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Maternal Active and Passive Smoking and Hypertensive Disorders of Pregnancy:

Risk with Trimester-Specific Exposures

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Abstract

Background—The inverse association between prenatal smoking and preeclampsia is puzzling, given the increased risks of prematurity and low birthweight associated with both smoking and preeclampsia. We analyzed the Norwegian Mother and Child Birth Cohort (MoBa) to determine whether the associations varied by timing of prenatal smoking.

Methods—We conducted an analysis of 74,439 singleton pregnancies with completed second- and third- trimester questionnaires. Active and passive smoke exposure by trimester were determined by maternal self-report, and covered the period of preconception through approximately 30 weeks' gestation. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Results—Rates of active smoking declined dramatically during pregnancy: for trimester 1, 23%; trimester 2, 9%; and trimester 3, 8%. Active smoking in the third trimester was associated with reduced odds of preeclampsia and gestational hypertension, with the strongest association among continuous smokers (for preeclampsia, OR = 0.57 [95% CI = 0.46–0.70]). Women who quit smoking before the third trimester had approximately the same risk of preeclampsia and gestational hypertension as nonsmokers. There was some evidence of dose-response, with the heaviest smokers (more than eight cigarettes per day) having the lowest risks of preeclampsia (0.48 [0.32–0.73]) and gestational hypertension (0.51 [0.28–0.95]). There was little evidence of an association with passive smoking exposure.

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Conclusion—The association between smoking and preeclampsia varies substantially according to the timing and intensity of exposure. A better understanding of the biologic pathways that underlie these associations may provide important clues to the etiology of preeclampsia and the development of effective clinical interventions.

The reduced risk of preeclampsia with maternal smoking during pregnancy is inconsistent with the many well-documented harmful effects of smoking, including increased risk of stillbirth and infant mortality.[1,2] The reduction in risk with maternal smoking is estimated to be 30%–50%.[3–5] However, arriving at a clear biologic mechanism to explain these findings has been complicated by the observation that maternal active smoking is also strongly associated with decrements in birthweight[6–8] and modest increases in risk for preterm delivery,[9,10] both of which also result from preeclampsia and should thus be decreased if preeclampsia is prevented by smoking.

Preeclampsia is not the only condition thought to be prevented by active smoking. Parkinson disease is another.[11] It is possible that some therapeutic intervention could evolve from a better understanding of the biological mechanism of such protective effects. Even though the net harm from smoking remains unarguable, understanding how an exogenous, modifiable factor affects preeclampsia risk could also shed light on the etiology of preeclampsia.

Despite the robust literature examining the influence of passive/environmental smoke exposure on birthweight or prematurity, to our knowledge there have been no studies on the influence of passive smoke exposure on preeclampsia or gestational hypertension. Additionally, there is very limited literature on trimester-specific effects of active smoking on hypertensive disorders of pregnancy, with one recent study based in the Swedish Medical Birth Registry finding that reduced risk of preeclampsia was limited to women who continued smoking into their late pregnancy.[5]

We undertook a prospective investigation of the trimester-specific effects of active and passive smoking on preeclampsia and gestational hypertension in the Norwegian Mother and Child cohort (MoBa), a population-based cohort recruited between 1999 and 2008, comprising about 18% of all deliveries in Norway during the study period.[12]

METHODS

Study Population and Design

The Norwegian Mother and Child cohort (MoBa) enrolled over 100,000 women between 1999 and 2008. Study design and selection characteristics have been described in detail elsewhere.[12,13] Briefly, women were invited to participate by mail prior to their routine ultrasound examination at their local hospital, which generally occurs around 18 weeks' gestation. Women consenting to participate completed two self-administered exposure questionnaires during their pregnancy. The first maternal and paternal questionnaires (Q1) were sent by mail with the consent form prior to the ultrasound appointment (95% completed). The mean gestational age at which the first questionnaire was completed was 17.6 weeks (standard deviation = 2.8). A second questionnaire covering maternal health status and habits since the first questionnaire was mailed to participants at approximately

week 30 (Q3) (92% completed, mean gestational age 30.7 [1.6] weeks). In some cases (0.4%), the last questionnaire was received following delivery. Women were allowed to participate for more than one pregnancy within the study period (15% with repeat pregnancies). Participation rate varied by study year,[12] but averaged 39%. The final MoBa population comprised approximately 18% of all deliveries in Norway during the study period. There were no differences between the enrolled MoBa population and the entire population with respect to prevalence of preeclampsia and chronic hypertension, although active smokers were under-represented among the MoBa participants (11% vs. 6%).[12]

