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Short-term, lagged association of airway inflammation, lung function, and asthma symptom score with $PM_{2.5}$ exposure among schoolchildren within a high air pollution region in South Africa

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Background: Asthma affects millions of people globally, and high levels of air pollution aggravate asthma occurrence. This study aimed to determine the association between short-term lagged $PM_{2.5}$ exposure and airway inflammation, lung function, and asthma symptom scores among schoolchildren in communities in the Highveld high-pollution region in South Africa.

Methods: A cross-sectional study was conducted among schoolchildren aged 9–14 years in six communities in the Highveld region in South Africa, between October 2018 and February 2019. A NIOX 200 instrument was used to measure fractional exhaled nitric oxide (FeNO). Lung function indices (forced expiratory volume in one second [FEV_1]; forced vital capacity [FVC] and FEV_1/FVC) were collected using spirometry and the percent of predicted of these was based on the reference equations from the Global Lung Initiative, without ethnic correction. These values were further analyzed as binary outcomes following relevant thresholds (lower limits of normal for lung function and a cutoff of 35 ppb for FeNO). Asthma symptoms were used to create the asthma symptom score. Daily averages of $PM_{2.5}$ data for the nearest monitoring station located in each community, were collected from the South African Air Quality Information System and created short-term 5-day lag $PM_{2.5}$ concentrations. Additional reported environmental exposures were collected using standardized instruments.

Results: Of the 706 participating schoolchildren, only 1.13% of the participants had doctor-diagnosed asthma, compared to a prevalence of 6.94% with an asthma symptom score suggestive of asthma. Lag 1 (odds ratio [OR]: 1.01; 95% confidence interval [CI]: 1.00, 1.02, $P = 0.039$) and 5-day average lagged $PM_{2.5}$ (OR: 1.02; 95% CI: 0.99, 1.04, $P = 0.050$) showed increased odds of the FeNO > 35 ppb. Lung function parameters (FEV_1 < lower limit of normal [LLN] [OR: 1.02, 95% CI: 1.00, 1.03, $P = 0.018$], and FEV_1/FVC < LLN [OR: 1.01; 95% CI: 1.00, 1.02, $P < 0.001$]) and asthma symptom score ≥ 2 (OR: 1.02; 95% CI: 1.00, 1.04, $P = 0.039$) also showed significant associations with lag 2, lag 4 and lag 1 of $PM_{2.5}$, respectively.

Conclusion: Lagged $PM_{2.5}$ exposure was associated with an increased odds of airway inflammation and an increased odds of lung function parameters below the LLN particularly for the later lags, but a significant dose–response relationship across the entire sample was not consistent.

Keywords: Air pollution; FeNO; Lung function; Asthma symptoms

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Introduction

Globally, asthma is estimated to affect more than 300 million individuals, increasing to about 400 million in 2025.[1–4] The prevalence in low- and middle-income countries is higher when compared with high-income countries.[5] Characterized by a variety of phenotypes, with different biochemical pathways, understanding the relationship between asthma and associated risk factors remains a challenge.[6,7]

Ambient air pollution, including respirable particulate matter 2.5 microns in diameter ($PM_{2.5}$), has been shown to have a significant association with a range of respiratory health effects particularly among those with asthma.[8,9] $PM_{2.5}$ has been

What this study adds:
Limited studies have looked at the association between airway inflammation and $PM_{2.5}$ exposure in children, in a lagged manner, particularly on the African continent. Our findings strongly suggest that $PM_{2.5}$ exposure contributes to airway inflammation, abnormal lung function, and asthma symptoms. This study adds to the existing literature providing evidence that short-term exposure to $PM_{2.5}$ has a lagged effect on airway inflammation and lung function and that this effect is stronger among those with compromised airways.

associated with acute and chronic respiratory symptoms, such as wheezing and shortness of breath, increased visits to emergency rooms, lung function declines, and increased adverse outcomes among asthmatics.[10,11] Studies describe these effects with either short-term (current or recent), longer-term, cumulative, or period-averaged (annual, seasonal) exposures.[11,12] Inconsistencies in findings may result from the specific outcome measure, the choice of the study sample (e.g., asthmatics vs. random sample), or the characterization of the metric of exposure.[13]

Measures of airway function are important indicators of pulmonary responses to external stimuli. Spirometry, as indicated by changes to forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and the ratio of these parameters (FEV_1/FVC), has frequently been reported with abnormal outcomes in the presence of exposure to air pollution. Airway inflammation, which if severe enough, results in asthma symptoms through various mechanisms including the immunoglobulin E (IgE)-mediated inhibition of innate antiviral responses to rhinovirus and production of cytokines leading to narrowing and swelling of the bronchial muscles.[14,15] The deposition of $PM_{2.5}$ in the airway and lung tissue through various biochemical pathways results in an inflammatory response.[8,9,16] A noninvasive quantitative biomarker of eosinophilic airway inflammation is fractional exhaled nitric oxide (FeNO).[17,18] FeNO, as a marker of airway inflammation, has been associated with increased $PM_{2.5}$ concentrations across several studies in Malaysia,[17] the United States,[18] and China.[19] Although using different estimates of exposure, per unit increase in pollutant exposures was associated with a same-day increase in FeNO in these studies. A systematic review identified only six studies that described the relationship between $PM_{2.5}$ and FeNO among children.[19] Among the studies that selected asthmatic children, associations varied, absent in some,[20–22] but were seen in others.[23–25] Studies among community-based samples of children including asthmatics and nonasthmatics showed $PM_{2.5}$-related increases in FeNO.[26–28] The inconsistencies among these studies may be related to the assumption of the temporal relationship between exposure and outcome. A limited number of studies have investigated the lagged effects between FeNO and $PM_{2.5}$ exposure among a random sample of children with and without asthma. Lagged effects have been reported among university students,[19] children,[29] and asthmatic children[21] including very short-term lags (<24 hours).[30]

