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Short- and medium-term air pollution exposure, plasmatic protein levels and blood pressure in children

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ABSTRACT

Exposure to air pollution influences children's health, however, the biological mechanisms underlying these effects are not completely elucidated. We investigated the association between short- and medium-term outdoor air pollution exposure with protein profiles and their link with blood pressure in 1170 HELIX children aged 6–11 years. Different air pollutants (NO_2, PM_{10}, $PM_{2.5}$, and $PM_{2.5abs}$) were estimated based on residential and school addresses at three different windows of exposure (1-day, 1-week, and 1-year before clinical and molecular assessment). Thirty-six proteins, including adipokines, cytokines, or apolipoproteins, were measured in children's plasma using Luminex. Systolic and diastolic blood pressure (SBP and DBP) were measured following a standardized protocol. We performed an association study for each air pollutant at each location and time window and each outcome, adjusting for potential confounders. After correcting for multiple-testing, hepatocyte growth factor (HGF) and interleukin 8 (IL8) levels were positively associated with 1-week home exposure to some of the pollutants (NO_2, PM_{10}, or $PM_{2.5}$). NO_2 1-week home exposure was also related to higher SBP. The mediation study suggested that HGF could explain 19% of the short-term effect of NO_2 on blood pressure, but other study designs are needed to prove the causal directionality between HGF and blood pressure.

1. Introduction

Air pollution is extensively known as a key contributor to the global burden of mortality and disease (Cohen et al., 2017). Nowadays, approximately 91% of the worldwide population is living in places where the levels of air quality exceed guideline limits established by the WHO (World Health Organization, 2021). Air pollution comprises different types of pollutants such as particulate matter (PM) or gaseous

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pollutants. PM can be classified according to their size: (a) particulate matter with an aerodynamic diameter of fewer than 2.5 μm ($PM_{2.5}$); (b) particulate matter with an aerodynamic diameter of fewer than 10 μm (PM_{10}). Besides particulate matter, other air pollutants are considered harmful for human health, such as nitrogen dioxide (NO_2), which is a gaseous air pollutant mainly used as a marker for traffic-related air pollution (WHO, 2003). These air pollutants together with sulphur dioxide (SO_2), carbon monoxide (CO), ozone (O_3), and organic compounds are considered as the top health-menacing air pollutants.

Previous evidence has shown that short- (=< 1week), medium- (>1 week, but =<1year), and long-term (>1year) air pollution exposure is related to a wide range of acute and chronic adverse health effects such as cardiovascular diseases in adults (Rajagopalan et al., 2018). Nowadays, cardiovascular diseases are one of the leading causes of death, responsible for more than 18 million deaths each year (Roth et al., 2018). Different modifiable risk factors for cardiovascular diseases are known such as smoking, diabetes, lipid abnormalities, or hypertension, which is one of the major contributors to cardiovascular diseases (Fuchs and Whelton, 2020). Emerging evidence, mainly in adults, has shown that short- and long-term exposure to air pollution can lead to higher blood pressure (BP) (Brook et al., 2011; Choi et al., 2019; Foraster et al., 2014). The early-life period is an important window of susceptibility to environmental exposures, and any alterations during pregnancy and childhood might permanently change the body's structure, metabolism and physiology (Barouki et al., 2012; Wright, 2017). In children, only a few studies have evaluated both short-, medium- and long-term effects of air pollutants on BP. However, the available studies in children reach similar conclusions to studies in adults (Huang et al., 2021; Sanders et al., 2018; Zhang et al., 2019). A recent meta-analysis concluded that both short-term (5 studies) and long-term (10 studies) exposure to ambient air pollution exposure can be associated with elevated BP in children (Huang et al., 2021). These are important findings as recent evidence found that children with higher BP are more likely to develop cardiovascular diseases during adulthood (Lurbe et al., 2009; Yang et al., 2020). Moreover, hypertension in children is related to other risk factors for cardiovascular diseases such as insulin resistance or hyperlipidemia (Martino et al., 2013).

