



Association between exhaled carbon monoxide and asthma outcomes in Peruvian children

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ABSTRACT

Background: Asthma prevalence continues to increase in low and middle-income countries, presenting challenges in assessing asthma control in resource-poor settings. Previous studies suggest that exhaled carbon monoxide (eCO) is higher with asthma severity and lower with treatment. We hypothesized that eCO levels may be elevated in children with asthma, particularly in children with partially controlled or uncontrolled asthma in a low-resource setting in Lima, Peru.

Methods: We compared average eCO levels between 248 children with asthma and 221 healthy controls as well as the odds of asthma by eCO quartiles (0–1, 2, 3, and ≥ 4 ppm) using multivariable linear and logistic regression. eCO quartiles were also used to compare the odds of partially controlled or uncontrolled asthma (score ≤ 19 on the Asthma Control Test) in a multivariable logistic regression model.

Findings: Average adjusted eCO level was 0.56 ppm (95% CI 0.07–1.05) higher in children with asthma. The adjusted odds of asthma were 1.22 (95% CI 0.75–1.97), 1.46 (0.81–2.63), and 1.76 (0.96–3.23) in the second, third, and fourth eCO quartiles compared to the first eCO quartile, respectively. Among children with asthma, the adjusted odds of partially controlled or uncontrolled asthma in those in the second, third, and fourth eCO quartiles, compared to the first, were 1.61 (95% CI 0.74–3.48), 3.66 (95% CI 1.51–8.87), and 2.50 (95% CI 1.06–5.90), respectively.

Interpretation: eCO may serve as an inexpensive biomarker for asthma control, particularly in low-resource settings.

1. Background

Asthma prevalence in low- and middle-income countries (LMIC) has been increasing, primarily due to growing urbanization [1]. This trend is evident in Peru, where asthma prevalence in adolescents is estimated to be 13%, with higher prevalence in urban compared to rural areas [2,3]. Characterized as a source of chronic airway inflammation, several markers for inflammation have been considered in detecting the presence of asthma and assessing the degree of asthma control [4]. One of these markers is exhaled carbon monoxide (eCO), which is a potential biomarker among children and adults with asthma [5]. In a 2010 meta-analysis of 18 studies, the weighted mean difference in eCO comparing subjects with asthma and healthy controls was 1.25 ppm (95% CI 0.92–1.58 ppm) [6]. The mechanism behind this difference in eCO could be the degradation of hemoglobin by the enzyme, heme oxygenase-1 [5]. As hemoglobin is degraded, it promotes the production of CO, which is then exhaled [7]. Factors such as oxidative stress, the presence of inflammatory cytokines, and nitric oxide (NO) can lead to upregulation of heme oxygenase-1 [8]. Cytokines are released and

NO is produced during asthmatic inflammation, which could influence the accumulation of heme oxygenase-1 and elevated production of eCO in individuals with asthma [8].

In addition to being non-invasive, eCO can be measured using devices that are generally simple to use and affordable, potentially making eCO a feasible asthma control assessment tool in low-resource settings in which access to primary healthcare is limited [5].

Studies have shown that during asthma exacerbations and prior to treatment with glucocorticosteroids, eCO levels are elevated, possibly due to induction of heme oxygenase-1 [9]. eCO could serve as a simple, adjunct measure that could provide healthcare workers and patients with a cheap alternative to assess asthma control.

The following analysis examines the relationship between eCO measurements and asthma status, as well as asthma control in children and adolescents with asthma living in a peri-urban community of Lima, Peru. We hypothesized that eCO levels would be higher in children with asthma compared to healthy controls and that higher levels of eCO would be associated with higher odds of asthma and increased odds of partially controlled or uncontrolled asthma.

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2. Materials and methods

2.1. Study population and setting

This study was carried out in Villa El Salvador (Villa), a coastal, peri-urban neighborhood approximately 25 km south of the city center of Lima, Peru. Villa consists largely of highland immigrants and has expanded in size as a result of increased urbanization over the last two decades. Surrounding roads are both paved and unpaved and trash burning is common. Smoking prevalence is low, with previous studies estimating daily smoking prevalence between 1.9 and 3.3% and occasional smoking (≤ 1 cigarette per day) between 8.9 and 9.1% [10,11]. Indoor household air pollution from biomass smoke exposure is also low, with a prevalence of 6.1% [12].

2.2. Study design

This study is an ancillary analysis carried out in a subset of children ages 9–19 years of age recruited as part of a parent study examining the role of gene-by-environment interactions in predicting asthma risk and severity [3].

