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Summary

Background Several single-exposure studies have documented possible effects of environmental factors on lung function, but none has relied on an exposome approach. We aimed to evaluate the association between a broad range of prenatal and postnatal lifestyle and environmental exposures and lung function in children.

Methods In this analysis, we used data from 1033 mother–child pairs from the European Human Early-Life Exposome (HELIX) cohort (consisting of six existing longitudinal birth cohorts in France, Greece, Lithuania, Norway, Spain, and the UK of children born between 2003 and 2009) for whom a valid spirometry test was recorded for the child. 85 prenatal and 125 postnatal exposures relating to outdoor, indoor, chemical, and lifestyle factors were assessed, and lung function was measured by spirometry in children at age 6–12 years. Two agnostic linear regression methods, a deletion-substitution-addition (DSA) algorithm considering all exposures simultaneously, and an exposome-wide association study (ExWAS) considering exposures independently, were applied to test the association with forced expiratory volume in 1 s percent predicted values (FEV_1%). We tested for two-way interaction between exposures and corrected for confounding by co-exposures.

Findings In the 1033 children (median age 8·1 years, IQR 6·5–9·0), mean FEV_1% was 98·8% (SD 13·2). In the ExWAS, prenatal perfluorononanoate (p=0·034) and perfluorooctanoate (p=0·030) exposures were associated with lower FEV_1%, and inverse distance to nearest road during pregnancy (p=0·030) was associated with higher FEV_1%. Nine postnatal exposures were associated with lower FEV_1%: copper (p=0·041), ethyl-paraben (p=0·029), five phthalate metabolites (mono-2-ethyl 5-carboxypentyl phthalate [p=0·016], mono-2-ethyl-5-hydroxyhexyl phthalate [p=0·023], mono-2-ethyl-5-oxohexyl phthalate [p=0·0085], mono-4-methyl-7-oxooctyl phthalate [p=0·040], and the sum of di-ethylhexyl phthalate metabolites [p=0·014]), house crowding (p=0·015), and facility density around schools (p=0·027). However, no exposure passed the significance threshold when corrected for multiple testing in ExWAS, and none was selected with the DSA algorithm, including when testing for exposure interactions.

Interpretation Our systematic exposome approach identified several environmental exposures, mainly chemicals, that might be associated with lung function. Reducing exposure to these ubiquitous chemicals could help to prevent the development of chronic respiratory disease.

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Introduction

The developmental period of a human, in both prenatal and early postnatal life, is likely to be particularly susceptible to environmental hazards. Exposures during this period could permanently affect body structure, physiology, and metabolism, leading to long-term health effects.[1] For instance, in-utero tobacco smoke exposure increases the risk of altered pulmonary function and asthma.[2]

Besides smoking, there is evidence of variable strengths that exposure to other environmental factors could affect lung health in childhood. For example, prenatal exposure to outdoor air pollution is associated with respiratory symptoms, asthma, and deficits of lung growth in newborn babies.[3] Among chemical exposures, there is moderate evidence for respiratory effects of some persistent organochlorine compounds, such as polychlorinated biphenyls (used in the 20th century as electric insulators), and dichlorodiphenyltrichloroethane and its metabolite dichlorodiphenyldichloroethylene, a pesticide, for which human exposure occurs predominantly via diet, including breastfeeding.[4,5] Emerging concerns for lung effects of other man-made substances, such as perfluoroalkyl substances (PFASs) used in

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Research in context

Evidence before this study

There is a large body of epidemiological literature on the effects of early-life exposures on respiratory health in children, but few studies have investigated several families of exposure, or applied an exposome approach—ie, one encompassing all environmental exposures from conception onwards. We searched PubMed for journal articles published in English up to Dec 17, 2018, with the search terms ((“Exposure” and “Environment”) OR (“Exposome”)) and (“Lung function” and “Epidemiology” and “Children”). We identified 295 articles, of which only 11 investigated at least two families of exposures and included few environmental exposures, and none relied on both exposure biomarkers and fine-scale environmental models. Populations are simultaneously exposed to a wide range of environmental factors, some of which are suspected to affect lung health. Therefore, the exposome approach warrants further investigation in respiratory epidemiology, particularly during early life, for which evidence is scarce.

Added value of this study

For the first time, to our knowledge, we were able to investigate the effect of a broad range of environmental exposures on lung function in children, by integrating 17 exposure families from the outdoor, indoor, chemical, and lifestyle domains of the exposome, assessed during pregnancy (85 exposures) and in childhood (125 exposures). We assessed pregnancy and childhood exposomes in 1033 mother–child pairs, with lung function measured by spirometry when children were aged 6–12 years. A lower forced expiratory volume in 1 s was associated with prenatal exposure to perfluoroalkyl substances, with postnatal exposure to ethyl-paraben and phthalate metabolites (used in the manufacture of plastics, solvents, and personal-care products), copper, facility density near school, and house crowding, although no exposure passed the correction for multiple testing.

Implications of all the available evidence

Our study strengthened the evidence for the contribution of chemical exposures (phenols, phthalate metabolites, and perfluoroalkyl substances) to the impairment of lung function development and highlights the need for larger prospective studies. Preventive measures aimed at lowering exposure to the identified ubiquitous chemicals, through stricter regulation and through informing the public by labelling these chemicals in consumer products, could help to prevent early-life lung function impairment, which in turn might have benefits for long-term health.

non-stick cookware, water-repellent clothing, stain-resistant fabrics, and carpets, or phthalate metabolites and phenols (including bisphenol A and ethyl-paraben)[6,7] used in the manufacture of plastics, solvents, and personal-care products, require further exploration. Few studies have considered the effects of metals on the developing respiratory system in humans.[8]

Pulmonary development in childhood is a key determinant for long-term respiratory function (as shown by studies of lung function deficits that have been tracked from childhood into adulthood—ie, the so-called tracking effect)[9,10] and has been linked to health outcomes beyond just respiratory health. Indeed, studies have shown that low peak lung function in early adulthood is associated with a higher prevalence of respiratory, cardiovascular, and metabolic abnormalities in later life, and premature death.[11] Therefore, it is essential to identify the environmental hazards affecting lung growth in childhood.

In daily life, populations are simultaneously exposed to a wide range of environmental factors that could affect health.[12] The exposome, a concept defined as encompassing all environmental exposures from conception onwards,[13] offers a new paradigm in environmental health research. By simultaneously considering a large set of exposures, the exposome approach can overcome the limitations of focusing on a single exposure or family of exposures in environmental studies done so far.[14] Specifically, exposome studies limit the risk of selective reporting (ie, testing many exposures and only reporting the most significant associations), and allow explicit reporting of multiple testing and correction for possible confounding by co-exposures.