Unlike the lagged PM effects of FeNO, the lagged effects of spirometry among children have been more regularly reported in the literature, affected by similar challenges of sample selection and exposure characterization. A recent meta-analysis of childhood studies with short-term exposure showed important $PM_{2.5}$-induced effects in the various lung function parameters, stronger for the same day as compared to the previous day lags. Although the meta-analysis did not stratify studies with exclusive asthmatics and mixed samples, the pooled estimates of reduced FEV_1 and peak expiratory flow were statistically significant across both lags.[31] Two-panel studies of asthmatic children showed a much stronger decline in lung function than those seen in the pooled estimates, with a greater effect associated with a 1-day moving average.[22,23]

Few studies found an increased risk of lagged $PM_{2.5}$ exposure in asthma exacerbation in children.[32,33] Huang et al showed in a meta-analysis that both adults and children were at an increased risk of asthma exacerbations in lag day 0 (risk ratio [RR] = 1.007, 95% confidence interval [CI]: 1.005, 1.010) and lag day 1 (1.005, 95% CI: 1.002, 1.008) from $PM_{2.5}$ exposure. There was a small increase in risk among children only (lag 0 [RR = 1.032, 95% CI: 1.025, 1.039] and lag 1 [RR = 1.014, 95% CI: 1.007, 1.021]).[34]

We hypothesized that there is a lagged $PM_{2.5}$ effect on airway inflammation in particular, as well as lung function and asthma symptom score generally in a sample of randomly selected schoolchildren. This study aimed to determine the association between lagged $PM_{2.5}$ exposure measures with airway inflammation, lung function, and asthma symptom score among schoolchildren living in communities in the Highveld High Pollution Priority Area (HPPA), a region with high ambient pollution concentrations in South Africa.[35,36]

Methods

Study setting and design

This study was conducted in the Highveld HPPA, a designated high air pollution region in inland South Africa (Figure 1).[37] This region is situated at an elevated altitude and is home to a range of high industrial emission sources, including coal mining and coal-fired power stations, among many other anthropogenic and natural emission sources. The Highveld HPPA has a climate with an average minimum temperature of 19 °C in summer and an average minimum temperature of 6 °C in winter.[38]

This was a cross-sectional study conducted among grade 4 schoolchildren aged 9–14 years. One school was selected (see selection criteria) from the following communities: Witbank, Secunda, Hendrina, Ermelo, Grootvlei, and Phola (Figure 2). These are similar with regard to environmental exposures (industrial emissions and burning of biomass fuels) and socioeconomic status. Two classes of grade four classes were randomly selected in the schools, except Grootvlei, Phola, and Hendrina, where all grade 4 classes were recruited within the selected school because of limited classes. The schools were selected based on proximity to an air quality monitoring station (within a 1–2 km radius of the monitoring station), sufficient numbers of grade 4 pupils, and a limited amount of "bussing in" of children from distant communities. Of the 714 schoolchildren eligible to participate, eight declined participation, resulting in a sample size of 706 participants.

Studies have reported that samples of at least 50 schools with an average of 10–30 children each will provide 90% power or more to describe outcome patterns and to fit models to test different hypotheses adjusting for appropriate covariates.[39] Given the small number of participating schools, we considered the Kenward–Roger correction for small clusters.[40,41] With this approach, an estimated sample size ranging from 500 to 1500 children would allow us to test our research question using generalized estimating equations (GEE) models with the correction for small clusters.[42] Thus, the available sample of approximately 700 children clustered into six schools had adequate power to test our hypothesis.

Collection of data

Child and caregiver interviews

Fieldworkers were recruited from the studied communities with previous experience in conducting community-based surveys. The questionnaire included demographic information; an assessment of the presence and severity of respiratory and other relevant symptoms and doctor-diagnosed disorders (Appendix I; http://links.lww.com/EE/A313). Questionnaires were available in English and Sotho, and interviews were conducted in the language of choice of the respondent. Data were collected electronically in the field and immediately uploaded onto remote servers using mobile technology.

An asthma symptom score was created from responses to specific respiratory symptoms questions from the caregiver's questionnaire: doctor-diagnosed asthma, shortness of breath when hurrying on level ground, too breathless during dressing, ever

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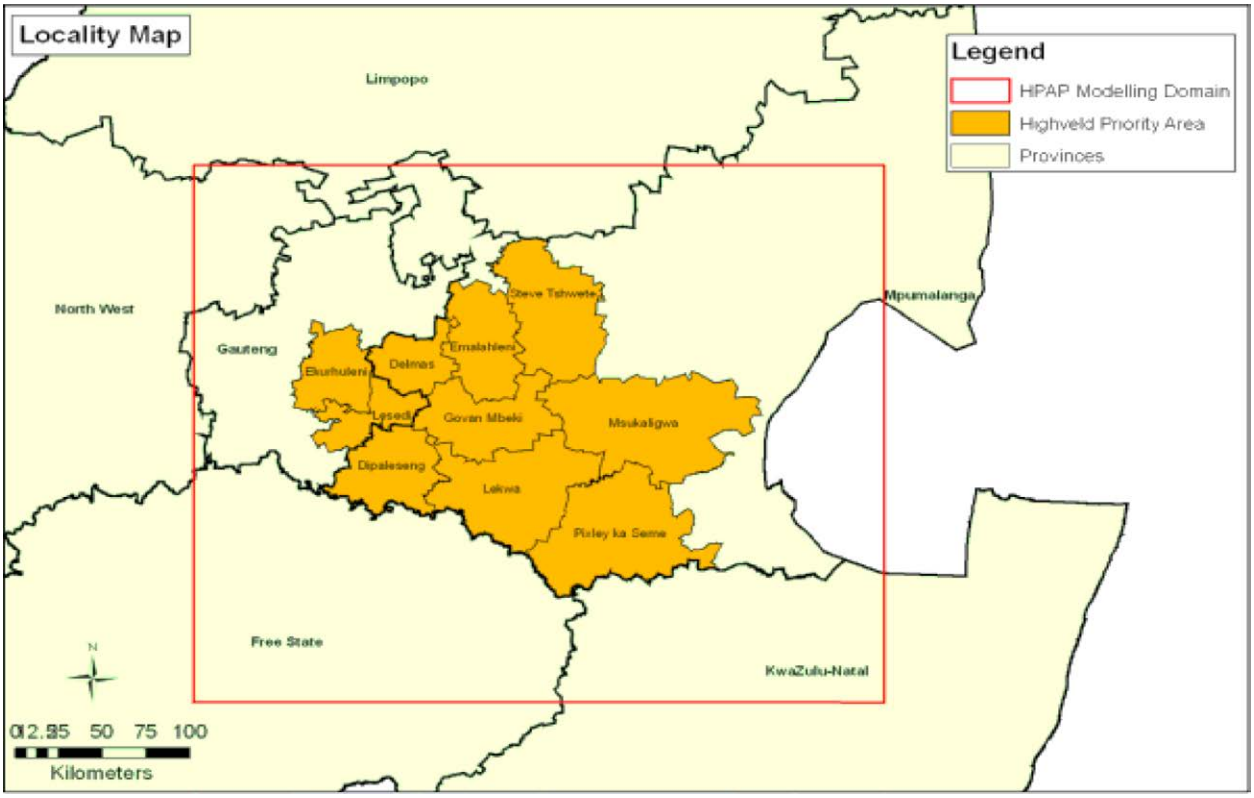

