



Preconception contraceptive use and miscarriage: prospective cohort study

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ABSTRACT

OBJECTIVES To evaluate the association between preconception contraceptive use and miscarriage.

DESIGN Prospective cohort study.

SETTING Residents of the United States of America or Canada, recruited from 2013 until the end of 2022.

PARTICIPANTS 13 460 female identified participants aged 21–45 years who were planning a pregnancy were included, of whom 8899 conceived.

Participants reported data for contraceptive history, early pregnancy, miscarriage, and potential confounders during preconception and pregnancy.

MAIN OUTCOME MEASURE Miscarriage, defined as pregnancy loss before 20 weeks of gestation.

RESULTS Preconception use of combined and progestin-only oral contraceptives, hormonal intrauterine devices, copper intrauterine devices, rings, implants, or natural methods was not associated with miscarriage compared with use of barrier methods. Participants who most recently used patch (incidence rate ratios 1.34 (95% confidence interval 0.81 to 2.21)) or injectable contraceptives (1.44 (0.99 to 2.12)) had higher rates of miscarriage compared with recent users of barrier methods, although results were imprecise due to the small numbers of participants who used patch and injectable contraceptives.

CONCLUSIONS Use of most contraceptives before conception was not appreciably associated with

miscarriage rate. Individuals who used patch and injectable contraceptives had higher rates of miscarriage relative to users of barrier methods, although these results were imprecise and residual confounding was possible.

Introduction

Nearly all women in the United States of America will use contraception in their lifetimes.¹ Given the high prevalence of contraceptive use, the potential reproductive effect of contraceptives after discontinuation is important to understand. Individual discontinuation of several hormonal contraceptives has been associated with transient delays in return to fertility of up to eight cycles.^{2–8} However, less is known about the potential impact of contraceptive use on pregnancy outcomes such as miscarriage (defined as pregnancy loss before 20 weeks of gestation).

Miscarriage occurs in about 20% of recognised pregnancies, but few modifiable risk factors have been identified.⁹ Several studies have evaluated the association between history of oral contraceptive use and miscarriage. Some^{10–12} but not all^{13 14} studies reported that use of oral contraceptives was associated with a lower risk of miscarriage compared with non-use, although these studies used various exposure definitions (eg, recent use v ever use). In mice, prolonged suppression of ovulation via use of a progestin implant slowed the physiological aging of oocytes, and may thereby reduce the risk of miscarriages associated with chromosomal abnormalities.¹⁵ Recent use of some hormonal contraceptives could plausibly increase risk of early miscarriage if the endometrium remains thin or endometrial receptivity is altered after cessation of the method.¹⁶ All hormonal contraceptives (oral contraceptives, intrauterine devices, injectable, patch, ring, and implant methods) administer progestin, either alone or with estrogen, and any of these methods could affect miscarriage risk through similar mechanisms. However, no research has been published on the risk of miscarriage associated with preconception use of other contraceptives.

In this study, we evaluated preconception use of a range of contraceptives and risk of miscarriage within a North American prospective cohort study of pregnancy planners.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Discontinuation of several hormonal contraceptives has been associated with temporary delays in return to fertility
- ⇒ Preconception use of oral contraceptives has been associated with a reduced risk of miscarriage in some but not all studies
- ⇒ Limited research is available on the association of miscarriage with preconception use of other contraceptive methods, particularly long-acting hormonal contraceptives

WHAT THIS STUDY ADDS

- ⇒ This study quantifies the rate of miscarriage after preconception use for various contraceptive methods
- ⇒ Compared with barrier methods, oral contraceptives, hormonal or copper intrauterine devices, rings, implants, and natural methods were not associated with miscarriage rate

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

- ⇒ These findings support individuals of reproductive aged and care providers in their contraceptive counseling and family planning efforts

Methods

We used data from the pregnancy study online (PRESTO), which is a prospective preconception cohort study of couples in the US and Canada (2013-ongoing).¹⁷ Eligible participants self-identified as female, were aged 21-45 years, and were trying to conceive without the use of fertility treatment at enrollment; although they could initiate fertility treatment during follow-up. Participants were recruited primarily via advertisements on social media and health related websites, and all questionnaires were administered online.^{17,18} Potential participants completed a screening questionnaire; those who were eligible were immediately sent an e-mail with a link to complete the online baseline questionnaire. After completion of the baseline questionnaire, participants completed follow-up questionnaires every eight weeks for up to 12 months or until pregnancy, cessation of pregnancy attempts, loss to follow-up, or study withdrawal. Participants who conceived completed two additional questionnaires at medians of 9 and 32 gestational weeks. We mailed residents of the contiguous US home pregnancy tests (Clearblue) immediately after enrolment.¹⁹ We excluded individuals who recently used sterilisation, emergency contraception, or douching as contraceptive methods. The Boston University Medical Campus Institutional Review Board approved the study protocol. All participants provided online informed consent.

Assessment of miscarriage

Miscarriage was defined as pregnancy loss occurring before 20 completed weeks of gestation; this definition included blighted ovum but not ectopic pregnancy. We used data up to and including the first observed pregnancy per participant; in other words, we assessed one pregnancy per participant.

On follow-up questionnaires, participants reported the date of their last menstrual period, whether they were currently pregnant, whether they had had a miscarriage, and the timing of their first home pregnancy test (whether negative or positive) relative to the day of expected menses. Participants who were currently pregnant completed the early pregnancy questionnaire on which they reported any pregnancy losses since their previous questionnaire, the due date of their current pregnancy, and the timing of their first positive pregnancy test relative to the day of expected menses. Miscarriages occurring after the early pregnancy questionnaire were identified on the late pregnancy questionnaire (online supplemental figure S1).

Participants who miscarried were asked to report how many weeks the pregnancy lasted and on what date the pregnancy ended. We used the participant's reported gestational weeks at loss where available. Among participants who did not report their gestational weeks at loss but reported a due date (10%, $n=192/1841$), we estimated gestational age as:

(pregnancy end date – (pregnancy due date–280 days))/7.²⁰ Among participants who reported neither their gestational weeks at miscarriage nor their due date (21%, $n=385/1841$), we estimated gestational weeks at loss as: (pregnancy end date – last menstrual period date)/7. For participants who were lost to follow-up, we attempted to collect outcome data by contacting them via email or phone, by linking to birth registries in selected states (CA, FL, MA, MI, OH, PA, TX, and NY), and by searching for baby registries and birth announcements online.