The aim of this study, based on a hypothesis-free approach, was to evaluate the association between prenatal and postnatal environmental exposures and forced expiratory volume in 1 s (FEV_1) in childhood in the large European Human Early-Life Exposome (HELIX) cohort.[15]

Methods

Study design and population

This study was part of the HELIX project, which is based on six existing longitudinal population-based European birth cohorts (Born in Bradford [BiB; UK], Étude des Déterminants Pré et Postnatals du Développement et de la Santé de l'Enfant [EDEN; France], Infancia y Medio Ambiente [INMA; Spain], Kaunas Cohort [KANC; Lithuania], Norwegian Mother and Child Cohort Study [MoBa; Norway], and Mother-Child Cohort in Crete [RHEA; Greece]). Children in the cohorts were born in 2007–08 for BiB and RHEA, 2003–05 for EDEN, 2005–07 for INMA and MoBa, and 2007–09 for KANC, and all cohorts are still ongoing. In this study, we analysed the subcohort of 1301 mother–child pairs from singleton pregnancies characterised by the HELIX project for a wide range of environmental exposures, including urban, chemical, and lifestyle exposures (inclusion and selection criteria have been described previously),[15] from which we included children who did a valid spirometry test between the

	Description
Atmospheric pollutants	NO_2, $PM_{2.5}$, PM_{10}, PM_{abs}
UV	Ambient UV radiation levels
Surrounding natural space	Average Normalized Difference Vegetation Index within buffers of 100 m; presence of a major green space (ie, grass, trees, vegetation) or blue space (ie, visible water) within a distance of 300 m
Meteorology	Air temperature as measured by meteorological stations (mean, minimum, and maximum); humidity percentage as measured by meteorological stations; atmospheric pressure data from the ESCAPE project
Built environment	Population density: inhabitants per km^2; building density: built area in m^2 of buildings per km^2 within a 300 m buffer; street connectivity: number of road intersections per km^2 within a 300 m buffer; accessibility: metres of bus public transport lines and number of bus public transport stops per km^2 within a 300 m buffer; facilities: facility richness index* and facility density index* within a 300 m buffer; land use evenness index†; walkability index‡ within a 300 m buffer
Traffic	Total traffic load of major roads within a 100 m buffer, total traffic load within a 100 m buffer, traffic density on nearest road, and inverse distance to nearest road
Road traffic noise	Night-time road noise levels, 24 h road noise levels
Organochlorine compounds	Blood concentrations of dichlorodiphenyldichloroethylene, dichlorodiphenyltrichloroethane, hexachlorobenzene, PCB-118, PCB-138, PCB-153, PCB-170, and PCB-180, with lipid adjustment
Brominated compounds	Blood concentrations of PBDE-47 and PBDE-153, with lipid adjustment
Perfluorinated alkylated substances	Blood concentrations of perfluorooctanoate, perfluorononanoate, perfluoroundecanoate, perfluorohexane sulphonate, and perfluorooctane sulphonate
Metals and essential elements	Whole blood concentrations of arsenic, cadmium, ceasium, cobalt, copper, lead, manganese, mercury, molybdenum, and thallium
Phthalate metabolites	Urine concentrations of monoethyl phthalate, mono-iso-butyl phthalate, mono-n-butyl phthalate, mono benzyl phthalate, mono-2-ethylhexyl phthalate, mono-2-ethyl-5-hydroxyhexyl phthalate, mono-2-ethyl-5-oxohexyl phthalate, mono-2-ethyl 5-carboxypentyl phthalate, mono-4-methyl-7-hydroxyoctyl phthalate, mono-4-methyl-7-oxooctyl phthalate, with creatinine adjustment
Phenols	Urine concentrations of methyl-paraben, ethyl-paraben, bisphenol A, propyl-paraben, N-butyl-paraben, oxybenzone, and triclosan, with creatinine adjustment
Organophosphate pesticide metabolites	Urine concentrations of dimethyl phosphate, dimethyl thiophosphate, dimethyl dithiophosphate, diethyl phosphate, diethyl thiophosphate, and diethyl dithiophosphate, with creatinine adjustment
Water disinfection by-products§	Total concentration of total trihalomethanes, chloroform, and total brominated trihalomethanes estimated in tap water from water company concentration and distribution data
Indoor air¶	Prediction models for indoor air concentrations of NO_2, $PM_{2.5}$, PM_{abs}, benzene, and TEX (toluene, ethylbenzene, xylene) using panel study data from indoor air samplers
Lifestyle	Diet, physical activity, sleep duration, pets in the home
Socioeconomic capital	Frequency of contact with family and friends, social participation, family affluence score, house crowding

ESCAPE=European Study of Cohorts for Air Pollution Effects. HELIX=Human Early-Life Exposome. NO_2=nitrogen dioxide. PBDE=polybrominated diphenyl ether. PCB=polychlorinated biphenyl. $PM_{2.5}$=particulate matter of less than 2·5 µm in aerodynamical diameter. PM_{10}=particular matter of less than 10 µm in aerodynamical diameter. PM_{abs}=absorbance of $PM_{2.5}$ filters. UV=ultraviolet. *Developed by HELIX; facilities included businesses, community services, educational institutions, entertainment, financial institutions, hospitals, parks and recreation, restaurants, shopping, transportation hubs, and travel destinations. †Defined on the basis of the mathematical concept developed by Shannon and Weaver,[17] using the FRAGSTATS software program. ‡Adapted from the previous walkability indices[18,19] for the purposes of the HELIX project. §Only estimated for the prenatal window of exposure. ¶Only estimated for the postnatal window of exposure.

Table 1: **List of prenatal and postnatal exposures[16] assessed in this study**

ages of 6 and 12 years. The full HELIX protocol and database are described in detail elsewhere.[16]

Characterisation of the exposome during pregnancy and childhood

A broad spectrum of environmental exposures covering 17 exposure families were assessed in each mother–child pair, totalling 85 prenatal and 125 postnatal exposure variables (table 1).[20] Briefly, exposures to outdoor factors were assessed from spatial and remote sensing data through a geographical information system. Chemical exposures were measured in plasma, serum, whole blood, or urine samples. During childhood, questionnaire information was collected on socioeconomic capital of the family, based on the Family Affluence Scale (FAS)[21] and through summary variables for social participation, social contact, and house crowding. Information on other lifestyle factors, including active and passive smoking, diet, or physical activity, was collected through questionnaires. Exposure assessment methods (appendix pp 3–15), levels, and correlation patterns for all exposure variables are described elsewhere[12,20] and exposure level of our study population is described in the appendix (pp 16–24).

