ORAL CONTRACEPTIVE USE AND BLOOD LEAD CONCENTRATIONS IN U.S. PREMENOPAUSAL INDIVIDUALS

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ABSTRACT

In the United States, the general population is ubiquitously exposed to toxic metal lead. Lead can adversely affect all organ systems. After exposure, lead is stored within bone, but can still transfer between bone and blood. Estrogen can induce a bone-sparing effect by suppressing osteoclast activity. Most oral contraceptives (OCs) contain estrogen and are the most commonly used form of contraception in the United States. Since lead is stored in bone, we hypothesized that current use of estrogen-containing oral contraceptives decreases skeletal mobilization of the toxic metal lead from bone to blood. To test this hypothesis, the aim of this study was to investigate the association between current OC use and blood lead concentrations in a U.S. nationally-representative sample of premenopausal individuals. We conducted a cross-sectional study using five data cycles (2003-2012) from the National Health and Nutrition Examination Survey (NHANES). The study population included premenopausal, non-pregnant individuals ages 20-44 with an intact uterus and at least one ovary who were not currently using injectable contraceptives, with information on current OC use and blood lead concentrations (unweighted n=3,973). We used multivariable linear regression to estimate the percent difference in geometric mean blood lead concentrations and 95% confidence intervals between current OC users and non-users based on self-report, accounting for the complex survey sampling design. We observed that current OC users had lower geometric mean blood lead concentrations (0.68 µg/dl, 95% CI: 0.66, 0.71) than non-users (0.81 µg/dl, 95% CI: 0.79, 0.83). After multivariable adjustment, current OC users had 9% lower (95% CI: -14%, -4%) blood lead concentrations than non-users. We also used prescription medication data to characterize combined oral contraceptive use in the past 30 days and observed a stronger association (-12% lower blood lead concentrations, 95% CI: -18%, -7%). As no safe level of blood lead exists, further research is warranted.

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INTRODUCTION

One of the World Health Organization's top ten chemicals of major public health concern is toxic metal lead (World Health Organization, 2020). Given its ability to substitute for calcium ions (Duan et al., 2021), lead can adversely affect almost every organ in the body, and result in serious consequences on neurological function, kidney function, and cardiovascular endpoints (Rădulescu & Lundgren, 2019; Rocha & Trujillo, 2019; Pirkle et al., 1985). In the United States, the general population is ubiquitously exposed to lead (Centers for Disease Control and Prevention, 2023). Exposure occurs from the inhalation of cigarette smoke, contaminated air, and dust from houses built before 1978 with lead-based paint; ingestion of contaminated food, beverages, and drinking water; as well as dermal application of cosmetics containing lead (Centers for Disease Control and Prevention, 2023). After exogenous exposure to lead, greater than 90% of it is stored in bone (Barry, 1975). Skeletal lead is an endogenous source of circulatory lead, with bone lead contributing to 45%-70% of lead in blood (Gulson et al., 1995).

The skeletal mobilization of lead to blood is affected by changes in bone metabolism. Bone is dynamic with the continual breakdown of bone tissue by osteoclasts and new bone formation by osteoblasts. An imbalance of these processes in bone remodeling that favors bone breakdown and osteoclast activity can increase skeletal mobilization of lead (Manton et al., 2008). One factor that suppresses osteoclast activity is estrogen (Streicher et al., 2017). Thus, estrogen may slow the skeletal mobilization of lead to blood. A common source of exogenous estrogen exposure is combined oral contraception which contains both estrogen and progestin (Cooper et al., 2022). Oral contraceptives are the most commonly used form of hormonal contraception in the world with 151 million users worldwide (United Nations, 2019). In the US, a quarter of current contraception users use oral contraception, making it the most common form of contraception (Centers for Disease Control and Prevention, 2019; Cooper et al., 2022). We hypothesize that current combined oral contraceptive use is associated with lower blood lead levels.

To our knowledge, only two previous studies have examined the association between oral contraceptive use and blood lead concentrations (Iglesias et al., 2008; Akinloye et al., 2011). Both studies had small samples sizes and adjustment for confounders was limited. Additionally, one study was conducted among adolescent patients (Iglesias et al., 2008), before peak bone mass accrual, and the other study used serum to quantify lead, which has a high potential for measurement error (Akinloye et al., 2011; National Research Council (US) Committee on Measuring Lead in Critical Populations). Therefore, the purpose of the present study was to investigate the association between current oral contraceptive use and blood lead concentrations in a nationally-representative sample of premenopausal U.S. individuals with detailed covariate data.

METHODS

Study design and population

Using data from five survey cycles (2003-2012) of the National Health and Nutrition Examination Survey (NHANES), we conducted a cross-sectional study. NHANES is a large population-based survey conducted by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC) that utilizes a complex survey sampling design to assess the health and nutritional status of the noninstitutionalized U.S. civilian population (National Center for Health Statistics, 2005). The two main survey components of NHANES are the household interview and the health examination. In the household interview, questionnaires are used to collect data on a range of topics including demographics, tobacco use, and medical conditions. NHANES examiners collect blood and urine samples, additional questionnaire data (e.g., reproductive health) as well as anthropometrics a during the health examination component (National Center for Health Statistics, 2005).