Assessment of contraceptive use

On the baseline questionnaire, participants reported the contraceptive method that they used most recently. The response categories included barrier methods (ie, condoms, diaphragm, sponge, jellies, creams, and suppositories), oral contraceptives, hormonal intrauterine devices, copper intrauterine devices, patches, injectable contraceptives, vaginal rings, implants, and natural methods (ie, withdrawal, avoiding sex when fertile, calendar methods, and monitoring cervical mucus or basal body temperature). The primary exposure was the contraceptive method used most recently (ie, the last or recently used method). Progestin-only and combined oral contraceptives were grouped for all analyses because only about 1%⁸ of participants used progestin-only oral contraceptives most recently.

Participants reported when they stopped using all contraception (month and year), whether they waited after discontinuing hormonal methods before trying to conceive, and if so, for how many months they waited. Participants also reported the name of any hormone containing contraceptive they had ever used, their age(s) at which they used each method, and their total duration of use (months, years, or both) for each method. We used these data to categorize participants who selected more than one most recent contraceptive method.

Statistical analysis

Participants were followed up from the date of their first positive pregnancy test until miscarriage, induced abortion, ectopic pregnancy, loss to follow-up, or 20 weeks' gestation, whichever came first. Participants who were lost to follow-up were censored at a median of 10 gestational weeks (interquartile range 6-14 weeks). Among participants who conceived, we fit age adjusted survival curves for miscarriage by contraceptive method. We fit a discrete analog to the Cox proportional hazards model stratified by gestational week to estimate incidence rate ratios for miscarriage, comparing use of oral contraceptives, hormonal intrauterine devices, copper intrauterine devices, rings, implants, patches, injectables, and natural methods as the last method of contraception with use of barrier methods. We

used an Andersen-Gill data structure with one row of data per gestational week per participant to account for potential bias due to left truncation.^{21 22}

We considered potential confounders based on a directed acyclic graph (online supplemental figure S2), prioritizing variables that could affect contraceptive use and miscarriage. We adjusted for the following non-reproductive covariates: age (years); body mass index (BMI); self-identified race and ethnicity (non-Hispanic white, non-Hispanic Black, non-Hispanic Asian, non-Hispanic other race or multiracial, or Hispanic); region (northeastern US, southern US, midwestern US, western US, or Canada); education level (high school, some college, college degree, or graduate school); household income (<50 000, 50 000-99 999, 100 000-149 999, or ≥150 000 USD); employment status (yes/no); hours per week of work; current smoking (yes/no); daily use of multivitamins or folate supplements (yes/no); sleep duration per night (<6 h, 6 to <9 h, ≥9 h); private health insurance (yes/no); number of primary care visits in the past year (0, 1, 2-3, or ≥4); 10-item Perceived Stress Scale score²³; Major Depression Inventory score²⁴; and diabetes (yes/no). We also adjusted for the following reproductive characteristics: lifetime duration of hormonal contraceptive use (months); parity (yes/no); prior miscarriage (yes/no); history of subfertility (yes/no); use of fertility treatment (yes/no); time to pregnancy (menstrual cycles); typical menstrual cycle length (days) and regularity (yes/no); history of a sexually transmitted infection (yes/no); endometriosis (yes/no); uterine leiomyomata (yes/no); and polycystic ovarian syndrome (yes/no). Most covariates were ascertained at baseline. However, smoking status, Perceived Stress Scale score, and daily use of multivitamins or folate supplements were updated on follow-up questionnaires. For these variables, we used the value that was assessed closest to the date of conception.

Selection bias occurs when selection into a study is related to both the exposure and outcome of interest. In this study, selection bias may arise due to conditioning on pregnancy, because preconception use of some contraceptives (exposure) is associated with pregnancy (selection),⁸ and common causes of pregnancy (selection) and miscarriage (outcome) exist. The role of selection bias due to conditioning on pregnancy in studies of miscarriage has been discussed widely (selection bias due to conditioning on live birth in studies of perinatal outcomes is an analogous issue in the literature).²⁵⁻²⁹ We used inverse probability weighting to account for this potential bias. In models using inverse probability weighting, each participant who is pregnant accounts for participants who are not pregnant who had similar characteristics (ie, similar probability of pregnancy). After weighting, the models are fit within a pseudo-population that is theoretically unaffected by

selection bias. To carry out inverse probability weighting, we calculated stabilized weights in the full sample of couples trying to conceive. We used logistic regression to estimate the probability of pregnancy given the exposure (n) and the probability of pregnancy given the exposure and covariates (d). The weight, w , was calculated as $w=n/d$ among participants who conceived, and $w=(1-n)/(1-d)$ among participants who did not conceive. The covariates in these models included those in the outcome model, plus frequency of intercourse and trying to improve chances of conception. We omitted use of fertility treatment to conceive the study pregnancy and time to pregnancy because we only collected data for those variables among participants who conceived. We then fit weighted models in the analytical population of participants who conceived.

We conducted several stratified analyses in the weighted population. We stratified by age at conception (<30 v ≥30 years), body mass index (<30 v ≥30), and gestational week at risk (<8 v ≥8 weeks). We stratified by age because age is the strongest known predictor of miscarriage, and ovarian aging could modify the effects of exogenous hormones. We stratified by body mass index because body size and adipose tissue may affect pharmacokinetics of contraceptives. Finally, we stratified by gestational age because the biological cause of miscarriage may vary across gestation, with earlier losses having a greater prevalence of chromosomal abnormalities than later losses.³⁰ Stratifying by gestational weeks at risk (online supplemental figure S3) allows us to evaluate differences in the effect of contraceptives on early v late miscarriage (ie, assessment of the proportional hazards assumption).

