HELIX BUILDING THE EARLY-LIFE EXPOSOME

"The Human Early-Life Exposome
novel tools for integrating early-life environmental exposures and child health across Europe"

ENV-FP7-2012-308333

Annex I to Project Final Report

Tables & Figures

References & List of Beneficiaries

Tables

Table 1: Characteristics of the cohorts contributing to the HELIX cohort

Cohort	Recruitment in original cohort	Exclusions made during recruitment	Years of birth	Region covered by HELIX	N of births in HELIX entire cohort
BiB, United Kingdom [5]	All pregnant women who attended the oral glucose tolerance test clinic at Bradford Royal Infirmary in weeks 26-28 of pregnancy.	Women who planned to move away from Bradford before birth were excluded.	2007-2010	Bradford	10,849
EDEN, France [6]	Pregnant women who attended prenatal care at the University hospitals of Nancy and Poitiers recruited before 24 weeks of amenorrhea.	Twin pregnancies, women with known diabetes before pregnancy, insufficient French language skills, and intention to move away from the recruitment area were excluded.	2003-2006	Nancy & Poitiers, urban areas	1900
INMA, Spain [7]	Pregnant women who attended a prenatal care centre in the study region during weeks 10-6 of pregnancy.	Women who resided or intended to deliver outside the study area, who were under 16 years old, who had twin or multiple pregnancies, who had assisted reproduction, or who had communication problems were excluded.	2003-2008	Gipuzkoa Sabadell Valencia	2063
KANC, Lithuania [8]	Pregnant women who attended one of four prenatal care clinics affiliated to the hospitals of the Kaunas University of Medicine during first trimester of pregnancy.	Women who lived outside Kaunas municipality, had medical records of pregnancy induced hypertension and/or diabetes were excluded.	2007-2008	Kaunas	4107
MoBa, Norway [9]	Recruitment at the first ultrasound (US) scan, i.e.during the 17-18 week of gestation. All women who gave singleton births in the participating maternity units.	None	1999-2008	Oslo	11,095
RHEA, Greece [10]	Pregnant women who attended US examination before 15 week of pregnancy with residence in and near Heraklion at Crete.	Women who were under 16 years old or who had communication problems were excluded	2007-2008	Heraklion	1458
TOTAL					31,472

Table 2 Overview of measurements of chemical biomarkers of exposure and correction factors in the sub cohort.

	Compound	Abbreviation
Persistent compounds	**Organochlorine compounds**	
	2.3'.4.4'.5-Pentachlorobiphenyl	CB 118
	2,2',3,4,4',5'-Hexachlorobiphenyl	CB 138
	2,2',4,4',5,5'-Hexachlorobiphenyl	CB 153
	2,2',3,3',4,4',5-Heptachlorobiphenyl	CB 170
	2,2',3,4,4',5,5'-Heptachlorobiphenyl	CB 180
	4,4'dichlorodiphenyltrichloroethane	DDT
	4,4'dichlorodiphenyldichloroethylene	DDE
	Hexachlorobenzene	HCB
	Polybrominated diphenylethers (PBDEs)	
	2,2',4,4'-Tetrabromodiphenyl Ether	BDE 47
	2,2',4,4',5,5'-Hexabromodiphenyl ether	BDE 153
	Perfluoroalkyl substances (PFASs)	
	Perfluorohexane sulfonate	PFHxS
	Perfluorohexane sulfonate	PFOS
	Perfluorooctanoate	PFOA
	Perfluorononanoate	PFNA
	Perfluoroundecanoate	PFUnDA
	Elements	
	Mercury	Hg
	Cadmium	Cd
	Lead	Pb
	Arsenic	As
	Cesium	Cs
	Copper	Cu
	Thallium	Tl
	Manganese	Mn
	Zinc	Zn
	Cobalt	Co
	Molybdenum	Mo
	Sodium	Na
	Potassium	K
	Magnesium	Mg

	Compound	Abbreviation
	Phthalate metabolites	
	Monoethyl phthalate	MEP

Non-persistent compounds	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
	Phenolic compounds	
	Methyl paraben	MEPA
	Ethyl-paraben	ETPA
	Propyl-paraben	PRPA
	N-Butyl paraben	BUPA
	Bisphenol-A	BPA
	Oxybenzone	OXBE
	Triclosan	TCS
	Organophosphate pesticide metabolites	
	Dimethyl phosphate	DMP
	Dimethyl thiophosphate	DMTP
	Dimethyl dithiophosphate	DMDTP
	Diethyl phosphate	DEP
	Diethyl thiophosphate	DETP
	Diethyl dithiophosphate	DEDTP
	Cotinine	
	Other compounds	
	Creatinine	
	Phospholipids	
	Total cholesterol	
	Triglycerides	
	High density lipoproteins	
	Low density lipoproteins	

Table 3 Concentrations of environmental contaminants in blood and urine samples from mothers and children in the HELIX subcohort.

