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Maternal smoking and gestational hypertension: Heterogeneous effect by timing of the exposure

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ABSTRACT

Objectives: The objective of this study was to examine whether the association between maternal smoking and gestational hypertension varies by the timing of exposure.
Study design: Retrospective cohort study of women identified in 2015 US natality records for singleton births.
Main outcome measures: Our outcome was whether a woman was diagnosed with gestational hypertension (GH) on the birth record, a category which includes preeclampsia.
Results: Women who smoked before and during pregnancy had a reduced risk for GH relative to non-smokers (adjusted RR 0.92, 95% CI 0.90–0.94). In contrast, women who apparently quit just before the start of pregnancy had higher risk than non-smokers (adjusted RR 1.02, 95% CI 1.00–1.05). When the trimester-specific effects were examined, only women who smoked before pregnancy and in all three trimesters had reduced risk for GH. Smoking mothers who quit just before the start of the 3rd trimester had an increased risk for GH compared to non-smokers (adjusted RR 1.08, 95% CI 1.02–1.16).
Conclusion: In our analysis, women who smoked before pregnancy and in all three trimesters have reduced risk of GH compared to non-smokers, while smokers who reported quitting before pregnancy were at an increased risk. Our results offer new insights into the importance of timing of smoking in pregnancy on risk of GH, and challenge the notion that any smoking during pregnancy has a protective effect.

1. Introduction

While maternal smoking during pregnancy is known to cause a variety of adverse pregnancy outcomes, such as spontaneous abortion and preterm birth [1], it is paradoxically known to be associated with a reduced risk of hypertensive disorders in pregnancy. Two systematic reviews agree on an inverse association between cigarette smoking during pregnancy and preeclampsia, with overall risk ratios (RR) of 0.68 (95% confidence interval (CI) of 0.67–0.69) [2] and 0.67 (95% CI 0.60–0.75) [3].

However, it is unknown what possible mechanism could explain these protective effects. In addition, there is uncertainty about importance of the timing of smoking to these associations, primarily because most studies did not differentiate the effects of smoking in different gestational ages. The pathogenesis of preeclampsia is thought to involve several stages: abnormal invasion of trophoblastic tissue occurs at early stage (at about 12–13 weeks' gestation); and the later disease development is considered to be caused by placental hypo-perfusion, hypoxia, and ischemia [4]. Understanding whether the effects vary by the timing of exposure could shed light onto the mechanism underlying the association between maternal smoking and the development of hypertensive disorders during pregnancy. If timing of quitting of smoking has material impact on risk, this may also influence how women are counselled when they plan pregnancy, especially if smoking at a specific time increases risk of gestational hypertension.

In this study, we aimed to examine the different effects of maternal smoking on gestational hypertension (GH), as identified on 2015 US birth certificates, by timing of the exposure.

2. Materials and methods

2.1. Study sample

We obtained the 2015 natality data file from the National Center for Health Statistics (NCHS), which includes all live births to US residents, and limited it to singletons. We excluded births in US territories and the

