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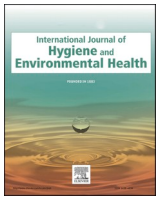

Personal exposure to particulate matter oxidative potential and airway inflammation: differences between asthmatic and non-asthmatic adults

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ABSTRACT

We aimed to determine whether exposure to particulate matter PM, measured as the oxidative potential (OP) of filters collected from 24 h personal samplers, is associated with increased airway inflammation in asthmatic and non-asthmatic volunteers. Forty-two adult asthmatic patients (25 women and 17 men) and 37 matched controls wore a personal sampler for a day collecting fine (PM2.5) and coarse (PM10–2.5) particles, and determining 24 h afterwards their fractional exhaled nitric oxide (FeNO). The PM-OP was determined by two methods: dithiothreitol (DTT) and ascorbic acid (AA) being OP levels dichotomized based on the median, to calculate adjusted mean differences (aMDs) and odds ratios (aORs) with sex, age, study level, body mass index and interleukin-6 (IL-6) levels as confounders. Statistically significant associations between PM-OP and FeNO levels in non-asthmatic volunteers were observed: aMD for OP-DTT PM2.5 = 11.64 ppbs; 95 %CI (0.13–22.79); aMD for OP-AA PM10–2.5 = 15.67; 95 %CI (2.91–28.43) with aORs = 4.87 and 18.18 respectively. In asthmatic patients an association was also observed in the form of aORs, but of lower magnitude (1.91 and 1.94 respectively). Non-significant higher FeNO levels (aMD = 5.22) and an aOR = 3.92 were also observed in non-asthmatic volunteers for OP-AA in the fine fraction. As a conclusion, the effect of personal PM-OP on airway inflammation appears to be differential between asthmatic and non-asthmatic volunteers suggesting a potential implication of inhaled corticosteroids diminishing the reactivity of airway epithelium since adjusted associations were higher in volunteers without asthma.

1. Introduction

Among the pollutants commonly monitored in air quality networks, particulate matter (PM) has potentially the greatest impact on human health (Guo et al., 2022; Kaufman et al., 2020). Their effects on the incidence and worsening of respiratory diseases are well known (Fan et al., 2016; Karakatsani et al., 2012). The toxicity of PM seems to be strongly related to its particle size and chemical composition (Kelly and Fussell, 2012), but in particular to the presence of PM-bound reactive oxygen species (ROS) and the ability of PM components to generate them, altering the balance of oxidants/antioxidants in the cells, and causing oxidative stress, leading to inflammation in the airways of the exposed population (Bates et al., 2019; Borlaza et al., 2024; Park et al., 2018; Verma et al., 2010; Xiang et al., 2016). As a result, in recent years the use of a global parameter that reflects the toxicity associated with PM and its capacity to deplete antioxidants and produce ROS, such as the oxidative potential (OP), has been considered. However, the PM-OP exposure estimates have been usually done by outdoor stationary PM

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samplers (Delfino et al., 2010; Janssen et al., 2015; Steenhof et al., 2013; Strak et al., 2012; Yang et al., 2016; Zhang et al., 2016), which could lead to underestimate/overestimate the PM-OP exposure, since people spend more than 80 % of their time indoors in Western countries (Avery et al., 2010). In this respect, the use of personal PM samplers reflects better the real exposure for a given period, since they make it possible to collect the particles to which a volunteer has been exposed to during a whole day. There are some published studies with the aim of determining the mass and chemical composition of PM based on personal PM sampling but to our knowledge few studies have also characterized the OP by using PM personal samplers (Borlaza et al., 2023; Brehmer et al., 2019, 2020; Marsal et al., 2023, 2024; Quinn et al., 2018; Secrest et al., 2016; Shang et al., 2022).

Regarding the measurement of specific airway inflammation, the fractional exhaled nitric oxide (FeNO) is the most important marker used in epidemiological studies with both healthy and asthmatic volunteers (Delfino et al., 2006, 2010, 2013; Janssen et al., 2015; Zhang et al., 2016), because of its established use in the clinical practice of the asthmatic patient (Global Initiative for Asthma, 2023; Plaza Moral et al., 2023). A recent review on the association between exposure to air pollutants and FeNO levels has shown some inconsistent results (Chen et al., 2020). This may be due to different designs (e.g. panel vs cross-sectional), but also to limitations in exposure estimates, mainly based on ambient (stationary) sampling. A more recent review on the associations between personal air pollution exposure and FeNO levels concluded that personal exposure assessment is recommended to study the effects of air pollution on FeNO response (Anand et al., 2024). To our knowledge, there are only four studies that have used PM personal samplers in asthmatic patients with an evaluation of FeNO (Delfino et al., 2006; Godri Pollitt et al., 2016; He et al., 2021; Maikawa et al., 2016). All of them were conducted in children, and only two measured the PM-OP (He et al., 2021; Maikawa et al., 2016).

In this context and with the rationale that PM may induce oxidative stress and airway inflammation that may be more prominent in asthmatic patients, we launched the ASTHMA-FENOP Study, including a group of controls without asthma, frequency matched by gender, age and smoking status with asthmatic patients. Our objective was to determine and compare between these two groups (asthmatic patients and control volunteers without asthma), the association between the OP of PM by using personal PM samplers and FeNO levels as a surrogate of airway inflammation. In this context, the ASTHMA-FENOP Study would be the first one on the association between the PM-OP obtained using personal samplers and FeNO levels in adult asthmatic patients.