See Online for appendix

Spirometry data

The children were examined once between the ages of 6 and 12 years as part of the HELIX subcohort follow-up visit according to common protocols across the six cohorts. Lung function was measured by a spirometry test (EasyOne spirometer; NDD [New Diagnostic Design], Zurich, Switzerland), by trained research technicians using a standardised protocol. The child, sitting straight and equipped with a nose clip, was asked to perform at

	Included mother–child pairs (n=1033)										Excluded mother–child pairs (n=268)	
	Imputed values	Range (min to max)	Overall distribution	By-cohort distribution						p value of equality between cohorts*	Overall distribution	p value of equality between included and excluded pairs†
				BiB	EDEN	INMA	KANC	MoBa	RHEA			
Cohort	0	..	..	..	..	..	..	..	..	NA	..	<0·0001
BiB	..	..	147 (14%)	147 (100%)	..	..	..	..	..	..	58 (22%)	..
EDEN	..	..	159 (15%)	..	159 (100%)	..	..	..	..	..	39 (15%)	..
INMA	..	..	185 (18%)	..	..	185 (100%)	..	..	..	..	38 (14%)	..
KANC	..	..	144 (14%)	..	..	..	144 (100%)	..	..	..	60 (22%)	..
MoBa	..	..	242 (23%)	..	..	..	..	242 (100%)	..	..	30 (11%)	..
RHEA	..	..	156 (15%)	..	..	..	..	..	156 (100%)	..	43 (16%)	..
Child sex	0	..	..	..	..	..	..	..	..	0·95	..	0·0058
Female	..	..	489 (47%)	75 (51%)	74 (47%)	85 (46%)	69 (48%)	115 (48%)	71 (46%)	..	101 (38%)	..
Male	..	..	544 (53%)	72 (49%)	85 (53%)	100 (54%)	75 (52%)	127 (52%)	85 (54%)	..	167 (62%)	..
Child age (years) ‡	0	5·4 to 12·1	8·1 (1·6)	6·6 (0·2)	10·8 (0·6)	8·8 (0·5)	6·5 (0·5)	8·5 (0·5)	6·5 (0·3)	<0·0001	7·7 (1·6)	0·0003
Child height (m)	7 (1%)	1·1 to 1·7	1·3 (0·1)	1·2 (0·1)	1·4 (0·1)	1·3 (0·1)	1·2 (0·1)	1·3 (0·1)	1·2 (0·1)	<0·0001	1·3 (0·1)	0·0067
Season of conception	9 (1%)	..	..	..	..	..	..	..	..	<0·0001	..	0·43
January–March	..	..	327 (32%)	92 (34%)	54 (34%)	36 (19%)	38 (26%)	96 (40%)	46 (29%)	..	92 (34%)	..
April–May	..	..	213 (21%)	49 (18%)	35 (22%)	42 (23%)	24 (17%)	47 (19%)	51 (33%)	..	50 (19%)	..
July–September	..	..	217 (21%)	65 (24%)	26 (16%)	51 (28%)	49 (34%)	36 (15%)	33 (21%)	..	64 (24%)	..
October–December	..	..	276 (27%)	62 (23%)	44 (28%)	56 (30%)	33 (23%)	63 (26%)	26 (17%)	..	62 (23%)	..
Breastfeeding duration (weeks)	23 (2%)	3·2 to 7·6	4·9 (1·1)	4·3 (1·2)	4·1 (0·9)	5·1 (1·1)	5·1 (1·1)	5·8 (0·7)	4·8 (1·0)	<0·0001	4·9 (1·1)	0·66
Postnatal passive smoking status	23 (2%)	..	..	..	..	..	..	..	..	<0·0001	..	0·62
Exposed to smoke	..	..	370 (36%)	46 (31%)	45 (28%)	58 (31%)	64 (44%)	46 (19%)	111 (71%)	..	91 (34%)	..
Not exposed to smoke	..	..	663 (64%)	101 (69%)	114 (72%)	127 (69%)	80 (56%)	196 (81%)	45 (29%)	..	177 (66%)	..
Number of older siblings	20 (2%)	..	..	..	..	..	..	..	..	<0·0001	..	0·69
None	..	..	476 (46%)	62 (42%)	75 (47%)	104 (56%)	62 (43%)	116 (48%)	57 (37%)	..	118 (44%)	..
One	..	..	375 (36%)	43 (29%)	57 (36%)	73 (39%)	43 (30%)	90 (37%)	69 (44%)	..	97 (36%)	..
Two or more	..	..	182 (18%)	42 (29%)	27 (17%)	8 (4%)	39 (27%)	36 (15%)	30 (19%)	..	53 (20%)	..
Maternal age at pregnancy (years)	10 (1%)	16·0 to 43·5	30·9 (4·7)	28·3 (5·4)	30·6 (4·9)	32·0 (4·0)	29·5 (4·7)	32·8 (3·7)	30·9 (4·7)	<0·0001	30·1 (5·2)	0·021
Maternal pre-pregnancy BMI (kg/m^2)	17 (2%)	15·9 to 51·4	24·6 (4·8)	28·0 (5·1)	23·1 (4·1)	24·0 (4·5)	27·8 (4·9)	22·6 (3·2)	24·2 (4·4)	<0·0001	25·8 (5·5)	0·01
Prenatal maternal active smoking status	37 (4%)	..	..	..	..	..	..	..	..	<0·0001	..	0·88
Smoker	..	..	144 (14%)	16 (11%)	38 (24%)	44 (24%)	9 (6%)	2 (1%)	35 (22%)	..	39 (15%)	..
Non-smoker	..	..	889 (86%)	131 (89%)	121 (76%)	141 (76%)	135 (94%)	240 (99%)	121 (78%)	..	229 (85%)	..