		Child samples				Maternal samples			
Compound	**Conc.unit**	**P50**	**Max**	**n reported samples**	**% quant. samples**	**P50**	**Max**	**n reported samples**	**% quant. samples**
CB 118	ng/g lipid	1.98	134	1279	99.8	2.64	39.0	829	79.1
CB 138	ng/g lipid	5.37	215	1279	99.8	9.10	132	1048	96.5
CB 153	ng/g lipid	11.6	217	1279	100	17.6	214	1048	99.6
CB 170	ng/g lipid	1.26	27.5	1279	90.7	3.69	84.5	826	99.5
CB 180	ng/g lipid	3.68	62.5	1279	99.2	10.4	201	1048	97.6
BDE 47	ng/g lipid	0.23	41.7	1279	90.8	0.43	34.74	684	80.8
BDE 153	ng/g lipid	0.16	16.5	1279	54.4	0.45	198	648	72.9
DDT	ng/g lipid	0.71	198	1279	79.8	1.33	94.1	826	65.6
DDE	ng/g lipid	21.8	2158	1279	100	52.3	1903	1048	99.9
HCB	ng/g lipid	8.19	88.1	1279	99.9	8.16	164	1048	99.1
PFOA	µg/L	1.55	6.66	1301	100	2.30	31.6	1240	99.7
PFNA	µg/L	0.47	11.5	1301	99.5	0.69	5.92	1240	97.9
PFUnDA	µg/L	0.03	1.51	1301	68.6	0.19	2.80	1032	95.4
PFHxS	µg/L	0.36	28.5	1301	99.7	0.55	21.0	1240	97.5
PFOS	µg/L	2.03	33.8	1301	99.8	6.41	48.0	1240	100
Hg	µg/L	0.86	20.1	1298	97.7	1.90	43.5	1020	98.9
Cd	µg/L	0.07	1.79	1298	86.5	0.22	27.9	833	99.6
Pb	µg/L	8.53	213	1298	100	9.66	187	833	100
As	µg/L	1.37	63.6	1298	67.1	1.19	90.1	833	58.5
Cs	µg/L	1.38	8.37	1298	100	1.56	10.9	833	100
Cu	µg/L	903	4460	1298	100	1420	2360	833	100
Tl	µg/L			1298	7.2			833	1.1
MEP	µg/g creat.	33.5	3197	1301	100	179	17733	1080	99.0
MiBP	µg/g creat.	41.8	861	1301	100	38.7	705	1088	99.9
MnBP	µg/g creat.	23.9	488	1301	100	29.6	6445	1089	100
MBzP	µg/g creat.	5.00	351	1301	99.9	7.33	775.1	1088	99.7
MEHP	µg/g creat.	2.88	282	1301	96.8	8.73	417	1085	99.5
MEHHP	µg/g creat.	20.1	2241	1301	99.8	18.2	967	1089	100
MEOHP	µg/g creat.	12.5	1289	1301	99.9	14.1	783	1089	100
MECPP	µg/g creat.	35.1	3681	1301	99.9	33.6	1361	913	99.9
oh-MiNP	µg/g creat.	5.36	548	1301	100	0.91	66.5	914	92.6
oxo-MiNP	µg/g creat.	2.83	680	1301	100	1.03	75.1	914	95.7
MEPA	µg/g creat.	6.50	23963	1301	99.7	167	39241	815	99.8
ETPA	µg/g creat.	0.67	2033	1301	99.3	6.26	6774	817	97.4