Pregnancy Smoking Information

Women were queried twice during pregnancy regarding their personal smoking habits and their exposure to passive/environmental tobacco smoke at work or home. In the first questionnaire (~18 weeks' gestation), mothers were asked whether they currently smoked (if so, how many cigarettes per day/week), or if they had stopped smoking after they became pregnant, and if so, at what gestational age. If a woman reported quitting smoking after she became pregnant but did not report the amount she smoked up until she quit (n = 10,073), we used the amount she reported in the 3 months before she became pregnant. If that was unavailable (n = 417), she was considered to be a smoker until the gestational week she reported quitting, but with a missing dose for that period. If a woman reported quitting but did not provide the gestational age at which she quit (n = 148), we assumed she quit at the midpoint of her current trimester. If a woman reported smoking during pregnancy, but did not report whether or not she quit (n = 5,852), we assumed she continued smoking. We used the dose information provided in the first questionnaire to cover the first- and second-trimester exposure, or up until a specified quit week. In the next questionnaire (~32 weeks' gestation), women were asked whether they currently smoked and how much, and, if they had quit at some point during pregnancy, at what gestational age. We used the dose information provided in this questionnaire to cover the third trimester until delivery, or until a specified quit week. Dose information was categorized into four groups: "None" and then ter-tiles rounded to the nearest whole cigarette above (>0 to <2, 2 to <8, ≥8 cigarettes per day). In both questionnaires, passive smoke exposure at work and home was reported, along with the number of hours exposed per day.

Birth Outcome Information

Birth outcome information was obtained by linkage with the Medical Birth Registry of Norway. The registry receives delivery information from hospitals using a standardized birth notification form.[14] This form provides demographic information on the mother and father, mother's health before and during pregnancy including chronic diseases and pregnancy complications, as well as infant birth defects and delivery characteristics. A designation of gestational hypertension alone, or preeclampsia/eclampsia, is completed by a hospital midwife using information from the mother's antenatal medical record and additional data recorded at the maternity department upon admission. Preliminary analyses of the positive predictive value of preeclampsia registrations as compared with blood pressure and protein measures on personal antenatal records and hospital discharge codes indicate that the preeclampsia registrations have strong validity (Klungsøyr K, unpublished data). Information on maternal chronic hypertension and diabetes is also contained in the registry.

Preeclampsia and gestational hypertension were considered separately in the analysis. Women with preexisting/chronic hypertension, including preeclampsia superimposed on chronic hypertension, were excluded from all analyses (n = 372). Overall, the risk of preeclampsia in this population was 3.5% (n = 2,564) and the risk of gestational hypertension was 1.9% (n = 1,935).

Statistical Analysis

MoBa data were from the version 4 release of quality-assured data. Of the 90,190 MoBa pregnancies in which Q1 was completed, 77,041 also had Q3 completed, of which 74,439 were singletons. Additionally, women who delivered prior to the onset of their third trimester (gestational age at delivery <27 weeks) were excluded (n = 2,378). There were 8,209 women who contributed two or more pregnancies to this analysis (7,890 with two pregnancies, 311 with three pregnancies, and eight with four pregnancies).