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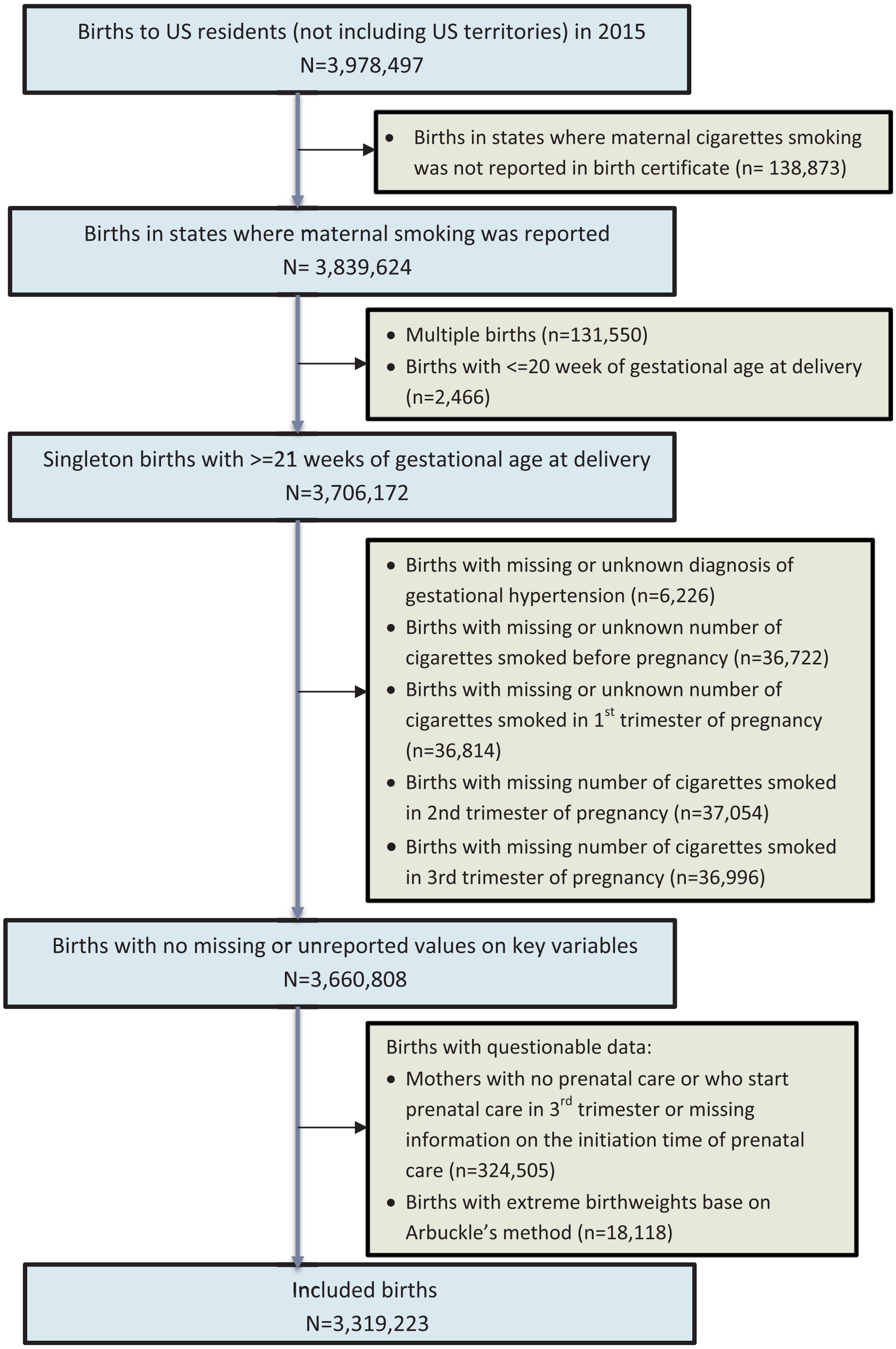

Fig. 1. Flow chart of sample derivation. This figure describes how the study sample were derived from the US 2015 births and depicts the number and reasons for the excluded births. Excluded groups are not mutually exclusive, so the numbers do not add up to total.

two states with no information on maternal cigarette smoking (Connecticut and New Jersey). We further excluded: (a) women with missing information on GH or maternal smoking; (b) women who delivered at ≤20 weeks of gestation (because GH, by clinical definition, occurs after 20 weeks' gestation [5]); (c) women who initiated their prenatal care visit after the start of their 3rd trimester and women who did not receive any prenatal care (to reduce potential bias from underdiagnosing of GH); and (d) births with extreme values of birthweight, using the method of Arbuckle et al. [6] (to reduce the number of erroneous gestational ages). Fig. 1 depicts the number of and reasons for the excluded births. The resulting study sample consisted of 3,319,223 births with ≥21 weeks of gestational age at delivery. In the analysis for trimester-specific effects, to ensure that we had potential for exposure in every trimester, we only included 3,308,786 with gestational age ≥27 weeks. All birth record data were de-identified, and the analysis was deemed exempt by the Institutional Review Board of Drexel University.

