AIRWAYS CHANGES RELATED TO AIR POLLUTION EXPOSURE IN WHEEZING CHILDREN

ONLINE SUPPLEMENT

MATERIAL AND METHODS

Population and protocol

The four included schools were selected from two different parts of Viseu: two main schools from the inner city (urban schools) and two main schools from the city area located outside the highway ring that surrounds Viseu (suburban schools).

The International Study of Asthma and Allergies in Childhood questionnaire (ISAAC) was fulfilled by parents.

Diagnoses of neuromuscular or psychiatric diseases and airways diseases other than asthma, constituted the exclusion criteria.

Skin prick tests

SPT were carried out with the following commercial extracts (Leti®): positive control (histamine 10 mg/ml), negative control (phenol-saline solution), *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, dog dander, cat dander, cockroach, alternaria, grass mix, olive tree, pellitory plant, cypress, birch and oak trees. Extracts were introduced into the skin using Stallerpoint® lancets. A wheal with erythema with mean diameter over 3 mm was considered a positive result. Atopy was considered if there was at least a positive result to an allergen tested.

Airways assessment

Spirometry was performed using a portable pneumotachograph (Vitalograph® Compact, Vitalograph, Buckingham, U.K.) according to standardized guidelines[1,2]. Lung function was measured both before and 15 minutes after administration of bronchodilator. Lung function was expressed as the percentage of the predicted normal value according to Polgar reference equations[3]. ΔFEV_1 is presented as the percentage of improvement considering the baseline FEV_1.

EBC collection was performed according to the recommendations of the American Thoracic Society and European Respiratory Society (ATS/ERS)[4], using a RTube® (Respiratory Research Inc., Austin Texas, U.S.A.). A nasal clip was used during the 15 minutes of the collection in order to achieve 1 to 3 mL of condensate. After collection, EBC was immediately frozen and stored until the pH measurement. pH analysis was performed two weeks after in the de-aerated samples (extraction of CO_2 with argon), using a glass microelectrode (HI9025C, HANNA® Instruments Inc., Woonsocket, U.S.A.). F_ENO measurement was performed before the spirometry, using a portable analyser, Niox® Mino (Aerocrine, Solna, Sweden), in which the expiratory flow rate is maintained at 50 mL/s. ATS/ERS recommendations were followed [5].

Air quality measurements

Concerning diffusive samplers, BTEX (benzene, toluene, ethylbenzene and xylenes) compounds were trapped by adsorption and recovered by carbon disulfide displacement and analysis was performed by flame ionization detector gas chromatography. For formaldehyde, the 2.4-dinitrophenylhydrazones were then extracted with acetronitrile and analyzed by reverse phase high-pressure liquid chromatography (HPLC) and UV detection. Both formaldehyde and BTEX measurements were done with Radiello® diffusive samplers (Tradate, Italy). NO_2 and O_3 diffusive samplers were produced in the University of Aveiro based on Palmes tubes [6,7] and analysed by spectrophotometry[8]. The detection limits for the diffusive samplers are: for BTEX and formaldehyde – 0.1 $\mu g.m^{-3}$; for O_3 – 2 $\mu g.m^{-3}$; for NO_2 – 1 $\mu g.m^{-3}$.

Diffusive samplers were exposed during 5 days. PM_{10} measurements were conducted during 2 weeks and the 5 x 24-hour measurements during the studied period were used.