Starting with the initial unweighted sample size of 50,912 participants, we restricted the study population to female participants aged 20-44 with information on blood lead concentrations and reproductive health characteristics (unweighted n = 5,007). The age range corresponds to the youngest age that NHANES participants were invited to complete adult questionnaires (age 20) and the oldest age that participants were asked about pregnancy status, starting in cycle year 2007-2008 (age 44). We excluded participants from the population who were menopausal (unweighted n=220) and those for whom information on menopause was missing (unweighted n=6), had a history of bilateral oophorectomy (unweighted n=11) and those for whom information on bilateral oophorectomy was missing (unweighted n=123) or hysterectomy (unweighted n=13) and those for whom information on hysterectomy was missing (unweighted n=5), or were currently pregnant (unweighted n=457) and those for whom information on pregnancy was missing (unweighted n=64) at the time of NHANES interview as these criteria would limit their eligibility to use oral contraceptives or are associated with altered blood lead concentrations (Abell, 2006; Ulrich et al., 2003; Symanski & Hertz-Picciotta, 1995; Mendola et al., 2013; Gulson et al, 2004; Rothenberg et al., 2000). We then excluded participants who were currently using the injectable contraceptive depot medroxyprogesterone acetate (DMPA) (unweighted n = 124) and those for whom information on DMPA use was missing (unweighted n=1) because DMPA is established to be associated with bone loss (American College of Obstetricians and Gynecologists, 2014; Bachrach, 2020; Beksinska et al., 2009; Beksinska et al., 2018; Johnson et al., 2015; Prior, 1990), and current use has been observed to be associated with increased blood lead concentrations (Upson et al., 2020). Finally, we excluded participants who were missing information on current oral contraceptive use (unweighted n = 10). Our final analytic sample comprised 3,973 participants (unweighted).

Oral contraceptive use

Information on oral contraceptive use was collected in the mobile examination center (MEC) using a computer assisted personal interview (CAPI), as part of the Reproductive Health Questionnaire in all female participants aged 12 years and older. Participants were asked, “Have you ever taken birth control pills for any reason?” (no, yes). If they answered “Yes”, they were then asked, “Are you taking birth control pills now?” (no, yes)(National Center for Health Statistics, 2005). Using this information, we created a binary variable to characterize current oral contraceptive use (no, yes). A total of 621 participants (unweighted) reported currently using oral contraception. Individuals not currently using oral contraceptives were defined as non-users (unweighted n = 3,352); the non-user comparison group included both past and never users of oral contraceptives.

For use in an exploratory analysis, we used prescription medication data to create a variable in which users of combined oral contraceptives (oral contraceptives containing both estrogen and progestin) in the 30 days prior to NHANES interview were considered exposed. We used data collected with the Prescription Medications Questionnaire administered to all participants during the household interview. Participants were asked for the name of their current prescription medication used in the past 30 days and the medication was recorded using the standard generic drug name (National Center for Health Statistics, 2005). Those using oral contraceptives containing both progestin and estrogen (desogestrel-ethinyl estradiol, drospirenone-ethinyl estradiol, ethynodiol-ethinyl estradiol, levonorgestrel-ethinyl estradiol, norethindrone-ethinyl estradiol, norgestimate-ethinyl estradiol, or norgestrel-ethinyl estradiol) were defined as current combined oral contraceptive users (unweighted n = 411). All others were considered non-users of current combined oral contraception (unweighted n = 3,495), including those using progestin-only oral contraceptive (norethindrone) (unweighted n = 21), progestin-only emergency contraception (levonorgestrel) (unweighted n = 1) and those who reported oral contraceptive use using the Reproductive Health Questionnaire but not did list the medication on the Prescription Medication Questionnaire (unweighted n = 210). Using the pharmacy data, we excluded those for whom the type of oral contraception was unspecified (unweighted n= 4), current users of other estrogen-containing contraception (contraceptive patch (unweighted n = 10) and contraceptive vaginal ring (unweighted n = 16)), and current users of non-contraceptive estrogen-containing medications (e.g., menopausal hormone therapy containing estrogen unweighted n = 37).

Blood lead concentrations

Given the change in laboratory methods starting in cycle year 2003 (National Center for Health Statistics, 2001; National Center for Health Statistics, 2005), the present analyses were conducted using blood lead measurements collected in cycle years 2003-2012. Whole blood samples collected from NHANES participants at least 1 year of age were measured for lead using inductively coupled plasma mass spectrometry (ICP-MS) by the Division of Laboratory Sciences at the National Center for Environmental Health, Centers for Disease Control and Prevention (National Center for Health Statistics, 2005). The limit of detection was 0.25 µg/dL, and none of the participants in the study population had blood lead concentrations below the limit of detection.

