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Multiple environmental exposures in early-life and allergy-related outcomes in childhood

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ABSTRACT

Introduction: Early onset and high prevalence of allergic diseases result in high individual and socio-economic burdens. Several studies provide evidence for possible effects of environmental factors on allergic diseases, but these are mainly single-exposure studies. The exposome provides a novel holistic approach by simultaneously studying a large set of exposures. The aim of the study was to evaluate the association between a broad range of prenatal and childhood environmental exposures and allergy-related outcomes in children.

Material and Methods: Analyses of associations between 90 prenatal and 107 childhood exposures and allergy-related outcomes (last 12 months: rhinitis and itchy rash; ever: doctor-diagnosed eczema and food allergy) in 6–11 years old children (n = 1270) from the European Human Early-Life Exposome cohort were performed. Initially, we used an exposome-wide association study (ExWAS) considering the exposures independently, followed by a deletion-substitution-addition selection (DSA) algorithm considering all exposures simultaneously. All the exposure variables selected in the DSA were included in a final multi-exposure model using binomial general linear model (GLM).

Results: In ExWAS, no exposures were associated with the outcomes after correction for multiple comparison. In multi-exposure models for prenatal exposures, lower distance of residence to nearest road and higher di-*iso*-nonyl phthalate level were associated with increased risk of rhinitis, and particulate matter absorbance (PM_{abs}) was associated with a decreased risk. Furthermore, traffic density on nearest road was associated with increased risk of itchy rash and diethyl phthalate with a reduced risk. DSA selected no associations of childhood exposures, or between prenatal exposures and eczema or food allergy.

Discussion: This first comprehensive and systematic analysis of many environmental exposures suggests that prenatal exposure to traffic-related variables, PM_{abs} and phthalates are associated with rhinitis and itchy rash.

Abbreviations: BiB, Born in Bradford; BMI, Body mass index; BUPA, N-butyl paraben; DAGs, Directed acyclic graphs; DEP, Diethyl phthalate; DiNP, Di-*iso*-nonyl phthalate; DSA, Deletion-substitution-addition selection (DSA); EDEN, Étude des Déterminants pré et postntals du development et de la santé de L'Énfant; ExWAS, Exposome-wide association study; GAM, Generalized linear models; GLM, General linear model; HELIX, The European Human Early-Life Exposome (HELIX) cohort; INMA, Infancia y Medio Ambiente; IQR, Interquartile range; KANC, Kaunus Cohort; MEP, Monoethyl phthalate; MoBa, Norwegian mother, father and childhood Study; NO_2, Nitrogen dioxide; OR, Odds ratio; Oxo-MiNP, Mono-4-methyl-7-oxooctyl phthalate; PFHxS, Perfluorohexane sulfonate; PFOA, Perfluorooctanoate; PFOS, Perfluorooctane sulfonate; OR, Particulate matter; PMabs, Particulate Matter absorbance; RHEA, RHEA Mother Child Cohort study; VIF, Variance inflation factor

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1. Introduction

The prevalence of allergy-related diseases, such as atopic dermatitis, rhinitis and food allergy, has increased the last decades (Platts-Mills 2015). In European children, the prevalence of these diseases are high (rhinitis: 9–23%; itchy rash; about 15%; eczema: 8–35% ; food allergy: 1–16%) (Austin et al. 1999, Garcia-Aymerich et al. 2015, Gupta et al. 2007, Mallol et al. 2013, Prescott et al. 2013, Williams et al. 1999). Additionally, allergic diseases often have an early onset and frequently develop into life-long chronic diseases with high individual and socio-economic burdens. Identification of factors affecting early immune system development and maturation is vital to reduce the prevalence of allergic diseases and the overall disease burden (Drucker 2017). Risk factors for allergic diseases are suggested to be genetic, lifestyle and/or environmental. The steep increase in prevalence of these diseases the last decades (Platts-Mills 2015) has been too rapid to be induced only by changes in the underlying genetic susceptibility of the population.

In daily life, individuals are exposed to a wide range of environmental factors simultaneously. The exposome concept, defined as encompassing all environmental exposures from conception onwards (Wild 2012), offers a new paradigm in environmental health research. By simultaneously considering a large set of exposures, the exposome approach overcomes some of the weaknesses of many existing studies focusing on a single or few exposures at a time (Siroux et al. 2016), by avoiding risk of selective reporting and allowing explicit reporting of multiple testing.

The aim of the present study was to evaluate the association between a broad spectrum of prenatal and childhood environmental exposures and allergy-related outcomes in children from the European Human Early-Life Exposome (HELIX) cohort, using an exposome approach.

2. Materials and methods

2.1. Study population

Six existing longitudinal population-based European birth cohorts were included in the HELIX project: the Born in Bradford (BiB) study (UK) (Wright et al. 2013), the Étude des Déterminants pré et postnatals du development et de la santé de l'Enfant (EDEN) (France) (Heude et al. 2016), the INfancia y Medio Ambiente (INMA) cohort (Spain) (Guxens et al. 2012), the Kaunus cohort (KANC) (Lithuania) (Grazuleviciene et al. 2009), the Norwegian Mother, Father and Child Cohort Study (MoBa) (Norway) (Magnus et al. 2016) and the RHEA Mother Child Cohort study (Greece) (Chatzi et al. 2017). The cohorts have large sets of previously collected longitudinal data from early pregnancy to

Table 1
List of prenatal and postnatal exposures included in the prenatal and/or childhood exposome.

