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A prospective study of maternal carboxyhemoglobin and preeclampsia risk

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Summary

We aimed to measure the relation between early-pregnancy maternal carboxyhemoglobin and subsequent preeclampsia risk. We conducted a nested case-control analysis using data from a western Washington State cohort study (1996–2004). We measured maternal whole blood carboxyhemoglobin in 128 women who developed preeclampsia and 419 normotensive controls (mean gestational age at blood draw, 14.8 weeks). After adjustment for confounders, high (≥1%) versus low (<0.7%) carboxyhemoglobin odds ratios [OR] and 95% confidence intervals [CI] were 4.09 [1.30, 12.9] in parous women, 0.53 [0.23, 1.26] in nulliparous women, and 1.11 [0.55, 2.25] in the overall study population (parity interaction p=0.01). The influence of parity on the association was unexpected. The association between high carboxyhemoglobin and preeclampsia risk in parous women implicates hypoxia at the fetal-maternal interface as a pathogenic mechanism. These results also suggest that the etiology of the disease may differ according to parity.

Keywords

carbon monoxide; carboxyhemoglobin; hypertension; preeclampsia; pregnancy

Introduction

Preeclampsia, an important cause of preterm delivery, intrauterine growth restriction, low birthweight, and perinatal death, is estimated to affect 5–8% of pregnant women in the United States.1 The clinical manifestations of the disorder, new onset hypertension and proteinuria, are thought to be of lesser pathogenic importance than the accompanying systemic maternal endothelial dysfunction, vasoconstriction, and reduced organ perfusion.2–4

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We hypothesized that maternal carbon monoxide exposure may increase preeclampsia risk. Ambient carbon monoxide exposure in early pregnancy has been associated with low birthweight,[5, 6] intrauterine growth restriction,[7–9] and preterm delivery[6] in diverse North American locations with relatively low ambient concentrations. Ambient carbon monoxide exposure has also been associated with cardiovascular disease outcomes and related physiological disturbances.[10] Preeclampsia shares many risk factors with cardiovascular disease and is itself a risk factor for future cardiovascular morbidity and mortality.[11, 12] It has been hypothesized that hypoxia at the fetal-maternal interface secondary to impaired placentation causes dissemination of free radicals that trigger preeclampsia in susceptible women.[4] Another potential cause of fetal hypoxia is carboxyhemoglobinemia caused by maternal carbon monoxide exposure. Inhaled carbon monoxide binds with high affinity to hemoglobin, forming carboxyhemoglobin.[13] Even fairly low maternal carboxyhemoglobin concentrations can impair fetal oxygen transport, because carbon monoxide bound to maternal hemoglobin shifts the oxygen/hemoglobin dissociation curve to the left, reducing oxygen transfer across the placenta.[14, 15]

Two small studies show cross-sectional associations between high maternal carboxyhemoglobin and preeclampsia.[16, 17] However, two others show lower breath carbon monoxide in women with preeclampsia versus normotensive controls.[18, 19] We aimed to contribute to this body of literature with a prospective assessment of maternal whole blood carboxyhemoglobin concentration and subsequent preeclampsia risk.

Methods

Study population

This nested case-control analysis uses data collected from participants of the Omega Study, an ongoing prospective cohort previously described in detail.[20] The primary purpose of this study was to identify dietary risk factors for preeclampsia. Omega Study participants were recruited from women attending prenatal care at clinics affiliated with Swedish Medical Center in Seattle and Tacoma General Hospital in Tacoma, Washington. Women who initiated prenatal care before 20 weeks gestation were eligible to participate. Women were ineligible if they were younger than 18 years of age, did not speak and read English, did not plan to carry the pregnancy to term, or did not plan to deliver at either of the two research hospitals. Participants completed a questionnaire administered in English by a trained interviewer at or near enrollment (mean gestational age and standard deviation [SD], 15.9 [4.8] weeks). This questionnaire was used to gather information on sociodemographic, anthropometric, and behavioral characteristics and reproductive and medical histories. Participants also provided a 20 ml non-fasting blood sample (mean gestational age and SD, 14.8 [3.1] weeks). Blood was fractionated using standard procedures and stored at −80°C until analysis. Seven to nine months after delivery, maternal and infant medical records were abstracted for information on the course and outcome of pregnancy. The procedures used in the Omega Study were approved by the Institutional Review Boards of Swedish Medical Center and Tacoma General Hospital. All participants provided written informed consent.

