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Maternal carbon monoxide exposure and its association with small-for-gestational-age newborns in an Andean city in Colombia

Exposición materna a monóxido de carbono y su asociación con recién nacidos pequeños para la edad gestacional en una ciudad andina colombiana

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Abstract

Introduction: Small-for-gestational-age (SGA) newborns, defined as birth weight below the 10th percentile, represent an adverse perinatal outcome with short- and long-term health implications. Prenatal exposure to carbon monoxide (CO), derived from vehicular traffic, has been associated with fetal growth restriction. This study aimed to determine the association between maternal exposure to CO and SGA in an Andean city in Colombia. **Methodology:** An analytical cross-sectional study was conducted. Newborns were classified as cases (SGA) and controls (non-SGA) and were matched by neonatal sex. Maternal exposure was estimated using an inventory of vehicular CO emissions (tons/year per 250 × 250 m grid cell). Descriptive analyses were performed, along with χ^2 and Student's t tests. Multivariable unconditional logistic regression models were fitted to examine the association with SGA, and robust linear regression models were used for birth weight. The models were adjusted for maternal age, parity, health insurance scheme, and marital status. A p-value <0.05 was considered statistically significant. **Results:** A total of 71 SGA cases and 142 controls were included. Mean CO exposure was higher among cases than controls (137 vs. 35 tons/year/250 × 250 m; $p<0.001$). Exposure above the fourth quartile of CO emissions was associated with an increased risk of SGA (adjusted OR: 15.2; 95% CI: 7.2–32; $p<0.001$). For each one-standard-deviation increase in emissions, birth weight decreased by a mean of 186 g. **Conclusions:** Prenatal exposure to vehicular CO is associated with an increased risk of SGA births. This finding supports the need for public policies aimed at controlling vehicular emissions as a preventive strategy for maternal and perinatal health. It also underscores the importance of studies incorporating direct measurements of pollutant concentrations and the assessment of gestational exposure windows.

Keywords: Infant, Small for Gestational Age; Carbon Monoxide; Maternal Exposure; Air Pollution.

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Introduction

Favorable pregnancy outcomes are considered direct indicators of the efficient functioning of health systems and the social development of a population. Therefore, the various factors leading to adverse obstetric outcomes have been the subject of ongoing scientific research[1].

Low birth weight (LBW) and small-for-gestational-age (SGA) newborns represent a significant public health concern due to their association with lifelong complications, including increased neonatal morbidity and mortality, prolonged hospital stays, intensive care unit admissions, disabling sequelae, and a higher risk of chronic diseases in adulthood[1–5]. Given their impact on human health, multiple strategies have been developed to reduce their incidence, such as the World Health Organization (WHO) Global Targets 2025 initiative, which aimed to achieve a 30% reduction in the LBW rate by that year[6].

The WHO defines LBW as a birth weight of less than 2,500 grams[2]; nevertheless, other definitions incorporate the relationship between birth weight and gestational age using population growth curves and percentile distributions[7–9]. A neonate is considered SGA when birth weight falls below the 10th percentile for their gestational age, a threshold used as a criterion to assess the risk of adverse events and perinatal mortality[2,9–12].

It is estimated that between 5% and 20% of live births are SGA[2]. In Colombia, various studies have reported the prevalence of SGA across different institutions and regions; however, official data adopt the WHO definition. For instance, the Ministry of Social Protection reported a national prevalence of 9% in 2014, whereas in Manizales the prevalence was estimated at 8.28%[13,14].

Over recent decades, the study of the relationship between environmental pollution exposure and the occurrence of various diseases has gained increasing relevance[15,16]. Numerous studies have demonstrated the association between prenatal exposure to chemical compounds present in atmospheric emissions and adverse obstetric outcomes, such as congenital malformations, preterm birth, perinatal mortality, stunted growth, alterations in infant psychomotor development, and fetal growth restriction [17–22].

Vehicular traffic is one of the primary sources of harmful emissions, releasing particulate matter, nitrogen oxides, heavy metals, halogenated and aromatic compounds, ozone, and carbon monoxide (CO), among others—all of which have been associated with SGA[23–25]. Among these pollutants, CO has been extensively studied due to its association with adverse obstetric outcomes. It is a byproduct of the combustion of organic and inorganic compounds, with motor vehicles representing one of the main emission sources. In response, health recommendations have been issued establishing regulatory limits for emissions to minimize environmental and health effects on exposed populations, along with measures to mitigate the impact of vehicular traffic[15–21].

