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ORIGINAL RESEARCH

Interaction Between Maternal Smoking Cessation Timing and Preexisting Hypertension on Fetal Growth Restriction: A Nationwide Population-Based Cohort Study

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Background: Maternal smoking is a major preventable cause of fetal growth restriction (FGR). Although cessation reduces risk, the benefit depends on its timing, and the role of preexisting hypertension—sharing vascular-placental mechanisms—remains underexplored.

Patients and methods: We conducted a population-based retrospective cohort study using US birth data (2020–2024). Maternal smoking was divided as nonsmokers, quit before pregnancy, quit in the first trimester, quit in the second trimester, or persistent smokers. FGR was defined using birth-weight-based percentiles derived from the NICHD fetal growth standards (<3rd, <5th, and <10th). Poisson regression with inverse probability of treatment weighting (IPTW) was used to estimate adjusted risk ratios (aRRs). Effect modification by preexisting hypertension was examined on multiplicative and additive scales.

Results: Among 17,381,709 singleton live births, FGR-3rd incidence increased across groups (3.3%, 4.5%, 6.1%, 7.5%, and 10.0%, respectively), showing a dose–response gradient. Compared with nonsmokers, the IPTW-aRRs for FGR-3rd were 1.20 (95% CI:1.17–1.23), 1.61 (1.57–1.66), 2.03 (1.95–2.11) and 2.01 (1.99–2.04) for women who quit before pregnancy, in the first trimester, in the second trimester, and persistent smokers. Preexisting hypertension increased absolute FGR risk but modified associations on the multiplicative scale, with attenuated relative risks among hypertensive women. No meaningful interaction was observed on additive scale. Notably, hypertensive women who quit before pregnancy achieved FGR risks comparable to hypertensive nonsmokers (aRR=0.98, 0.88–1.08). Similar patterns were observed for <5th and <10th percentiles.

Conclusion: Earlier smoking cessation is associated with lower risk of FGR. Preexisting hypertension modifies associations on the multiplicative scale, where relative risks were attenuated among hypertensive women, but not on the additive scale, suggesting the independence on the additive scale (a lack of departure from risk additivity). These findings support integrating smoking cessation into preconception and antenatal care, especially for high-risk women.

Keywords: maternal smoking cessation, fetal growth restriction, preexisting hypertension, modification, inverse probability of treatment weighting

Introduction

Maternal smoking is a well-established and preventable risk factor for fetal growth restriction (FGR), contributing to neonatal morbidity, stillbirth, and long-term cardiometabolic and neurodevelopmental disorders.[1–3] FGR mainly originates from placental dysfunction.[4,5] Tobacco components such as nicotine and carbon monoxide disrupt vascular and trophoblastic development, collectively reducing nutrient and oxygen transfer to the fetus and leading to FGR.[5,6]

Numerous population-based studies have shown that maternal smoking cessation reduces the risk of FGR.[7–10] The timing of cessation is critical: quitting before pregnancy or in the first trimester yields the greatest benefit, whereas cessation after

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first trimester confers only modest or diminishing benefit.[6–10] This dose–response gradient is consistent with biological vulnerability during early placentation and organogenesis, when placental vascular development is most susceptible to toxic exposures.[10,11] However, the extent of benefit from cessation may differ according to maternal vascular health.

Hypertensive disorders in pregnancy, particularly preexisting (chronic) hypertension, are independently linked to FGR through chronic uteroplacental insufficiency and impaired vascular remodeling.[12–15] These mechanisms overlap with those from smoking, suggesting potential interaction or effect modification. Yet, very few studies have examined whether maternal hypertension modifies the association between smoking cessation timing and FGR risk. One previous study found synergistic effect between trimester-specific smoking and hypertension on small for gestational age (SGA)/FGR,[16] whereas another study did not.[17] Preexisting hypertension and gestational hypertension or preeclampsia have different etiologies and potentially different interactions with smoking. And gestational hypertension or preeclampsia could be potential intermediate conditions along the causal pathway between maternal smoking and fetal growth restriction. Therefore, we focused mainly on maternal preexisting hypertension whether it will interact with maternal smoking cessation timing in relation to fetal growth restriction.

In epidemiologic study, it is important to distinguish biological interaction from statistical effect modification. Biological interaction refers to that two exposures jointly influence disease mechanisms, whereas statistical effect modification refers to variation of an exposure-outcome association across levels of another exposure. Interaction can be assessed on different statistical scales: interaction on the multiplicative scale evaluates whether the relative risk of an exposure differs across strata of another variable, reflecting differences in relative effects; whereas interaction on the additive scale examines whether the combined effect of two exposures exceeds the sum of their individual effects, reflecting departures from risk additivity. Additive interaction is often directly relevant for public health and etiologic interpretation because it captures excess risk attributable to the joint presence of exposures. As a result, an exposure pair may appear to interact on one scale but not the other, leading to different explanations regarding synergistic or independent effects.

Accordingly, we aimed to investigate whether preexisting hypertension modifies the association between the timing of maternal smoking cessation and FGR risk in a large national population-based cohort, examining potential modification on both multiplicative and additive scales.

Methods

Study Design and Data Source

We conducted a population-based retrospective cohort study using the US National Vital Statistics System (NVSS) data between 2020 and 2024 from the National Center for Health Statistics (NCHS). The datasets include all live births in the United States and Washington DC, and provide detailed maternal demographic, behavioral, and clinical information derived from birth certificates. All personal identifiers are removed and released publicly, so no ethics approval was obtained from the institutional review board.

Study Population

We restricted to singleton live births between 20 and 42 weeks of gestation, and excluded records with multiple gestations, congenital anomalies, missing data on birth weight or gestational age, as well as missing or inconsistent information on maternal smoking status. Births to non-US residents were also excluded in accordance with NCHS analytic recommendations.[18]

Exposures: Maternal Smoking Cessation

Maternal smoking status was derived from four trimester-specific self-reported smoking variables on the birth certificate, including: average number of cigarettes smoked per day (in the three months) before pregnancy, in the first trimester, second trimester, and third trimester, as well as gestational age at delivery, according to "User Guide to the 2024 Natality".[18] Generally, the cohort was divided into five exposure groups: 1) nonsmokers – no smoking before pregnancy and in all three trimesters; 2) quit before pregnancy – smoked before pregnancy but not in any trimester; 3) quit in the first trimester – smoked before pregnancy and the first trimester but not the second or third; 4) quit in

the second trimester – smoked before pregnancy, in the first and second trimesters but not the third; and 5) persistent smokers – smoked before and in all 3 trimesters. For each period, women who smoked an average of ≥1 cigarette a day were considered to have smoked. Women with missing, unknown or inconsistent smoking status before pregnancy or for any trimester were classified as missing for exposure,[18] and were excluded from the study.