Different underlying biological mechanisms have been proposed to mediate the effect of air pollution and adverse health outcomes such as oxidative stress and systemic inflammation (Clemente et al., 2017; Johnson et al., 2021; Z. Li et al., 2019b). It is known that circulating proteins such as adipokines and cytokines are related to inflammation processes and their levels can be increased by air pollution exposure (Dadvand et al., 2014; Yang et al., 2017). In general, epidemiological studies have focused on a few specific proteins such as interleukins (IL1, IL6, IL8, or IL10), tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP) (Yang et al., 2017), and adipokines (leptin or adiponectin) (Dauchet et al., 2018). Moreover, most of the studies have investigated either short- or long-term exposure to air pollution. Thus, there is a paucity of studies considering multiple windows of exposure and air pollutants, and multiple plasmatic proteins. Finally, the majority of the evidence of biological mechanisms refers to the adult population (Elbarbary et al., 2021; Fiorito et al., 2018; Pilz et al., 2018; Riggs et al., 2020a; Su et al., 2017; Sun et al., 2020; Tsai et al., 2019; Zhang et al., 2020a), with only a few studies available in children (Alderete et al., 2018; Gruzieva et al., 2017; X. Li et al., 2019a).

Within the framework of the HELIX project, we have shown that short- and medium-term air pollution exposure during the childhood period was related to higher diastolic blood pressure (DBP) at age 4–5 years (Warembourg et al., 2021), and a similar not statistically significant trend was observed for systolic blood pressure (SBP) at the age of 8 years (Warembourg et al., 2019). In this study, we expanded previous association studies to additional exposure windows and locations in 1170 HELIX children aged 6–11 years and explored potential biological mechanisms. In particular, we aimed to investigate the relationship of residential and school short- and medium-term (1 day, 1 week, and 1 year) outdoor air pollution exposure to NO_2, $PM_{2.5}$, PM_{10}, and absorbance of PM2.5 filters (PM_{abs}) with 36 plasmatic protein levels (including cytokines, apolipoproteins, adipokines and other proteins such as growth factors) and blood pressure in HELIX children, and to evaluate the potential mediating role of selected proteins.

2. Materials and methods

2.1. Study population

This study was conducted in the context of the HELIX project, which was based on six on-going longitudinal population-based birth cohorts established in six countries across different parts of Europe (Born in Bradford [BiB; UK](Wright et al., 2013), Étude des Déterminants Pré et Postnatals du Développement et de la Santé de l'Enfant [EDEN; France](Heude et al., 2016), Infancia y Medio Ambiente [INMA; Spain](Guxens et al., 2012), Kaunas Cohort [KANC; Lithuania](Grazuleviciene et al., 2009), Norwegian Mother, Father and Child Cohort Study [MoBa; Norway](Magnus et al., 2016), and Mother-Child Cohort in Crete [RHEA; Greece](Chatzi et al., 2017)). Before the start of HELIX, all six cohorts had undergone the required evaluation by national ethics committees and obtained all the required permissions for their cohort recruitment and follow-up visits. The work in HELIX was covered by new ethic approvals in each country and at enrolment in the new follow-up, participants were asked to sign a new informed consent form. The HELIX project included 31,472 mother-child pairs of which 1301 children, around 200 from each of the cohorts, were selected to create a subcohort based on some criteria of eligibility explained elsewhere (Warembourg et al., 2019). A clinical examination, a computer-assisted interview with the mother, and the collection of additional biological samples were carried out during the second follow-up in 2014–2015 of the HELIX subcohort. For this study, we sub-selected 1170 children from the subcohort aged between 6 and 11 years (mean age of 7.4 years) which had information on air pollution exposure, plasmatic proteins, and blood pressure (Figure A 1).

2.2. Childhood outdoor air pollution exposure assessment

The following atmospheric pollutants were assessed for different locations and time windows: NO_2, $PM_{2.5}$ and PM_{10}, and PM_{abs}. A detailed exposure assessment was previously explained elsewhere (Tamayo-Uria et al., 2019; Warembourg et al., 2019). Briefly, outdoor air pollution exposures were assessed using estimates based on land use regression (LUR) modelling approach developed within the framework of the European Study of Cohorts for Air Pollution Effects (ESCAPE) (Beelen et al., 2009; Cyrys et al., 2012; Eeftens et al., 2012a, 2012b; Sellier et al., 2014), which were temporally adjusted to measurements made in local background monitoring stations (Tamayo-Uria et al., 2019). Estimates on air pollutants were assigned to each subcohort individual within GIS techniques considering their residential and school geocoded addresses, which was collected through the last available follow-up survey for each cohort. Moreover, different time windows were calculated for the evaluated air pollutants by averaging them over 1 day, 1week and, 1 year before the clinical and molecular assessment (see Supplementary material for a more extensive explanation of the air pollution exposure assessment, appendix A, section S1).