Exposure group	Exposure variables[a]
Built environment	Population density : inhabitants per km^2 (home and school) Building density : built area in m^2 per km^2 within 300 m buffer (home and school) Street connectivity : number of road intersections per km^2 within 300 m buffer (home and school) Accessibility : Meters of bus public transport lines and number of bus public transport stops per km^2 within 300mbuffer (home and school) Facilities: facility richness index & facility density index in a 300 m buffer (home and school) Land Use Evenness Index (home and school) Walkability index within 300 m buffer
Air pollution	Nitrogen dioxide (NO_2), PM_{10}, $PM_{2.5}$, PM_{abs} (PM_{10} and $PM_{2.5}$ = mass concentration of particles less than 10 and 2.5 μm in aerodynamical diameter, respectively; PM_{abs} = absorbance of $PM_{2.5}$ filters)
Traffic variables	Total traffic load of major roads in a 100 m buffer (home and school)Total traffic load in a 100 m buffer Traffic density on nearest road Inverse distance to nearest road
Noise	Day (home and school) and night time road noise levels
Natural space	Average Normalized Difference Vegetation Index (NDVI) within 100 m buffer (home and school) Presence of a major green or blue space in a distance of 300 m (home and school)
Meteorology	Mean temperature from meteorological stations (pregnancy, last month before follow-up) Humidity percentage (average) from meteorological stations (pregnancy, last month before follow-up) Atmospheric pressure data (average) from the ESCAPE project (pregnancy) Vitamin D UV dose (last month before follow-up)
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
Tobacco smoke	Urine levels of cotinine, and questionnaire on active and passive smoking
Lifestyle and diet	Alcohol consumption, diet and physical activity during pregnancy Breastfeeding duration, diet, physical activity and pet keeping during childhood
Metals	Whole blood concentrations of arsenic (As), cadmium (Cd), ceasium (Cs), cobalt (Co), copper (Cu), lead (Pb), manganese (Mn), mercury (Hg), molybdenum (Mo), thallium (Tl)
Organochlorine compounds (OC)	Lipid adjusted blood concentrations of dichlorodiphenyldichloroethylene (DDE), dichlorodiphenyltrichloroethane (DDT), hexachlorobenzene (HCB), and polychlorinated biphenyl (PCB) – 118, 138, 153, 170 and 180, and sum of PCBs
Polybrominated diphenyl ether (PBDE)	Lipid adjusted blood concentrations of polybrominated diphenyl ether (PBDE) – 47, 153
Organophosphate pesticide (OP) metabolites	Urine concentrations of dimethyl phosphate (DMP), dimethyl thiophosphate (DMTP), dimethyl dithiophosphate (DMDTP), diethyl phosphate (DEP), diethyl thiophosphate (DETP) adjusted for creatinine
Perfluoroalkyl substances (PFASs)	Blood concentrations of perfluorooctanoate (PFOA), perfluorononanoate (PFNA), perfluoroundecanoate (PFUnDA), perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS)
Phenols	Urine concentrations of methyl paraben (MEPA), ethyl paraben (ETPA), bisphenol A (BPA), propyl paraben (PRPA), N-butyl paraben (BUPA), oxybenzone (OXBE), triclosan (TRCS) adjusted for creatinine
Phthalate metabolites	Urine concentrations of monoethyl phthalate (MEP), mono-*iso*-butyl phthalate (MiBP), mono-n-butyl phthalate (MnBP), mono benzyl phthalate (MBzP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), mono-2-ethyl 5-carboxypentyl phthalate (MECPP), mono-4-methyl-7-hydroxyoctyl phthalate (oh-MiNP), mono-4-methyl-7-oxooctyl phthalate (oxo-MiNP), sum of di-ethylhexyl phthalate (DEHP) metabolites. All adjusted for creatinine
Water disinfection by-products (WDB)	Total concentration of total trihalomethanes (THMs), chloroform, and total brominated THMs estimated in tap water from water company concentration and distribution data
Socio-economic capital	Family affluence score, social contact with friends and family, house crowding

[a] See Text S2 in Supplementary material for more detailed information of the variables. Exposure levels are described in Tables S1–S2 in Supplementary material.

childhood. Background information on the HELIX cohorts is described elsewhere (Haug et al. 2018, Maitre et al. 2018, Robinson et al. 2018, Tamayo-Uria et al. 2019) and in Text S1 Supplementary material. The HELIX subcohort consists of 1301 mother child-pairs that were additionally characterized for a wide range of chemical exposures (Vrijheid et al. 2014). The subcohort was established at the follow-up examination when the children were 6–11 years of age using common protocols for all the cohorts. The full HELIX protocol and cohorts are described in Maitre et al. (Maitre et al. 2018). After excluding participants with missing information on the allergy-related outcomes, 1270 mother–child pairs were included in the present study. Local ethical committees approved the studies that were conducted according to guidelines laid down in the Declaration of Helsinki. Written consents were provided from all parents.