This analysis is based on women recruited into the Omega Study between December 1996 and December 2004. During this period, 3,000 (77%) of 3,899 invited women consented to participate. Of these participants, 60 women experienced early pregnancy losses and 152 were lost to follow-up due to unknown delivery outcome or a missing medical record.

Preeclampsia diagnosis

We identified 136 women (4.9%) who developed preeclampsia in the remaining cohort. Diagnosis was made according to American College of Obstetricians and Gynecologists

(ACOG) guidelines using data obtained from medical record abstraction. The guidelines, which were current at the study onset, defined preeclampsia as sustained pregnancy-induced hypertension with proteinuria.2 Hypertension was defined as sustained blood pressure readings of ≥140/90 mm Hg (with readings performed ≥6 hours apart) and/or a sustained 30 mm Hg systolic rise or 15 mm Hg diastolic rise above first trimester blood pressure values. Proteinuria was defined as urine protein concentrations of ≥30 mg/dl or 1+ on a urine dipstick on ≥2 specimens collected ≥4 hours apart. The control group consisted of 443 women randomly selected from the 2,652 remaining cohort participants who did not develop preeclampsia according to the ACOG guidelines.2 We aimed to select at least 3 controls per case. Women with multiple gestations were not excluded from the study population.

Carboxyhemoglobin measurement

We measured whole blood carboxyhemoglobin in 135 preeclampsia cases and 443 controls. One case participant had insufficient blood sample volume for testing. Carboxyhemoglobin was measured in whole blood collected in tubes containing ethylene diamine tetraacetic acid (EDTA). We used a previously described measurement method with slight modification.21 Briefly, we used head-space capillary gas chromatography-mass spectrometry with a HP-Molesieve PLOT column (19091P-MS4, 30 m, 0.32 mm id and 12.0 μm film thickness; Agilent Technologies, Santa Clara CA). The assay provides a lower detection limit of 0.2%. 21 Carboxyhemoglobin is expressed as percent hemoglobin. Hemoglobin was measured with a Quantichrom colorimetric assay kit using the cyanmethemoglobin method (BioAssay Systems, Hayward CA).22

Statistical analysis

For this analysis, we excluded 5 (3.7%) cases and 16 (3.6%) controls who did not complete the early-pregnancy interview and thus had missing covariate data. We excluded another 2 cases and 8 controls who provided blood samples after 20 weeks gestation, when preeclampsia may first be diagnosed. The final analytical population includes 128 preeclampsia cases and 419 controls. We tested the difference in median carboxyhemoglobin between cases versus controls using a rank sum test. We tested the difference in the proportion of cases and controls with high carboxyhemoglobin using a chi-square test. We examined carboxyhemoglobin distributions according to maternal characteristics within case and control groups. We used multivariable logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CI). We modeled carboxyhemoglobin concentration both continuously and categorically. We defined categories of <0.7% (low), 0.7–0.99% (moderate), and ≥1% (high). The 0.7% cutpoint approximates the upper bound of endogenous carboxyhemoglobin concentration in healthy humans, typically 0.4–0.7%.13 The 1% cutpoint roughly distinguishes endogenous exposure from exposure due to environmental sources such as tobacco smoke or urban air pollution. 13 Carboxyhemoglobin concentrations in nonsmokers living in moderately polluted urban areas are about 1–2%; concentrations in smokers are typically 4–7%.13, 23

We evaluated the following characteristics, reported in interviews, as potential confounders: maternal age, parity (any prior live births), pre-pregnancy body mass index (BMI), race/ethnicity, education, employment in early pregnancy, marital status, household income, smoking before and during pregnancy, environmental tobacco smoke exposure in and outside of the home in the year before pregnancy, regular recreational physical activity before pregnancy, and histories of asthma, diabetes, and chronic hypertension. We evaluated multiple gestation and gestational age at blood draw as potential confounders. We also evaluated year and month of blood draw as confounders due to secular and seasonal changes in regional ambient carbon monoxide.24 We included in the final model those covariates that altered unadjusted carboxyhemoglobin ORs by 10% or more.