Most epidemiological studies estimate exposure through measured or modeled ambient concentrations (e.g., μg/m3). In this study, we utilized a spatial model of vehicular emissions (tons/year/cell) as a proxy for residential exposure. Although these measures were related, they are not equivalent; therefore, any direct comparison of effect estimates with literature based on concentration measures should be interpreted with caution.

In 2018, Gómez et al. conducted a study in the Colombian city of Manizales that estimated the temporal and spatial emissions of particulate matter smaller than 10 microns (PM_{10}) and CO from vehicular traffic, using a 250 × 250 m grid cell to identify areas with higher pollutant concentrations[25,26]. These data allowed the definition of CO exposure in the city and the analysis of its association with the occurrence of SGA births. While regional studies have examined the relationship between air pollution and perinatal outcomes, our study provides evidence using a geospatial approach to vehicular emissions, thereby complementing previous studies based on ambient pollutant concentrations.

Methodology

Study design

An analytical cross-sectional study was conducted based on a retrospective review of medical records of births at a tertiary care institution in Manizales, Colombia, between January 1 and December 31, 2014.

The sample size was determined based on previous studies comparing exposure to various concentrations of particulate matter, which reported a probability of exposure to high concentrations of 10% in the control group (p_1) and 26% in the case group (p_2)[27]. For the present study, an expected odds ratio (OR) of 1.5 (w) was assumed. A confidence level of 95% (α) and a statistical power (1–β) of 80% were established. A control-to-case ratio of 2:1 was adopted (controls = m; cases = n). Based on these parameters, the required sample size was estimated at 69 cases and 139 controls.

Inclusion criteria

a. Women who had a vaginal delivery or cesarean section between January 1 and December 31, 2014.
b. Mothers of newborns with birth weight below the 10th percentile for gestational age, calculated using the INTERGROWTH-21st tool.
c. Residents of the city's urban area with georeferenced residential addresses.

Exclusion criteria

a. Incomplete medical records.
b. History of thyroid disease, pregestational or gestational diabetes, hypertensive disorders of pregnancy, chronic hypertension, psychoactive substance use, autoimmune or oncological diseases, maternal malnutrition, congenital malformations, Rh incompatibility, or multiple gestations.

Exposure assessment

Data on the spatial and temporal disaggregation of PM10 and carbon monoxide (CO) emissions for the year 2014, as described by Gómez et al.26, were used. A gridded geographic layer with a spatial resolution of 250 × 250 m was created using ArcGIS® software for the urban area of Manizales, allowing visualization of the spatial distribution of PM10 and CO concentrations by grid cell. Participants' residential addresses were geolocated in a separate layer using ArcGIS® and overlaid for visualization on the Google My Maps® platform. Exposure was defined as the estimated CO emission value corresponding to the grid cell where each case and control was located.

Statistical analysis

Data were analyzed using Stata IC version 14.2 (StataCorp LLC, College Station, TX, USA). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Variables with $p > 0.05$ were summarized as means and standard deviations (SD), while those with $p < 0.05$ were reported as medians and interquartile ranges (IQR). For bivariate comparisons in this analytical cross-sectional study, χ^2 tests were used for categorical variables, and either Student's t test or the Mann-Whitney U test was applied for continuous variables, depending on their distribution.

Crude odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were estimated. Subsequently, unconditional multivariable logistic regression models were fitted to evaluate the association between CO emissions (exposure) and SGA births (outcome), adjusting for maternal age, parity, marital status, and health insurance scheme. As a complementary analysis, birth weight was modeled as a continuous variable using linear regression with robust standard errors (Huber-White sandwich estimator). Gestational age was not included in the SGA models, as it is inherently part of the outcome definition. Statistical significance was set at $p<0.05$.

Results

A total of 213 patients were included, comprising 71 cases and 142 controls. The mean age of the participants was 25 years. No statistically significant differences were observed between cases and controls regarding socioeconomic characteristics (marital status and health insurance scheme) or clinical factors (gravidity and history of miscarriages). In both groups, the contributory health insurance scheme was the most prevalent, accounting for 60% of cases and 64% of controls; four patients in each group were enrolled in a special health insurance regime (military or teachers' union) **(Table 1).**

