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Short-term exposure to ultrafine particles is associated to bronchial inflammation in schoolchildren

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Running title: Ultrafine particles exposure affects FeNO

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Conflict of interest

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I. INTRODUCTION

Ultrafine particles (UFP, particulate matter PM_{<100 nm}), through their small size, high number and surface area, and their chemical composition¹, can induce serious health effects². UFP are able to reach lung alveoli³ and are toxic through mechanisms of oxidative stress, cell signalling and activation, and release of mediators initiating inflammatory processes in the respiratory tract and in the cardiovascular system^{3, 4}. Moreover, asthmatic/allergic children are likely to be more susceptible to UFP exposure than healthy children². However, epidemiological data on the short-term respiratory health effects of UFP exposure, especially on the

fraction of exhaled nitric oxide (FeNO) as a marker of eosinophilic airway inflammation⁵ in children remains limited². Only one study used personal measurements of UFP exposure on a daily basis, taking into account all the microenvironments attended by children⁶.

The aim of this study was to investigate the relationship between personal measurements of UFP exposure and FeNO in 9-year-old children with and without persistent respiratory symptoms from PARIS (*Pollution and Asthma Risk: an Infant Study*) birth-cohort (Paris, France).

II. MATERIAL AND METHODS

A cross-sectional study nested in the PARIS birth-cohort⁷ took place between June 2014 and December 2015 on a random sample of children with ($N=45$) and without ($N=51$) persistent respiratory symptoms till the age of 6 years, and whose parents accepted a 9-year health check-up and gave their informed consent. Children **with persistent respiratory symptoms** were participants with asthma-like symptoms reported by parents as persistent wheezing and/or asthma attacks at two or more time points from 4 years of age, or with doctor-diagnosed asthma until the age of 6 years. **Children without persistent respiratory symptoms** were participants without any lower airways respiratory symptoms between the ages of 18 months and 6 years.

Exposure measurement. Personal measurement of UFP exposure was realized during the 24 hours preceding the health check-up, as described by Paunescu et al. (2017)⁸, with a portable device DiSCmini® (Diffusion Size Classifier miniature, Testo SE & Co. KGaA, Titisee-Neustadt, Germany), that gives the number of particles per cubic centimeter of aspirated air ("particle number concentration", PNC, pt/cm^3), and estimates automatically using an internal algorithm, the surface coming into contact with the lung mucosa ("lung-deposited surface area", LDSA, $\mu\text{m}^2/\text{cm}^3$). The LDSA concentration is defined as the particle surface area concentration per unit volume of air, weighted by the deposition probability in the lung⁹.

Health check-up. FeNO was measured by the direct "On-line" method using a NIOX MINO® electrochemical nitric oxide (NO) analyzer (Circassia Pharmaceuticals Inc., Chicago, USA), and was expressed continuously and dichotomized with reference to 20 ppb or 35 ppb thresholds⁵. Spirometry tests (maximum expiratory volume in 1 second, FEV₁) were performed by trained technicians in two tertiary referral children hospitals in Paris. The children did not have any respiratory infections at the time of the check-up, and were advised to stop their medication to improve breathing between 5 and 10 days (according to the half-life of the drugs) before the lung function testing (except in cases of serious disease and doctor contraindication). The specific level of immunoglobulin E (IgE) directed to 7 aeroallergens (mites, Timothy grass, cat, birch, dog, *Alternaria* and cockroach) was assessed by ImmunoCAP® (Phadia, Thermo Fisher Scientific, Uppsala, Sweden). Allergic sensitization was defined as an allergen-specific IgE antibody level of 0.35 kU_A/l or greater. A health questionnaire documented respiratory/allergic morbidity and treatment in children; characteristics of parents' lifestyle and habits at home (Table I).