In *post-hoc* exploratory analyses, we discovered that nulliparity, a preeclampsia risk factor, strongly influenced the relation between early-pregnancy carboxyhemoglobin concentration and preeclampsia risk. Therefore, we fit multivariable logistic regression models with a product term for the interaction between nulliparity (no versus any prior live births) and categorized carboxyhemoglobin (<0.7%, 0.7–0.99%, and ≥1.0%). We calculated ORs and 95% CIs comparing risk across carboxyhemoglobin categories within parous and nulliparous women, separately. We also fit models with an interaction term between nulliparity and carboxyhemoglobin modeled as a continuous variable.

We repeated analyses after excluding 36 current smokers to determine whether the findings were driven by smoking-associated carbon monoxide exposure. We also performed analyses after excluding 35 women with self-reported chronic hypertension. Finally, we excluded 34 cases who met the then-current ACOG diagnostic criteria, but who did not meet the current criteria established by the National High Blood Pressure Education Working Group in 2000: these women experienced a sustained blood pressure rise that did not reach the 140/90 mm Hg cutpoint.25

Results

Table 1 shows distributions of characteristics within case and control groups. Median carboxyhemoglobin concentration was slightly higher among cases than controls (p=0.07). The proportions of cases and controls with high carboxyhemoglobin (≥1%) were 31.3% and 26.3%, respectively (p=0.27). Median carboxyhemoglobin concentrations were highest among Hispanic and African-American women, those with no more than high school education, smokers, women who were employed in early pregnancy, unmarried women, and those exposed to environmental tobacco smoke in the year before pregnancy. Median concentrations were also highest among women who enrolled and provided a blood sample during the first two years of the study. Among controls but not cases, carboxyhemoglobin was higher in nulliparas than in parous women.

The estimated association between early-pregnancy carboxyhemoglobin and preeclampsia risk is shown in Table 2. Each 1% increase in carboxyhemoglobin was non-significantly associated with increased preeclampsia risk in a univariate model (OR=1.48 [95% CI 0.90–2.41). This association decreased toward the null after adjustment for maternal age, nonwhite race/ethnicity, chronic hypertension, pre-pregnancy BMI, nulliparity, smoking before or during pregnancy, and date of blood draw (adjusted OR=1.07 [0.58, 1.95]). Similarly, moderate (0.7–0.99%) and high carboxyhemoglobin (≥1.0%) were not strongly associated with preeclampsia risk after adjustment for confounders. Adjusted ORs [95% CI] were 1.39 [0.76, 2.54] and 1.11 [0.55, 2.25] for moderate and high exposure categories, respectively.

After stratification of study participants according to parity, we observed differences in the relation between carboxyhemoglobin concentration and preeclampsia risk (Table 3). Among nulliparous women, each 1% increase in carboxyhemoglobin was associated with non-significantly decreased risk (adjusted OR=0.44 [0.16, 1.25]). The high versus low category adjusted OR was 0.53 [0.23, 1.26]. However, among parous women, each 1% increase in carboxyhemoglobin was associated with non-significantly increased preeclampsia risk (adjusted OR=2.30 [0.79, 6.72]). Parous women with high carboxyhemoglobin (≥1%) had significantly greater odds of preeclampsia than parous women with low carboxyhemoglobin (adjusted OR=4.09 [1.30, 12.9]). The influence of parity on the carboxyhemoglobin/preeclampsia relationship was statistically significant (interaction p=0.01).