Air quality modelling

The CHIMERE multi-scale model is primarily designed to produce daily forecasts of ozone, aerosols and other pollutants and make long-term simulations for emission control scenarios. CHIMERE runs over a range of spatial scale from the regional scale (several thousand kilometers) to the urban scale (100-200 Km) with resolutions from 1-2 Km to 100 Km. This air quality modelling system based on the chemistry-transport model CHIMERE[9] forced by the mesoscale model MM5[10], has been widely applied and validated and is currently used as the Portuguese air quality forecasting system[11]. The modelling system was applied first at the European scale (with 27 x 27 km resolution), then over Portugal using the same physics and a one-way nesting technique with 9 x 9 km, and 3 x 3 km, and finally over Viseu, at 1 x 1 km horizontal resolution. The assessment of the model performance was made by comparison of the modelling results with air quality measurements from a fixed air quality station. The statistical parameters used for the model evaluation are recommended by the Forum for air quality modelling for Europe (FAIRMODE)[12] and have been used in various air quality assessment studies[11,13]. The model results showed reasonable agreement with observations, with correlation coefficients around 0.7 and normalised errors between 10% and 30%.

Exposure assessment estimation

Microenvironments where it was not possible to measure pollutants were geo-referenced and outdoor concentrations were obtained directly from modelling while for indoor concentrations indoor-outdoor relations from literature were used[14,15]. Details on methodology and results concerning air pollutants concentration measurements and modelling as well as exposure calculations were published elsewhere[16]. The exposure of

BTEX and formaldehyde were calculated entirely based on measured concentrations. O_3, NO_2 and PM_{10} exposure was estimated using both measurements and results from modelling. For O_3 and NO_2 the calculation included measured values of outdoor concentrations in schools and air quality modelling results since the measured concentrations were undetectable, namely in the indoors. Concerning PM_{10}, measured concentrations were used for schools (indoor and outdoor), while for the other microenvironments (houses) concentrations were provided by air quality modelling.

RESULTS

Children who did not accept to participate did not differ significantly in age (p=0.298) and sex (p=0.868) from the others. During the period of study, three children dropped out (two abandoned the study and one moved to another city) after the first visit.

Forty nine children had the four complete medical visits and two children had three. In the follow-up, we performed 202 spirometries, 202 F_ENO evaluations and collected 204 breath samples. There were no missing data for PM_{10}, O_3 and NO_2 neither for BTEX at schools. Overall we obtained 166 measurements of BTEX in the houses of the participating children, as some participants did not accept always the equipment at their houses while in others technical problems occurred.

The most common SPT positivities were to house dust mite (21 children) and grass pollen (18 children). Twenty percent of children had at least one smoking parent at home.

Differences between January and June were found with January showing the higher values of PM_{10}, benzene, toluene, xylene and ethylbenzene. According to the Portuguese legislation concerning air quality, most of the pollutants concentrations were considered low and did not cause concern, with the exception of ambient air PM_{10} that surpassed the limits. Relative humidity was higher and average temperature was lower in January, namely in the first year. Despite this, in the second year, the temperature was unexpected low in June.

Correlation matrixes for pollutants are presented for each season in Tables 1s, 2s, 3s and 4s. PM_{10} was negatively correlated with individual exposure to NO_2 and ozone as consequence of the trend presented by NO_2 and ozone to be negatively correlated with the time spent indoors, where low levels of those pollutants were found.

In the univariable analysis we found associations between spirometric outcomes and most of the pollutants (Table 5s), with exception of xylene and formaldehyde. Some of those associations achieved a high statistical significance.

Univariable analysis for clinical outcomes is presented in Table 6s. Univariable analysis studying associations between spirometric outcomes and variables selected *a priori* and other variables included in the model, are presented in Tables 7s and 8s.

Two-pollutant models in order to take into account the correlations between pairs of pollutants were performed for FEV_1 (Figure 1s) and pH on EBC (Figure 2s). Generally the results presented the same trend of associations achieved in the one pollutant models, although without reaching statistical significant associations. The exceptions were for benzene (FEV_1 as outcome) and PM_{10} (pH as outcome), that persisted statistically significant also in the two-pollutant models. In the case of FEV_1, the application of two-pollutant models for PM_{10} and NO_2 was not conclusive because of fitting problems.

Reported wheezing symptoms, need of rescue medication and emergency department visits decreased along the study. At the end of the study, less than half of the participants mentioned symptoms in the previous months, namely “wheezing” that was the symptom that motivated the inclusion in the study.

