)	18,292 (44.5)	101,202 (41.7)	30,485 (56.8)	42,615 (52.7)
Missing	15,693 (5.1)	4,821 (5.3)	2,713 (6.6)	13,286 (5.5)	2,528 (4.7)	3,097 (3.8)
Epilepsy‡	818 (0.3)	220 (0.24)	215 (0.5)	531 (0.2)	99 (0.2)	245 (0.3)
Corticosteroid use†§	49 (0.02)	7 (0.01)	3 (0.01)	40 (0.02)	8 (0.01)	5 (0.01)
Prior fracture‡	2,279 (0.7)	717 (0.8)	396 (1.0)	1,881 (0.8)	300 (0.6)	583 (0.7)

DMPA, depomedroxyprogesterone acetate; OCP, oral contraceptive pills; IUD, intrauterine device; BMI, body mass index.
Data are n, mean±SD, or n (%).
* Women may have used one or more methods; categories overlap and add to more than 100%.
† Closest visit within 12 months before or after the index date.
‡ In the 12 months before the index date.
§ Oral prednisone equivalent 1,825 mg or more.

Table 2. Incident Fractures Over the Study Period by Fracture Site (n=7,659)*

Fracture Site	n (%)
Spine	271 (3.5)
Chest	203 (2.7)
Pelvis	81 (1.1)
Clavicle	209 (2.7)
Scapula	22 (0.3)
Humerus	357 (2.7)
Radius or ulna	1,412 (18.4)
Carpal or metacarpal	1,205 (15.7)
Hip	24 (0.3)
Femur	25 (0.3)
Patella	104 (1.4)
Tibia or fibula	595 (7.8)
Ankle	1,123 (14.7)
Tarsal or metatarsal	2,028 (26.5)

* Incident fracture was defined as the first nontraumatic fracture occurring after the index date through December 31, 2017. Fractures were not counted as incident if there was a prior fracture in the same site in the 12 months before the index date.

DMPA being adolescents. Greater proportions of women who used DMPA were African American (16.7%) than those who used combined or progestin-only OCPs or IUDs (8.1%, 8.3%, and 8.8%, respectively). A smaller proportion of women who used combined OCPs (12.9%) were current or former smokers than women who used DMPA, progestin-only OCPs or IUDs (17.6%, 17.0%, and 17.5%, respectively). Greater proportions of women who used IUDs (52.7%) and progestin-only OCPs (56.8%) were overweight or obese than women who used combined OCPs (41.7%).

There were 7,659 fractures over the study period; the largest proportion of fractures in this premenopausal cohort were tarsal and metatarsal (26.5%), and radius and ulnar fractures (18.4%); less than 1% of fractures were hip or femur fractures (Table 2). The total incidence of fractures was 5.5 per 1,000 person-years (n=1,391,251; 95% CI 5.4–5.6) (Table 3). The median age of women with fractures was 30 years (SD 11.3, range 12–58). The incidence of fractures was greatest in women with known risk factors including corticosteroid use (18.2/1,000 person-years [95% CI 5.0–46.6]) and prior fracture (15.6/1,000 person-years [95% CI 13.2–18.3]) (Table 3). Fracture rates were also higher among adolescents and women 50 years and older (9.0 and 8.1/1,000 person-years, respectively). Most women who used DMPA used it for 2 years or less. Women who had recent use of DMPA and cumulative exposure of more than 2 years had the highest incidence of fractures among contraceptive use exposure categories with 7.8 fractures per 1,000 person-years (95% CI 6.0–10.0) (Table 4).

After controlling for age, race, and clinical risk factors, corticosteroid use (adjusted HR 2.72 [95% CI 1.02–7.24]) and prior fracture (adjusted HR 2.45 [95% CI 2.09–2.88]) had the strongest association with fracture. Smoking, alcohol use disorder, epilepsy, adolescence, and older age were all independent risk factors for fracture. All racial and ethnic minorities were at lower risk of fracture compared with white women. Association with contraceptive method exposure was weaker. Women with recent use and 2 years or less, or more than 2 years of cumulative DMPA exposure were at higher fracture risk compared with women with no DMPA use (adjusted HR 1.15 [95% CI 1.01–1.31] and 1.42 [95% CI 1.10–1.83], respectively). However, fracture risk was not increased in women with past DMPA use. Women with more than 2 years of combined OCP exposure and women with any progestin-only OCP exposure were slightly less likely to have a fracture compared with women with no OCP use (adjusted HR 0.85 [95% CI 0.76–0.96] and 0.88 [95% CI 0.80–0.97], respectively) (Table 4). Intrauterine device exposure was not associated with fracture risk. The main estimates of fracture risk for the hormonal contraceptive groups did not materially change in the sensitivity analyses with multivariate models without the covariates of epilepsy, corticosteroid use, and prior fracture.