These associations were robust to exclusion of current smokers, women with chronic hypertension, and cases who did not meet current diagnostic criteria. After exclusion of 36 smokers, high (≥1%) versus low (<0.7%) carboxyhemoglobin adjusted ORs were 3.96 [1.23, 12.7] and 0.60 [0.25, 1.49] among parous and nulliparous women, respectively (interaction p=0.02). After exclusion of 32 women with chronic hypertension, high versus low adjusted ORs were 5.89 [1.43, 24.4] among parous women and 0.43 [0.18, 1.06] among nulliparas (interaction p=0.003). After exclusion of 34 cases who met the 1996 criteria but not current criteria,25, 26 high versus low adjusted ORs were 3.23 [0.95, 11.0] and 0.61 [0.20, 1.87] among parous and nulliparous women, respectively (interaction p=0.03).

Discussion

We found a strong association between high early-pregnancy carboxyhemoglobin and preeclampsia risk only among parous women. This relation was not evident among nulliparous women, and the difference in the relationship between these two groups was statistically significant. The estimates of association were robust to adjustment for several confounding characteristics, exclusion of women who reported chronic hypertension or smoking during early pregnancy and those cases who did not meet the current diagnostic criteria.

The strengths of this study included prospective measurement of maternal carboxyhemoglobin using a highly sensitive assay, information on numerous potential confounders including active and passive smoking, and use of standardized diagnostic criteria to define cases. However, the limitations of this analysis should be considered when interpreting the results. First, these findings may be due to chance. The subgroup results were based on small numbers. Our finding of interaction by parity, though statistically significant, was not based on an *a priori* hypothesis. Second, carboxyhemoglobin was measured at only one timepoint. Incidental carbon monoxide exposure close to the time of sampling may have influenced concentrations. However, because of its short half-lives (biphasic elimination, half-lives 3.6 and 4.5 hours),27 carboxyhemoglobin would rapidly return to a concentration governed by typical ambient levels and endogenous production. Furthermore, misclassification arising from atypical incidental exposure is likely unrelated to future preeclampsia development. Estimated associations would therefore be biased toward rather than away from the null. Third, maternal smoking and other characteristics were based on self-report. Errors in these data are unlikely to be related to subsequent preeclampsia risk. Therefore, misclassification of estimated associations due to such errors is also likely toward the null. Fourth, although we hypothesized that carboxyhemoglobin would influence preeclampsia risk via fetal hypoxia, we could not directly measure fetal carboxyhemoglobin concentrations. However, maternal carboxyhemoglobin concentrations are highly correlated with cord blood concentrations obtained from cordocentesis during the third trimester ($0.52 \leq \rho \leq 0.72$).28, 29 Finally, because available medical record information regarding preeclampsia severity was limited, we could not evaluate the influence of disease severity on the relation of interest. However, the associations between carboxyhemoglobin and preeclampsia associated with preterm delivery were not substantially different than associations with preeclampsia associated with term delivery (data not shown).

Adjustment for date of blood draw weakened estimated associations somewhat, though not entirely. The strong inverse relation between year of blood draw and carboxyhemoglobin initially caused us to question whether sample degradation during storage might have influenced the measurements. One study showed that carboxyhemoglobin in postmortem EDTA-preserved blood did not meaningfully change after two years of storage at 3°C.30 While exposure to air and heat during storage can cause carbon monoxide liberation and decreased carboxyhemoglobin concentration,31 we could find no evidence in the literature

of increased carboxyhemoglobin concentration after storage in any condition. Degradation of hemoglobin could feasibly cause an artifactual increase in carboxyhemoglobin over time in storage, though only if hemoglobin bound to carbon monoxide degraded at a slower rate, which seems unlikely. Glycosylated hemoglobin has been shown to be stable for up to 20 years in frozen storage.[32, 33] Two types of mammalian blood collected aseptically and stored at room temperature in the dark did not show signs of hemoglobin degradation after 20 years.[34] Furthermore, hemoglobin concentration was not correlated with duration of storage of these samples ($\rho=0.03$, $p=0.44$). An alternative explanation for the decrease in median carboxyhemoglobin over the study period is the decrease of about 40% in ambient carbon monoxide in western Washington between 1996 and 2005.[24] Previous studies have shown that carboxyhemoglobin concentrations measured in blood donated by non-smokers correlated with declining air pollution within one city[35] and differences in ambient air pollution across four American cities.[36]

