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Relation of Whole Blood Carboxyhemoglobin Concentration to Ambient Carbon Monoxide Exposure Estimated Using Regression

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Exposure to carbon monoxide (CO) and other ambient air pollutants is associated with adverse pregnancy outcomes. While there are several methods of estimating CO exposure, few have been evaluated against exposure biomarkers. The authors examined the relation between estimated CO exposure and blood carboxyhemoglobin concentration in 708 pregnant western Washington State women (1996–2004). Carboxyhemoglobin was measured in whole blood drawn around 13 weeks' gestation. CO exposure during the month of blood draw was estimated using a regression model containing predictor terms for year, month, street and population densities, and distance to the nearest major road. Year and month were the strongest predictors. Carboxyhemoglobin level was correlated with estimated CO exposure ($\rho = 0.22$, 95% confidence interval (CI): 0.15, 0.29). After adjustment for covariates, each 10% increase in estimated exposure was associated with a 1.12% increase in median carboxyhemoglobin level (95% CI: 0.54, 1.69). This association remained after exclusion of 286 women who reported smoking or being exposed to secondhand smoke ($\rho = 0.24$). In this subgroup, the median carboxyhemoglobin concentration increased 1.29% (95% CI: 0.67, 1.91) for each 10% increase in CO exposure. Monthly estimated CO exposure was moderately correlated with an exposure biomarker. These results support the validity of this regression model for estimating ambient CO exposures in this population and geographic setting.

air pollutants; carbon monoxide; carboxyhemoglobin; pregnancy

Abbreviations: CI, confidence interval; SD, standard deviation.

Ambient carbon monoxide exposure during pregnancy has been associated with preterm delivery, intrauterine growth restriction, and reduced birth weight in diverse settings (1–6). Carbon monoxide exposures have been estimated using data from local air pollutant monitoring networks in several ways: by averaging concentrations across all local monitors (3, 6), using concentrations measured at the monitor nearest the maternal residence (1, 4), or calculating inverse-distance weighted averages of nearby concentrations (2, 5). These approaches are limited by the assumption that all persons residing within a given distance of a monitoring site are equally exposed.

Land-use regression is an exposure estimation method designed to overcome this limitation by exploiting the fact that intraurban variations in many air pollutants are related to nearby environmental characteristics, such as traffic, population density, and land use (7–9). The model quantifies the relations between local characteristics and the concentration of an air pollutant measured at a network of stationary monitors. The model is then used to estimate local residents' exposures (7–9). Previous regression models have explained 16%–76% of the variability in annual air pollutant concentrations (7, 10–13). Some model-based exposure estimates have been validated against independently obtained air pollutant measurements (11, 14). However, because of the expense and difficulty of this process, most estimates have not been directly compared with other exposure measures.

In contrast to many air pollutants (15), there exists a sensitive and specific biomarker of carbon monoxide exposure: whole blood carboxyhemoglobin concentration, resulting from the displacement of oxygen from hemoglobin by carbon monoxide (16, 17). Carboxyhemoglobin concentrations reflect recent exposures (biphasic elimination, half-lives of 3.6 and 4.5 hours) (18). In previous studies, carboxyhemoglobin concentrations measured in nonsmokers were correlated with declining air pollution levels within 1 city (19) and with differences in pollution across 4 cities (20). In 2 small studies, carboxyhemoglobin levels in infant umbilical cord blood were correlated with ambient carbon monoxide concentrations (21, 22). However, to our knowledge, no investigators have examined the correlation between regression model-based estimates of ambient carbon monoxide exposure and carboxyhemoglobin concentrations.

As part of our agenda to examine pregnancy-related effects of air pollution, we designed a regression model incorporating land use and temporal terms to estimate monthly and trimester-specific ambient carbon monoxide exposures among pregnant women in western Washington State. We aimed to quantify the relation between model-based exposure estimates and contemporaneous carboxyhemoglobin concentrations. This information should provide evidence of the degree to which our model captures biologically meaningful variations in ambient carbon monoxide exposure.

MATERIALS AND METHODS

Study population

In this cross-sectional analysis, we used data collected for the Omega Study (1996–2008), a previously described prospective cohort study (23). Participants were women attending prenatal care clinics affiliated with Swedish Medical Center in Seattle, Washington, 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 less than 18 years old, did not speak and read English, or did not plan to deliver at either hospital. Participants completed a questionnaire administered by a trained interviewer (mean gestational age = 15.9 weeks (standard deviation (SD), 4.8)). This questionnaire gathered information on sociodemographic, anthropometric, behavioral, medical, and reproductive characteristics. Participants provided a 20-mL nonfasting blood sample (mean gestational age = 14.8 weeks (SD, 3.1)). Blood was fractionated using standard procedures and stored at −80°C. After delivery, medical records were abstracted for information on the course and outcome of pregnancy. Study procedures were approved by the institutional review boards of both hospitals. All participants provided written informed consent.