2.2. *Gestational hypertension*

Beginning with the 2003 revision of the US standard birth certificate, pre-pregnancy (chronic) hypertension, GH (pregnancy-induced hypertension *OR* preeclampsia), and eclampsia were included under "Risk factors in this pregnancy" [7]. Our outcome variable included both diagnoses of pregnancy-induced hypertension (below the threshold for preeclampsia) and preeclampsia; we had no means to differentiate these two diagnoses with birth certificate data.

2.3. Maternal smoking

Smoking information on birth certificates captured daily average quantities of cigarettes smoked during the three months before pregnancy and during each trimester. These questions were asked on maternal worksheets, which were designed by NCHS to collect information directly from mothers after giving birth. A 2015 study reported that smoking information on birth certificates had 'almost perfect' agreement with maternal worksheets and 'substantial' agreement with medical records [8], implying that the vast majority of data on smoking is derived from standardized worksheets. Based on this data, we categorized maternal smoking into four mutually exclusive trajectories: (a) smokers before and during pregnancy (i.e., in the three months prior to pregnancy and during any trimester); (b) smokers before pregnancy only (i.e., in the three months prior to pregnancy but not during pregnancy); (c) smokers during pregnancy only (i.e., during any trimester but not in the three months prior to pregnancy); and (d) nonsmokers (i.e., no smoking in either the three months prior to pregnancy or during pregnancy). We also constructed indicator variables for report of smoking in any of the four time periods. We further categorized women who smoked before and during pregnancy into three finer mutually exclusive groups based on the combination of their smoking status in each trimester: (a) smokers before pregnancy and in 1st trimester only; (b) smokers before pregnancy and in 1st and 2nd trimesters only; and (c) "persistent smokers" before pregnancy and in all trimesters.

2.4. Covariates

Potential confounders were selected *a priori*, including parents' demographic characteristics (race, Hispanic origin, education, mother's age), parity, gravidity, interval since last pregnancy, previous preterm delivery, previous cesarean section, adequacy of prenatal care, maternal pre-pregnancy body mass index (BMI), gestational weight gain, pre-pregnancy diabetes, gestational diabetes, infertility treatment, payment source, and child's sex. Using BMI-based guidelines for gestational weight gain developed by the Institute of Medicine, gestational weight gain was categorized as inadequate, appropriate, or excessive [9]. An index of adequacy of prenatal care visits was calculated based on the initiation time and number of prenatal care visits, and women were categorized as receiving intensive, adequate, intermediate, or inadequate prenatal care [10].

2.5. Statistical method

We estimated the RR for GH by maternal smoking status using Poisson regression with robust variance estimator [11]. All *a priori* considered covariates were included in the regression models to control for confounding. We evaluated exposure-response trends across the categories of the number of cigarettes smoked per day, categorized as 1–3, 4–6, 7–10, and ≥11. All analyses were performed using SAS 9.3 (SAS Institute, Cary NC).

3. Results

Among 3,319,223 women with singleton births at ≥21 weeks of gestation at delivery, 183,035 (5.51%) had GH. In this study sample, 9.86% of mothers smoked during the 3 months before pregnancy, 7.27% smoked during the 1st trimester, 6.16% smoked during the 2nd trimester, and 5.85% smoked during the 3rd trimester. Table 1 presents the incidence of GH by maternal smoking status and gestational age at delivery, as well as other covariates. In general, smokers during

Table 1
Incidence of Gestational Hypertension by Smoking Status, Demographic, Obstetric and Neonatal Characteristics, Among Women Who Delivered at Gestational Age ≥21 Weeks.