Statistical analysis. Comparisons between children with and without persistent respiratory symptoms were tested by Student *t*-test, and frequency comparisons, by Chi-2 test or Fisher Exact test. Multivariate linear regression models were used to relate children's FeNO to their UFP exposure, adjusting for sex, age, height, and potential confounders, including personal black carbon exposure. The inter-quartile range (IQR between first and third quartile) of the UFP exposure was used to express the subsequent change in FeNO levels. The significance level was 0.05. Analyses were performed using Stata 11.2 software (StataCorp LP, College Station, Texas, USA).

III. RESULTS

The results deal with 71 children presenting data for both, UFP exposure and FeNO: 35 children with and 36 without persistent respiratory symptoms. The two groups of children were comparable with regard to all characteristics / parameters given in Table I (including UFP exposure), except FEV₁ (lower in children with persistent respiratory symptoms). About 80% and 9% of children with persistent

respiratory symptoms were diagnosed with asthma and allergic rhinitis (AR), respectively until 9 years. At the time of health check-up, 40% of children with persistent respiratory symptoms still reported wheezing in the chest, 34% asthma attacks and 51% had taken medication to improve their breathing in the last year, inhaled and/or oral corticosteroids for most of them (72%).

The increase in 24-hr IQR personal UFP exposure (PNC 7 069 pt/cm³ or LDSA 15 µm²/cm³) was related to higher FeNO in all children, particularly in those with persistent respiratory symptoms, and most specifically in children with asthma/AR diagnosis (Figure 1).

IV. DISCUSSION

Our study shows that after adjusting on the main confounders including another particulate indicator – personal exposure to black carbon (resulting from incomplete combustion of biomass, oil/diesel), measured continuously, simultaneously to UFP – higher prior 24-hr personal exposure to PNC/LDSA was related to higher FeNO in all children, particularly in those with respiratory symptoms. The associations with LDSA were slightly weaker than those with PNC, more likely due to the greater imprecision in the estimate of this surface assessed by calculation from PNC⁹. No other study considered LDSA in relation with FeNO.

The actual exposure must take into account not only outdoor (mostly traffic-related air pollution), but also indoor exposure, mainly due to families' activities (such cooking which led to the highest peaks of PNC) and habits/lifestyle. As previously reported⁸, children from PARIS-cohort spent daily 91% of the time indoor (at home and in the school), and these indoor exposure accounted for 88% of the total 24-hr PNC exposure⁸. Consequently the exposure assessment in all children's life-microenvironments is needed; this constitutes one of the strengths of our study. However it must be noted that the ambient temperature has not been assessed. Nevertheless, we used the season as a proxy for this parameter and exposure measurements covered equally all periods of the year⁸. Moreover there was no heat wave during the study period to expect a major implication of temperature on the studied association.

Studies investigating the relationship between UFP exposure and FeNO are scarce⁶. Only Buonanno et al. (2013) reported in 103 Italian children (healthy and asthmatic/atopic) aged 8-11 years, a crude positive correlation between UFPs (personal measurements) and FeNO only in subgroups of asthmatics, and to a lesser extent, in children allergic to house dust mites⁶. Although these associations were not adjusted on confounders, they are in line with our results. In both studies, asthmatics appear to be more vulnerable to personal UFP exposure. This is consistent with the fact that in asthmatics, compared to healthy subjects, the UFP lung deposition is increased¹⁰. The increased FeNO we observed in asthmatic/allergic children suggested an increased airway inflammation which is supported by the pathogenic mechanisms showing that inhalational exposure to UFP was commonly associated with enhanced pulmonary inflammation that is characterised by the rapid influx of neutrophils and induction of pro-inflammatory cytokines⁴. The relationship with eosinophilic inflammation suggested by our results needs to be better understood.

Finally, after adjustment our findings showed that 24-hr personal UFP exposure was positively associated with the level of FeNO in children and more particularly in those with asthma-like symptoms. Further studies are needed to better understand the potential impact of PNC/LDSA on FeNO in children, especially in those with asthma or allergy. Reducing UFP levels, especially indoors, could help to improve respiratory health of children.