We conducted a house-by-house census survey of Villa from 2011 to 2012. During the census, potential cases were identified using the child's birthdate and a positive response to questions regarding (1) wheezing or having experienced symptoms of asthma in the past 12 months or (2) use of an asthma medication within the past 12 months. Children who responded negatively to both of these questions were identified as potential healthy controls. Healthy controls were selected by simple random sample and screened using the following criteria: 1) no self- or parentally-reported wheezing or asthma symptoms within the past 12 months, 2) no asthma medication use within the past 12 months, 4) $FEV_1/FVC \geq 85\%$, and 5) $FEV_1\%$ predicted $> 80\%$. A total of 221 healthy controls were enrolled.

Following the census survey, disease status was confirmed during the baseline visit, which occurred between July and November 2013. Children were excluded if they had a history of ocular, abdominal, or thoracic surgery within the past 3 months, a history of hospitalization for cardiac reasons in the past 3 months, a diagnosis of tuberculosis, a prescription for tuberculosis treatment, a chronic respiratory condition other than asthma, or were pregnant at enrollment. Final enrollment resulted in 248 children with asthma.

2.3. Demographic questionnaire

Demographic questionnaires were administered to all participants during the baseline visit. The baseline questionnaire provided date of birth, sex, medication status, BMI, smoking status, as well as whether or not the participant had close friends or family who smoked, lived in a household that burned trash outside, or had neighbors that burned trash outside.

2.4. Exhaled carbon monoxide assessment

We measured eCO using the Micro CO Meter (Micro Direct, Lewiston, ME). The eCO monitor was calibrated monthly using a calibration gas concentration of 20 ppm. Participants were instructed to inhale for 20 s, then exhale for 20 s with lips forming a tight seal around the eCO meter, as per monitor instructions. Measurements were carried out in the morning for 160 children, and in the afternoon for 279 children. Time of eCO measurement was considered a dichotomous variable consisting of morning or afternoon measurements.

2.5. Asthma outcomes

We used the Asthma Control Test (ACT), a 5-item validated questionnaire, to measure asthma control at the baseline visit [13]. Asthma

control was dichotomized with an ACT score > 19 indicating well-controlled asthma and an ACT score ≤ 19 denoting partially controlled or uncontrolled asthma [14].

2.6. Statistical analyses

The primary analytical objectives were to evaluate the potential relationship between eCO and asthma status and to determine the association between eCO and asthma control. Sex, age, BMI, smoking status of the participant, smoking status of close friends and family, trash burning by neighbors, time of day of the eCO measurement were considered *a priori* as potential confounders in adjusted models. Due to low numbers within our sample, we could not adjust for participant smoking, household trash burning, and long-term controller medication in our analysis.

In addressing the first objective, multivariable linear regression was used to compare average eCO in children with asthma and healthy controls during the baseline visit. Multivariable logistic regression was also used to model the odds of asthma by eCO quartile. In logistic regression models, eCO level was analyzed by quartile as 90% of eCO measurements were less than 4 ppm. Quartiles consisted of eCO values of 0–1 ppm, 2 ppm, 3 ppm, and ≥ 4 ppm, respectively. In addressing the second objective, multivariable logistic regression was used to model the odds of partially controlled or uncontrolled asthma by eCO quartile at the baseline visit. Data were analyzed using STATA 13 statistical software (Stata Corp., College Station, TX) [12].

3. Results

3.1. Characteristics of study population

Of the 545 children screened within Villa for the parent case-control study, 469 were included in the current analysis. eCO measurements were obtained for 439 of the 469 children and ranged from 0 to 26 ppm with an average of 2.2 ppm. Of all the children enrolled, 248 had self or parental-reported asthma, 92.3% of which reported receiving an asthma diagnosis from a physician. There were no significant differences in age, sex, BMI, or asthma status between children with and without eCO measurements (Table 1). Children with and without asthma were similar in terms of sex, smoking status, and exposure to secondhand tobacco smoke through family and friends. Few children reported smoking ($n = 5$), while more than half of children reported

Table 1
Participant characteristics among children with asthma and healthy controls.