2. Methods

2.1. Study design

The study design and population have been described elsewhere (Santibáñez et al., 2024). We conducted an observational study from November 2022 to February 2024 involving 44 adult asthmatic patients with different stages of severity according to the international GINA and national GEMA v5.3 guidelines on the management of asthma (Global Initiative for Asthma, 2023; Plaza Moral et al., 2023) and 37 control volunteers (without asthma), frequency matched by gender, age (±5 years) and smoking status. Recruitment was done in collaboration with the Pneumology Service of Hospital Universitario Marqués de Valdecilla (HUMV) and Hospital de Liencres (HL). The inclusion criteria for both asthmatic patients and controls are detailed in Table S1. While stable treatment with inhaled corticosteroids (ICS) over the previous three months was required for asthmatic patients, any treatment with oral or ICS for any reason was an exclusion criterion for controls.

Candidates were selected based on pre-determined different outdoor PM levels. Most participants resided in the urban area of Santander (50.0 % of cases and 48.6 % of controls). A second subgroup (13.6 % of cases and 13.5 % of controls) lived in the Maliaño area (near metallurgical plants), forming an urban-industrial mixed area. At these locations, two stationary PM sampling campaigns were conducted in a previous study (Expósito et al., 2025), which indicated higher levels of PM-bound metals and OP at the urban-industrial site. The places of residence for the rest of volunteers were distributed in more distant and rural locations. Overall, no differences in geographical distribution of places of residence were observed between asthmatic and non-asthmatic volunteers ($p = 0.990$). The residences of the volunteers, the PM-OP results, and the locations of the two stationary samplers are shown in Fig. 1.

2.2. PM sampling and recruitment scheme

After signing the informed consent, each volunteer received a personal sampler upon arrival on the first day (visit 1). Four similar PM personal samplers were used to collect over 24 h each personal exposure. The sampler pumps were programmed to sample for 24 h to avoid mishandling and were returned during the second day's visit. Each Personal sampler included a two-stage personal modular impactor (SKC PMI coarse), which can separately sample PM2.5 and PM10–2.5 filters, connected to a personal pump (SKC Aircheck XR5000) operating at a flow rate of 3 L per minute (lpm). Thirty-seven- and 25-mm polytetrafluoroethylene (PTFE) membrane filters were used for the PM2.5 and PM10–2.5 fractions, respectively.

The protocol for the first 41 asthmatic patients and the rest of volunteers is outlined in Tables S2 and S3. In summary, for the first 41 asthmatic patients, the stability of FeNO levels during three consecutive days (day 2 to day 4) was corroborated. After that verification, the recruitment process was reduced from four to three consecutive days. Overall, on day 3 (lag 1, 24 h after returning the personal sampler), all patients had at least one FeNO determination as well as a fasting blood sample.

2.3. OP analysis

The OP assay procedure including the methodology to calculate the detection limits (D.L.), and the arithmetic means of blank filters, has been described in detail elsewhere (Santibáñez et al., 2024). Briefly, the PM2.5 and PM10–2.5 filters were extracted with a phosphate buffer (PB) solution and filtered with a syringe cartridge. Then, they were stored at 4 °C until oxidative potential (OP) analysis, with a maximum storage time of 24 h. Two OP assays were conducted: dithiothreitol (DTT) and ascorbic acid (AA) using a Multiskan Skyhigh microplate spectrophotometer (Thermo Fisher Scientific). The AA consumption of the PM sample extract/AA solution was determined by measuring the change in absorbance of ascorbate at 265 nm for a total reaction time of 2 h. For the DTT assay, the DTT concentration was calculated after adding dithiobisnitrobenzoic acid (DTNB) to the reaction mixture to convert the remaining DTT to 2-nitro-5-thiobenzoic acid (TNB), by reading the absorbance of TNB at 412 nm over time (at 10, 20, 30, and 40 min). Both, extractions and OP measurements were conducted at 37 °C.

The OP values were initially calculated from the slope of the linear part of the DTT/AA depletion curve (μM/min). These values were then normalized by the corresponding filtered air sample volume (m^3) for both assays (OP_v), due to its higher relevance to health, so OP-DTT_v/OP-AA_v values were expressed as nmol $min^{-1}m^{-3}$. Samples were analyzed in triplicate and the depletion rates of 5 blank filters were used for the D. L. calculation. These D.L., along with the mean values of blank filters, and percentage of samples higher than the D.L. are shown in Table S4.

2.4. FeNO measurements as marker of airway inflammation

Single-breath, online measurements of FeNO were conducted using the same device (FeNO NIOX VERO® FeNO meter) and by the same researcher (JA) from the HUMV Pneumology Service. This was done in accordance with the standardized procedures recommended by the

