

Prior hormonal contraceptive use and preeclampsia in Angola: a hospital- based, individually matched case-control study

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Research Article

Keywords: Preeclampsia, hormonal contraception, medroxyprogesterone acetate, Angola, case-control studies

Posted Date: October 20th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11411535/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background: Evidence on whether prior hormonal contraceptive use is associated with preeclampsia is sparse and inconsistent, particularly for progestogen-only injectables, and no data exist from Angola. We aimed to estimate this association overall and by method, duration and time since discontinuation.

Methods: In this hospital-based case–control study with incidence-density sampling at Hospital Geral de Benguela, Angola, incident cases of preeclampsia (2021 International Society for the Study of Hypertension in Pregnancy criteria with confirmed proteinuria, adjudicated blind to exposure) were each matched to two randomly sampled controls on age, parity group, gestational age and calendar time. The primary exposure was any hormonal contraceptive use before the index pregnancy, obtained by structured calendar interview and verified against records; secondary exposures were method, cumulative duration and time since discontinuation. The primary outcome was preeclampsia; secondary outcomes were early-onset, late-onset and severe preeclampsia. Conditional logistic regression was adjusted for confounders prespecified with a causal diagram.

Results: Between January and June 2026, we enrolled 165 cases and 330 controls. Prior hormonal contraceptive use was reported by 54 (32.7%) cases and 62 (18.8%) controls (adjusted odds ratio [aOR] 2.19, 95% CI 1.35–3.57; $p = 0.0016$). Compared with never use, the aOR was 3.03 (95% CI 1.59–5.78) for depot medroxyprogesterone acetate, which did not differ clearly from other hormonal methods (aOR 1.85, 95% CI 0.83–4.13), and 3.12 (95% CI 1.50–6.50) for discontinuation less than three months before conception; among users, cumulative duration was not associated with preeclampsia. The association was attenuated with documented exposure only (aOR 1.84, 95% CI 0.99–3.44), in a post hoc analysis excluding referred cases (aOR 1.58, 95% CI 0.87–2.86) and against users of non-hormonal methods only (aOR 1.68, 95% CI 0.73–4.11).

Conclusions: Prior hormonal contraceptive use was associated with higher odds of preeclampsia, but referral, selection, information or indication bias may explain part of this association, and there was no clear evidence that depot medroxyprogesterone acetate differed from other hormonal methods. These findings do not justify changes to contraceptive counseling and require prospective confirmation.

Background

Hypertensive disorders of pregnancy account for about one in seven maternal deaths worldwide, and preeclampsia is the most serious of them [1]. Preeclampsia also causes fetal growth restriction, iatrogenic preterm birth and stillbirth, and its burden is greatest in low- and middle-income countries, where diagnosis is often late and access to timely delivery is limited [2]. Hypertensive disorders of pregnancy are common across Africa [3], yet most evidence on their risk factors comes from high-income settings.

Established risk factors, including previous preeclampsia, chronic hypertension, pregestational diabetes, high body mass index (BMI), nulliparity and a family history of preeclampsia, are largely fixed by the time

of conception [4]. Exposures before conception that alter vascular, metabolic or immune function could also influence placentation and maternal endothelial function [2].

Hormonal contraception is one such exposure. Combined oral contraceptives increase blood pressure, partly through activation of the renin–angiotensin–aldosterone system [5], and progestogen-only methods, in particular depot medroxyprogesterone acetate (DMPA), have been associated with changes in weight and lipid profile [6, 7]. Whether such effects persist after discontinuation and influence the risk of preeclampsia in a later pregnancy is unknown. Studies of prior contraceptive use and preeclampsia are few, were conducted in high-income countries and examined mainly oral contraceptives [8–10]. A 2024 meta-analysis of three studies of contraceptive use of any type found no association (pooled estimate about 6% lower, 95% confidence interval [CI] 0.82–1.13) [11], whereas a Dutch prospective cohort reported a higher risk of late-onset preeclampsia after periconceptional oral contraceptive use (adjusted risk ratio 1.38, 95% CI 0.99–1.93), most marked when use stopped within three months before conception [10]. An immunological hypothesis has also implicated barrier methods, which limit exposure to paternal antigens before conception [8, 12].

Evidence on progestogen-only injectables, which dominate the method mix in many sub-Saharan African countries, is almost absent. In Angola, use of modern contraception is low, injectables and oral pills are among the most used methods [13], and no data exist on contraceptive history and preeclampsia. We aimed to estimate the association between prior hormonal contraceptive use and incident preeclampsia among women attending Hospital Geral de Benguela, overall and by method, cumulative duration, time since discontinuation and preeclampsia subtype.

Methods

Study design and setting

We conducted a hospital-based case–control study with individual 1:2 matching and incidence-density (risk-set) sampling of controls at Hospital Geral de Benguela (HGB), the referral hospital of Benguela province, Angola. Participants were recruited between January and June 2026. A pilot study of 11 cases and 19 controls, not included in the analysis, was used to test the procedures. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [14]; the completed STROBE checklist is provided in Additional file 1. Full methodological details are given in Additional file 2, Appendix S1.

Participants

The source population comprised pregnant women resident in Benguela province for at least 12 months who attended HGB for antenatal care, emergency care or delivery. Eligible women were aged 16–49 years and had completed at least 20 weeks of gestation. We excluded women with chronic hypertension,

pregestational diabetes, chronic kidney disease, systemic autoimmune disease, multiple pregnancy or pregnancy after assisted reproduction.

Cases were all eligible women with an incident diagnosis of preeclampsia at HGB during the recruitment period, enrolled consecutively. Women with suspected preeclampsia are triaged directly to the obstetric emergency department or the maternity ward, so cases were identified in these services rather than at the antenatal clinic. Preeclampsia was defined by the 2021 criteria of the International Society for the Study of Hypertension in Pregnancy [15]: new-onset hypertension after 20 weeks ($\geq 140/90$ mmHg on two occasions at least four hours apart) with proteinuria (urine protein/creatinine ratio ≥ 30 mg/mmol or, when unavailable, dipstick $\geq 2+$ confirmed on a second sample). The definition adopted in the protocol also allows a diagnosis based on maternal organ or uteroplacental dysfunction without proteinuria; however, on the advice of the study's specialist obstetrician and to reduce outcome misclassification, only women with confirmed proteinuria (the standard investigation at HGB for pregnant women with signs of preeclampsia) were enrolled as cases (Additional file 2: Table S1). Two obstetricians, blinded to exposure, independently adjudicated each case from an anonymized record extract abstracted before the exposure interview; a third resolved disagreements. The primary outcome was incident preeclampsia; secondary outcomes were its subtypes, classified as early (< 34 weeks) or late onset, and with or without severe features.