DISCUSSION

The results of this U.S. population study, which is based on more than 300,000 women who used DMPA, copper or levonorgestrel IUDs, or combined or progestin-only OCPs including 25,847 women and 15,252 adolescents who used DMPA, provide evidence in support of the safety of DMPA. After controlling for potential confounders and other method use, women with DMPA use within the previous 2 years had a modestly increased fracture risk compared with women with no DMPA use (but had used OCPs, IUDs, or both). However, given the HRs of less than 2.0 in an observational study, it is most likely that the finding of increased fracture risk with DMPA use is due to unmeasured bias.[17] Women who use DMPA may be at increased risk for behaviors that increase fracture risk compared with women who use other methods. The strength of the association between DMPA use and fracture was notably weaker than the association with other well-established risk factors that were observed in our study and the past literature including corticosteroid

Table 3. Incident Fracture Rates and Unadjusted and Adjusted Fracture Risk by Demographic and Clinical Characteristics Estimated With Cox Proportional Hazards Model*

Characteristic	No. of Fractures	Person-Years	Fracture Rate/1,000 Person-Years (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Total	7,659	1,391,251	5.5 (5.4–5.6)	n/a	n/a
Age category at outcome (y)					
18–29	2,899	557,573	5.2 (5.0–5.4)	Ref.	Ref.
12–17	913	101,520	9.0 (8.4–9.6)	1.70 (1.58–1.84)	1.61 (1.49–1.75)
30–39	1,705	379,745	4.5 (4.3–4.7)	0.87 (0.82–0.92)	0.91 (0.85–0.96)
40–49	1,820	312,900	5.8 (5.6–6.1)	1.13 (1.06–1.20)	1.11 (1.05–1.19)
50 and older	322	39,513	8.1 (7.3–9.1)	1.60 (1.41–1.82)	1.48 (1.30–1.69)
Race–ethnicity					
Non-Hispanic white	4,462	619,178	7.2 (7.0–7.4)	Ref.	Ref.
African American	530	114,203	4.6 (4.3–5.1)	0.64 (0.59–0.70)	0.63 (0.57–0.69)
Asian or Pacific Islander	680	261,327	2.6 (2.4–2.8)	0.36 (0.33–0.39)	0.39 (0.36–0.42)
Hispanic	1,480	295,712	5.0 (4.8–5.3)	0.69 (0.65–0.74)	0.71 (0.66–0.75)
Other or unknown	507	100,831	5.0 (4.6–5.5)	0.69 (0.63–0.76)	0.71 (0.65–0.78)
Smoking status†					
Never	4,817	910,837	5.3 (5.1–5.4)	Ref.	Ref.
Current or former	1,371	184,814	7.4 (7.0–7.8)	1.40 (1.32–1.49)	1.32 (1.24–1.40)
Missing	1,471	295,600	5.0 (4.7–5.2)	0.94 (0.88–0.99)	0.94 (0.88–1.00)
Alcohol use disorder diagnosis‡	60	4,859	12.3 (9.4–15.9)	2.26 (1.75–2.91)	1.67 (1.29–2.16)
BMI category (kg/m^2)†					
Normal or underweight (25 or less)	3,631	676,601	5.4 (5.2–5.5)	Ref.	Ref.
Overweight or obese (greater than 25)	3,662	643,079	5.7 (5.5–5.9)	1.06 (1.02–1.11)	1.07 (1.02–113)
Missing	366	72,572	5.0 (4.5–5.6)	0.94 (0.84–1.05)	0.95 (0.85–1.07)
Epilepsy‡	35	3,468	10.1 (7.0–14.0)	1.84 (1.32–2.56)	1.61 (1.15–2.24)
Corticosteroid use†§	4	220	18.2 (5.0–46.6)	3.31 (1.24–8.81)	2.72 (1.02–7.24)
Prior fracture‡	151	9,698	15.6 (13.2–18.3)	2.86 (2.44–3.37)	2.45 (2.09–2.88)