(Table 2 continues on next page)

	Included mother–child pairs (n=1033)										Excluded mother–child pairs (n=268)	
	Imputed values	Range (min to max)	Overall distribution	By-cohort distribution						p value of equality between cohorts*	Overall distribution	p value of equality between included and excluded pairs†
				BiB	EDEN	INMA	KANC	MoBa	RHEA			
(Continued from previous page)												
Prenatal maternal active smoking (number of cigarettes per smoker per day)§	37 (4%)	0·0 to 33·3	3·9 (3·9)	4·5 (6·3)	1·2 (1·6)	3·9 (3·3)	4·8 (3·8)	4·9 (4·4)	2·2 (1·6)	0·0080	4·9 (6·5)	0·33
Prenatal maternal passive smoking status	14 (1%)	..	..	..	..	..	..	..	..	<0·0001	..	0·61
Exposed to smoke	..	..	408 (39%)	37 (25%)	39 (25%)	106 (57%)	75 (52%)	9 (4%)	142 (91%)	..	111 (41%)	..
Not exposed to smoke	..	..	625 (61%)	110 (75%)	120 (75%)	79 (43%)	69 (48%)	233 (96%)	14 (9%)	..	157 (59%)	..
Highest parental education level¶	15 (1%)	..	..	..	..	..	..	..	..	<0·0001	..	0·50
Tertiary	..	..	575 (56%)	109 (74%)	80 (50%)	83 (45%)	71 (49%)	183 (76%)	49 (31%)	..	153 (57%)	..
Upper secondary and post-secondary non-tertiary education	..	..	420 (41%)	24 (16%)	75 (47%)	92 (50%)	69 (48%)	58 (24%)	102 (65%)	..	109 (41%)	..
Less than primary, or primary and lower secondary	..	..	38 (4%)	14 (10%)	4 (3%)	10 (5%)	4 (3%)	1 (0%)	5 (3%)	..	6 (2%)	..
Both parents native to the cohort country	22 (2%)	..	..	..	..	..	..	..	..	<0·0001	..	0·60
Yes	..	..	868 (84%)	66 (45%)	143 (90%)	176 (95%)	140 (97%)	195 (81%)	148 (95%)	..	221 (82%)	..
No	..	..	165 (16%)	81 (55%)	16 (10%)	9 (5%)	4 (3%)	47 (19%)	8 (5%)	..	47 (18%)	..
FEV_1%‖	0	60·9 to 139·2	98·8 (13·2)	93·8 (14·1)	91·6 (9·1)	99·8 (11·9)	111·7 (12·6)	97·6 (10·6)	99·9 (12·7)	<0·0001	NA	NA
FEV_1 Z score‖	0	−3·8 to 3·0	−0·1 (1·1)	−0·6 (1·3)	−0·7 (0·8)	−0·0 (1·0)	0·9 (1·0)	−0·2 (0·9)	0·0 (1·0)	<0·0001	NA	NA
Asthma (doctor diagnosed)	6 (1%)	..	..	..	..	..	..	..	..	<0·0001	..	0·57
Yes	..	..	123 (12%)	27 (18%)	34 (21%)	8 (4%)	12 (8%)	29 (12%)	13 (8%)	..	28 (10%)	..
No	..	..	904 (88%)	120 (82%)	125 (79%)	173 (96%)	130 (92%)	213 (80%)	143 (92%)	..	239 (90%)	..

Data are number (%), range, or mean (SD), unless otherwise specified; distribution is presented as mean (SD) for continuous variables and number (%) for categorical variables computed on the imputed dataset. Mother–child pairs were excluded if they did not have a valid FEV_1 value. 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 and Child Cohort Study. RHEA=Mother-Child Cohort in Crete. NA=not applicable. BMI=body-mass-index. FEV_1=forced expiratory volume in 1 s. FEV_1%=forced expiratory volume in 1 s in percent predicted. *ANOVA tests were applied to compare means; χ^2 tests were applied to compare proportions. †t tests were applied to compare means; χ^2 tests were applied to compare proportions. ‡Child age varies across cohorts because the enrolment years differed between cohorts. §The value is computed over declared smokers in the second trimester of gestation only. ¶Education was defined using the International Standard Classification of Education. ‖FEV_1 was not imputed; distribution is given over all mother–child pairs with a valid FEV_1 value.

Table 2: **Population characteristics in all mother–child pairs, by cohort, and comparison between included and excluded mother–child pairs**

least six manoeuvres (if possible). Data from unacceptable manoeuvres as a result of errors, including hesitation or false starts, cough, variable efforts, glottis closure, early termination, and leaks, were not retained by the technicians. The protocol required that at least three acceptable manoeuvres were obtained, and that they were reproducible, defined as a difference of less than 200 mL between the two highest values for forced vital capacity (FVC) and FEV_1 taken from the acceptable manoeuvres.

We then applied the following validation criteria on the spirometer curves retained by the technicians. We defined a manoeuvre as acceptable if there was no hesitation or false start (defined as a ratio of backward extrapolated volume [BEV] to FVC of <5% or a BEV of <100 mL if FVC was <1000 mL) and if the forced expiratory time was in an acceptable range (>1·5 s and <10 s). The two highest values for FEV_1 taken from acceptable forced expiratory manoeuvres could not vary by more than 150 mL or by more than 5% from the second FEV_1. To address the efficiency of the FEV_1 data cleaning, the 243 examinations from the INMA cohort (185 of which were included in the HELIX study) were further investigated by trained investigators who looked at the shape of the curves; for 192 (79%) of the 243 examinations, the same curve was selected, and for the remaining 51 (21%), the Pearson correlation between the FEV_1 of the two different curves was 0·96.

We used the reference equations estimated by the Global Lung Initiative[22] for computing the FEV_1 percent predicted values (ie, values standardised by age, height, sex, and ethnicity of the patient) and FEV_1 Z scores. After excluding extreme values (ie, FEV_1 <60% or >140%, which were probably due to measurement error in our young population), we selected the greatest FEV_1 value at an individual level among all accepted curves, hereafter referred to as FEV_1%.

Statistical analysis

Exposures were transformed to approach normality. After imputing missing data for all exposures and adjustment factors, exposures were standardised by the IQR (appendix p 12).[20] We did statistical analyses for the prenatal (85 exposure variables) and the postnatal (125 exposure variables) exposome separately, using two approaches: a deletion-substitution-addition (DSA) algorithm, considering all exposures simultaneously, and an exposome-wide association study (ExWAS), considering exposures independently.[23]

DSA is an iterative linear regression model search algorithm, allowing at each iteration the removal of a term, substitution of one term for another, or addition of a term to the model. The final model is selected by minimising the value of the root-mean-squared error of predictions using five-fold cross-validated data. To stabilise estimates, the DSA was fitted 100 times on the data, and exposures were retained if they were selected in at least 5% of the runs. We repeated the DSA estimation testing for two-way interactions.[24]