	Children with Asthma	Healthy Controls	p-value
Sample size	248	221	
Demographics			
Age in years, mean (SD)	13.1 (2.5)	12.6 (2.5)	0.05
n, (%) boys	128 (51.6)	108 (48.9)	0.55
Anthropometry			
BMI in kg/m^2 , mean (SD)	22.4 (4.7)	21.4 (4.0)	0.02
Underweight and Normal weight (%)	126 (50.8)	132 (59.7)	0.14
Overweight (%)	82 (33.1)	62 (28.1)	
Obese (%)	40 (16.1)	27 (12.2)	
Socioeconomic status, n (%)			
Current smokers	2 (1.0)	3 (1.4)	0.55
Reports having one close friend who smokes	188 (75.8)	170 (76.9)	0.68
Reports family member who smokes	57 (23.0)	43 (19.5)	0.33
Reports trash burning by family members within the household	2 (0.8)	5 (2.3)	0.20
Reports trash burning by neighbors	48 (19.4)	27 (12.2)	0.04

Table 2

Participant characteristics among children with controlled, partially controlled, and uncontrolled asthma.

	Controlled Asthma	Partially Controlled or Uncontrolled Asthma	p-value
Sample size, n	176	72	
Demographics			
Age in years, mean (SD)	13.1 (2.6)	13.0 (2.3)	0.80
n, (%) boys	95 (54.0)	33 (45.8)	0.24
Anthropometry			
BMI in kg/m ² , mean (SD)	22.3 (4.8)	22.7 (4.3)	0.57
Underweight and Normal weight (%)	93 (52.8)	33 (45.8)	0.53
Overweight (%)	57 (32.4)	25 (34.7)	
Obese (%)	26 (14.8)	14 (19.4)	
Socioeconomic status, n (%)			
Current smokers	2 (1.1)	0 (0.0)	0.36
Reports having one close friend who smokes	132 (75.0)	56 (77.8)	0.75
Reports family member who smokes	40 (23.3)	17 (23.6)	0.96
Reports trash burning by family members within the household	1 (0.6)	1 (1.4)	0.53
Reports trash burning by neighbors	38 (22.1)	10 (13.9)	0.14
Medication status, n (%)	3 (1.7)	6 (8.3)	0.01

having at least one close friend or family member who smoked; however, there was no significant difference in the number of close family or friends who smoked between children with asthma and healthy controls. Few households reported burning trash outside their home while 16% reported having neighbors that did. At 64%, a higher proportion of children in households where the neighbors burned trash also had asthma ($p < 0.05$). Children with asthma were slightly older with an average age of 13.1 years compared to 12.6 years in healthy controls ($p = 0.05$). Those with asthma had a slightly higher average BMI at 22.4 kg/m² compared to 21.4 kg/m² in healthy controls ($p < 0.05$).

Between children with controlled and partially controlled or uncontrolled asthma, there was no difference in sex, age, and BMI (Table 2). Similar to the overall study population, few participants smoked cigarettes ($n = 2$) while a fair number had friends ($n = 188$) or family members ($n = 57$) who smoked. Only two households reported burning their own trash while 48 reported having neighbors that burned trash. There was no difference in asthma control among households in which the family or surrounding neighbors burned trash or among participants who reported having friends and family who smoked. Very few children reported taking asthma medication ($n = 9$), with six using albuterol and three using oral prednisone. Of these children, six had partially controlled or uncontrolled asthma while the remaining had reported controlled asthma.

3.2. eCO levels and asthma status

In an unadjusted analysis, children with asthma had an eCO measurement that was on average 0.58 ppm higher than that of children without asthma ($p = 0.02$) (Table 3). After adjustment for confounders, children with asthma still had an eCO level that was 0.56 ppm higher compared to children without asthma ($p = 0.03$).

There was also an upward trend in the odds of asthma with eCO quartile in the unadjusted analysis. Compared to the first eCO quartile, the odds ratio for asthma in the second, third, and fourth quartiles were 1.19 (95% CI 0.75 to 1.89), 1.37 (95% CI 0.79 to 2.38), and 1.91 (95% CI 1.07 to 3.39), respectively (Table 3). Significant results were only evident in the fourth eCO quartile. The adjusted analysis followed a similar trend: odds of asthma in the second, third, and fourth quartiles were 1.22 (95% CI 0.75 to 1.97), 1.46 (95% CI 0.81 to 2.63), and 1.76 (95% CI 0.96 to 3.23), respectively when compared to the first quartile (Table 3).