Sensitivity analysis

We conducted several exploratory analyses in the unweighted population. We described the distribution of time since discontinuation of the most recently used contraceptive, defined as months from discontinuing until conception, and the frequency of miscarriage by time since discontinuation.

We then evaluated the effect of recency of use for all hormonal methods in the unweighted population. For oral contraceptives and hormonal intrauterine devices, we fit restricted cubic spline models to assess the possibly non-linear relation between months since discontinuing and rate of miscarriage.^{31 32} To accommodate sparse data among less commonly used contraceptives, we then re-categorized recency of use based on participants' entire contraceptive histories, regardless of the most recent method used. We compared the rate of miscarriage for those who discontinued 0-6 months and 7-12 months before conception, with

Table 1 | Baseline characteristics of 8899 participants according to most recent method of contraception used

Characteristic	Barrier (n=2166)	Oral contraceptive (n=2506)	Hormonal IUD (n=1284)	Copper IUD (n=353)	Ring (n=349)	Implant (n=196)	Patch (n=61)	Injectable (n=112)
Gestational age at first positive pregnancy test (weeks), mean (SD)	4.1 (0.8)	4.2 (0.9)	4.1 (1.0)	4.1 (0.7)	4.1 (0.9)	4.1 (0.8)	4.1 (0.7)	4.5 (1.0)
Age (years), mean (SD)	30.4 (3.8)	29.9 (3.9)	30.6 (3.6)	31.2 (3.9)	30.2 (3.6)	28.5 (3.6)	28.3 (3.3)	28.5 (4.2)
BMI, mean (SD)	26.4 (6.2)	27.0 (6.8)	27.3 (6.8)	26.7 (6.2)	27.2 (6.2)	28.9 (8.0)	27.4 (7.7)	29.6 (7.5)
Race/ethnicity, no (%):								
White, non-Hispanic	1850 (85.4)	2186 (87.2)	1127 (87.8)	301 (85.3)	293 (84.0)	157 (80.1)	50 (82.0)	85 (75.9)
Hispanic	132 (6.1)	138 (5.5)	70 (5.5)	26 (7.4)	23 (6.6)	23 (11.7)	1 (1.6)	13 (11.6)
Black, non-Hispanic	22 (1.0)	42 (1.7)	28 (2.2)	9 (2.6)	16 (4.6)	5 (2.6)	2 (3.3)	7 (6.3)
Asian, non-Hispanic	59 (2.7)	52 (2.1)	17 (1.3)	5 (1.4)	4 (1.2)	1 (0.5)	2 (3.3)	1 (0.9)
Multiracial/other race	103 (4.8)	88 (3.5)	42 (3.3)	12 (3.4)	13 (3.7)	10 (5.1)	6 (9.8)	6 (5.4)
Region of residence, no (%):								
Northeastern U.S.	519 (24.0)	644 (25.7)	285 (22.2)	89 (25.2)	83 (23.8)	31 (15.8)	12 (19.7)	18 (16.1)
Southern US	423 (19.5)	577 (23.0)	260 (20.3)	69 (19.6)	81 (23.2)	63 (32.1)	13 (21.3)	37 (33.0)
Midwestern US	439 (20.3)	557 (22.2)	270 (21.0)	70 (19.8)	74 (21.2)	63 (32.1)	23 (37.7)	31 (27.7)
Western US	372 (17.2)	361 (14.4)	250 (19.5)	74 (21.0)	65 (18.6)	36 (18.4)	4 (6.6)	18 (16.1)
Canada	413 (19.1)	367 (14.6)	219 (17.1)	51 (14.5)	46 (13.2)	3 (1.5)	9 (14.8)	8 (7.1)
Educational attainment ≤ high school, no (%)	52 (2.4)	66 (2.6)	32 (2.5)	9 (2.6)	5 (1.4)	17 (8.7)	4 (6.6)	13 (11.6)
Annual household income <50 000 USD, no (%)	289 (13.3)	322 (12.9)	143 (11.1)	41 (11.6)	36 (10.3)	57 (29.1)	16 (26.2)	33 (29.5)
Currently employed, no (%)	1862 (86.0)	2271 (90.6)	1154 (89.9)	320 (90.7)	329 (94.3)	158 (80.6)	49 (80.3)	82 (73.2)
Hours per week of work, mean (SD)	32.7 (16.2)	35.6 (14.3)	35.8 (15.4)	34.7 (15.5)	36.9 (12.5)	30.6 (17.7)	30.2 (17.4)	28.9 (19.6)
Current smoker, no (%)	97 (4.5)	166 (6.6)	83 (6.5)	17 (4.8)	16 (4.6)	26 (13.3)	6 (9.8)	26 (23.2)
Daily use of multivitamins/folic acid, no (%)	1912 (88.3)	2157 (86.1)	1147 (89.3)	314 (89.0)	303 (86.8)	156 (79.6)	46 (75.4)	81 (72.3)
<6 h per night of sleep, no (%)	65 (3.0)	99 (4.0)	61 (4.8)	16 (4.5)	16 (4.6)	14 (7.1)	5 (8.2)	10 (8.9)
≥4 primary care visits in past year, no (%)	292 (13.5)	365 (14.6)	161 (12.5)	42 (11.9)	46 (13.2)	28 (14.3)	9 (14.8)	26 (23.2)
Ever diagnosed with diabetes, no (%)	23 (1.1)	25 (1.0)	23 (1.8)	3 (0.9)	3 (0.9)	1 (0.5)	0 (0.0)	0 (0.0)
Total lifetime duration of any hormonal contraceptive use (years), mean (SD)	7.1 (4.6)	9.7 (4.6)	10.2 (4.5)	9.2 (4.3)	8.8 (4.6)	8.1 (4.3)	8.3 (4.3)	7.0 (4.6)
Menstrual cycle length (days), mean (SD)	29.8 (3.5)	29.8 (4.0)	29.4 (3.6)	29.5 (3.1)	29.4 (3.9)	29.5 (3.1)	29.7 (3.4)	29.1 (4.3)
Menstrual cycle regularity, no (%):								
Regular	1530 (70.6)	943 (37.6)	482 (37.5)	299 (84.7)	140 (40.1)	75 (38.3)	27 (44.3)	59 (52.7)
Irregular	114 (5.3)	308 (12.3)	112 (8.7)	46 (13.0)	37 (10.6)	30 (15.3)	14 (23.0)	22 (19.6)
Unknown due to hormone use	322 (14.9)	1255 (50.1)	690 (53.7)	8 (2.3)	172 (49.3)	91 (46.4)	20 (32.8)	31 (27.7)
Parous, no (%)	726 (33.5)	613 (24.5)	508 (39.6)	141 (39.9)	83 (23.8)	88 (44.9)	23 (37.7)	53 (47.3)
Total number of menstrual cycles tried to conceive, mean (SD)	6.0 (5.6)	6.8 (5.7)	5.8 (5.3)	5.5 (4.5)	7.0 (6.2)	6.4 (4.6)	7.7 (6.1)	10.3 (7.5)