PRPA	µg/g creat.	0.22	1758	1301	67.3	44.2	12463	1083	97.3
BUPA	µg/g creat.	0.08	96.8	1301	96.6	3.37	371	1083	97.0
BPA	µg/g creat.	4.06	362	1301	98.3	2.82	107	1084	99.4
TrCS	µg/g creat.	0.61	702	1301	100	6.28	1653	1085	98.5
OXBE	µg/g creat.	2.16	7985	1301	99.9	4.90	12837	1085	99.3
DMP	µg/g creat.	0.78	83.3	1301	49.3	8.37	321	1080	90.8
DMTP	µg/g creat.	2.99	405	1301	90.4	4.96	220	1084	88.9
DMDTP	µg/g creat.			1301	18.2	0.19	134	969	41.6
DEP	µg/g creat.	1.83	665	1301	80.9	3.33	198	1082	97.8
DETP	µg/g creat.	0.18	78.5	1301	43.5	0.58	44.3	1037	50
DEDTP	µg/g creat.			1301	1.5			1084	1.7
Cotinine	µg/g creat.			1301	17.4	5.25	15410	1093	43.7

Table 4 List of spatial exposure variables

TOPIC	INDICATOR	DESCRIPTION
air pollution	NO_X, NO_2, $PM_{2.5}$, PM_{10}, PM_{abs}, PMcoarse	LUR exposures backextrapolated in time
UV	Erythemal UV, DNA damage UV and Vitamin-D UV dose	Erythemal UV, DNA damage UV and Vitamin-D UV dose
noise	L_{den} and L_{night}	Noise values from closest street or point location
green spaces	Greenness	Average NDVI within buffers of 100, 300 and 500m
green spaces	Major green/blue spaces	Straight line distance to nearest major space > 5,000m^2
green spaces	Major green/blue spaces	Distance and size of clostest major space
meteorology	Spatial resolution data	Land Surface Temperature (ºC)
meteorology	Temporal resolution data	Average meanTemperature, minTemperature, maxTemperature (ºC), humidity (%), pressure (bar)
built environment	Population density	inhabitans/km^2
built environment	Building density	m^2 built/km^2 within buffers of 100, 300 and 500 m
built environment	Connectivity density	number of intersections / km^2 within buffers of 100 and 300m
built environment	Accessibility	Meters of public transport mode lines inside each 100m buffer, divided by the buffer area in km^2
built environment	Accessibility	Number of bus public transport mode stops inside each 100m buffer, divided by the buffer area in km^2
built environment	Facility richness index	number of different facility types present divided by the maximum potential number of facility types specified, in a buffer of 300 meters
built environment	Facility density index	number of facilities present divided by the area of the 300 meters buffer
built environment	Land Use Evenness Index	minus the sum, across all land use types, of the proportional abundance of each land use type multiplied by that proportion, divided by the logarithm of the number of land use types, in a buffer of 300 meters
built environment	Walkability index	how 'walkable' is a buffer of 300 meters around each geocode
built environment	Trafmajorload	Total traffic load of major roads in a 100m buffer
built environment	Trafload	Total traffic load in a 100m buffer
built environment	Trafnear	Traffic density on nearest road
built environment	Distinvnear	Inverse distance to the nearest road

Table 5.1 Final number of samples and features in –omics datasets after the quality control process

			HELIX (N=1301)			
Omics	Platform	Features	1X	1A	1B	Subcohort (1X+1A)
Proteomics	Luminex	36	1020	150	154	1170
Methylation	450K, Illumina	386518	1024	149	153	1173
Transcriptomics	HTA v2.0, Affymetrix	35841	889	121	127	1010
miRNA	SurePrint Human miRNA rel 21, Agilent	330	821	120	123	941
Urinary metabolomics	1H NMR	44	1043	155	153	1198
Sera metabolomics	AbsoluteIDQ p180 kit, Biocrates	177	1044	154	154	1198
Telomer lenght (TL)	qPCR	1	1016	150	153	1166
Mitochondrial DNA content (mt DNA content)	qPCR	1	1016	150	153	1166
Cell counts	blood smear	6	1111	154	147	1265

Table 5.2 Overlap of samples with several omics data.

Data overlap	N HELIX
HELIX children health outcomes (follow up)	1630
HELIX children with health outcomes (follow up) and exposome data (NIPH biomarkers)	1301
+ urinary metabolomics	1198
+ urinary metabolomics + sera metabolomics	1192
+ urinary metabolomics + sera metabolomics + proteomics	1152
+ urinary metabolomics + sera metabolomics + proteomics + DNA methylation	1122
+ urinary metabolomics + sera metabolomics + proteomics + DNA methylation + transcriptomics	880
+ urinary metabolomics + sera metabolomics + proteomics + DNA methylation + transcriptomics + miRNA	874
+ urinary metabolomics + sera metabolomics + proteomics + DNA methylation + transcriptomics + miRNA + TL + mtDNA content	866
+ urinary metabolomics + sera metabolomics + proteomics + DNA methylation + transcriptomics + miRNA + TL + mtDNA content + cell counts	843

Table 6 List of exposures estimated for HELIX subcohort for the pregnancy and postnatal periods.