2.2. Allergy-related outcomes

Information on the allergy-related outcomes were obtained through questions adapted from the International Study on Asthma and Allergy in Childhood (ISAAC) during the interview with the mother at the follow-up examination (i.e. 6–11 years of the child): “In the last year, has your child had problems with sneezing, or a runny, or blocked nose when he/she did not have a cold or the flu?” (hereafter called rhinitis); “Has your child had an itchy rash which was intermittently coming and going at any time in the past 12 months?” (hereafter called itchy rash); “Has your child ever been diagnosed by a doctor as having eczema or atopic dermatitis or neurodermatitis?” (hereafter called eczema); “Has your child ever had an allergic reaction to food, diagnosed by a doctor?” (hereafter called food allergy). Since itchy rash is a common feature in eczema, itchy rash will be regarded as “possible eczema” in the present study.

2.3. The prenatal and childhood exposomes

The HELIX project measured a broad spectrum of outdoor, urban, and contaminant exposures covering 18 exposure groups during pregnancy and at the subcohort follow-up: built environment, air pollution, traffic variables, road traffic noise, natural spaces, meteorology, indoor air, tobacco smoke, lifestyle and diet, metals, organochlorine compounds (OCs), polybrominated diphenyl ethers (PBDEs), organophoshate pesticide (OP) metabolites, perfluoroalkyl substances (PFASs), phenols, phthalate metabolites, water disinfection by-products and socio-economic capital (Table 1). In short, outdoor factors (built environment, air pollution, traffic, noise, natural spaces and meteorology) were estimated from monitoring stations, geospatial models, land use databases and satellite data, and were assigned to study participants according to their geocoded home address (pregnancy and childhood follow-up) and school address (childhood follow-up) using a Geographic Information System (GIS) platform. Chemicals were analysed in serum, plasma, whole blood or urine samples from the mother during pregnancy, cord whole blood and newly collected samples from the children at follow-up. Information on socioeconomic capital and lifestyle factors was collected through questionnaires. For the pregnancy period, exposure to water disinfection by-products was estimated in tap water from water company concentration and distribution data. For the childhood period, estimations were made for indoor air pollutants.

Methods, levels and correlation patterns for the exposures are described elsewhere (Haug et al. 2018, Maitre et al. 2018, Robinson et al. 2018, Tamayo-Uria et al. 2019) and in Text S2 and Tables S1–S2 in Supplementary material. In short, correlations between exposures were much lower between exposure groups compared to within exposure groups, which have important implications for co-exposure confounding in multiple exposure studies. Some correlations between exposures in the same exposure group reached high values above 0.8. The median correlation within exposure groups was > 0.3 for many exposure groups. Median correlations between different exposure groups rarely reached 0.3. Some correlations were driven by cohort-level associations. It should be noted that despite some high correlations, redundancy in the exposome data was still low. Ten principal components explained 45% and 39% of the total variance in the pregnancy and childhood exposome, respectively, while 65 and 90 components were required to explain 95% of the exposome variability (Tamayo-Uria et al. 2019).

More exposure variables than included in the present study were available in the HELIX project, but were not included in the current analysis for the following reasons: they had more than 70% missing values; they were calculated for several exposure windows (only the longest exposure window was included); or they had a correlation of 0.9 or higher with another similar variable within the exposure group (only one exposure variable representative of the group was included) (Tamayo-Uria et al. 2019).

Due to high correlation coefficients between the same exposure variable measured during pregnancy and childhood for many of the exposures (Tamayo-Uria et al. 2019), separate statistical analyses were performed for the prenatal and childhood exposomes. A total of 90 and 107 exposures were included in the prenatal and childhood exposome, respectively (Tables S1–S2 in Supplementary material).

2.4. Statistical analyses

For all exposures and covariates, the optimal transformation to approach normality was applied. Missing values for all exposures and covariates were imputed using the method of chained equations (White et al. 2011) (Text S3, Supplementary material). A total of 20 imputed datasets were generated and used in the statistical analyses; Rubin’s rule were used to aggregate the results (White et al. 2011). After imputation, continuous exposure variables were standardized by the interquartile range (IQR) for a better comparability of the association estimates across exposures.

The statistical methods, identified a priori through simulation studies (Agier et al. 2016), were:

(1) Exposome-wide association study (ExWAS) analyses using logistic regression models fitted independently for each exposure, avoiding the issue of collinearity amongst exposures. 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 (Li et al. 2012), which is an estimate of the number of truly independent tests that are performed, given the correlation structure of P-values (48.1 and 58.6 effective numbers of tests for the prenatal and postnatal exposome, respectively). This provided the corrected thresholds of 0.001 and 0.0009 for prenatal and childhood exposures, respectively.
(2) A deletion/substitution/addition algorithm (DSA) to select a reduced number of statistically significant exposures to be included in a final multi-exposure model using binomial general linear model (GLM). DSA uses cross-validation and has been shown to provide a lower proportion of false-positive findings compared to ExWAS (Agier et al. 2016, Barrera-Gomez et al. 2017). It is an iterative regression model search algorithm, allowing at each iteration to remove a term, substitute one term by another, or add a term to the model. The final model is selected by minimizing the value of the root mean squared error of predictions using 5-fold cross-validated data. DSA was applied to the 20 imputed dataset stacked one after the other using weight. The DSA algorithm is based on cross-validation, and repeating the selection process can lead to different sets of exposures retained. To stabilise the selection, DSA was fitted 50 times. Lastly, a multi-exposure binomial GLM was run including the exposures selected in at least 6% of the runs (n ≥ 3 runs) of the DSA models.

The final multi-exposure model is considered as our main analysis

and has been given most emphasis in the discussion.