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Table 1s: Spearman rank order correlation coefficients of individual exposure to pollutants, for Visit 1

	PM_{10}	**O_3**	**NO_2**	**Benzene**	**Toluene**	**Xylene**	**Ethylbenzene**	**Formaldehyde**
PM_{10}		-0.277(*)	-0.642(**)	0.356(*)	0.082	0.020	0.046	-0.038
O_3			0.822(**)	-0.294(*)	-0.164	0.013	-0.061	-0.511(**)
NO_2				-0.423(**)	-0.151	0.003	-0.075	-0.357(*)
Benzene					0.190	0.394(*)	0.424(**)	0.284
Toluene						0.576(**)	0.660(**)	0.071
Xylene							0.961(**)	0.050
Ethylbenzene								0.133

** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed)

Table 2s: Spearman rank order correlation coefficients of individual exposure to pollutants, for Visit 2

	PM_{10}	**O_3**	**NO_2**	**Benzene**	**Toluene**	**Xylene**	**Ethylbenzene**	**Formaldehyde**
PM_{10}		-0.251	-0.719(**)	-0.065	-0.103	-0.115	-0.111	-0.035
O_3			0.223	-0.069	0.502(**)	0.429(**)	0.406(*)	-0.250
NO_2				-0.038	-0.075	0.007	-0.020	0.025
Benzene					0.319	0.345(*)	0.345(*)	0.416(**)
Toluene						0.652(**)	0.607(**)	0.123
Xylene							0.936(**)	0.419(**)
Ethylbenzene								0.326(*)

** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed)

Table 3s: Spearman rank order correlation coefficients of individual exposure to pollutants, for Visit 3

	PM_{10}	O_3	NO_2	Benzene	Toluene	Xylene	Ethylbenzene	Formaldehyde
PM_{10}		0.063	-0.547(**)	-0.105	-0.194	-0.134	-0.147	-0.113
O_3			-0.517(**)	-0.043	0.502(**)	0.429(**)	0.406(*)	-0.250
NO_2				-0.102	-0.194	-0.100	-0.227	-0.261
Benzene					0.527(**)	0.149	0.586(**)	-0.028
Toluene						0.451(**)	0.632(**)	0.214
Xylene							0.500(**)	0.250
Ethylbenzene								0.163

** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed)

Table 4s: Spearman rank order correlation coefficients of individual exposure to pollutants, for Visit 4

	PM_{10}	O_3	NO_2	Benzene	Toluene	Xylene	Ethylbenzene	Formaldehyde
PM_{10}		-0.528(**)	-0.816(**)	-0.003	0.131	0.262	0.253	0.033
O_3			0.528(**)	0.019	-0.181	-0.297(*)	-0.264	-0.235
NO_2				0.138	-0.176	-0.221	-0.029	-0.226
Benzene					0.326(*)	0.503(**)	0.448(**)	-0.055
Toluene						0.483(**)	0.462(**)	0.262
Xylene							0.977(**)	0.065
Ethylbenzene								0.045

** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed)

Table 5s: Relationships between different pollutants exposure and spirometry / airways inflammation outcomes (Crude regression coefficients, CI 95%, p value)

