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Alexandra-Cristina Paunescu[a], Maribel Casas[b,c,d], Amparo Ferrero[d,e], Pau Pañella[b,d], Nicolas Bougas[a], Nicole Beydon[f], Jocelyne Just[g], Guillaume Lezmi[h], Jordi Sunyer[b,c,d], Ferran Ballester[d,e,i], Isabelle Momas[a,j,*]

[a] Inserm U1153-CRESS HERA Team, Faculté de Pharmacie de Paris, Université Paris Descartes, France
[b] ISGlobal, Barcelona, Spain
[c] Universitat Pompeu Fabra, Barcelona, Spain
[d] CIBER Epidemiologia y Salud Publica (CIBERESP), Spain
[e] Epidemiology and Environmental Health Joint Research Unit, FISABIO-Universitat Jaume I-Universitat de València, Spain
[f] Unité Fonctionnelle de Physiologie - Explorations Fonctionnelles Respiratoires, AP-HP, Hôpital d'Enfants Armand-Trousseau, Paris, France
[g] Service d'Allergologie Pédiatrique, AP-HP, Hôpital d'Enfants Armand-Trousseau, Paris, France
[h] Service de Pneumologie et d'Allergologie Pédiatriques, AP-HP, Hôpital Necker-Enfants Malades, Université Paris Descartes, Paris, France
[i] School of Nursing, University of Valencia, Spain
[j] Ville de Paris, Direction de l'Action Sociale, de l'Enfance et de la Santé, Cellule Cohorte PARIS, Paris, France

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ABSTRACT

Background: Few studies have investigated the 24-hour respiratory health effects of personal black carbon (BC) and ultrafine particles (UFP) exposure in schoolchildren. The objective of this study was to investigate these associations with the lung function in children 10-years old with and without persistent respiratory symptoms.
Methods: We conducted a cross-sectional study in 305 children (147 and 158 with and without persistent respiratory symptoms, respectively) from three European birth-cohorts: PARIS (France) and INMA Sabadell and Valencia (Spain). Personal 24-hour measurements of exposure concentrations to BC and UFP were performed by portable devices, before lung function testing. Forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and the fraction of exhaled nitric oxide (FeNO) were determined.
Results: There was no association of UFP with lung function parameters or FeNO whereas the increase in 24-hour BC exposure concentrations was related to a statistically significant decrease in lung function parameters only among children with persistent respiratory symptoms [−96.8 mL (95% Confidence Interval CI: −184.4 to −9.1 mL) in FVC, and −107.2 mL (95% CI: −177.5 to −36.9 mL) in FEV_1 for an inter-quartile range of 1160 ng/m^3 exposure increase]. A significant positive association between BC and FeNO was observed only in children with persistent respiratory symptoms with current wheezing and/or medication to improve breathing [FeNO increases with +6.9 ppb (95% CI: 0.7 to 13.1 ppb) with an inter-quartile range BC exposure increase].
Conclusion: Children suffering from persistent respiratory symptoms appear to be more vulnerable to BC exposure.

1. Introduction

Exposure to ambient air particulate matter (PM) produced by a wide variety of natural and anthropogenic activities (Poschl, 2005) is associated with various adverse health effects, especially pulmonary, cardiovascular, and cancer (Cohen et al., 2017; Mukherjee and Agrawal, 2018; WHO, 2016). Among parameters that play an important role for eliciting health effects are the size and surface of particles, their number and their composition as they can absorb and transfer a multitude of pollutants (HEI Perspectives, 2013; Kampa and Castanas, 2008; Valavanidis et al., 2008).

Smaller particles such as black carbon (BC, constituent of $PM_{2.5}$ resulting from the incomplete combustion of biomass, oil/diesel) (Janssen et al., 2012), and ultrafine particles (UFP, PM < 100 nm) are of recent health interest (Heinzerling et al., 2016). They are able to reach lung alveoli (Kampa and Castanas, 2008) and are toxic through

* Corresponding author at: Inserm U1153-CRESS, HERA Team, Faculté de Pharmacie de Paris, 4 Avenue de l'Observatoire, 75006 Paris, France.
E-mail address: Isabelle.Momas@parisdescartes.fr (I. Momas).

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mechanisms of oxidative stress, cell signalling and activation, and release of mediators initiating inflammatory processes in the respiratory tract and in the cardio-vascular system (Kampa and Castanas, 2008; Meldrum et al., 2017).

Children with lung disease are likely to be more susceptible to lung function changes following exposure to PM compared to healthy children (Paulin and Hansel, 2016). Studies focusing on the short-term effects of PM on objective measurements of lung function in children have mainly dealt with PM_{10} and $PM_{2.5}$ (Li et al., 2012; Paulin and Hansel, 2016) and more rarely, BC (Cornell et al., 2012; Jacobson et al., 2014; Yoda et al., 2017). While a series of publications have already shown the relationship between PM_{10}, $PM_{2.5}$ and BC exposures and decreased lung function (Gauderman et al., 2007; Jacobson et al., 2014; Paulin and Hansel, 2016; Urman et al., 2014; Ward and Ayres, 2004; Xu et al., 2018; Yoda et al., 2017), they generally used ecological exposure measurements from the air quality monitoring network and rarely personal measurements (Trenga et al., 2006). Handheld devices were recently developed which can provide personal measurements of different pollutants, including BC and UFP, integrated on all the microenvironments attended by individuals. However, few studies have investigated the short-term respiratory health effects on lung function and/or on fractional exhaled nitric oxide (FeNO, as marker of bronchial inflammation), of BC (Jung et al., 2017) and/or UFP exposure (Buonanno et al., 2013) measured by personal monitors in schoolchildren.