	N	Gestational Hypertension	
		n	%
Mother's Smoking Status			
Smoked in the 3 months before pregnancy			
Yes	327,161	19,358	5.92
No	2,992,062	163,677	5.47
Smoked in the 1st trimester			
Yes	241,146	13,168	5.46
No	3,078,077	169,867	5.52
Smoked in the 2nd trimester			
Yes	204,328	10,626	5.20
No	3,114,895	172,409	5.53
Smoked in the 3rd trimester			
Yes	194,198	9847	5.07
No	3,125,025	173,188	5.54
Gestational Age at Delivery			
21–26 weeks	10,437	925	8.86
27–33 weeks	49,600	9362	18.88
34–36 weeks	182,265	24,638	13.52
37–39 weeks	2,115,933	123,377	5.83
40–47 weeks	960,988	24,733	2.57
Mother's Demographic Characteristics			
Mother's Age			
< 20 years	190,555	11,647	6.11
20–39 years	3,032,644	164,323	5.42
40–54 years	96,024	7065	7.36
Mother's Race			
White	2,552,180	138,471	5.43
Black	498,653	34,143	6.85
American Indian or Alaskan Native	35,951	2400	6.68
Asian or Pacific Islander	232,439	8021	3.45
Mother's Hispanic Origin			
Non-Hispanic	2,529,814	147,355	5.82
Hispanic	643,933	28,158	4.37
Unknown	145,476	7522	5.17
Mother's Education			
Less than high school	451,277	21,628	4.79
High school	813,791	45,305	5.57
Some college	710,072	44,513	6.27
Associate degree	276,930	17,919	6.47
Bachelor degree	653,912	34,173	5.23
Graduate school	376,777	17,895	4.75
Unknown	36,464	1602	4.39
Father's Demographic Characteristics			
Father's Race			
White	2,138,076	116,161	5.43
Black	391,467	25,406	6.49
American Indian or Alaskan Native	29,486	1943	6.59
Asian or Pacific Islander	195,619	6196	3.17
Unknown or not stated	564,575	33,329	5.90
Father's Hispanic Origin			
Non-Hispanic	2,233,969	126,115	5.65
Hispanic	913,047	48,170	5.28
Unknown	134,016	6684	4.99
Father's Education			
Less than high school	404,854	20,209	4.99
High school	836,173	49,107	5.87
Some college	572,927	34,929	6.10
Associate degree	210,789	12,915	6.13
Bachelor degree	549,490	26,841	4.88
Graduate school	309,032	12,241	3.96
Unknown	435,958	26,793	6.15
Obstetric History			
Parity (Number of Previous Live Births)			
0 (nulliparous)	1,298,950	95,877	7.38
1–2	1,628,192	68,991	4.24
3 or more	384,879	17,801	4.63
Unknown	7202	366	5.08

(*continued on next page*)

Table 1 (*continued*)