Figure 1. A map illustrating Highveld High Pollution Priority Area (as defined in reference [37]).

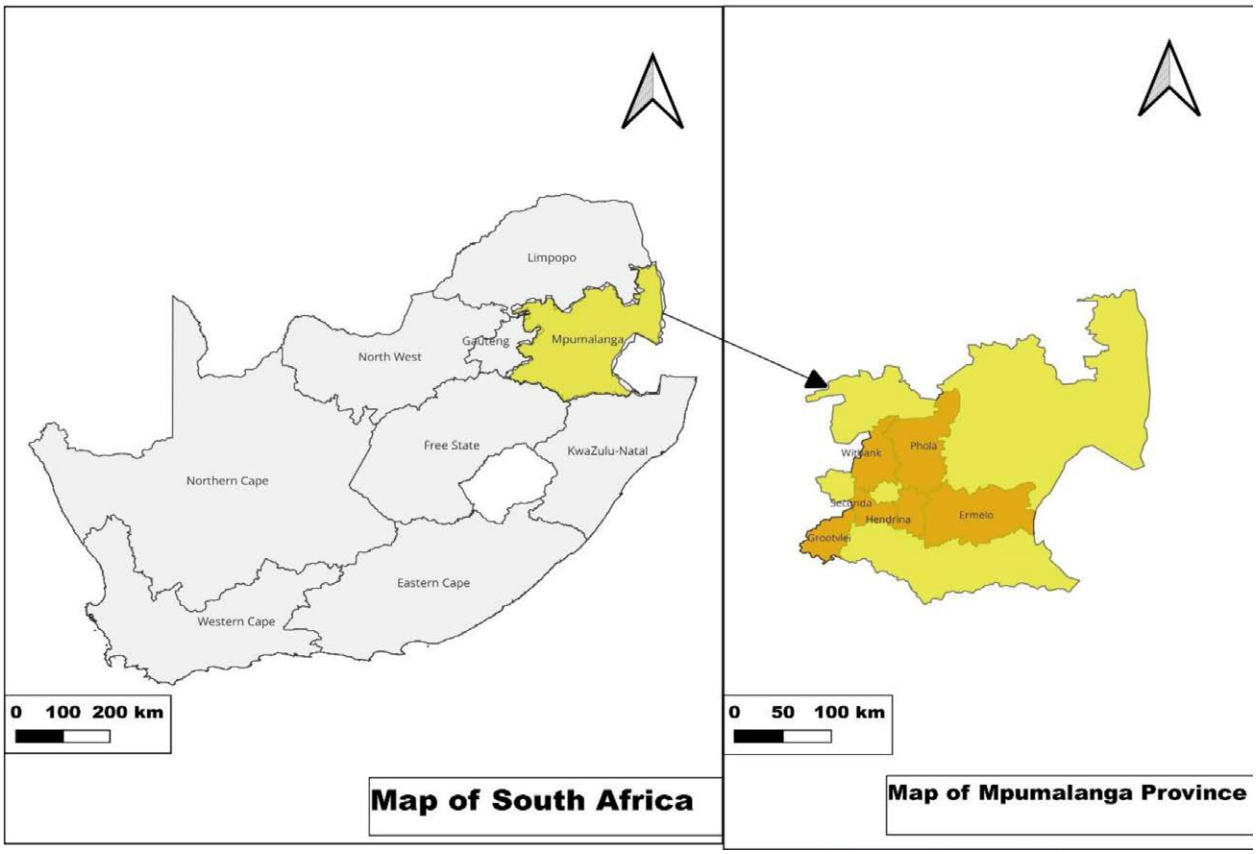

Figure 2. An exploded map showing the studied communities.

wheezing in the past 12 months, wheezy apart from cold, and wheezing leading to shortness of breath. These asthma symptoms questions were combined into an asthma symptom score consisting of a sum of positive answers to these questions as previously reported.[43–45] The asthma symptom score was categorized into "less likely" (score = 0 or 1) and "more likely" (score ≥2) for the presence of asthma.

The child and child caregiver questionnaire provided indirect measures of environmental exposures. These included household cooking fuel type, use of a heater, heater fuel, and environmental tobacco smoke (ETS) exposure. ETS exposure was determined from positive responses to either of the following questions "Are there any household smokers?" and "Do you (the child's caregiver) smoke cigarettes, even occasionally?."

Fractional exhaled nitric oxide

FeNO measurements were conducted before spirometry following procedures described by the American Thoracic Society and European Respiratory Society (2005). Briefly, FeNO was measured using the NIOX 200 (Circassia Inc, Uppsala, Sweden), where the learners were asked to empty their lungs by breathing away from the machine. Then, the new sensor was inserted into their mouth and the learner sealed their lips tightly around the opening. The learner then inhaled deeply until the lungs were filled up, and then exhaled at a normal rate through the sensor. The test was stored automatically in the machines. The learners completed a previous day's 24-hour food and medication intake screening questionnaire. Moreover, learners were asked to not consume drinks or food an hour before the test.

Spirometry

A qualified spirometry technologist conducted a once-off baseline spirometry assessment for 347 schoolchildren. Among the 359 participants without a spirometry test, some were not available on the days on which the spirometry test was conducted, and some participants refused to participate.