For each case, the date of diagnosis was the index date. A field coordinator who did not conduct interviews kept a time-stamped daily list of all eligible women attending antenatal care, the obstetric emergency department or the maternity ward. Candidate controls were women on this list within seven days of the index date, within three years of the case's age, in the same parity group (0, 1–2 or ≥ 3 previous births) and within two weeks of the case's gestational age, who were normotensive and free of preeclampsia and proteinuria at the index date; women with gestational hypertension were therefore not eligible as controls. Candidates were randomly ordered with a seeded script by a person without access to exposure data, and the first two were approached; replacements and any prespecified relaxation of matching criteria were logged. Under incidence-density sampling, a control who later developed preeclampsia remained a control in her original set and was also enrolled as a case; the odds ratio (OR) therefore estimates the incidence rate ratio [16, 17]. Controls were followed until six weeks postpartum.

Exposure

Five trained midwives or nurses, independent of the investigators and unaware of the directional hypothesis, interviewed participants in private with an identical structured electronic questionnaire: cases within 72 hours of diagnosis and controls at enrollment. A contraceptive calendar from first intercourse to the last menstrual period (LMP), anchored on life events and supported by photographs of locally available methods, was used. Reported use was checked against family planning cards and registers and classified as documented or self-reported only.

The primary exposure was any use of hormonal contraception for at least one month before the LMP of the index pregnancy, compared with never use; emergency contraception was not counted. Secondary exposures were the predominant method (longest cumulative use), cumulative duration (< 12, 12–59 and ≥ 60 months, and per 12 months) and the interval from the end of contraceptive coverage (for DMPA, last injection plus 13 weeks; for implants, removal) to conception (LMP plus 14 days), categorized as conception during coverage, 0 to < 3, 3 to < 12 and ≥ 12 months. Use of non-hormonal methods only served as an active comparator, and ever condom use as a negative-control exposure [18].

Covariates

The adjustment set was defined in advance with a directed acyclic graph included in the protocol (Additional file 2: Figure S1). The primary model (Model 1) included pre-pregnancy BMI, first-degree family history of preeclampsia or hypertension, previous preeclampsia, education, urban or rural residence and smoking in the year before pregnancy, plus age and parity as continuous terms to remove residual confounding within matching strata. Pre-pregnancy weight was taken from the first antenatal visit when this occurred at or before 14 weeks, and was otherwise self-reported; height was measured. Variables that may be affected by the exposure or the outcome (BMI during pregnancy, lipids, fetal growth, gestational age at delivery) were not used for adjustment. Gestational age was assigned by a prespecified hierarchy (first-trimester ultrasound, LMP confirmed by ultrasound, second-trimester ultrasound, LMP alone), and blood pressure was measured with an oscillometric device validated in pregnancy (Omron M3 Comfort, HEM-7134-E; Omron Healthcare, Kyoto, Japan) following standard recommendations [19].

Statistical analyses

Assuming a 20% prevalence of prior hormonal contraceptive use among controls, two controls per case, a two-sided α of 0.05 and 80% power to detect an OR of 2.0 with the conditional method for matched studies [20], 128 cases were required; after inflation by 15% for adjustment and 10% for incomplete data, the target was 165 cases and 330 controls. In the prespecified blinded re-estimation after the first 100 controls, the prevalence of prior hormonal contraceptive use was 18%, within the prespecified range of 15%–30%, so the target was not changed.

Analyses followed the prespecified statistical analysis plan and were independently reproduced by a statistician who was not involved in data collection. Cases and controls were compared with absolute standardized mean differences rather than tests that ignore matching [21]. The primary analysis used conditional logistic regression stratified by matched set to estimate crude and adjusted ORs with Wald 95% CIs; pre-pregnancy BMI was modeled with a three-knot restricted cubic spline [22]. Model 1 had 12 parameters for 165 matched sets (13.8 events per parameter) [23], so we also fitted it with Firth's penalized conditional likelihood, which was prespecified for models with separation; for Firth estimates, 95% CIs and p values were obtained from the profile penalized likelihood [24, 25], and Wald intervals are

shown for comparison in Additional file 2: Table S2. We examined collinearity (variance inflation factors) and influence (leave-one-out deletion).

Prespecified exploratory analyses estimated ORs by method (and DMPA vs other hormonal methods), by duration (categories, per 12 months with never users coded 0, and a restricted cubic spline), by interval since discontinuation and by preeclampsia subtype (each subtype with its own matched controls); ORs for hormonal users against users of non-hormonal methods only and for the negative-control exposure; and effect modification by pre-pregnancy BMI (< 25 vs ≥ 25 kg/m²). A post hoc model added an ever-use indicator to duration per 12 months, to separate a dose–response among users from the ever–never contrast.

Prespecified sensitivity analyses excluded women with hormonal exposure after the LMP; restricted exposure to documented use; retained only antenatal-clinic controls; excluded sets with relaxed matching; excluded minors and the sets of referred cases; excluded women with a recorded cardiovascular contraindication; added physical activity, interpregnancy interval and HIV infection (extended model, with complete cases and with multiple imputation); and used unconditional logistic regression. A prespecified analysis excluding influential observations (those changing the OR by more than 10%) was identical to the primary analysis, because no observation met this criterion. Post hoc, we excluded the sets of referred cases and minors separately. A prespecified analysis using BMI measured at enrollment was not performed (Additional file 2: Table S1). No Model 1 covariate was missing; for the extended model (13 sets with missing data, 7.9%) we used multiple imputation by chained equations with 20 imputations and Rubin's rules [26].

Quantitative bias analysis comprised E-values [27] and a record-level probabilistic bias analysis for exposure misclassification [28], with sensitivity and specificity drawn from beta distributions informed by a validation substudy in which self-report was compared with records in a random sample of participants (planned as 10%; 55 participants, 11.1%), with Wilson 95% CIs, under non-differential and differential scenarios and a fixed worst case (better recall in cases). Selection bias was explored with bias factors of 0.8–1.5 (Additional file 2: Table S3).