This is the first study, to our knowledge, to assess the relation between maternal blood carboxyhemoglobin in early pregnancy and the subsequent risk of preeclampsia. In a cross-sectional study of nonsmokers at or near term, whole blood carboxyhemoglobin was higher among 15 preeclamptic women than among 15 normotensive controls (means 2.8% versus 0.7%, $p<0.001$).[17] Another cross-sectional study of 13 women with mild preeclampsia and 24 normotensive controls, most of whom were in labor, showed very similar results. Mean carboxyhemoglobin was 2.72% and 0.65% in cases and controls, respectively ($p<0.001$).[16] In contrast, two cross-sectional studies of carbon monoxide measured in exhaled breath demonstrated lower concentrations among non-smokers with pregnancy-induced hypertension or preeclampsia versus normotensive non-smoking controls.[18, 19] Both studies of exhaled carbon monoxide adjusted for ambient carbon monoxide concentrations, which may have precluded their ability to detect associations arising from exogenous sources. None of these studies adjusted for parity or other maternal characteristics. The distributions of participants according to parity were not reported in sufficient detail to evaluate the influence of this characteristic on these studies' results.

The difference in the association between parous and nulliparous women was unexpected and is difficult to explain. Some researchers believe that preeclampsia in parous women arises from different mechanisms than in nulliparas.[37, 38] Two small studies demonstrated higher concentrations of antilymphocyte antibodies and white cell counts, both markers of immune maladaptation, in multiparous compared with nulliparous preeclamptic women.[39, 40] We are aware of no other examinations of differences in preeclampsia risk factors according to parity.

Paradoxically, cigarette smoking, a major influence of carboxyhemoglobin concentration, is generally associated with a reduced risk of preeclampsia.[41, 42] Some investigators have hypothesized that carbon monoxide in cigarette smoke reduces preeclampsia risk by decreasing placental inflammation and promoting spiral artery remodeling.[43] Interestingly, in a large prospective study, Ness et al. found that smoking was associated with an inverse risk of preeclampsia in underweight and normal weight women, but was unassociated with preeclampsia risk in overweight or obese women.[41] The authors hypothesized that the prometabolic and adverse effects of obesity counteract the protective, antimetabolic effects of smoking. Similarly, we speculated that prometabolic characteristics associated with parity may oppose any anti-inflammatory effects of ambient carbon monoxide exposure. However, our analyses provide no evidence that prometabolic characteristics associated with parity, such as increased maternal age and adiposity, explain the influence of parity on the relation between carboxyhemoglobin and preeclampsia risk. Alternatively, cigarette smoke constituents other than carbon monoxide may be responsible for the putative protective effect of smoking.

Carboxyhemoglobin can arise from endogenous and exogenous sources. Endogenous carboxyhemoglobin formation results primarily from hemolysis and to a much smaller extent from oxidation of organic molecules.44 Carboxyhemoglobin also forms after exposure to inhaled carbon monoxide arising from incomplete combustion of organic materials. Outdoor sources include automobile exhaust and industrial combustion activities. Indoor sources include tobacco smoke and improperly vented home fireplaces, water heaters, and other appliances.45

An association between elevated early-pregnancy carboxyhemoglobin and preeclampsia could be due to increased endogenous carboxyhemoglobin formation or increased exogenous carbon monoxide exposure. Increased endogenous production may be a result of early increased hemolysis in women who later develop preeclampsia. A few cross-sectional studies support associations between hemolysis and preeclampsia, as evidenced by increased serum iron or ferritin concentrations.16, 46–48 However, there is no corroborative prospective evidence, to our knowledge. We hypothesized that hemolysis may be more evident in parous women who later develop preeclampsia because they more commonly have comorbidities such as chronic hypertension.37 However, our results did not meaningfully change after excluding 35 women with self-reported chronic hypertension, four with self-reported sickle cell anemia or thalassemia, 28 with medical record indication of antepartum anemia, and eight who developed HELLP syndrome according to the medical record (data not shown). Perhaps other comorbidities that we were unable to account for in this study population may help explain the differences in associations observed in parous versus nulliparous women.