The spirometer was calibrated daily. The lung function indices of interest were FEV_1, FVC, and the ratio of FEV_1/FVC. All tests were performed per the American Thoracic Society Guidelines,[46] but without nose clips. Our previous experience with schoolchildren has indicated discomfort with nose clips, and given the evidence in the literature of minimal effect, we elected to omit its use.[47,48] No bronchodilator reversibility assessments were performed. A minimum of three consecutive maneuvers were performed, up to a maximum of eight at a particular trial. The prediction equations from the Global Lung Initiative (GLI) were used in our analysis,[49] without race or ethnicity correction. Each maneuver performed by the learner for the lung function measurements was assessed for meeting acceptability criteria. The dates of the spirometry data were used to align with the $PM_{2.5}$ exposure data.

Allergy testing (Phadiatop)

Allergy or atopy tests (Phadiatop) were conducted to screen allergic sensitization in individuals. The blood was drawn by a qualified medical doctor, stored in the cooler box with an ice pack, and then sent to the National Institute of Occupational Health in Johannesburg on the same day for analysis. Informed consent was obtained from both the caregiver and the child to have their blood drawn for the test.

Environmental exposure assessment

Data for $PM_{2.5}$ were obtained from South African Weather Services air monitoring stations located in each of the five communities: Witbank, Secunda, Hendrina, Ermelo, Phola, and Eskom air monitoring stations in Grootvlei. The monitoring stations used similar monitoring equipment, methods of sampling, and quality control. The communities were similar in terms of environmental exposures (industrial emissions and burning of biomass fuels) and socioeconomic status. The daily mean of $PM_{2.5}$ concentrations from these monitoring stations was downloaded from the South African Air Quality Information System (SAAQIS, https://saaqis.environment.gov.za/) as Excel spreadsheets to match the study period of October 2018–February 2019. The spreadsheets were exported and merged in STATA/IC version 18 (StataCorp., College Station, TX). Data from the SAAQIS network are validated according to the South African Weather Services' Standard Operating Procedures during the quality control process. Outliers are identified if they are outside the range of three standard deviations (SDs) of the mean and removed from the validated dataset unless these are legitimate spikes in the concentration. In such instances, they were retained. The data were also checked for zero shift, which were corrected to correspond with the values from the recent calibration if identified.[50]

IVEware is a package used to perform multiple imputations, variance estimation, and draw inferences from missing data as described previously.[51] The code "IMPUTE" uses a multivariate sequential regression approach called Chained Equations. This approach is used to impute missing data and can create multiple imputed datasets. Continuous and categorical variables can be handled using this approach. Furthermore, linear and logistic regression models can be fitted using data resulting from this multiple imputation analysis.

Statistical analysis

Initial exploratory data analysis techniques, such as means and SD, medians, and interquartile ranges (IQRs) and percentages, were used as appropriate to describe the data. Histograms and QQ plots were used to assess the distributions of primary and secondary outcomes. All outcomes were modeled as continuous and binary following relevant thresholds. Our models included lag effects for the preceding days (lags 1–5, as well as 5-day average lag) of $PM_{2.5}$ exposure.

Tukey fences method was used to identify outliers and their removal from the analysis was determined. Data analysis was performed in STATA/IC version 18 and SAS (SAS Institute Inc., Cary, NC). Multiple imputation using the Chain equation (MICE) method provided in the IVEware software was used since more than 5% of the data was missing for all the variables used in the analysis. Five imputed datasets were used. "Missingness" was assessed for exposure and outcome for bias due to confounding and missing mechanisms, respectively. We compared variables across the strata of missing $PM_{2.5}$, and it was determined that some confounders were unbalanced for those with exposure compared to those without exposure. When comparing groups by presence or absence of the outcome, it was determined that the data were missing at random. Based on these preliminary analyses, we anticipated that the analysis of the original dataset without imputation would be biased and less precise. Several imputation methods were considered, and because of the nature of this dataset, including a modest set of variables and missingness and the fewer set of assumptions required with this method, the MICE approach was seen as the most appropriate. Individual distributions of each relevant variable were assessed to determine bounds for continuous variables. We performed sensitivity analyses of both datasets (complete and imputed) and present the findings of the imputed data here.

Dependent variables

The continuous outcomes were FeNO and the lung function parameters (FEV_1 percent predicted [pp], FVCpp, and FEV_1/

FVCpp) that were calculated from the GLI equations, without race or ethnicity correction.[49] To determine whether effects were greater among those with abnormal parameters, FeNO > 35 ppb was used as the definition of airway inflammation[17,52] and FEV_1 < lower limit of normal (LLN), FEV_1/FVC < LLN,[53] and asthma symptom score ≥ 2 were used as dichotomized variables in the analysis based on internationally standardized definitions.[45,54,55]

Independent variables

The $PM_{2.5}$ and its 5-day lag estimates were used as the key exposure variable. Missing $PM_{2.5}$ concentrations were also imputed using the IVEware multiple imputation method and the resulting dataset was used for further analysis.

To address the objectives of this study, we used the GEE approach with exchangeable correlation matrix. The exchangeable correlation matrix structure was selected because it has a reduced number of parameters to be estimated. We used the identity link for continuous outcomes, such as FeNO, FEV_1pp, FVCpp, and FEV_1/FVCpp, and the logit link for binary outcomes. These models were adjusted for relevant covariates, such as sex, age, ETS exposure, and household energy fuels. The GEE approach was considered to be appropriate because of the clustering of our data by school, and the need for fixed effects methods.

Ethics approval

The study protocol was approved by the Research Ethics Committee of Council for Scientific and Industrial Research (reference number: 177/2016). Informed consent was obtained from all the primary caregivers of the participants, while the latter assented to participation.

Results

The ambient $PM_{2.5}$ concentrations monitored in the Highveld communities during the study period are shown in Table 1. The median concentrations of $PM_{2.5}$ in Witbank, Secunda, Hendrina, Ermelo, Grootvlei, and Phola were 41.0 μg/m^3 (range: 11.4–60.4), 38.7 μg/m^3 (range: 9.92–66.5), 10.7 μg/m^3 (range: 9.32–55.9), 39.9 μg/m^3 (range: 11.6–70.0), 26.7 μg/m^3 (range: 11.9–60.8), and 31.2 μg/m^3 (range: 10.5–72.2), respectively (Table 1).