For rhinitis and itchy rash, statistical analyses were performed separately for the prenatal and childhood exposomes, whereas only the prenatal exposome was analysed with regard to eczema and food allergy. Directed acyclic graphs (DAGs) were used to define the minimal sufficient adjustment sets to be included in all the statistical analyses (Figure S1 in Supplementary material). For the prenatal exposome, cohort, child's sex and ethnicity, trimester of conception, parity, maternal and paternal education, pre-pregnancy maternal body mass index (BMI) and maternal age were adjusted for. For the childhood exposome, cohort, child's sex, ethnicity and age, parity, nursery attendance in the first two years of life, and maternal and paternal education were adjusted for.

2.4.1. Sensitivity analyses

The following sensitivity analyses were performed on the final multi-exposure models.

Multiple cohorts: Since there are cohort-differences with regard to both exposures and outcomes, between-cohort heterogeneity was evaluated by means of the I^2 statistic. I^2 statistics quantifies the proportion of the variation in the effect estimates for each cohort that is due to heterogeneity rather than chance. What constitutes a large I^2 value is subjective. In the present study, we used the GRADE definition of an I^2-value < 40% as indicating a low degree of heterogeneity (GRADE 2013).

Collinearity: Collinearity, which can adversely affect the regression results, can occur when there is correlation between exposure variables in the statistical model. The variance inflation factor (VIF) estimates how much the variance of the regression coefficient is inflated due to collinearity in the model. A VIF greater than 10 indicates collinearity.

Linearity: The significant exposure-health associations were tested for linearity using generalized additive models (GAM) with or without smooth terms. The fit between the models were assessed using the Akaike Information Criteria (AIC), with difference in AIC > 3 defining different models. Since GAM cannot cope with multiple imputations, the linearity tests were applied on an one-imputed dataset.

Heredity: As parental history of allergic disease has been shown to induce a greater risk of disease development in the child, parental atopy was included as a covariate in the final multi-exposure model.

Statistical analyses were performed using the R software version 3.4 and 3.5 (www.r-project.org). The package *rexposome* was used for drawing plots, *mice* for multiple imputations, *DSA* for the DSA algorithm, *jtools* for collinearity check and *mgcv and gam* for linearity check in R. Between-cohort heterogeneity check was performed in Stata version 15 (www.stata.com) using the metan package.

3. Results

3.1. Population description

The prevalence of the allergy-related outcomes was 25% (range: (15–34%)) for rhinitis, 17% (7–27%) for itchy rash, 21% (16–35%) for eczema, and 10% (4–20%) for food allergy (Table 2). Except for itchy rash, there were statistical differences in the prevalence between cohorts for all outcomes.

Table 3
Description of the study population (N = 1270).

Covariate	Non-imputed values		Imputed values
	n (SD)	Missing (n)	n (SD)
Child's age yrs (IQR)	8.0 (2.4)	0	8.0 (2.4)
	n (%)		**n (%)**
Gender		0	
Female	571 (45)		571 (45)
Child's ethnicity[a]		27	
No native parents	136 (11)		142 (11)
Only one native parent	63 (5)		66 (5)
Both parents native	1044 (84)		1062 (84)
Parity		30	
No child	568 (45)		579 (46)
1 child	447 (35)		458 (36)
≥2 children	225 (18)		233 (18)
Season of conception		13	
Jan-March	401 (32)		407 (32)
April-June	253 (20)		255 (20)
July-Sept	274 (22)		277 (22)
Oct-Dec	329 (26)		331 (26)
Nursery attendance		26	
Yes	515 (41)		734 (58)
Pre-pregnancy maternal BMI		23	
< 18.5	49 (4)		49 (4)
18.5–24.9	711 (56)		724 (57)
25–29.9	305 (24)		309 (24)
≥30	182 (14)		188 (15)
Maternal education		43	
Low	170 (13)		180 (14)
Middle	427 (34)		437 (34)
High	630 (50)		653 (51)
Paternal education		87	
Low	207 (16)		236 (19)
Middle	465 (37)		486 (38)
High	511 (40)		548 (43)

[a] Defined as the parents' country of birth (country of the cohort or not).

At the time of examination, the childrens' average age was 8 years (SD: 2.4), 45% were females and 45% were first born (Table 3). In the first two years of life, 41% of the children had attended a nursery. Eleven percent of the children had no parents born in the cohort country. With regard to the mothers, 38% had a pre-pregnancy BMI above 25 (defined as overweight or obese (WHO 2018)), and 50% had high education. There were no statistically significant differences between the non-imputed and imputed values for any of the covariates. With regard to cohort differences, there was statistically significant differences for all covariates except gender (Table S3 in Supplementary material).

3.2. Rhinitis

Out of the 90 prenatal exposures studied, three were associated with rhinitis in the single-exposure ExWAS analyses at $p < 0.05$. None of these associations passed the multiple testing corrected p-value threshold of 0.001 (Table 4, Table S4 in Supplementary material). The DSA algorithm followed by the multi-exposure GLM identified the same prenatal exposures as the ExWAS: inverse distance of residence to

Table 2
Prevalence of the health outcomes in the total cohort and for the separate cohorts.