Exposure family (Number of exposure variables)	Exposure indicator	Unit	Exposure window or spatial buffer (IQR)
Outdoor exposome			
Built environment (15)	Length of public transport mode lines	Meter per km^2	100m buffer ([b]) [a] 300m buffer ([b]) 500m buffer ([b]) [a]
	Number of bus public transport mode stops	Number of stops /km^2	100m buffer ([b]) [a] 300m buffer (14.2) 500m buffer (15.4) [a]
	Number of facility [c] types		300m buffer (0.1)
	Number of facilities [c]	Number of facilities / km^2	300m buffer (49.5)
	Land use Shannon's Evenness Index [d]		300m buffer (0.2)
	Walkability index [e]		At pregnancy address (0.1)
	Connectivity density	Number of intersections /km^2	100m buffer (192.2) [a] 300m buffer (167.3)

	Build density	Square meter with buildings / km^2	100m buffer (164,685) [a] 300m buffer (149,341)
	Population density [f]	People / km^2	At pregnancy address (6,874)
Air pollution (16)	NO_2 [g]	Microgram per cubic meter	T1(13.3) [a] T2 (13.0) [a] T3(12.4) [a] Preg (11.2)
	PM_{10} [g]		T1 (11.2) [a] T2 (11.4) [a] T3 (11.8) [a] Preg (11.2)
	$PM_{2.5}$ [g]		T1 (5.1) [a] T2 (5.2) [a] T3 (4.5) [a] Preg (3.8)
	$PM_{2.5}$ absorbance [g]		T1 (1.0) [a] T2 (1.0) [a] T3 (1.0) [a] Preg (1.0)
Noise (2)	Day and night noise [h]	Decibel	At pregnancy address ([b])
	Night noise [h]		At pregnancy address ([b]) [a]
Meteorology (13)	Temperature [g]	Celsius degrees	T1(10.9) [a] T2 (11.0) [a] T3(10.2) [a] Preg (5.7)
	Pressure [g]	Bar	T1 (23.6) [a] T2 (21.5) [a] T3(23.2) [a] Preg (21.2)
	Humidity [g]	Percentage	T1 (19.3) [a] T2 (18.1) [a] T3 (18.1) [a] Preg (15.1)
	Land surface temperature from satellite image [i]	Degrees Celsius	At pregnancy address (3.0) [a]
Natural space (5)	NDVI [jg]		100m buffer (0.3) 300m buffer (0.2) [a] 500m buffer (0.2) [a]
	Green space [k]	Squared meter for	Presence in 300m buffer ([b])

		size, m for distance	
	Blue space [k]	meter	Presence in 300m buffer ([b])
Traffic variables (4)	Traffic load of major roads	Number of vehicles per day	100m buffer ([b]) [a]
	Traffic load of all roads	Number of vehicles per day	100m buffer (1,655,702)
	Traffic density on nearest road	Number of vehicles/day	From pregnancy address (3,500)
	Inverse distance to nearest road	Inverse meter	From pregnancy address (0.1)
Metals [l] (10)	Arsenic	Microgram per litter	Pregnancy measure (2.2)
	Cadmium		Pregnancy measure (0.2)
	Cobalt		Pregnancy measure (0.2)
	Caesium		Pregnancy measure (1.0)
	Copper		Pregnancy measure (350.0)
	Mercury		Pregnancy measure (2.6)
	Manganese		Pregnancy measure (5.7)
	Molybdenum		Pregnancy measure (0.3)
	Lead		Pregnancy measure (5.9)
	Thallium (dichotomized)		Pregnancy measure ([b])
Lifestyle (14)	Meat consumption [g]		Pregnancy measure ([b])
	Fish consumption [g]		Pregnancy measure ([b])
	Vegetables consumption [g]		Pregnancy measure ([b])
	Fruit consumption [g]		Pregnancy measure ([b])
	Dairy consumption [g]		Pregnancy measure ([b])
	Legume consumption [g]		Pregnancy measure ([b])
	Cereal consumption [g]		Pregnancy measure ([b])
	Fast food consumption [g]		Pregnancy measure ([b])
	Folic acid supplementation during pregnancy		Pregnancy measure ([b])
	Walking and/or cycling activity during pregnancy [m]		T1 ([b]) [a] T3 ([b])
	Exercise or sport activity during pregnancy [m]		T1 ([b]) [a] T3 ([b])
	Alcohol consumption during pregnancy		Pregnancy measure ([b])
Organochlorine compounds (OC) [n,o] (9)	Dichlorodiphenyldichloroethylene (DDE)	Nanogram per gram of lipids	Pregnancy measure (90.3)
	Dichlorodiphenyltrichloroethane (DDT)		Pregnancy measure (2.4)
	Hexachlorobenzene (HCB)		Pregnancy measure (6.6)