Women with gestational hypertension without preeclampsia at the index date belonged to the risk set but were not eligible as controls and were not interviewed. In a post hoc deterministic bias analysis, we assumed that they made up 5%–20% of the risk set and that 18.8% (the prevalence among enrolled controls) to 50% of them had used hormonal contraception, calculated the exposure prevalence expected in a control group sampled from the full risk set, and divided the adjusted OR and its confidence limits by the resulting bias factor (Additional file 2: Table S4). We also calculated the prevalence of use among these women at which the lower confidence limit would reach 1.

The single primary hypothesis was confirmatory and was tested at a two-sided α of 0.05; all other analyses were exploratory, were not adjusted for multiplicity and are interpreted by effect sizes and CIs. Analyses used Python 3.13 (Python Software Foundation, Wilmington, DE, USA) with NumPy, SciPy and

statsmodels 0.15; the conditional likelihood, including Firth's penalty, was implemented directly and verified against statsmodels (maximum absolute coefficient difference < 0.001).

Use of artificial intelligence

The authors used Claude Opus 5.5 (Anthropic, San Francisco, CA, USA) to translate the manuscript from Portuguese into English. The translation was reviewed by a professional translator, and the authors checked the final text and take full responsibility for its content. No artificial intelligence tool was used to collect, analyze or interpret the data.

Results

Between January and June 2026, of 213 women with preeclampsia screened, 30 were ineligible (17 with chronic hypertension and 13 with other exclusion criteria), 11 declined (participation 94.0% of eligible cases) and seven were not confirmed at adjudication, leaving 165 cases. To enroll 330 controls, 467 randomly ordered candidates were identified; 58 were ineligible on approach and 79 declined (participation 80.7% of eligible candidates) (Fig. 1). All matched sets contained one case and two controls; six sets (3.6%) required relaxation of matching criteria. Five women sampled as controls later developed preeclampsia and were also enrolled as cases, so the 495 participants corresponded to 490 women; 17 controls (5.2%) were lost before the six-week postpartum contact. Most controls (262, 79.4%) were recruited at the antenatal clinic, whereas all cases were recruited at the obstetric emergency department (86, 52.1%) or the maternity ward (79, 47.9%). Of the cases, 60 (36.4%) had early-onset preeclampsia and 94 (57.0%) had severe features, including 13 with eclampsia and 12 with HELLP syndrome; proteinuria was confirmed by protein/creatinine ratio in 69 (41.8%) and by repeated dipstick in 96 (58.2%). Only 60 participants (12.1%) had pregnancies dated by first-trimester ultrasound; dating methods were distributed similarly in cases and controls (Additional file 2: Table S5).

Cases and controls were balanced on the matching variables (Table 1). Cases had a higher pre-pregnancy BMI (mean 26.1 vs 24.8 kg/m²) and more often reported a family history of preeclampsia or hypertension (26.1% vs 15.5%) or previous preeclampsia (9.1% vs 3.0%), and they were much more often referred from another facility (30.9% vs 4.8%). No Model 1 covariate had missing data.

Table 1
Characteristics of cases with preeclampsia and matched controls

Characteristic	Cases (n = 165)	Controls (n = 330)	SMD
Matching variables			
Age, years, mean (SD)	28.2 (5.5)	28.2 (5.6)	0.00
Parity group, n (%)			0.00
Nulliparous	49 (29.7)	98 (29.7)	
1–2 previous births	52 (31.5)	104 (31.5)	
≥3 previous births	64 (38.8)	128 (38.8)	
Gestational age at index date, weeks, mean (SD)	34.9 (2.6)	35.0 (2.7)	0.03
Sociodemographic characteristics			
Education, n (%)			0.19
None	22 (13.3)	45 (13.6)	
Primary	49 (29.7)	114 (34.5)	
Secondary	68 (41.2)	139 (42.1)	
Higher	26 (15.8)	32 (9.7)	
Area of residence, n (%)			0.17
Urban	121 (73.3)	217 (65.8)	
Rural	44 (26.7)	113 (34.2)	
Household asset index, quintile, n (%)			0.20
Q1 (poorest)	32 (19.4)	67 (20.3)	
Q2	25 (15.2)	72 (21.8)	
Q3	33 (20.0)	52 (15.8)	
Q4	39 (23.6)	72 (21.8)	
Q5 (wealthiest)	34 (20.6)	60 (18.2)	
Missing	2 (1.2)	7 (2.1)	
Age < 18 years, n (%)	6 (3.6)	14 (4.2)	0.03
Clinical and behavioral characteristics			
Pre-pregnancy BMI, kg/m ² , mean (SD)	26.1 (3.9)	24.8 (3.5)	0.35

Characteristic	Cases (n = 165)	Controls (n = 330)	SMD
Matching variables			
Pre-pregnancy BMI category, n (%)			0.38
<18.5 kg/m ²	7 (4.2)	16 (4.8)	
18.5–24.9 kg/m ²	52 (31.5)	148 (44.8)	
25.0–29.9 kg/m ²	78 (47.3)	144 (43.6)	
≥30.0 kg/m ²	28 (17.0)	22 (6.7)	
Family history of preeclampsia or hypertension ^a , n (%)	43 (26.1)	51 (15.5)	0.26
Preeclampsia in a previous pregnancy, n (%)	15 (9.1)	10 (3.0)	0.26
Smoking in year before pregnancy, n (%)	7 (4.2)	16 (4.8)	0.03
Alcohol use in year before pregnancy, n (%)	25 (15.2)	49 (14.8)	0.01
Physical activity (IPAQ), n (%)			0.02
Low	53 (32.1)	109 (33.0)	
Moderate	65 (39.4)	129 (39.1)	
High	45 (27.3)	88 (26.7)	
Missing	2 (1.2)	4 (1.2)	
HIV infection, n (%)	3 (1.8)	10 (3.0)	0.08
Sickle cell disease, n (%)	1 (0.6)	3 (0.9)	0.03
Planned pregnancy, n (%)	74 (44.8)	161 (48.8)	0.08
Referred from another facility, n (%)	51 (30.9)	16 (4.8)	0.72
Contraceptive history			
Any prior hormonal contraception, n (%)	54 (32.7)	62 (18.8)	0.32
Non-hormonal methods only, n (%)	37 (22.4)	78 (23.6)	0.03
Ever condom use, n (%)	59 (35.8)	132 (40.0)	0.09
Ever emergency contraception, n (%)	8 (4.8)	11 (3.3)	0.08

Data are n (%) or mean (SD). BMI, body mass index; IPAQ, International Physical Activity Questionnaire; SD, standard deviation; SMD, absolute standardized mean difference (for variables with more than two

categories, the multivariate SMD); values above 0.10 indicate imbalance. No hypothesis tests are presented because they would ignore the matched design. ^aFirst-degree relative.