	Total (1270)	MoBa (264)	BIB (200)	KANC (191)	EDEN (197)	INMA (219)	RHEA (199)	P-value
Outcomes*								
Rhinitis n(%)	213 (25)	40 (15)	52 (26)	65 (34)	61 (31)	38 (17)	56 (28)	< **0.001**
Itchy rash n(%)	218 (17)	72 (27)	31 (16)	13 (7)	45 (23)	30 (14)	27 (14)	0.24
Eczema n(%)	262 (21)	50 (19)	42 (21)	30 (16)	33 (17)	76 (35)	31 (16)	< **0.001**
Food allergy n(%)	131 (10)	38 (14)	7 (4)	39 (20)	15 (8)	20 (9)	12 (6)	< **0.001**

* Parent-reported rhinitis and itchy rash the last year; Parent-reported doctor-diagnosed eczema and food allergy ever.

nearest road (OR per IQR increase [95%CI]: 1.3[1.1; 1.6]) and di-*iso*-nonyl phthalate (DiNP)-metabolite oxo-MiNP (OR per IQR increase: 1.2[1.0; 1.4]) were associated with an increased risk of rhinitis and PM_{abs} with a decreased risk (0.5[0.3; 0.9]) (Table 4). Associations between the covariates and the exposure variables that were significantly associated with rhinitis are shown in Table S5.

Of the 107 childhood exposures, six variables were associated with rhinitis in the ExWAS analyses at $p < 0.05$. Population density at home, blood cadmium and urinary BUPA levels were associated with an increased risk of rhinitis (OR per IQR increase [95% CI]: 1.3[1.0;1.6], 1.2[1.0;1.4] and 1.2[1.1;1.3], respectively) (Table 4, Table S6 in Supplementary material). Having a cat at home (0.7[0.5;1.0]), level of molybdenum and PFOS (OR per IQR increase: 0.9[0.8;1.0] and 0.8[0.6;1.0], respectively) were associated with a reduced risk of rhinitis . None of these associations remained statistically significant after correction for multiple comparisons ($p \leq 0.0009$). The DSA algorithm did not identify any childhood exposures associated with rhinitis.

3.3. Itchy rash

Out of the 90 prenatal exposures studied, three were associated with itchy rash in the ExWAS analyses at $p < 0.05$. None of these associations passed the multiple testing corrected p-value threshold of 0.001 (Table 4, Table S4 in Supplementary material). The DSA algorithm followed by the multi-exposure GLM identified the same prenatal exposures as the ExWAS. Traffic density on nearest road (OR per IQR

Table 4
Association between prenatal and childhood exposures, and allergy-related outcomes (N = 1270). The exposure variables with uncorrected ExWAS* p-value < 0.05 or those selected in ≥ 6% DSA runs are shown. IQR: for untransformed and unimputed data. Tables S4 and S6 in Supplementary material show ExWAS* results for all exposures and outcomes.

Exposure variable[a]	Exposure group	IQR	ExWAS		DSA	multi-exposure model	
			OR[95% CI][a]	p value	Frequency of selection (%)	OR[95% CI][a]	p value
Rhinitis							
Prenatal[b]							
PM_{abs} μg/m^3)	Air pollution	1.01	0.6 [0.4;0.9]	0.02	34	0.5 [0.3;0.9]	0.01
Inverse distance to nearest road (m^{-1})	Traffic	0.09	1.2 [1.0;1.5]	0.02	34	1.3 [1.1;1.6]	0.01
oxo-MiNP (μg/g)	Phthalates	1.01	1.2 [1.0;1.4]	0.04	32	1.2 [1.0;1.4]	0.05
Childhood[c]							
Population density at home address (inhabitants/km^2)	Built environment	6180	1.3 [1.0;1.6]	0.02	ns		
Cat at home	Lifestyle		0.7 [0.5;1.0]	0.03	ns		
Molybdenum (μg/L)	Metals	1.34	0.9 [0.8;1.0]	0.03	ns		
Cadmium (μg/L)	Metals	0.06	1.2 [1.0;1.4]	0.03	ns		
PFOS (μg/L)	PFASs	1.97	0.8 [0.6;1.0]	0.01	ns		
BUPA (μg/L)	Phenols	0.11	1.2 [1.1;1.3]	0.007	ns		
Itchy rash							
Prenatal[b]							
Traffic density on nearest road (vehicles/day)	Traffic	3500	1.3 [1.0;1.5]	0.03	14	1.3 [1.0;1.6]	0.02
Exposure to tobacco smoke during pregnancy (No exposure)	Tobacco smoke				16		
Only passive exposure			0.5 [0.3; 0.9]	0.01		0.5 [0.3; 0.9]	0.01
Smoker			0.9 [0.5; 1.5]	0.62		0.9 [0.5; 1.4]	0.56
MEP (μg/g)	Phthalates	375	0.8 [0.6; 1.0]	0.04	14	0.8 [0.6; 1.0]	0.03
Childhood[c]							
NO_2 (indoors) (μg/cm^3)	Air pollution	11	1.5 [1.0;2.3]	0.04	ns		
Total hours of sleep (hours)	Lifestyle	0.9	0.8 [0.6;1.0]	0.02	ns		
Sedentary behaviour (min/day)	Lifestyle	129	1.2 [1.0;1.5]	0.05	ns		
Arsenic (μg/L)	Metals	2.05	1.4 [1.0;1.8]	0.03	ns		
PFOA (μg/L)	PFASs	0.78	0.8 [0.6;1.0]	0.03	ns		
PFHxS (μg/L)	PFASs	0.42	0.7 [0.5;1.0]	0.04	ns		
BUPA (μg/g)	Phenols	0.11	1.2 [1.0;1.4]	0.04	ns		
Eczema							
Prenatal[b]							
None					ns		
Food allergy							
Prenatal[b]							
Traffic density on nearest road (vehicles/day)	Traffic	3500	0.8 [0.6;1.0]	0.02	ns		
Inverse distance to nearest road (m^{-1})	Traffic	0.09	1.4 [1.0;1.8]	0.04	ns		