3.3. eCO levels and asthma control

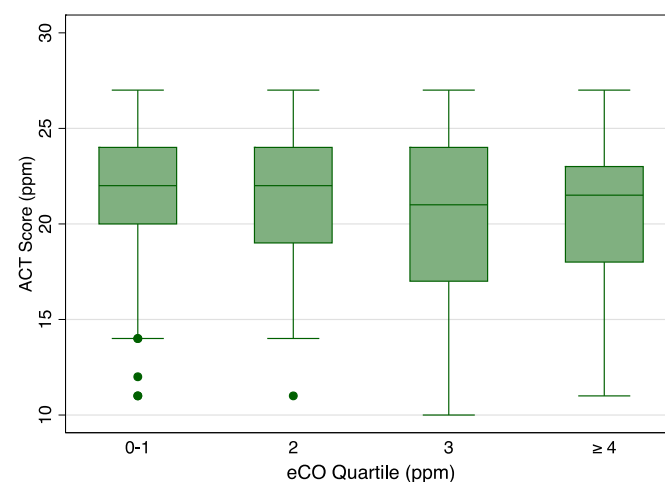
We plotted boxplots of ACT scores by eCO quartiles in Fig. 1, and

Table 3

Linear and logistic regression results relating eCO to asthma status.

eCO by asthma status	Unadjusted analysis (95% CI)	Adjusted analysis (95% CI) ^a
Average difference in eCO comparing children with asthma to healthy controls (ppm)	0.58 (0.11–1.05)	0.56 (0.07–1.05)
Odds ratio of Asthma by eCO quartile		
0–1 ppm (ref)	1.0	1.0
2ppm	1.19 (0.75–1.89)	1.22 (0.75–1.97)
3ppm	1.37 (0.79–2.38)	1.46 (0.81–2.63)
4 ppm and higher	1.91 (1.07–3.39)	1.76 (0.96–3.23)

^a Adjusted for age, sex, BMI, smoking status of close friends and family, household trash burning by friends and family, and time of day of the eCO measurement.

**Fig. 1.** Average ACT score by eCO quartile.

found that ACT scores were overall lower in higher eCO quartiles. In an unadjusted analysis, the odds of partially controlled or uncontrolled asthma for those with eCO values in the third and fourth quartile were higher when compared to the first quartile (Table 4). The odds ratio comparing the odds of partially controlled or uncontrolled asthma in the second eCO quartile to the first was 1.71 (95% CI 0.80 to 3.65). The third eCO quartile had the most pronounced increase in the odds of partially controlled or uncontrolled asthma compared to the first

Table 4

Logistic regression results for the association between partially controlled or uncontrolled asthma with eCO.

Odds ratio of partially controlled or uncontrolled asthma by eCO quartile		
	Unadjusted analysis (95% CI)	Adjusted analysis (95% CI) ^a
0–1 ppm (ref)	1.0	1.0
2ppm	1.71 (0.80–3.65)	1.61 (0.74–3.48)
3ppm	2.78 (1.22–6.32)	3.66 (1.51–8.87)
4 ppm and higher	2.46 (1.10–5.53)	2.50 (1.06–5.90)

^a Adjusted for age, sex, BMI, smoking status of close friends and family, household trash burning by friends and family, and time of day of the eCO measurement.

quartile with an odds ratio of 2.78 (95% CI 1.22 to 6.32, $p = 0.02$). Although less prominent than the third eCO quartile, the effect of eCO on the odds of partially controlled or uncontrolled asthma was statistically significant in the fourth quartile compared to the first quartile, as evidenced by an odds ratio of 2.46 (95% CI 1.10 to 5.53, $p = 0.03$).

After adjusting for confounders, eCO remained significantly associated with higher odds of partially controlled or uncontrolled asthma for the third and fourth eCO quartiles. The odds ratio of partially controlled or uncontrolled asthma in the second quartile compared to the first was not significant at 1.61 (95% CI 0.74 to 3.48), after adjustment. The third eCO quartile showed a significant increase in the odds of partially or uncontrolled asthma with an adjusted odds ratio of 3.66 (95% CI 1.51 to 8.87, $p < 0.01$). The fourth eCO quartile showed a less pronounced increase in the odds of partially controlled asthma with an odds ratio of 2.50 (95% CI: 1.06 to 5.90, $p = 0.04$) after adjustment.

4. Discussion

While the odds of asthma did not increase significantly with eCO quartile, we found that mean eCO levels were higher in children with asthma when compared to children without asthma. Higher eCO levels were also associated with greater odds of partially controlled or uncontrolled asthma.