Outcome: Fetal Growth Restriction

The primary outcome was fetal growth restriction (FGR). Clinically, the FIGO initiative defines FGR based on a combination of fetal size (commonly estimate fetal weight or abdominal circumference <10th percentile for gestational age) and Doppler abnormalities, with all fetuses of estimated weight below 3rd percentile for gestational age considered as FGR.[19] Since small for gestational age (SGA) reflecting FGR is often taken as a surrogate in practice, and birth certificate data provide only birth weight, we used SGA—birth weight below a given percentile for gestational age—as a proxy for FGR.

As birth-weight-based references may underestimate the incidence of SGA/ FGR and substantial racial/ethnic differences exist in fetal growth,[20,21] we defined FGR according to the NICHD fetal growth standards, which were based on sonographic data of low-risk US pregnancies.[21] The NICHD standards were developed for four major US racial/ethnic groups and are applicable for 14–40 weeks of gestation; births at 41–42 weeks were therefore assigned to the 40-week reference category.[21] Given fetal growth slows substantially and limited growth increment after 41 weeks in addition to its relatively small proportion, the potential impact on fetal growth classification is expected to minimal.[18,21,22] To match with these standards, maternal race/ethnicity in NVSS was categorized as non-Hispanic White, non-Hispanic Black, Hispanic, Asian, and Other (the latter using the non-Hispanic White standards). We used three thresholds to define FGR: FGR-3rd (birth weight <3rd percentile), FGR-5th (<5th percentile), and FGR-10th (<10th percentile) for gestational age and race/ethnicity. We mainly focused on FGR-3rd, the true "FGR", with FGR-5th and FGR-10th as the sensitivity analysis.

Covariates

Following potential confounders were considered and obtained from the NVSS, including year of birth, maternal age, education level, race/ethnicity, marital status, parity, pre-pregnancy body mass index (BMI), preexisting hypertension, preexisting diabetes, initiation of prenatal care, payment source for delivery, gestational weight gain (GWG), and neonatal sex. According to NVSS, risk factors in pregnancy, including preexisting hypertension, were recommended to collected from medical record.[23] Maternal race/ethnicity was divided into five groups as described above. GWG was categorized as inadequate, adequate, and excessive according to Institute of Medicine (IOM) criteria.[24] Although GWG and timing of prenatal care initiation may also partially lie on the causal pathway between smoking and fetal growth, they were included as covariates as proxy for broader maternal health behaviors to improve comparability across groups. All missing/unknown data for each covariate were assigned as an indicator, respectively.

Statistical Analysis

The incidence of FGR (FGR-3rd, FGR-5th, and FGR-10th) was presented for five exposure groups. Risk ratios (RRs) and 95% confidence intervals (CIs) of FGR (FGR-3rd, FGR-5th, and FGR-10th) were estimated using log-link Poisson regression models, with nonsmokers as the reference group. Owing to the extremely large data and computational burden, standard errors were adjusted using the Pearson-based parameter (robust-like error variance estimation) as a conservative approximation to account for potential overdispersion.

Propensity scores predicting smoking status were calculated using multinomial logistic regression after adjusting for above maternal demographic, behavioral, and medical covariates.[25,26] Stabilized inverse probability of treatment weighting (IPTW) based on propensity scores was applied, balancing covariates across smoking categories, to estimate adjusted risk ratios (IPTW-aRRs). IPTW-weighted marginal incidences were calculated to balance above maternal covariates across smoking groups.

To evaluate potential effect modification by preexisting hypertension, we (1) introduced interaction terms between smoking categories and preexisting hypertension in IPTW-weighted Poisson models, (2) performed stratified analyses to

estimate weighted marginal incidences and IPTW-aRRs, and (3) assessed additive-scale interaction using the relative excess risk due to interaction (RERI) and absolute risk differences (ARDs) (exposed minus nonsmokers), which may better capture the public-health impact of cessation and reveal whether joint effects are synergistic or independent. RERI was computed as $RERI=RR_{11} - RR_{10} - RR_{01} + 1$, where RR_{11} is the risk ratio for the joint exposure (smoking category + hypertension), RR_{10} for smoking only, and RR_{01} for hypertension only. Confidence intervals for RERI were obtained by delta method.

Several sensitivity analyses were conducted to test the robustness of the results. First, pregnancies complicated by gestational hypertension or preeclampsia were excluded. Second, we further assessed the impact of smoking intensity as well as potential misclassification by classifying each exposure group into light (1–10 cigarettes/day) and heavy (≥11 cigarettes/day) smokers based on average number of cigarettes per day. The average number of cigarettes per day for each group was estimated by multiplying the reported average daily cigarette consumption in each period by the duration of that period (assumed as 91 days), summing across all periods, and dividing by the total duration. All analyses were done in SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Baseline Characteristics of the Cohort by Exposure Groups

A total of 18,170,648 live births were obtained from US National Vital Statistics System (NVSS) between 2020 and 2024. After exclusions based on prespecified criteria (Figure 1), 17,381,709 singleton live births remained in the study cohort: 16,553,017 (95.2%) were born to nonsmoking mothers, 192,269 (1.1%) to mothers who quit smoking before pregnancy, 87,754 (0.5%) to those who quit in the first trimester, 35,315 (0.2%) to those who quit in the second trimester, and 513,354 (3.0%) to persistent smokers.

Table 1 presents the baseline characteristics by smoking groups. Women who quit smoking before or during pregnancy (in the first/second trimester) were generally younger (about 30% aged ≤24 years), whereas older mothers (≥35 years) were more prevalent among nonsmokers and persistent smokers. Nonsmokers had higher proportions of

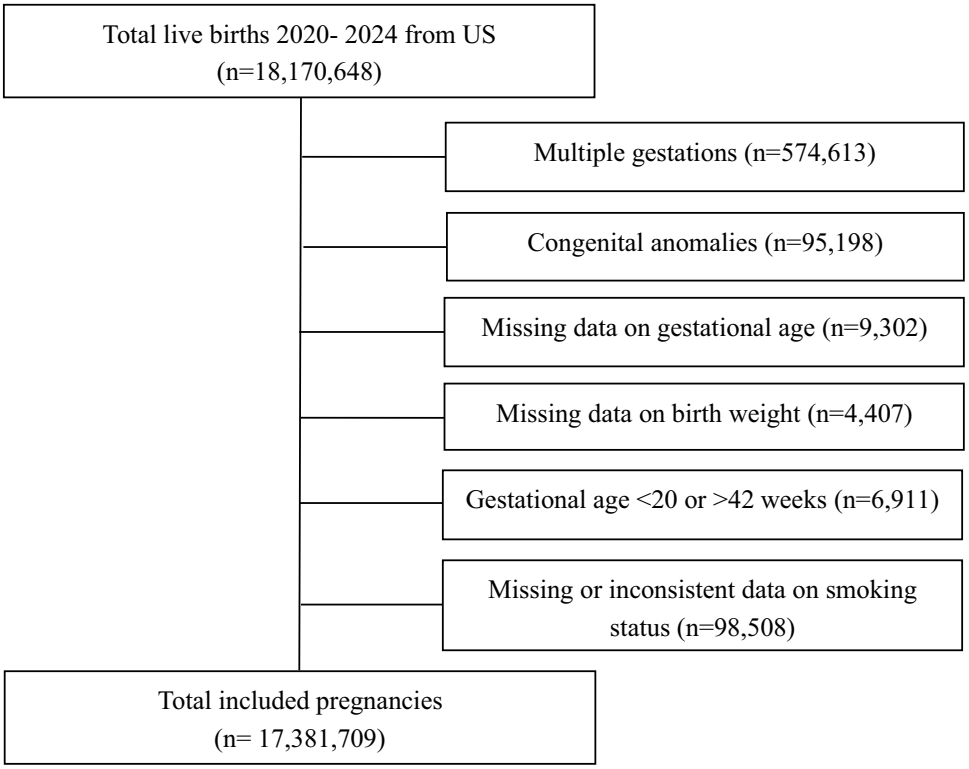

Figure 1 Flow chart for exclusion of the study population.