In this context, the aim of this study was to investigate the relationship between personal measurements of exposure concentrations to BC and UFP and lung function and FeNO in 10-year-old children with and without persistent respiratory symptoms from three European birth-cohorts: PARIS (*Pollution and Asthma Risk*: *an Infant Study*) in Paris (France) and INMA (*INfancia y Medio Ambiente*) in Sabadell and Valencia (Spain).

2. Methods

2.1. Study design

This research was a cross-sectional study nested in three birth-cohorts. The study consisted of a personal 24-hour measurement of BC and UFP exposure concentrations in children from Paris (Paunescu et al., 2017), Sabadell (Pañella et al., 2017) and Valencia, prior to a health check-up (including lung function testing and FeNO measurement). The study took place between June 2014 and December 2015 in Paris, between January 2014 and June 2015 in Sabadell, and between November 2015 and October 2016 in Valencia.

2.2. Study population

Participants were children respectively with and without persistent respiratory symptoms defined according to the information available in self-administered questionnaires till the age of 6/7 years, in the three birth-cohorts and whose parents accepted a 9/11-year (depending on cohort) health check-up and gave their informed consent.

The **PARIS**-cohort consists of 3840 full-term healthy newborn babies recruited between February 2003 and June 2006 in five Parisian maternity hospitals, their parents having to reside in inner Paris or in the suburbs (Clarisse et al., 2007).

The **INMA**-cohort is composed of 3768 newborns (Guxens et al., 2012) whose mothers were recruited in seven geographical areas of Spain during the first prenatal visit in the main public hospital or health centre in each zone. This study deals more specifically with those recruited in Sabadell between July 2004 and July 2007 and in Valencia (34 municipalities within Valencia province) between November 2003 and June 2005.

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 6/7 years. **Children without persistent respiratory symptoms** were participants without any lower airways respiratory symptoms between the ages of 12/18 months and 6/7 years.

In each cohort, around 50 children with and 50 children without persistent respiratory symptoms were recruited among children reaching their 8th year and meeting the inclusion criteria above-mentioned. They were selected at random leading to the recruitment of 149 children with persistent respiratory symptoms (45 from Paris, 50 from Sabadell, and 54 from Valencia) and 160 children without persistent respiratory symptoms (51 from Paris, 50 from Sabadell, and 59 from Valencia).

2.3. Personal exposure measurements

Portable devices were used to measure continuously BC concentrations and UFP for 24-h with measuring points every minute. The methodology was previously published (Pañella et al., 2017; Paunescu et al., 2017). The 24-h exposure time was chosen because of the technical performance of the measuring devices used.

Before starting the field study, we carried out laboratory validation experiments for our devices and we conducted a pilot study applying the design of the study to a group of 15 volunteers from the Paris area in order to ensure the correct procedures (Paunescu et al., 2017).

For **BC**, an Aethalometer-microAeth® Model AE51 (AethLabs, San Francisco, California, USA) that analyzes the BC concentration expressed as ng/m^3 was used (AethLabs, 2011), with a precision assessed at 19.4% in our previous study (Paunescu et al., 2017).

For **UFP**, a DiSCmini® (Diffusion Size Classifier miniature, Testo SE & Co. KGaA, Titisee-Neustadt, Germany) was used. It gives the number of particles per cubic centimeter of aspirated air ("particle number concentration", PNC, pt/cm^3), with an accuracy around 30% according to the manufacturer (Matter Aerosol, 2012). Our preliminary study showed that the computed precision of the measured values by DiSCmini® for aerosols containing a different number of particles per cm^3 of air with particle diameters varying between 30 and 100 nm was 24.8% (Paunescu et al., 2017). DiSCmini® also automatically estimates using an internal algorithm, the surface of UFP supposed to come into contact with the lung mucosa ("lung-deposited surface area", LDSA, $\mu m^2/cm^3$). The LDSA concentration is defined as the particle surface area concentration per unit volume of air, weighted by the deposition probability in the lung. The precision for particle sizes between 20 and 240 nm was evaluated as smaller than ~20% (Fierz et al., 2011).

2.4. Lung function and airway inflammation determination

Spirometry tests (i.e. flow-volume curves) were carried out by trained technicians, in two tertiary referral children hospitals in Paris, in a Primary Care Center in Sabadell and in the FISABIO-Public health research Center in Valencia. The measured maximum expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) values were reported to theoretical values based on sex, age, height and ethnicity, according to the Global Lung Initiative equations (Quanjer et al., 2012) and expressed as a percentage of the predicted value. The measurement of the fraction of exhaled nitric oxide (FeNO) was carried out by the direct "On-line" method using a NIOX MINO® electrochemical nitric oxide (NO) analyzer (Circassia Pharmaceuticals Inc., Chicago, USA). Pulmonary function measurements were performed immediately, within 1 h after the end of the exposure measurements. The children did not have any respiratory infections at the time of the check-up. The parents received information to stop the drug treatment for airway disease of children, 24-h before lung function testing (except in cases of serious disease and doctor contraindication). Weight (kg) and height (cm) were measured.