The following covariates were considered as potential confounders or effect modifiers: maternal age (linear and quadratic term), prepregnancy body mass index, parity, marital status, maternal education, educational disparity between mother and father, household income, and any diabetes prior to or during pregnancy. We constructed directed acyclic graphs to explore the possible relations between active and passive smoking, the above covariates, and preeclampsia or gestational hypertension. We adjusted for covariates indicated by an inspection of directed acyclic graphs, although we also included highly predictive covariates that improved the overall precision of the model. We evaluated the final model for parsimony after inspecting changes in the main effect estimate. Women who were missing active or passive smoking exposure information were dropped from the models. For the main analysis of active and passive smoking in relation to preeclampsia and gestational hypertension, multiple imputation (five replications) was used to impute missing values for body mass index (BMI) and education. Specifically, in SAS, we first used the Markov Chain Monte Carlo method to construct five data sets, just enough missing values to have a monotone missing value, and then used the discriminant function on each of these data sets to impute education. The imputed continuous values for BMI were placed in discrete categories. We evaluated the interaction between smoking and maternal BMI, smoking and maternal age, and smoking and parity, including any interactions in the model if the *P* value for the product term was less than 0.10. Multivariable logistic regression using Proc Genmod was implemented in SAS 9.2 (Cary, NC), using the repeated statement to account for multiple observations per woman.

RESULTS

There were 74,067 singleton pregnancies with complete pregnancy questionnaire data (Table 1). Among these, 17,014 (23%) reported active smoking at some point during pregnancy. Among women who reported any smoking during pregnancy, 47% reported quitting in the first trimester, 6% reported quitting in the second trimester, and 1% reported quitting in the third trimester. In general, smokers tended to be younger, primiparous, less educated, more likely to be single at the time of pregnancy, and have smaller personal

incomes. Smokers were also much more likely to report passive smoke exposure at home or work.

Rates of smoking declined dramatically during pregnancy. Approximately 23% of women reported active smoking in trimester 1, which declined to 9% in trimester 2 and 8% in trimester 3. Patterns of smoking behavior and their associated risks for preeclampsia and gestational hypertension are described in Table 2. Women who quit smoking prior to the onset of their third trimester had roughly the same risk of preeclampsia and gestational hypertension as non-smokers. In general, smoking during the third trimester was required to produce a substantial decrement in risk of disease. Because few third-trimester smokers take up the habit in the third trimester, we cannot separate the effect of continuous exposure from exposure during the third trimester alone. For both preeclampsia and gestational hypertension, women with continuous exposure throughout pregnancy had the strongest reduction in risk of disease (Table 2).

We estimated the associations of trimester 1, trimester 2, and trimester 3 active and passive smoking with preeclampsia and gestational hypertension (Table 3). In models considering each trimester separately (model 1), active smoking only (ever vs. never) was associated with lower odds of preeclampsia in all trimesters, with the strongest associations in trimesters 2 and 3. Passive smoke exposure alone was also associated with minor decrements in risk across pregnancy. Although consistent in direction with active smoking, the passive smoking estimates were weak. Active and passive smoke exposure together was also associated with reduced odds of preeclampsia in every trimester—again most strongly in trimesters 2 and 3. Women who smoked throughout the pregnancy also tended to smoke more heavily (40% of women who quit smoking before their second trimester reported smoking less than 1 cigarette per day, whereas only 13% of women who smoked throughout pregnancy reported smoking so little in the first trimester). We conducted a sensitivity analysis in an attempt to isolate the effect of timing from that of dose in early pregnancy. We reran the third-trimester model 1 (Table 3), including the additional adjustment variable of dose in trimester 1, and found no appreciable change in the estimate of relative risk or the precision of the overall association. This suggests that there is some independent effect of exposure timing on the overall association of smoking with preeclampsia.

To shed additional light on the association with exposure in trimester 3, we performed additional analyses (model 2) that adjusts the trimester 3 association for smoking in trimester 2. (We limited ourselves to adjusting trimester 3 results because, in general, smoking status in trimesters 1 and 2 were correlated in the sense that exposure history was ascertained during the same interview, and there were no nonsmokers at trimester 1 who reported starting smoking at trimester 2.) The analysis suggests that adjusting for prior trimesters did not substantially change the trimester 3 effects, although the association became much less precise (eg, for the association of active smoking with preeclampsia, odds ratio [OR] = 0.56 unadjusted for prior history vs. 0.63 adjusting for trimester 2 smoking, which is a 13% change in OR).