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Table I

Comparison of characteristics and other parameters in children from PARIS birth-cohort (global results and stratified by type of persistent respiratory symptoms)

Characteristics	Global	Persistent respiratory symptoms		Comparison
		Yes	No	
	Arithmetic mean (SD)	Arithmetic mean (SD)	Arithmetic mean (SD)	t-Test p-value
Children	N = 71	N = 35	N = 36	
Anthropometric characteristics				
Age (years)	9.05 (0.20)	9.08 (0.25)	9.01 (0.13)	0.1282
Size (cm)	135.2 (6.0)	136.3 (5.8)	134.1 (6.1)	0.1188
Weight (kg)	31.0 (4.7)	31.9 (4.6)	30.2 (4.7)	0.1311
	N (%)	N (%)	N (%)	p-value
Sex	71	35	36	0.3900 [†]
Male	41 (57.8)	22 (62.9)	19 (52.8)	
Female	30 (42.2)	13 (37.1)	17 (47.2)	
Parents				
Ethnic origin of the mother	71	35	36	0.9999 [‡]
"Caucasian"	67 (94.4)	33 (94.3)	34 (94.4)	
"Other" (Asian / Black)	4 (5.6)	2 (5.7)	2 (5.6)	
Ethnic origin of the father	71	35	36	0.4930 [‡]
"Caucasian"	70 (98.6)	34 (97.1)	36 (100)	
"Other" (Asian / Black)	1 (1.4)	1 (2.9)	0 (0)	
Parents highest education level	71	35	36	0.4290 [‡]
"Secondary"	6 (8.5)	4 (11.4)	2 (5.6)	
"University"	65 (91.5)	31 (88.6)	34 (94.4)	
Parental history of allergy [§]	71	35	36	0.1056 [†]
Yes	44 (62)	25 (71.4)	19 (52.8)	
No	27 (38)	10 (28.6)	17 (47.2)	
Lifestyle and habits				
Parental smoking in the past 12 months	68	34	34	0.0719 [†]
Yes	14 (20.6)	4 (11.8)	10 (29.4)	
No	54 (79.4)	30 (88.2)	24 (70.6)	
Pets at home	71	35	36	0.4921 [†]
Yes	12 (16.9)	7 (20)	5 (13.9)	
No	59 (83.1)	28 (80)	31 (86.1)	
Localization of the home	71	35	36	0.5559 [†]
Inner Paris	37 (52.1)	17 (48.6)	20 (55.6)	
Suburbs	34 (47.9)	18 (51.4)	16 (44.4)	
Children respiratory / allergic status				
Diagnosed asthma and/or allergic rhinitis (until 9 years)	71	35	36	<0.0001 [†]
Yes	29 (40.9)	28 (80)	1 (2.8)	
No	42 (59.1)	7 (20)	35 (97.2)	
Diagnosed eczema (until 9 years)	70	34	36	0.1361 [†]
Yes	19 (27.1)	12 (35.3)	7 (19.4)	
No	51 (72.9)	22 (64.7)	29 (80.6)	
Allergic sensitization to aeroallergens (at 9 years) [†]	70	35	35	0.2289 [†]
Yes	31 (44.3)	18 (51.4)	13 (37.1)	
No	39 (55.7)	17 (48.6)	22 (62.9)	
Lung function and FeNO	N total	Adjusted mean	Adjusted mean	t-Test