A health questionnaire documented respiratory/allergic morbidity

of children and their treatment [ever doctor diagnosis of asthma/eczema/allergic rhinitis or medication against rhinitis; wheezing in the chest in the last year; medication to improve breathing in the last year (yes/no)]. Other data were collected such as: information at birth/early childhood [caesarean delivery; breastfeeding during the first 3 months of life; mother's smoking during pregnancy (yes/no)]; socio-demographic characteristics of parents [ethnic origin of the mother/father (Caucasian vs. Other); mothers'/fathers' level of education (university vs. primary, secondary)]; parental history of allergy (asthma/eczema/allergic rhinitis (yes/no)); lifestyle and habits at home [parental smoking in the last year, pets at home, gas cookers, heating or water heater gas/fuel (yes/no)].

2.5. Statistical analysis

Normality of exposure variables was tested and if necessary, the variables were log-transformed. Distributions were provided for continuous variables: exposures (BC, PNC and LDSA), and outcome variables (lung function parameters, % of predicted values, and FeNO). The dependent variables were also dichotomized according to the reference ATS 2005/ERS 2011 criteria (Pellegrino et al., 2005), as follows: % of predicted FVC (< 85% vs. ≥85%), % of predicted FEV_1 (< 85% vs. ≥85%), FEV_1/FVC ratio (< 80% vs. ≥80%) and FeNO (≥20 ppb vs. < 20 ppb) (Dweik et al., 2011).

Comparisons between cohorts were tested with application of the Bonferroni Adjustment for Multiple Comparisons test; comparisons between children with and without persistent respiratory symptoms from the three pooled cohorts 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 lung function to their particle exposure, adjusting for sex, age, height, weight, and the potential confounders [especially cohort and season of measurements (cold, autumn-winter vs. warm, spring-summer)]. The inter-quartile range (IQR between first and third quartile) of the exposure variables was used to express the subsequent change in lung function parameters and FeNO levels. Two multivariate models including a single exposure or two-pollutant were alternatively built. Pearson correlations between exposure variables were calculated. Interactions (*p*-value for interaction < 0.10) were tested between exposure variables and "persistent respiratory symptoms" status, current symptoms and/or medication, with the aim of studying possible modifying effects. The significance level was 0.05. Analyses were performed using Stata 11 (StataCorp LP, College Station, Texas, USA) software.

3. Results

During the health check-up at 9/11 years, among 309 recruited children 92% were able to realize lung function testing (for FVC and FeNO measurements, respectively: 141/149 and 137/149 children with persistent respiratory symptoms; 144/160 and 147/160 children without persistent respiratory symptoms). BC concentrations were recorded for 269 (87%) and PNC/LDSA for 295 (96%) children. Finally the results of this study dealt with 305 children presenting data for at least one exposure (BC or PNC) and one explained variable (lung function parameters or FeNO): 147 children with persistent respiratory symptoms and 158 children without persistent respiratory symptoms. Until the age of 6/7 years about 42% and 44% of children with persistent respiratory symptoms were diagnosed with asthma and eczema, respectively and 69% had a personal history of allergy (asthma/eczema/allergic rhinitis or reported taking medication against rhinitis). At the time of lung function testing (9/11 years of age), 35% of children with persistent respiratory symptoms still reported wheezing in the chest and 43% had taken medication to improve their breathing in the past year.

Participants from the three cohorts were different with regard to several characteristics, such as age (children were older in Valencia),