Table 1 Baseline Characteristics of Cohort, n(%)

Characteristics	Nonsmoker (n=16553017)	Quit before pregnancy (n=192269)	Quit in 1st trimester (n=87754)	Quit in 2nd trimester (n=35315)	Persistent smoker (n=513354)
Birth year					
2020	3216071(19.4)	56625(29.5)	26194(29.9)	9976(28.3)	146945(28.6)
2021	3301473(19.9)	47783(24.9)	21428(24.4)	8735(24.7)	123949(24.1)
2022	3349554(20.2)	35958(18.7)	16755(19.1)	6798(19.3)	98951(19.3)
2023	3314733(20.0)	28844(15.0)	13065(14.9)	5412(15.3)	79779(15.5)
2024	3371186(20.4)	23059(12.0)	10312(11.8)	4394(12.4)	63730(12.4)
Maternal age (years)					
<20	681609(4.1)	8766(4.6)	4854(5.5)	1779(5.0)	16877(3.3)
20–24	2877053(17.4)	48672(25.3)	23061(26.3)	9073(25.7)	106543(20.8)
25–29	4574696(27.6)	59563(31.0)	26494(30.2)	10887(30.8)	157929(30.8)
30–34	5040299(30.5)	48117(25.0)	21241(24.2)	8682(24.6)	144020(28.1)
35–39	2732619(16.5)	22502(11.7)	9934(11.3)	3984(11.3)	72013(14.0)
≥40	646741(3.9)	4649(2.4)	2170(2.5)	910(2.6)	15972(3.1)
Marital status					
Married	9004976(54.4)	65080(33.9)	22660(25.8)	7985(22.6)	126588(24.7)
Unmarried	5584112(33.7)	121491(63.2)	62418(71.1)	26430(74.8)	377454(73.5)
Missing	1963929(11.9)	5698(3.0)	2676(3.1)	900(2.6)	9312(1.8)
Maternal Race					
Non-Hispanic white	8128795(49.1)	128845(67.0)	59423(67.7)	24732(70.0)	391930(76.4)
Non-Hispanic black	2288758(13.8)	23352(12.2)	12039(13.7)	4829(13.7)	57393(11.2)
Asian	1056032(6.4)	2369(1.2)	651(0.7)	160(0.5)	1737(0.3)
Hispanic	4397389(26.6)	24366(12.7)	9081(10.4)	2804(7.9)	28916(5.6)
others	682043(4.1)	13337(6.9)	6560(7.5)	2790(7.9)	33378(6.5)
Educational level					
Lower than high school	1766914(10.7)	25464(13.2)	14704(16.8)	7310(20.7)	130251(25.4)
High school graduate	4199690(25.4)	76145(39.6)	37519(42.8)	15688(44.4)	232785(45.4)
College and bachelor	8009357(48.4)	84931(44.2)	34119(38.9)	11904(33.7)	143162(27.9)
Higher than bachelor's degree	2314851(14.0)	4974(2.6)	1069(1.2)	245(0.7)	2535(0.5)
Unknown	262205(1.6)	755(0.4)	343(0.4)	168(0.5)	4621(0.9)
Parity (live born)					
Nulliparous	6647050(40.2)	84325(43.9)	34788(39.6)	11896(33.7)	117707(22.9)
Parous	9866275(59.6)	107538(55.9)	52802(60.2)	23328(66.1)	394034(76.8)
Missing	39692(0.2)	406(0.2)	164(0.2)	91(0.3)	1613(0.3)
Prepregnancy BMI, kg/m^2					
Underweight (<18.5)	424342(2.6)	6788(3.5)	3810(4.3)	1715(4.9)	25364(4.9)
Normal (18.5–24.9)	6289249(38.0)	60995(31.7)	28578(32.6)	12213(34.6)	180914(35.2)
Overweight (25.0–29.9)	4504655(27.2)	48139(25.0)	21112(24.1)	8488(24)	120488(23.5)
Obesity (≥ 30.0)	5003926(30.2)	74123(38.6)	33147(37.8)	12311(34.9)	173743(33.8)
Unknown or not stated	330845(2.0)	2224(1.2)	1107(1.3)	588(1.7)	12845(2.5)
Gestational weight gain					
Inadequate	3463345(20.9)	31238(16.3)	15466(17.6)	7361(20.8)	142601(27.8)
Adequate	5006907(30.3)	41476(21.6)	19390(22.1)	8097(22.9)	128087(25.0)
Excessive	7611840(46.0)	115123(59.9)	50834(57.9)	18728(53.0)	221185(43.1)
Missing	470925(2.8)	4432(2.3)	2064(2.4)	1129(3.2)	21481(4.2)
Initiate of prenatal care (GA)					
1st to 3rd month	12592065(76.1)	145851(75.9)	61303(69.9)	22021(62.4)	311262(60.6)
4th month and after	3331620(20.1)	39871(20.7)	23026(26.2)	11330(32.1)	155012(30.2)
No prenatal care	313923(1.9)	3243(1.7)	1965(2.2)	1250(3.5)	36263(7.1)
Missing	315409(1.9)	3304(1.7)	1460(1.7)	714(2.0)	10817(2.1)
Payment source					
Medicaid	6497648(39.3)	110944(57.7)	58618(66.8)	26024(73.7)	399438(77.8)
Private Insurance	8668076(52.4)	69938(36.4)	24248(27.6)	7390(20.9)	86096(16.8)
Self Pay	711933(4.3)	3394(1.8)	1547(1.8)	631(1.8)	11458(2.2)
Other	555686(3.4)	6383(3.3)	2697(3.1)	966(2.7)	11935(2.3)
Missing	119674(0.7)	1610(0.8)	644(0.7)	304(0.9)	4427(0.9)

(*Continued*)

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Table 1 (Continued).