	PCB118; PCB138; PCB153; PCB170		Pregnancy measure (2.8;10.2;19.2;5.6)
	PCB180		Pregnancy measure[a] (12.2)
	Sum of PCBs		Pregnancy measure (46.3)
Polybrominated diphenyl ether (PBDE) [n,o] (2)	PBDE47, PBDE153	Nanogram per gram of lipids	Pregnancy measure (0.9,0.6)
Organophosphate pesticides (OP) [n,p] (6)	Dimethyl phosphate (DMP)	Microgram per gram of creatinine	Pregnancy measure (11.4)
	Dimethyl thiophosphate (DMTP)		Pregnancy measure (9.9)
	Dimethyl dithiophosphate (DMDTP)		Pregnancy measure (4.9) [a]
	Diethyl phosphate (DEP)		Pregnancy measure (4.5)
	Diethyl thiophosphate (DETP)		Pregnancy measure (2.2)
	Dichotomous variable of diethyl dithiophosphate (DEDTP)		Pregnancy measure ([b])
Perfluoroalkyls (PFA) (5)	Perfluorooctanoate	Microgram per litter	Pregnancy measure (2.0)
	Perfluorononanoate		Pregnancy measure (0.7)
	Perfluoroundecanoate		Pregnancy measure (0.2)
	Perfluorohexane sulfonate		Pregnancy measure (0.6)
	Perfluorooctane sulfonate		Pregnancy measure (5.5)
Phenols [n,p] (7)	Methyl paraben (MEPA)	Microgram per gram of creatinine	Pregnancy measure (354.1)
	Ethyl paraben (ETPA)		Pregnancy measure (29.7)
	Propyl paraben (PRPA)		Pregnancy measure (130.3)
	Bisphenol A (BPA)		Pregnancy measure (4.9)
	N-Butyl paraben (BUPA)		Pregnancy measure (12.4)
	Oxybenzone (OXBE)		Pregnancy measure (23.7)
	Triclosan (TRCS)		Pregnancy measure (62.7)
Phthalates [n,p] (11)	Monoethyl phthalate (MEP)	Microgram per gram of creatinine	Pregnancy measure (387.3)
	Mono-iso-butyl phthalate (MiBP)		Pregnancy measure (39.1)
	Mono-n-butyl phthalate (MnBP)		Pregnancy measure (30.1)
	Mono benzyl phthalate (MBzP)		Pregnancy measure (14.1)
	Mono-2-ethylhexyl phthalate (MEHP)		Pregnancy measure (10.0)
	Mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP)		Pregnancy measure (20.5)
	Mono-2-ethyl-5-oxohexyl phthalate (MEOHP)		Pregnancy measure (15.3)
	Mono-2-ethyl 5-carboxypentyl phthalate (MECPP)		Pregnancy measure (29.6)
	Sum of Di-EthylhexylPhthalate		Pregnancy measure (118.3)

	(DEHP) metabolites		
	Mono-4-methyl-7-hydroxyoctyl phthalate (OHMiNP)		Pregnancy measure (0.9)
	Mono-4-methyl-7-oxooctyl phthalate (OXOMiNP)		Pregnancy measure (1.2)
Water disinfection by-products [q] (12)	Total concentration of trihalomethanes (THM)	Microgram per liter	T1 (53.2) [a] T2(49.5) [a] T3(62.2) [a] Preg (39.8)
	Chloroform		T1(25.8) [a] T2 (26.0) [a] T3 (26.0) [a] Preg (13.4)
	Brominated THMs		T1 (84.0) [a] T2 (15.0) [a] T3 (16.1) [a] Preg (15.2)

IQR: inter-quantile range of the (untransformed) exposure variable; NDVI: normalized difference vegetation index; NO_2: nitrogen dioxide; PBDE: polybrominated diphenyl ether; PCB: polychlorinated biphenyl; $PM_{2.5}$: particulate matter in the ambient air with an aerodynamical diameter below 2.5 micrometers; PM_{10}: particulate matter in the ambient air with an aerodynamical diameter below 10 micrometers; preg: whole pregnancy average; T1: averaged during trimester 1 of pregnancy; T2: averaged during trimester 2 of pregnancy; T3: averaged during trimester 3 of pregnancy.