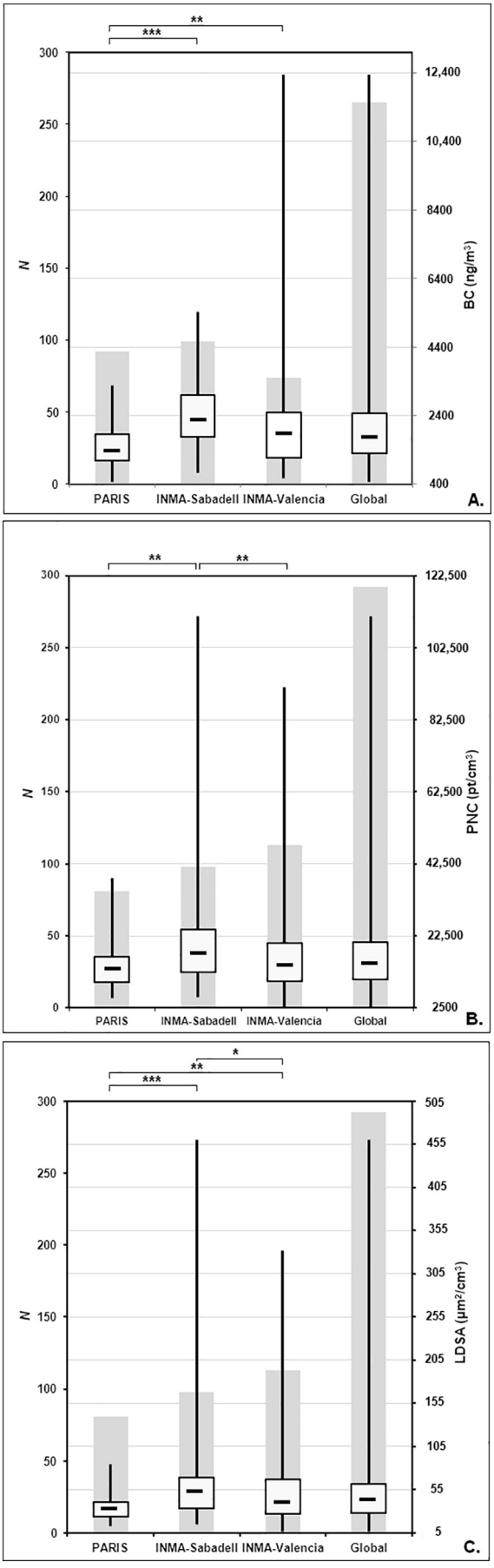

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Fig. 1. Plots of exposure concentrations to A. black carbon (ng/m^3), B. particles number concentrations (pt/cm^3) and C. LDSA (μm^2/cm^3) in children from PARIS, INMA-Sabadell and INMA-Valencia cohorts.
Each box represents the first and third quartile concentrations, the whiskers indicate the minimum and maximum concentration values, and the small lines indicate the geometric means. The shadow bars represent the number of participants. The lines above the graphs represent the side-by-side comparisons between cohorts and p is the significance level resulting from the comparisons: $*p < 0.05$; $**p < 0.01$; $***p < 0.0001$.
Notations: BC – black carbon; PNC – particles number concentrations; LDSA – lung deposition surface area; N – number of participants.

habits and lifestyle at home (breastfeeding, smoking, presence of pets and gas/fuel heating more frequent in Spanish cohorts), educational level of parents (higher level in Paris) and parental history of allergy (more frequent in Sabadell) (Appendix A). The frequency of doctor-diagnosed asthma and eczema were statistically different between cohorts, with more asthma diagnosed in Paris, and more eczema in Spanish children, particularly in Valencia (Appendix B). Lung function parameters were different between cohorts: Parisians had the highest average of % of predicted FEV_1, and children from Sabadell, the lowest FVC and FEV_1 (Appendix B). However, regarding the adjusted FeNO values, children from the three cohorts had similar values (Appendix B). Spanish children, especially Sabadell's ones, had the highest exposure concentrations (Fig. 1; Appendix C). Exposure variables were moderately correlated [BC and PNC $r = 0.44$; BC and LDSA $r = 0.60$, $p < 0.0001$, $n = 252$].

The two groups of children with and without persistent respiratory symptoms at age of 9/11 years were comparable with regard to individual characteristics (Table I). Regarding lung function, children with persistent respiratory symptoms had respectively the lowest averages of lung function parameters and the highest proportion of FEV_1/FVC ratio < 80%, and the highest FeNO values (Table II). The exposure to BC and PNC/LDSA did not differ between children with and without persistent respiratory symptoms, although PNC and LDSA were slightly higher in persistent respiratory symptoms children (Table III).

"Persistent respiratory symptoms" status had no modifying effect on the relationship between exposure to BC or PNC/LDSA and lung function parameters or FeNO (p-value of the interaction term ≥0.30 and 0.14, respectively). Higher exposure to BC (increase per IQR of 1160 ng/m^3) was associated with reduced FVC, FEV_1 and percentages of their predicted values in children from both groups, particularly in those with persistent respiratory symptoms (Table IV), and more specifically in children with persistent respiratory symptoms with "current wheezing and/or medication to improve breathing" (p-value of the interaction term ≥0.18) (Table V). These effects remained significant after adjustment on PNC (Appendices D and E). No association was observed between PNC or LDSA and lung function parameters (Table IV).

No association was observed between exposure to BC or PNC/LDSA and FeNO in children with or without persistent respiratory symptoms (Table IV). Only among children with persistent respiratory symptoms and "current wheezing and/or medication to improve breathing" (interaction term p-value of 0.06), higher exposure to BC was associated with increased FeNO (Table V).

4. Discussion

Our study shows that the increase in 24-h BC exposure concentrations was related to lower lung function parameters in all children, particularly in children with persistent respiratory symptoms. A significant positive association between BC concentrations and FeNO was observed only in children with persistent respiratory symptoms and current wheezing and/or medication to improve breathing. No association was observed between PNC or LDSA and lung function or FeNO.

No team, except Jung et al. (2017) who described the effect of acute

Table I
Comparison of characteristics of children from PARIS, INMA Sabadell and Valencia pooled cohorts with and without persistent respiratory symptoms.