Characteristics	Nonsmoker (n=16553017)	Quit before pregnancy (n=192269)	Quit in 1st trimester (n=87754)	Quit in 2nd trimester (n=35315)	Persistent smoker (n=513354)
Preexisting diabetes mellitus	188800(1.1)	2705(1.4)	1352(1.5)	567(1.6)	7991(1.6)
Preexisting hypertension	463378(2.8)	7774(4.0)	3894(4.4)	1572(4.5)	23123(4.5)
Neonatal Sex					
Female	8091999(48.9)	94555(49.2)	42653(48.6)	17204(48.7)	250824(48.9)
Male	8461018(51.1)	97714(50.8)	45101(51.4)	18111(51.3)	262530(51.1)

Abbreviations: BMI, body mass index; GA, gestational age.

Hispanic (26.6%) or Asian (6.4%) compared with other exposure groups. Nonsmokers were more often married (54.4%), whereas about two-thirds of smokers were unmarried (62.2~74.8%).

Persistent smokers (76.8%) and those who quit in the second trimester (66.1%) were more likely to be parous, whereas nonsmokers and those who quit before pregnancy or in the first trimester had proportions of nulliparous women. Pre-pregnancy obesity (BMI ≥30.0 kg/m^2) was slightly more frequent in those who quit before pregnancy (38.6%) or in the first trimester (37.8%). Similarly, excessive gestational weight gain was more common among quitters (59.9%, 57.9%, and 53.0% for those who quit before pregnancy, in the first and second trimester, respectively). Nonsmokers had lower proportion of preexisting hypertension (2.8%) and preexisting diabetes mellitus (1.1%).

Nonsmokers (62.4%) and women who quit before pregnancy (46.8%) or in the first trimester (40.1%) had higher proportion of college and above. Nonsmokers tended to have private insurance (52.4%), whereas smokers relied more heavily on Medicaid (57.7–77.8%). Early initiation of prenatal care (1st to 3rd month) was most frequent among nonsmokers (76.1%) and those who quit before pregnancy (75.9%), but least common among persistent smokers (60.6%).

After IPTW weighting, the distribution of demographic and clinical variables was well balanced across five exposure groups and almost all post-weighting maximum standardized mean difference were below 0.1, suggesting reducing differences in measured confounders (Supplementary Table S1).

Risk of Fetal Growth Restriction by Smoking Status

Figure 2 shows FGR incidence (FGR-3rd, FGR-5th, and FGR-10th) across five smoking groups. The unweighted (crude) incidence of FGR-3rd was 3.3% among nonsmokers, 4.5% among women who quit before pregnancy, 6.1% among those who quit in the first trimester, 7.5% among those who quit in the second trimester, and 10.0% among persistent smokers, respectively, demonstrating a clear dose–response pattern (Figure 2a); corresponding weighted marginal incidences, balancing covariates by IPTW, were 3.3%, 4.0%, 5.4%, 6.8% and 6.7%, respectively (Figure 2b), showing consistent gradients. Similar patterns were observed for FGR-5th and FGR-10th (Figure 2).

Table 2 summarizes the risk ratios (RR) of FGR from IPTW-weighted Poisson regression. Compared with non-smokers, both persistent smokers and women who quit smoking in the second trimester had significantly increased and nearly identical risks (eg, for FGR-3rd, aRR= 2.01, 95% CI: 1.99–2.04; and 2.03, 1.95–2.11, respectively). Quitting before pregnancy (aRR = 1.20, 95% CI: 1.17–1.23) or in the first trimester (aRR=1.61, 95% CI: 1.57–1.66) substantially reduced risk relative to persistent smoking (Table 2). Although cessation before pregnancy lowered risk considerably, women who quit before pregnancy still had slightly higher FGR risk than nonsmokers. These results confirm a robust dose–response relationship between timing of smoking cessation and risk of FGR, with the greatest benefit from quitting before pregnancy.

When pregnancies with gestational hypertension or preeclampsia were excluded from the analyses, the results were comparable to the main analyses (Supplementary Table S2), suggesting the robustness of the findings. In additional analyses stratified by smoking intensity within each exposure group, the overall trends were broadly consistent with the primary findings (Supplementary Table S3), with heavy smokers showing slightly higher risks of FGR than light smokers.