Covariates

NHANES had data available on various covariates used in the present analyses including age, race/ethnicity, education, poverty income ratio [Demographics Data]; body mass index [Body Measures Data]; birth in the past year, number of live births, current breastfeeding, and current use of estrogen-containing hormone replacement (estrogen-only hormonal pills, combination pills, estrogen-only patches, or combination patches) [Reproductive Health Questionnaire]; current cigarette smoking [Smoking and Tobacco Use Questionnaire]; current alcohol use [Alcohol Use Questionnaire]; whole blood hemoglobin (g/dL) and serum 25-hydroxy vitamin D (25(OH)D) concentrations (nmol/L) [Laboratory Data]; daily dietary intake of calcium (mg/day) and total energy intake (kcal/day) [24-hour dietary recall interview]; health conditions (diabetes, thyroid condition, congestive heart failure, leukemia, lymphoma, emphysema, hypertension, heart attack, ischemic/coronary heart disease, diabetes-induced retinopathy, stroke, liver disease, and breast cancer) [Medical Conditions Questionnaire][Diabetes

Questionnaire][Blood Pressure Questionnaire]; and prescription medications used in the past 30 days (glucocorticoids, thyroxines, anticonvulsants, and hormonal contraception) [Prescription Medications Questionnaire]. We used this information on health conditions and prescription medication use to create a composite variable on health conditions or medications associated with bone loss (Office of the Surgeon General, 2004). Additionally, we used information on health conditions (hypertension, congestive heart failure, heart attack, ischemic/coronary heart disease, diabetes-induced retinopathy, stroke, liver disease, breast cancer, diabetes for over 20 years, or smoking more than 15 cigarettes per day while over the age of 35) to create a composite variable on health conditions that are contraindications for oral contraception use (Centers for Disease Control and Prevention, 2023).

Statistical analyses

We used descriptive statistics to compare current oral contraceptive users and non-users regarding sociodemographic, reproductive, medical, and lifestyle characteristics. To understand the distribution of blood lead concentrations across participant characteristics, we estimated the geometric mean blood lead concentrations and 95% confidence intervals adjusting for factors strongly associated with blood lead concentrations (age, current smoking, and cycle year). This descriptive analysis was conducted among current non-users of oral contraception (unweighted n=3,352).

We examined the association between current oral contraceptive use and blood lead concentrations using multivariable linear regression. To estimate the percent difference in blood lead concentrations and 95% confidence intervals (CI) between current users and non-users of oral contraception, we used the natural log of blood lead concentrations and the formula [exp(beta)-1] x 100. We selected covariates *a priori* for adjustment based on associations between the covariates and oral contraceptive use or blood lead exposure in prior studies (Agency for Toxic Substances and Disease Registry, 2020; Ulrich et al., 2003; Office of the Surgeon General, 2004; Arshad et al., 2022; Lazarević et al., 2012; Hegazy et al., 2010; Kutllovci-Zogaj et al., 2014; Jangid et al., 2012; Watts, 2017). All analyses were adjusted for age (continuous), education (<high school education, high school graduate, >high school education), smoking (current), alcohol use (current), birth in the past year (no, yes), and cycle year (2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012) (Model 1). We repeated the analyses additionally adjusting for total calcium intake (<1000 mg/day, ≥ 1000 mg/day), total energy intake (continuous), and a history of conditions or medications associated with bone loss (no, yes) (Model 2). We conducted an exploratory analysis by repeating the main analyses using prescription medication data to characterize combined oral contraceptive use in the 30 days before NHANES interview as the exposure (described above). Although the prescription medication data ascertained combined oral contraceptive use, the timing of use was in the prior 30 days rather than current use at the NHANES interview. For this reason, we did not use this exposure for the main analysis.