Figure S1; http://links.lww.com/EE/A313 shows the monthly variation of $PM_{2.5}$ across a calendar year. While a distinct peak concentration is seen in the coldest months (June–August) for Witbank and Secunda, a variable pattern is seen in the other communities. Hendrina experienced a peak in May, and Grootvlei in September, while a fairly narrow range was noted for Phola.

The descriptive statistics of participating child characteristics are shown in Table 2. The mean age of the participants of this study was 10.3 (SD: 0.92) years ranging from 9 to 14 years. Most of the participants were males (53.4%) (Table 2). In their households, participants used clean (electricity or gas, n = 486 [69%]) and dirty cooking fuels (paraffin, wood, and/or coal, n = 220 [31%]). About 28.8% of the households used wood stoves, while 12.8% of the households had a fireplace. More than 50% of the participants were exposed to ETS.

A small number of the participants reported that they were diagnosed with asthma (1.13%), chronic bronchitis (0.85%), and allergy (3.82%) by a medical doctor (Table 3). The prevalence of participants with an asthma symptoms score ≥ 2 was 6.94%, a measure suggestive of more likely to have asthma. An obstructive pattern (FEV_1/FVC < LLN) of lung function was observed in 2.41% of the participants. Airway inflammation as indicated by FeNO >35ppb was 17.3% (Table 3).

The characteristics of schoolchildren were similarly distributed across schools (Table S1; http://links.lww.com/EE/A313).

Although no significant differences in the mean $PM_{2.5}$ concentrations were observed among the various dichotomized respiratory outcomes, there were consistently higher concentrations among those with abnormal outcomes (FeNO > 35 ppb; lung function < LLN and asthma symptom score ≥ 2) and among those who reported wheeze-related symptoms (Table S2; http://links.lww.com/EE/A313).

Lags 4 and 5, as well as the preceding 5-day averaged $PM_{2.5}$ exposure, were associated with a statistically significant odds ratio for FeNO>35ppb, FEV_1 <LLN, and FEV_1/FVC < LLN. Additionally, lags 1 (FeNO>35ppb) and lag 2 (FEV_1 and FEV_1/FVC < LLN) showed increased odds with exposure (Figure 3; Table S3; http://links.lww.com/EE/A313). Furthermore, lag 1, lag 4, and 5-day average lagged $PM_{2.5}$ were significantly associated with increased odds of an asthma symptom score greater than 2 (Figure 3; Table S3; http://links.lww.com/EE/A313).

After adjusting for relevant covariates, the GEE linear regression models showed no significant associations between lagged $PM_{2.5}$ and FeNO levels. Increased estimates of FeNO levels were noted for lags 0–4 and the 5-day average lags of $PM_{2.5}$. Similarly, the 5-day lag effect and the 5-day average for all the lung function parameters were in the direction suggesting an

Table 1.

Descriptive statistics of ambient $PM_{2.5}$ (μg/m^3) from the monitored communities (n = 706)

		$PM_{2.5}$ concentration (μg/m^3)					
Community	n	Mean (SD)	Min	p25	Median	p75	Max
Witbank	118	38.8 (13.5)	11.4	31.0	41.0	54.8	60.4
Secunda	101	37.7 (14.6)	9.92	25.7	38.7	49.5	66.5
Hendrina	135	21.6 (20.0)	9.32	9.32	10.7	55.9	55.9
Ermelo	99	39.8 (13.0)	11.6	30.4	39.9	49.6	70.0
Grootvlei	95	27.9 (8.91)	11.9	23.3	26.7	29.4	60.8
Phola	158	38.5 (19.0)	10.5	27.4	31.2	44.6	72.2
Total	706	34.0 (17.3)	9.32	19.4	31.2	46.1	72.2

Table 2.

Demographics and household characteristics of participating school children (n = 706)

Variables	n (%)
Age (years) (mean ± SD)	10.3 ± 0.92
Sex	
Male	377 (53.4)
Female	329 (46.6)
School	
Witbank	118 (16.7)
Secunda	101 (14.3)
Hendrina	135 (19.1)
Ermelo	99 (14.0)
Grootvlei	95 (13.5)
Phola	158 (22.4)
Cooking fuel	
Clean fuel (electricity + gas)	486 (68.8)
Dirty fuel (paraffin + wood + coal)	220 (31.2)
Use of an electric heater	102 (14.5)
Heater fuel	
None	604 (85.6)
Clean fuel (electricity)	88 (12.5)
Dirty fuel (paraffin + coal)	14 (1.98)
Wood stove	203 (28.8)
Heating with electric stove	391 (55.4)
Cooking with an electric stove	570 (80.7)
Fireplace	90 (12.8)
ETS exposure	379 (53.7)

Table 3.

Respiratory health outcomes among the participating children (n = 706)

Health outcome	
Doctor-diagnosed asthma, n (%)	8 (1.13)
Doctor-diagnosed chronic bronchitis, n (%)	6 (0.85)
Doctor-diagnosed allergy, n (%)	27 (3.82)
Doctor-diagnosed bronchitis, n (%)	2 (0.28)
Chronic cough, n (%)	52 (7.37)
Phlegm, n (%)	88 (12.5)
Chronic phlegm, n (%)	21 (2.97)
Shortness of breath when hurrying on level ground, n (%)	30 (4.25)
Shortness of breath when dressing or undressing, n (%)	9 (1.27)
Ever wheezing, n (%)	30 (4.25)
Wheeze apart from colds, n (%)	17 (2.41)
Wheeze leading to shortness of breath, n (%)	366 (51.8)
Asthma symptom score,[a] n (%)	
Less likely (0–1)	657 (93.1)
More likely (≥2)	49 (6.94)
FEV_1 (L), mean ± SD	1.73 ± 0.66
FVC (L), mean ± SD	1.84 ± 0.78
FEV_1/FVC, mean ± SD	0.96 ± 0.09
FEV_1 percent predicted (%), mean ± SD	105.6 ± 40.7
FVC percent predicted (%), mean ± SD	99.2 ± 43.2
FEV_1/FVC percent predicted, mean ± SD	108.8 ± 12.9
FEV_1/FVC < LLN, n (%)	17 (2.41)
FEV_1 < LLN, n (%)	189 (26.8)
FeNO (ppb), median (IQR)	15.8 (10–27)
Airway inflammation (FeNO > 35 ppb), n (%)	122 (17.3)
Atopy (PAU/l), median (IQR)	1.13 (0.07–13.1)
Atopy > 0.35 PAU/l, n (%)	399 (56.5)

[a]Asthma symptom score was created from specific respiratory symptoms questions from the caregiver's questionnaire.

exposure-related risk (Figure 4; Table S4; http://links.lww.com/EE/A313).