	FEV_1%	FEV_1/FVC	FEF25-75%	ΔFEV_1%	pH EBC	F_ENO ppb
PM_{10}						
	-0.43 (-1.32 to 0.47), NS	-0.62 (-1.07 to -0.17), p=0.008	-0.75 (-2.11 to 0.62), NS	0.63 (0.03 to 1.23), p=0.039	0.00 (-0.06 to 0.07), NS	-0.99 (-2.14 to 0.15), p=0.089
O_3						
	-1.68 (-2.95- to -0.44), p=0.008	0.72 (0.07 to 1.38), p=0.031	-1.21(-3.16 to 0.69), NS	-0.09 (-0.97 to 0.77), NS	-0.22 (-0.29 to -0.13), p<0.001	3.37 (1.80 to 4.93), p<0.001
NO_2						
	-4.36 (-6.70 to -2.01), p<0.001	0.12 (-1.15 to 1.39), NS	-4.66 (-8.34 to -0.98), p=0.013	1.05 (-0.61 to 2.72), NS	-0.44 (-0.60 to -0.28), p<0.001	5.11 (2.04 to 8.18), p=0.001
Benzene						
	-4.78 (-7.18 to -2.37), p<0.001	-1.72 (-3.12 to -0.32), p=0.016	-6.02 (-9.79 to -2.25), p=0.002	3.06 (1.42 to 4.70), p<0.001	-0.23 (-0.40 to 0.05), p=0.011	3.10 (-3.93 to 6.60), p=0.082
Toluene						
	-0.83 (-1.63 to - 0.03), p=0.041	-0.42 (-0.87 to 0.02), p=0.063	-0.99 (-2.23 to 0.25), NS	0.96 (0.46 to 1.45), p<0.001	0.01 (-0.04 to 0.07), NS	0.36 (-0.74 to 1.48), NS
Xylene						
	-0.26 (-1.07 to 053), NS	0.09 (-0.36 to 0.55), NS	-0.21 (-1.45 to 1.03), NS	-0.25 (-0.79 to 0.29), NS	-0.00 (-0.06 to 0.05), NS	0.82 (-0.29 to 1.93), NS
Ethylbenzene						
	-1.98 (-3.29 to -0.67), p=0.003	-0.33 (-1.10 to 0.45), NS	-2.41 (-4.47 to -0.35), p=0.022	1.23 (0.32 to 2.16), p=0.008	-0.16 (-0.25 to -0.06), p=0.001	2.55 (0.68 to 4.42), p=0.007
Formaldehyde						
	-0.22 (-3.61 to 3.18), NS	-0.33 (-2.08 to 1.41), NS	-0.82 (-5.95 to 4.31), NS	-0.02 (-1.96 to 1.92), NS	0.02(-0.19 to 0.23), NS	0.23 (-4.02 to 4.49), NS

FVC: Forced Vital Capacity; :FEV_1: Forced Expiratory Volume in 1 second; FEF25-75%: Forced Expiratory Flow between 25-75% of vital capacity; ΔFEV_1: The increase of FEV_1 as a percentage of the initial value, after bronchodilator; EBC: Exhaled Breath Condensate; F_ENO: Fraction of exhaled nitric oxide; CI: Confidence interval; NS: p-value > 0.100

Regression coefficients (CI 95%) represent the mean change in spirometric and inflammatory parameters for increments of 10 µg.m^3 of air pollutant

Table 6s: Relationships between different exposures to pollutants and clinical outcomes (Crude regression coefficients, CI 95%, p value)

	Wheezing	Need of rescue medication	Emergency Department
PM_{10}			
	0.07(0.03 to 0.11), p=0.002	0.03(-0.00 to 0.07), p=0.127	0.04(-0.00 to 0.08), p=0.059
O_3			
	-0.20 (-0.25 to -0.14), p=0.000	-0.06(-0.12 to 0.01), p=0.021	-0.10(-0.15 to -0.44), p=0.000
NO_2			
	-0.27 (-0.39 to -0.16), p=0.000	-0.07(-0.18 to 0.03), p=0.175	-0.13 (-0.24 to -0.03), p=0.012
Benzene			
	-0.03 (-0.08 to 0.02), p=0.269	0.01 (-0.03 to 0.06), p=0.555	0.03(-0.01 to 0.07), p=0.162
Toluene			
	0.04(0.00 to 0.07), p=0.023	0.01 (0.02 to 0.04), p=0.474	0.01(-0.01 to 0.04), p=0.304
Xylene			
	-0.04 (-0.12 to 0.05), p=0.382	-0.00(-0.08 to 0.07), p=0.921	0.00(-0.067 to 0.08), p=0.866
Mp-Xylene			
	0.10 (-0.04 to 0.17), p=0.002	0.1 (0.04 to 0.16), p=0.001	0.09(0.03 to 0.14), p=0.002
Ethylbenzene			
	-0.01(0.05 to 0.03), p=0.534	-0.00(-0.04 to 0.02), p=0.589	0.02(-0.01 to 0.05), p=0.240
Formaldehyde			
	0.10(0.01 to 0.18), p=0.025	0.02 (-0.06 to 0.10), p=0.642	0.03(-0.36 to 0.10), p=0.338