Continued

Table 1 Continued									
Characteristic	Barrier (n=2166)	Oral contraceptive (n=2506)	Hormonal IUD (n=1284)	Copper IUD (n=353)	Ring (n=349)	Implant (n=196)	Patch (n=61)	Injectable (n=112)	
Conceived current pregnancy with the use of fertility treatment, no (%)	134 (6.2)	226 (9.0)	84 (6.5)	17 (4.8)	36 (10.3)	10 (5.1)	8 (13.1)	13 (11.6)	
History of subfertility or infertility*, no (%)	300 (13.9)	297 (11.9)	132 (10.3)	48 (13.6)	45 (12.9)	23 (11.7)	16 (26.2)	27 (24.1)	
History of miscarriage, no (%)	587 (27.1)	536 (21.4)	265 (20.6)	96 (27.2)	77 (22.1)	64 (32.7)	19 (31.2)	34 (30.4)	
Reproductive health diagnoses, no (%):									
Endometriosis	42 (1.9)	75 (3.0)	48 (3.7)	5 (1.4)	11 (3.2)	5 (2.6)	2 (3.3)	5 (4.5)	
Uterine leiomyomata	52 (2.4)	45 (1.8)	23 (1.8)	4 (1.1)	5 (1.4)	3 (1.5)	1 (1.6)	4 (3.6)	
Polycystic ovarian syndrome	127 (5.9)	179 (7.1)	53 (4.1)	21 (6.0)	20 (5.7)	10 (5.1)	5 (8.2)	10 (8.9)	
Any sexually transmitted infection	211 (9.7)	332 (13.3)	178 (13.9)	58 (16.4)	46 (13.2)	35 (17.9)	12 (19.7)	26 (23.2)	
Chlamydia	120 (5.5)	176 (7.0)	99 (7.7)	32 (9.1)	23 (6.6)	20 (10.2)	9 (14.8)	19 (17.0)	
Herpes	59 (2.7)	105 (4.2)	45 (3.5)	17 (4.8)	18 (5.2)	7 (3.6)	2 (3.3)	8 (7.1)	

Baseline characteristics of individuals who used natural methods most recently are presented in online supplemental table S1. BMI=body mass index. IUD=intrauterine device; SD=standard deviation; USD=United States dollars.
*History of subfertility or infertility was defined as having taken ≥6 months to conceive in a prior pregnancy attempt.

those who discontinued more than 12 months before conception. These models were adjusted only for age due to the small sample sizes within each exposure level.

Missing data

We used fully conditional specification methods to impute missing values for covariates and gestational age at miscarriage. In SAS, we created 20 imputed datasets using SAS PROC MI. We included the following variables with complete data in the imputation model: age, education, geographical region, history of miscarriage, history of diabetes, history of a thyroid disorder, history of endometriosis, history of polycystic ovarian syndrome, history of a sexually transmitted infection, daily use of multivitamins or folate supplements, and race and ethnicity. A small amount of missingness (n≤10) was noted for marital status, use of marijuana, use of pain medications, use of antibiotics, and use of asthma medication. We performed simple imputation for these variables before including them in the multiple imputation model. We fit regression models for each imputation, and then averaged the coefficients across imputations using SAS PROC MIANALYZE. This procedure also estimates robust standard errors for the pooled estimates. Missingness was less than 3% for all variables except for type of health insurance, which was missing for 35% (3193/8899) of participants because this variable was added to the baseline questionnaire in 2018 and was therefore not asked of all participants. We used SAS statistical software (version 9.4, SAS Institute) and R (R Core Team, 2021) to perform statistical analyses.

Interpretation

To interpret our results, we focused on the size of the effect estimates, the width of their confidence intervals, and the consistency of results across models. This approach is aligned with American Statistical Association guidelines, which strongly caution against the dichotomization of P values into significant and not significant.³³

Patient and public involvement

No participants were involved in developing the research question, study design, or outcome measures, nor in the implementation of this study. Results of the study will be accessible to participants and the public through the study website.

Results

Approximately 87% of individuals who completed the screener questionnaire were eligible, of whom 56% enrolled and completed the baseline questionnaire. Median follow up from the date of their first positive pregnancy test was four weeks (range 3-13 weeks); women were followed up until miscarriage (n=1841), induced abortion (n=44), ectopic