HR, hazard ratio; n/a, not applicable; Ref., reference; BMI, body mass index.
* Model includes covariates in Table 3 (age, race–ethnicity, smoking status, alcohol use disorder, BMI, epilepsy, corticosteroid use, and prior fracture) and Table 4 (contraceptive exposure).
† Closest visit within 12 months before or after the index date.
‡ In the 12 months before the index date.
§ Oral prednisone equivalent 1,825 mg or more.

use, prior fracture, alcohol use disorder, and epilepsy.[14,15]

If the observed association between recent DMPA use and fracture risk reflects a true causal relationship, it is reassuring to note that the difference in fracture rate for women with recent use of DMPA or more than 2 years compared with women with no use was low, at approximately two fractures per 1,000 person-years. In addition, the observed association between DMPA use and fractures was not observed if the last injection was more than 2 years ago. The finding of increase fracture risk with recent use but not past use is biologically plausible given the known recovery of BMD loss seen with DMPA use. Several investigators have demonstrated recovery of BMD after discontinuation of DMPA with complete recovery as early as 1 year after discontinuation.[18–20] The estimate of risk for women with past DMPA use for more than 2 years is not statistically significant and the CI does not exceed 2.0, suggesting a clinically significant effect of past use is also not likely. There were a small number of fractures and a shorter observation time for women with more than 2 years of DMPA use in the past. Longer follow-up time of our cohort may be helpful to confirm our results.

Our findings suggest OCP use may be protective; after controlling for potential confounders and other method use, we observed a slightly decreased fracture risk in women with more than 2 years of combined OCP use and women with any progestin-only OCP use compared with women who did not use OCPs (but used DMPA, IUDs, or both). Although a protective effect of combined OCPs is biologically plausible given the known inhibitory effect of estrogen on bone resorption, a biological explanation for reduced risk in women with progestin-only OCP use

Table 4. Incident Fracture Rates and Unadjusted and Adjusted Fracture Risk by Cumulative Contraceptive Use Estimated With Cox Proportional Hazards Model*

Characteristic	Fractures	Person-Years	Fracture Rate/1,000 Person-Years (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Total	7,659	1,391,252	5.5 (5.4–5.6)	n/a	n/a
DMPA cumulative exposure					
No use	7,010	1,293,518	5.4 (5.3–5.5)	Ref.	Ref.
Recent use†					
2 y or less	415	61,657	6.7 (6.1–7.4)	1.22 (1.11–1.35)	1.15 (1.01–1.31)
More than 2 y	65	8,317	7.8 (6.0–10.0)	1.49 (1.17–1.91)	1.42 (1.10–1.83)
Past use‡					
2 y or less	163	26,567	6.1 (5.2–7.2)	1.16 (0.99–1.35)	1.09 (0.91–1.30)
More than 2 y	6	1,192	5.0 (1.8–11.0)	0.91 (0.41–2.03)	0.88 (0.39–1.96)
Any use	649	97,733	6.6 (6.1–7.2)	1.22 (1.13–1.32)	1.18 (1.06–1.32)
Combined OCP cumulative exposure					
None	2,716	485,918	5.6 (5.4–5.8)	Ref.	Ref.
2 y or less	3,891	687,962	5.7 (5.5–5.8)	1.1 (0.96–1.06)	1.00 (0.91–1.09)
More than 2 y	1,052	217,371	4.8 (4.6–5.1)	0.89 (0.82–0.96)	0.85 (0.76–0.96)
Any use	4,943	905,333	5.5 (5.3–5.6)	0.98 (0.93–1.03)	0.99 (0.90–1.09)
Progestin-only OCP cumulative exposure					
None	6,920	1,231,457	5.6 (5.5–5.7)	Ref.	Ref.
2 y or less	611	133,458	4.6 (4.2–5.0)	0.81 (0.75–0.88)	0.86 (0.77–0.95)
More than 2 y	128	26,336	4.9 (4.1–5.8)	0.89 (0.74–1.06)	0.87 (0.72–1.05)
Any use	739	159,794	4.6 (4.3–5.0)	0.82 (0.76–0.89)	0.88 (0.80–0.97)
IUD cumulative exposure					
None	5,745	1,053,787	5.5 (5.3–5.6)	Ref.	Ref.
2 y or less	1,106	188,075	5.9 (5.5–6.2)	1.06 (0.99–1.13)	1.05 (0.95–1.10)
More than 2 y	808	149,390	5.4 (5.0–5.8)	1.02 (0.94–1.10)	0.96 (0.86–1.07)
Any use	1,914	337,464	5.7 (5.4–5.9)	1.04 (0.99–1.10)	1.04 (0.95–1.14)