CI: Confidence interval

Regression coefficients (CI 95%) represent the mean change in clinical outcomes for increments of 10 µg.m^3 of air pollutant

Table 7s: Relationships between different variables included *a priori* and spirometry / airways inflammation outcomes (Crude regression coefficients, CI 95%, p value)

	FEV_1%	FEV_1/FVC	FEF25-75%	ΔFEV_1%	pH EBC	F_ENO ppb
Age (years)	-3.04 (-4.74 to -1.34), p<0.001	0.62 (-0.24 to 1.49), p=0.159	-2.36 (-5.00 to 0.29), p=0.081	-0.90 (-0.02 to 1.83), p=0.056	-0.15 (-0.25 to -0.60), p=0.001	4.41 (2.37 to 6.45), p<0.001
Sex						
Women	-10.12 (-17.29 to -2.95), p=0.006	1.16 (-2.43 to 4.75), p=0.526	-5.39 (-17.95 to 7.15), p=0.399	1.63 (-1.25 to 4.50), p=0.269	0.03 (-0.25 to 0.31), p=0.830	-7.34 (-15.14 to 0.47), p=0.065
Parental education						
High School or University	5.87 (-1.65 to 13.39), p=0.127	1.85 (-1.72 to 5.41), p=0.311	10.19 (-2.12 to 22.50), p=0.102	-2.80 (-5.59 to - 0.00), p=0.050	-0.08 (-0.35 to 0.20), p=0.585	-0.03 (-8.09 to 8.02), p=0.994
Passive smoking						
Yes	-3.90 (-13.49 to 5.68), p=0.425	-0.91 (-5.42 to 3.60), p=0.691	-6.41 (-22.15 to 9.32), p=0.424	0.72 (-2.90 to 4.34), p=0.697	-0.11 (-0.46 to 0.23), p=0.585)	0.10 (-9.99 to 10.20), p=0.984
Atopy						
Yes	-3.34 (-8.01 to 7.34), p=0.932	-1.18 (-4.76 to 2.40), p=0.518	-0.32(-12.92 to 12.27), p=0.960	0.81 (-2.80 to 3.70), p=0.583	-0.24 (-0.51 to 0.02), p=0.073)	20.69 (15.10 to 26.28), p<0.001
Average temperature						
One Cº increase	0.14 (-0.08 to 0.37), p=0.208	0.08(-0.03 to 0.20), p=0.161	0.21 (-0.13 to 0.56), p=0.224	-0.08 (-0.23 to 0.07), p= 0.297	-0.00(-0.02 to 0.01), p=0.668	0.10 (-0.19 to 0.40), p=0.476
Average humidity						
% increase	-0.00 (-0.15 to 0.15), p=0.971	-0.06 (-0.14 to 0.01), p=0.117	-0.08 (-0.31to 0.15), p=0.504	0.04 (-0.06 to 0.14), p= 0.415	0.01 (-0.00 to 0.02), p=0.100	-0.21(-0.40 to -0.03), p=0.025
Time	-1.41 (-2.48 to -0.35), p=0.009	0.063 (0.07 to 1.19), p=0.029	-0.98 (-2.61 to 0.68), p=0.246	-0.12 (-0.86 to -0.62), p=0.746	-0.19 (-0.26 to -0.12), p<0.001	2.94 (1.60 to 4.27), p<0.001