In this analysis, we used data from women recruited between 1996 and 2004. During this period, 3,000 (77%) of the 3,899 invited women participated. Of these, 60 experienced early pregnancy losses and 152 were lost to follow-up because of an unknown delivery outcome or a missing medical record.

Analytical sample

Carboxyhemoglobin level was measured in 789 of the remaining 2,788 participants' blood samples. As part of our research agenda, we aimed to examine carboxyhemoglobin in relation to preeclampsia and preterm delivery. Therefore, we oversampled women who experienced these outcomes for carboxyhemoglobin measurement. We selected all women who developed preeclampsia or preterm delivery ($n = 390$) and a random sample of 399 who remained normotensive and delivered at term. From the 789 women with carboxyhemoglobin measurements, we excluded 35 women who did not complete an interview, from whom we obtained covariate data. We excluded 36 women with a nongeocodable address, which prevented estimation of carbon monoxide exposures. We also excluded 10 women who lived outside the Puget Sound region (King, Kitsap, Pierce, or Snohomish county) because the carbon monoxide exposure model may not be generalizable to other locations (8). The analytical population included 708 women.

Carboxyhemoglobin measurement

We measured carboxyhemoglobin in whole blood collected in tubes containing ethylenediaminetetraacetic acid. We used head-space capillary gas chromatography-mass spectrometry with an HP-Molesieve PLOT column (Agilent Technologies, Santa Clara, California). The assay provides a lower detection limit of 0.2% (16). Carboxyhemoglobin is expressed as percent hemoglobin. Hemoglobin was measured with a Quantichrom colorimetric assay (BioAssay Systems, Hayward, California) (24).

Estimation of ambient carbon monoxide exposure

We estimated monthly ambient carbon monoxide exposure using a multivariable linear regression model that included terms for land-use characteristics, month, and year. Our model was constructed using carbon monoxide measurements collected from 1996 to 2006 at 15 regional monitoring sites administered by the Puget Sound Clean Air Agency (see Web Figure 1, which is posted on the *Journal*'s Web site (http://aje.oxfordjournals.org/)) (25). The Puget Sound Clean Air Agency describes 12 sites as urban and 2 as suburban (1 is not described). Fourteen sites are in commercial areas; 3 of these areas are also described by the Puget Sound Clean Air Agency as residential. The sites are located using Environmental Protection Agency criteria to ensure a consistent and representative measure of air quality (25). We collapsed daily measurements into 890 monthly average concentrations. The average number of measurements taken per month was 29.9 (range, 18–31). The average number of monthly measurements taken per site was 59.3 (range, 4–123). Four sites operated for 10 years or more, 5 sites operated for 4–9 years, and 6 sites operated for less than 4 years. Within each month, the average difference in carbon monoxide concentrations across monitoring sites was 0.78 ppm (range, 0.18–1.67). Within each monitoring site, the average difference across months was 1.19 ppm (range, 0.31–2.01).

Table 1. Characteristics of Pregnant Women Receiving Prenatal Care and Distribution of Median Carboxyhemoglobin Concentrations According to Those Characteristics, Western Washington, 1996–2004

Characteristic	No. of Subjects	%	Median Carboxyhemoglobin Concentration, % Hemoglobin
Entire study population	708	100.0	0.85 (0.72–1.04)[a]
Age, years			
≤20	10	1.4	0.89 (0.82–1.23)
21–34	466	65.8	0.86 (0.72–1.05)
35–39	180	25.4	0.84 (0.74–1.05)
≥40	52	7.3	0.81 (0.68–0.99)
Parity			
Nulliparous	461	65.1	0.88 (0.75–1.09)
Parous	247	34.9	0.79 (0.68–0.94)
Prepregnancy body mass index[b,c]			
<18.5	32	4.6	0.78 (0.68–0.95)
18.5–24.9	460	65.4	0.85 (0.72–1.05)
25.0–29.9	117	16.6	0.86 (0.73–1.00)
≥30.0	94	13.4	0.86 (0.73–1.14)
Race/ethnicity[c]			
Non-Hispanic white	601	85.1	0.84 (0.71–1.03)
Non-Hispanic black	19	2.7	0.93 (0.79–1.13)
Hispanic	19	2.7	0.93 (0.72–1.15)
Asian/Pacific Islander	50	7.1	0.85 (0.75–1.05)
Other	17	2.4	0.86 (0.78–1.08)
Education			
Completion of high school	29	4.1	0.90 (0.72–1.16)
Vocational school or some college	138	19.5	0.87 (0.75–1.09)
Completion of college	299	42.2	0.83 (0.71–1.01)
Postgraduate education	242	34.2	0.85 (0.72–1.03)
Employed during early pregnancy[c]			
Yes	584	82.8	0.87 (0.73–1.06)
No	121	17.2	0.79 (0.69–0.90)
Marital status			
Married	644	91.0	0.84 (0.72–1.02)
Unmarried	64	9.0	0.93 (0.80–1.26)