Table 1. Maternal and neonatal characteristics

Characteristic	Total	Cases	Controls	p-value
	(n=213)	(n=71)	(n=142)	
Maternal characteristics				
Maternal age (years),				0.801
Mean (SD)	25.80 ± 5.50	25.60 ± 4	26 ± 2.40	
Marital status				0.222
Single	48.82 (104)	50.7 (36)	47.88 (68)	
Married	18.77 (40)	19.71 (14)	18.3 (26)	
Cohabiting / common-law union	30.98 (66)	29.57 (21)	31.69 (45)	
Separated	0.46 (1)	0	0.7 (1)	
Widowed	0.93 (2)	0	1.4 (2)	
Health insurance scheme				0.270
Contributory	62.91 (134)	60.56 (43)	64.08 (91)	
Subsidized	30.98 (66)	33.8 (24)	29.57 (42)	
Special regime	3.75 (8)	5.63 (4)	2.81 (4)	
Uninsured	2.34 (5)	0	3.52 (5)	
Gravidity				0.299
0	64.78 (138)	69.01 (49)	62.67 (89)	
1	24.41 (52)	23.94 (17)	24.64 (35)	
≥2	10.78 (23)	7.04 (5)	12.67 (18)	
Previous miscarriages				0.829
Yes	10.79 (23)	11.26 (8)	10.56 (15)	
No	89.2 (190)	88.73 (63)	89.43 (127)	
Neonatal characteristics				
Sex				0.700
Male	33.80 (72)	33.80 (24)	33.80 (48)	
Female	66.19 (141)	66.19 (47)	66.19 (94)	
Birth weight (grams)				<0.001
Mean (SD)	2970 ± 474	2534 ± 473	3187 ± 470	
Median	3000	2600	3182	
Interquartile range (IQR)	2685–3325	2450–2705	3000–3407	
Mode of delivery				0.1
Vaginal	57.3 (122)	50.7 (36)	60.6 (86)	
Cesarean section	40.8 (87)	46.5 (33)	38 (54)	
Instrumental delivery	1.9 (4)	2.8 (2)	1.4 (2)	
Gestational age at birth				
30–34 weeks	1.9 (4)	1.4 (1)	2.1 (3)	
35–37 weeks	5.1 (11)	7 (5)	4.2 (6)	
≥ 37 weeks	93 (198)	91.6 (65)	93.7 (133)	

Note: p-values were calculated using the χ^2 test, Student's t-test, or Mann-Whitney U test, as appropriate based on variable type and distribution.

Carbon monoxide (CO) emissions followed a normal distribution (Kolmogorov-Smirnov test, p=0.61). The mean CO exposure among cases was 137 tons/year per 250 × 250 m grid cell, with a median of 108 (interquartile range [IQR]: 73–195). In contrast, controls had a mean exposure of 35 tons/year per 250 × 250 m grid cell, with a median of 25.31 (IQR: 7.5–43). Student's t-test revealed significantly higher exposure to vehicular CO emissions among cases (mean = 136.84) compared with controls (mean = 36.97) ($t(82.1) = 9.56$, $p < 0.05$) **(Table 2).**

Table 2. Vehicular CO emissions in cases and controls.

Group	Mean (SD)	Median (IQR)	p-value
SGA cases (n=71)	136.8 ± 90.4	108 (73–195)	
Controls (n=142)	36.92 ± 26,3	25.3 (7.5–43)	
Total (n=213)	—	—	<0.001

Vehicular CO emissions are expressed in tons/year per 250 × 250 m grid cell; p-values were obtained using Student's t-test for the comparison between cases and controls. CI, confidence intervals (95 % CI) are provided. CO: Carbon monoxide; SGA: small-for-gestational-age (<10th percentile according to INTERGROWTH-21st standards).

Bivariate analysis revealed a statistically significant association between CO exposure levels above the fourth quartile and a higher risk of SGA births, with more than 15-fold increase in risk (crude OR = 15.2; 95% CI: 7.2–32; p < 0.0001). No statistically significant associations were found between other sociodemographic or clinical variables and SGA **(Table 3)**.

Table 3. Bivariate analysis (crude ORs) for SGA births

Variable	Crude OR (95% CI)	p-value
CO emissions		
Q1–Q3 (73 - 195)	1	
Quartile 4 (>195)	15.2 (7.2–32)	<0.001
Maternal age ≥	—	0.2
Marital status		
Single	1	
Cohabiting / Common-law union	0.88 (0.46–1.70)	0.23
Marital status		
Single	1	
Married	1.02 (0.47–2.19)	0.11
Health insurance scheme		
Contributory	1	
Subsidized	1.21 (0.65–2.25)	0.21
Health insurance scheme		
Contributory	1	
Special regime	2.12 (0.51–8.87)	0.33
Gravidity		
0	1	
1	0.88 (0.45–1.73)	0.32
≥2	0.50 (0.18–1.44)	0.11
Previous miscarriages		
No	1	
Yes	1.08 (0.43–2.67)	0.2

Vehicular CO emissions are expressed in tons/year per 250 × 250 m grid cell. Crude odds ratios (ORs) with 95% confidence intervals (CIs) are presented. SGA, small-for-gestational-age (<10th percentile according to INTERGROWTH-21st standards).