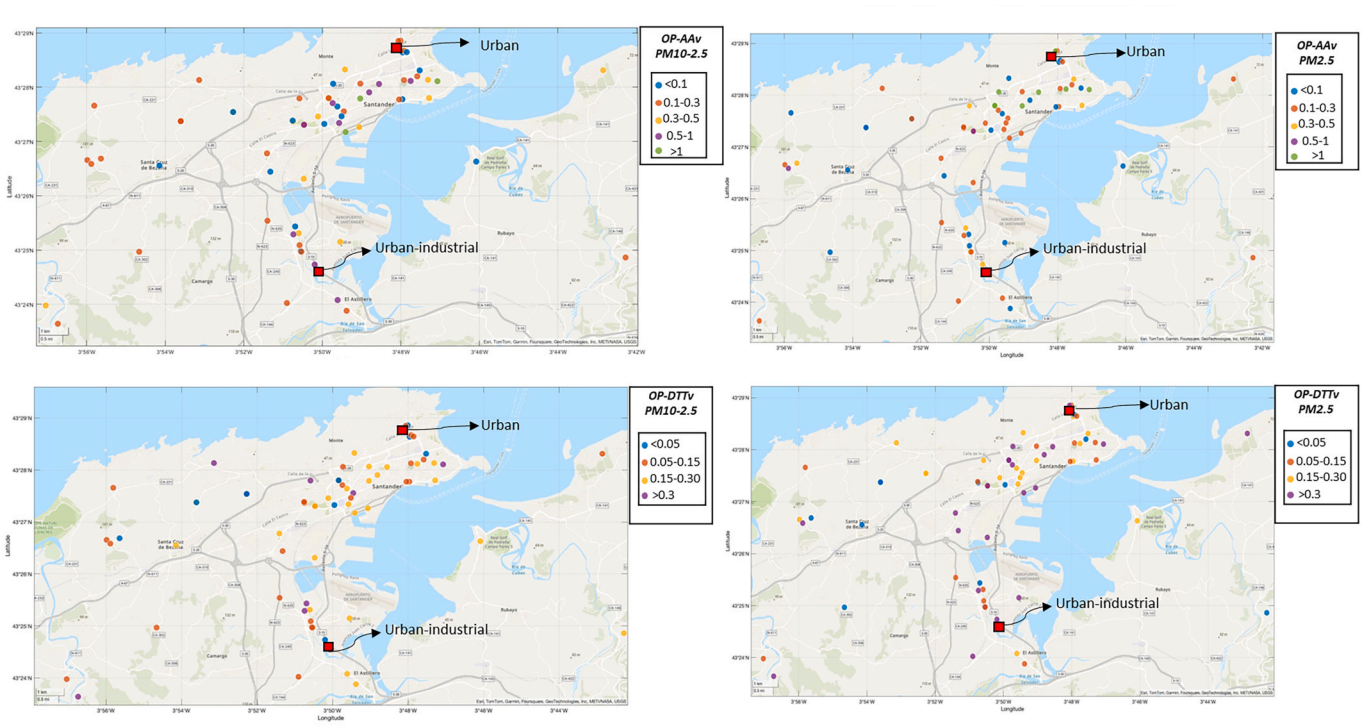

Fig. 1. Location of volunteers' residences and the two stationary sampling points (urban and urban-industrial) used in a previous study (Expósito et al., 2025). Levels of OP-DTT$_v$ and OP-AA$_v$ (nmol min^{-1} m^{-3}) of PM10–2.5 and PM2.5 samples are also shown in the map.

American Thoracic Society, the European Respiratory Society, and the Spanish Respiratory Society. It was ensured that spirometry, physical exercise, and the consumption of certain foods or beverages were avoided for 1 h prior to each measurement (Dweik et al.,). As FeNO is a non-invasive determination, for the first 41 asthma patients we protocolized three FeNO repeated measurements during three consecutive days with the first FeNO determination after 24 h wearing the personal sampler, in Visit 2 = lag 0; and the rest every 24 h thereafter (lag 1, 25–48 h, Visit 3; lag 2, hours 49 to 72, Visit 4). FeNO levels were very stable, with Spearman's rhos >0.95, mean differences for each comparison of days of less than 1 ppb, and repeated measures ANOVA results also supporting it: F(2.0; 80) = 0.205, p = 0.815; Partial Eta squared = 0.005. As they were so stable, we decided to simplify to an only one FeNO determination on Visit 3 for the rest of volunteers.

2.5. Serum interleukin-6 (IL-6) levels

Fasting blood samples were collected from all participants on day 3 from the beginning of the recruitment (from 8:00–9:00 a.m.) and serum was then separated and stored at −80°. IL-6 determination was performed utilizing the human IL-6 enzyme-linked immunosorbent assay (ELISA) kit ENZ-KIT178-0001 IL-6 according to the manufacturer's protocols; the concentration of serum IL-6 was used as confounding variable for the adjusted statistical models described below.

2.6. Statistical analysis

Continuous variables were described as mean and SD and/or median and interquartile ranges (IQR). Statistical differences between groups were compared using the Student's *t*-test in the case of mean comparisons and using the Mann Whitney *U* test for median comparisons. Categorical and discrete variables were expressed as percentages, and comparisons were performed with the Chi-square test, using Fisher's exact test, when appropriate.

OP$_v$ metrics were dichotomous categorized according to the median (lower versus higher values) and adjusted mean differences (MDs) with their 95 % confidence intervals (CI) were calculated by using a linear regression model in which the quantitative FeNO results were treated as the dependent variable, and each OP exposure as a binary variable (0 = lower values; 1 = higher values). Age (as a continuous variable), sex, study level (ordinal categorized), body mass index (BMI) and IL-6 levels are pre-established as confounders to obtain adjusted MDs. In addition, to estimate the strength of associations, FeNO levels were also dichotomous divided into lower and higher values according to medians and crude and adjusted odds ratios (ORs) with their 95 % CI were calculated by using unconditional logistic regression models.