The ExWAS consisted of a covariate-by-covariate estimation of the exposure–outcome association by independent linear regression models. For each exposure variable, results from the 20 imputed datasets were aggregated using Rubin's rules for multiple imputed data such that a unique p value was obtained.[25] To correct for multiple hypothesis testing, each p value was compared with a threshold, defined as 0·05 divided by the effective number of tests,[26] which estimates the number of truly independent tests that are done given the correlation structure of p values (46·5 and 70·8 effective numbers of tests for the prenatal and postnatal exposome, respectively). To account for potential co-exposure confounding, we further included in a multivariable linear regression (MLR) model all the

	Exposure family	Transformation before IQR standardisation	IQR	ExWAS*		ExWAS-MLR adjusting for potential confounding by co-exposure*†	
				Estimate (95% CI)‡	p value	Estimate (95% CI)‡	p value
PFNA (µg/L)	Perfluoroalkyl and polyfluoroalkyl substances	Log_2	0·83	−1·4 (−2·7 to −0·1)	0·034	−0·8 (−2·8 to 1·2)	0·42
PFOA (µg/L)	Perfluoroalkyl and polyfluoroalkyl substances	Log_2	0·77	−1·4 (−2·7 to −0·1)	0·030	−0·6 (−2·6 to 1·3)	0·52
Inverse distance to nearest road (m^{-1})	Traffic	Log_e	1·17	1·2 (0·1 to 2·2)	0·030	1·1 (0·1 to 2·2)	0·030

ExWAS=exposome-wide association study. FEV_1%=forced expiratory volume in 1 s in percent predicted. HELIX=Human Early-Life Exposome. IQR=interquartile range of the (transformed to approach normality) exposure variable. MLR=multivariable linear regression. PFNA=perfluorononanoate. PFOA=perfluorooctanoate. *Results are presented only for exposures with an (uncorrected for multiple hypothesis testing) p value of <0·05 in ExWAS. †Results from a multivariate linear regression model including all nine exposures with a (uncorrected for multiple hypothesis testing) p value of <0·20 in ExWAS except those that were too highly correlated (absolute correlation coefficient >0·90)—ie, PFOA, PFNA, inverse distance to nearest road, facility richness and facility density indexes, particular matter of less than 10 µm in aerodynamical diameter, presence of a major green or blue space, and total brominated trihalomethanes estimated in tap water. ‡Coefficient estimates are given for a change in mean FEV_1% for an IQR change in the given exposure.

Table 3: **Adjusted association between the prenatal exposome (85 exposures) and FEV_1% in 1033 children from the HELIX cohort (ExWAS analysis)**

exposure variables associated with FEV_1% with a p value of less than 0·20.

In previous simulation studies,[23,24] DSA had better model selection efficiency than several other regression-based methods in an exposome context similar to ours, mainly in terms of the false-positive rate (28%). However, the complementary ExWAS approach allowed an improved sensitivity (96% for ExWAS *vs* 73% for DSA), at the cost of a higher false-positive rate (86%).[23]

We adjusted all our models for a set of adjustment factors that were selected from the literature: the centre of recruitment (with a fixed effects model, which provides unbiased estimates [unlike a random effects model, which can lead to biased estimates], and which DSA can cope with), the child's sex, age, and height and parental country of birth (to avoid any residual confounding effect despite the fact that we accounted for these factors a priori when computing the percent predicted values), breastfeeding duration, season of conception, presence of older siblings, parental education level, maternal age, maternal pre-pregnancy body-mass index (BMI), postnatal passive smoking status, and prenatal maternal active and passive smoking status.

The cohort-specific estimates were computed independently for each exposure in an exposure–cohort interaction ExWAS, and used to compute the I^2 statistic,[27] measuring the between-cohort heterogeneity of the association between the exposure and FEV_1% (the lower the I^2 value, the most consistent the association).

We also did sensitivity ExWAS analyses to address the robustness of our results to the following factors: (1) the choice of adjustment factors (first, not adjusting for the child's age, sex, and height, and second, further adjusting for birth mode, gestational age, and the child's BMI, although these factors could act as mediators in the association between the exposure and FEV_1); (2) the outcome definition, by considering the FEV_1 Z score; and (3) specific subpopulations (considering first, exposure-specific complete data; second, children who did not report a [nose] cold at the time of the spirometry test; third, children who had never been diagnosed with asthma by doctors; and fourth, children who had been diagnosed with asthma at least once). We did not adjust for asthma in our main analysis because asthma could be an intermediate variable in the causal link between the prenatal exposome and lung function.

All analyses were done using R software (version 3.4). We used the software packages rexposome for drawing plots, mice for multiple imputation, and DSA for the DSA algorithm.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 1301 children in the HELIX project, 1033 (79%) had a valid FEV_1% value (≥70% of each cohort). FEV_1% ranged from 60·9% to 139·2%, with a median value of 98·6% (IQR 89·6–107·4) and a mean value of 98·8% (SD 13·2). At the time of the spirometry test, the median age of the 1033 children was 8·1 years (IQR 6·5–9·0). Variations were observed between cohorts for both median FEV_1%, from 91·4% (84·9–98·6) in EDEN to 113·9% (103·9–120·2) in KANC, and age (table 2; appendix p 42).

The median maternal age at pregnancy was 31·0 years (IQR 27·7–34·1) and the infants were breastfed for a median of 5·2 weeks (3·9–6·0). 544 (53%) of 1033 were boys and 476 (46%) had no older sibling. Most clinical and demographic characteristics were similar between the 1033 included and 268 excluded (because FEV_1% was not valid) mother–child pairs, but differed between cohorts (table 2).

With regard to the prenatal exposome, the ExWAS identified two perfluoroalkyl compounds—perfluorooctanoate and perfluorononanoate—associated with lower FEV_1% ($p<0·05$), with a mean FEV_1% change for each doubling in exposure level of –1·7% (95% CI –3·2 to –0·1) for perfluorooctanoate and –1·8% (–3·5 to –0·2) for perfluorononanoate. Table 3 and figure 1 present the results for an IQR increase in transformed exposure, for better comparability across exposures. Unexpectedly, the inverse distance to the nearest road during pregnancy was associated with an increased FEV_1% (mean change for a unit increase in $\log_e$-transformed exposure level was 1·0, 95% CI 0·1–1·9). None of the exposure–FEV_1% associations remained statistically significant when correcting for multiple testing (p value threshold of 0·001). Coefficients were consistent across cohorts (appendix pp 25–30, 43–44), although for the inverse