Average eCO concentration was 0.56 ppm higher, after adjustment, in children with asthma compared to healthy controls. These findings are consistent with much of the existing literature, which demonstrate higher concentrations of eCO among adult and pediatric asthmatic populations [4,6]. Higher eCO levels among children with asthma might be the result of inflammation and resulting degradation of hemoglobin by heme oxygenase-1 [15]. In a cross-sectional study by Horváth et al., those with asthma who had expired more eCO also exhibited higher levels of heme oxygenase-1 proteins in airway macrophages compared to healthy controls [15]. While other studies indicate that environmental triggers such as tobacco smoke can also lead to higher eCO readings, smoking status of participants and close family and friends was low overall and relatively balanced between children with asthma and children without asthma [16–18]. Children who reported smoking ($n = 5$) had a slightly higher average eCO measurement of 3.20 ppm compared to 2.17 ppm among those who did not report smoking; however, this difference was not significant. In addition, we adjusted for sources of nearby pollution, such as trash burning by neighbors and tobacco smoking by friends and family. Thus, the source of eCO is likely to be endogenous in nature, rather than the result of external factors such as tobacco smoke or burning trash.

Prior studies generally compared average eCO level between individuals with and without asthma. When evaluating the odds of asthma by eCO quartile, both the unadjusted and adjusted analyses followed an upward trend, suggesting that the odds of asthma increase with eCO quartile. While the odds ratio was only significant within the fourth quartile of the unadjusted analysis, the positive trend may be

worth evaluating through further analyses using a larger sample size.

Regarding asthma control, we found higher odds of partially controlled or uncontrolled asthma within the third and fourth eCO quartiles compared to the first, with and without adjustment for confounders. Although not statistically significant, the odds of having partially controlled or uncontrolled asthma were higher in those with eCO levels in the second quartile compared to the first quartile. The odds of partially controlled or uncontrolled asthma were highest in the third eCO quartile compared to the first. This may suggest that rather than using eCO as a continuous indicator of asthma control, eCO measurements at 3 ppm or higher may serve as a cutoff point for partially controlled or uncontrolled asthma. This may be particularly useful in clinical settings for more severe cases of asthma in which symptoms are not immediately apparent or fully communicated, or in research settings to assist in the identification of potential cases of uncontrolled asthma.

Previous studies outlined below show conflicting findings in describing the association between eCO and asthma control. A cross-sectional study by Uasuf et al. found a significant difference in average eCO levels between children with persistent asthma and infrequent episodic asthma; however, there was no significant difference between those with infrequent episodic asthma and healthy controls [19]. Similarly, a cross-sectional study by Yamaya et al. that examined average eCO among 71 asthmatic adults with controlled to unstable severe asthma found a highly significant inverse correlation between eCO and FEV₁ [20]. In contrast, a 2014 study of 241 children with asthma in Slovak Republic found no significant association between ACT score and eCO levels [4]. A similar study that employed the Asthma Control Questionnaire (ACQ) found no correlation between asthma control and eCO among 23 Dutch children with mild to moderate asthma [21]. While notable, the aforementioned studies were carried out in high-resource settings in which asthma medications are readily prescribed and available. The present study appears to be the first to examine asthma control and eCO in children in a low-resource setting or a middle-income country.

While other markers for asthma control, such as exhaled nitric oxide (eNO), are conventionally used in western clinical settings, eCO is cheaper to measure than eNO [22]. As such, use of an eCOMeter may be favorable in a low-resource setting, such as Villa [23]. In addition, studies comparing various respiratory disease indicators have shown significant correlations between eCO and eNO among individuals with asthma [4,21].

Limitations of the present study include a lack of repeated eCO measurements, increasing the potential for uncertainty in eCO measurements for each child. Our study also lacked objective measures for tobacco smoke exposure. While smoking rates were low, potential confounders such as the participant's smoking status and exposure to secondhand smoke from friends and family were self-reported, rather than confirmed through objective measures such as urine cotinine. Additionally, as a cross-sectional study, temporality could not be assessed in the relationship between eCO and asthma status or asthma control.

Further research is warranted to assess the degree to which eCO is associated with asthma control, particularly in low-resource settings. Studies should evaluate the mechanisms behind eCO and asthma and how these mechanisms differ based on treatment status. In high-resource settings, studies relating eCO and asthma medication adherence could be considered to evaluate the potential role of eCO as an indicator of behaviors that impact asthma control. In addition, longitudinal studies assessing the effect of eCO and the frequency of reports of partially controlled or uncontrolled asthma may be helpful.

5. Conclusion

In summary, the results of this study suggest a positive association between average eCO level and asthma status. eCO levels are elevated

in children with asthma compared to healthy controls and appear to increase as asthma control decreases. Further study is merited to consider the potential role of eCO as a marker for asthma control, particularly in low-resource settings.

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Ethics, consent, and permissions

All participants provided written informed consent or assent. This study was approved by the Institutional Review Boards at the Johns Hopkins University School of Medicine, Baltimore, USA, and A.B. PRISMA in Lima, Peru.

Conflicts of interest

The authors have no competing interests to declare.

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