A stratified analysis as a function of the asthma and non-asthma statuses was pre-established as well as multivariate regression models with the variable asthma and non-asthma including its interaction term with each PM-OP$_v$ metric. Lastly, an additional multivariate model restricted to asthma patients was computed in which results in the Asthma Control Test (ACT), Test of Adherence to Inhalers (TAI), dosage of ICS and use of biologics (GEMA v5.3 stages), were also included as confounding factors.

The level of statistical significance was set at 0.05 and all tests were two-tailed. We used the SPSS statistical software package 22.0 (SPSS, Inc., Chicago, IL, USA) for statistical analyses.

3. Results

3.1. Description of the sample

The overall mean age was 52.26 years; [SD = 16.99] with similar mean ages for both asthmatics (mean = 52.03) and controls (mean = 52.45) as a result of matching. 56.8 % were women in asthmatics and controls and the rest men (43.2 %). Most of volunteers were non-smoker (77.8 %). University study level was different between asthmatic and controls volunteers, with a higher prevalence of University studies in controls ($p < 0.001$). Regarding BMI, 56.8 % of non-asthmatic volunteers were on Healthy Weight according to WHO classification (cut off

points 18.5–24.9). Prevalence of Overweight (BMI 25–29.9) and Obesity (BMI≥30) was slightly higher among asthmatic volunteers (p = 0.096). Two asthma patients had oral corticosteroids prescribed for other reason than asthma (for Rheumatologic reasons). However, as it was an exclusion control criteria, none control was on oral or ICS for any reason. Median levels of blood eosinophils were similar between asthmatics and controls (200 cells/mm^3) but means and % of volunteers with blood eosinophils ≥150 cells/mm^3 were higher among asthmatic patients. As expected, FeNO levels were higher among asthmatic patients. See Table 1.

Additional clinical characteristics of the asthmatic volunteers are summarized in Table S5. Five patients (11.4 %) were in GINA and GEMA stage 3 with low-dose ICS combined with long-acting beta-agonists (LABA). Eighteen patients (40.9 %) were with medium dose maintenance of ICS-LABAs prescriptions (GEMA stage 4) and the rest (n = 21, 47.7 %) were with high dose maintenance of ICS (GEMA stages 5 and 6). Nine out of these 21 patients were also on biologic treatment (GEMA stage 6). Adherence to their inhaled maintenance therapy according to the Test of Adherence to Inhalers (TAI) was good in the majority of patients (n = 33/44, 75.0 %). Their mean score in the Asthma Control Test (ACT) was 22.16 points; [SD = 3.8]. Based on the ACT scores, 81.8 % had their asthma controlled (≥ 20 points).

3.2. OP_v levels of participants in their PM personal samplers

The distribution of PM-OP_v levels presented some positive asymmetry with means of 0.24, 0.55, 0.16 and 0.40 and medians of 0.16, 0.18, 0.13 and 0.20 nmol min^{-1} m^{-3} for the fine and coarse PM fractions according to OP-DTT and OP-AA methods, respectively. Medians and means of OP_v determinations were higher among asthmatic patients compared to controls, yielding statistical significance in some cases, although as it is shown in Fig. 1, no differences in OP_v values according to the geographic distribution of volunteers' residences were observed. See Table 1 and Fig. 1.

3.3. Adjusted associations between OP_v and FeNO levels

Statistically significant higher FeNO levels after adjusting for the predefined variables were observed among those controls with higher OP_v in their PM fine fraction according to the DTT method, and among those controls with higher OP_v in their PM coarse fraction according to the AA method: aMD for OP-DTT_v PM2.5 = 11.46; 95 %CI (0.13–22.79), p = 0.048. aMD for OP-AA_v PM10–2.5. = 15.67; 95 %CI (2.91–28.43), p = 0.018. In the form of aORs, the results were similar, but lost significance, with a 4.87 and 18.18-fold increase of having higher FeNO levels

Table 1
Description of the sample as a function of asthma or control statuses.