Some air pollutants could not be assessed in some cohorts because land use regression (LUR) models were not available. In those cohorts that had air pollution measurements, missing values were imputed following a process previously described (Tamayo-Uria et al., 2019). Imputed values represented a maximum of 2% of the values within each cohort. Sample sizes after imputation were: (a) 1170 individuals for NO_2 and $PM_{2.5}$ models; (b) 1020 individuals for PM_{10} models (missing in EDEN cohort); and (c) 828 individuals for PM_{abs} models (missing in EDEN and RHEA cohorts). To enable the comparison of results between different pollutants, air pollution exposure variables were standardized

by their interquartile range (IQR).

2.3. Measurement of plasmatic proteins levels

Blood samples were collected from HELIX subcohort children at a mean age of 7.4 years during the clinical examination, thus simultaneously to the blood pressure measurement (Maitre et al., 2018). Plasma samples were analysed to detect and quantify a panel of relevant proteins. Three Luminex kits commercially available from Life Technologies and Millipore were selected, which assessed a total of 50 measurements (43 unique proteins): Cytokines 30-plex (Cat #. LHC6003M), Apolipoprotein 5-plex (LHP0001M), and Adipokine 15-plex (LHC0017M). Plasma analyses were performed following the standard protocol defined by the vendor. The % of coefficients of variation (% CV) for each protein estimated by plate and then averaged ranged from 3.4% to 36%. For each protein, the limit of detection (LOD) was determined and the lower and upper quantification limits (LOQ1 and LOQ2, respectively) were obtained from the calibration curves. For those proteins that passed the quality control, data were log2 transformed to reach normal distribution. Afterwards, the plate batch effect was corrected by subtracting for each individual and each protein the difference between the overall protein average minus the plate-specific protein average. Finally, values below LOQ1 and above LOQ2 were imputed using a truncated normal distribution implemented in the truncdist R package (Nadarajah and Kotz, 2006) (see details on the QC in the Supplementary material (Appendix A, section S2)) and a descriptive table of the proteins evaluated in the study in Supplementary Excel (Appendix B) file (Table B 1)). A final dataset with the log2-transformed, imputed, and normalized levels for 36 proteins of the 1170 individuals of the HELIX subcohort.

2.4. Blood pressure measurement

A standardized protocol was followed to measure BP during the clinical examination. After 5 min of rest in the sitting position, 3 consecutive measurements, separated by 1-min intervals, were taken using an oscillometric device (OMRON 705-CPII, Omron, Kyoto, Japan). The children were in a pre-defined posture and the right arm was used preferably. The cuff sizes were chosen considering each child's arm length and circumference. Each measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP) was recorded, and the mean of the second and third measurements was calculated and used in further analyses. In the following manuscript measures of 1167 individuals were evaluated.

2.5. Covariates

During pregnancy and in the childhood follow-up examination information on the following key covariates was collected: self-reported maternal education (primary school, secondary school and university degree or higher), self-reported ancestry (European, Asian and Pakistani, or other), child age at blood sample collection (continuous in years), self-reported maternal pre-pregnancy body mass index (BMI) (continuous in kg/m^2), child's BMI z-score (based on continuous BMI in kg/m^2) (De Onis et al., 2007; WHO), child's height (continuous in meters), maternal smoking during pregnancy (no smoker, only passive smoker, or smoker), smoking status of parents during childhood (none, one, or both), mean outdoors temperature (one day, one week and one month before blood and protein measurements) at residential and at school addresses (continuous in °C), exposure to outdoor air pollution during pregnancy (NO_2, PM_{10}, $PM_{2.5}$ and PM_{abs} as an average of the whole pregnancy period estimated at maternal residential addresses). Missing values in covariates (<3%) were imputed as described above.

2.6. Statistical analyses

2.6.1. Descriptive analyses and correlations

For categorical variables, we calculated frequency and percentage; and for continuous variables, we calculated median and interquartile range (IQR). We used Spearman's correlation coefficients to quantify the correlation between plasmatic proteins data and Pearson's correlation coefficient to quantify the correlation between the different air pollutant measurements.