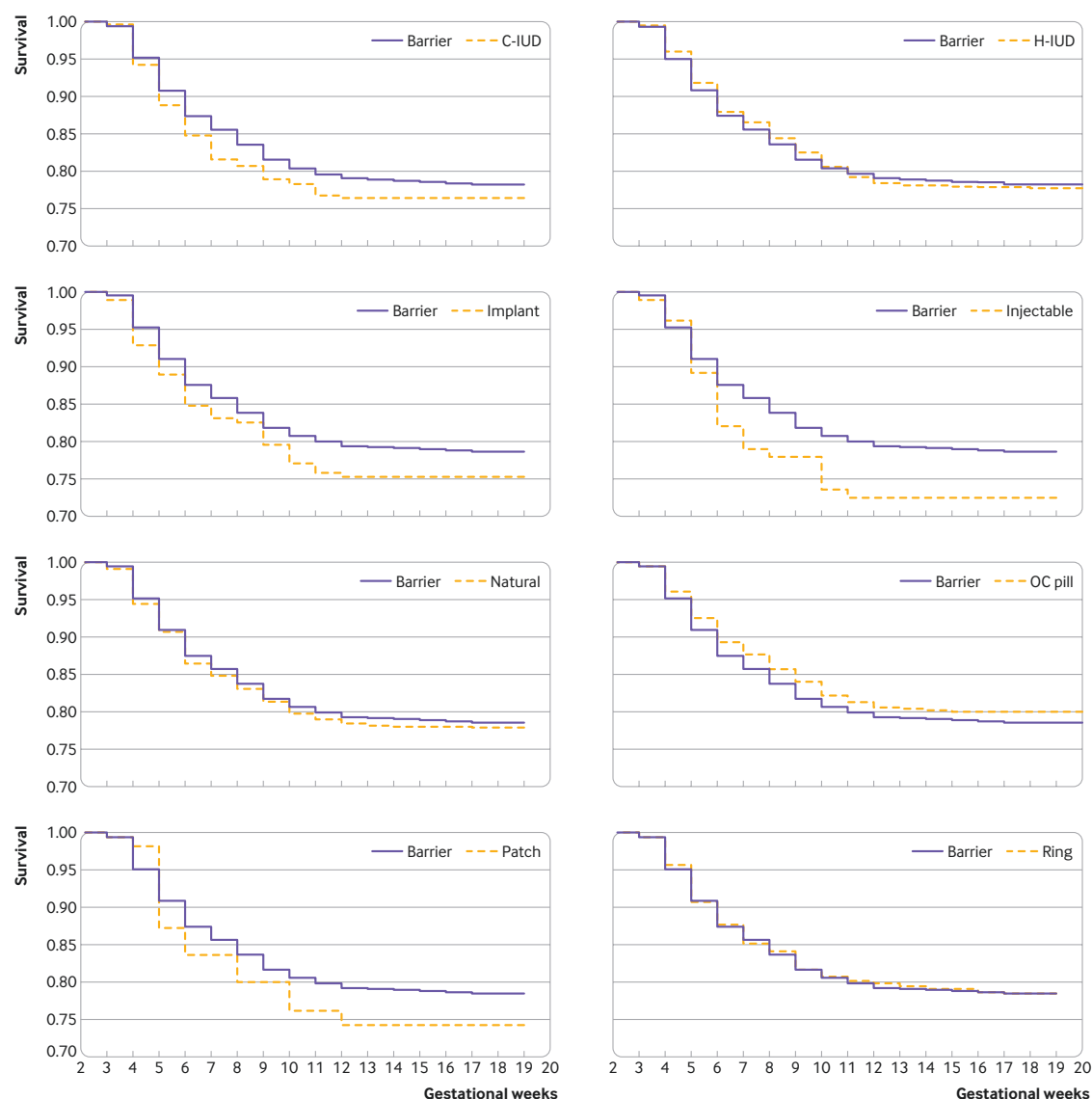


Figure 1 | Age adjusted survival curves for miscarriage stratified by most recent contraceptive method. C-IUD=copper intrauterine device; H-IUD=hormonal intrauterine device; OC=oral contraceptive. Survival curves were adjusted for maternal age at conception

pregnancy (n=72), loss to follow-up (n=1043), or 20 weeks' gestation (n=5714). Participants lost to follow-up were censored at a median of 10 gestational weeks (interquartile range 6-14 weeks).

Among the 13 460 eligible participants, 8899 conceived during the study period. More than 95% (6597 of 6935 participants with data on this variable) of participants used a home pregnancy test to confirm their pregnancy. Among those who conceived, 24% (2166/8899) reported recent use of barrier methods, 28% (2506/8899) used oral contraceptives, 14% (1284/8899) used hormonal intrauterine device, 4% (353/8899) used copper intrauterine device, 4% (349/8899) used a ring, 2% (196/8899) used an implant, 1% (61/8899) used a patch, 1% (112/8899) used injectable contraceptives, and 21% (1872/8899) used natural methods (table 1, online supplemental table S1). Users of

natural and barrier methods had the lowest body mass index on average, whereas users of implant and injectable contraceptives had the highest body mass index. Hormonal intrauterine device users had substantially higher household income and educational attainment than injectable users on average. Participants who used implants and injectables were more likely to report current smoking than users of other methods; they were also more likely to be parous. Users of injectable contraceptives had the longest time to pregnancy, were more likely to have used fertility treatment to conceive the pregnancy reported in the study, and were more likely to have diagnoses of endometriosis, uterine leiomyomata, polycystic ovarian syndrome, or sexually transmitted infections.

Risk of miscarriage ranged from 19% among participants who used oral contraceptives to 24% among

Table 2 | Most recent method of contraception and rate of miscarriage with inverse probability weighting for pregnancy

Contraceptive method	No. of individuals	No. of gestational weeks contributed	No. of miscarriages (%)	Age adjusted IRR (95% CI)	Primary adjusted IRR (95% CI)	Fully adjusted IRR (95% CI)
Barrier	2166	27 969	452 (20.9)	Reference	Reference	Reference
Oral contraceptive	2506	32 802	482 (19.2)	0.93 (0.82 to 1.06)	0.91 (0.80 to 1.04)	0.92 (0.80 to 1.04)
Hormonal IUD	1284	16 342	273 (21.3)	1.00 (0.86 to 1.16)	0.98 (0.84 to 1.14)	1.02 (0.88 to 1.19)
Copper IUD	353	4233	82 (23.2)	1.14 (0.90 to 1.43)	1.13 (0.90 to 1.43)	1.14 (0.91 to 1.44)
Ring	349	4434	72 (20.6)	0.94 (0.73 to 1.21)	0.90 (0.70 to 1.16)	0.89 (0.69 to 1.15)
Implant	196	2434	43 (21.9)	1.18 (0.87 to 1.62)	1.11 (0.81 to 1.53)	1.12 (0.81 to 1.54)
Patch	61	759	14 (23.0)	1.36 (0.83 to 2.24)	1.38 (0.84 to 2.28)	1.34 (0.81 to 2.21)
Injectable	112	1243	27 (24.1)	1.51 (1.04 to 2.18)	1.40 (0.96 to 2.05)	1.44 (0.99 to 2.12)
Natural	1872	23 201	396 (21.2)	1.04 (0.91 to 1.19)	1.03 (0.90 to 1.18)	1.01 (0.89 to 1.16)