	N	Gestational Hypertension	
		n	%
Gravidity (Number of Previous Pregnancies)			
0	1,067,797	76,980	7.21
1–3	1,896,440	87,678	4.62
4 or more	343,842	17,851	5.19
Unknown	11,144	526	4.72
Interval Since Last Pregnancy			
4–11 months	89,542	5274	5.89
12–23 months	512,400	21,626	4.22
24–71 months	960,760	39,269	4.09
≥72 months	308,534	17,867	5.79
No previous pregnancy	1,067,797	76,980	7.21
Unknown	380,190	22,019	5.79
Previous Preterm Birth			
No	3,224,858	174,711	5.42
Yes	94,365	8324	8.82
Previous Cesarean Section			
No	2,818,735	157,316	5.58
Yes	500,488	25,719	5.14
Characteristics of This Pregnancy			
Adequacy of Prenatal Care			
Intensive	222,342	19,611	8.82
Adequate	1,467,482	95,671	6.52
Intermediate	1,430,964	59,256	4.14
Inadequate	172,239	7036	4.09
Missing	26,196	1461	5.58
Pre-pregnancy Body-Mass-Index			
Underweight < 18.5 kg/m^2	116,526	2943	2.53
Normal 18.5–24.9 kg/m^2	1,471,204	50,419	3.43
Overweight 25.0–29.9 kg/m^2	837,658	47,042	5.62
Obesity I 30.0–34.9 kg/m^2	452,479	36,013	7.96
Obesity II 35.0–39.9 kg/m^2	219,004	22,375	10.22
Extreme Obesity III ≥40.0 kg/m^2	152,106	20,413	13.42
Unknown or not stated	70,246	3830	5.45
Gestational Weight Gain			
Inadequate	672,406	26,872	4.00
Appropriate	1,023,090	42,783	4.18
Excessive	1,518,141	107,523	7.08
Existing Diabetes (Diagnosis prior to this pregnancy)			
No	3,293,811	179,352	5.45
Yes	25,412	3683	14.49
Gestational Diabetes			
No	3,130,503	162,051	5.18
Yes	188,720	20,984	11.12
Infertility Treatment Used			
No	3,281,092	179,575	5.47
Yes	38,131	3460	9.07
Principle Source of Payment			
Medicaid	1,397,556	76,767	5.49
Private Insurance	1,655,235	94,716	5.72
Self-pay	112,413	3190	2.84
Other	133,392	7493	5.62
Unknown	20,627	869	4.21
Neonatal Characteristics			
Sex of the child			
Female	1,620,572	88,195	5.44
Male	1,698,651	94,840	5.58

pregnancy had a lower incidence of GH than non-smokers, and the largest risk difference was in the 3rd trimester between smokers (5.07%) and non-smokers (5.54%). However, smokers before pregnancy had a higher incidence of GH compared to non-smokers (5.92% vs 5.47%). The incidence of GH peaked among mothers who delivered at 27–33 weeks of gestational age (18.88%), while the incidence was 2.57% among women who delivered at > 40 weeks of gestational age. Mothers with the following characteristics had higher incidences of GH: 40–54 years of age, non-Caucasian, educational level of some college or associate degree, no previous live births, no previous pregnancy, history of preterm birth, received either intensive or adequate prenatal care, obese before pregnancy, excessive weight gain during pregnancy, existing diabetes or gestational diabetes, or received infertility treatment.

We observed differences in risk of GH by timing of mothers' smoking (Table 2). Smokers before and during pregnancy had a reduced risk for GH compared to non-smokers (RR = 0.92, 95% CI 0.90–0.94). Only 4265 women reported initiating smoking after the start of pregnancy ("smoked during pregnancy only") and they also had a reduced risk of GH relative to non-smokers. However, among the 84,452 mothers who reported quitting smoking just before the start of pregnancy ("smoked before pregnancy only"), the risk of GH was higher than that of non-smokers (adjusted RR = 1.02, 95% CI 1.00–1.05). There is evidence that quitting just before pregnancy (RR = 1.11, 95% CI 1.08–1.14) and never smoking (RR = 1.09, 95% CI 1.07–1.11) confer similarly elevated risks of GH compared to "smoked before and during pregnancy".

Among women who delivered at ≥27 weeks of gestation, we evaluated trimester-specific effects by dividing "smoked before and during pregnancy" into finer groups based on their reported smoking in each trimester (Table 3). The 186,950 women who smoked before pregnancy and during all three trimesters, referred to as "persistent smokers", had a clearly reduced risk of GH (RR = 0.89, 95% CI 0.87–0.91). Smoking mothers who quit just before the start of the 3rd trimester ("smoked before pregnancy and 1st and 2nd trimesters only") had a slightly increased risk for GH relative to non-smokers (RR = 1.08, 95% CI 1.02–1.16).