	Non-asthma		Asthma		All		*p value*
	N = 37		N = 44		N = 81		
Age, yrs. Mean [SD]	52.03	16.69	52.45	17.42	52.26	16.99	*0.911*
Age, yrs. Median [IQR]	54	39–67	50	40–69	52	39.5–68.5	*0.794*
Sex at birth							
Female	21	56.8 %	25	56.80 %	46	56.8 %	*1*
Male	16	43.2 %	19	43.20 %	35	43.2 %	
No smoker	29	78.4 %	34	77.3 %	63	77.8 %	*0.905*
Former smoker	8	21.6 %	10	22.7 %	18	22.2 %	
Study level							
Primary education	1	2.7 %	5	11.4 %	6	7.4 %	*<0.001*
Secondary education	3	8.1 %	13	29.5 %	16	19.8 %	
High school level	2	5.4 %	16	36.4 %	18	22.2 %	
University studies	31	83.8 %	10	22.7 %	41	50.6 %	
BMI (WHO classification)							
Healthy Weight 18.5–24.9	21	56.8 %	16	36.4 %	37	45.7 %	*0.096*
Overweight 25–29.9	13	35.1 %	18	40.9 %	31	38.3 %	
Obesity ≥30	3	8.1 %	10	22.7 %	13	16.0 %	
Blood Eosinophils (Visit 3), cells/mm^3, Mean [SD]	208.11	108.98	331.82	412.46	275.31	317.23	*0.062*
Blood Eosinophils (Visit 3), cells/mm^3, Median [IQR]	200	100–300	200	100–400	200	100–300	*0.183*
Blood Eosinophils (Visit 3) ≥150 cells/mm^3							
No	13	35.1 %	12	27.3 %	25	30.9 %	*0.445*
Yes	24	64.9 %	32	72.7 %	56	69.1 %	
Blood Neutrophils (Visit 3) ≥5000 cells/mm^3							
No	35	94.6 %	37	84.1 %	72	88.9 %	*0.134*
Yes	2	5.4 %	7	15.9 %	9	11.1 %	
Oral corticosteroids (for Rheumatologic reason)							
No	37	1	42	0.955	79	0.975	*0.189*
Yes	0	0	2	0.045	2	0.025	
Systemic inflammation							
IL-6 (Visit 3) pg/mL. Mean [SD]	30.33	40.45	18.08	32.57	23.68	36.66	*0.135*
IL-6 (Visit 3) pg/mL. Median [IQR]	7.86	10.56–38.9	5.84	2.06–15.25	9.24	0.01–125	*0.009*
Airway inflammation							
FeNO (Visit 3), ppb. Mean [SD]	24.43	14.49	37.27	24.23	31.41	21.25	*0.004*
FeNO/Visit 3), ppb. Median [IQR]	21	15–29.5	27	19–52	23	16–40.5	*0.013*
FeNO (Visit 3)≥20 ppb							
No	17	*45.9 %*	12	27.3 %	29	*35.8 %*	*0.081*
Yes	20	*54.1 %*	32	72.7 %	52	*64.2 %*	
PM-OP_v metrics (nmol/min/m3)							
OP-DTT_v PM2.5. Mean [SD]	0.17	0.25	0.30	0.29	0.24	0.27	*0.029*
OP-DTT_v PM2.5. Median [IQR]	0.10	0.03–0.18	0.24	0.15–0.34	0.16	0.1–0.31	*<0.001*
OP-AA_v PM2.5. Mean [SD]	0.34	0.89	0.72	1.29	0.55	1.14	*0.127*
OP-AA_v PM2.5. Median [IQR]	0.15	0.06–0.28	0.23	0.12–0.49	0.18	0.07–0.37	*0.027*
OP-DTT_v PM10–2.5. Mean [SD]	0.14	0.11	0.18	0.11	0.16	0.11	*0.058*
OP-DTT_v PM10–2.5. Median [IQR]	0.11	0.06–0.19	0.17	0.10–0.26	0.13	0.08–0.22	*0.052*
OP-AA_v PM10–2.5. Mean [SD]	0.17	0.11	0.59	1.38	0.40	1.04	*0.051*
OP-AA_v PM10–2.5. Median [IQR]	0.20	0.1–0.20	0.22	0.10–0.55	0.20	0.1–0.39	*0.029*

(above median), respectively. For OP-AA_v in the fine fraction non-significant higher FeNO levels (aMD = 5.22) and a positive OR (aOR = 3.92) were obtained. For the OP-DTT_v in the coarse fraction, negative aMDs and aORs lower than 1 were observed in controls. In contrast, non-significant negative or near zero aMDs were obtained in asthmatic patients. In the form of aORs, values higher than 1 but non-significant were obtained only for OP_v in their PM fine fraction according to the DTT method (aOR = 1.91), and in their PM coarse fraction according to the AA method (aOR = 1.94). Considering the whole sample (n = 81), statistically significant aORs higher than 1 were obtained for these two PM-OP_v metrics: aOR = 3.64 for OP-DTT_v PM2.5 and aOR = 3.47 for OP-AA_v PM10–2.5. See Fig. 2 and Tables S6–S9. The interpretation of the associations between PM-OP_v metrics and FeNO did not change when restricted to asthmatic patients and after adjusting for specific clinical confounding variables such as ACT, TAI scores, and GEMA stages (as indicators of ICS dosage and biologic use). See Table S10.

The differences between both groups are more deeply depicted in Tables 2 and 3, where the interaction results between each PM-OP_v metric and the asthma and non-asthma condition are shown. Positive adjusted interaction terms were obtained in both linear and logistic regression models in all PM-OP_v metrics with the exception of OP-DTT_v in the coarse fraction, indicating that the effect of PM-OP_v on the increase of FeNO is greater in controls (without ICS) for OP-DTT_v PM2.5, OP-AA_v PM 2.5 and OP-AA_v PM 10–2.5.

4. Discussion

We have found high magnitude associations between PM-OP_v and FeNO levels in non-asthmatic volunteers. In asthmatic patients an association was also observed for OP-DTT_v and OP-AA_v in the fine and coarse fractions respectively, but of lower magnitude. Our asthmatic population is on maintenance therapy with ICS with a good adherence to treatment according to TAI test. As FeNO is a well-recognized biomarker for type 2-driven asthma which is characterized by its response to ICS (Fahy, 2015; Gauthier et al., 2015; Robinson et al., 2017), it is reasonable to think that the response of FeNO to ICS in some way could buffer the possibility of increasing FeNO levels, slowing down or decreasing the reactivity of airway epithelium in the presence of increased exposure to ROS. In contrast, in the absence of inhaled or oral corticosteroids as is the case in the control group, this buffering would not occur, increasing without limitations the FeNO levels to a greater extent. The differences between asthmatic and non-asthmatic subjects regarding the effects of air pollutant exposure on FeNO levels are consistent with some findings in the literature [see e.g. the study by Liu et al. (2014) with asthmatic and non-asthmatic children]. A review by Anand et al. (2024) revealed that medications used by asthmatic patients can reduce the inflammatory response to exposure to air pollutants.