Among the 116 users, the predominant method was DMPA in 58 (50.0%); the median cumulative duration was 30 months (interquartile range 14–53) and the median interval from the end of coverage to conception 5.2 months (interquartile range 1.3–11.5). Use was documented for 29 of 54 exposed cases (53.7%) and 41 of 62 exposed controls (66.1%) (Additional file 2: Table S6).

Prior hormonal contraceptive use was reported by 54 cases (32.7%) and 62 controls (18.8%) (crude OR 2.22, 95% CI 1.41–3.50; adjusted OR [aOR] 2.19, 95% CI 1.35–3.57; $p = 0.0016$) (Table 2). Results were similar with BMI modeled linearly (aOR 2.15, 95% CI 1.33–3.49) and with Firth's penalized likelihood (aOR 2.12, 95% profile penalized-likelihood CI 1.33–3.44). Variance inflation factors were below 4.8, and no observation changed the OR by more than 6.8% (Additional file 2: Table S7).

Table 2

Prior hormonal contraceptive use and preeclampsia overall and by method, duration and interval to conception

Exposure	Cases, n (%) (n = 165)	Controls, n (%) (n = 330)	Crude OR (95% CI)	Adjusted OR (95% CI) ^a
Any prior hormonal contraception				
Never used (reference)	111 (67.3)	268 (81.2)	1.00	1.00
Ever used	54 (32.7)	62 (18.8)	2.22 (1.41–3.50)	2.19 (1.35–3.57)
Predominant method^b				
DMPA	28 (17.0)	30 (9.1)	2.44 (1.36–4.40)	3.03 (1.59–5.78)
Progestogen-only pill	6 (3.6)	6 (1.8)	2.59 (0.81–8.22)	2.36 (0.64–8.69)
Combined oral contraceptive	8 (4.8)	10 (3.0)	1.89 (0.74–4.88)	1.56 (0.54–4.49)
Implant	9 (5.5)	9 (2.7)	2.66 (0.95–7.44)	1.91 (0.60–6.08)
Other ^c	3 (1.8)	7 (2.1)	1.09 (0.28–4.30)	0.81 (0.18–3.66)
DMPA vs other hormonal methods			1.20 (0.59–2.43)	1.85 (0.83–4.13)
Cumulative duration of use				
<12 months	7 (4.2)	14 (4.2)	1.21 (0.47–3.13)	1.15 (0.40–3.28)
12–59 months	34 (20.6)	37 (11.2)	2.37 (1.38–4.05)	2.32 (1.28–4.18)
≥60 months	13 (7.9)	11 (3.3)	3.34 (1.37–8.14)	3.58 (1.36–9.44)
Per 12 months (never users = 0)			1.23 (1.08–1.39)	1.22 (1.07–1.40)
Per 12 months among users ^d			–	1.09 (0.88–1.34)
Interval from end of coverage to conception				
Conception during coverage	3 (1.8)	6 (1.8)	1.45 (0.35–6.00)	1.21 (0.26–5.61)

Exposure	Cases, n (%) (n = 165)	Controls, n (%) (n = 330)	Crude OR (95% CI)	Adjusted OR (95% CI) ^a
Any prior hormonal contraception				
0 to < 3 months	22 (13.3)	18 (5.5)	2.99 (1.54–5.79)	3.12 (1.50–6.50)
3 to < 12 months	19 (11.5)	20 (6.1)	2.38 (1.21–4.66)	2.41 (1.13–5.12)
≥12 months	10 (6.1)	18 (5.5)	1.47 (0.66–3.27)	1.43 (0.61–3.32)

All ORs were estimated by conditional logistic regression stratified by matched set (165 sets); each category is compared with never use within the same model. CI, confidence interval; DMPA, depot medroxyprogesterone acetate; OR, odds ratio. ^aModel 1: adjusted for pre-pregnancy body mass index (restricted cubic spline, three knots), first-degree family history of preeclampsia or hypertension, previous preeclampsia, education, urban or rural residence, smoking in the year before pregnancy, and age and parity as continuous terms. ^bMethod with the longest cumulative use. ^cTransdermal patch, vaginal ring or levonorgestrel intrauterine system. ^dPost hoc model including an indicator of ever use, so that the estimate reflects duration among users only.

Compared with never use, DMPA was associated with an aOR of 3.03 (95% CI 1.59–5.78), and estimates for other methods were imprecise (Table 2); the direct comparison of DMPA with other hormonal methods gave an aOR of 1.85 (95% CI 0.83–4.13). Odds were higher with 12–59 months (aOR 2.32, 95% CI 1.28–4.18) and ≥ 60 months of use (aOR 3.58, 95% CI 1.36–9.44) but not with less than 12 months (aOR 1.15, 95% CI 0.40–3.28); the aOR per 12 months of use was 1.22 (95% CI 1.07–1.40) with never users coded 0 (Fig. 2), but 1.09 (95% CI 0.88–1.34) among users when ever use was included in the model. The aOR was 3.12 (95% CI 1.50–6.50) when coverage ended less than three months before conception, 2.41 (95% CI 1.13–5.12) at 3 to < 12 months and 1.43 (95% CI 0.61–3.32) at 12 months or more.

Associations were similar for early-onset (aOR 2.09, 95% CI 0.98–4.45) and late-onset preeclampsia (aOR 2.26, 95% CI 1.16–4.39), and the point estimate was larger for preeclampsia with severe features (aOR 3.14, 95% CI 1.45–6.79) than without (aOR 1.84, 95% CI 0.89–3.80) (Table 3). Compared with users of non-hormonal methods only, hormonal users had an aOR of 1.68 (95% CI 0.73–4.11), based on 63 informative sets with 36 exposed cases and 35 exposed controls (Firth's estimate with profile penalized-likelihood CI, because of separation). There was no evidence of effect modification by BMI (p for interaction = 0.87), and the negative-control exposure was not associated with preeclampsia (aOR 0.73, 95% CI 0.47–1.13).