Exposure to ambient carbon monoxide may increase risk of preeclampsia via fetal hypoxia. Hypoxia at the fetal-maternal interface has been hypothesized to trigger the disease through free radical generation.4 One study provides some evidence that air pollutant exposure may increase preeclampsia risk via hemoglobin alteration. This was a cross-sectional study of 61 women of ≥24 weeks gestation who lived in an area heavily polluted by oxidized nitrogen compounds in drinking water, food, and ambient air.49 Fourteen women had toxemia, a historical term used to describe a group of disorders including pregnancy-induced hypertension and preeclampsia. Blood methemoglobin was higher among toxemic women compared to those with normotensive pregnancies. The relation between toxemia and ambient nitrogen compounds, of which methemoglobin is a putative marker, was not directly assessed. However, a subsequent report showed a strong correlation between maternal methemoglobin concentrations and ambient sulfur dioxide concentrations during a period of coal-powered plant operation in an industrial city.50 It is difficult to speculate why parity would increase a woman's susceptibility to ambient carbon monoxide exposure. We cannot distinguish between endogenous and exogenous influence of carboxyhemoglobin in our study population. However, carboxyhemoglobin concentrations were associated with environmental tobacco smoke exposure, smoking, and employment, which may be a rough surrogate for time spent in traffic.

We look forward to future examinations of carboxyhemoglobin and preeclampsia in other populations. Investigation of ambient carbon monoxide exposures in relation to preeclampsia risk can also aid in determining whether exogenous sources play a role in this relationship. Should these findings be replicated, they may help elucidate differences in the etiology of preeclampsia occurring in nulliparous and parous women.

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Table 1

Distributions of carboxyhemoglobin (%) according to pregnancy characteristics within preeclampsia cases and controls.

Characteristic	Preeclampsia cases (N=128)		Controls (N=419)	
	No. (%)	Median (IQR)[a]	No. (%)	Median (IQR)[a]
Overall	128 (100.0)	0.85 (0.74–1.07)	419 (100.0)	0.82 (0.70–1.00)
Age (years)				
≤ 20	3 (2.3)	0.82 (0.67–1.11)	6 (1.4)	0.88 (0.86–1.23)
21–34	79 (61.7)	0.87 (0.74–1.17)	284 (37.8)	0.82 (0.69–1.00)[c]
35–39	36 (28.1)	0.82 (0.73–0.98)	99 (23.6)	0.84 (0.74–1.02)
≥ 40	10 (7.8)	0.87 (0.72–1.10)	30 (7.2)	0.81 (0.67–0.99)
Parity				
Nulliparous	87 (68.0)	0.85 (0.74–1.04)	261 (62.3)	0.88 (0.75–1.07)
Parous	41 (32.0)	0.86 (0.74–1.07)	158 (37.7)	0.77 (0.66–0.88)[c]
Pre-pregnancy body mass index (kg/m^2)[b]				
< 18.5	7 (5.5)	0.74 (0.66–0.80)	21 (5.0)	0.84 (0.68–1.05)
18.5–24.9	51 (39.8)	0.85 (0.71–1.12)	290 (69.5)	0.83 (0.71–1.01)
25–29.9	33 (25.8)	0.87 (0.80–1.04)	68 (16.3)	0.81 (0.69–0.98)[c]
≥ 30	37 (28.9)	0.85 (0.73–1.17)	38 (9.1)	0.81 (0.67–1.08)
Race/ethnicity[b]				
Non–Hispanic white	107 (84.3)	0.85 (0.74–1.12)	357 (85.4)	0.82 (0.70–1.00)
Non–Hispanic black	5 (3.9)	1.11 (0.84–1.22)	9 (2.2)	0.90 (0.79–1.13)
Hispanic	3 (2.4)	1.01 (0.70–1.08)	11 (2.6)	0.94 (0.81–1.15)
Asian/Pacific Islander	6 (4.7)	0.83 (0.74–0.90)	32 (7.7)	0.81 (0.70–1.02)
Other	6 (4.7)	0.86 (0.82–0.98)	9 (2.1)	0.82 (0.75–1.03)
Education				
≤ 12 years	11 (8.6)	1.11 (0.82–1.18)	13(3.1)	0.86 (0.72–0.95)
> 12 years	117 (91.4)	0.85 (0.74–1.04)	406 (96.9)	0.82 (0.70–1.00)
Employed in early pregnancy[b]				
Yes	108 (85.7)	0.86 (0.74–1.07)	345 (82.7)	0.85 (0.72–1.02)
No	18 (14.3)	0.82 (0.75–1.06)	72 (17.3)	0.77 (0.64–0.86)[c]
Marital status				
Married	112 (87.5)	0.84 (0.74–1.05)	387 (92.4)	0.82 (0.70–1.00)
Unmarried	16 (12.5)	0.94 (0.75–1.21)	32 (7.6)	0.90 (0.76–1.24)
Annual household income[b]				
< $30,000	6 (4.8)	0.83 (0.67–1.55)	10 (2.4)	0.87 (0.71–1.24)
$31,000–69,999	28 (22.4)	0.88 (0.67–1.18)	95 (23.0)	0.85 (0.72–1.00)
≥ $70,000	87 (69.6)	0.86 (0.73–1.04)	299 (72.2)	0.82 (0.70–1.01)
Refused	4 (3.2)	0.82 (0.74–1.35)	10 (2.4)	0.84 (0.63–0.87)
Smoking status[b]				
Never	97 (76.4)	0.83 (0.73–1.04)	296 (70.8)	0.82 (0.68–1.00)