Our results epidemiologically support this hypothesis since positive adjusted interaction terms were found when comparing results between asthmatic and control volunteers in MDs and ORs for OP-DTT_v PM2.5, OP-AA_v PM2.5 and OP-AA_v PM10–2.5. For ease of understanding and interpretation, the meaning of these interaction terms is explained. Thus, the interaction coefficient for aMDs is in an additive context. It denotes the amount of ppm of FeNO to be added in the control group (without ICS) with respect to the asthma group (with ICS); e.g., for OP-DTT_v PM2.5: 5.06 ppb + 16.35 ppb = 11.29 ppb (i.e., in the absence of ICS, the aMD increases 16.35 ppb in those with higher exposure). The interaction coefficient for aOR is in a multiplicative context. It denotes the amount of OR necessary to multiply to obtain the result in the control group; e.g., for the same OP metric, 2.02 multiplied by 2.58 equals 5.21 (i.e., in the absence of ICS, the aOR increases 2.58 times in those with higher exposure).

This increase in FeNO levels after PM exposure found in our non-asthmatic group is also supported by published studies. In the respiratory system nitric oxide (NO) is mainly produced by constitutive nitric oxide synthetase (NOS) and inducible NOS (iNOS) (Ricciardolo, 2014). Several studies show an increased expression of iNOS in the lung tissues of mice after exposure to PM2.5 (Li et al., 2017; Zhang et al., 2018). In primary school children (n = 130), the exposure to black carbon was positively associated with FeNO (De Prins et al., 2014), and air pollution (without measuring specifically PM-OP) is also been shown to be associated with increased FeNO in children (with asthma) (Brown et al., 2012; Delfino et al., 2006; Godri Pollitt et al., 2016), young adults (Huang et al., 2012) and elderly people (Adamkiewicz et al., 2004; Delfino et al., 2010). In terms of specific PM-OP results, Delfino et al. (2013) found an association also in asthmatic children; in this study,

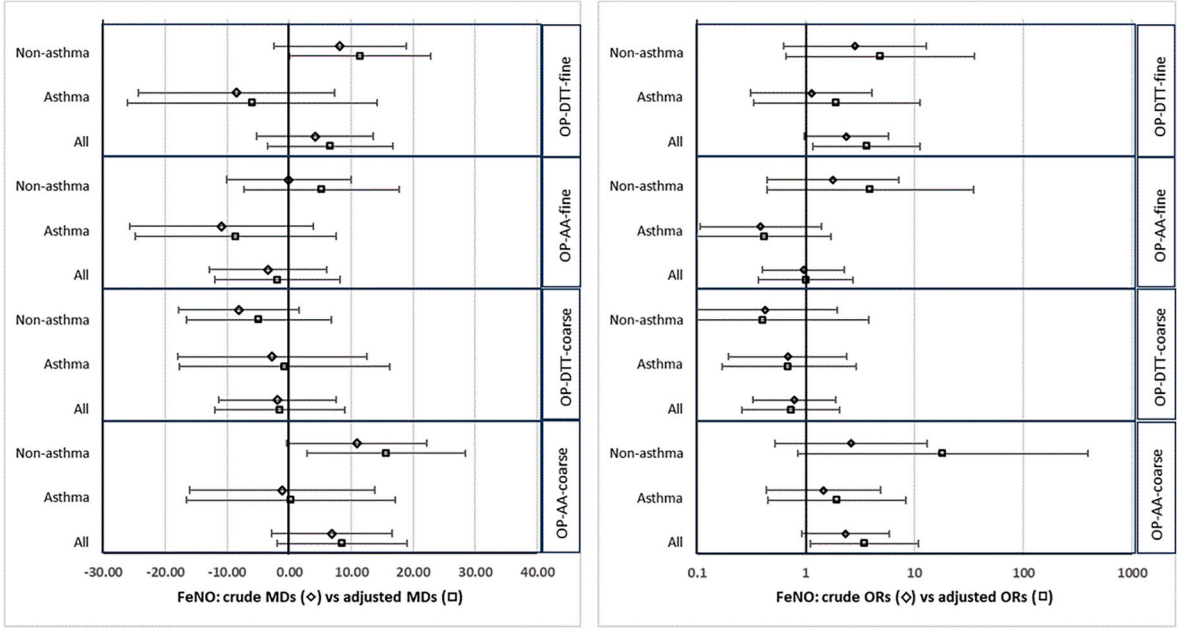

Fig. 2. Forest plot of crude and adjusted Mean Differences (MDs) (on the left) and odds ratios (ORs) (on the right); between higher values of OP-AA_v and OP-DTT_v (for the coarse and fine PM fractions) and higher FeNO levels (above median). MDs and ORs adjusted for age, sex, educational level, BMI according to WHO classification, and IL-6 levels.

Table 2
Study of the interaction (effect of being without ICS because non-asthma) on the Mean Differences of FeNO levels between higher and lower OP values.