Table 3

Secondary analyses: preeclampsia subtypes, active comparator, effect modification and negative-control exposure

Analysis	Informative matched sets	Exposed cases/controls	Crude OR (95% CI)	Adjusted OR (95% CI) ^a
Preeclampsia subtype				
Early onset (< 34 weeks)	60	20/23	2.11 (1.03–4.30)	2.09 (0.98–4.45)
Late onset (≥ 34 weeks)	105	34/39	2.31 (1.28–4.15)	2.26 (1.16–4.39)
With severe features	94	32/36	2.37 (1.29–4.35)	3.14 (1.45–6.79)
Without severe features	71	22/26	2.05 (1.03–4.06)	1.84 (0.89–3.80)
Active comparator				
Hormonal users vs users of non-hormonal methods only ^b	63	36/35	1.89 (0.86–4.17)	1.68 (0.73–4.11)
Effect modification by pre-pregnancy BMI^c				
BMI < 25 kg/m ²	–	18/26	–	2.30 (1.11–4.75)
BMI ≥ 25 kg/m ²	–	36/36	–	2.13 (1.16–3.90)
Negative-control exposure				
Ever condom use	165	59/132	0.83 (0.57–1.23)	0.73 (0.47–1.13)

Conditional logistic regression; the reference category is never use of hormonal contraception unless otherwise stated. Exposed cases/controls refers to women exposed to hormonal contraception (or, for the negative control, to condoms). BMI, body mass index; CI, confidence interval; OR, odds ratio. ^aModel 1 (see Table 2). ^bRestricted to hormonal users and users of non-hormonal methods only; matched sets without a case or without a control in this subset are uninformative. Exposed cases/controls are those in the 63 informative sets. Because of separation, the adjusted OR was estimated with Firth's penalized

conditional likelihood, with a profile penalized-likelihood CI. ^cStratum-specific ORs from a model with a product term; p for interaction = 0.87.

Estimates were stable in six prespecified sensitivity analyses, with aORs of 1.98–2.33 (Fig. 3; Additional file 2: Table S8). The association was attenuated with documented exposure only (aOR 1.84, 95% CI 0.99–3.44) and after excluding minors and the sets of referred cases (aOR 1.53, 95% CI 0.85–2.77); post hoc analyses showed that this was due to the exclusion of referred cases (aOR 1.58, 95% CI 0.87–2.86) rather than of minors (aOR 2.16, 95% CI 1.33–3.51).

In the validation substudy (55 participants, 11.1%), agreement between self-report and records was high (kappa 0.95). Sensitivity was 0.90 (95% CI 0.60–0.98) in cases and 1.00 (95% CI 0.44–1.00) in controls, the latter based on only three controls with documented use; specificity was 1.00 in cases (95% CI 0.77–1.00) and in controls (95% CI 0.88–1.00) (Additional file 2: Table S9). Bias-adjusted ORs were 2.45 (95% simulation interval 1.44–4.53) for non-differential, 2.08 (0.47–7.84) for differential and 1.85 (1.12–3.04) for worst-case misclassification. The E-value was 3.81 for the point estimate and 2.03 for the lower confidence limit. In the post hoc bias analysis for the exclusion of women with gestational hypertension from the control pool, the corrected aOR was 2.19 when their prevalence of prior hormonal contraceptive use equaled that of enrolled controls and fell to 1.52 (95% CI 0.93–2.47) in the most extreme scenario (20% of the risk set, 50% exposed) (Additional file 2: Table S4). For the lower confidence limit to reach 1, these women would have needed a prevalence of use of at least 69% if they made up 10% of the risk set, 52% if 15% and 44% if 20%; no prevalence could do so if they made up 5%.

Discussion

In this individually matched case–control study from Angola, prior hormonal contraceptive use was associated with about twice the odds of preeclampsia after adjustment for prespecified confounders. Point estimates were highest for DMPA and for discontinuation within three months before conception, although DMPA did not differ clearly from other hormonal methods. However, duration was not associated with preeclampsia among users, so the apparent dose–response largely reflected the ever–never contrast, and the association was attenuated, with CIs including the null, when exposure was restricted to documented use, when referred cases were excluded (post hoc) and when hormonal users were compared with users of non-hormonal methods. These results are compatible with a modest association but do not exclude that it is partly or wholly explained by bias.

Earlier studies were conducted in high-income countries and focused on oral contraceptives [8–10], and a meta-analysis that pooled contraceptive methods of any type found no association [11]. Our estimate for any hormonal method was larger than that reported for oral contraceptives in the Dutch PRIDE cohort (adjusted risk ratio 1.38, 95% CI 0.99–1.93, late-onset preeclampsia only) [10], but that cohort also found the highest risk when use stopped within three months before conception (adjusted risk ratio 1.56, 95% CI 1.03–2.37), a pattern similar to ours. Our study adds evidence on DMPA and from sub-Saharan Africa. A stronger association with DMPA is biologically plausible, given its associations with weight gain and

adverse lipid changes [6, 7], but the direct comparison with other hormonal methods was imprecise and did not show a clear difference. Combined oral contraceptives raise blood pressure during use [5], yet few participants used them. Whether vascular or metabolic effects persist after discontinuation, as the higher estimate for recent discontinuation might suggest, cannot be determined from these data.

Four patterns deserve attention. First, the association was weaker for documented use, and a smaller proportion of exposure was documented in cases than in controls, which could reflect better recall of undocumented past use by cases. In the validation substudy, self-report agreed closely with records in both groups, but the sample was small, and the differential bias analysis accordingly gave a wide interval.

Second, nearly a third of cases but few controls had been referred, and excluding the sets of referred cases in a post hoc analysis reduced the aOR to about 1.6. We consider referral the main potential source of bias in this study. Because HGB is the provincial referral hospital, referred women with preeclampsia may differ from the population that gave rise to the controls, for example in access to family planning, and this could inflate the association [16, 17]; restriction also removed a third of the informative sets. Because this exclusion was not prespecified on its own and greatly reduced precision, we report the prespecified primary estimate as the main result but interpret it together with this analysis. Cases and controls were also recruited from different services: no case came from the antenatal clinic, whereas most controls did; however, restricting controls to the antenatal clinic did not change the estimate (aOR 2.14).