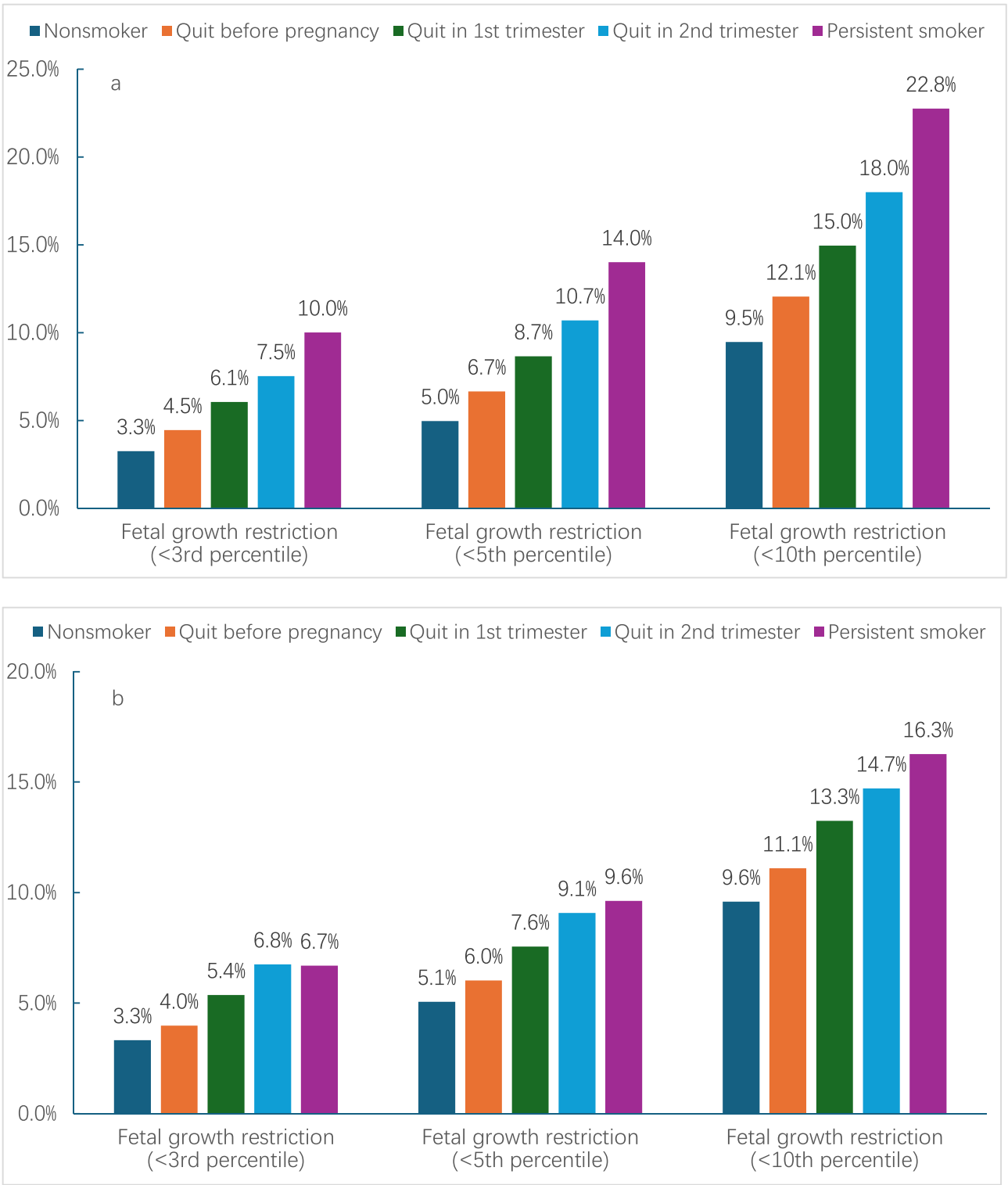

Figure 2 Incidence of fetal growth restriction (FGR) by smoking-cessation group. (**a**) Unweighted (crude) incidences and (**b**) IPTW-weighted marginal incidences of FGR < 3rd, < 5th, and < 10th percentiles among nonsmokers, women who quit before pregnancy, during the first or second trimester, and persistent smokers. Both panels demonstrate a consistent dose–response relationship, with earlier cessation associated with substantially lower FGR incidence.

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Table 2 Risk of Fetal Growth Restriction Births by Exposure Groups

Fetal growth restriction	Nonsmoker	Quit before pregnancy	Quit in 1st trimester	Quit in 2nd trimester	Persistent smoker
<3rd percentile					
Unadjusted RR (95% CI)	Ref	1.36(1.34, 1.39)	1.86(1.81, 1.91)	2.31(2.22, 2.40)	3.07(3.04, 3.10)
Adjusted RR (95% CI)[a]	Ref	1.16(1.14, 1.19)	1.50(1.46, 1.54)	1.75(1.69, 1.82)	2.22(2.20, 2.25)
IPTW-adjusted RR (95% CI)[b]	Ref	1.20(1.17, 1.23)	1.61(1.57, 1.66)	2.03(1.95, 2.11)	2.01(1.99, 2.04)
<5th percentile					
Unadjusted RR (95% CI)	Ref	1.34(1.31, 1.36)	1.74(1.70, 1.78)	2.15(2.09, 2.22)	2.82(2.80, 2.84)
Adjusted RR (95% CI) [a]	Ref	1.16(1.14, 1.18)	1.43(1.40, 1.47)	1.68(1.62, 1.73)	2.11(2.09, 2.12)
IPTW-adjusted RR (95% CI) [b]	Ref	1.19(1.17, 1.21)	1.50(1.46, 1.53)	1.80(1.74, 1.86)	1.90(1.89, 1.92)
<10th percentile					
Unadjusted RR (95% CI)	Ref	1.27(1.26, 1.29)	1.58(1.55, 1.60)	1.90(1.86, 1.94)	2.40(2.39, 2.42)
Adjusted RR (95% CI) [a]	Ref	1.14(1.12, 1.15)	1.35(1.33, 1.37)	1.54(1.51, 1.58)	1.89(1.88, 1.90)
IPTW-adjusted RR (95% CI) [b]	Ref	1.16(1.14, 1.17)	1.38(1.36, 1.41)	1.53(1.49, 1.57)	1.70(1.69, 1.71)

Notes: [a]Adjusted RR: risk ratio adjusted for year of birth, maternal age, marital status, race/ethnicity, education, parity, pre-pregnancy BMI, Preexisting hypertension, Preexisting diabetes, gestational weight gain, initiation of prenatal care, payment source for delivery, and neonatal sex. [b]IPTW-adjusted RRs: Poisson regression applying inverse probability of treatment-weighted (IPTW) based on propensity scores.

Effect Modification by Preexisting Hypertension

Weighted marginal incidences showed that women with preexisting hypertension had higher absolute FGR risks across all smoking groups. For FGR-3rd, the IPTW-weighted incidences among women without preexisting hypertension were 3.2%, 3.9%, 5.2%, 6.7%, and 6.6% for nonsmokers, those who quit before pregnancy, in the first and second trimester, and persistent smokers, respectively, which were closely similar to those in the whole cohort; corresponding incidences among hypertensive women were 6.1%, 5.9%, 10.2%, 9.0%, and 9.1%, respectively (Figure 3a, b). Notably, among hypertensive women, quitting before pregnancy showed comparable weighted incidence of FGR to that of hypertensive nonsmokers. The unweighted crude incidences were presented in supplementary Figure S1a and b) for comparison.

Stratified IPTW-weighted Poisson regression showed generally consistent dose-response gradients and greater protection for early cessation in both strata (Table 3). Among normotensive women, the risk ratios (IPTW-aRRs) were essentially similar to that in the whole cohort. In contrast, among hypertensive women, the aRRs were numerically attenuated due to higher baseline FGR incidence (rather than biological reduction or loss of cessation benefit), except for those who quit in the first trimester showing comparable aRRs. Among hypertensive women, quitting before pregnancy yielded an aRR of 0.98 (FGR-3rd: 95% CI: 0.88–1.08) relative to hypertensive nonsmokers, whereas quitting in the first or second trimester, and persistent smokers still showed higher aRRs (1.67, 95% CI: 1.50–1.87; 1.47, 95% CI: 1.22–1.78; and 1.49, 95% CI: 1.43–1.57, respectively). Similar patterns were observed for FGR-5th and FGR-10th.

Significant interactions terms between preexisting hypertension and timing of smoking cessation (except quitting in the first trimester) were detected on multiplicative scale across all FGR definitions (betas(β) for interaction were −0.21, 95% CI: −0.32- −0.11; 0.05, 95% CI: −0.07–0.16; −0.33, 95% CI: −0.53- −0.14; and −0.31, 95% CI: −0.36- −0.26, respectively), indicating attenuation of relative risks among hypertensive women (Supplementary Table S4), whereas part of the differences in adjusted risk estimates across strata were relatively modest (Table 3). However, absolute risk differences (ARDs) between each smoking group and nonsmokers were generally comparable across hypertensive and normotensive strata (except that hypertensive women who quit in the first trimester had a higher ARD), indicating similar absolute benefits of cessation in both strata (Table 4). Furthermore, additive interaction analyses yielded RERI estimates close to zero across most comparisons (eg, RERI ranging from −0.26 to +0.23), with only a modest positive value for FGR-3rd among women quitting in the first trimester (RERI=0.67, 95% CI: 0.29–1.04), suggesting limited evidence of synergistic interaction (Table 4).

Overall, these findings indicate scale-dependent effect modification: significant interaction on the multiplicative scale (attenuation of relative risks among hypertensive women) accompany near-null synergistic interaction, while gradients for weighted incidences and IPTW-aRRs suggested greater benefits from early cessation across both strata, especially quitting before pregnancy.