CI=confidence interval; IRR=incidence rate ratio; IUD=intrauterine device.
Age adjusted model adjusted for maternal age at conception (years).
Primary adjusted model adjusted for maternal age at conception; body mass index; race/ethnicity; geographical region of residence; educational attainment; employment status; hours per week of work; current smoking; use of multivitamins and folate supplements; sleep duration; private health insurance; number of primary care visits in the past year; 10 item Perceived Stress Scale score; Major Depression Inventory score; and ever diagnosed with diabetes.
Fully adjusted model additionally adjusted for time to pregnancy; parity; menstrual cycle length; irregular menstrual cycles; history of sexually transmitted infection; ever diagnosed with endometriosis; ever diagnosed with polycystic ovarian syndrome; ever diagnosed with uterine leiomyoma; history of miscarriage; history of subfertility or infertility; use of fertility treatment in conceiving the study pregnancy; and total lifetime duration of hormonal contraceptive use.

participants who used injectable contraceptives (online supplemental table S2). Based on age adjusted survival curves, recent users of injectables and the patch had the highest rates of miscarriage (figure 1). In the unweighted models (online supplemental table S2), little evidence suggested confounding: estimates were similar for models adjusted for age only, for all non-reproductive characteristics, and for all non-reproductive and reproductive characteristics. We compared the Akaike's information criterion statistic across models and found that the Akaike's information criterion decreased with each successive model, indicating improved fit for the fully adjusted model compared with more parsimonious models. In the fully adjusted models, the most recently used method and miscarriage did not show an association for oral contraceptives (incidence rate ratio 0.94 (95% confidence interval 0.82 to 1.07)), hormonal intrauterine devices (1.02 (0.87 to 1.19)), copper intrauterine devices (1.10 (0.87 to 1.40)), rings (0.98 (0.77 to 1.27)), implants (1.13 (0.83 to 1.56)), or natural methods (1.02 (0.89 to 1.17)) compared with barrier methods. The incidence rate ratio for use of patch contraceptives compared with barrier methods was 1.23 (0.72 to 2.10). The corresponding incidence rate ratio for use of injectables was 1.40 (0.94 to 2.09).

Results were similar or slightly stronger when we accounted for selection bias due to conditioning on pregnancy (table 2; online supplemental figure S4). The fully adjusted incidence rate ratio for use of patch contraceptives compared with barrier methods was 1.34 (95% confidence interval 0.81 to 2.21). The corresponding incidence rate ratio for injectable contraceptives was 1.44 (0.99 to 2.12).

All stratified analyses were weighted to account for selection bias due to conditioning on pregnancy. When we stratified by age (<30 v ≥30 years),

associations were consistent across groups for hormonal intrauterine devices, rings, patches, injectables, and natural methods (table 3). Associations differed across age groups for oral contraceptives, copper intrauterine devices, and implants: recent use of copper intrauterine devices and implants was associated with an increased rate of miscarriage among older participants but not among younger participants; and recent use of oral contraceptives was associated with a reduced rate of miscarriage among older participants but not among younger participants. When we stratified by body mass index (<30 v ≥30), associations for use of patch and injectable contraceptives were consistent across groups. Among participants who were overweight (body mass index ≥30), use of ring contraceptives was associated with a reduced rate of miscarriage. When we stratified by gestational week at risk (<8 v ≥8 weeks), substantial differences across gestational timing were noted, but these differences were inconsistent across contraceptive methods.

Sensitivity analyses

In unadjusted analyses of the most recent contraceptive method, participants who used oral contraceptives had a slightly lower rate of miscarriage if they conceived three months or earlier after discontinuing contraception relative to conceiving more than three months after discontinuing contraception (online supplemental table S3). However, age adjusted restricted cubic splines were consistent with no effect of recent discontinuation of oral contraceptives use on miscarriage (figure 2). The splines for hormonal intrauterine device use were similarly consistent with no effect. When we evaluated time since discontinuation for other methods, the stratum specific numbers (at months 0-3, 4-6, 7-12, >12) were small and no consistent trend was noted.

Table 3 | Most recent method of contraception and miscarriage, stratified analyses