ExWAS: Exposome-wide association study using logistic regression by each exposure independently.
DSA: Deletion/substitution/addition algorithm.
ns: not selected in the DSA model.
IQR: interquartile range.
* Significant after p-value correction based on the number of effective tests (i.e., p-value correction for multiple testing). Threshold for effective number of test = 0.001 for prenatal exposures, and 0.0009 for childhood exposures.
[a] Reference category as indicated inside brackets for the categorical variables. For continuous variables, estimates are calculated per IQR increase in exposure, as indicated inside brackets; IQRs calculated on the first imputed dataset after back transforming the variables.
[b] Adjusted for cohort, child's sex and ethnicity, trimester of conception, parity, maternal and paternal education, pre-pregnancy maternal body mass index (BMI) and maternal age.
[c] Adjusted for cohort, child's sex, ethnicity and age, parity, nursery attendance in the first two years of life, and maternal and paternal education.

increase [95%CI]: 1.3[1.0; 1.6]) was associated with increased risk of itchy rash and diethyl phthalate (DEP)-metabolite MEP (OR per IQR increase [95% CI]: 0.8[0.6; 1.0]) and passive exposure to smoke during pregnancy (OR[95% CI]: 0.5[0.3;0.9]; reference category "no exposure") were associated with a decrease in itchy rash (Table 4). Active smoking showed no association with itchy rash (OR[95% CI: 0.9[0.5;1.5]; reference category: "no exposure"). Associations between the covariates and the exposure variables that were significantly associated with itchy rash are shown in Table S5.

For childhood exposures, the ExWAS showed NO_2 levels indoors, sedentary behaviour of the child, arsenic levels and BUPA to be associated with an increase in itchy rash at $p < 0.05$ (OR per IQR increase [95% CI]: 1.5[1.0:2.3], 1.2[1.01;1.5], 1.4[1.0;1.8] and 1.2[1.;1.4], respectively. The child's total hours of sleep and the blood level of perfluoroalkyl substances PFOA and PFHxS were associated with a decrease in itchy rash (0.8[0.6;1.0], 0.8[0.6;1.0] and 0.7[0.5;1.0], respectively) (Table 4, Table S6 in Supplementary material). None of these associations remained statistically significant after correction for multiple comparisons ($p \leq 0.0009$). No childhood exposures were associated with itchy rash using the DSA algorithm.

3.4. Eczema

No prenatal exposures were associated with doctor-diagnosed eczema in the ExWAS ($p < 0.05$) or selected using the DSA algorithm (Table 4, Table S4 in Supplementary material).

3.5. Food allergy

For prenatal exposures, traffic density at the nearest road was associated with a decreased risk of food allergy, whereas inverse distance to the nearest road was associated with an increased risk of food allergy (OR per IQR increase [95% CI]: 0.8[0.6;1.0] and 1.4[1.0;1.8], respectively) (Table 4, Table S4 in Supplementary material). None of these associations remained statistically significant after correction for multiple comparisons ($p \leq 0.001$). No prenatal exposures were associated with food allergy using the DSA algorithm.

3.6. Sensitivity analyses

We found little evidence for heterogeneity of the associations between cohorts: for rhinitis and itchy rash, the I^2-values were all below 40% (Figs. S2–S3 in Supplementary material). Furthermore, we found little evidence for collinearity in the multiple exposure models in that VIFs were in the range of 1.1–4.6. The difference between the AICs from GAM with and without the smooth terms were below 3 for both rhinitis and itchy rash with regard to the prenatal exposure variables (1.5 and 0, respectively), indicating linear relationships between the exposure variables and the health outcomes. The final multi-exposure GLMs including parental atopy as a covariate showed similar risk estimates as in the main model (Table S7 in Supplementary material).

4. Discussion

The present study is a comprehensive and systematic investigation of associations between a broad spectrum of environmental exposures and allergy-related outcomes in childhood. Based on the final multi-exposure models our results suggest that prenatal exposure to inverse distance to nearest road and DiNP, which is the parent compound of the metabolite oxo-MiNP, are associated with an increased risk of rhinitis, whereas exposure to PM_{abs} is associated with decreased risk. Our findings further suggest that prenatal exposure to the traffic related variable traffic density on nearest road is associated with increased risk of itchy rash, whereas DEP, the parent compound of the phthalate metabolite MEP, and exposure to passive smoking during pregnancy are associated with a decreased risk. No significant associations were found between the prenatal exposome and eczema or food allergy, or the childhood exposome and any of the included health outcomes.