	FeNO ppb											
	Asthma (ICS prescribed)								Non-Asthma (Without ICS)			
PM-OP$_v$ nmol min^{-1} m^{-3}	aMD	95 %	CI	*p value*	**Interaction term (β)**	95 %	CI	*p interaction*	aMD	95 %	CI	*p value*
OP-DTT$_v$ PM2.5												
Lower values	0								0			
Higher values	−5.06	−19.23	9.12	*0.479*	**16.35**	−4.51	37.21	*0.122*	11.29	−4.10	26.68	*0.148*
OP-AA$_v$ PM2.5												
Lower values	0								0			
Higher values	−8.78	−21.47	3.91	*0.172*	**11.94**	−6.72	30.61	*0.206*	3.16	−11.27	17.59	*0.664*
OP-DTT$_v$ PM10-2.5												
Lower values	0								0			
Higher values	−0.85	−14.05	12.35	*0.898*	**−3.72**	−22.95	15.51	*0.701*	−4.58	−19.48	10.33	*0.542*
OP-AA$_v$ PM10-2.5												
Lower values	0								0			
Higher values	0.78	−11.89	13.45	*0.903*	**13.50**	−6.96	33.97	*0.192*	14.29	−2.81	31.38	*0.100*

ICS= Inhaled corticosteroids. aMD = Mean Differences adjusted for age, sex, educational level, IL-6 levels, BMI according to WHO classification and asthma and non-asthma status including its interaction term with each PM–OP metric.

Table 3
Study of the interaction (effect of being without ICS because non-asthma) in the association between OP and FeNO levels.

	FeNO ppb (Median)											
	Asthma (ICS prescribed)								Non-Asthma (Without ICS)			
PM-OP$_v$ nmol min^{-1} m^{-3}	**aOR**	95 %	CI	*p value*	**Interaction term EXP(β)**	95 %	CI	*p interaction*	**aOR**	95 %	CI	*p value*
OP-DTT$_v$ PM2.5												
Lower values	1								1			
Higher values	2.02	0.43	9.59	*0.375*	**2.58**	0.28	24.15	*0.407*	5.21	0.95	28.56	*0.057*
OP-AA$_v$ PM2.5												
Lower values	1								1			
Higher values	0.43	0.11	1.69	*0.228*	**5.95**	0.79	45.01	*0.084*	2.57	0.55	12.10	*0.232*
OP-DTT$_v$ PM10-2.5												
Lower values	1								1			
Higher values	0.77	0.20	2.97	*0.708*	**0.73**	0.09	5.86	*0.768*	0.57	0.11	3.00	*0.502*
OP-AA$_v$ PM10-2.5												
Lower values	1								1			
Higher values	2.10	0.54	8.15	*0.284*	**2.96**	0.31	28.69	*0.35*	6.21	0.84	46.16	*0.075*

ICS= Inhaled corticosteroids. aOR= Odds Ratios adjusted for age, sex, educational level, IL-6 levels, BMI according to WHO classification and asthma and non-asthma status including its interaction term with each PM–OP metric.

OP-DTT and cellular OP (ROS induced using rat alveolar macrophage cells) were determined in PM samples collected by stationary samplers; later, Zhang et al. (2016) with the same approach found positive but non-significant associations in elderly people. Janssen et al. (2015) exposed 31 volunteers for 5 h to ambient air pollution at five locations: an underground train station, two traffic sites, a farm and an urban background site. They measured pre and post FeNOs and characterized the on site PM-OP-DTT and OP-AA of each location, showing increased FeNO levels after more OP exposed settings. In addition to the above-mentioned studies, as it is also mentioned in the introduction there are two studies with personal PM-OP characterization in asthmatic children: one uses an in vitro rat alveolar macrophage cell model to characterize it without finding significant association between its OP cellular assay and FeNO levels (He et al., 2021). The other study determined PM-OP by the AA acellular method as we do, and by glutathione (GSH) finding some association for OP-GSH PM2.5, but no association between OP-AA PM2.5 and FeNO levels. OP in PM10–2.5 was not measured (Maikawa et al., 2016). ICS usage in these studies ranged from 27.8 % to 48.6 % and probably the doses of ICS were lower than in our adult population, which is mostly on medium doses of ICS (GEMA stage 4). Since our study is the first one on the association between the PM-OP obtained using personal samplers and FeNO levels in asthmatic and non-asthmatic adults, future studies including a larger number of subjects in each group, would be needed to create further evidence on this hypothesis.