Table continues

We evaluated local characteristics as potential predictors of monthly carbon monoxide concentrations at the monitoring sites. Characteristics were mapped and measured at each site using ArcMap 9.2 software (ESRI, Redlands, California). Using 2001 traffic-count data from the Washington State Department of Transportation, we estimated annual average traffic volume on the nearest major road (federal or state highway) within circular buffers with radii of 250 m and 500 m (26). We also measured distance to the nearest major road. Using US Census 2000 TIGER line files, we estimated street density (km/km^2) within 100-, 250-, 500-, and 1,000-m buffers (27). We used census measures of population density (persons/km^2) and housing density (housing units/km^2) within each site's census block group (27). We used monthly averages of daily high and low temperatures and precipitation collected by the Western Regional Climate Center at 31 weather stations (28). We used measurements taken at the nearest weather station; the average distance between each monitoring site and the nearest station was 6.8 km (range, 0.7–32 km). We used year and month terms to capture secular and seasonal variations in carbon monoxide concentrations.

We fitted multivariable linear regression models for the relation between each environmental characteristic (independent variables) and monthly average carbon monoxide (dependent variable). We used a stepwise procedure to determine the final model. First, we fitted models including a single environmental characteristic, year, and month as predictors. (All of these ''single-predictor'' models included year and month to allow estimation of monthly carbon monoxide concentrations). We coded continuous predictors

Table 1. Continued

Characteristic	No. of Subjects	%	Median Carboxyhemoglobin Concentration, % Hemoglobin
Annual household income[c]			
<$30,000	23	3.3	0.87 (0.71–1.38)
$31,000–$69,999	170	24.3	0.88 (0.75–1.11)
≥$70,000	492	70.2	0.84 (0.71–1.01)
Refused to respond	16	2.3	
Smoking status[c]			
Never smoked	508	71.8	0.84 (0.71–1.01)
Smoked before pregnancy	154	21.8	0.85 (0.75–1.08)
Smoked before and during pregnancy	46	6.5	0.91 (0.76–1.41)
SHS exposure in home during year before pregnancy			
No	680	96.0	0.85 (0.72–1.04)
Yes	28	4.0	0.93 (0.78–1.31)
SHS exposure outside home during year before pregnancy			
No	430	60.7	0.82 (0.71–1.00)
Yes	278	39.3	0.89 (0.74–1.11)
Regular recreational physical activity during early pregnancy[c]			
Yes	642	90.8	0.85 (0.72–1.05)
No	65	9.2	0.84 (0.73–1.00)
Year of blood draw			
1996–1998	144	20.3	1.09 (0.84–1.29)
1999–2001	249	35.2	0.88 (0.76–1.01)
2002–2004	315	44.5	0.78 (0.66–0.91)
Season of blood draw			
Winter (December–February)	166	23.5	0.88 (0.76–1.06)
Spring (March–May)	167	23.6	0.81 (0.69–0.95)
Summer (June–August)	183	25.9	0.84 (0.71–1.08)
Autumn (September–November)	192	27.1	0.86 (0.73–1.08)
Gestational week of blood draw			
5.7–12.9 (first trimester)	402	56.8	0.87 (0.74–1.10)
13.0–27.7 (second trimester)	306	43.2	0.82 (0.71–0.98)

Abbreviation: SHS, secondhand smoke.
[a] Numbers in parentheses, interquartile range (25th–75th percentiles).
[b] Weight (kg)/height $(m)^2$.
[c] Numbers in subgroups do not sum to overall number because of missing data.

linearly, log-transformed, and as a set of indicators or splines based on quartiles or other cutpoints suggested by exploratory analyses. First, for each predictor, we selected the model with the largest adjusted R^2 value. If multiple coding schemes produced similar R^2 statistics, the most parsimonious model was selected. Second, we chose the most predictive spatial scale (buffer) for street and bus densities and traffic volume by comparing single-predictor models and choosing the model with the largest adjusted R^2. Third, we included in the final model all characteristics with a Wald P value less than 0.10 in single-predictor models.