FVC: Forced Vital Capacity; :FEV_1: Forced Expiratory Volume in 1 second; FEF25-75%: Forced Expiratory Flow between 25-75% of vital capacity; ΔFEV_1: The increase of FEV_1 as a percentage of the initial value, after bronchodilator; EBC: Exhaled Breath Condensate; F_ENO: Fraction of exhaled nitric oxide; CI: Confidence interval

Table 8s:Relationships between other variables and spirometry / airways inflammation outcomes (Crude regression coefficients, CI 95%, p value)

	FEV_1%	FEV_1/FVC	FEF25-75%	ΔFEV_1%	pH EBC	F_ENO ppb
Height						
(1 cm increase)	-0.52 (-0.83 to -0.21), p=0.001	0.11 (-0.04 to 0.26), p=0.177	-0.40 (-0.88 to 0.09), p=0.108	0.01 (-0.14 to 0.17), p=0.872	-0.02 (-0.04 to - 0.00), p= 0.010	0.74 (0.39 to 1.09), p<0.001
Weight						
(1 Kg increase)	-0.39 (-0.76 to -0.02), p=0.040	-0.08 (-0.10 to 0.26), p=0.399	-0.22 (-0.80 to 0.36), p=0.447	0.04 (-0.14 to 0.22), p= 0.640	-0.02(-0.04 to 0.00), p=0.048	0.76 (0.34 to 1.17), p<0.001
Pets at home						
Yes	-1.94 (-9.62 to 5.73), p=0.620	1.46 (-2.04 to 4.96), p=0.415	3.18 (-9.22 to 15.59), p=0.615	-1.31(-4.22 to 1.60), p=0.378	0.22 (-0.05 to 0.49), p=0.118	-7.27 (-15.06 to 0.52), p=0.067
Older siblings						
Yes	4.82 (-2.63 to 12.30), p=0.206	2.38 (-1.05 to 5.80), p=0.174	10.85 (-1.09 to 22.80), p=0.075	-1.04 (-3.92 to 1.84), p=0.481	-0.10 (-0.37 to 0.17), p=0.482	-7.33 (-15.03 to 0.36), p=0.062
Mold or dampness at home						
Yes	-14.20 (-25.20 to -3.21), p=0.011	-5.99 (-11.08 to -0.88), p=0.021	-24.93 (-42.55 to -7.31), p=0.006	8.16 (4.33 to 11.98), p<0.001	-0.04 (-0.45 to 0.38), p=0.871	-2.60 (-14.79 to 9.58), p=0.675
Fireplace at home						
Yes	2.66 (-4.97 to 10.08), p=0.506	2.95 (-0.429 to 6.33), p=0.087	11.21 (-0.66 to 23.08), p=0.064	-3.07 (-5.84 to -0.31), p=0.029	-0.13 (-0.40 to 0.14), p=0.338	-2.66 (-10.54 to 5.21), p=0.500

FVC: Forced Vital Capacity; :FEV_1: Forced Expiratory Volume in 1 second; FEF25-75%: Forced Expiratory Flow between 25-75% of vital capacity; ΔFEV_1: The increase of FEV_1 as a percentage of the initial value, after bronchodilator; EBC: Exhaled Breath Condensate; F_ENO: Fraction of exhaled nitric oxide; CI: Confidence interval