For each group, our study has shown important differences on the associations between PM-OP$_v$ and FeNO levels between both OP assays and as a function of the PM fraction: whereas the highest associations were found in controls and for OP-AA$_v$ in PM10–2.5 and OP-DTT$_v$ in PM2.5, and to a lower extent for OP-AA$_v$ in PM2.5, no positive associations were found for the OP-DTT assay in PM10–2.5 neither in controls nor in asthmatic volunteers. We attribute this to the different sensitivity of these assays to the particle size and chemical composition of PM. Most epidemiological studies have only assessed the OP in the fine fraction. While OP-DTT in PM2.5 has been usually positively associated with FeNO (Janssen et al., 2015; Yang et al., 2016; Zhang et al., 2016), an association for OP-AA in PM2.5 is less consistent (Maikawa et al., 2016; Steenhof et al., 2013; Strak et al., 2012). According to the literature, the PM components that are active in the OP-AA assay varied with the particle size; in particular, AA assay was found to be mainly sensitive to coarse particles (Massimi et al., 2020; Simonetti et al., 2018). This may explain the highest effect sizes of OP-AA in PM10–2.5 on FeNO levels found in our work. Regarding the sensitivity of OP assays to the chemical composition of PM, both OP-DTT and OP-AA are very sensitive to soluble Cu, whereas OP-DTT is sensitive to Mn but not to Fe, while Fe is an important driver of OP-AA (Bates et al., 2019; Guo et al., 2020; Expósito et al., 2024). In the area of study, a recent work displayed high levels of PM-bound Fe and Mn in both size fractions, due to the presence of local industrial sources of both metals (a ferromanganese alloy plant and a non-integrated steel plant). In addition, Cu was also found in this area mainly due to road traffic, but at relatively low concentrations (Expósito et al., 2025). Literature also shows that OP-DTT is in general very sensitive to organic compounds, especially to photochemically aged organic

species, which are mostly present in the fine fraction (Bates et al., 2019; Pietrogrande et al., 2019). This probably explains the higher relevance of OP-DTT in epidemiological studies compared to OP-AA (Bates et al., 2019; Øvrevik, 2019) but as we have mentioned, this analysis is mainly based on the PM2.5 fraction and our study reveals that the OP-AA assays can be as relevant as OP-DTT when the coarse fraction is considered.

When we analyzed PM-OP_v by stationary ambient samplers located in Maliaño and Santander (the urban-industrial and urban site, respectively, shown in Fig. 1), differences were obtained, with higher levels of PM-OP_v and metals in the urban-industrial site compared to the urban site (Expósito et al., 2025). However, in the case of personal samples assessed in the present work, no spatial pattern has been found, suggesting that work and leisure activities (hobbies) outside the place of residence have a substantial contribution to the individual personal exposure. Thus, since no differences in geographic distribution of places of residence were observed between asthmatic and non-asthmatic volunteers, the explanation of the lower levels of PM-OP_v in non-asthmatic volunteers may be related with the different educational level (higher University studies in non-asthmatics), which denotes different occupations or hobbies. Our results, based mainly on a population living in a relatively low polluted mixed urban–industrial area, show lower levels of PM-OP_v than those reported in other studies (In 't Veld et al., 2023). It would be reasonable to think that associations of higher magnitude would have been found in a more exposed population, or in a population with more variability in terms of PM-OP exposure with higher median cut-off points.

Lastly, as it is an observational study, we have presented MDs and ORs adjusted for several potential confounding variables such as sex, age, study level, BMI and IL-6 levels in both asthmatic and non-asthmatic volunteers, and adding clinical specific variables such as dosage of ICS and use of biologics (GEMA v5.3 stages), ACT and TAI results in a multivariate regression model restricted to asthma patients. It minimizes the existence of a confounding bias in our results, and highlights the importance of controlling for it using multivariate regression models. The concordance between the two approaches (aMDs by linear regression and aOR by logistic regression) would support the internal validity of our findings.

Regarding limitations, an important caveat of our study is the sample size and the statistical power to detect positive associations as statistically significant. Because of this, few statistically significant associations were obtained for the total sample (n = 81), with some of them losing statistical significance in the stratified analysis (n = 44 asthmatics and n = 37 controls) with wider 95 % confidence intervals. A larger sample size of asthmatics on low-dose ICS (n = 5 in our sample) would have allowed for a specific analysis within this group to determine the extent to which low-dose ICS can buffer airway inflammation (as indicated by FeNO levels) in response to PM-OP. Our cross-sectional approach with only one PM-OP_v determination per volunteer is another shortcoming that needs to be improved in future larger prospective studies.

5. Conclusion

We have found differential associations between the OP_v of PM and FeNO levels between asthmatic and non-asthmatic volunteers. Adjusted associations were higher in volunteers without asthma. It suggests a potential implication of ICS in diminishing the reactivity of airway epithelium to ROS from PM that should be confirmed by further studies.

CRediT authorship contribution statement

Miguel Santibáñez: Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Juan José Ruiz-Cubillán:** Resources, Investigation, Funding acquisition, Data curation. **Juan Agüero:** Resources, Investigation, Funding acquisition, Data curation. **Andrea Expósito:** Resources, Investigation, Funding acquisition, Data curation. **Beatriz Abascal:** Resources, Investigation, Funding acquisition, Conceptualization. **Juan Luis García-Rivero:** Resources, Investigation, Funding acquisition, Data curation. **Carlos Antonio Amado:** Resources, Investigation, Funding acquisition, Data curation. **Maria Mercedes Hernando:** Resources, Investigation, Funding acquisition, Data curation. **Laura Ruiz-Azcona:** Investigation, Formal analysis. **Esther Barreiro:** Resources, Investigation, Formal analysis, Conceptualization. **Adriana Núñez-Robainas:** Resources, Investigation, Data curation. **José Manuel Cifrián:** Resources, Investigation, Funding acquisition, Data curation. **Ignacio Fernandez-Olmo:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Cantabria (CEIC) (internal codes 2020.475 and 2023.412), and the ethics committee of the UC (CEPI) (internal code: 16.2021). All personal data were anonymized. Informed consent was obtained from all subjects involved in the study.

Data availability

Data will be made available on request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2025.114589.

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