Given the cross-sectional study design, we performed an extensive series of sensitivity analyses to investigate other explanations for an association yielded in the main analysis, using self-reported current oral contraceptive use. First, we repeated the main analysis additionally adjusting for anemia status, defined as hemoglobin <12 mg/dL. Compared with non-users, current oral contraceptive users tend to have lighter menstrual flow and less frequently experience anemia (American College of Obstetricians and Gynecologists, n.d.). As lead is stored in red blood cells, the lack of red blood cell loss in current oral contraceptive users may give the appearance of greater blood lead concentrations (Arshad et al., 2022; Kutllovci-Zogaj et al., 2014). Next, we performed seven sensitivity analyses, restricting the study population as follows: (i) to never smokers (unweighted n=2,613) to address potential confounding from cigarette smoking, a substantial contributor to blood lead concentrations (Lazarević et al., 2012); (ii) to ever users of oral contraception (unweighted n=2,979) to compare current and past oral contraceptive users and address unmeasured confounding that may be associated with both oral contraceptive use and lead exposure; (iii) to those not using non-contraceptive estrogen-containing hormonal medication (e.g., menopausal hormone therapy such as estrogen pill, estrogen-progestin combination pill, estrogen patch, or estrogen-progestin combination patch) (unweighted n = 3,937) as these estrogen-containing preparations may also decrease bone remodeling and skeletal mobilization of lead to blood (Streicher et al., 2017; Garnero et al., 1995; Nappi et al., 2003; Almstedt et al., 2020; Grandi et al., 2014; Ott et al., 2001; Mazess et al, 1991; Bachrach, 2020; Beksinska et al., 2009; Beksinska et al., 2018; Johnson et al., 2015; Prior, 1990); (iv) to those that have not given birth in the past year (unweighted n= 3,428) as skeletal mobilization of calcium during pregnancy and lactation can increase the mobilization of lead from bone to blood (Winter et al., 2020; Rothenberg et al., 2000); (v) to those without a history of conditions or current medication use associated with bone loss (unweighted n = 3,464) to address potential confounding from health conditions or medication use that may have the unintended consequence of mobilizing lead from bone to blood (Office of the Surgeon General, 2004); (vi) to participants without a history of medical conditions that are contraindications for oral contraceptive use (unweighted n = 3,142); these contraindications would limit the opportunity to use oral contraceptives (Centers for Disease Control and Prevention, 2023) and are also associated with altered blood lead concentrations (Abell, 2006; Ulrich et al., 2003; Symanski & Hertz-Picciotto, 1995; Mendola et al., 2013; Gulson et al., 2004; Rothenberg et al., 2000); and (vii) to participants aged 25 and older (unweighted n = 3,111); peak bone mass accrual is typically achieved by age 25 in females (American Academy of Orthopaedic Surgeons, n.d.), therefore those under the age of 25 may not have reached peak bone mass and may have greater blood lead concentrations.

RESULTS

In the analytic sample, the weighted prevalence of current oral contraceptive use was 19% (unweighted n=621). Compared to non-users, current oral contraceptive users tended to be younger, non-Hispanic White, have higher educational attainment (college graduate or more), and have a higher poverty income ratio (>1.3, indicating higher income status) (Table I). Current oral contraceptive users also tended to report never smoking cigarettes, current alcohol use, having a lower BMI (<25 kg/m^2), and having a history of no live births compared to non-users. Additionally, current oral contraceptive users less frequently had anemia (hemoglobin (<12 g/dl)), tended to consume more calcium daily (≥1000 mg/day), and have higher 25-hydroxy vitamin D concentrations (≥17.76 ng/mL, the median concentration in this analytic sample) compared to non-users.

In the study population, the unadjusted geometric mean blood lead concentration was 0.78 µg/dL (95% CI: 0.77, 0.80). There were 25 participants in the study population with blood lead levels above the CDC's action level (5 µg/dL); only 1 of these participants was currently using oral contraception (Centers for Disease Control and Prevention, 2023). Among oral contraceptive non-users (unweighted n = 3,352), those with higher blood lead concentrations tended to be older, racialized as Mexican American, Non-Hispanic Black, or other/more than one race, have lower educational attainment (< high school graduate), and have a lower poverty income ratio (≤1.3, indicating lower income status). They also tended to be current smokers (≥20 cigarettes/day), report never consuming alcohol, have a lower BMI (<25 kg/m^2), have a history of ≥4 prior births, and report currently breastfeeding at the time of NHANES interview.

The geometric mean blood lead concentration was lower for current oral contraceptive users (0.68 µg/dL 95% CI: 0.66, 0.71) than non-users (0.81 µg/dL, 95% CI: 0.79, 0.83) (Table

II). After adjustment for age, education, current smoking status, current alcohol consumption status, birth in the past year, and NHANES cycle year (Model 1), we observed that participants who were currently using oral contraceptives had blood lead concentrations that were 10% lower than those not currently using oral contraceptives (95% CI: -14%, -5%). After additionally adjusting for total calcium intake, total energy intake, and medical conditions and medication use associated with bone loss (Model 2), the association was attenuated; we observed that current oral contraceptive users had 9% lower blood lead concentrations compared to non-users (95% CI: -15%, -4%). In our exploratory analyses using prescription medication information to characterize combined oral contraceptive use in the 30 days prior to NHANES interview, we observed a slightly stronger magnitude of the association; those currently using combined oral contraceptives had 12% lower blood lead concentrations compared to all others (12% lower, 95% CI: -17%, -6%) (Table III)).

In each sensitivity analysis we conducted, we observed a similar percent difference in blood lead concentrations to that of our main analyses (Table IV.). This included our analysis additionally adjusting for anemia status (10% lower, 95% CI: -14%, -5%) and after restricting the study population to (i) never smokers (10% lower, 95% CI: -16%, -5%); (ii) ever oral contraceptive users (7% lower, 95% CI: -12%, -3%); (iii) those not currently using non-contraceptive estrogen-containing hormonal medication (10% lower, 95% CI: -15%, -5%); (iv) those who have not given birth in the past year (10% lower, 95% CI: -15%, -5%); (v) participants without a history of medical conditions or current prescription medication use associated with bone loss (9% lower, 95% CI: -14%, -5%); (vi) participants without a history of medical conditions that are contraindications for oral contraceptive use (10% lower, 95% CI: -14%, -5%); and (vii) participants aged 25 years and older (10% lower, 95% CI: -15, -5%).