2.6.2. Outdoor air pollution exposures and plasmatic proteins analyses

We assessed the association between childhood outdoor exposure to air pollution and protein levels using the *omicRexposome* R package (Bioconductor - omicRexposome,). Each air pollutant exposure (at different locations, windows, and pollutants) was related to the plasmatic levels of each protein through linear regressions adjusted for covariates using the *omicRexposome* based on *limma* R package (Ritchie et al., 2015). Models were adjusted for a common set of confounders identified a priori based on literature: child's sex, cohort, self-reported maternal education, self-reported ancestry child's age and mean outdoors temperature of each participant at residential or school addresses. The effect size was expressed as log2 fold change (log2FC) in protein levels per IQR change of the exposure. Nominal significance was established at nominal p-value <0.05. Multiple testing correction was addressed by applying the effective number of tests (ENT) (Li et al., 2012) method, which estimates the number of independent tests considering the correlation among proteins: ENT = 31.54, p-value threshold = 0.0016.

2.6.3. Sensitivity analyses

We conducted several sensitivity analyses. First, we run additional models adjusted for other covariables that could be confounding the associations. Models were further adjusted for: (i) maternal smoking and outdoor air pollution exposure during pregnancy, or (ii) for parental smoking during childhood and child BMI z-score. Second, for the air pollutants that survived multiple-testing correction, we ran mutually adjusted models (NO_2 models were further adjusted for $PM_{2.5}$, and vice versa) to determine if the estimated effects remained statistically significant. We selected NO_2 and $PM_{2.5}$ as they were not strongly correlated (Figure A 6) and had data available in the whole sample (n = 1170 individuals). Third, we conducted a cohort-by-cohort analysis for each statistically significant association in the main model, to check the pattern of association within each cohort. The *meta* R package (Schwarzer, 2007) was used to conduct the fixed-effects inverse variance weighted meta-analyses based on the estimates and standard errors of the associations. We looked at the I^2 statistics to describe heterogeneity across cohorts.

2.6.4. Mediation analyses

We hypothesized that part of the association between exposure to air pollution and blood pressure could be mediated by the change in protein levels. Therefore, first, linear regression models were conducted to examine the associations between each of the childhood outdoor air pollution exposures (different locations, windows, and air pollutants) and SBP and DBP, respectively. Models were adjusted for a common set of confounders identified a priori based on literature: child's sex, cohort, self-reported maternal education, self-reported ancestry, mean temperature of each participant at residential or school addresses, child's age, and child's height. Effect size is reported as the change in blood pressure (millimeters of mercury (mmHg)) by IQR of exposure levels. Then, we investigated the potential mediating role of selected proteins in the association between air pollutants and blood pressure. This was restricted to statistically significant associations between air pollutants and proteins and blood pressure. To do so, we conducted a formal mediation analysis using the function '*mediate*' from the R package *mediation* (Tingley et al., 2014). This package allows the calculation of various

quantities: the total effect, the average direct effect (ADE), indirect effect or average causal mediation effects (ACME), and the proportion mediated (Imai et al., 2010).

The statistical framework R (version 3.6.0) was used to perform all the analyses (R Core Team, 2021).

3. Results

3.1. Study population

Descriptive statistics of the sociodemographic characteristics of the study participants are presented in Table 1. From the 1170 participants included in the study, the median age at the clinical examination was 7.4 (2.4) years old. Of these children 89.6% were of European ancestry, 45.4% were female, and 50.6% were born from mothers with a university degree or higher education level. The median average SBP and DBP was 98 (15) and 57 (10) mmHg, respectively.

Within each pollutant and time window, correlations between home and school were very high ($r > 0.772$) (Figure A 2-A 5). Regarding time windows, higher correlations were detected between 1- day and 1-week than for 1-week and 1-year within each pollutant. For instance, for the exposure to $PM_{2.5}$ at home, the correlation between 1-day and 1-week was $r = 0.665$, while for 1-week and 1-year it was $r = 0.591$. Finally, we found higher correlations among $PM_{2.5}$, PM_{10} and lower correlations or no correlation between PMs subtypes and NO_2. For instance, the correlation between 1-week exposure at home to $PM_{2.5}$ and to PM_{10} was $r = 0.835$, however, its correlation with NO_2 was $r = -0.051$. A graphical display of the correlation matrix between all air pollution exposures is shown in Figure A 6.

Table 1
Characteristics of study population (N = 1170).