We also examined the dose-response relationship between number of cigarettes smoked per day and the risk of GH (Table 4). There was no evidence of a dose-response for smoking before pregnancy only. Among the persistent smokers, after adjusting for the amount smoked before pregnancy and during other trimesters, there is evidence of a trend towards lower levels of risk with higher smoking intensity (p-trend < 0.001). For example, compared to smoking 1–3 cigarettes/day, smoking more than 11 cigarettes/day was associated with stronger protective effects on GH (RR = 0.81, 95% CI 0.71–0.92).

4. Discussion

Our findings are in agreement with a large body of literature showing that women who smoked cigarettes during pregnancy had a reduced risk of GH [2,3]. However, we observed that this protective effect was confined to persistent smokers who smoked before pregnancy and in all three trimesters. Indeed, among women who smoked before pregnancy and up to the 2nd trimester but quit smoking before the start of the 3rd trimester, the risk was higher than that in non-smokers. Our sample size was sufficiently large for analysis of different smoking patterns and suggests heterogeneity of effects by time of smoking.

4.1. Comparison to literature

Although a large body of literature exists showing that women who smoked cigarettes during pregnancy had a reduced risk for GH [2,3], the importance of timing of exposure is understudied primarily because most studies only examined the effect of *any* smoking in pregnancy. Few studies have examined the trimester-specific effects of maternal smoking. Engel et al. reported similar patterns as ours using data from a Norwegian cohort [12]. Their study found that women who smoked in all trimesters had a reduced risk of GH with an OR of 0.62 (95% CI 0.46–0.83), while women who smoked in the 1st and 2nd trimesters only had approximately the same risk for preeclampsia (OR = 0.99, 95% CI 0.87–1.11) and GH (excluding preeclampsia, OR = 0.97, 95% CI 0.62–1.51) as non-smokers [12]. Similarly, a study using data from the Swedish Birth Register on all singleton births in Sweden during 1999–2006 (n = 612,712) found that persistent smoking during pregnancy reduced the risk of term preeclampsia or GH (OR = 0.48, 95% CI

Table 2
Association Between Mother's Smoking Status and Risk of Gestational Hypertension (GH), Among Women Who Delivered at Gestational Age ≥21 Weeks.

	n	Incidence of GH (%)	Adjusted [a] Risk Ratio (RR) for GH			
			RR	(95% CI)	RR	(95% CI)
Mother's Smoking Status						
Smoked before and during pregnancy	242,709	5.46	**0.92**	**(0.90–0.94)**	Reference	
Smoked before pregnancy only	84,452	7.23	**1.02**	**(1.00–1.05)**	**1.11**	**(1.08–1.14)**
Smoked during pregnancy only	4,265	5.06	**0.85**	**(0.74–0.97)**	0.92	(0.81–1.05)
Non-smoker	2,987,797	5.47	Reference		**1.09**	**(1.07–1.11)**

The statistical significance was defined as alpha = 0.05. In the table, bold indicates $p < 0.05$.
[a] Adjusted for mother's demographic characteristics (age, race, Hispanic origin, education), father's demographic characteristics (race, Hispanic origin, education), parity, gravidity, interval since last pregnancy, previous preterm, previous cesarean section, adequacy of prenatal care, maternal pre-pregnancy BMI, gestational weight gain, pre-pregnancy diabetes, gestational diabetes, infertility treatment, payment source, and child sex.

Table 3
Association Between the Combination of Trimester-Specific Mother's Smoking Status and Risk of Gestational Hypertension (GH), Among Women Who Delivered at Gestational Age ≥27 Weeks.

	n	Incidence of GH (%)	Adjusted [a] Risk Ratio (RR) for GH	
			RR	(95% CI)
Smoked before and during pregnancy				
Before pregnancy and in 1st trimester only	36,579	6.88	1.00	(0.96–1.04)
Before pregnancy and in 1st and 2nd trimesters only	13,340	6.98	**1.08**	**(1.02–1.16)**
Before pregnancy and in all trimesters	186,950	5.07	**0.89**	**(0.87–0.91)**
Non-smokers	2,978,146	5.46	Reference	

The statistical significance was defined as alpha = 0.05. In the table, bold indicates $p < 0.05$.
[a] Adjusted for mother's demographic characteristics (age, race, Hispanic origin, education), father's demographic characteristics (race, Hispanic origin, education), parity, gravidity, interval since last pregnancy, previous preterm, previous cesarean section, adequacy of prenatal care, maternal pre-pregnancy BMI, gestational weight gain, pre-pregnancy diabetes, gestational diabetes, infertility treatment, payment source, and child sex.