In the multivariable models, vehicular CO emissions remained significantly associated with SGA births. Specifically, for every one-standard-deviation increase in vehicular CO emissions (74.9 tons/year per 250 × 250 m grid cell) at the maternal residence, birth weight decreased by an average of 186 g, according to the linear regression model with robust standard errors.

Discussion

Prenatal exposure to carbon monoxide (CO) has been associated with multiple health conditions occurring both during the perinatal period and later in adulthood. Evidence suggests an increased risk of developing diseases such as cancer, diabetes, respiratory disorders, cardiovascular disease, cognitive impairment, and mental health disorders in later life[15–18]. Similarly, prenatal CO exposure has been associated with pregnancy complications, including preterm birth, congenital malformations, hypertensive disorders of pregnancy, and low birth weight[25–32].

This effect may be mediated by a reduction in the oxygen-carrying capacity of maternal hemoglobin, thereby decreasing oxygen delivery to the fetus. Furthermore, CO crosses the placental barrier and directly affects fetal hemoglobin, leading to hypoxia and reduced fetal growth potential[28–31]. It has also been proposed that CO may affect smooth muscle tone, immune system regulation, and contribute to oxidative stress and cellular damage[30,33,34].

The magnitude of the association observed in our study was greater than that reported in the international literature, possibly due to the high dispersion of emissions and spatial heterogeneity within the city. For instance, Qian et al. reported that for every 100 $\mu g/cm^3$ increase in maternal CO exposure in Wuhan, China, the risk of SGA births increased by 15% (OR: 1.15; 95% CI: 1.1–1.2)[35]. Guo et al. found an increased risk, particularly during the second and third trimesters of pregnancy (OR = 1.04; 95% CI: 1.02–1.05)36. In Latin America, a study conducted in the Brazilian Amazon reported a 49% increase in the risk of low birth weight associated with CO exposure above the fourth quartile, using the WHO definition (<2,500 g)[37]. Nonetheless, some national studies contradict these findings: González et al. found no association between exposure to PM_{10} and CO and preterm birth, and Narváez et al. reported no association with preeclampsia[38,39].

Manizales, located in the Andes Mountains at an average altitude of 2,150 m above sea level (m a.s.l.), has a population of nearly 400,000 inhabitants, with a high population density (6,800 inhabitants per 17 km^2) and a high motorization rate (455 vehicles per 1,000 inhabitants in 2018), surpassing even larger cities, including the national capital. These conditions favor increased population exposure to potentially harmful compounds[40–44]. Interest in air quality in Manizales arose following the eruption of the Nevado del Ruiz volcano on November 13, 1985—a natural disaster that claimed more than 25,000 lives and remains one of the most severe tragedies in recent history[45]. Since then, air quality monitoring stations, atmospheric concentration modeling, and active research groups have been established[45,46].

A potential confounding factor is the altitude of Manizales; however, while the city is located in the Andean region, its elevation of 2,150 m a.s.l. is below the 2,500 m threshold considered a risk factor for SGA births due to hypobaric hypoxia[47]. Therefore, the association observed in this study is not necessarily explained by the city's altitude.

When assessing the impact of exposure to environmental pollutants on gestational health, multiple interrelated variables must be considered, as they complicate the analysis of causality. For instance, ambient temperature also influences air quality and clinical outcomes. Ha et al. reported an increase in relative risk of up to 2.49 (95% CI: 2.3–2.83) when exposure occurs during heatwave periods throughout pregnancy [47].

A limitation of this study is the inability to accurately differentiate the specific source of CO, whether vehicular, industrial, or derived from volcanic emissions from the Nevado del Ruiz. Additionally, isolating the effects of a single pollutant is challenging because exposure involves a complex mixture of atmospheric compounds, including nitrogen oxides (NOx), sulfur oxides (SOx), halogenated compounds, and particulate matter, among others[48]. Exposure was estimated based on maternal residence, although individual variations due to daily mobility may

exist. However, a study by Choe et al. found no significant differences in exposure to $PM_{2.5}$ and PM_{10} between women who work outside the home and those who did not, with respect to the occurrence of SGA births[49,50]. These findings support the validity of using maternal residence as the primary proxy for exposure in our analysis.