Variable	N (%) or median (IQR)
Cohort	
BIB	196 (16.8%)
EDEN	150 (12.8%)
INMA	210 (17.9%)
KANC	199 (17%)
MOBA	223 (19.1%)
RHEA	192 (16.4%)
Ethnicity	
Asian and Pakistani	95 (8.1%)
European	1.048 (89.6%)
Other	27 (2.3%)
Sex of the child	
Female	531 (45.4%)
Male	639 (54.6%)
Child age at blood collection, in years	7.4 ± 2.4
Child z-score BMI	0.3 ± 1.5
Child SBP, mmHg*	98 ± 15
Child DBP, mmHg*	57 ± 10
Maternal age, in years	31 ± 6.8
Maternal pre-pregnancy BMI	24 ± 5.9
Maternal education	
Primary school	172 (14.7%)
Secondary school	406 (34.7%)
University degree or higher	592 (50.6%)
Maternal smoking during pregnancy	
No smoker	633 (54.1%)
Only passive smoker	363 (31%)
Smoker	174 (14.9%)
Parental smoking during childhood	
Neither	721 (61.6%)
One parent	322 (27.5%)
Both parents	127 (10.9%)

Note: BIB = Born in Bradford; EDEN = Étude des Déterminants Pré et Postnatals du Développement et de la Santé de l'Enfant; INMA = Infancia y Medio Ambiente; KANC = Kaunas Cohort; MoBa= Norwegian Mother, Father and Child Cohort Study; RHEA = Mother-child Cohort in Crete; BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure. *For systolic and diastolic blood pressure the sample size was 1167 individuals.

Plasmatic proteins were classified into 4 groups according to their function: adipokines, apolipoproteins, cytokines, and other proteins, including growth factors, hormones, and the C-reactive protein (CRP) (See Supplementary Excel (Appendix B) for further information, Table B 1). Their average concentrations can be found in Table B 1, and their pair-wise correlation is shown in Figure A 7. The heatmap suggests 4 clusters, which are mostly consistent with the four groups of proteins previously created based on their biological function. Higher correlations can be found within most of the cytokines, adipokine PAI1(Plasminogen activator inhibitor-1) and some growth factors (EGF (Epidermal growth factor), GSCF (Granulocyte colony-stimulating factor), and FGFBasic (Basic fibroblast growth factor)), all of them related with inflammatory processes. The group of apolipoproteins was correlated between them and with adiponectin and CRP. Moreover, leptin, interleukin-1 beta (ILbeta), interleukin-6 (IL6), all produced by the fat tissue, and insulin were quite correlated among them. Finally, we observed correlations within a smaller group of cytokines (Interleukin-8 (IL8), tumor necrosis factor alfa (TNF-α) and monocyte chemoattractant protein-1m (MCP1)), the B-cell activating factor (BAFF) which is an adipokine, the hepatocyte growth factor (HGF) and one hormone (Cpeptide), all of them with anti-inflammatory properties.

3.2. Outdoor air pollution exposures and plasmatic proteins analyses

Higher 1-week NO_2, $PM_{2.5}$, and PM_{10} home levels were associated with increased levels of HGF (Table 2). In addition, higher 1-week $PM_{2.5}$ and PM_{10} school levels were also related to increased levels of HGF. Finally, exposure to 1-week PM_{10} at home and school was associated with higher IL8 concentration (Table 2). The beforementioned associations are the ones that passed the multiple testing correction threshold ($p < 0.0016$) based on the effective number of tests (ENTs) considering

Table 2
Results of the association between outdoor air pollution exposures and plasmatic proteins levels (main model).

Exposure	Outcome	N	log2FC (95%CI) [a]	P-value	Adjusted p-value
NO_2 home exposure (1 week) (IQR = 0.57)	HGF	1170	0.06 (0.02, 0.10)	0.001	0.036
$PM_{2.5}$ home exposure (1 week) (IQR = 6.89)	HGF	1170	0.04 (0.01, 0.06)	0.001	0.035
$PM_{2.5}$ school exposure (1 week) (IQR = 6.78)	HGF	1170	0.04 (0.01, 0.06)	0.001	0.036
PM_{10} home exposure (1 week) (IQR = 15.28)	HGF	1020	0.04 (0.02, 0.06)	8.08×10^{-05}	0.003
PM_{10} school exposure (1 week) (IQR = 15.15)	HGF	1020	0.04 (0.01, 0.06)	0.001	0.027
PM_{10} home exposure (1 week) (IQR = 15.28)	IL8	1020	0.05 (0.02, 0.07)	1.74×10^{-04}	0.005
PM_{10} school exposure (1 week) (IQR = 15.15)	IL8	1020	0.05 (0.02, 0.08)	0.001	0.006