Table 4
Association Between Number of Cigarettes Smoked Per Day and Risk of Gestational Hypertension (GH), Among Women Who Delivered at Gestational Age ≥27 Weeks.

	n	Incidence of GH (%)	Adjusted [a] Risk Ratio (RR) for GH (95% CI)
Smokers before pregnancy only			
Smoked 1–3 cigarettes/day before pregnancy	18,236	6.75	Reference
Smoked 4–6 cigarettes/day before pregnancy	20,596	6.91	0.97 (0.90–1.05)
Smoked 7–10 cigarettes/day before pregnancy	24,677	7.59	1.05 (0.98–1.12)
Smoked ≥11 cigarettes/day before pregnancy	20,650	7.54	1.01 (0.94–1.09)
Test for dose–response by quartiles of cigarettes/day: p-trend = 0.4 [b]			
Persistent Smokers [c]			
Smoked 1–3 cigarettes/day during 3rd trimester	37,872	5.73	Reference
Smoked 4–6 cigarettes/day during 3rd trimester	51,159	4.95	**0.82 (0.76–0.89)**
Smoked 7–10 cigarettes/day during 3rd trimester	67,517	4.90	**0.83 (0.75–0.91)**
Smoked ≥11 cigarettes/day during 3rd trimester	30,402	4.82	**0.81 (0.71–0.92)**
Test for dose-response by quartiles of cigarettes/day: p-trend < **0.001** [d]			

The statistical significance was defined as alpha = 0.05. In the table, bold indicates $p < 0.05$.
[a] Adjusted for mother's demographic characteristics (age, race, Hispanic origin, education), father's demographic characteristics (race, Hispanic origin, education), parity, gravidity, interval since last pregnancy, previous preterm, previous cesarean section, adequacy of prenatal care, maternal pre-pregnancy BMI, gestational weight gain, pre-pregnancy diabetes, gestational diabetes, infertility treatment, payment source, child sex, cigarettes smoked per day before pregnancy and in 1st and 2nd trimesters.
[b] Quartiles of cigarettes/day was included as a continuous variable with values of 1, 2, 3, 4. The RR for one increase in quartile is 1.01 (0.99–1.03), p-trend = 0.4.
[c] Persistent smokers: women who smoked before pregnancy and in all three trimesters.
[d] Quartiles of cigarettes/day was included as a continuous variable with values of 1, 2, 3, 4. The RR for one increase in quartile is 0.94 (0.90–0.97); p-trend < 0.001.

0.44–0.53), whereas the risk among women who smoked at first antenatal visit but stopped smoking before 30–32 weeks was similar to that of non-smokers (OR = 0.94, 95% CI 0.83–1.05) [13]. In contrast, two hospital-based case-control studies in Canada reported that women who stopped smoking in the first 20 weeks of pregnancy had somewhat elevated risk of GH [14] and preeclampsia [15], although effect estimates were imprecise and inconsistent across various outcome definitions. Two similarly-powered cohort studies in the US reported that pregnant women who stopped smoking before study enrollment in early pregnancy, compared to never-smokers, exhibited associations that suggested either protective or aggravating effects on hypertensive disorders, depending on definition of the outcomes [16,17].