DISCUSSION

In a sample of US premenopausal individuals, we observed that current oral contraceptive use was associated with lower blood lead concentrations. The observed association is biologically plausible. Estrogen represses pro-osteoclastic cytokines, activates estrogen receptor alpha, and disrupts the RANKL:OPG ratio (Streicher et al., 2017). These processes ultimately lead to apoptosis of osteoclasts, resulting in decreased bone breakdown. In humans, current use of oral contraceptives has been associated with decreased bone turnover rates in multiple studies (Garnero et al., 1995; Nappi et al., 2002; Almstedt et al., 2020; Grandi et al., 2014; Ott et al., 2001; Mazess & Barden, 1991). The most compelling results of bone turnover rates and contraceptive use come from a randomized controlled trial where participants, aged 22-34 years, were randomly assigned to a low-dose combined oral contraceptive (n=20), an ultra-low-dose combined oral contraceptive (n=20), or placebo (n=20) to evaluate the effect of combined oral contraceptives on bone turnover and bone mineral density. The trial reported significant reductions in bone turnover markers after 6, 9, and 12 months of oral contraceptive use when compared to with baseline values, suggesting that combined oral contraceptives have a protective effect on bone (Nappi et al., 2003). In multiple epidemiologic studies, skeletal mobilization of lead to blood has been observed during periods of increased bone resorption; these studies observed increased blood lead concentrations during pregnancy, lactation, and menopause. (Gulson et al., 2003; Rothenberg et al., 1994; Hertz-Picciotta et al., 2000; Tellez-Rojo et al., 2002; Gulson et al., 1998; Gulson et al., 1997; Schell et al., 2000; Moura et al., 2002; Latorre et al., 2003; Hernandez-Avila et al., 2000). A longitudinal study, conducted among 15 pregnant migrants to Australia and 6 pregnant Australian controls, aimed to evaluate blood lead concentrations pre-pregnancy, during pregnancy, and at least 6 months postpartum. The investigators reported an overall 20% increase in blood lead concentrations during pregnancy and postpartum, with skeletal mobilization of lead being greater during postpartum (Gulson et al., 2003).

To our knowledge, the association between oral contraceptives and blood lead concentrations has only been examined in two prior cross-sectional studies (Iglesias et al., 2008) (Akinloye et al., 2011). The first study was conducted among 174 adolescent clinic patients, aged 13-21 years, in the Bronx, New York (Iglesias et al., 2008). The authors reported slightly lower mean blood lead concentrations among current oral contraceptive users (n=25, 1.2 µg/dL) than nonhormonal contraceptive users (n=121, 1.5 µg/dL). However, this study did not adjust for important factors that may confound the association, such as current smoking status. Additionally, an association may be difficult to detect in an adolescent population who have not yet reached peak bone mass accrual (achieved around 25 years of age); rather than decreased bone turnover rates observed with oral contraceptive use in studies of adults, oral contraceptive use during adolescence has been associated with increased bone turnover rates (Bachrach, 2020), which may increase skeletal mobilization of lead. The second study was conducted among 150 family planning patients, aged 18-40 years, in Nigeria (Akinloye et al., 2011) comparing lead concentrations across three different contraception methods and those not currently using any contraception methods. The authors observed similar mean lead concentrations between those using oral contraception (n=50) compared with those not currently using contraception (n=50). However, in that study, concentrations of lead were quantified in serum samples. Serum is not recommended for the measurement of lead as serum does not measure red blood cells, which is where lead is stored in blood (Arshad et al, 2022; Kutllovici-Zogaj et al., 2014; Hu et al., 2007; Smith et al., 1998). Therefore, more sensitive analytic methods are needed to accurately quantify low lead concentrations in blood (Chemnitzer, 2019; Hu et al., 2007; National Research Council (US) Committee on Measuring Lead in Critical Populations, 1993; Smith et al., 1998). For this reason, whole blood is used for the measurement of lead (National Research Council (US) Committee on Measuring Lead in Critical Populations, 1993; Smith et al., 1998).