To our knowledge, we are the first to report on the relationship between traffic-related exposures during pregnancy and the risk of developing allergy-related health outcomes in childhood. However, when it comes to exposure to traffic-related variables during childhood, similar findings have been reported in a German study where a distance dependent relationship between living near a major road and both hay fever (rhinitis) and eczema were observed, with the highest risk for children (aged 4–6 years) living < 50 m from a busy street (Morgenstern et al. 2008). Furthermore, in two cross-sectional studies, an increased risk of eczema with road density and road proximity were seen in South Korean children aged 1–12 years (Yi et al. 2017) and an increased risk of allergic rhinitis with frequency of truck traffic in German children aged 12–15 years (Duhme et al. 1996). In the present study and in a study by Pujades-Rodriguez et al. examining children aged 2–15 years from UK (Pujades-Rodriguez et al. 2009), no statistically significant associations were found between childhood traffic-related exposures and risk of allergy development. However, in the present study there was a tendency of traffic density on nearest road being associated with an increased risk of itchy rash in the ExWAS analysis (OR[95% CI]: 1.3[1.0;1.8] for an IQR increase, $P = 0.09$) (Table S6 in Supplementary material).

With regard to prenatal exposure to soot particles outdoors (measured as PM_{abs}), a decreased risk of rhinitis was observed (OR[95% CI]: 0.5 [0.3;0.9] per IQR increase). In a German birth cohort study, similar finding were reported for estimates of PM_{abs} at the child's birth address and a decreased risk of rhinitis at age 10 years (OR[95% CI]: 0.75[0.58;0.96] per IQR increase) (Fuertes et al. 2013). Neither in the present nor the German study statistically significant associations were seen between childhood exposures and rhinitis. Furthermore, in a Dutch study, no associations were reported between PM_{abs} in childhood and itchy rash or eczema (Brauer et al. 2007). Childhood exposure to NO_2 and PM_{10} have been reported to increase the risk of rhinitis and eczema, as well as allergic sensitisation (Deng et al. 2016, Patel et al. 2011, Penard-Morand et al. 2010, Sbihi et al. 2015). The present study gives little support for these findings in that childhood exposure to outdoor NO_2, PM_{10} and $PM_{2.5}$, as well as indoor $PM_{2.5}$ was not associated with rhinitis or itchy rash (Table S6 in Supplementary material). Indoor NO_2 was associated with an increased risk of itchy rash in the ExWAS analysis, but only before correcting for multiple comparisons.

In the present study, inverse distance to nearest road during pregnancy was associated with an increased risk of rhinitis whereas PM_{abs} was associated with a reduced risk. Since PM_{abs}, a measure of soot particles, can be associated with vehicle traffic (Boogaard et al. 2010, China et al. 2014), our findings may seem conflicting. However, PM_{abs} was only weakly to moderately correlated to the traffic-related variables (Pearson's coefficient: 0.14–0.39, Table S8 in Supplementary material) (Robinson et al. 2018). Since PM_{abs} estimates also includes other primary combustion sources not related to traffic (*e.g.* wood-burning, coal-burning, heating, industry), this may explain the weak to moderate correlations coefficients.

In the present study, prenatal exposure to DiNP was associated with an increased risk of rhinitis. With regard to prenatal exposure to DEP, we observed a decreased risk of itchy rash. In two other studies on prenatal exposure to DEP, no significant association with eczema was observed (Gascon et al. 2015, Wang et al. 2014). There are, however, two studies reporting a decreased risk of eczema with prenatal exposure to DEHP and a principal component reflecting DiNP (Ait Bamai et al. 2018, Smit et al. 2015). Findings from animal studies with intraperitoneal or subcutaneous injections with DiNP suggest a Th2-dependent adjuvant effect on IgG1 and IgE in antigen-primed mice. These findings are supported by *in vitro* experiments where DiNP enhanced the expression of interleukin 4. It should be noted, however, that animal studies with either topical treatment or oral exposure to DiNP have failed to impact on cytokine expression (Bornehag and Nanberg, 2010;

Kimber and Dearman, 2010).

Since phthalates are high-production volume chemicals used in a large variety of consumer products, the general population is continuously exposed to phthalates. Due to their non-persistent nature with half-lives ranging from hours to days (Meeker et al. 2009), phthalate exposures are chronic but highly variable. Thus, the use of one spot urine, as in the present study for prenatal exposures and most other epidemiological studies, for analysing phthalate metabolites may lead to a high level of exposure misclassification reducing the ability to observe true significant associations. This may explain the inconsistent findings in the effects of prenatal phthalate exposure on the allergy-related outcomes in childhood.

The impact of maternal exposure to tobacco smoke during pregnancy on allergy-related outcomes is uncertain with some studies reporting no associations, whereas other studies report an increased risk of eczema and/or rhinitis (Kantor et al. 2016, Lee et al. 2012, Murray et al. 2004, Parazzini et al. 2014, Tanaka et al. 2017, Wang et al. 2008). In the present study, active maternal smoking during pregnancy was not associated with any of the allergy-related outcomes. However, there was a decreased risk of itchy rash in children of mothers passively exposed to smoke during pregnancy. There was a good accordance between reported status of exposure to smoke during pregnancy and maternal urine cotinine levels (biomarker of tobacco smoke exposure), indicating correct reporting by the mothers. On the contrary, there was no statistically significant association between the cotinine levels and children's itchy rash status (results not shown). The inconsistencies between itchy rash, reported smoke exposure and maternal cotinine levels may indicate that the association seen between maternal passive exposure to smoke during pregnancy and itchy rash can be due to other factors than smoke exposure, and that passive smoking may be a proxy for an unobserved variable. Furthermore, we consider the finding on smoke exposure and itchy rash as not being robust due to the lack of an "exposure–response" relation since the association with active smoking was not statistically significant, and since the estimates were not precise (wide confidence intervals). In addition, our findings are not concordant with the literature.