HR, hazard ratio; n/a, not applicable; Ref., reference; DMPA, depomedroxyprogesterone acetate; OCP, oral contraceptive pills; IUD, intrauterine device.

* Model includes covariates in Table 3 (age, race–ethnicity, smoking status, alcohol use disorder, body mass index, epilepsy, corticosteroid use, and prior fracture) and contraceptive exposure in Table 4.

† Recent use—last injection 2 or fewer years ago.

‡ Past use—last injection more than 2 years ago.

is less plausible. Bias due to predominate use of progestin-only OCP use in lactating postpartum women, who may be a lower risk population, is possible. The observed associations between OCP use and fracture were weak and previous studies have not shown a consistent relationship between OCP use and fracture risk.[12,21] Future analyses of our data examining timing of use and estrogen dose may be useful.

This study of a community-based U.S. population provides realistic estimates of fracture risk associated with DMPA use. Prior U.S. studies have also demonstrated weak associations between DMPA use and fracture risk; however, these studies were in select populations of military recruits and girls with developmental disabilities.[7,8] Vestergaard et al[11] reported increased fracture risk in Danish women for DMPA ever-use (odds ratio [OR] 1.44, 95% CI 1.01–2.06) and more than 4 years of use (OR 2.16, 95% CI 1.32–3.53); however, the number of DMPA users was small (n=163). Meier et al[9] also reported effect sizes similar to those in our study for associations with fracture using data from the UK-based General Practice Research Database for any past use, including one or two injections (OR 1.17, 95% CI 1.07–1.29) and for current use of three to nine prescriptions (OR 1.36, 95% CI 1.15–1.60) or 10 or more (OR 1.54, 95% CI 1.33–1.78).

There are several strengths and limitations to our study. We used one of the largest U.S pharmacy databases with linked clinical information on fractures and important potential confounders. Although we controlled for many factors associated with increased fracture risk, we could not possibly control for all factors. For example, we did not control for rheumatoid arthritis or hyperthyroidism, conditions which occur less commonly in reproductive age women.

We did use a time-varying approach, accounting for real life contraceptive use in which women use multiple methods and have periods of nonuse over time. To identify contraceptive method start dates and assess for confounders, women with health plan membership of less than 12 months were excluded, which limits generalizability as they may have higher fracture risk. Although the greatest public health burden of fragility fractures is among older women with fragility fractures of the hip and pelvis, and to a lesser degree, the spine, humerus, and wrist due to low BMD and other aging-related factors, fragility fractures also occur in other bones, among younger, and more active populations. Hence, we assessed the risk of all clinical fractures, given our relatively short follow-up time and the age demographic of our cohort, most of whom were premenopausal during the study period.

We did not perform clinical adjudication for fractures; we may have included nonfragility fractures despite selection of fractures from specific sites and clinical departments and exclusion of major trauma among hospitalized women. Also, we may not have captured incident fractures that were diagnosed outside of an emergency, urgent care or surgical ambulatory clinic visit. Information on BMI and smoking was not uniformly collected in the electronic health records before 2006, which led to missing data. Finally, we did not differentiate between copper and levonorgestrel IUDs because there is less biological plausibility and previous studies have not shown an association.[12] Despite these limitations, we hope our results inform providers who counsel women who use DMPA or are considering initiating a contraceptive. Patients and providers should consider DMPA a safe method. Use of DMPA beyond 2 years as cautioned in the FDA "black box" warning should not be considered an absolute contraindication. The risk of DMPA use on bone health demonstrated in this study is small and should be weighed against adverse risk of mistimed and unwanted pregnancy for adolescents and women.

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PEER REVIEW HISTORY

Received April 5, 2019. Received in revised form June 3, 2019. Accepted June 13, 2019. Peer reviews and author correspondence are available at http://links.lww.com/AOG/B480.