Characteristic	Preeclampsia cases (N=128)		Controls (N=419)	
	No. (%)	Median (IQR)[a]	No. (%)	Median (IQR)[a]
Before pregnancy	23 (18.1)	1.01 (0.75–1.28)	93 (22.3)	0.82 (0.74–1.01)[c]
Before and during	7 (5.5)	0.83 (0.67–1.17)	29 (6.9)	0.94 (0.76–1.28)
Environmental tobacco smoke exposure in the home in the year before pregnancy				
No	121 (94.5)	0.85 (0.74–1.06)	404 (96.4)	0.82 (0.69–1.00)
Yes	7 (5.5)	0.98 (0.63–1.21)	15 (3.6)	0.90 (0.77–1.41)
Environmental tobacco smoke exposure outside of home in the year before pregnancy				
No	74 (57.8)	0.84 (0.74–1.01)	261 (62.3)	0.80 (0.68–0.98)
Yes	54 (42.2)	0.88 (0.73–1.18)	158 (37.7)	0.87 (0.74–1.08)
Regular participation in recreational physical activity in year before pregnancy (%)				
Yes	109 (85.8)	0.86 (0.74–1.04)	386 (92.3)	0.82 (0.70–1.01)
No	18 (14.2)	0.93 (0.74–1.22)	32 (7.7)	0.84 (0.71–0.93)
History of asthma				
No	103 (80.5)	0.86 (0.75–1.11)	377 (90.2)	0.83 (0.70–1.01)[c]
Yes	25 (19.5)	0.80 (0.68–0.94)	41 (9.8)	0.81 (0.71–0.99)
History of diabetes (excluding gestational diabetes)				
No	119 (93.0)	0.86 (0.74–1.08)	406 (97.4)	0.83 (0.70–1.01)
Yes	9 (7.0)	0.76 (0.71–0.87)	11 (2.6)	0.80 (0.62–0.93)
History of chronic hypertension (excluding pregnancy–associated hypertension)				
No	107 (83.6)	0.86 (0.74–1.11)	405 (96.7)	0.83 (0.71–1.01)[c]
Yes	21 (16.4)	0.84 (0.68–0.98)	14 (3.3)	0.80 (0.61–0.94)
Multiple gestation				
No	112 (87.5)	0.86 (0.74–1.09)	409 (97.6)	0.82 (0.70–1.00)[c]
Yes	16 (12.5)	0.82 (0.74–0.99)	10 (2.4)	0.84 (0.65–1.01)
Year of blood draw				
1996–1998	42 (32.8)	1.12 (0.79–1.34)	74 (17.7)	1.01 (0.84–1.27)
1999–2001	50 (39.1)	0.84 (0.74–1.00)	141 (33.7)	0.84 (0.75–1.01)
2002–2004	36 (28.1)	0.79 (0.70–0.87)	204 (48.7)	0.77 (0.64–0.93)
Month of blood draw				
Dec.–Feb.	32 (25.0)	0.84 (0.73–1.04)	92 (22.0)	0.87 (0.74–1.05)
Mar.–May	24 (18.8)	0.79 (0.68–0.89)	106 (25.0)	0.80 (0.68–0.94)
Jun.–Aug.	37 (28.9)	0.98 (0.79–1.25)	111 (26.5)	0.81 (0.70–1.03)[c]
Sep.–Nov.	35 (27.3)	0.86 (0.77–1.05)	110 (26.3)	0.84 (0.72–1.01)