The sensitivity analyses performed on the final multi-exposure GLMs strengthens the exposure-health associations observed in the present study with regard to the prenatal exposures and rhinitis and itchy rash (low to moderate heterogeneity between cohorts; no collinearity between the exposure variables in the final models; linear exposure-health associations; parental atopy did not moderate the estimates in the final models).

The present study has several strengths such as: (1) The multicentre design with mother–child pairs from six European countries; (2) The use of standardised protocols to measure environmental exposures, including sensitive biomarkers for many chemical exposures and wide-range geospatial modelling of the outdoor and built environment; (3) The broad number of simultaneously assessed exposures both prenatally and in childhood is an approach representing a step forward; (4) The use of an optimal combination of *a-priori* selected statistical approach based on results of simulation studies (Agier et al. 2016, Barrera-Gomez et al. 2017). We used the ExWAS screening method that is characterised by its low false negative rate and high sensitivity, and the DSA that has a relatively low false positive rate and allowed adjustment for confounding by multiple exposures. Even though ExWAS is expected to give a higher false positive rate compared to DSA, statistically significant associations were only detected in the final multi-exposure GLMs including the exposure variables selected in the DSA algorithm. This could be related to the fact that the simulation studies were performed with linear regression models, whereas logistic regression models were applied in the present study, which may have led to different false positive rates than those found in the simulation studies.

Limitations of the study include: (1) The main limitation of the study is the small sample size increasing the likelihood of false negative findings (type 2 error). Statistical power in an exposome context is limited given by the heterogeneity of the exposures and the correction for multiple testing performed. However, it has recently been demonstrated that the ExWAS approach combined with false discovery rate correction for multiple comparisons, requires a sample size of 1000–2000 subjects to deal with 100 exposures and achieve power of 80% (Chung et al. 2019); (2) In longitudinal observational studies there is a risk of both reporting and recall bias. In addition, the parental-reported health outcomes used in the present study were not confirmed by the study personnel at the follow-up examination, increasing the risk of misclassification of the health outcomes; 3) With regard to environmental exposure assessment, misclassification bias is likely varying in type and magnitude between exposures. This is difficult to avoid (requiring repeated biosamples or more precise measurement tools). In the context of the exposome approach, the comparisons of strength of the exposure-health associations between exposures should, therefore, be interpreted cautiously; and 4) Unmeasured residual confounding cannot be excluded. In order to reduce the risk of biased effect estimates due to confounding, covariates to be included in the statistical analyses were carefully selected based on DAGs in which is regarded as an effective means of presenting expert-knowledge assumptions when selecting adjustment variables.

The exposome approach used in the present study aimed at systematically publishing all exposure-outcome associations, independently of their magnitude or statistical significance, thus avoiding publication bias. In addition, this approach corrected for multiple testing to reduce false positive results. This is not done when studies publish results in a series of papers each focusing on a single exposure or exposure group. Lastly, confounding by other exposures is usually not tackled in single exposure studies, whereas exposome studies, by including many exposure variables, can account for this. The first exposome studies have made a significant progress in understanding how multiple exposures correlate and co-exist, how the exposome varies geographically between European countries and over time, and how we may explore associations between multiple exposures and health. They have outlined the next set of exposome-related challenges, paving the way for the development of next-generation tools and data. Ideally, the statistical methods should be capable of handling a large set of exposures from different exposure groups, while considering correlation structures and accounting for multiple comparisons (Santos et al. 2020). With large number of comparisons, however, statistical power is an issue and novel approaches are needed not only to increase sample sizes, but also to improve accuracy of exposure estimates and reduce exposome dimensions.

5. Conclusions

By using a systematic exposome approach that avoids the issue of selective reporting, as well as confounding by other exposures and false positive findings, the present study suggests that prenatal exposure to traffic-related variables, PM_{abs} and phthalates can affect development of the allergy-related health outcomes rhinitis and itchy rash. The exposome approach can be used to prioritize environmental exposures to be included in further investigations.

CRediT authorship contribution statement

Berit Granum: Writing - original draft, Formal analysis, Investigation. **Bente Oftedal:** Writing - review & editing, Formal analysis. **Lydiane Agier:** Writing - review & editing, Methodology. **Valerie Siroux:** Writing - review & editing. **Philippa Bird:** Writing - review & editing. **Maribel Casas:** Writing - review & editing. **Charline Warembourg:** Writing - review & editing, Formal analysis. **John Wright:** Writing - review & editing, Conceptualization. **Leda Chatzi:** Writing - review & editing. **Montserrat de Castro:** Writing - review & editing. **David Donaire:** Writing - review & editing. **Regina**

Grazuleviciene: Writing - review & editing. **Line Småstuen Haug:** Writing - review & editing. **Lea Maitre:** Writing - review & editing. **Oliver Robinson:** Writing - review & editing. **Ibon Tamayo:** Writing - review & editing. **Jose Urquiza:** Writing - review & editing. **Mark Nieuwenhuijsen:** Writing - review & editing. **Remy Slama:** Writing - review & editing. **Cathrine Thomsen:** Writing - review & editing. **Martine Vrijheid:** Project administration, Funding acquisition, Supervision, Writing - review & editing, Conceptualization.

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 material

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