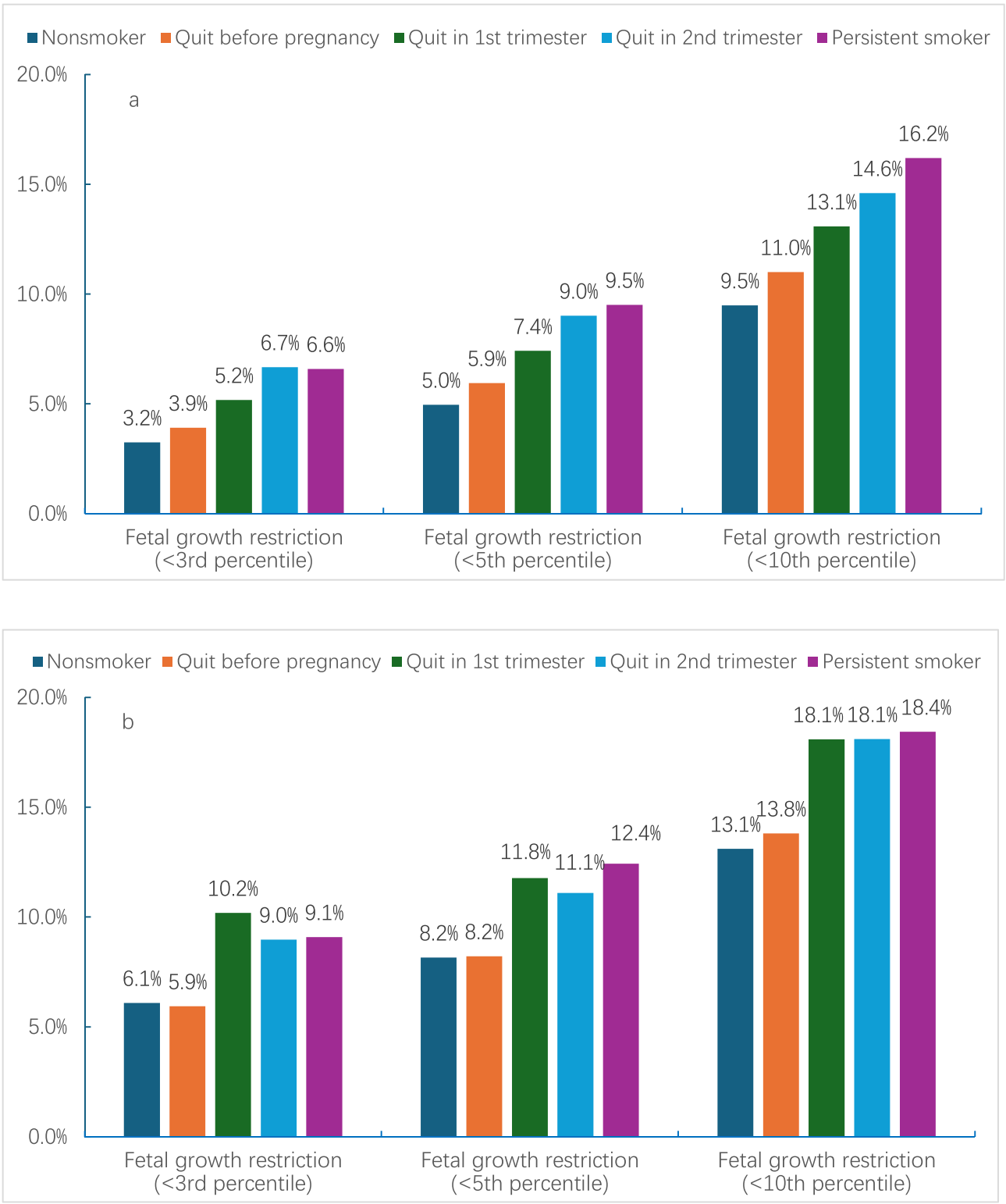

Figure 3 Weighted marginal incidence of fetal growth restriction (FGR) by smoking-cessation group, stratified by preexisting hypertension. (**a**) Women without preexisting hypertension and (**b**) women with preexisting hypertension. Incidences of FGR < 3rd, < 5th, and < 10th percentiles were estimated using IPTW to balance covariates across smoking groups. Absolute FGR risk was higher in hypertensive women across all groups. Among hypertensive women, quitting before pregnancy showed comparable FGR incidence to that of hypertensive nonsmokers.

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Table 3 Risk of Fetal Growth Restriction by Exposure Groups Stratified by Maternal Preexisting Hypertension

Fetal Growth Restriction Thresholds	Nonsmoker	Quit Before Pregnancy	Quit in 1st trimester	Quit in 2nd trimester	Persistent Smoker
Without Preexisting hypertension					
<3rd percentile					
Unadjusted RR (95% CI)	ref	1.37(1.34, 1.40)	1.87(1.82, 1.92)	2.32(2.23, 2.41)	3.11(3.08, 3.14)
Adjusted RR (95% CI) [a]	ref	1.17(1.15, 1.20)	1.52(1.48, 1.56)	1.77(1.70, 1.84)	2.27(2.25, 2.29)
IPTW-adjusted RR (95% CI) [b]	ref	1.21(1.18, 1.24)	1.60(1.55, 1.65)	2.06(1.98, 2.14)	2.04(2.01, 2.06)
<5th percentile					
Unadjusted RR (95% CI)	ref	1.34(1.32, 1.37)	1.75(1.71, 1.79)	2.16(2.09, 2.23)	2.85(2.83, 2.87)
Adjusted RR (95% CI) [a]	ref	1.17(1.15, 1.19)	1.45(1.42, 1.48)	1.69(1.63, 1.74)	2.14(2.12, 2.16)
IPTW-adjusted RR (95% CI) [b]	ref	1.20(1.18, 1.22)	1.49(1.46, 1.53)	1.82(1.75, 1.88)	1.92(1.90, 1.93)
<10th percentile					
Unadjusted RR (95% CI)	ref	1.28(1.26, 1.29)	1.59(1.56, 1.61)	1.91(1.86, 1.96)	2.42(2.41, 2.44)
Adjusted RR (95% CI)	ref	1.14(1.13, 1.16)	1.36(1.33, 1.38)	1.55(1.51, 1.59)	1.91(1.90, 1.92)
IPTW-adjusted RR (95% CI) [b]	ref	1.16(1.14, 1.17)	1.38(1.35, 1.40)	1.54(1.50, 1.58)	1.71(1.70, 1.72)
With Preexisting hypertension					
<3rd percentile					
Unadjusted RR (95% CI)	ref	1.04(0.96, 1.14)	1.40(1.26, 1.56)	1.76(1.52, 2.04)	2.02(1.95, 2.10)
Adjusted RR (95% CI) [a]	ref	0.98(0.90, 1.07)	1.26(1.13, 1.40)	1.52(1.31, 1.76)	1.65(1.59, 1.72)
IPTW-adjusted RR (95% CI) [b]	ref	0.98(0.88, 1.08)	1.67(1.5, 1.87)	1.47(1.22, 1.78)	1.49(1.43, 1.57)
<5th percentile					
Unadjusted RR (95% CI)	ref	1.08(1.01, 1.16)	1.32(1.20, 1.44)	1.70(1.50, 1.93)	1.97(1.90, 2.03)
Adjusted RR (95% CI) [a]	ref	1.02(0.95, 1.10)	1.20(1.09, 1.31)	1.49(1.31, 1.70)	1.64(1.58, 1.69)
IPTW-adjusted RR (95% CI) [b]	ref	1.01(0.93, 1.09)	1.44(1.30, 1.59)	1.36(1.15, 1.60)	1.52(1.46, 1.58)
<10th percentile					
Unadjusted RR (95% CI)	ref	1.07(1.01, 1.13)	1.30(1.21, 1.39)	1.53(1.38, 1.70)	1.82(1.77, 1.87)
Adjusted RR (95% CI) [a]	ref	1.02(0.96, 1.08)	1.20(1.11, 1.29)	1.37(1.23, 1.52)	1.56(1.51, 1.60)
IPTW-adjusted RR (95% CI) [b]	ref	1.05(0.99, 1.12)	1.38(1.28, 1.49)	1.38(1.22, 1.57)	1.41(1.36, 1.45)