Third, the active-comparator analysis, intended to reduce confounding by indication and care-seeking, gave a smaller and imprecise estimate. The null result for the negative-control exposure argues against strong general reporting bias, although condom use is an imperfect negative control, because limited preconception exposure to paternal antigens has been hypothesized to increase the risk of preeclampsia [8, 12].

Fourth, women with gestational hypertension without preeclampsia at the index date were not eligible as controls, although under incidence-density sampling they belonged to the risk set from which cases arose. If hormonal contraception is associated with hypertension in pregnancy more generally, their exclusion would lower the prevalence of exposure among controls and bias the OR away from the null. In the post hoc bias analysis, the association was attenuated, but its lower confidence limit remained above 1 unless such women made up at least 10% of the risk set and had a much higher prevalence of prior hormonal contraception (44%–69%, depending on their share of the risk set) than enrolled controls (18.8%).

Strengths include a protocol and statistical analysis plan prespecified and approved by the ethics committee before recruitment; consecutive incident cases defined by international criteria with confirmed proteinuria and adjudicated blind to exposure; random sampling of controls from a complete daily sampling frame by incidence-density sampling; independent interviewers; record verification and a

validation substudy; confounders chosen in advance with a directed acyclic graph and measured before pregnancy; and extensive prespecified sensitivity and bias analyses.

Limitations include ascertainment of exposure after diagnosis, with 40% of reported use undocumented, and interviewers who could not be blinded to case status. Controls were hospital-based and the study was conducted in a single referral hospital, which limits generalizability and may introduce referral bias. Women with gestational hypertension were excluded from the control pool, and requiring proteinuria may have excluded women diagnosed by organ or uteroplacental dysfunction alone, which limits generalizability to those presentations. Residual confounding, particularly by indication and by factors such as duration of cohabitation, is possible. Model 1 had 13.8 events per parameter, below the planned 15, although Firth's estimates were nearly identical. Analyses by method, interval and subtype had limited power and were not adjusted for multiplicity. More than half of pre-pregnancy weights were self-reported, proteinuria was confirmed by repeated dipstick in 58.2% of cases, and 17 controls were lost before the six-week postpartum contact. Because few pregnancies were dated by first-trimester ultrasound, gestational age, used for matching and for classifying early-onset disease, may have been misclassified, although dating methods were distributed similarly in cases and controls. Recruitment ended after six months instead of the planned minimum of 12 once the target sample size was reached, and a case-control design cannot provide absolute risks.

These findings should not be used to discourage hormonal contraception, which prevents unintended pregnancies and averts many maternal deaths [29]; current eligibility criteria do not consider a later risk of preeclampsia [30]. Prospective cohorts following women from contraceptive use to pregnancy, with exposure recorded before the outcome, and multicenter studies in sub-Saharan Africa are needed to establish whether the association is causal.

Conclusions

Among women attending a referral hospital in Angola, prior hormonal contraceptive use was associated with higher odds of preeclampsia. Attenuation of the association in analyses designed to detect referral, information and indication bias indicates that the evidence is not conclusive. Contraceptive counseling should not change on the basis of these findings, and prospective confirmation is needed.

Abbreviations

aOR
Adjusted odds ratio
BMI
Body mass index
CI
Confidence interval
DMPA

Depot medroxyprogesterone acetate
HELLP
Hemolysis, elevated liver enzymes and low platelets
HGB
Hospital Geral de Benguela
HIV
Human immunodeficiency virus
IPAQ
International Physical Activity Questionnaire
LMP
Last menstrual period
OR
Odds ratio
SD
Standard deviation
SMD
Standardized mean difference
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committee of the Scientific and Pedagogical Directorate of Hospital Geral de Benguela (reference 2972DG/DPC/DFPI/2025) on October 30, 2025. All participants gave written informed consent. For participants younger than 18 years, the participant's assent and the written consent of a parent or legal representative were obtained. For women too unwell to consent at enrollment, a legal representative gave consent, and the participant confirmed her consent after recovery.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available because they contain confidential health information on participants and their release is restricted by the terms of the ethics approval granted by the Scientific and Pedagogical Directorate of Hospital Geral de Benguela. De-identified data, together with the data dictionary, the study protocol, including the statistical analysis plan

and the analysis code, are, however, available from the corresponding author upon reasonable request and with the permission of the Scientific and Pedagogical Directorate of Hospital Geral de Benguela.

Competing interests

The authors declare that they have no competing interests.

Funding

This study received no specific funding.

Authors' contributions

RFT contributed to conceptualization, methodology, data curation, validation and visualization, wrote the original draft and reviewed and edited the manuscript. HP performed the formal analysis and software implementation, contributed to visualization and reviewed and edited the manuscript. TL provided resources and supervision and reviewed and edited the manuscript. AK provided resources and reviewed and edited the manuscript. RFT and HP accessed and verified the underlying data. All authors read and approved the final manuscript.

Acknowledgements

We thank the women who took part in the study, the interviewers, the field coordinator and the staff of the maternity department of Hospital Geral de Benguela. We are grateful to Dr Divane Marcolino, obstetrician-gynecologist and Director of Hospital Geral de Benguela, for his support with administrative procedures and authorizations.