Characteristics	Children		Comparison
	With persistent respiratory symptoms	Without persistent respiratory symptoms	
	Arithmetic mean (SD)	Arithmetic mean (SD)	t-Test p-Value
	N = 147	N = 158	
Anthropometric characteristics			
Age (years)	9.5 (0.9)	9.7 (0.9)	0.118
Size (cm)	137.9 (7.4)	138.2 (7.1)	0.674
Weight (kg)	35.53 (8.81)	35.42 (8.67)	0.909
BMI (kg/m^2)	18.5 (3.4)	18.4 (3.3)	0.659
Birth weight (kg)	3.29 (0.51)	3.30 (0.45)	0.817
Other characteristics	N (%)	N (%)	p-Value
Cohort	147	158	0.834[a]
PARIS	43 (29.3)	50 (31.7)	
INMA-Sabadell	50 (34.0)	49 (31.0)	
INMA–Valencia	54 (36.7)	59 (37.3)	
Sex	147	158	0.906[a]
Male	81 (55.1)	86 (54.4)	
Female	66 (44.9)	72 (45.6)	
Information at birth			
Caesarean delivery	140	154	0.869[a]
Yes	28 (20.0)	32 (20.8)	
No	112 (80.0)	122 (79.2)	
Breastfeeding during the first 3 months of life	147	158	0.736[a]
Yes	93 (63.3)	97 (61.4)	
No	54 (36.7)	61 (38.6)	
Mother's smoking during pregnancy	142	158	0.380[a]
Yes	26 (18.3)	23 (14.6)	
No	116 (81.7)	135 (85.4)	
Socio-demographic characteristics of parents			
Ethnic origin of the mother	143	158	0.999[b]
"Caucasian"	140 (97.9)	155 (98.1)	
"Other" (Asian/Black/Gipsy/Native American)	3 (2.1)	3 (1.9)	
Ethnic origin of the father	142	158	0.670[b]
"Caucasian"	139 (97.9)	156 (98.7)	
"Other" (Asian/Black/Gipsy/Native American)	3 (2.1)	2 (1.3)	
Mothers' level of education	145	158	0.488[a]
"Primary"	26 (17.9)	21 (13.3)	
"Secondary"	51 (35.2)	55 (34.8)	
"University"	68 (46.9)	82 (51.9)	
Fathers' level of education	145	157	0.345[a]
"Primary"	44 (30.3)	36 (22.9)	
"Secondary"	45 (31.0)	54 (34.4)	
"University"	56 (38.6)	67 (42.7)	
Parental history of allergy (asthma/eczema/allergic rhinitis)[c]	141	142	0.101[a]
Yes	90 (63.8)	77 (54.2)	
No	51 (36.2)	65 (45.8)	
Lifestyle			
Parental smoking in the past 12 months	146	154	0.514[a]
Yes	46 (31.5)	54 (35.1)	
No	100 (68.5)	100 (64.9)	
Pets at home	147	158	0.071[a]
Yes	67 (45.6)	56 (35.4)	
No	80 (54.4)	102 (64.6)	

(*continued on next page*)

Table I (*continued*)

Characteristics	Children		Comparison
	With persistent respiratory symptoms	Without persistent respiratory symptoms	
	Arithmetic mean (SD)	Arithmetic mean (SD)	*t*-Test *p*-Value
Gas cookers	147	156	0.513[a]
Yes	61 (41.5)	59 (37.8)	
No	86 (58.5)	97 (62.2)	
Heating or water heater gas/fuel	137	149	0.686[a]
Yes	112 (81.8)	119 (79.9)	
No	25 (18.3)	30 (20.1)	

[a] Comparison between cohorts by the Chi^2 test.
[b] Comparison between cohorts by the Fisher Exact test.
[c] If the mother or the father was "allergic".

Table II
Comparison of lung function parameters and FeNO in children from PARIS, INMA Sabadell and Valencia pooled cohorts with and without persistent respiratory symptoms.

Lung function		Children		Comparison
		With persistent respiratory symptoms	Without persistent respiratory symptoms	
Continuous variables	*N* total	Adjusted mean [95% CI]	Adjusted mean [95% CI]	*t*-Test *p*-Value
Lung function parameters				
FVC (L)	285	2.254 [2.208; 2.300]	2.282 [2.237; 2.326]	0.385[a]
FEV_1 (L)	298	1.886 [1.847; 1.926]	1.957 [1.919; 1.995]	0.011[a]
FEV_1/FVC	285	0.834 [0.820; 0.848]	0.865 [0.852; 0.878]	0.001[a]
% predicted FVC	285	101.5 [99.3; 103.6]	102.2 [100.1; 104.4]	0.637[b]
% predicted FEV_1	298	98.7 [96.7; 100.8]	102.12 [100.1; 104.2]	0.022[b]
FeNO (ppb)	284	20.3 [17.6; 22.9]	15.7 [13.2; 18.1]	0.012[a]
Dichotomized variables		*N* (%)	*N* (%)	Chi^2 test *p*-Value
FEV_1/FVC		141	144	0.0004[a]
< 0.80		38 (26.9)	17 (11.8)	
≥0.80		103 (73.1)	127 (88.2)	
% predicted FVC		141	144	0.089[b]
< 85%		15 (10.6)	7 (4.9)	
≥85%		126 (89.4)	137 (95.1)	
% predicted FEV_1		146	152	0.142[b]
< 85%		16 (11)	9 (5.9)	
≥85%		130 (89)	143 (94.1)	
FeNO (ppb)		137	147	0.002[a]
< 20 ppb		89 (65)	120 (81.6)	
≥20 ppb		48 (35)	27 (18.4)	

Notations: CI - confidence interval; FVC - Forced vital capacity; FEV_1 - Forced expiratory volume in 1 s; FeNO – Fraction of exhaled nitric oxide.
[a] Adjusted model on: age (years), sex (male vs. female), height (cm), weight (kg), cohort (Valencia, Sabadell, Paris - reference), and season (cold – autumn and winter vs. warm – spring and summer).
[b] Adjusted model on: weight (kg), cohort (Valencia, Sabadell, Paris - reference), and season (cold vs. warm).

Table III
Comparison of exposure concentrations to BC (ng/m^3), PNC (pt/cm^3) and LDSA (μm^2/cm^3) in children from PARIS, INMA Sabadell and Valencia pooled cohorts with and without persistent respiratory symptoms.