Notes: [a]Adjusted RR: risk ratio adjusted for year of birth, maternal age, marital status, race/ethnicity, education, parity, pre-pregnancy BMI, preexisting hypertension, Preexisting diabetes, gestational weight gain, initiation of prenatal care, payment source for delivery, and neonatal sex. [b]IPTW-adjusted RRs: Poisson regression applying inverse probability of treatment-weighted (IPTW) based on propensity scores.

Table 4 Weighted Incidence, Absolute Risk Difference (ARD), and Additive-Scale Interaction (RERI) Between Smoking Cessation Timing and Preexisting Hypertension for FGR

Smoking Status	Weighted Incidence of FGR (%) Without Hypertension	Weighted Incidence of FGR (%) With Hypertension	Absolute Risk Difference (ARD, %) (vs Nonsmokers)	RERI (95% CI)*
FGR (<3rd percentile)				
Nonsmokers	3.2	6.1	Reference	—
Quit before pregnancy	3.9	5.9	+0.7 (no hypertension), −0.2 (hypertension)	−0.26(−0.45, −0.06)
Quit in 1st trimester	5.2	10.2	+2.0 (no hypertension), +4.1 (hypertension)	0.67(0.29, 1.04)
Quit in 2nd trimester	6.7	9.0	+3.5 (no hypertension), +2.9 (hypertension)	−0.17(−0.72, 0.38)
Persistent smokers	6.6	9.1	+3.4 (no hypertension), +3.0 (hypertension)	−0.11(−0.25, 0.04)

(*Continued*)

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Table 4 (Continued).

Smoking Status	Weighted Incidence of FGR (%) Without Hypertension	Weighted Incidence of FGR (%) With Hypertension	Absolute Risk Difference (ARD, %) (vs Nonsmokers)	RERI (95% CI)*
FGR (<5th percentile)				
Nonsmokers	5.0	8.2	Reference	—
Quit before pregnancy	5.9	8.2	+0.9 (no hypertension), −0.0 (hypertension)	−0.19(−0.34, −0.04)
Quit in 1st trimester	7.4	11.8	+2.4 (no hypertension), +3.6 (hypertension)	0.23(−0.02, 0.49)
Quit in 2nd trimester	9.0	11.1	+4.0 (no hypertension), +2.9 (hypertension)	−0.22(−0.62, 0.17)
Persistent smokers	9.5	12.4	+4.5 (no hypertension), +4.2 (hypertension)	−0.06(−0.17, 0.05)
FGR (<10th percentile)				
Nonsmokers	9.5	13.1	Reference	—
Quit before pregnancy	11.0	13.8	+1.5 (no hypertension), +0.7 (hypertension)	−0.08(−0.18, 0.01)
Quit in 1st trimester	13.1	18.1	+3.6 (no hypertension), +5.0 (hypertension)	0.15(−0.02, 0.31)
Quit in 2nd trimester	14.6	18.1	+5.1 (no hypertension), +5.0 (hypertension)	−0.01(−0.27, 0.25)
Persistent smokers	16.2	18.4	+6.7 (no hypertension), +5.3 (hypertension)	−0.14(−0.21, −0.08)

Notes: *RERI, relative excess risk due to interaction = $RR_{11} - RR_{10} - RR_{01} + 1$; RRs were derived from inverse probability of treatment–weighted Poisson regression models. Positive RERI indicates additive interaction between smoking and hypertension on FGR risk.

Discussion

In this national cohort of more than 17 million US singleton live births (2020–2024), we observed a robust dose–response association between the timing of maternal smoking cessation and the risk of FGR. Earlier cessation—especially before pregnancy—was consistently associated with lower risk, whereas quitting after the first trimester conferred only modest or diminishing benefit. Preexisting hypertension modified this relationship: significant interaction was observed on the multiplicative scale (attenuation of relative risks among hypertensive women) but not on the additive scale, suggesting independence on the additive scale (a lack of departure from risk additivity) rather than synergistic interaction. Notably, among hypertensive women, quitting before pregnancy showed comparable FGR risk to that of hypertensive nonsmokers. Our results corroborate the well-established evidence that maternal smoking is a major preventable cause of FGR, and reveal a clear dose-response relationship between the timing of cessation and FGR risk, underscoring the critical importance of early cessation. Consistent with prior studies, cessation before pregnancy yielded the greatest reduction in risk, and quitting in the first trimester also conferred meaningful benefit though to a lesser extent, whereas quitting in the second trimester provided only modest or no protection.[6–8] This temporal gradient is biologically plausible, as the first trimester is a critical window for placental implantation, trophoblast invasion, and uteroplacental vascular remodeling, processes that are highly vulnerable to toxic exposures, such as smoking.[2,5,27] Exposure to smoking during this critical developmental window may have lasting effects on placental function. Consistent with this biological framework, quitting in the second trimester and persistent smoking yield nearly identical risk estimates suggested that cessation after the first trimester may confer little or no measurable benefit for severe FGR (FGR-3rd), which further corroborated that early pregnancy may represent a particularly vulnerable period for placental development.

Our novel contribution is the demonstration that preexisting hypertension modifies the smoking-FGR associations on the multiplicative scale but not on the additive scale. Among hypertensive women, the risk ratios were numerically

attenuated, reflecting higher baseline FGR risk and compression of ratios on the multiplicative scale. The near zero RERI estimates indicate limited synergistic effect, suggesting that smoking and hypertension contribute largely independently rather than synergistically on additive scale to FGR when coexisting. Nevertheless, it should not be interpreted as absence of biological interplay between maternal smoking and hypertension, as statistical interaction on a specific scale may not fully reflect underlying biological mechanisms. The phenomenon that quitting before pregnancy normalized FGR risk (a greater reduction in relative risk) in hypertensive women is biologically plausible given that the placenta with impaired vascular may be more susceptible to both the impairment of smoking and the benefits of cessation. Another possible explanation is speculated to be associated with more intensive perinatal or antenatal care,[15] and stronger motivation for behavioral change among high-risk pregnancies.