We measured the environmental characteristics included in the final model at each participant's self-reported, geocoded residential address (Web Figure 1). We used model coefficients and these measurements to estimate participants' monthly carbon monoxide exposures. We estimated exposures within each calendar month of pregnancy after approximating the date of conception to the nearest calendar month. We measured date of conception using the maternal report of the date of the last menstrual period and ultrasonography performed at ≤20 weeks' gestation. Information on the last menstrual period and ultrasound results was gathered by interview and medical record abstraction,

respectively. If both the last-menstrual-period and ultrasound-based dates agreed within 14 days, we used the former date. Among 4% of participants with dates differing by more than 14 days, we used the ultrasound-based date.

For this analysis, we used carbon monoxide exposures estimated in the calendar month and trimester of blood draw (e.g., the first trimester was defined as pregnancy calendar months 1–3). We chose these exposure windows because many studies suggest that adverse outcomes are most strongly associated with monthly- or trimester-specific exposures (1–6).

Statistical analysis

Because the carboxyhemoglobin distribution was skewed, we examined median concentrations and interquartile ranges according to participant characteristics (shown in Table 1), assessed during early-pregnancy interviews. We also examined distributions across groups classified by year, season, and trimester of blood draw.

We quantified the fit of the model in several ways. We calculated R^2 to quantify the proportion of the variance in carbon monoxide concentrations explained by the model. We calculated a root mean square prediction error to quantify the average absolute difference between observed and predicted concentrations at monitoring sites. We calculated 2 cross-validated coefficients of correlation between observed and estimated concentrations (11). First, we fitted the model using a randomly selected sample of half of the concentrations measured at the monitoring sites. We used this model to predict the remaining half, used the same procedure to predict concentrations in the first half of the sample, and calculated a ''random-half R^2.'' Second, we fitted the model using data from all but 1 of the carbon monoxide monitoring sites and then applied it to estimate concentrations at the remaining site; we performed this procedure for every site in turn and then calculated the ''remaining-site R^2.''

We fitted a weighted linear regression model to quantify the relation between log-transformed carboxyhemoglobin concentration and the characteristics used as predictors of ambient carbon monoxide exposure in the land-use regression model. We report model coefficients (β) as the $X\%$ (i.e., $(1 + X/100)$-fold) difference in median carboxyhemoglobin levels observed when comparing 2 groups of participants classified according to each predictor (29). We used frequency weights to account for the overrepresentation of preterm delivery and preeclampsia cases in the study sample. Subgroup analyses provided no evidence that the relations of interest differed according to preterm delivery or preeclampsia (data not shown). We calculated R^2 to quantify the proportion of variance in log-transformed carboxyhemoglobin concentration explained by the model predictors.

We quantified the agreement between estimated carbon monoxide exposure and carboxyhemoglobin concentration using a Pearson's ρ (Spearman's ρ values were similar). We used a multivariable linear regression model weighted to account for the overrepresentation of preterm delivery and preeclampsia, with log-transformed carboxyhemoglobin level as the dependent variable and log-transformed estimated carbon monoxide exposure as the independent variable. We estimated the percent difference in median carboxyhemoglobin concentration associated with each 10% increase in estimated carbon monoxide exposure. We log-transformed carbon monoxide values to maintain consistency in scale with carboxyhemoglobin values. We evaluated the characteristics listed in Table 1 as potential confounders. We included those that changed the association of interest by 10% or more (cigarette smoking, secondhand smoke exposure, and gestational age at blood draw) in the final model. We repeated analyses after stratifying women according to smoking and/or secondhand smoke exposure.

RESULTS

Participants were typically 21–34 years old, nulliparous, white, and married. Only 7% reported current smoking (Table 1). Median carboxyhemoglobin levels were higher among younger women, women without previous livebirths, black or Hispanic women, employed women, unmarried women, current smokers, women reporting secondhand smoke exposure, earlier participants, and those with first-trimester blood draws. As expected given the low prevalence of smoking and the geographic setting, distributions of local ambient carbon monoxide concentrations, estimated carbon monoxide exposures, and carboxyhemoglobin concentrations were generally low (Table 2).

The exposure estimation model included terms for year and month (indicators), street density within 500 m (quartile-based indicators), distance to the nearest major road (<100 m, 101–1,000 m, >1,000 m), and census tract population density (continuous). R^2 was 0.73. The root mean square error was 0.22 ppm (10% of the range). A scatterplot of observed versus predicted concentrations is shown in Figure 1. The random-half and remaining-site R^2 values were 0.71 and 0.31, respectively. Model coefficients showed that concentrations at monitoring sites were highest in 1996 and declined thereafter (Table 3). Concentrations were highest in February and lowest in July, on average. Concentrations were highest at sites with third-quartile street density but lower at sites with fourth-quartile density. Concentrations were inversely related to distance to the nearest major road and were not strongly related to population density.