Particulate exposure	Children		Comparison *t*-Test
	With persistent respiratory symptoms	Without persistent respiratory symptoms	
	N AM (SDa) [GM]	*N* AM (SDa) [GM]	*p*-Value[a]
BC (ng/m^3)	129 1983 (823) [1816]	136 2122 (1448) [1789]	0.810
PNC (pt/cm^3)	142 18,062 (12,724) [15,598]	150 15,762 (8431) [13,890]	0.053
LDSA (μm^2/cm^3)	142 54.80 (50.79) [44.02]	150 45.68 (30.81) [38.67]	0.064

Notations: AM - arithmetic mean; SDa - standard deviation of AM; GM - geometric mean; BC – black carbon; PNC – particle number concentration; LDSA – lung-deposition surface area.
[a] Calculated on log-transformed values.

BC exposure on epigenetic changes and FeNO (Jung et al., 2017), documented in children the respiratory effects of BC assessed by personal measurements. The authors considered either outdoor BC measured continuously by stations from monitoring networks (Cornell et al., 2012; De Prins et al., 2014) or by devices placed at the children's schools (Jacobson et al., 2014; Sarnat et al., 2012; Yoda et al., 2017) or indoor BC in schools (Sarnat et al., 2012) or at home (Cornell et al., 2012).

Only few studies dealt with the impact of BC on lung function: peak expiratory flow (PEF) (Jacobson et al., 2014; Yoda et al., 2017), FEV_1 (Yoda et al., 2017) or FEV_1/FVC (Cornell et al., 2012). Two panel studies showed associations between outdoor BC at fairly low levels (IQR ≤1 μg/m^3) and short-term changes in PEF (Jacobson et al., 2014), FEV_1 (Yoda et al., 2017) in mainly healthy children. Thus Yoda et al. (2017) reported a significant decrease in FEV_1 (−27.28 mL; 95% CI: −54.1 to −0.46; $p = 0.046$) measured every morning for about 1 month, with an IQR increase of 0.23 μg/m^3 outdoor 24-h BC, before the pulmonary function test, in 43 healthy Japanese children aged 15–16 years living in an isolated island (Yoda et al., 2017). Although direct comparisons are not possible given differences in exposure metrics and study designs, our findings are consistent with these previous studies, confirming for an IQR increase in personal BC exposure, lowering lung function parameters of the same order of magnitude. We did not find any association with FEV_1/FVC ratio, like Cornell et al. (2012) in a case-control study in 218 New York City (NYC) children aged 7–8 years old, with high or low prevalence of asthma (Cornell et al., 2012).

The greater association we observed in children with persistent respiratory symptoms supports that these are more vulnerable to air pollution, as previously described for asthmatics (Heinzerling et al., 2016; Li et al., 2012; Paulin and Hansel, 2016). BC seems to have an acute effect on the inflammation of the airways which may be involved in a reduction of pulmonary function (Yoda et al., 2017). Using personal BC measurements, we corroborate the short-term positive associations previously reported between indoor BC at fairly low levels (≤1.6 μg/m^3) and markers of airway inflammation in exhaled breath in asthmatic children (Cornell et al., 2012; Sarnat et al., 2012). In our study, we found a significant relationship between 24-h BC exposure concentrations and FeNO, only in children currently suffering from asthma-like symptoms. In these children, even a small increase in BC

Table IV
Relationship between exposure concentrations to BC/PNC/LDSA and lung function parameters/FeNO in children from PARIS, INMA Sabadell and Valencia pooled cohorts with and without persistent respiratory symptoms.