A similar pattern was found for gestational hypertension (approximately 11% change in estimated effect) (Table 3). We found no evidence of effect modification of these

associations by parity, maternal age, or body mass index. Moreover, results were unchanged when adjusted for the length of the third trimester (in order to account for the possibility that smokers delivered prior to development symptoms of preeclampsia). Overall, active smoking in trimester 2 and trimester 3 appeared to be associated with the strongest reductions in risk for both preeclampsia and gestational hypertension.

We used multiple imputation to account for missing data on key covariates in Table 3. When observations with missing data for key covariates were instead excluded, in general, the point estimates and confidence limits of the smoking effects were consistent to the second decimal place (data not shown).

For both preeclampsia and gestational hypertension, odds of disease dropped markedly from the lightest to the heaviest smokers (Table 4). However, overall there were few “light” smokers during this period, and a substantial number reporting no daily cigarette usage.

DISCUSSION

In this population-based study of Norwegians, we observed a strong reduction in risk of preeclampsia and, to a lesser degree, gestational hypertension, among women who reported smoking in their third trimester of pregnancy. Moreover, the associations were stronger among women who reported heavier smoking in this period, both for preeclampsia and for gestational hypertension. It is notable that women who quit smoking prior to the onset of their third trimester experienced roughly the same risk of preeclampsia as nonsmokers. This is somewhat inconsistent with a recent study indicating that women who smoke in the first trimester have a steeper increase in mean systolic blood pressure throughout pregnancy, and a steeper increase in mean diastolic blood pressure in later pregnancy, compared with nonsmokers.[15] However, their study was much smaller than ours, with only 49 exposed gestational hypertension cases and 20 exposed preeclampsia cases.

Trimester-specific associations with smoking have not been widely studied. In a small hospital-based case-control study, Xiong et al[16] found smoking in pregnancy to be inversely related to risk, but there were too few exposed cases to distinguish early versus late effects. Marcoux et al,[17] also in a hospital-based case-control study, reported that smoking cessation prior to 20 weeks’ gestation resulted in an attenuation of the apparent protection provided by maternal smoking. England et al[18] analyzed smoking data collected from a randomized clinical trial, and found that prepregnancy smoking was not protective, while smoking at the enrollment visit (which occurred at some point between 13 and 21 weeks) was. Very similar results were found by Zhang and colleagues,[19] in historical data from the Collaborative Perinatal Project (CPP) (smoking information collected at ~18 weeks), and also by Sibai et al[20] in an analysis of a randomized clinical trial with personal smoking history: prepregnancy smoking was not associated with reduced risk, but current smoking at enrollment was. However, none of these studies was able to describe smoking patterns continuously across trimesters. It is also likely that in each of these studies, except perhaps the CPP, a large proportion of first-trimester smokers were misclassified because the largest drop in smoking rates occurred between the second and third trimesters. Few women appear

to quit smoking later in pregnancy, making it difficult to disentangle second and third trimester-specific effects.

Wikström and colleagues[5] recently reported results from the Swedish Birth Register, using all singleton births in Sweden during the years 1999–2006. Information on smoking and snuff use was collected at two time points: at the first antenatal visit (approximately 15 weeks' gestation) and at approximately week 30–32. Information on first-trimester smoking was not available (eg, if a woman was not a current smoker at 15 weeks). Wikström et al[5] analyzed smoking in discrete categories: smoking or smokeless tobacco use at the first interview and smoking or smokeless tobacco use at the second interview. In that study, continuous smokers and smokers at the second interview had the greatest reduction in risk, both for preeclampsia and gestational hypertension, with no reduced risk associated with snuff use (suggesting that the causal agent is not nicotine, but rather some product of combustion).