Our study had several limitations. First, due to the cross-sectional nature of NHANES data collection, the temporal ordering of oral contraceptive use and blood lead concentrations cannot be determined. However, the concern that the outcome, blood lead concentrations, precedes the exposure, oral contraceptive use, is minimized as lead measured in whole blood reflects exposure over the past month (Agency for Toxic Substances and Disease Registry, 2023). Second, information on oral contraceptive use relied on self-report, which can result in exposure misclassification. In addition, in the reproductive health questionnaire, participants were asked about oral contraceptive use in general, and not the type of oral contraception (combined or progestin-only oral contraception). Interestingly, the weighted prevalence of oral contraceptive use (19%) observed in our study population is similar to the frequency of oral contraceptive use (14%) reported among US women aged 15-49 years in the CDC National Survey of Family Growth (Centers for Disease Control and Prevention, 2019). Furthermore, data from a study of women aged 15-44 from the National Survey of Family Growth suggest that combined oral contraception is most commonly used, with progestin-only oral contraception only being used by 2% of oral contraceptive users (Hall et al., 2012). To address potential exposure misclassification due to both reliance on self-report and lack of self-reported data on oral contraceptive type, we specifically investigated combined oral contraceptive use in our exploratory analysis using pharmacy medication data; as expected, we observed a stronger association with combined oral contraceptives. Third, we were not able to evaluate the dose-response relationship considering duration, frequency (e.g., cyclic, extended, or continuous use of combined oral contraception) or estrogen dose due to a lack of data on this information in NHANES. Lastly, some data on sources of lead exposure were not collected in NHANES, including exposure to lead paint chips as a child, aspects of housing in addition to housing age to characterize exposure to lead (Office of Lead Hazard Control and Health Homes, 2012), and source of drinking water. However, in our sensitivity analysis comparing current oral contraceptive users to past users to account for unmeasured confounding factors, we observed similar results to the main analysis.

Our study had several strengths. We conducted the largest study to date on the association between oral contraceptive use and blood lead concentrations. Our results are generalizable to the premenopausal U.S. population due to NHANES's sampling scheme which recruits a nationally representative sample of the U.S. population (National Center for Health Statistics, 2005). We also benefitted from the measurement of whole blood lead concentrations by the laboratory at the CDC, a globally-recognized leader in the methods to quantify lead. Furthermore, the wide range of detailed data collected in NHANES allowed us to conduct a series of sensitivity analyses to evaluate other possible explanations for the observed results; across the sensitivity analyses, the observed association of lower blood lead concentrations with current oral contraceptive use persisted.

CONCLUSION

Among a nationally representative sample of U.S. premenopausal individuals, current oral contraceptive use was associated with lower blood lead concentrations. The observed association was stronger in magnitude when we specifically investigated combined oral contraceptive use. As no safe level of blood lead exists, and lead can adversely affect all organ systems, even in adulthood, further research is warranted to replicate our findings and to investigate the dose-response relationship between oral contraceptive use and blood lead concentrations.

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APPENDIX

Table I. Participant characteristics by current oral contraceptive use and blood lead concentrations, National Health and Nutrition Examination Survey (NHANES), 2003-2012.[a]

Participant characteristic	Current oral contraceptive use		Blood lead (µg/dL)
	Yes (unweighted n = 621) n[b](%)[c]	No (unweighted n = 3,352) n[b](%)[c]	Among women not currently using oral contraception (unweighted n= 3,352) Adjusted GM (95% CI)[d]
Age at sample collection, years[e]			
20-29	350 (56)	1253 (36)	0.73 (0.70, 0.76)
30-39	210 (34)	1358 (41)	0.82 (0.79, 0.85)
40-44	61 (10)	741 (23)	0.96 (0.92, 1.01)
Race/Ethnicity			
Mexican American	82 (6)	684 (11)	1.15 (1.07, 1.23)
Other Hispanic	38 (4)	319 (6)	1.00 (0.90, 1.11)
Non-Hispanic White	370 (79)	1335 (61)	0.90 (0.86, 0.95)
Non-Hispanic Black	97 (7)	725 (14)	1.11 (1.04, 1.18)
Other/More than one race	34 (4)	289 (8)	1.26 (1.16, 1.36)
Education			
<HS graduate	74 (8)	708 (15)	1.13 (1.06, 1.20)
HS graduate	82 (12)	691 (20)	0.95 (0.88, 1.01)
Some college or AA degree	228 (37)	1168 (36)	0.92 (0.87, 0.98)
≥College graduate	237 (43)	783 (29)	0.95 (0.89. 1.01)
Poverty Income Ratio			
≤1.3	163 (19)	1155 (27)	1.07 (1.00, 1.14)
>1.3 - 3.5	210 (35)	1173 (38)	0.91 (0.86, 0.96)
>3.5	226 (46)	823 (35)	0.95 (0.90, 1.01)
Smoking status[f]			
Never	451 (69)	2162 (62)	0.93 (0.89, 0.99)
Former	71 (13)	379 (14)	0.92 (0.85, 0.99)
Current, <20 cigarettes/day	80 (14)	618 (18)	1.21 (1.12, 1.32)
Current, ≥20 cigarettes/day	19 (3)	189 (6)	1.40 (1.29, 1.53)

Table I. (cont'd)