Our findings agree with a large body of evidence showing that smoking cessation before or early in pregnancy substantially reduces tobacco-related adverse perinatal outcomes, including fetal growth restriction, preterm birth, low birth weight and stillbirth. Moore et al reported that trimester-specific smoking patterns were strongly associated with preterm birth, with the lowest risks among women who quit before or in the first trimester.[28] Similarly, Polakowski et al, using US birth certificate data, showed that cessation in the first trimester achieved comparable risks of preterm birth and SGA to that of nonsmokers.[7] Blatt et al analyzing nearly one million Ohio births, likewise found that smoking of any duration during pregnancy increased the risk of FGR, with earlier cessation conferring the greatest protection.[6] In a larger study of about five million California births, Ratnasiri et al confirmed that cessation before pregnancy or in the first trimester substantially reduced the risks of low birth weight, preterm birth, and SGA.[29] Consistent findings from international cohorts, including the Japan Environment and Children's Study (Tatsuta et al) and Generation R and Born in Bradford cohorts from Europe (Brand et al) further support that cessation before or early in pregnancy lower the impairment on birth weight and other anthropometrics, whereas cessation later provides only minimal or no meaningful effect.[8,30]

However, very few studies have examined whether maternal comorbidities modify the association between smoking and FGR. Lewandowska et al observed additive risks of maternal smoking and obesity, showing that cessation before pregnancy reduced FGR risk, whereas quitting later offered no protection, and excessive maternal weight further increased the risk.[9] Allen et al, in a Canadian population-based study, reported that smoking modified the hypertension-FGR association, hypertensive women who smoked had a less than expected increase risks of SGA.[15] And Luke and Kirby reported synergistic effect between trimester-specific smoking and hypertension on SGA.[16] In contrast, Rasmussen and Irgens, in a Norwegian registry, found no synergistic interaction between smoking and pregnancy-induced hypertension on FGR; each factor may act largely independently.[17]

Specifically, previous studies have reported that maternal smoking is associated with a reduced risk of preeclampsia,[31] but increases the risk of adverse fetal growth outcomes among pregnancies complicated by preeclampsia.[17] The mechanism underlying this paradoxical association remain incompletely understood and may involve multiple biological pathways affecting placental function and vascular development.[32] Although our primary analyses focused on preexisting hypertension, gestational hypertension or preeclampsia may also interact with maternal smoking and fetal growth. However, the results in sensitivity analyses excluding gestational hypertension or preeclampsia were similar to main analyses, which suggested the robustness of the main findings. Nevertheless, future studies should further investigate potential interactions between maternal smoking and gestational hypertension or preeclampsia. Our study extends this literature by explicitly quantifying the scale-dependent effect modification by preexisting hypertension. Specially, we found that hypertensive women had higher absolute FGR risks across all smoking groups, yet cessation before pregnancy seems effectively eliminated the excess FGR risk attributable to smoking, showing comparable to that of hypertensive nonsmokers. These findings highlight the critical importance of early smoking cessation—preferably before pregnancy or within the first trimester—in preventing FGR, particularly among hypertensive women. At the population level, they reinforce the need for preconception and early-pregnancy cessation interventions targeting women of reproductive age, consistent with ACOG and public health guidance.[33,34] Clinically, integrating cessation counseling into preconception and early antenatal care—especially for women with hypertension—may help eliminate the excess risk of FGR from smoking and improve perinatal outcomes.

By integrating trimester-specific smoking cessation with hypertensive status, this national study demonstrates that preexisting hypertension not only increases the absolute risk of FGR but also modifies the relative benefit of early

cessation. Strengths include the large, nationally representative cohort; use of race/ethnicity-specific fetal growth standards to define FGR; consistent findings across different FGR thresholds; and application of IPTW to minimize confounding. However, given the very large sample size, small numerical differences may not reflect clinically meaningful differences, and interpretation of interaction findings should consider the magnitude and potential clinical relevance of the observed effects in addition to statistical significance.

Nevertheless, several limitations should be noted. First, smoking status was self-reported without biochemical verification, which could lead to underreporting and potential misclassification. However, women who reported smoking are likely true smokers,[35] and this misclassification could likely bias the association towards null. In addition, residual misclassification of smoking intensity may still dilute the associations. Second, as with all observational studies, particularly those based on registry data such as NVSS, residual confounding by unmeasured factors, such as alcohol use, diet and other behavioral changes, cannot be entirely excluded. Although we adjusted for a range of maternal characteristics, no formal sensitivity analyses were conducted to quantify the potential impact of unmeasured confounding. Third, the use of live births may introduce selection bias. Both maternal smoking and preexisting hypertension are associated with an increased risk of fetal loss, including stillbirth; thus, conditioning on survival to birth may selectively excluding more severe cases, which may underestimate the true effect of smoking and hypertension. In addition, adjustment for gestational weight gain and timing of prenatal care initiation may have resulted in overadjustment, potentially further underestimate the associations. Finally, the study period (2020–2024) overlapped with the COVID-19 Pandemic, which may have influenced maternal health behaviors and healthcare utilization. Although we have adjusted for year of birth, the findings may partly reflect pandemic-related conditions and may differ under non-pandemic settings. Future studies should incorporate objective biomarkers of tobacco exposure and investigate the mechanisms linking smoking, hypertension, and placental dysfunction.[9,11,17]

Conclusions

This national cohort identified a clear dose–response association between the timing of maternal smoking cessation and FGR risk. Earlier cessation—especially before pregnancy—was consistently associated with lower risk, whereas quitting after the first trimester provided diminishing benefit. Preexisting hypertension modifies these association: interactions were significant on the multiplicative scale, where relative risks were attenuated among hypertensive women, but not additive scale, suggesting independence on the additive scale (a lack of departure from risk additivity). Notably, hypertensive women who quit before pregnancy achieved FGR risk comparable to hypertensive nonsmokers. These findings underscore the need for early, targeted smoking cessation interventions integrated into preconception and antenatal care, particularly for high-risk women.

Use of Generative AI Tools

ChatGPT was used to polish the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Abbreviations

FGR, Fetal growth restriction; SGA, Small for gestational age; HDP, Hypertensive disorders of pregnancy; NVSS, The US National Vital Statistics System; IOM, Institute of Medicine; GWG, Gestational weight gain; RR(s), Risk ratio(s); 95% CI, 95% Confidence intervals; IPTW, Inverse probability of treatment-weighted; RERI, Relative excess risk due to interaction; ARD(s), Absolute risk difference(s).

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available in the National Center for Health Statistics repository: https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm#Downloadable.

Ethics Approval and Informed Consent

This study involved secondary analysis of the National Vital Statistics System (NVSS) datasets, which has its own ethical approval with patient informed consent and were publicly available with deidentified information. According to the "Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects" issued by the Chinese government on February 18, 2023 (Article 32, items 1 and 2), this type of research, which utilizes publicly available human information data, causes no harm to human subjects, and does not involve sensitive personal information or commercial interests, is exempt from institutional ethical review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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