It remains plausible that residual or unmeasured confounding partly explains the consistently inverse associations of prenatal smoking with preeclampsia. One possible pathway is that genetic traits associated with addiction to smoking are also directly associated with preeclampsia through another unblocked pathway. A similar concern has arisen in the literature linking prenatal smoking with childhood attention deficit hyperactivity disorder (ADHD). Although maternal prenatal smoking has been consistently associated with increased risks of ADHD in offspring in a number of human[21,22] and animal[23,24] studies, the use of a sib-pair design to control for unmeasured confounding reduced the magnitude of the association dramatically.[25] Likewise, the CPP (conducted when smoking was far more prevalent during pregnancy) found no association between maternal smoking and ADHD.[26] However, a protective and dose-response association between antenatal smoking and preeclampsia was reported in the CPP,[19] dispelling some of the concerns that residual confounding might entirely explain the association of smoking with preeclampsia. Preeclampsia studies using designs that are more robust to genetic or other unmeasured confounders, such as the sib-pair design, should be explored, but may be challenging to implement given the strong association between parity and preeclampsia.

Preeclampsia is considered a two-stage disease.[27] The first stage is caused by abnormal placentation due to insufficient invasion of extravillous cytotrophoblasts, leading to insufficient remodeling of the maternal spiral arteries and a reduced placental perfusion.[28,29] The second stage of preeclampsia (the maternal systemic disorder) is likely to develop as a consequence of placental ischemia. Because sufficient uteroplacental blood flow is a key element in successful implantation and reproductive outcome, increased attention has been devoted to altered angiogenesis in preeclampsia. Recent research has focused on angiogenic factors and their role in the development of preeclampsia. Placental ischemia is believed to release endothelial damaging factors to the maternal circulation,[27] and antiangiogenic factors are likely to play a role in the development of preeclampsia. Decreased concentrations of circulating angiogenic factors, free placental growth factor and free vascular endothelial growth factor, have been reported in preeclamptic pregnancies,[30] as have increased concentrations of the antiangiogenic factors soluble fms-like tyrosine kinase

1 (sFlt-1) (which is an inhibitor of placental growth factor and vascular endothelial growth factor) and soluble endoglin (sENG).[31,32]

The inverse association between smoking during pregnancy and risk of preeclampsia could be causal. Various biologic mechanisms have been proposed to explain this association, including carbon monoxide–mediated inhibition of inflammation,[33] enhanced vasodilation,[34] and suppression of platelet aggregation,[35] plasminogen activation,[35] apoptosis,[36,37] reactive oxygen species formation[38], and sFlt-1, an antiangiogenic factor.[39,40] Altered function of sFlt-1 has been associated with well-established risk factors for preeclampsia. Primiparity and twin pregnancy are major risk factors, separately[2] and together.[41] Wolf et al[42] reported a decrease in circulating sFlt-1 from first to second pregnancy, suggesting that higher levels of sFlt-1 may predispose to preeclampsia. Higher levels of sFlt-1 have also been found in twin pregnancies,[43] and lower sFlt-1 levels have been found in pregnancies of smokers,[44] further supporting this hypothesis. A recent nested case-control study demonstrated higher gestational age–specific birthweights and lower sFlt-1 levels in smokers with preeclampsia as compared with nonsmokers with preeclampsia.[45] The authors suggest smoking may exert this effect by reducing levels of sFlt-1.

Heterogeneity in associations of smoking with preeclampsia risk according to trimester of exposure may provide some clues as to the underlying mechanism. Clinical preeclampsia usually emerges after the middle of the second trimester, coincident with substantial rises in sFlt-1 and sENG, and may explain why smoking during the latter half of the pregnancy as demonstrated in our study and others seems more beneficial.[46]

There is likely to be some misclassification of outcome in our study (eg, gestational hypertension labeled preeclampsia or the reverse). In general, the patterns of association for these outcomes were similar, and thus it is difficult to argue that the smoking effect is specific to preeclampsia, although the magnitude of associations was stronger for this outcome. Differential recall of smoking behavior is made less likely by the prospective design of exposure ascertainment, with the first-trimester smoking behaviors reported prior to 20 weeks' gestation. Smoking behaviors during late pregnancy may have been reported coincident with the symptoms or diagnosis of disease. Biomarkers of smoking exposure (such as cotinine levels)—unless they were collected at multiple times during pregnancy—would be unlikely to substantially improve estimates of exposure, given the significant variability in smoking patterns across pregnancy in this population and others.[47] Additionally, the analytic approach would be improved by time-to-event modeling, in which competing risks for delivery (eg, prematurity) could be explicitly accounted for. Unfortunately, this approach requires the availability of gestational age at onset of symptoms, which is rarely available.