	MA [95% CI]	[95% CI]	[95% CI]	p-value
FeNO (ppb)	71 19.5 [15.7; 23.3]	16.8 [9.6; 24]	18.4 [9.7; 27.2]	0.7291 ^{ll, #} (N = 66)
FEV ₁ (L)	70 1.877 [1.82; 1.94]	1.806 [1.734; 1.879]	1.986 [1.899; 2.072]	0.0015 ^{††} (N = 66)
FeNO threshold values	Total N (%)	N (%)	N (%)	Chi-2 Test p-value
FeNO (ppb)	71	35	36	0.0742 ^{ll, #}
< 20 ppb	48 (67.6)	19 (54.3)	29 (80.6)	
≥ 20 ppb	23 (32.4)	16 (45.7)	7 (19.4)	
FeNO (ppb)	71	35	36	0.1957 ^{ll, #}
< 35 ppb	63 (88.7)	29 (82.9)	34 (94.4)	
≥ 35 ppb	8 (11.3)	6 (17.1)	2 (5.6)	
Particulate exposure	N Total AM (SDa) [GM]	N AM (SDa) [GM]	N AM (SDa) [GM]	t-Test p-value ^{††}
PNC (pt/cm ³)	71 14 259 (6 314) [13 227]	35 14 356 (7 163) [13 095]	36 14 164 (5 467) [13 227]	0.8948
LDSA (μm ² /cm ³)	71 35.01 (15.05) [32.46]	35 35.93 (16.44) [32.79]	36 34.11 (13.73) [31.82]	0.7163
BC (ng/m ³)	70 1 447 (559) [1 339]	35 1 466 (523) [1 367]	35 1 429 (601) [1 300]	0.6441
Season of measurements	Total N (%)	N (%)	N (%)	p-value
Cold (autumn–winter)	71 36 (50.7)	35 20 (57.1)	36 16 (44.4)	0.2846 [†]
Warm (spring–summer)	35 (49.3)	15 (42.9)	20 (55.6)	

[†] Comparison between subgroups by Chi-2 test.

[‡] Comparison between subgroups by Fisher Exact test.

[§] If the mother or the father was "allergic" (asthma / eczema / allergic rhinitis).

[¶] Allergic sensitization to aeroallergens (IgE testing).

^{||} Adjusted model on: age (years), sex (male vs. female), height (cm), sensitization to aeroallergens (yes/no), medication to improve breathing in the past year (yes/no), forced expiratory volume in one second (FEV₁; L), parental smoking in the last year (yes/no), parental history of allergy (asthma/eczema/allergic rhinitis; yes/no), season (cold vs. warm).

p-value was calculated on log-transformed FeNO values.

[#] p-value was calculated on log-transformed FeNO values.

^{††} Model adjusted on the same variables as ^(||) excepting FEV₁.

^{††} p-value was calculated on log-transformed exposure values.

Notations: AM - arithmetic mean; BC – black carbon; CI - confidence interval; FeNO – Fractional exhaled nitric oxide; FEV₁ - Forced expiratory volume in one second; GM - geometric mean; LDSA – lung-deposition surface area; PNC – particle number concentration; SDa - standard deviation of AM.