Participants' carboxyhemoglobin concentrations were generally similarly related to model predictors (Table 3). This set of characteristics explained 28% of the variance in carboxyhemoglobin level (adjusted $R^2 = 0.28$). Year and month accounted for almost all of the explained variance in carboxyhemoglobin: The adjusted R^2 statistic for a model without the land-use terms was 0.27. Concentrations were generally higher among earlier participants, those who had winter blood draws, and those with higher street or population density. Unlike ambient carbon monoxide, carboxyhemoglobin was not strongly associated with distance to the nearest major road.

Carboxyhemoglobin was correlated with estimated carbon monoxide exposures in the calendar month ($\rho = 0.22$, 95% confidence interval (CI): 0.15, 0.29) and trimester ($\rho = 0.21$, 95% CI: 0.14, 0.28) of blood draw (Table 4). Each 10% increase in estimated carbon monoxide exposure

Table 2. Ambient Carbon Monoxide Concentrations[a] and Study Participants' Estimated Carbon Monoxide Exposures and Carboxyhemoglobin Concentrations ($n = 708$), Western Washington, 1996–2004

	Mean	Minimum	Percentile				Maximum
			25th	50th	75th	95th	
Local monthly CO concentration, ppm	1.08 (0.4)[b]	0.38	0.80	1.08	1.38	1.87	2.64
Estimated CO exposure in month of blood draw, ppm	1.00 (0.40)	0.12	0.71	0.97	1.28	1.70	2.14
Estimated CO exposure in trimester of blood draw, ppm	1.01 (0.39)	0.16	0.73	0.99	1.27	1.68	2.07
Carboxyhemoglobin level, % hemoglobin	0.93 (0.43)	0.17	0.72	0.85	1.04	1.55	5.92

Abbreviation: CO, carbon monoxide.
[a] Local concentrations measured at 15 monitoring sites.
[b] Numbers in parentheses, standard deviation.

during the month of blood draw was associated with a 1.42% (95% CI: 0.83, 2.02) difference in median carboxyhemoglobin concentration. This relation weakened slightly after adjustment ($\beta = 1.12\%$, 95% CI: 0.54, 1.69). The adjusted relation with estimated carbon monoxide in the trimester of blood draw was similar (per 10% increase in exposure, $\beta = 1.10\%$, 95% CI: 0.52, 1.69). Comparing 2 groups with 75th percentile carbon monoxide exposure versus 25th percentile carbon monoxide exposure in the month of blood draw, the adjusted difference in median carboxyhemoglobin level was 6.92% (95% CI: 3.35, 10.52). Relations of interest did not meaningfully differ after exclusion of the highest 1% of carboxyhemoglobin concentrations (data not shown).

Current smoking or exposure to secondhand smoke during the year before pregnancy did not strongly affect the association (Table 4). Among unexposed women, each 10% increase in estimated carbon monoxide exposure during the month of blood draw was associated with a 1.29% (95% CI: 0.67, 1.91) increase in median carboxyhemoglobin concentration. The relation within the subgroup of smoke-exposed women was somewhat weaker ($\beta = 0.90\%$, 95% CI: −0.01, 2.02).

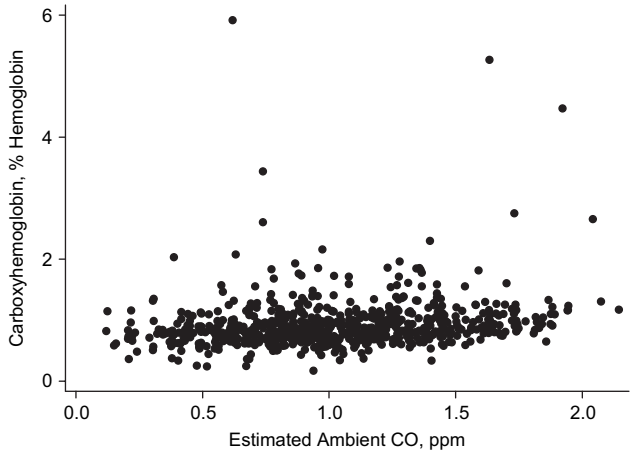

Figure 1. Carboxyhemoglobin concentration versus estimated ambient carbon monoxide (CO) concentration in the month of blood draw, Western Washington, 1996–2004.