In conclusion, our results add to the weight of evidence implicating smoking exposure during late pregnancy as the critical determinant of the inverse association between antenatal smoking and preeclampsia. Although the pathways underlying the association remain unknown, eventual elucidation may help to identify treatment options for this dangerous and enigmatic disorder.

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TABLE 1

Participant Characteristics According to Maternal

	Active Smoker (n = 17,014)		Nonsmoker (n = 57,053)	
	No.	(%)	No.	(%)
Age (years)				
≥20	790	(4.6)	645	(1.1)
21–30	9,689	(57.0)	28,475	(49.9)
31–40	6,401	(37.6)	27,280	(47.8)
≥41	134	(0.8)	653	(1.1)
BMI (kg/m^2)[a]				
<18.5	644	(3.9)	1,527	(2.8)
18.5–25	10,063	(61.1)	37,058	(66.7)
26–30	3,848	(23.4)	12,027	(22.6)
≥30	1,911	(11.6)	4,988	(9.0)
Parity				
0	8,789	(51.7)	25,430	(44.6)
1	5,427	(31.9)	20,996	(36.8)
≥2	2,798	(16.4)	10,627	(18.6)
Marital status[b]				
Married/cohabitating	15,747	(93.2)	55,622	(97.9)
Single/divorced/widowed/separated	863	(5.1)	785	(1.4)
Other	292	(1.7)	414	(0.7)
Education[c]				
<High school	6,082	(37.9)	9,172	(16.9)
High school	3,286	(20.5)	7,463	(13.8)
>High school	6,661	(41.6)	37,576	(69.3)
Past year personal income				
<200 NOK	7,456	(43.8)	17,618	(30.9)
200–299 NOK	5,782	(34.0)	20,430	(35.8)
≥300 NOK	3,776	(22.2)	19,005	(33.3)
Passive smoke exposure[d]	2,841	(16.9)	2,400	(4.2)
Preeclampsia	604	(3.6)	1,960	(3.4)
Gestational hypertension	299	(1.8)	1,096	(1.9)

NOK, Norwegian currency (Krone).

[a] 2,001 women were missing information on BMI.

[b] 344 women were missing information on marital status.

[c] 3827 women were missing information on education.

[d] 397 women were missing information on passive smoke exposure.

TABLE 2

Risk of Preeclampsia and Gestational Hypertension According to Patterns of Active Smoking[a]

	Preeclampsia[b]			Gestational Hypertension[c]		
Trimester of Exposure	**No. (n = 70,729)**	**No. Cases (n = 2,474)**	**OR (95% CI)**	**No. (n = 69,544)**	**No. Cases (n = 1,357)**	**OR (95% CI)**
Never[d]	54,163	1,878	1.00	53,291	1,062	1.00
Trimester 1 only	9,947	417	0.99 (0.87–1.11)	9,728	207	0.97 (0.82–1.14)
Trimester 1 and 2 only	1,193	46	0.89 (0.64–1.23)	1,170	24	0.97 (0.62–1.51)
Trimester 1 and 3 only	383	8	0.62 (0.31–1.27)	380	5	0.64 (0.24–1.71)
Trimester 3 only	86	2	0.78 (0.20–3.09)	86	2	1.57 (0.38–6.43)
All trimesters	4,957	123	0.57 (0.46–0.70)	4,889	57	0.62 (0.46–0.83)

CI indicates confidence interval.

[a] Patterns were only among women with complete smoking information in all trimesters: 1,144 women were missing smoking for the first and second trimesters, and 1,249 for the third trimester (total missing = 2,345). Adjusted models included parity, maternal education, prepregnancy body mass index, maternal age (linear and quadratic terms), and any diabetes, and accounted for multiple observations per woman.