Discussion

In this study among primary schoolchildren living in communities within a known high-pollution region in South Africa, we found lagged $PM_{2.5}$ exposure-related effects with FeNO, a marker of airway inflammation, as well as lung function and asthma symptoms score. Although we found dose–response relationships between exposure and continuous outcomes, these did not reach statistical significance.

Airway inflammation is a critical pathological response in asthma, resulting from the immunological reactions that characterize the disease, and in turn, influence airway obstruction.[14] FeNO has been used as a marker of airway eosinophilic inflammation in asthmatic patients.[56,57] Chemokines involved in airway inflammation increase with increasing ambient $PM_{2.5}$ in the airways of asthmatic patients.[58,59]

The association between $PM_{2.5}$ and airway inflammation has been shown to be dose-related, although inconsistent across studies. A one SD (2.0 μg/m^3) increase in the annual average of $PM_{2.5}$ was shown to be associated with a 4.55% (95% CI: 2.33%, 6.82%) increase in FeNO levels in US schoolchildren.[18] Dose–response effects are seen among asthmatic samples, with shorter-term, same-day IQR increases in $PM_{2.5}$ resulting in an increase of FeNO from 1% to 3% increase[23] through to 18.7%.[25] The effects reported among randomly selected community-based samples tend to be smaller, ranging from 1.1 ppb[28] through to 5 ppb.[26] Our findings are within the range reported by these latter studies but did not reach statistical significance.

The inconsistencies seen across studies for a $PM_{2.5}$-related airway inflammation effect may be related to the lack of understanding between the exposure-biochemical reaction-biological effect and outcome pathway. These may occur within a few hours, as have been reported in some studies where effects of 6.9 and 6.3 ppb increase in FeNO were shown within 1 and 4 hours of exposure,[30] or 24–48 hour lags[21,29] or even longer lags, as found in our study. A meta-analysis reported a pooled estimate of 2.25% (95% CI: 1.51%, 2.99%) change in FeNO per 10 μg/m^3 increase in short-term $PM_{2.5}$, exposure across a 0–24-hour lag.[20] However, this analysis did not discriminate between studies of exclusive asthmatic children and random samples, suggesting a possible smaller effect in the general population, and a larger effect among asthmatics is likely. The lag analysis is important when assessing the effects of $PM_{2.5}$ on the airways, especially for short-term exposure.[60]

A significant association between $PM_{2.5}$ and FeNO was observed for lag 6 in a panel study that investigated associations between ambient air pollution and FeNO in university students in an urban area of China.[61] This provided evidence that FeNO can be influenced by short-term variation of $PM_{2.5}$ and was supported by our findings of significant association for lag 1- and 5-day average lags of $PM_{2.5}$.

We saw similar dose–response effects with lung function, as was seen with FeNO. This was in keeping with the reports in the literature. A meta-analysis indicated that a 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 25.7 ml decrease (95% CI: 14.9, 36.5) in FEV_1. This was also observed at lag 1, where FEV_1 decreased by 14.8 ml (95% CI: 2.24, 27.4).[21] Similarly, a 10 μg/m^3 increase in $PM_{2.5}$ concentrations was shown to be associated with a decrease in FEV_1 on the current day (–22.0 ml, 95% CI: –32.5, –11.6) and lag 1 (–32.6 ml, 95% CI: –43.7, –21.4) among schoolchildren in China.[62] This delayed effect was also observed for FEV_1 on lag day 0–2, where a 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 1.67% decrease in FEV_1 (95% CI: –3.05, –0.26).[63,64]

Our data seemed to suggest that the effect of $PM_{2.5}$ on the various measures of lung health is likely to be strongest among those with existing evidence of poor lung health. This may explain why our findings were statistically significant when dichotomized between normal and abnormal (FeNO > 35 ppb; lung function parameters < LLN). Those with normal lungs are resilient to these exposure-related effects. The linear models incorporating the full sample may then tend to dilute out significant effects.

There is strong evidence that an asthma symptom score can be used in characterizing and quantifying asthma symptoms in individuals who have never been labeled as asthmatics.[43,55,65] Asthma symptom score ≥ 2 (more likely to have asthma) was positively associated with long-term exposures to $PM_{2.5}$ concentrations, but this lacked significant association.[55,65] In this study, asthma symptom score ≥ 2 was also positively associated significantly with lag 1, in addition to lag day 4 and 5-day average lags of $PM_{2.5}$.

Our findings for lagged effects have important health systems implications. The delayed response to $PM_{2.5}$ exposure could result in health surveillance systems failing to associate health outcomes with exposures or providing exposed communities with adequate warnings to those at particular risk for adverse respiratory health outcomes. Health services and schools should take necessary precautions for asthmatic children or those with features of poor lung health in the days after such elevation or exceedances. Development of these early warning systems will assist in reducing mortality and morbidity from $PM_{2.5}$-related asthma.[66,67]

We reported a prevalence of doctor-diagnosed asthma of 1.1% in this sample, which is much lower than that described in other South African studies, ranging from 5% to 34%.[68,69] This may suggest poor access to health care services in these communities. This is contrasted with the asthma symptoms score, with approximately 7% more likely to have asthma. The asthma symptoms score combines several asthma-associated symptoms.[45,55] The asthma symptoms score also has a good predictive ability for asthma-related outcomes and can also assist in detecting environmental risk factors.[44,65]