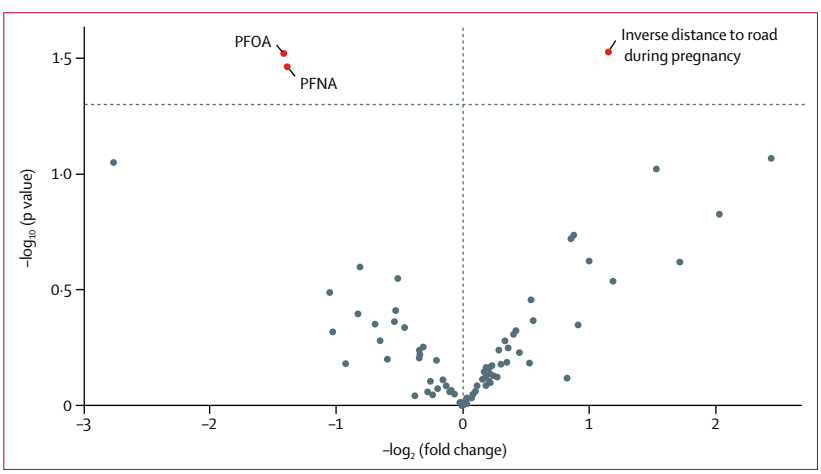

Figure 1: **Volcano plot of the coefficient estimates for prenatal exposure variables versus p value (uncorrected for multiple hypothesis testing) in the ExWAS analysis of the exposure–FEV_1% association**
Coefficient estimates are given in FEV_1% fold change for an IQR change in the given exposure, which was previously transformed to approach normality. The dashed horizontal line shows where p=0·05. ExWAS=exposome-wide association study. FEV_1%=forced expiratory volume in 1 s in percent predicted. PFNA=perfluorononanoate. PFOA=perfluorooctanoate.

	Exposure family	Transformation before IQR standardisation	IQR	ExWAS*		ExWAS-MLR adjusting for potential confounding by co-exposure*†	
				Estimate (95% CI)‡	p value	Estimate (95% CI)‡	p value
Facility density around school (number per km²)	Built environment	Log_e	1·32	−1·2 (−2·3 to −0·1)	0·027	−1·1 (−2·6 to 0·4)	0·16
Copper (μg/L)	Metals and elements	Log_2	0·16	−1·0 (−1·9 to −0·0)	0·041	−0·9 (−1·8 to 0·1)	0·064
Ethyl-paraben (μg/g of creatinine)	Phenols	Log_2	0·98	−0·5 (−1·0 to −0·1)	0·029	−0·6 (−1·2 to −0·1)	0·030
Sum of DEHP metabolites (μg/g of creatinine)	Phthalate metabolites	Log_2	0·85	−1·3 (−2·3 to −0·3)	0·014	−1·3 (−3·0 to −0·5)	0·15
MECPP (μg/g of creatinine)	Phthalate metabolites	Log_2	0·87	−1·3 (−2·3 to −0·2)	0·016	§	..
MEHHP (μg/g of creatinine)	Phthalate metabolites	Log_2	0·87	−1·2 (−2·2 to −0·2)	0·023	§	..
MEOHP (μg/g of creatinine)	Phthalate metabolites	Log_2	0·84	−1·3 (−2·3 to −0·3)	0·0085	§	..
OXOMiNP (μg/g of creatinine)	Phthalate metabolites	Log_2	1·34	−0·9 (−1·7 to 0·0)	0·040	−0·4 (−1·6 to 0·8)	0·50
House crowding (number of people)	Socioeconomic capital	None	1·00	−1·1 (−1·9 to −0·2)	0·015	−0·9 (−1·7 to 0·0)	0·039

DEHP= diethylhexyl phthalate. ExWAS=exposome-wide association study. FEV_1%=forced expiratory volume in 1 s in percent predicted. HELIX=Human Early-Life Exposome. IQR=interquartile range of the (transformed to approach normality) exposure variable. MECPP=mono-2-ethyl 5-carboxypentyl phthalate. MEHHP=mono-2-ethyl-5-hydroxyhexyl phthalate. MEOHP=mono-2-ethyl-5-oxohexyl phthalate. MLR=multivariable linear regression. OXOMiNP=mono-4-methyl-7-oxooctyl phthalate. *Results are presented only for exposures with an (uncorrected for multiple hypothesis testing) p value of <0·05 in ExWAS. †Results from a multivariate linear regression model including all 22 exposures with a (uncorrected for multiple hypothesis testing) p value of <0·20 in ExWAS except those that were too highly correlated (absolute correlation coefficient >0·90)—ie, facility density, building density around school, bus public transport lines around school, benzene in indoor air, presence of pets other than cats or dogs at home, house crowding, traffic density on nearest road to home address, presence of blue space around home address, copper, thallium, ethyl-paraben, methyl-paraben, oxybenzone, monobenzyl phthalate, mono-2-ethylhexyl phthalate, mono-4-methyl-7-hydroxyoctyl phthalate, OXOMiNP, sum of DEHP metabolites, diethyl phosphate, dimethyl thiophosphate, polybrominated diphenyl ether 153, and perfluorononoate. ‡Coefficient estimates are given for a change in mean FEV_1% for an IQR change in the given exposure. §The exposure variable was removed from the multivariate analyses because it was correlated at r>0·9 in absolute value with another exposure.

Table 4: **Adjusted association between the postnatal exposome and FEV_1% in 1033 children from the HELIX cohort (ExWAS analysis)**

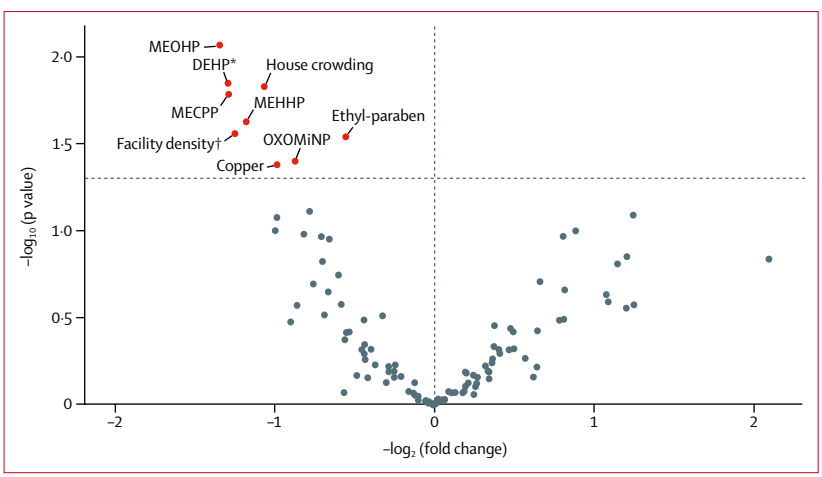

Figure 2: **Volcano plot of the coefficient estimates for postnatal exposure variables versus p value (uncorrected for multiple hypothesis testing) in the ExWAS analysis of the exposure–FEV_1% association** Coefficient estimates are given as the FEV_1% fold change for an IQR change in the given exposure, which was previously transformed to approach normality. The dashed horizontal line shows where p=0·05. ExWAS=exposome-wide association study. MECPP=mono-2-ethyl 5-carboxypentyl phthalate. MEHHP=mono-2-ethyl-5-hydroxyhexyl phthalate. MEOHP=mono-2-ethyl-5-oxohexyl phthalate. OXOMINP=mono-4-methyl-7-oxooctyl phthalate. *Sum of di-ethylhexyl phthalate metabolites. †Facility density within a 300 m buffer around school.