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Figures

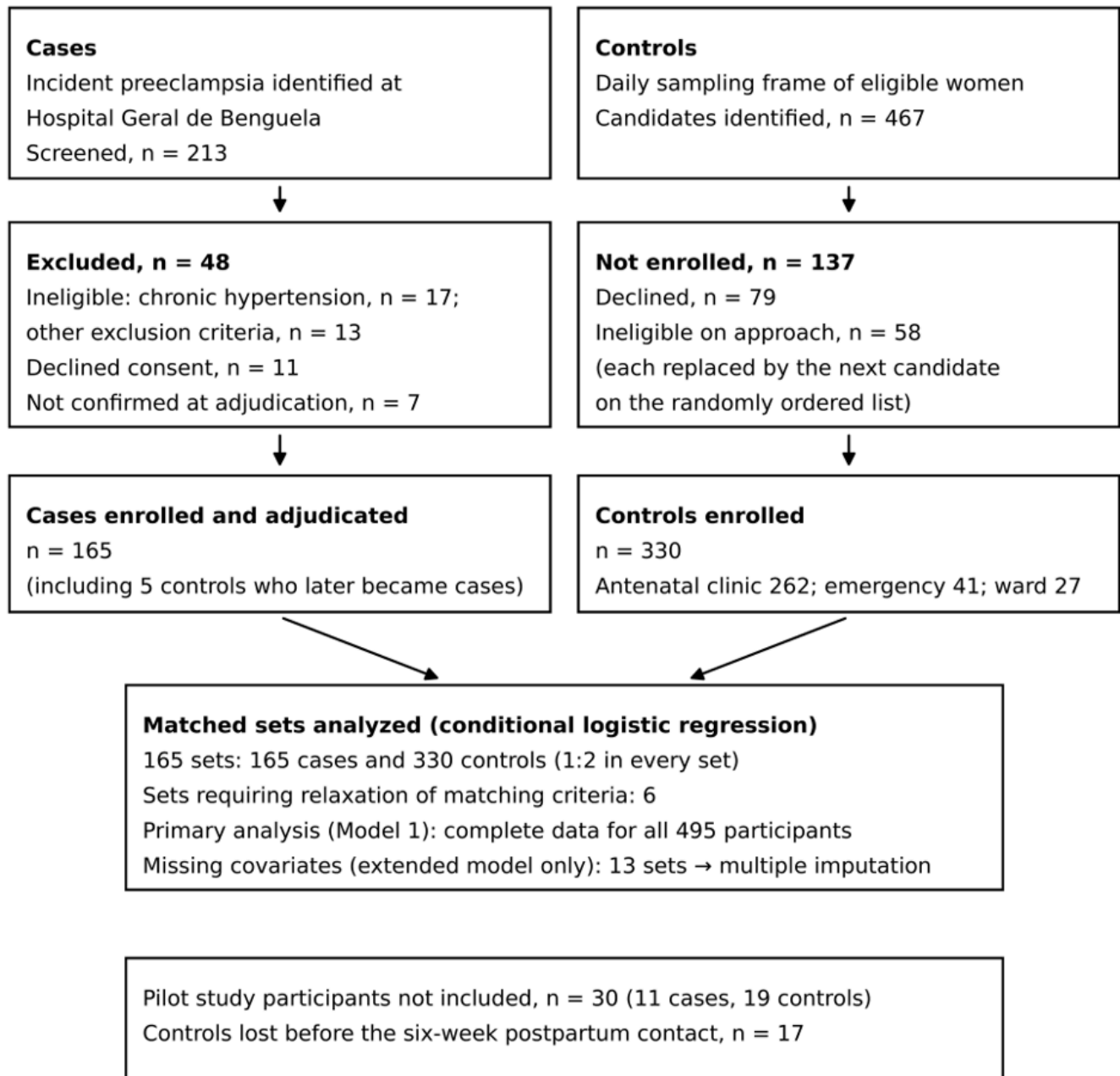


Figure 1

Flow of participants through the study. Cases were enrolled consecutively, and each was matched to two controls sampled at random, by incidence-density sampling, from a daily list of all eligible pregnant women. Five women sampled as controls later developed preeclampsia and were also enrolled as cases, so the 495 participants correspond to 490 women.