[a] IQR = intraquartile range.

[b] Numbers in subgroups do not total to overall number due to missing data.

[c] Ranksum p-value <0.05 for difference in median carboxyhemoglobin between cases and controls within characteristic stratum.

Table 2

Associations between early-pregnancy carboxyhemoglobin and risk of preeclampsia.

Carboxyhemoglobin exposure	No. cases[a]	No. controls[a]	Unadjusted OR [95% CI]	Adjusted[b] OR [95% CI]
Per 1% increase	126	416	1.48 [0.90, 2.41]	1.07 [0.58, 1.95]
Categorized				
0.17–0.69%	23	105	1.00 Reference	1.00 Reference
0.70–0.99%	63	201	1.37 [0.81, 2.32]	1.39 [0.76, 2.54]
1.00–5.27%	40	110	1.59 [0.88, 2.82]	1.11 [0.55, 2.25]
			p_{trend}: 0.12	p_{trend}: 0.87[3]

[a] Numbers included in final adjusted model.

[b] Adjusted for nulliparity, age, nonwhite race/ethnicity, chronic hypertension, pre-pregnancy body mass index, smoking before and during pregnancy, and date of blood draw.

Table 3

Association between early-pregnancy carboxyhemoglobin and risk of preeclampsia within groups classified by parity.

Carboxyhemoglobin exposure	No. cases[a]	No. controls[a]	Unadjusted OR [95% CI]	Adjusted[b] OR [95% CI]
Nulliparous women				
Per 1% increase	85	261	0.71 [0.32, 1.59]	0.44 [0.16, 1.25]
Categorized				
0.17–0.69%	16	46	1.00 Reference	1.00 Reference
0.70–0.99%	46	129	0.99 [0.52, 1.89]	0.92 [0.43, 1.96]
1.00–5.27%	23	86	0.72 [0.35, 1.49]	0.53 [0.23, 1.26]
			p_{trend}: 0.33	p_{trend}: 0.11
Parous women				
Per 1% increase	41	155	3.57 [1.54, 19.1]	2.30 [0.79, 6.72]
Categorized				
0.17–0.69%	7	59	1.00 Reference	1.00 Reference
0.70–0.99%	17	72	1.91 [0.74, 4.91]	2.33 [0.83, 6.54]
1.00–5.27%	17	24	5.97 [2.20, 16.2]	4.09 [1.30, 12.9]
			p_{trend}: <0.001	p_{trend}: 0.02
			$p_{interaction}$: 0.001[c]	$p_{interaction}$: 0.01[c]

[a] Numbers included in final adjusted model.

[b] Adjusted for age, nonwhite race/ethnicity, chronic hypertension, pre-pregnancy BMI, smoking before and during pregnancy, and date of blood draw.

[c] Interaction p-value from model with categorized carboxyhemoglobin.