NO_2 = Nitrogen dioxide; $PM_{2.5}$ = Particulate matter with an aerodynamic diameter of less than 2.5 μm; PM_{10} = Particulate matter with an aerodynamic diameter of less than 10 μm; HGF = Hepatocyte growth factor; IL8 = Interleukin 8; log2FC = log2 fold change of protein levels by IQR or air pollutant; IQR = Interquartile range. Results are presented only for the exposure-protein associations that surpassed the multiple testing correction threshold considering correlated proteins (ENT = 31.54). The main model was adjusted for: child's sex, cohort, self-reported maternal education, self-reported ancestry, and mean temperature. The analyses were conducted in 1170 children from the HELIX subcohort for the NO_2 and $PM_{2.5}$ models and in 1020 for the PM_{10} models. exposure.

all the proteins. The rest of the associations are shown in the supplementary information (see Supplementary Excel for the full set of results, Table B 4-B.7).

When further adjusting the models for maternal smoking and outdoor air pollution exposure during pregnancy and, for parental smoking during childhood and child BMI z-score plus the main covariates considered before, the associations remained significant and still passed the multiple testing correction threshold (see Supplementary Excel (Appendix B) file for the full set of results, Table B 4-B 6). Then, in the mutually adjusted models, the associations were not statistically significant anymore, however effect sizes were only slightly smaller, and all maintained the same direction (see Supplementary Excel (Appendix B) file for the full set of results, Table B 4- B.5). Finally, we conducted fixed-effects inverse variance weighted meta-analyses of the results by the cohort of the exposure-omics associations that passed the multiple testing correction (Figure A 8). For 1-week NO_2 exposure estimated effects were consistent across cohorts (Figure A 8A). For the other associations the pattern was slightly more heterogeneous with some cohorts going in the opposite direction (Figure A 8B, A 8C, and A 8D). Nevertheless, the statistic I^2 was equal to 0 for all exposure variables.

3.3. Mediation analyses

Linear regression models adjusted for covariates showed marginally significant associations between 1-week exposure to NO_2 at home and school and higher SBP (beta = 1.21, p-value = 0.091; and beta = 1.24, p-value = 0.081, respectively), and for 1-year exposure to NO_2 and to PM_{abs} at school (beta = 1.77, p-value = 0.063; and beta = 1.91, p-value = 0.079, respectively). For the other air pollutants and regards to DBP non-significant associations were found (see Supplementary Excel (Appendix B) file for the full set of results, Table B 8-B 9).

Associations between air pollution and BP did not change substantially after further adjusting the models for (a) maternal smoking and outdoor air pollution exposure during pregnancy, and for (b) parental smoking during childhood and child BMI z-score (see Supplementary Excel (Appendix B) file for the full set of results, Table B 8-B 9). The only exception was the association between 1-week NO_2 exposure at home and SBP, where a statistically significant effect was observed when further adjusting the models for variables related to pregnancy (beta = 1.53, p-value = 0.040). In the mutually adjusted models, stronger estimates were observed between NO_2 exposure and higher SBP; on the contrary, $PM_{2.5}$ exposure was related to a decrease in SBP (see Supplementary Excel (Appendix B) file for the full set of results, Table B 8-B 9).

Finally, we conducted mediation analyses for those exposures, proteins, and outcomes that were involved in marginally significant associations, namely 1-week NO_2 exposure at home, HGF, and SBP. The results of the mediation analyses showed that 19% of the effect of the exposure to 1-week NO_2 levels at home on SBP could be partly mediated via the HGF concentrations (see Table B 10).

4. Discussion

To our knowledge, this is one of the first studies to simultaneously evaluate the possible influence of different time windows of air pollution exposure (1-day, 1-week, and 1-year) and various pollutants on the levels of various cytokines, apolipoproteins, adipokines, and other proteins such as growth factors in children, and their link with blood pressure. We showed that higher levels of 1-week exposure to NO_2, $PM_{2.5}$, and PM_{10} at home or school were associated with higher levels of HGF. A similar association, but only for PM_{10} was observed for IL8. Finally, higher levels of 1-week exposure to NO_2 were related to higher SBP, and the mediation analysis suggests that HGF might be implicated in this link.