	IQR increase of BC (ng/m^3)							
	Children with persistent respiratory symptoms				Children without persistent respiratory symptoms			
	N	β (SE)	95% CI	*p*-Value	*N*	β (SE)	95% CI	*p*-Value
Lung function parameters								
FVC (mL)	123	−96.8 (44.2)	[−184.4; −9.1]	0.031[a]	123	−21.2 (18.3)	[−57.4; 15.0]	0.248[a]
FEV_1 (mL)	128	−107.2 (35.5)	[−177.5; −36.9]	0.003[a]	131	−30.7 (16.3)	[−62.9; 1.5]	0.062[a]
FEV_1/FVC	123	−12.3 (12.1)	[−36.3; 11.7]	0.310[a]	123	−10.2 (5.2)	[−20.4; 0.9]	0.052[a]
% predicted FVC	123	−4.70 (2.20)	[−9.06; −0.35]	0.035[b]	123	−0.68 (0.86)	[−2.38; 1.02]	0.431[b]
% predicted FEV_1	128	−5.52 (1.995)	[−9.48; −1.55]	0.007[b]	131	−1.37 (0.84)	[−3.03; 0.28]	0.103[b]
FeNO (ppb)	122	1.59 (2.10)	[−2.58; 5.77]	0.451[a]	128	−0.65 (1.12)	[−2.88; 1.57]	0.562[a]
	IQR increase of PNC (pt/cm^3)							
	Children with persistent respiratory symptoms				Children without persistent respiratory symptoms			
	N	β (SE)	95% CI	*p*-Value	*N*	β (SE)	95% CI	*p*-Value
Lung function parameter								
FVC (mL)	136	2.8 (20.9)	[−38.5; 44.1]	0.894[a]	136	−2.7 (25.2)	[−52.5; 47.1]	0.915[a]
FEV_1 (mL)	141	−4.5 (17.7)	[−39.6; 30.6]	0.801[a]	144	−5.8 (22.2)	[−49.7; 38.1]	0.796[a]
FEV_1/FVC	136	2.1 (6.2)	[−10.2; 14.5]	0.732[a]	136	4.0 (7.7)	[−11.2; 19.2]	0.607[a]
% predicted FVC	136	0.27 (1.01)	[−1.73; 2.27]	0.790[b]	136	−0.29 (1.13)	[−2.53; 1.95]	0.797[b]
% predicted FEV_1	141	−0.05 (0.96)	[−1.95; 1.86]	0.963[b]	144	−0.51 (1.12)	[−2.71; 1.70]	0.649[b]
FeNO (ppb)	135	−0.05 (1.11)	[−2.24; 2.15]	0.967[a]	140	−2.54 (1.56)	[−5.63; 0.54]	0.105[a]
	IQR increase of LDSA (μm^2/cm^3)							
	Children with persistent respiratory symptoms				Children without persistent respiratory symptoms			
	N	β (SE)	95% CI	*p*-Value	*N*	β (SE)	95% CI	*p*-Value
Lung function parameter								
FVC (mL)	136	−39.0 (17.3)	[−37.9; 30.3]	0.824[a]	136	−2.1 (22.7)	[−45.0; 43.0]	0.928[a]
FEV_1 (mL)	141	−12.8 (14.7)	[−42.0; 16.3]	0.386[a]	144	−8.9 (20.5)	[−49.4; 31.7]	0.666[a]
FEV_1/FVC	136	0.2 (5.2)	[−10.0; 10.4]	0.969[a]	136	−0.4 (6.9)	[−14.1; 13.3]	0.954[a]
% predicted FVC	136	−0.12 (0.84)	[−1.78; 1.53]	0.884[b]	136	−0.18 (1.03)	[−2.21; 1.86]	0.863[b]
% predicted FEV_1	141	−0.54 (0.80)	[−2.12; 1.04]	0.499[b]	144	−0.50 (1.04)	[−2.54; 1.55]	0.634[b]
FeNO (ppb)	135	−0.13 (0.92)	[−1.94; 1.69]	0.892[a]	140	−1.91 (1.42)	[−4.72; 0.90]	0.180[a]

Note: Interquartile range (IQR): BC 1160 ng/m^3; PNC 10,195 pt/cm^3 and LDSA 33.57 μm^2/cm^3.
[a] Adjusted model on: age (years), sex (male vs. female), height (cm), weight (kg), cohort (Sabadell, Valencia, Paris - reference), and season (cold vs. warm).
[b] Adjusted model on: weight (kg), cohort (Sabadell, Valencia, Paris - reference), and season (cold vs. warm).

Table V
Relationship between exposure concentrations to BC and lung function parameters/FeNO in children with persistent respiratory symptoms from PARIS, INMA-Sabadell and INMA-Valencia pooled cohorts, depending on whether they had or not "wheezing in the chest and/or medication to improve breathing in the past 12 months".

	IQR increase of BC (ng/m^3)							
	Children with persistent respiratory symptoms							
	With wheezing and/or medication				Without wheezing and/or medication			
	N	β (SE)	95% CI	*p*-Value	*N*	β (SE)	95% CI	*p*-Value
Lung function parameters								
FVC (mL)	55	−124.6 (49.0)	[−223.1; −26.0]	**0.014**[a]	61	−88.6 (72.8)	[−234.8; 57.6]	0.229[a]
FEV_1 (mL)	56	−110.8 (48.7)	[−208.6; −13.0]	**0.027**[a]	63	−68.9 (56.8)	[−182.8; 45.1]	0.231[a]
FEV_1/FVC	55	−8.5 (18.3)	[−45.2; 28.3]	0.645[a]	61	−3.5 (17.0)	[−37.7; 30.7]	0.839[a]
% predicted FVC	55	−5.95 (2.40)	[−10.78; −1.14]	**0.016**[b]	61	−4.92 (3.61)	[−12.15; 2.30]	0.178[b]
% predicted FEV_1	56	−5.81 (2.70)	[−11.24; −0.38]	**0.037**[b]	63	−4.39 (3.18)	[−10.75; 1.98]	0.174[b]
FeNO (ppb)	54	6.88 (3.10)	[0.66; 13.11]	**0.031**[a]	61	−3.54 (3.20)	[−9.96; 2.88]	0.273[a]

Note: Interquartile range (IQR): BC 1160 ng/m^3.
[a] Adjusted model on: age (years), sex (male vs. female), height (cm), weight (kg), cohort (Sabadell, Valencia, Paris - reference), and season (cold vs. warm).
[b] Adjusted model on: weight (kg), cohort (Sabadell, Valencia, Paris - reference), and season (cold vs. warm).

concentrations (1.16 μg/m^3) led to a significant increase in FeNO (about +7 ppb). In the case-control study of Cornell et al. (2012), the association between indoor 7-day BC and FeNO was also somewhat stronger among asthma cases than among controls (Cornell et al., 2012). Some of the studies that investigated the relationship between outdoor BC and FeNO showed strong associations in the study sample as a whole (gathering healthy and asthmatics), perhaps because they dealt with much higher BC (IQR ≥ 4 μg/m^3). They noted a similar increase in FeNO of respectively +16.6% (De Prins et al., 2014)/+16.7% (Lin et al., 2011) per 24-h average outdoor BC IQR increase of 4.0 μg/m^3 (De Prins et al., 2014)/4.5 μg/m^3 (Lin et al., 2011) in Chinese (De Prins et al., 2014)/Belgium (Lin et al., 2011) schoolchildren.