Method	Comparator 1				Comparator 2			
	No of individuals	No of GW	No of miscarriages (%)	Adjusted IRR (95% CI)*	No of individuals	No of GW	No of miscarriages (%)	Adjusted IRR (95% CI)*
Age <30 years (n=3936) v age ≥30 years (n=4963)								
Barrier	900	11 972	155 (17.2)	Reference	1266	15 997	297 (23.5)	Reference
Oral contraceptive	1203	15 955	212 (17.6)	1.02 (0.82 to 1.27)	1303	16 848	270 (20.7)	0.84 (0.71 to 0.99)
Hormonal IUD	506	6477	93 (18.4)	1.10 (0.85 to 1.44)	778	9866	180 (23.1)	0.98 (0.81 to 1.19)
Copper IUD	122	1576	18 (14.8)	0.83 (0.50 to 1.37)	231	2658	64 (27.7)	1.25 (0.96 to 1.62)
Ring	152	1975	29 (19.1)	1.00 (0.65 to 1.51)	197	2459	43 (21.8)	0.86 (0.62 to 1.19)
Implant	120	1577	21 (17.5)	0.97 (0.61 to 1.56)	76	857	22 (29.0)	1.29 (0.83 to 2.00)
Patch	39	500	7 (18.0)	1.36 (0.70 to 2.63)	22	259	7 (31.8)	1.35 (0.60 to 3.00)
Injectable	75	834	16 (21.3)	1.44 (0.83 to 2.51)	37	410	11 (29.7)	1.49 (0.85 to 2.61)
Natural	819	10 488	150 (18.3)	1.12 (0.89 to 1.41)	1053	12 713	246 (23.4)	0.97 (0.82 to 1.15)
BMI <30 (n=6712) v BMI ≥30 (n=2187)								
Barrier	1658	21 748	326 (19.7)	Reference	508	6222	126 (24.8)	Reference
Oral contraceptive	1886	24 931	355 (18.8)	0.99 (0.84 to 1.16)	620	7872	127 (20.5)	0.80 (0.63 to 1.00)
Hormonal IUD	924	11 954	192 (20.8)	1.07 (0.88 to 1.29)	360	4389	81 (22.5)	0.97 (0.74 to 1.28)
Copper IUD	267	3216	62 (23.2)	1.19 (0.90 to 1.57)	86	1017	20 (23.3)	1.11 (0.73 to 1.69)
Ring	258	3300	55 (21.3)	1.08 (0.80 to 1.45)	91	1134	17 (18.7)	0.64 (0.39 to 1.05)
Implant	134	1709	28 (20.9)	1.17 (0.78 to 1.76)	62	725	15 (24.2)	1.06 (0.63 to 1.79)
Patch	44	565	9 (20.5)	1.32 (0.65 to 2.65)	17	194	5 (29.4)	1.31 (0.62 to 2.77)
Injectable	67	771	15 (22.4)	1.47 (0.83 to 2.60)	45	473	12 (26.7)	1.42 (0.83 to 2.45)
Natural	1474	18 374	307 (20.8)	1.09 (0.93 to 1.28)	398	4827	89 (22.4)	0.87 (0.67 to 1.12)
<8 gestational weeks (n=8877) v ≥8 gestational weeks (n=7192)								
Barrier	2164	8066	306 (14.1)	Reference	1755	19 903	146 (8.3)	Reference
Oral contraceptive	2499	9291	301 (12.0)	0.87 (0.73 to 1.02)	2084	23 512	181 (8.7)	1.02 (0.81 to 1.29)
Hormonal IUD	1282	4882	169 (13.2)	0.96 (0.79 to 1.17)	1044	11 460	104 (10.0)	1.15 (0.88 to 1.50)
Copper IUD	353	1283	65 (18.4)	1.33 (1.02 to 1.73)	263	2950	17 (6.5)	0.73 (0.44 to 1.20)
Ring	348	1304	51 (14.7)	0.92 (0.68 to 1.26)	281	3130	21 (7.5)	0.85 (0.53 to 1.36)
Implant	195	721	30 (15.4)	1.15 (0.79 to 1.69)	155	1714	13 (8.4)	1.06 (0.59 to 1.92)
Patch	61	230	9 (14.8)	0.95 (0.47 to 1.92)	50	529	5 (10.0)	2.28 (1.11 to 4.69)
Injectable	112	382	21 (18.8)	1.68 (1.06 to 2.66)	83	862	6 (7.2)	0.88 (0.34 to 2.26)
Natural	1863	6869	278 (14.9)	1.08 (0.91 to 1.27)	1477	16 332	118 (8.0)	0.89 (0.69 to 1.14)

BMI=body mass index; CI=confidence interval; GW=gestational weeks; IRR=incidence rate ratio; IUD=intrauterine device.

*Models were fully adjusted. That is, all models were adjusted for maternal age at conception; body mass index; race/ethnicity; geographical region of residence; educational attainment; employment status; hours per week of work; current smoking; use of multivitamins and folate supplements; sleep duration; private health insurance; no of primary care visits in the past year; daily to item perceived stress scale score; major depression inventory score; ever diagnosed with diabetes; time to pregnancy; parity; menstrual cycle length; irregular menstrual cycles; history of sexually transmitted infection; ever diagnosed with endometriosis; ever diagnosed with polycystic ovarian syndrome; ever diagnosed with uterine leiomyoma; history of miscarriage; history of subfertility or infertility; use of fertility treatment in conceiving the study pregnancy; and total lifetime duration of hormonal contraceptive use.

When we considered total contraceptive history in the 8899 participants, we identified 6212 participants who had ever used oral contraceptives (70%), 2032 who had used a hormonal intrauterine device

(23%), 1625 who had used ring contraceptives (18%), 472 who had used implant contraceptives (5%), 545 who had used patch contraceptives (6%), and 948 who had used injectable contraceptives

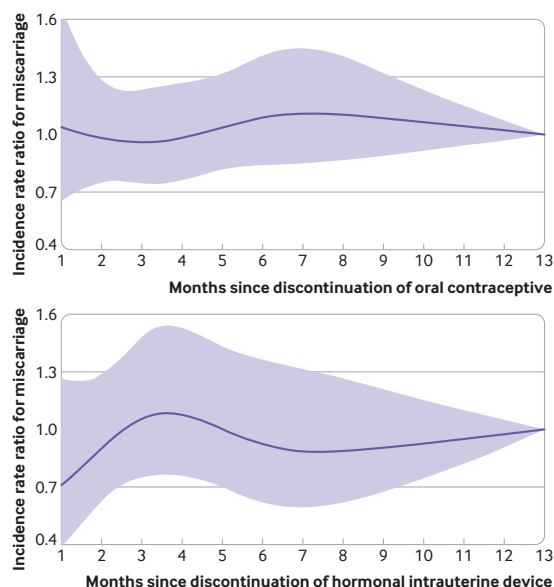


Figure 2 | Restricted cubic spline for associations of months since discontinuing oral contraceptives or a hormonal intrauterine device with miscarriage incidence. These figures relied on data for the most recently used method. Splines were adjusted for maternal age at conception (years) and were modelled with knots at months 1, 3, 6, and 9. Months since discontinuing was calculated as (conception date – discontinuation date)/30

(11%). Results were imprecise when we estimated incidence rate ratios for miscarriage comparing individuals who discontinued 0-6 months or 7-12 months before conception with participants who discontinued >12 months before conception for each method (using total contraceptive history) (figure 3). Individuals who discontinued injectable, patch, or implant contraceptives zero to six months before conception had a higher rate of miscarriage compared with those who discontinued more than 12 months before conception. However, the findings indicated that any potential increased rate of miscarriage

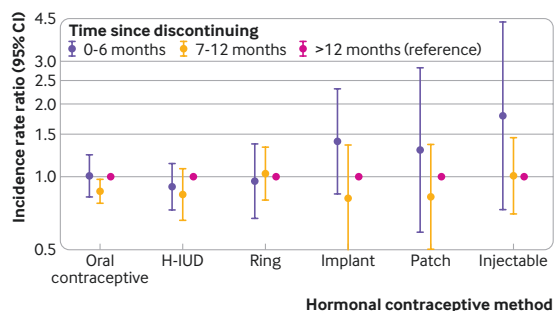


Figure 3 | Time since discontinuation of each hormonal contraceptive and miscarriage, based on total contraceptive history. IRR=incidence rate ratio; OC=oral contraceptive; H-IUD=hormonal IUD. This figure relied on data for total contraceptive history, regardless of most recent method. Models were adjusted for maternal age at conception

following use of these contraceptives did not persist longer than six months after discontinuation.