distance to nearest road the association was driven by the RHEA cohort (the association p value increased to 0·79 when excluding this cohort, whereas all other leave-one-cohort-out analyses of exposures identified in the prenatal and postnatal ExWAS gave p values of <0·30; data not shown). When adjusting for potential confounding due to co-exposure (jointly including the nine exposure variables associated at p<0·20), results remained consistent, but the magnitude of the association with perfluorooctanoate and perfluo-rononanoate decreased (table 3), probably because of their correlation with one another (r=0·61). The DSA model did not select any exposure–FEV_1% association, whether we tested for interaction terms or not.

For the postnatal exposome, the ExWAS identified nine exposure variables that were associated with a decrease in FEV_1%: four di-ethylhexyl phthalate (DEHP) metabolite exposures (mono-2-ethyl-5-oxohexyl phthalate [MEOHP], mono-2-ethyl-5-hydroxyhexyl phthalate [MEHHP], mono-2-ethyl 5-carboxypentyl phthalate [MECPP], and the sum of all DEHP metabolites; these four variables were strongly correlated, with all absolute r values of >0·9; mean FEV_1% change for a doubling in exposure level between −1·6 [95% CI −2·8 to −0·4] and −1·3 [−2·5 to −0·2]); one di-iso-nonylphthalate (DINP) metabolite (mono-4-methyl-7-oxooctyl phthalate [OXOMiNP], −0·6%, 95% CI −1·3 to −0·0); ethyl-paraben (−0·6%, −1·1 to −0·1); copper (−6·1%, −12·0 to −0·2); house crowding (mean FEV_1% change for a unit exposure increase, −1·1, −1·9 to −0·2); and facility density around school (mean FEV_1% change for a unit increase in log_e-transformed exposure level −0·9, −1·8 to −0·1). Table 4 and figure 2 present results for an IQR increase in transformed exposure, for better comparability across exposures. None of the exposure–FEV_1% associations remained statistically significant when correcting for multiple testing (p value threshold of 0·0007). No strong between-cohort heterogeneity (I^2>0·40) was observed, except for facility density (I^2=0·76), for which both negative (BiB, EDEN) and positive (RHEA) cohort-specific associations were observed (appendix pp 31–40, 45–47). When adjusting for potential confounding due to co-exposure, coefficient estimates remained similar but p values increased, and only those associated to ethyl-paraben and house crowding

had a p value of less than 0·05. The DSA model did not select any significant exposure–FEV_1% associations, whether we tested for interaction terms or not.

All ExWAS results for the prenatal and postnatal exposures (reported for an IQR increase in transformed exposure, for better comparability across exposures) are presented in the appendix (pp 25–40), including results of the exposure–FEV_1% association by cohort.

All exposures identified in ExWAS had less than 5% imputed values (<15% at the cohort level; appendix p 41). Each exposure displayed no absolute correlation above an *r* value of 0·7 with an exposure variable from another exposure family.

ExWAS results were robust to the choice of adjustment factors (appendix pp 48–49), to the outcome definition (when using FEV_1 Z scores; appendix pp 50–51) and to specific subpopulation (including to exposure-specific complete data; appendix pp 52–53). In the analysis of children with asthma, coefficients of the exposures remained consistent, but the 95% CIs increased given the lower sample size, and a stronger association between FEV_1% and perfluorooctanoate was observed.

Discussion

To our knowledge, this is the first study to address the effect of the exposome on lung function in children by considering a broad range of prenatal and postnatal environmental factors. Our results suggest that prenatal exposure to PFASs (perfluorononanoate and perfluorooctanoate) and postnatal exposure to copper, ethyl-paraben, DEHP and DINP metabolites, and house crowding are associated with a lower FEV_1 in childhood.

Regarding the chemical exposures, we observed associations between lung function in childhood and prenatal perfluorooctanoate and perfluorononanoate exposures, which are ubiquitous synthetic fluorinated compounds typically used as stain repellents because of their surfactant properties and hydrophobicity. The majority of exposure to PFASs can be attributed to diet, in-utero exposure through placental transfer, and breastfeeding. Our findings are in line with experimental studies reporting immunosuppressive effects of PFASs,[28] and animal models showing impaired lung development associated with exposure to PFASs—more specifically, induced airway inflammation and altered airway function[29]—possibly through oxidative stress mechanisms.[7] To date, epidemiological evidence for a role of PFAS exposure in respiratory outcomes in humans is scarce; only two studies relying on objective measures of lung function have been published.[7,30] One reported that postnatal concentrations of perfluorooctane sulphonate, perfluorooctanoate, perfluorohexane sulphonate, and perfluorononanoate were significantly negatively associated with spirometry measures in 132 children with asthma, but not in children without asthma.[7] Consistently, we noted a stronger association with prenatal perfluorooctanoate in children with asthma than in those without. Impinen and colleagues[30] did not observe significant associations between prenatal exposure to PFASs and lung function at birth assessed from tidal breathing variables (ratio of time taken to achieve peak tidal expiratory flow to total expiratory time).[30] Notably, Haug and colleagues[12] showed that perfluorooctane sulphonate and perfluorooctanoate exposures in mothers and children in the HELIX cohort often exceeded the HBM-I value (ie, the concentration of a substance in human biological material, above which individuals are considered at risk for adverse health effects according to the Human Biomonitoring Commission of the German Federal Environment Agency).[12] From a public health perspective, our findings, combined with the observations from Haug and colleagues, advocate the reduction of exposure to PFASs.