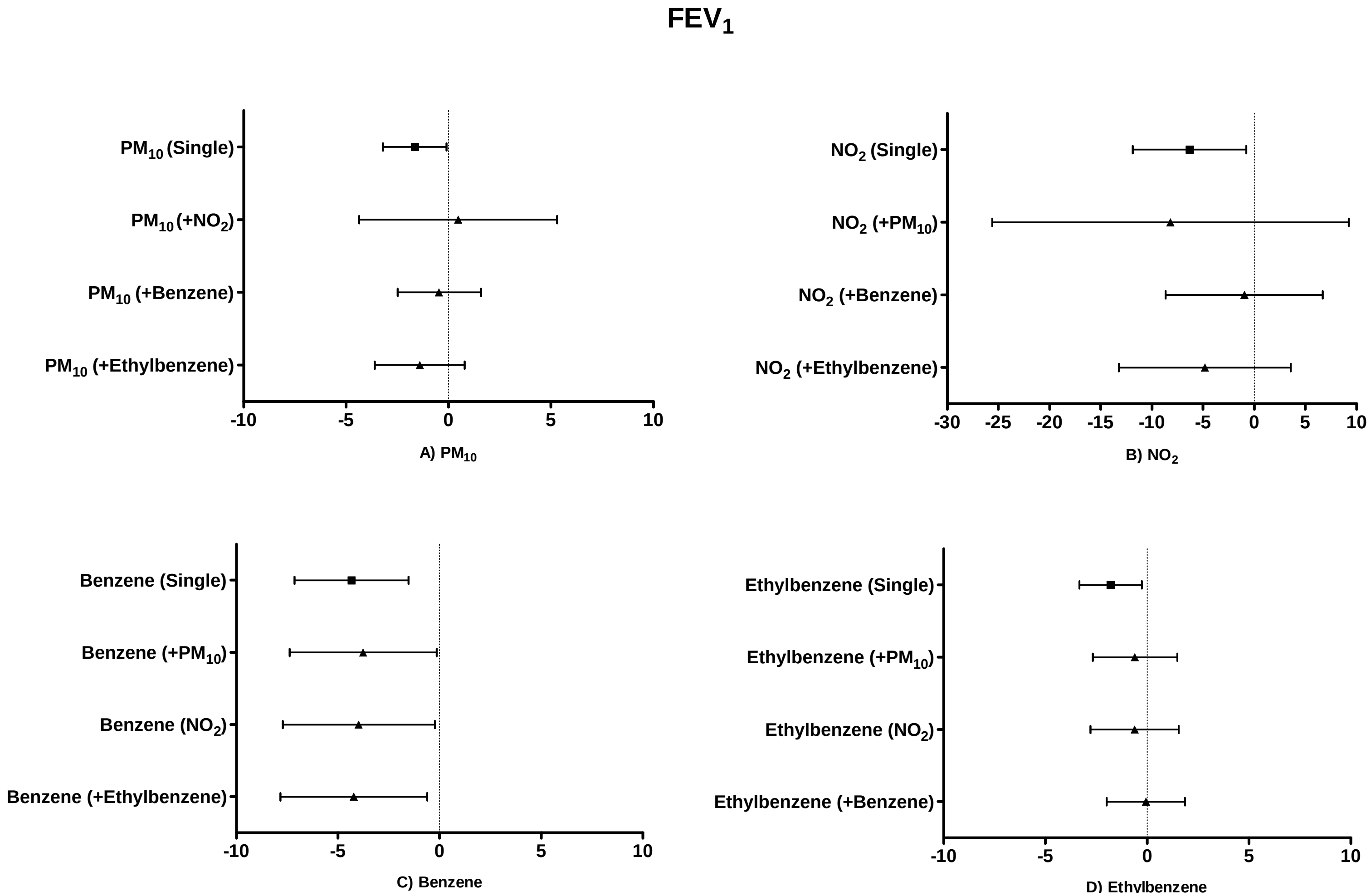

Figure 1s: Percent changes and corresponding 95% confidence intervals in FEV_1 for 10 $\mu g.m^{-3}$.h increments of air pollutant, after adjustment, in one (single) and two pollutants model. Results are presented for each pollutant - A) PM_{10} B) NO_2 C) benzene and D) ethylbenzene - adjusted for the second pollutant (+).