[b] Preeclampsia rates excluded women with gestational hypertension and model additionally adjusted for educational disparity.

[c] Gestational hypertension rates excluded women with preeclampsia and model additionally adjusted for native language of grandparents.

[d] Reference category.

TABLE 3

Associations of Trimester-Specific Prenatal Active and Passive Smoking with Preeclampsia and with Gestational Hypertension in the Norwegian Mother and Child Birth Cohort

	Preeclampsia					Gestational Hypertension				
		Model 1[a]		Model 2[b]			Model 3[d]		Model 4[e]	
Smoking Classifications	**Total No.**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**Total No.**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
First trimester										
No smoke exposure[c]	44,482	1.00				43,846	1.00			
Active smoking only	10,545	0.88	(0.78–0.98)			10,367	0.88	(0.76–1.03)		
Passive smoking only	3,596	0.90	(0.76–1.07)			3,521	0.92	(0.73–1.17)		
Active and passive smoking	3,306	0.82	(0.78–0.98)			3,237	0.86	(0.67–1.12)		
Second trimester										
No smoke exposure[c]	52,081	1.00				51,305	1.00			
Active smoking only	3,034	0.60	(0.48–0.75)			2,998	0.64	(0.47–0.88)		
Passive smoking only	4,919	0.94	(0.81–1.09)			4,806	0.94	(0.76–1.15)		
Active and passive smoking	1,895	0.69	(0.54–0.88)			1,862	0.75	(0.52–1.08)		
Third trimester										
No smoke exposure[c]	53,381	1.00		1.00		52,566	1.00		1.00	
Active smoking only	2,541	0.56	(0.43–0.72)	0.62	(0.44–0.89)	2,516	0.64	(0.46–0.90)	0.69	(0.42–1.13)
Passive smoking only	4,249	0.90	(0.78–1.05)	0.91	(0.76–1.10)	4,160	0.86	(0.69–1.07)	0.84	(0.64–1.09)
Active and passive smoking	1,758	0.59	(0.44–0.78)	0.60	(0.40–0.90)	1,729	0.57	(0.38–0.87)	0.51	(0.28–0.90)

CI indicates confidence interval.

[a] Model 1: Adjusted for parity, maternal education, educational disparity, prepregnancy body mass index, maternal age (linear and quadratic terms), any diabetes, and excluding gestational hypertension.

[b] Model 2: As above, but adjusting for smoke exposure in the previous trimester.

[c] Reference category.

[d] Model 3: Adjusted for parity, maternal education, native language of grandparents, prepregnancy body mass index, maternal age (linear and quadratic terms), any diabetes, and excluding preeclampsia.

[e] Model 4: As above, but adjusting for smoke exposure in the previous trimester.

TABLE 4

Smoking Dose in Third Trimester in Relation to Preeclampsia and Gestational Hypertension

	Preeclampsia[a]				Gestational Hypertension[b]			
Smoking Classification by Dose (cigarettes/day)	**Total No. (n = 61,817)**	**(% Cases)**	**OR**	**(95% CI)**	**Total No. (n = 60,861)**	**(% Cases)**	**OR**	**(95% CI)**
0[c]	57,640	(3.57)	1.00		56,737	(2.04)	1.00	
>0–1.7 (light)	1,026	(3.12)	0.78	(0.55–1.12)	1,009	(1.49)	0.76	(0.46–1.27)
>1.7–8.0 (moderate)	2,107	(2.28)	0.52	(0.39–0.70)	2,084	(1.20)	0.59	(0.40–0.89)
>8.0–20 (heavy)	1,044	(2.30)	0.48	(0.32–0.73)	1,031	(1.07)	0.51	(0.28–0.95)

CI indicates confidence interval.

[a] Adjusted for parity, maternal education, educational disparity, prepregnancy body mass index, maternal age, any diabetes, and excluding gestational hypertension.

[b] Adjusted for parity, maternal education, native language of grandparents, educational disparity, prepregnancy body mass index, maternal age, any diabetes, and excluding preeclampsia.

[c] Reference category.