Alcohol consumption			
Never	64 (7)	560 (14)	1.09 (1.01, 1.17)
Former	71 (11)	546 (14)	0.95 (0.89, 1.02)
Current	486 (82)	2244 (72)	0.96 (0.91, 1.01)
BMI (kg/m^2)			
<25	320 (56)	1221 (41)	1.04 (0.98, 1.10)
25-<30	151 (23)	877 (26)	0.96 (0.90, 1.03)
30-<35	80 (12)	606 (16)	0.93 (0.87, 0.99)
35-<40	39 (6)	325 (9)	0.91 (0.85, 0.98)
≥40	28 (3)	305 (8)	0.85 (0.78, 0.93)
Number of live births			
0	324 (58)	1012 (34)	0.99 (0.91, 1.08)
1	114 (17)	568 (17)	0.96 (0.89, 1.03)
2	114 (18)	857 (26)	0.96 (0.90, 1.02)
3	52 (6)	588 (16)	0.96 (0.89, 1.09)
≥4	17 (1)	327 (7)	1.09 (1.00, 1.17)
Birth in the past year			
No	553 (92)	2875 (88)	0.93 (0.89, 0.97)
Yes	62 (8)	448 (12)	1.00 (0.93, 1.08)
Currently breastfeeding			
No	604 (99)	3178 (96)	0.93 (0.89, 0.97)
Yes	11 (1)	145 (4)	1.06 (0.96, 1.17)
Anemia (hemoglobin (<12 g/dl))			
No	577 (96)	2910 (90)	0.96 (0.91, 1.01)
Yes	41 (4)	437 (10)	1.01 (0.94, 1.09)
Daily total calcium intake			
<1000 mg/day	372 (60)	2274 (68)	0.98 (0.93, 1.04)
≥1000 mg/day	242 (40)	1012 (32)	0.92 (0.87, 0.97)
25(OH)D[g]			
<17.76 ng/mL	199 (25)	2027 (54)	0.99 (0.93, 1.05)
≥17.76 ng/mL	402 (75)	1201 (46)	0.94 (0.89, 0.99)

Table I. (cont'd)

Conditions or medications associated with bone loss[h]			
No	560 (90)	2904 (87)	0.98 (0.93 1.03)
Yes	58 (10)	417 (13)	0.91 (0.84, 0.98)

Abbreviations: AA, Associate in Arts; BMI, body mass index; CI, confidence interval; GM, geometric mean; HS, high school; 25(OH)D, serum 25-hydroxyvitamin D concentrations.

[a]Study population restricted to non-pregnant, premenopausal female participants ages 20-44 years with an intact uterus and at least one ovary who are not currently using injectable contraceptive depot medroxyprogesterone acetate.

[b]Unweighted n; missing data for education (n=2), poverty income ratio (n=223), smoking status (n=4), alcohol consumption (n=2), BMI (n=21), birth in the past year (n=35), current breastfeeding status (n=35), anemia status (n=8), calcium (n=73), 25(OH)D (n=144), and conditions or medications associated with bone loss (n=34).

[c]Weighted percent.

[d]Geometric mean blood lead concentration adjusted for age (continuous), current smoking status (yes, no), and NHANES cycle year (2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012).

[e]Geometric mean blood lead concentration adjusted only for current smoking (yes, no).

[f]Geometric mean blood lead concentration adjusted only for age (continuous).

[g]Median in study population is 17.76 ng/mL.

[h]History of conditions (diabetes, thyroid disease, congestive heart failure, leukemia, lymphoma, emphysema) or current medication use (glucocorticoids, thyroxines, anticonvulsants) associated with bone los

Table II. Percent difference (95% CI) in geometric mean of blood lead concentrations between current oral contraceptive (OC) users and nonusers, National Health and Nutrition Examination Survey (NHANES), 2003-2012 (unweighted n = 3,973).

Current OC Use	n^a (%)[b]	Crude blood lead (µg/dL) GM (95% CI)	Model 1 % difference (95% CI)[d]	Model 2 % difference (95% CI)[e]
No	3,352 (81)	0.81 (0.79, 0.83)	Reference	Reference
Yes	621 (19)	0.68 (0.66, 0.71)	-10% (-14%, -5%)	-9% (-14%, -4%)

Abbreviations: CI, confidence interval; GM, geometric mean; OC, oral contraceptive use.

[a]Study population restricted to non-pregnant, premenopausal female participants ages 20-44 years with an intact uterus and at least one ovary who are not currently using injectable contraceptive depot medroxyprogesterone acetate.

[a]Unweighted n.

[b]Weighted percent.

[c]Adjusted for age (continuous), current smoking (yes, no), and NHANES cycle year (2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012).

[d]Adjusted for age (continuous), education (< high school education, high school graduate, some college or associate degree or college graduate or above), smoking (current), alcohol use (current), birth in the past year, and cycle year.

[e]Adjusted for age (continuous), education (< high school education, high school graduate, some college or associate degree or college graduate or above), smoking (current), alcohol use (current), birth in the past year, cycle year, total calcium intake, total energy intake, and conditions and medications associated with bone loss.

Table III. Exploratory Analyses of the percent difference (95% CI) in geometric mean of blood lead concentrations between combined oral contraceptive (COC) users in the 30 days before interview and nonusers, National Health and Nutrition Examination Survey (NHANES), 2003-2012 (n = 3,906).