pH

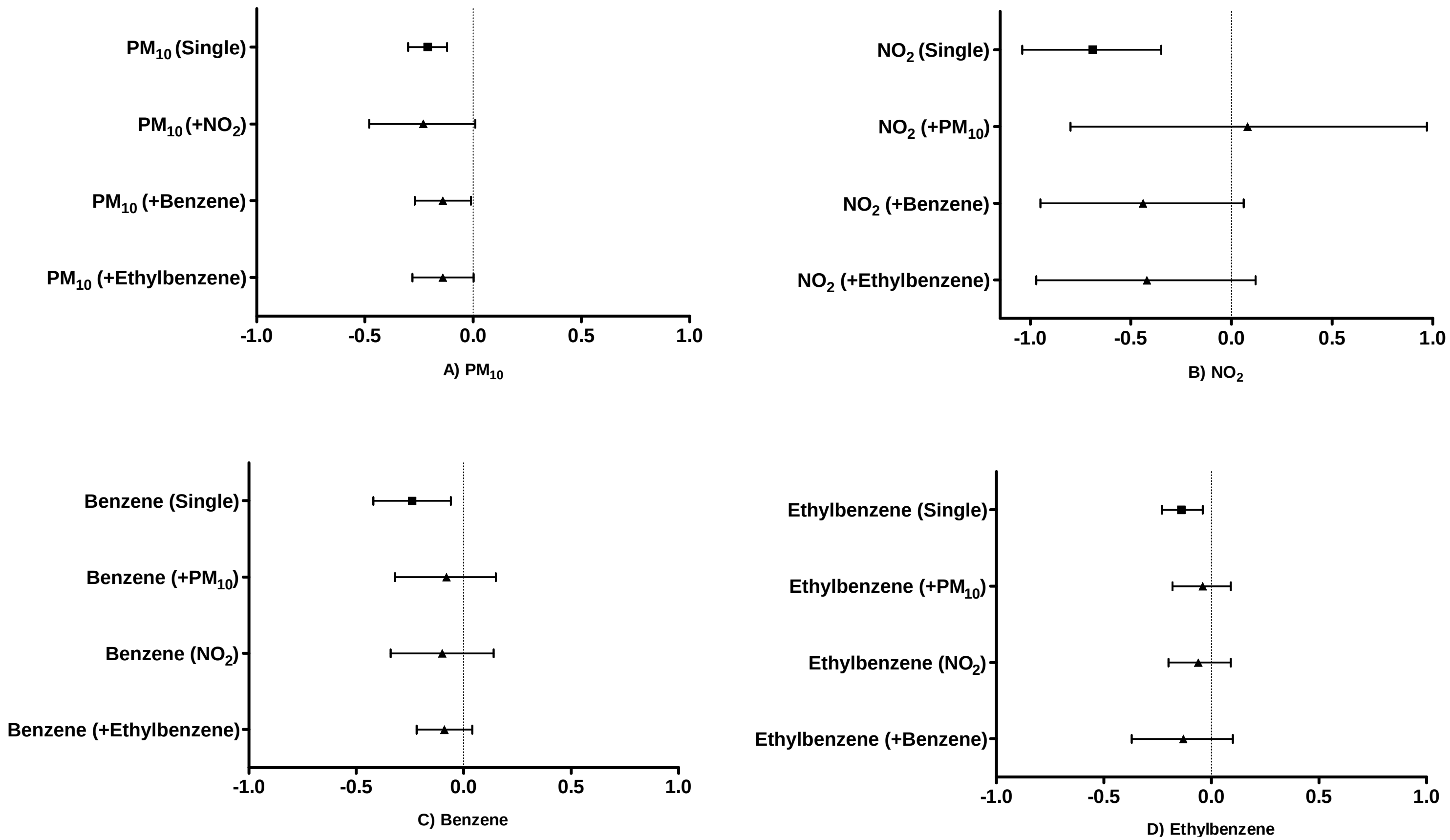

Figure 2s: Exhaled breath condensate pH changes and corresponding 95% confidence intervals for 10 µg.m^{-3}.h increments of air pollutant, after adjustment, in one (single) and two pollutants model. Results are presented for each pollutant - A) PM_{10} B) NO_2 C) benzene and D) ethylbenzene - adjusted for the second pollutant (+).