DISCUSSION

Within this population of pregnant women in western Washington State, estimated residence-based carbon monoxide exposures were moderately correlated with carboxyhemoglobin concentrations. The association was slightly stronger within the subgroup of women who reported no smoking or secondhand smoke exposure.

Ours is the first study, to our knowledge, to demonstrate a relation between an air pollutant exposure estimated using a regression model and a contemporaneous exposure biomarker. However, 5 previous studies have suggested that ambient carbon monoxide concentrations influence carboxyhemoglobin concentrations. In a study by Stewart et al. (20), carboxyhemoglobin concentrations among nonsmoking blood donors in Chicago (Illinois), Los Angeles (California), Milwaukee (Wisconsin), and New York City were higher ($0.7\% \leq$ median $\leq 2.7\%$ across locations) than those measured among study volunteers breathing carbon monoxide-free air (median, 0.5%). The median carboxyhemoglobin concentration declined from 1.7% to 1.4% in nonsmoking Chicago blood donors from 1970 to 1974, correlating with reduced ambient carbon monoxide concentrations (19). Among 176 nonsmoking traffic police in Milan, Italy, Bono et al. (30) showed that each 10% increase in ambient carbon monoxide exposure was associated with a 2.4% increase in median carboxyhemoglobin level (95% CI: 0.0, 4.9). Ambient exposure (geometric mean = 3.0 ppm) was estimated using the average of the past-24-hour values measured at 6 monitoring sites. Ziaei et al. (22) measured umbilical cord blood carboxyhemoglobin in newborns delivered to 41 women living in a high-pollution area of Tehran, Iran, and 32 women living in a lower-pollution area. Average carbon monoxide exposures, measured at the nearest of 2 sites in the month of delivery, were 16 ppm (SD, 6.7) and 2.7 ppm (SD, 0.8) in the 2 groups. Cord-blood carboxyhemoglobin was correlated with carbon monoxide exposures ($\rho = 0.86$

Table 3. Comparison of the Exposure Model and Predictor/Biomarker Relations, Western Washington, 1996–2006[a]

CO Model Predictor Term	Coefficient for the CO Exposure Estimation Model (n = 890 Monthly Concentrations)				Adjusted[b] % Difference in Median Carboxyhemoglobin Concentration Across Participants (n = 708 Participants)		
	No. of Site-Months	No. of Sites	β, ppm	95% CI	No. of Study Participants	% Hemoglobin	95% CI
Year							
1996	103	8	0.77	0.68, 0.85	3	78.2	50.0, 106.6
1997	96	8	0.73	0.64, 0.81	75	56.6	46.8, 66.4
1998	102	10	0.60	0.51, 0.68	66	21.1	13.0, 29.3
1999	81	8	0.57	0.48, 0.65	76	37.7	27.9, 47.4
2000	102	9	0.57	0.48, 0.66	60	13.9	5.2, 22.6
2001	83	8	0.39	0.30, 0.49	113	6.8	−0.9, 14.5
2002	92	9	0.25	0.17, 0.34	104	4.4	−4.6, 13.3
2003	63	6	0.17	0.08, 0.26	128	10.9	1.4, 20.4
2004	64	6	0.17	0.08, 0.26	83	0	
2005	67	6	0.14	0.05, 0.23	0		
2006	37	6	0		0		
Month							
January	78	14	0		59	0	
February	77	14	0.03	−0.04, 0.10	41	1.0	−10.9, 12.9
March	77	14	−0.18	−0.25, −0.11	55	−13.1	−24.6, −1.6
April	73	15	−0.28	−0.35, −0.21	64	−11.7	−25.3, 1.9
May	73	15	−0.37	−0.44, −0.30	48	−11.9	−26.0, 1.9
June	73	15	−0.43	−0.50, −0.36	58	−7.6	−21.6, 6.4
July	73	15	−0.45	−0.52, −0.38	64	−13.2	−25.8, −0.7
August	70	13	−0.36	−0.43, −0.29	61	−4.6	−17.2, 8.0
September	68	13	−0.21	−0.28, −0.13	59	−10.1	−24.1, 3.8
October	73	13	−0.03	−0.10, 0.04	61	−6.9	−19.7, 5.9
November	73	13	0.10	0.03, 0.17	72	−9.4	−21.7, 2.9
December	73	13	0.03	−0.04, 0.10	66	−6.9	−20.3, 6.4
Street density within a 500-m buffer[c], km/km^2							
≤9.07	226	4	0		278	0	
9.08–11.87	246	4	0.31	0.25, 0.36	178	−0.2	−7.4, 7.2
11.88–14.37	114	4	0.66	0.56, 0.76	189	−3.3	−10.4, 3.7
≥14.38	304	3	0.19	0.13, 0.24	63	−5.6	−18.0, 6.8
Distance to the nearest major road[d], m							
≤100	89	2	0		28	0	
101–1,000	759	12	−0.30	−0.36, −0.23	326	6.1	−3.8, 16.1
≥1,001	42	1	−0.49	−0.57, −0.40	354	0.9	−8.7, 10.6
Population density[e] per 1,000 persons/km^2			0.40	−1.52, 2.35		0.6	−1.8, 2.9

Abbreviations: CI, confidence interval; CO, carbon monoxide.