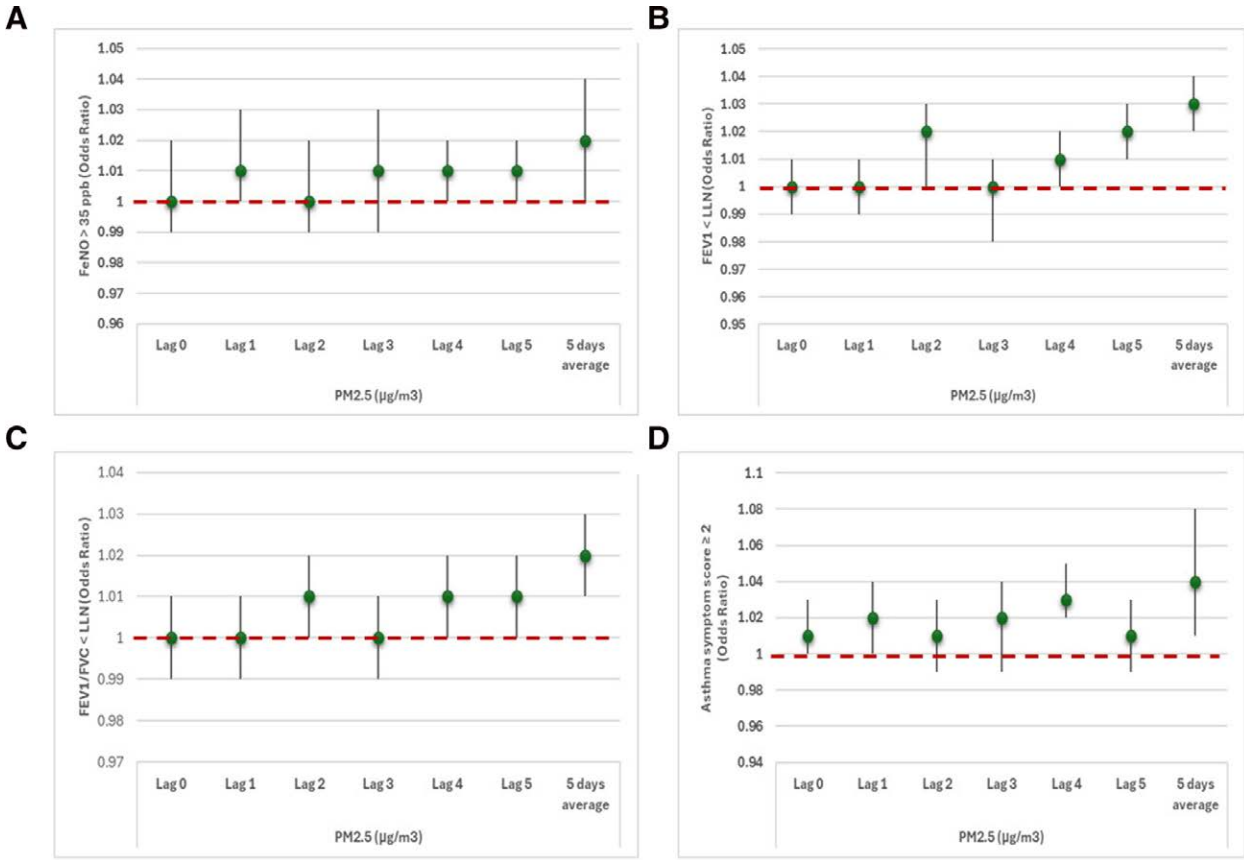

Figure 3. Adjusted logistic regression GEE models estimates for respiratory health outcomes including (A) FeNO > 35 ppb, (B) FEV_1 < LLN, (C) FEV_1/FVC < LLN, and (D) asthma symptom score ≥ 2 in association with $PM_{2.5}$ for current day exposure, lag 1–5 days, and 5-day average. Adjusted for age, sex, heating fuel, ETS exposure, and atopy (positive Phadiatop). Odds ratios are depicted by green dots, 95% CI is represented by tails, and the dashed line indicates the level of null effect.

The daily mean ambient $PM_{2.5}$ over the course of the study ranged from 21.6 to 39.8 µg/m^3 in the communities included in the present study, which were all above the World Health Organization (WHO) 24-hour guideline of 15 µg/m^3.[70] Nevertheless, these concentrations were below the South African National Ambient Air Quality Standards 24-hour guidelines of 40 µg/m^3.[36] While there is extensive evidence that elevated levels of $PM_{2.5}$ are associated with adverse lung function outcomes,[71,72] levels of $PM_{2.5}$ below the WHO guidelines are still associated with respiratory illness.[73,74] This provides support for the case that lower levels of air pollution still present with adverse outcomes among those children with compromised lung health. Thus the WHO and South African National Ambient Air Quality Standards strategy for a continued reduction in these standards is necessary.

The Highveld region was declared an Air Pollution Priority Area in terms of Section 19(1) of the National Environmental Management: Air Quality Act (Act 39 of 2004).[75] This is one of the three HPPAs in South Africa, all of which experience high levels of pollution mostly from a range of sources including industrial sources, community-based sources (such as burning of domestic fuels), vehicles, etc. As designated areas, they have their own Priority Area networks of air monitoring.

Our study presented with several limitations. For logistical reasons, our study was conducted between October and February months. Typically, these are the months overlapping the spring months of the year October–November, and the summer months (December–January) in the Highveld region. Air pollution is affected by seasons, and PM generally peaks in the cold months in the Highveld region.[38,76] Pollutant levels in some communities may have been generally lower than the peak annual levels, during this period. This may have resulted in an underestimation of the effect estimates. However, for several of the communities, the annual variability was not substantial nor consistent.[38] For example, the Phola community has fairly consistent seasonal pollutant levels,[77] (https://saaqis.environment.gov.za/) while reports of other Highveld communities describe geographical differences across seasons.[38,76,78] Thus, while it is likely that if our study was conducted in the coldest months with higher $PM_{2.5}$ levels, the changes in effects would have been modest, and at worst, our findings are biased toward the null. Nevertheless, the presence of effects despite these lower levels of pollution provides grounds for stronger intervention.