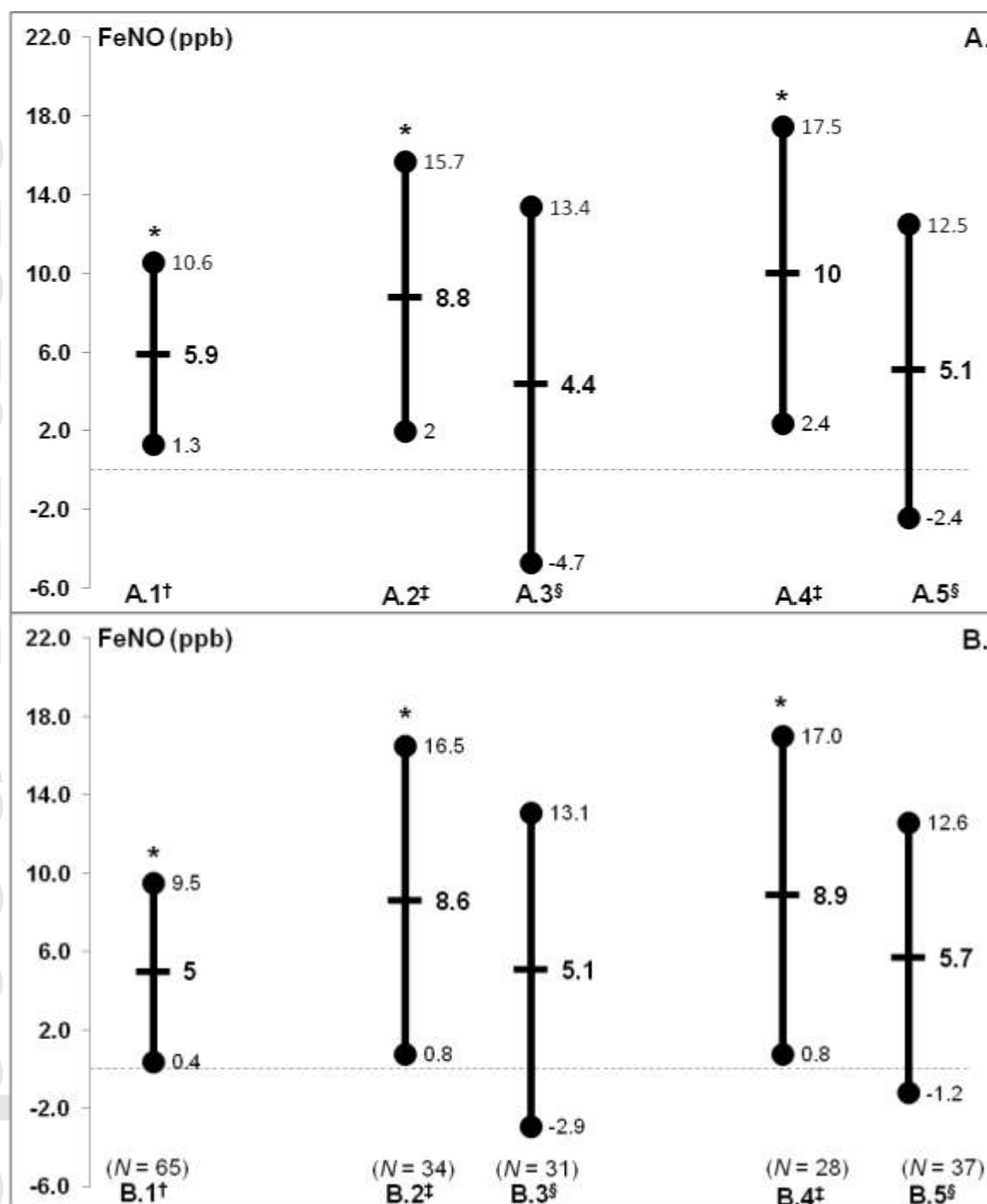


Figure 1.

Relationship between exposure concentrations to PNC (Figure A) / LDSA (Figure B) and FeNO (ppb) in children from PARIS birth-cohort: global results (Figure A.1 and B.1) and stratified by type of children with (Figure A.2 and B.2) and without (Figure A.3 and B.3) persistent respiratory symptoms, and with (Figure A.4 and B.4) and without (Figure A.5 and B.5) diagnosed asthma and/or allergic rhinitis

The sticks delimit the lower and upper limits of the 95% confidence interval (95% CI), the small lines indicate the β coefficients of the linear regression models and * indicate the significance level: * $p < 0.05$.

[†] Adjusted model on: age (years), sex (male vs. female), height (cm), sensitization to aeroallergens (yes/no), persistent respiratory symptoms (yes/no), medication to improve breathing in the past year (yes/no), forced expiratory volume in one second (FEV₁; L), parental smoking in the last year (yes/no), parental history of allergy (asthma/eczema/allergic rhinitis; yes/no), season (cold vs. warm) and black carbon exposure (BC; ng/m³).

[‡] Adjusted model on the same variables as ^(†) except persistent respiratory symptoms.

[§] Adjusted model on the same variables as ^(†) except persistent respiratory symptoms and medication to improve breathing in the past year.

Notations: PNC – particles number concentrations; LDSA – lung deposition surface area; FeNO – fraction of exhaled nitric oxide.