The duration of exposure and its variations across gestational trimesters are critical factors for establishing associations. Since emission estimates in this study were conducted for the 2014 calendar year, it was not possible to precisely determine variations for participants whose pregnancies began in 2013. Nevertheless, it was assumed that emission patterns remain stable between consecutive years. These methodological limitations introduce confounding factors that should be considered when interpreting the results. Even so, studies by Lu Jia et al.[51] and Van den Hooven et al.[52] support the use of estimated monthly or annual averages, as these facilitate the analysis of epidemiological associations.

Although a matched design was initially considered, the analysis was performed using an analytical cross-sectional approach with unconditional models. This decision was based on the risk of overmatching described by Pearce[53], given that the place of residence is a strong determinant of exposure to CO emissions. By employing adjusted conventional logistic regression models, loss of statistical power was avoided, allowing for a more robust estimation of odds ratios (ORs), in line with the recommendations by Rose and Laan[54] regarding efficiency in study designs involving geographically confounding variables.

Vehicular CO emission exposure was estimated using data published by Gómez et al.[26]. In that study, emissions were modeled based on vehicle counts, estimates by vehicle type, and proximity to primary and secondary roads, using atmospheric dispersion and mass transport models to generate a 250 × 250 m grid cell. This indirect measurement may introduce imprecision in emission estimates; therefore, future studies incorporating direct measurements are warranted.

In this study, emissions are reported in tons per year per 250 × 250 m grid cell, whereas other studies report pollutant concentrations in ambient air units ($\mu g/m^3$)[13–20,26,28,32–34,44–47]. It is fundamental to distinguish that the former represent the production and ground-level spatial distribution of the pollutant, whereas the latter reflect its atmospheric dilution and transport. This study focused on a specific emission source (mobile sources) and its direct effects[40–42,47]; future research should incorporate both methodological approaches to explore differences and clinical implications. Furthermore, it is crucial to study the effects of industrial emissions on SGA births, given that their chemical composition differs from vehicular emissions and their perinatal toxicity has been previously demonstrated[13,15,20]. Despite the age of the data, traffic patterns, urban topography, and meteorological conditions in Manizales have remained relatively stable over the past decade, supporting the validity of these findings.

The statistical analysis revealed high dispersion in vehicular CO emission values, with differences exceeding 100-fold between minimum and maximum values. This wide variability may explain the higher ORs observed compared with those reported in previous studies. A potential spatial imbalance between cases and controls is suggested, with the presence of pollution clusters that should be identified in future research. Regarding the spatial distribution in Manizales, cases appear to be concentrated in areas with high traffic density characterized by suboptimal sanitary conditions, poverty, and exposure to industrial pollutants and waste—factors that could not be fully evaluated using this methodology. This combination of factors, along with others not included in the model, may have acted synergistically, leading to the elevated risk observed[12].

The impact of vehicular emissions on birth weight represents a significant knowledge gap in the region. This study constitutes one of the first in Latin America to explore the association between vehicular emissions and SGA births, providing novel evidence from an Andean urban context and complementing previous findings that have primarily employed atmospheric concentrations as the exposure metric.

Conclusions

Prenatal exposure to vehicular carbon monoxide emissions was associated with an increased likelihood of small-for-gestational-age (SGA) neonates, regardless of maternal factors such as age, parity, marital status, and health

insurance scheme. These findings are consistent with international literature and provide additional evidence from an Andean urban context in Latin America.

Further studies incorporating direct measurements of atmospheric concentrations, co-pollutants, and stratified analyses by gestational trimester are warranted to determine the magnitude of the association and critical exposure windows. Our results suggest that vehicular emissions, as a potentially modifiable factor, should be considered in the development of government and public health policies aimed at reducing the incidence of adverse obstetric outcomes such as SGA.

Author Contributions

FA and NE designed and conducted the study and drafted the report and the manuscript. LD provided subject-matter expertise and thematic guidance. NE and LD supervised the statistical and methodological analyses. All authors have reviewed, edited, and approved the final version of the manuscript.

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Ethical Considerations

This research adheres to the ethical principles governing studies involving human subjects, in accordance with national and international regulations and current Colombian legislation. This manuscript is based on the results of the principal investigator's thesis conducted as part of the specialization program in Gynecology and Obstetrics. The study protocol was approved by the Ethics Committee of the Universidad de Caldas. Data confidentiality was ensured in accordance with applicable legal standards for the protection of privacy.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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During the preparation of this work, the authors did not use artificial intelligence. The authors reviewed and edited the content according to academic standards and assume full responsibility for the final content of the manuscript.

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