We were dependent on the air quality monitoring network for our exposure data. SAAQIS provided data of 24-hour $PM_{2.5}$ averages. Despite the rigor of quality control, this network is subject to challenges. Missing data are common due to electrical shutdown or breakdown of monitoring equipment.[50] This is not uncommon among monitoring networks. To overcome the missing data for the specific periods, we performed data imputation using well-established techniques.[51] This approach was used to impute missing data to create five multiple imputed datasets. Through various sensitivity analyses, we believe that the imputed estimates were robust for the analysis we conducted.

An important shortcoming in our study design was the cross-sectional approach we adopted. Both our respiratory health outcomes and our exposure measures were taken at single points in time, driven by the dates of the objective respiratory assessments (FeNO and spirometry). While among schoolchildren with normal respiratory health, this is likely to have a limited impact on our findings, schoolchildren with asthma are likely to have variable lung function. Thus, once-off

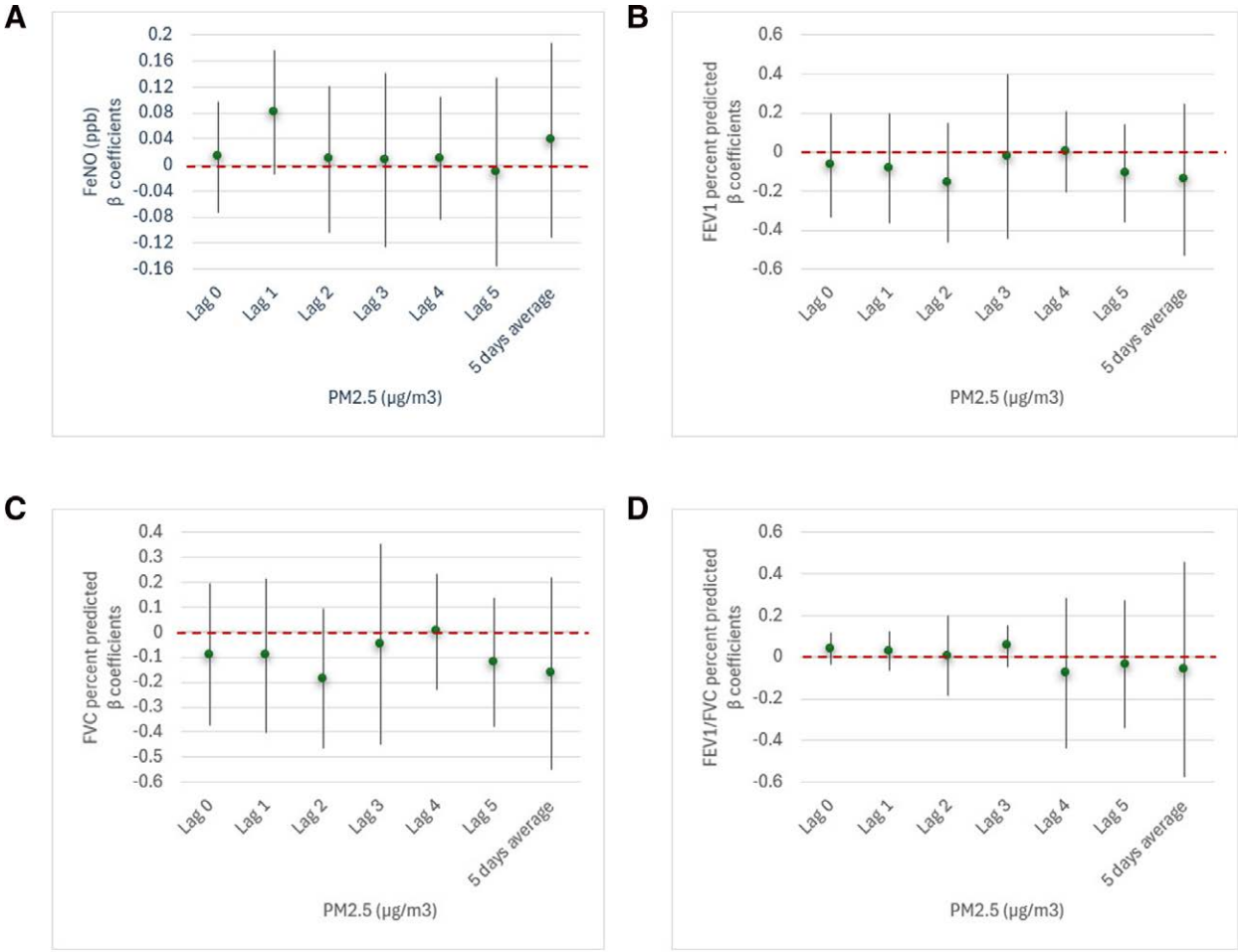

Figure 4. Adjusted multivariate linear regression GEE models estimates for (A) FeNO, (B) FEV_1pp, (C) FVCpp, and (D) FEV_1/FVCpp in association with $PM_{2.5}$ for current day exposure, lag 1–5 days, and 5-day average. Adjusted for age, sex, heating fuel, ETS exposure, and atopy (positive Phadiatop). Green dots depict the point estimate and tails depict the 95% CI.

measurements are probably inadequate to describe their true respiratory health status, resulting in a nonrandom misclassification, with more children classified as normal than is truly the case.[79] Our findings of approximately 27% having abnormal FEV_1 (using the GLI equations and the LLN cut point) suggest that the prediction equations may not be appropriate for this sample, and the associations using this index must be interpreted with caution. It is likely that the ratio is a more robust measure.

Despite these shortcomings, our study has numerous strengths. This is one of the few such studies to describe a lagged effect of $PM_{2.5}$ with FeNO, lung function, and asthma on the African continent. We had well-collected health outcome measures, with both objective assessments of lung health, as well as reporting of outcomes using standardized instruments. Our ability to access quality air pollution data within an established network in six communities located in a designated high air pollution area is an important opportunity to describe the exposure effects on health in these vulnerable communities.

In conclusion, our findings strongly suggest that air pollution, in a lagged manner, results in airway inflammation and decreased lung function. These findings are likely to be more substantial among schoolchildren with asthma or asthma-like symptoms associated with increased $PM_{2.5}$ levels.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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