[a] CO exposure model coefficients and percent differences in median carboxyhemoglobin concentration across study participants according to exposure model predictor terms.

[b] Adjusted for all other covariates in the table. Estimates and confidence intervals are weighted to account for oversampling of preeclampsia and preterm delivery cases from the underlying cohort.

[c] Street density ranged from 1.90 km/km^2 to 17.93 km/km^2 at monitoring sites and from 1.90 km/km^2 to 18.65 km/km^2 at participants' residences.

[d] Distance to the nearest major road ranged from 0.3 m to 29,786 m at monitoring sites and from 3 m to 1,449 m at participants' residences.

[e] Population density ranged from 237 persons/km^2 to 4,872 persons/km^2 at monitoring sites and from 1.3 persons/km^2 to 17,035 persons/km^2 at participants' residences.

Table 4. Relations Between Estimated Ambient Carbon Monoxide Exposure and Carboxyhemoglobin Concentration, According to Cigarette Smoke Exposure, Western Washington, 1996–2004

Analytic Sample and Window of CO Exposure	Pearson's ρ	95% CI	Difference in Median CBH Level per 10% Increase in CO Exposure			
			Unadjusted		Adjusted	
			%	95% CI	%	95% CI
Entire study population ($n = 708$)[a,b]						
Month of blood draw	0.22	0.15, 0.29	1.42	0.83, 2.02	1.12	0.54, 1.69
Trimester of blood draw	0.21	0.14, 0.28	1.41	0.81, 2.01	1.10	0.52, 1.69
Nonsmokers with no SHS exposure ($n = 422$)[a,c]						
Month of blood draw	0.24	0.15, 0.33	1.44	0.80, 2.08	1.29	0.67, 1.91
Trimester of blood draw	0.21	0.12, 0.30	1.27	0.62, 1.91	1.12	0.49, 1.76
Women reporting smoking and/or SHS exposure ($n = 286$)[a,c]						
Month of blood draw	0.16	0.04, 0.27	1.11	0.01, 2.23	0.90	−0.01, 2.02
Trimester of blood draw	0.17	0.05, 0.28	1.30	0.04, 2.57	1.16	−0.01, 2.41

Abbreviations: CBH, carboxyhemoglobin; CI, confidence interval; CO, carbon monoxide; SHS, secondhand smoke.

[a] Number included in adjusted model. Estimates and confidence intervals are weighted to account for oversampling of preeclampsia and preterm delivery cases from the underlying cohort.

[b] Adjusted model included covariates for smoking (never, before, or during early pregnancy), SHS exposure (yes or no), and gestational age at blood draw (weeks; continuous).

[c] Adjusted model included a covariate for gestational age at blood draw (weeks; continuous).

and $\rho = 0.36$ in high- and low-pollution groups; both P's $\leq$ 0.01). In the highly polluted and less polluted areas, each 0.1-ppm increase in carbon monoxide was associated with 0.07% and 0.06% rises in carboxyhemoglobin level, respectively (confidence intervals were not reported). As Pereira et al. (21) reported, among 47 newborns of nonsmoking women in São Paulo, Brazil, each 1-ppm increase in carbon monoxide was associated with a 0.29% (95% CI: 0.17, 0.40) increase in cord-blood carboxyhemoglobin. Carbon monoxide exposure was measured as the past 24-hour average of concentrations at 5 monitoring sites. Average exposure was 5.7 ppm (SD, 1.9).

Because of differences in modeling of carboxyhemoglobin concentrations and carbon monoxide exposures, it is difficult to quantitatively compare relations in the studies by Ziaei et al. (22) and Pereira et al. (21) with those estimated here. The association in Bono et al.'s study (30) was stronger than ours, perhaps because carbon monoxide concentrations were much higher in that setting. Nonetheless, like our findings, these studies show a positive relation between ambient carbon monoxide exposure and blood carboxyhemoglobin levels.