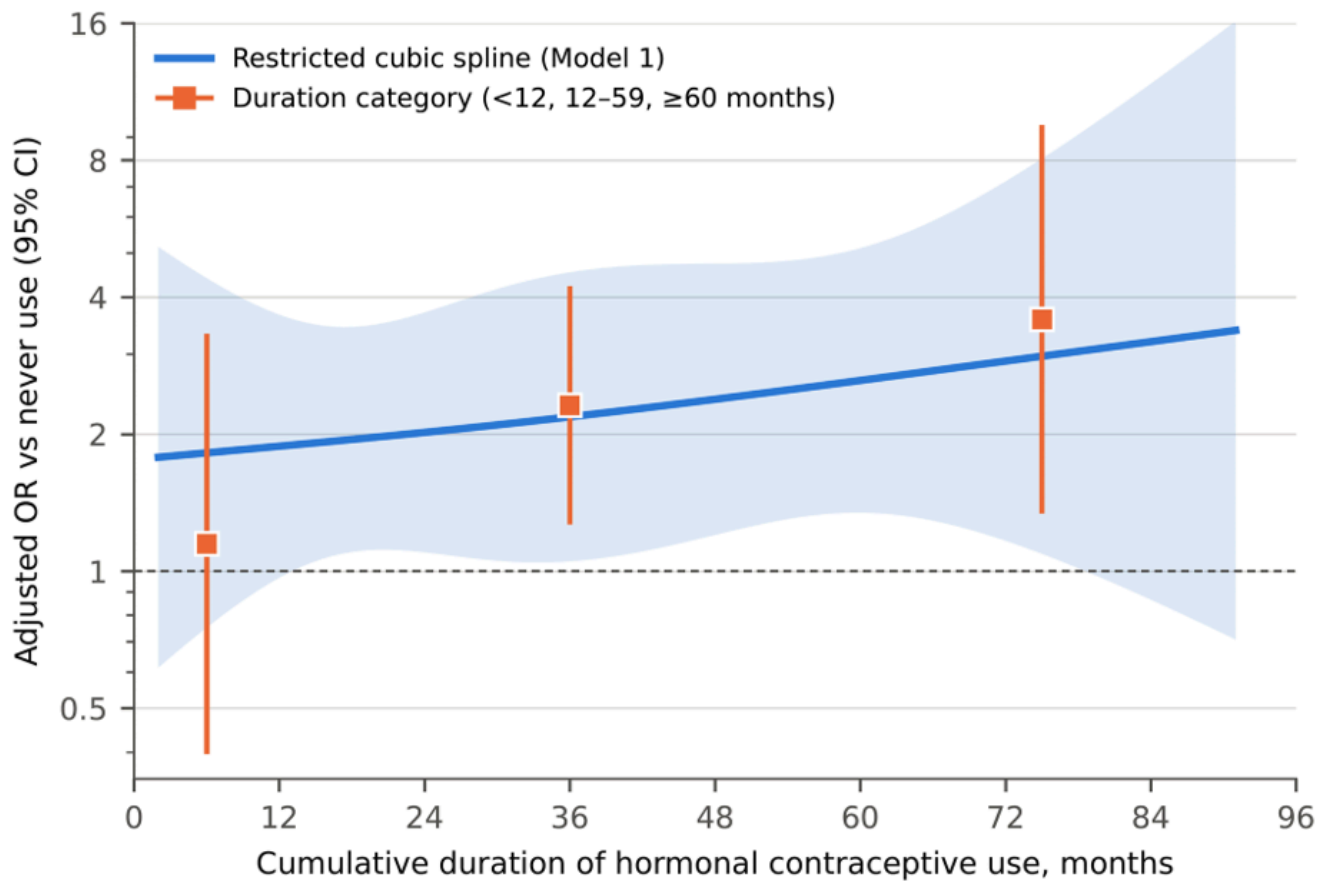


Figure 2

Adjusted odds ratio of preeclampsia by cumulative duration of hormonal contraceptive use. Duration is compared with never use. The line and shaded band show the estimate and 95% confidence interval (CI) from a restricted cubic spline (knots at 7.5, 30 and 68 months) combined with an indicator of ever use; squares and bars show adjusted odds ratios (ORs) for the duration categories, plotted at the category midpoint (or at 75 months for ≥ 60 months). Both are adjusted for the Model 1 covariates (Table 2). Logarithmic vertical axis.

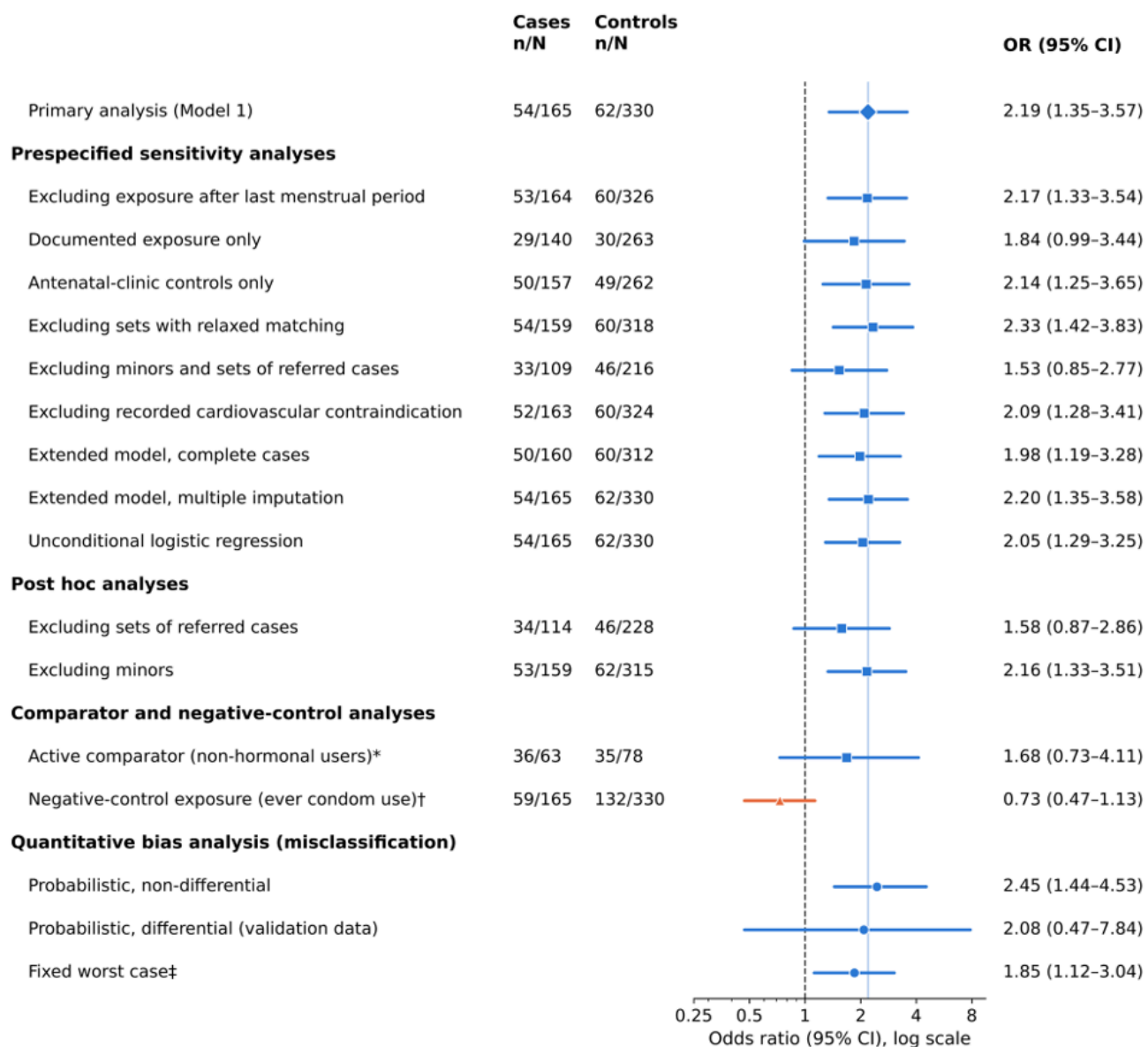


Figure 3

Primary, sensitivity, comparator, negative-control and bias analyses for hormonal contraception and preeclampsia. The panel shows the primary, prespecified sensitivity, post hoc, comparator, negative-control and quantitative bias analyses. Odds ratios (ORs) are adjusted for the Model 1 covariates (Table 2), except for the unconditional analysis, which also includes the matching variables. n/N, exposed participants/participants included in the analysis (for conditional analyses, those in informative matched sets). Bias-analysis estimates are medians with 95% simulation intervals from record-level probabilistic correction for exposure misclassification. The dashed vertical line marks the null value, and the shaded vertical line marks the primary estimate. CI, confidence interval. *Firth's penalized conditional likelihood (separation), with profile penalized-likelihood CI. †n/N refers to ever condom use. ‡Sensitivity 0.95 and specificity 0.98 in cases; sensitivity 0.80 and specificity 0.98 in controls.

Supplementary Files

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