Discussion

Principal findings

In this prospective study of nearly 9000 individuals, most contraceptives had little effect on the rate of miscarriage. Recent use of patch and injectable contraceptives was associated with a slightly higher rate of miscarriage, although these results were based on small numbers of individuals. Many behavioural and sociodemographical differences were reported across users of different contraceptives, yet, results were consistent across models adjusted for confounders.

Comparison with other studies

Hormonal contraception can be divided into progestin-only methods (implant, injectable, and some oral contraceptives (known as the minipill) and combined methods, which contain both progestin and a synthetic estrogen (vaginal ring, transdermal patch, and combined oral contraceptives) (online supplemental table S4). Continuous administration of progestins in hormonal contraceptives prevents normal fluctuations in steroid hormones and blocks the proliferative effects of oestrogen. Progestins prevent pregnancy by suppressing ovulation, thickening cervical mucus, and causing the endometrium to become atrophic. The addition of estrogen in combined contraceptives provides stability to the endometrium to prevent breakthrough bleeding and increases the potency of the progestin component.

Use of certain hormonal contraception is associated with transient delays in return to fertility,²⁸ which suggests effects on endogenous hormonal rhythms and that the endometrial milieu persists after discontinuation. The longest delays in return to fertility have been observed for injectable contraceptives.²⁸ Injectables contain substantially higher dosages of progestin compared with other types of hormonal contraception³⁴ and thus cause large reductions in endogenous concentrations of estradiol and progesterone.^{35 36} In addition to these effects, the progestin component of injectable contraceptives (medroxyprogesterone acetate) has strong immunological effects³⁷ that could impact the establishment of pregnancy.

We observed a possible association with miscarriage for recent users of injectable and patch contraceptives relative to barrier methods, but no consistent association for copper or hormonal intrauterine devices, oral contraceptives, the ring, or the implant. Although injectables have a plausible mechanism for this effect, why the use of patch contraceptives, but not other combined hormonal contraceptives, would increase miscarriage risk is not clear. Differences in the risk of miscarriage across various contraceptives could

be due to the generation and androgenicity of the progestin component.^{38 39} However, our data were insufficient to evaluate the role of different progestins. Our findings could also be explained by chance; the two methods for which we observed an increased rate of miscarriage (injectable and patch) were also the two methods with the smallest amount of data. Additionally, the associations for injectable and patch contraceptives may have been most susceptible to residual confounding because the baseline characteristics of uses showed that participants who used injectables and patches tended to differ more from those of barrier methods or of other hormonal methods.

In stratified analyses, use of patch and injectable contraceptives was associated with an increased rate of miscarriage regardless of age or body mass index. Use of oral contraceptives and ring contraceptives was associated with a reduced rate of miscarriage among participants with a body mass index of ≥ 30 . The explanation for this is unclear. When we stratified by gestational timing of miscarriage, recent use of the copper intrauterine device was associated with an increased risk of early miscarriage (< 8 weeks). A potential explanation is that the inflammatory state induced by copper intrauterine devices persists after removal and selectively affects early miscarriages.^{40 41} Of note, use of patch contraceptives was related to later miscarriages only, whereas use of injectable contraceptives was related with early miscarriages only, although, these findings were based on small numbers.

Limitations

Limitations of this study include possible residual confounding. Individuals with a history of reproductive health problems may be advised to use specific contraceptives over others based on treatment guidelines. Although we adjusted for a range of reproductive factors, misclassification of these covariates or other reproductive factors that were unmeasured is possible. Bias could also arise if the frequency and timing of pregnancy testing were related to cycle regularity, which is related to contraceptive use. However, results were similar before and after adjusting for cycle regularity. Additionally, the timing of pregnancy testing was similar between participants with and without irregular cycles. Furthermore, measurement error in the timing of miscarriage is possible. In a validation study of PRESTO participants who had delivered singletons, gestational age calculated using the clinician provided due date and participant reported gestational age had greater accuracy than that calculated using last menstrual period when compared with birth certificate data.⁴² We relied on the date of the last

menstrual period to calculate gestational age for 21% of miscarriages. Lastly, our findings may not be generalizable to all couples at risk for pregnancy. PRESTO participants were actively trying to conceive, were recruited mainly via social media and health related websites, and all participation was online. As such, PRESTO participants report higher socioeconomic position on average compared with the general population. They may also have more health seeking behaviors given that they enrolled in a research study. However, we expect that the biological mechanisms of action for various contraceptives to be largely consistent among those who participated and those who did not.

Conclusions

This epidemiological study investigated the effects of preconception use of non-oral contraceptives on future miscarriage. Our findings indicate that recent use of oral contraceptives, intrauterine devices, the ring, and implant contraceptives has little to no effect on miscarriage. Findings for use of patch and injectable contraceptives were uncertain but may indicate a positive association with miscarriage, relative to barrier methods. Given the degree of imprecision of these findings, the results should be viewed as tentative.

Contributors JJY was responsible for formulation of the study hypotheses and study design, statistical analyses, results interpretation, manuscript writing, revision, and finalization. AKW, EEH, KJR, and LAW were responsible for study design, development, and implementation of the study cohort. All authors were responsible for providing input on analytic methods, interpretation of results, and manuscript writing revision. LAW is the guarantor and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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