Inflammation and oxidative stress are known to be the main biological mechanisms by which air pollution induces health effects, which might be translated to an inflammation cascade, and oxidation stress process in the lung, vascular, or heart tissue (Lodovici and Bigagli, 2011), together with dysfunction of vascular endothelium (Araujo and Nel, 2009; Brook et al., 2009; Zhong et al., 2015). In line with previous studies, we have shown a positive association between IL8 levels and PM, specifically, PM_{10}. IL8 is a chemotactic factor that can be produced by a wide range of cells such as epithelial, fibroblasts endothelial, macrophages, or lymphocytes in response to inflammation (Benakanakere et al., 2016). It is considered a pro-inflammatory mediator that intermediates in host responses to tissue damage and inflammation (Mehrbani et al., 2016). In particular, it is involved in mitogenesis, inhibition of angiogenesis, chemotaxis, neutrophil degranulation, calcium homeostasis, and leukocyte activation (Brennan and Zheng, 2007). Two observational studies in adults have shown that short-term exposure to $PM_{2.5}$ increased levels of circulating MCP1, IL8, and TNF-α (Zhang et al., 2020b), and also of IL6 (Pope et al., 2016). A study carried out with children (8- to 10-year-old) found higher levels of saliva IL8 in a region with higher air pollution (Mehrbani et al., 2016). In vitro studies using primary human bronchial epithelial cells (HBECs) exposed to PM_{10} have confirmed an increase in IL8 concentrations in 24h after exposure, which goes in line with our results (Fujii et al., 2001). Moreover, in response to air pollution exposure it has been seen that IL8 gene expression increases in the macrophages located in the pulmonary alveoli (Drumm et al., 1999). An elevated expression of this cytokine has been previously associated with some conditions as hypertension (Martynowicz et al., 2014), carcinogenesis (Gales et al., 2013) or chronic obstructive pulmonary diseases (Gilowska, 2014). Thus, elevated IL8 levels in response to air pollution might lead to other adverse health effects, besides blood pressure. However, in our study PM_{10} exposure, which was associated with IL8, was not related to BP, therefore, we did not conduct a formal mediation analysis between this exposure and BP.

In relation to HGF, we found that plasma levels of this protein were related to 1-week exposure to NO_2, PM_{10}, and $PM_{2.5}$. Results were consistent across cohorts and not modified when adjusting for other covariates, which suggests a robust association. However, there is scarce evidence regarding the influence of air pollution on HGF levels. One of the available studies so far, found a positive association between short-term exposure to NO_2 and HGF in the adult population (Dadvand et al., 2014). In contrast, another study in adults did not find any association between short-term exposure to $PM_{2.5}$ and HGF (Riggs et al., 2020b). HGF is not usually considered as an inflammatory marker, and it was first described as a liver-regenerative circulating factor. Currently, it is thought to be an angiogenic growth factor by its participation in the HGF/c-Met signaling cascade (Neuss et al., 2004). This cascade regulates proliferation, differentiation, survival, and mitogenesis of endothelial cells that are linked to the reparation of tissues in different organs such as the heart (Mungunsukh et al., 2014; Oliveira et al., 2018). Previous evidence has shown positive associations between HGF and BP(Hayash et al., 2002). In our study, we ran a mediation analysis between air pollution, HGF levels, and blood pressure. We found that 19% of the effect of air pollution on SBP could be mediated through HGF. However, we need to interpret the results cautiously as the direction of the relationship between HGF and BP is uncertain. In vitro models, suggest that HGF could be a downstream product of increased blood pressure (Nakamura et al., 1996). Other studies in humans suggest that HGF would be produced to counteract the endothelial damage induced by hypertension (Morishita et al., 1998, 2002; Shimizu et al., 2016) as HGF/c-Met pathway could have a role in cardiovascular remodeling after tissue injury (Gallo et al., 2015). Thus, further studies should address the causal connection between HGF and blood pressure in the context of air pollution.