Our results related to BC exposure over 24-h are consistent with previous works regarding effects of lagged exposure to BC on FeNO. Lin et al. (2011) reported that FeNO was significantly and positively associated with IQR increases in 0–48-h outdoor BC but the estimated effect was dominated by the first 0–24-h (Lin et al., 2011). These authors showed that IQR increases in BC during the 10-h before FeNO measurements have the strongest associations with FeNO (Lin et al., 2011). This finding might explain why Jung et al. (2017) did not observe any association between personal 24-h averaged BC exposure and FeNO measured 5 days later in 163 NYC children (Jung et al., 2017).

Few studies have assessed the short-term associations of UFP exposure with lung function parameters and FeNO in schoolchildren. Among them (Heinzerling et al., 2016), only Buonanno et al. (2013) used personal measurements of UFP (Buonanno et al., 2013). The other authors considered central ambient monitor measurements (Li et al., 2016; Pekkanen et al., 1997; Tiittanen et al., 1999) or indoor/outdoor air sampling near children (Newcomb et al., 2012). Results are contradictory depending on the exposure metrics, the studied population and subgroups [both healthy and asthmatic/atopic children (Buonanno et al., 2013) or only asthmatics or children with chronic respiratory symptoms (Li et al., 2016; Newcomb et al., 2012; Pekkanen et al., 1997; Tiittanen et al., 1999)], and the statistical analyses (univariable vs. multivariable models).

Like most of previous studies whatever their design [longitudinal panel (Li et al., 2016; Pekkanen et al., 1997; Tiittanen et al., 1999), case-crossover (Newcomb et al., 2012)], our study did not find any relationship between PNC or LDSA and lung function parameters. Conversely, in 103 Italian children (healthy and asthmatic/atopic) aged 8–11 years, Buonanno et al. (2013) found a negative correlation between the daily dose of alveolar surface area and FEV_1 ($p = 0.02$) and mean forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75}$) ($p = 0.004$) (Buonanno et al., 2013). This last result on $FEF_{25–75}$ which may reflect small airways disease must be interpreted with caution due to its variability noticeably larger than for FEV_1 and to its dependency to FVC value. These correlations were not adjusted on confounders, which limit the strength of any conclusion that could be drawn from it. Buonanno et al. (2013) also reported a crude positive correlation between UFP and FeNO only in subgroups of asthmatics, and to a lesser extent, in children allergic to house dust mites (Buonanno et al., 2013). In our study we did not find any relationship between PNC or LDSA and FeNO in children with persistent respiratory symptoms may be because they suffered from asthma-like symptoms of different severity, so that effects might be diluted. The weaker precision of UFP measurement with DiSCmini® compared to BC could also explain to some extent why UFP were not associated with lung function parameters or FeNO. Moreover concerning LDSA, even if this parameter seems relevant regarding respiratory health, its estimate through a computation might be less accurate than PNC measurement.

Our study has several advantages: 1/ it is one of the few studies on the relationship between personal BC exposure concentrations and PNC or LDSA and objective respiratory outcomes including FeNO in schoolchildren; 2/ it was conducted following the standardized operating procedures developed in the MeDALL program and the ATS/ERS standards for lung function test and FeNO measurement (Dweik et al., 2011; Pellegrino et al., 2005); 3/ exposure concentrations were measured continuously over 24-h according to a previously validated procedure (Paunescu et al., 2017) and using the same portable devices; 4/ the study covered equally, both hot and cold periods of the year, known to have a role on particulate distribution and lung function parameters; 5/ pooling data from three cohorts allowed having more variation in traffic-related air pollution exposure concentrations and resulted in higher statistical power.

However, our study has some weaknesses. First, the study design was cross-sectional and the 24-h measurement of BC exposures and PNC/LDSA and pulmonary function testing were made only once for each subject, so that the reported associations cannot prove definitely causality. Second, study experienced some difficulties: in the field, technical problems with measuring devices sometimes occurred (some families have forgotten to load the devices), so that for a number of children, exposures could not be recorded; and some children have difficulty to perform satisfactorily spirometry and/or FeNO measurements, results depending heavily on the children's cooperation (Moshammer et al., 2006). Therefore, both factors reduced the initial sample size. Third, some factors were not taken into account in the adjustment of models, such as ambient temperature and relative humidity. These meteorological factors have not been assessed. Nevertheless, we used the season as a proxy for the temperature and exposure measurements covered equally all periods of the year. Moreover there was no heat wave during the study periods to expect a major implication of temperature on the studied association.

In **conclusion**, our study brings new insights on the effects of personal BC concentrations and UFP exposures on respiratory health of European schoolchildren. It quantifies the relationship between 24-h BC exposure concentrations and lung function, especially in young children suffering from persistent respiratory symptoms. In terms of public health, the effects of such BC exposure concentrations, although relatively small, might be clinically meaningful when these exposures are repeated in children, involving a reduction in lung function and consequently an increase in the risk of developing asthma (Bowatte et al., 2015). Therefore, our findings highlight the relevance to consider BC as an air quality indicator in monitoring networks and the importance to develop strategies to reduce its concentrations, as previously recommended by the WHO (Janssen et al., 2012). Further studies are needed to better understand the potential impact of BC and UFP on respiratory health in children, especially in those with asthma or allergy.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.104984.

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