The strongest exposure–FEV_1% associations identified in our study were with postnatal exposure to DEHP metabolites (MECPP, MEHHP, MEOHP, and sum of DEHP metabolites), and one DINP metabolite (OXOMiNP), which are mainly used as plasticisers and can be either ingested, inhaled, or absorbed through dermal contact. Several of these phthalates have been highlighted in the literature for their negative association with FEV_1 in adults[31] and in children, and with other respiratory outcomes in children, including when exposed prenatally.[6,32,33] DEHP metabolites are suspected to affect the respiratory system, especially in the paediatric age group, possibly by promoting immunological and inflammatory mediators.[34] Our findings for DINP are of particular public health importance because the use of DINP is increasing in Europe as a substitute to DEHP, and it is now one of the most commonly used plasticisers.

Regarding phenols, we observed an inverse association with postnatal ethyl-paraben exposure, a compound used as a preservative in cosmetics; this is in line with a previous observation of an association between ethyl-paraben and FEV_1 at age 5 years in boys from the EDEN cohort, although for prenatal instead of postnatal exposure.[6] Other epidemiological studies have suggested that bisphenol A could contribute to the development of respiratory disorders in children,[35,36] but the timing of exposure and associated effects are conflicting. In the HELIX cohorts we did not identify an association between FEV_1 and prenatal or postnatal exposure to bisphenol A (0·4 [95% CI –0·7 to 1·6] and 0·4 [–0·4 to 1·2], respectively). This absence of association might partly be due to the exposure assessment from a single spot urine, which, for a compound with such a short half-life, leads to measurement error.[35] This measurement error could considerably bias dose–response functions towards the null, especially because the compound has high within-person variability.[37] Regarding metals, we found that copper, which in the general population is mainly ingested through drinking water and diet, was associated with lower FEV_1; this observation is in line with previous studies in adults, and might relate to the pro-oxidant activity of copper.[38]

Regarding socioeconomic factors, we found that a higher number of people living in the same house was associated with a lower FEV_1. The association between house crowding (median of four people per household in our population) and respiratory function is difficult to interpret, and epidemiological evidence is inconsistent.[39] On the one hand, in agreement with the hygiene hypothesis, house crowding is suspected to protect against allergic diseases.[40] On the other hand, it might be a risk factor for asthma and lower lung function through increased contact with pathogens that cause lower respiratory infections.[41]

This study covered many more exposures related to the urban and outdoor environment than most previous epidemiological studies. Of these new indicators, only facility density around schools was associated with a lower FEV_1. Greater facility density or diversity is expected to create a more walkable environment, but could also be related to higher exposure to hazardous factors in the urban environment, such as air pollution, noise, and reduced green space,[42] which could explain our association with a lower FEV_1. Regarding the atmospheric pollutants, meteorological factors, and green space indicators, which have rather well documented roles in child respiratory health,[43–46] none was linked to lung function in children in the HELIX cohort, except for inverse distance to the nearest road during pregnancy; the lack of robustness of this association across the cohorts suggests that this association might be spurious, as can be expected from large exposome studies.[23]

The main strengths of this study include its reliance on prospectively collected data from six European countries, with detailed and comprehensive assessment of the internal and external exposome, both prenatally and in childhood. An objective measurement of lung function in childhood was used for this study, assessed using a standardised protocol. The association study was done in accordance with a statistical protocol that was based on simulation studies identifying the most efficient statistical approaches to be used in the exposome context.[23,24] We relied on two regression methods that are complementary in terms of avoidance of false-positive and false-negative findings. The exposure–FEV_1 association estimates were reported for each exposure that was tested, avoiding problems of selective reporting.

Our study has several limitations. One relates to application of the exposome to real settings: with few financial and measurement tool resources, we had to make a choice in terms of the exposures that were investigated. This list does not include all exposures relevant for lung function (eg, exposure to volatile organic compounds or pollens was not included), but it does cover the largest set of exposures studied thus far. Additionally, the data collected in HELIX did not allow us to analyse trimester-specific effects of the exposures assessed by biomarkers. Secondly, the statistical power is limited by the multiplicity of the exposures that were tested (and even more when testing for two-way interaction effects)[24] and the rather small effect on lung function that is expected for these exposures; a larger population sample size could help to partly overcome this issue. Accounting for multiple comparisons in an exposome approach is not straightforward. However, compared with single-polluteant approaches, in which articles are independently published in a given cohort for several exposures without accounting for multiple exposure testing, the exposome approach represents a major step forward; it helps to avoid publication bias and allows better adjustment of exposure–health associations for potential co-exposure confounding, possibly at the cost of power because of multiple comparison corrections. Third, regarding environmental exposure assessment, measurement error bias is unavoidable and certainly of a different type and magnitude across the exposures. Therefore, in the context of the exposome approach, the comparison of the exposure–health association between exposures should be interpreted cautiously. Fourth, regarding the outcome assessment, although the spirometry tests were done by trained technicians following standardised protocols and current guidelines, forceful spirometry manoeuvres require strong patient cooperation, which is likely to be an issue for young children. Although we attempted to reduce this measurement error by refining acceptability and reproducibility criteria, the FEV_1 might have been underestimated for part of the study population; how this underestimation might have biased our estimate is difficult to say. Because young children are not always able to produce prolonged expirations to properly estimate lung volume, we did not analyse the ratio of FEV_1 to FVC, which might be more prone to measurement errors than FEV_1. We expect that the between-cohort variation in the FEV_1% values, for which the age difference across cohorts might partly be an explanation, would not have affected our results because our statistical analyses were all adjusted for centre of recruitment. Furthermore, each association observed at a p value of less than 0·05 was further investigated cohort by cohort to ensure that a similar pattern of association was observed across the cohorts. Finally, although a study of toxicological interactions between exposures would add to the holistic understanding of early environmental effects on lung function, many types of effects could be considered (eg, synergistic or antagonistic interactions), which we did not investigate in this study.

In conclusion, our study is, to our knowledge, the first to use a comprehensive exposome approach to report that specific prenatal and postnatal chemical exposures (phenols, phthalate metabolites, perfluoroalkyl substances) might be associated with the impairment of lung function development. These findings have important public health implications because they

suggest that preventive measures aimed at lowering exposure to the identified ubiquitous chemicals, through stricter regulation and informing the public by labelling these chemicals in consumer products, could help to prevent lung function impairment, which in turn should prevent the development of chronic respiratory disease in adulthood.

Contributors

LA, XB, RS, MV, and VS designed the analytical and statistical methods. LA analysed the data. LA, MV, and VS interpreted the results and wrote the paper. MV, OR, and LM coordinated the HELIX data collection. All authors contributed to the data collection and to the manuscript, and approved the manuscript.

Declaration of interests

We declare no competing interests.

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