Finally, we did not find any association between short- and medium-term exposure to air pollutants and CRP, PAI1, TNF-α, IL6, and IL10, previously related to air pollution in other studies (Liu et al., 2019; Tang et al., 2020; Wu et al., 2012). A meta-analyses of 40 studies conducted in adults confirmed a positive association between being exposed to $PM_{2.5}$

or PM_{10} and levels of circulating CRP, with stronger associations when considering long-term exposures (more than 6 months) (Liu et al., 2019). In children, it was found that exposure to traffic-related pollutants (PM_{10} and NO_2) during the first year of life was associated with the levels of IL6 and IL10 measured at 8 years of age (Gruzieva et al., 2017). Besides measurement error problems, which do not seem to be the case, the lack of replication of some air pollution-protein associations in our study might have other explanations. First, our levels of air pollution could be lower compared to other studies. Previous evidence have shown that the production of some pro-inflammatory mediators such as IL8 could be more sensitive to air pollution exposure than others (Mehrbani et al., 2016), which might explain why we found an association between PM and IL8, and not with IL6. Second, existing evidence have also found that exposure to PM was associated with an increased production of inflammatory mediators (IL6 or CRP) by stimulated immune cells, but not with their circulating levels (Tripathy et al., 2021), and in our study circulating protein levels in plasma were considered as the outcome. Additionally, the influence on protein concentrations might not be just affected by PM levels, but also by the proportion of each chemical component found in PM, as it has been seen that the effect of each component can differ (Li et al., 2020; Xu et al., 2020). According to it, future studies should determine the chemical composition of PM to clearly evaluate which are the components with a higher impact in protein levels. Third, most of the studies have been conducted in adults and our study is based on children, which might develop a different response to this risk factor as their inflammatory response could be lower due to the chronic exposure is lower compared to adults. Finally, based on our results, we observed that stronger associations are found within one-week of exposure before the clinical and molecular assessment, thus suggesting acute effects of air pollution on these traits. In the way our exposure was assessed, the 1-year average exposure to air pollution is not collecting information on the 1-day or 1-week peaks of air pollution through that period, which could be the main contributors to the increased levels of protein or BP measurements. Therefore, the evaluation of these peaks of air pollution and, the potential chronical influence on health outcomes would require further analyses based on longitudinal studies.

The main strengths of our study are the comprehensive assessment of the air pollution exposure in six populations across Europe with different cultures and settings, the evaluation of different air pollutants and time windows in the same analyses, the harmonized protocols used for the measurement of blood pressure and plasmatic proteins levels, and the adjustment of the statistical models for covariates. Moreover, the analyses investigated the influence of air pollution exposure in children, which are considered as one of the most vulnerable population groups. Finally, we reported the estimates obtained through the analyses of each exposure-protein association to avoid selective reporting bias.

However, our results should be interpreted in the context of its limitations. First, we were not able to consider children's behavior throughout day-to-day life as we have only estimated air pollution values at home and school. Second, we need to consider that the sources of the different air pollutants are unknown and might be different from cohort to cohort, and that we were not able to determine the chemical composition of PM. Moreover, we cannot clearly identify which are the most sensitive windows of exposure because of the low within-subject variability. Third, we have evaluated only thirty-six plasmatic proteins, which is limited considering all the circulating proteins that are present in the human body. However, within the sample of proteins investigated, we have considered acute phase proteins and the most involved in systemic inflammation. Finally, we acknowledge that our study had a cross-sectional design, and we cannot establish a causal link between protein levels and blood pressure. Importantly, the mediation analyses do not imply causality as the relationship could be due to reverse causation. We believe that future studies should investigate the molecular and cellular response to air pollution to elucidate underlying biological mechanisms involved in the relation between air pollution and health outcomes.

Overall, we found that short-term exposure to air pollutants was related to increased levels of HGF, IL8, and systolic blood pressure. HGF seems to be connected to higher blood pressure in the context of air pollution, but direct causation is not proven. These findings reinforce the adverse cardiovascular effects of air pollution in children, a potentially susceptible group. Moreover, considering that elevated blood pressure during childhood impacts on health across the lifespan, reducing the exposure to this environmental risk factor could be also an important prevention strategy. Considering all the above, this study might provide more evidence to promote and implement new strategies and public policies to reduce exposure to air pollution.

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permissions for their cohort recruitment and follow-up visits. The work in HELIX was covered by new ethic approvals in each country and at enrolment in the new follow-up, participants were asked to sign a new informed consent form.

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.

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Appendix A. Supplementary data

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