In addition, we observed that women who smoked before pregnancy but reported to have quit before the start of their 1st trimester did not have a protective effect on GH compared to non-smokers. In fact, our findings suggest that such exposure timing may be associated with elevated risk of GH by an average of about 10% compared to women who continued to smoke throughout pregnancy. There is some tendency for risk to increase with heavier smoking before pregnancy, but it is not as compelling as the exposure-response for persistent smokers. Previous studies on women who quit smoking just before the beginning of pregnancy, if examined individually, appear to have mixed results. Our effect estimate is most comparable to that of England et al. and is of similar magnitude [17]. England et al. reported that women who quit smoking before their last menstrual period did not have a reduced risk of GH (adjusted RR = 1.1, 95% CI 0.9–1.3) [17]. In contrast, Marcoux et al. and Zhang et al. reported that women who stopped smoking before pregnancy had a slightly decreased risk of GH, but the associations were not statistically significant [14,16].

Synthesis of the literature is challenging because of variations in definitions of outcome and in definitions of timing of smoking. Application of prior literature to understanding current risk in the US is further complicated by the fact that none of these research definitions is identical to those used in US birth records. Overall, our results point to the heterogeneity in risk of GH by timing of smoking during pregnancy and adds support to the hypothesis that smoking very early in pregnancy increases the risk of GH.

4.2. Implications

Examining the different effects by timing of exposure could provide insight into the mechanism underlying maternal smoking and the development of GH. Preeclampsia is thought to involve abnormal placentation, followed by placental ischemia [4]. Our results on the possible adverse effect of maternal smoking before and during early pregnancy on GH imply that maternal smoking may be involved in conferring elevated risk of GH by disrupting placentation. In addition, our findings that only smokers in all three trimesters exhibit a protective effect suggests that maternal smoking may affect placental ischemia.

Researchers have proposed some potential action ingredients of cigarette that confers the protective effect of maternal smoking on GH [2]. Our study found that quitting either before pregnancy or before the 3rd trimester did not have residual protective effects, which may suggests that any component of cigarette or any biochemical change caused by cigarette smoking that persists in women's body for weeks or months after smoking cessation is unlikely to be involved.

The observation that quitting just before the start of pregnancy confers a higher risk than being a non-smoker at that time, if true, may have clinical implications. It must be noted that "non-smokers" in our sample is a mixture of never-smokers and those who smoked only before the time window captured in birth records. This highlights the possibility of preventive measures by counselling quitting earlier than our data allowed to observe, such that risk for former smokers becomes indistinguishable to that of never-smokers.

4.3. Limitations

Our study has several limitations to consider. Self-report of maternal smoking is not fully reliable and is bound to introduce misclassification of exposure [8,18–22]. It is hard to predict how such misclassification could bias the results, because misclassification probabilities at different times in pregnancy are unknown, and the misclassification is likely to be differential by the outcome variable [8,21]. Differential misclassification would also occur when categorizing an imperfectly measured continuous trait (maternal smoking) that is associated with the outcome (GH) [23]. Another source of misclassification is the possible variations in the gestational ages used by the mother to define each trimester when reporting smoking status, which may also be different from the clinician's best obstetric estimate of gestational age.

In addition to exposure measurement issues, several limitations regarding the outcome measure should be considered. Our work suffers from uncertainty about classification of GH that is a mixture of preeclampsia and pregnancy-induced hypertension (not meeting clinical criteria for preeclampsia).

Lastly, there is no assurance that we captured all of the important confounders. Thus, bias from unmeasured confounding remains a possibility, especially those arising from access to care that is of special concern in the diverse healthcare provision landscape of the US. However, consistency with prior literature that included different populations and confounders reassures us that our results are not due to confounding unique to our sample. Formal sensitivity analyses for exposure misclassification and latent confounding lie outside the scope of the current work, but should shed light on the magnitude of variability in the associations we report [24,25].

5. Conclusion

We offer new insights into the importance of timing of smoking in pregnancy on risk of gestational hypertension, and further challenge the notion that any smoking during pregnancy has an apparent protective effect. Understanding of such patterns may be helpful in the search for mechanistic explanations for this epidemiologic phenomenon and better clinical care.

6. Disclosure of interest

The authors report no conflict of interest.

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