COC use in past 30 days	n^a (%)[b]	Crude blood lead (µg/dL) GM (95% CI)	Model 1 % difference (95% CI)[d]	Model 2 % difference (95% CI)[e]
No	3,495 (85)	0.81 (0.79, 0.83)	Reference	Reference
Yes	411 (15)	0.66 (0.63, 0.68)	-12% (-18%, -7%)	-12% (-17%, -6%)

Abbreviations: CI, confidence interval; COC, combined oral contraceptive use; GM, geometric mean.

[a]Unweighted n.

[b]Weighted percent.

[c]Adjusted for age (continuous), current smoking (yes, no), and NHANES cycle year (2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012).

[d]Adjusted for age (continuous), education (< high school education, high school graduate, some college or associate degree or college graduate or above), smoking (current), alcohol use (current), birth in the past year, and cycle year.

[e]Adjusted for age (continuous), education (< high school education, high school graduate, some college or associate degree or college graduate or above), smoking (current), alcohol use (current), birth in the past year, cycle year, total calcium intake, total energy intake, and conditions and medications associated with bone loss.

Table IV. Sensitivity Analyses of the percent difference (95% CI) in geometric mean of blood lead concentrations between current oral contraceptive (OC) users and nonusers, National Health and Nutrition Examination Survey (NHANES), 2003-2012.

Sensitivity Analyses	Current OC Use	*n*[a] (%)[b]	Crude blood lead (µg/dL) GM (95% CI)	Model 1 % difference (95% CI)[c]	Model 2 % difference (95% CI)[d]
Additional adjustment for anemia status (unweighted n=3,965)	No	3,347 (81)	0.81 (0.79, 0.83)	Reference	Reference
	Yes	618 (19)	0.68 (0.66, 0.71)	-10% (-14%, -5%)	-9% (-14%, -4%)
Restricted to never smokers (unweighted n=2,613)	No	2,162 (79)	0.75 (0.73, 0.78)	Reference	Reference
	Yes	451 (21)	0.65 (0.62, 0.68)	-10% (-16%, -5%)	-11% (-17%, -4%)
Restricted to ever OC users (unweighted n=2,979)	No	2,358 (83)	0.80 (0.78, 0.82)	Reference	Reference
	Yes	621 (17)	0.68 (0.66, 0.71)	-7% (-12%, -3%)	-7% (-12%, -2%)
Restricted to those not currently using non-contraceptive estrogen-containing hormonal medication (unweighted n=3,937)[e]	No	3,320 (81)	0.81 (0.79, 0.83)	Reference	Reference
	Yes	617 (19)	0.68 (0.66, 0.71)	-10% (-15%, -6%)	-10% (-15%, -5%)
Restricted to those that have not given birth in the past year (unweighted n=3,428)	No	2,875 (80)	0.81 (0.78, 0.84)	Reference	Reference
	Yes	553 (20)	0.68 (0.65, 0.71)	-10% (-15%, -5%)	-9% (-14%, -4%)
Restricted to participants without history of medical conditions or current medication use associated with bone loss (unweighted n=3,464)[f]	No	2,904 (80)	0.81 (0.79, 0.83)	Reference	Reference
	Yes	560 (20)	0.69 (0.66, 0.71)	-9% (-14%, -5%)	-9% (-14%, -5%)
Restricted to participants without history of medical conditions that are contraindications for OC use (unweighted n= 3,142)[g]	No	2,608 (79)	0.79 (0.76, 0.81)	Reference	Reference
	Yes	534 (21)	0.67 (0.64, 0.70)	-10% (-14%, -5%)	-10% (-15%,-5%)
Restricted to participants aged 25 and older (unweighted n=3,111)	No	2,683 (83)	0.83 (0.81, 0.86)	Reference	Reference
	Yes	428 (17)	0.70 (0.67, 0.73)	-10% (-15%, -5%)	-11% (-17%, -5%)

Abbreviations: CI, confidence interval; GM, geometric mean; OC, oral contraceptive use.

[a]Unweighted n.

[b]Weighted percent.

Table IV. (cont'd)

[c]Adjusted for age (continuous), education (< high school education, high school graduate, some college or associate degree or college graduate or above), smoking (current), alcohol use (current), birth in the past year, and cycle year.

[d]Adjusted for age (continuous), education (< high school education, high school graduate, some college or associate degree or college graduate or above), smoking (current), alcohol use (current), birth in the past year, cycle year, total calcium intake, total energy intake, and conditions and medications associated with bone loss.

[e]Non-contraceptive hormonal medications included estrogen pill, estrogen-progestin combination pill, estrogen patch, and estrogen/progestin combination patch.

[f]History of conditions (diabetes, thyroid condition, congestive heart failure, leukemia, lymphoma, emphysema) or current medications (glucocorticoids, thyroxines, or anticonvulsants).

[g] History of conditions (hypertension, congestive heart failure, heart attack, ischemic/coronary heart disease, diabetes-induced retinopathy, stroke, liver disease, breast cancer, diabetes for over 20 years, or smoking more than 15 cigarettes per day while over the age of 35.)

[h]Adjusted for age (continuous), current smoking (yes, no), and NHANES cycle year (2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012).