Two cross-validation procedures show that our model explained 31%–71% of the variance in local carbon monoxide concentrations. The R^2 value for the non-cross-validated model, 0.73, was similar to or higher than others in the literature (7, 10–12). The average error in our estimates was small compared with the range of concentrations. Both traffic measures were associated with carbon monoxide, though distance to the nearest major road explained little of their variance (adjusted R^2 values were 0.19 and 0.01, respectively). In 1996–2005, on-road vehicles caused approximately 65% of regional ambient carbon monoxide emissions (31, 32). Street density was not linearly associated with carbon monoxide. This may be due to the fact that all monitoring sites with highest-quartile density were located within 1 km of the waterfront; traffic may influence local concentrations differently near large bodies of water. However, in post hoc analyses, adding an interaction term for nearness to water and street density neither improved model fit nor meaningfully changed the carbon monoxide–street density relation.

Month and year were the strongest predictors of carbon monoxide concentration: Adjusted R^2 statistics were 0.20 and 0.30, respectively. The final model including temporal and land-use terms explained more variance in ambient carbon monoxide than a model with only temporal terms (adjusted R^2 values were 0.73 and 0.50, respectively). However, the temporal terms accounted for nearly the same amount of variance in carboxyhemoglobin concentrations as the full model (adjusted R^2 values were 0.28 and 0.27, respectively). Regional carbon monoxide concentrations are typically highest in winter, and concentrations declined steadily from 1996 to 2006 (25). These secular and seasonal fluctuations probably improved the model's ability to predict carbon monoxide concentrations. Models designed for short or fixed time periods in regions without declining carbon monoxide levels, or models designed to estimate annual concentrations, may be less strongly predictive.

Endogenous and exogenous carbon monoxide sources influence carboxyhemoglobin concentrations. Endogenous carboxyhemoglobin (typically 0.4%–0.7%) results primarily from hemolysis (33, 34). Exogenous sources include automobile exhaust, industrial combustion, tobacco smoke, and home appliances (35). In the absence of indoor sources,

indoor and ambient concentrations are highly correlated (36, 37). Carboxyhemoglobin concentrations in urban nonsmokers are approximately 1%–2%; concentrations in smokers are typically 4%–7% (17, 34).

Given carboxyhemoglobin's short half-lives, incidental carbon monoxide exposure shortly before blood draw may have influenced concentrations, resulting in misclassification of longer-term exposures that may have weakened our estimates of association. Inaccuracies in residential geocoordinates may have introduced misclassification. Errors in self-reported smoking and secondhand smoke exposure may have also influenced our results. To the extent that such errors are unrelated to ambient carbon monoxide exposure, they would attenuate estimated associations toward the null.

The random-half R^2 between observed and estimated carbon monoxide levels at monitoring sites was stronger than the remaining-site R^2, suggesting that individual sites influenced model fit. Within monitoring sites, R^2 ranged from 0.03 to 0.85. Excluding the 2 sites with the smallest R^2 values did not meaningfully improve the model fit. Sources of error in our model included rounding of exposure windows to the nearest month, imprecision in geocoding, and inaccurate land-use measures. Changes in traffic characteristics during the study period may not have been captured because of our reliance on 2001 traffic density data. Furthermore, the accuracy and precision of our residence-based model was probably hampered by our inability to estimate exposures outside the home. If these errors were unrelated to ambient exposures, they would have biased our estimates of association toward the null.

Another limitation of the model is its reliance on data collected from monitors sited for local monitoring purposes. While this approach is convenient and cost-effective because it takes advantage of existing data, the monitoring sites may not be optimally located for purposes of prediction. For instance, few monitors were located in residential areas, only 2 were located near a major road, and some participants lived in areas more densely populated than the monitoring sites. Differences between sites and participants' residences such as these may have led to exposure misclassification. The small numbers of sites in close proximity to a major road may have adversely limited our ability to capture traffic-related variations in carbon monoxide concentrations.

Our relatively simple model probably does not capture all of the spatial and temporal dependence in ambient carbon monoxide concentrations. The model's predictive ability may be improved by incorporating residual dependence using universal kriging or other methods. Nevertheless, measures of model fit and the relations between exposure estimates and carboxyhemoglobin are strong, though they appear to be driven primarily by temporal rather than spatial characteristics. These results support the validity of this easily implementable model for estimating monthly and trimester-specific carbon monoxide exposures and examining their influences on pregnancy-related health outcomes in this setting. We look forward to future studies designed to relate model-based air pollutant exposure estimates to other exposure biomarkers such as DNA adducts and carbon in airway macrophages (38, 39). Such studies may provide additional evidence to support the increasingly common use of air pollution prediction models in estimating exposures for epidemiologic research.

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