[a] Removed from the multivariate analyses for being redundant with or being highly correlated with another exposure variable.

[b] Dichotomous or categorical variable, or variable that was dichotomized because >60% of subjects had the same value.

[c] Facilities from each study area were obtained using NAVTEQ. Facilities were all points of interest for pedestrians as part of their daily life activities, like restaurants, shops, medical centers, schools, libraries, etc (https://wego.here.com/. Accessed: 19th December 2016).

[d] Land Use Evenness Index equals minus the sum, across all land use types, of the proportional abundance of each land use type multiplied by that proportion, divided by the logarithm of the number of land use types, in a buffer of 300 meters. In other words, the observed Shannon Diversity Index(Shannon 1948) divided by the maximum Shannon's Diversity Index for that number of land use types.

[e] A walkability index for HELIX was developed by ISGlobal to quantify how 'walkable' is a location. It is based on the methods of Frank et al.(Frank et al. 2006) and Walk Score (https://www.walkscore.com/terms-of- use.shtml, Accessed: 19th December 2016).

[f] Population density is the number of inhabitant per square kilometer. It used local layers but if they were not available we used raster data on population density using Corine Land Cover

2000 inventory (Gallego 2010) produced by European Environment Agency (EEA).

[g] Averaged value over the given exposure windows.

[h] Noise values from closest street or point location. The noise assessment was carried out with the help of existing European road traffic noise maps, which were generated for larger agglomerations >250,000 inhabitants) during the first round of strategic noise mapping under EC Directive 2002/49/EC (Assessment and Management of Environmental Noise) in the framework of the European Noise Directive.

[i] Land surface temperature is derived from the Landsat 4-5 Thematic Mapper (TM) and Landsat 8 Thermal Infrared Sensor (TIRS) data at 30m x 30m resolution. The first process was to convert the Digital Numbers (DN) to at-Sensor Radiance from thermal infrared band (band 6 in Landsat 4-5 TM and band 10 in Landsat 8 TIRS) and then convert radiance to brightness temperature. Finally, Land Surface Temperature was obtained by performing correction of

brightness temperature against Land Surface Emissivity through Planck Equation (Artis and Carnahan 1982; Sinha et al. 2014).

[j] NDVI is derived from the Landsat 4–5 Thematic Mapper (TM), Landsat 7 Enhanced Thematic Mapper Plus (ETM+), and Landsat 8 Operational Land Imager (OLI)/Thermal Infrared Sensor (TIRS) with 30m x 30m resolution. Landsat data was acquired for the study period and averaged.

[k] The Europe-wide "Urban Atlas" (prepared by European Environmental Protection Agency) was used to extract maps of urban and natural green and blue spaces across HELIX study regions (http://www.eea.europa.eu/data-and-maps/data/urban-atlas, Accessed: 28th November 2016).

[l] Measured in blood.

[m] Categorical variable.

[n] The biomarker measure were adjusted for creatinine/lipids.

[o] Measured in serum or plasma.

[p] Measured in urine.

[q] We collected routine DBP measurements from water companies. This has built on the work of the EC FP-6 HiWate project (Health Impacts of long-term exposure to disinfection byproducts in drinking Water) that previously modelled exposure levels in the water supply of the residence of each participating family.

Table 7 Description of the study population

	All (N=1301)	BIB (N=205)	EDEN (N=198)	INMA (N=223)	KANC (N=204)	MOBA (N=272)	RHEA (N=199)
Age	4.57 (0.72)	4.26 (0.86)	4.54 (0.72)	4.75 (0.59)	4.33 (0.73)	4.85 (0.55)	4.58 (0.71)
Gender							
Female	710 (54.62)	113 (55.12)	113 (57.07)	120 (53.81)	111 (54.68)	142 (52.21)	111 (55.78)
Male	590 (45.38)	92 (44.88)	85 (42.93)	103 (46.19)	92 (45.32)	130 (47.79)	88 (44.22)
Education							
Low	173 (13.76)	87 (48.07)	12 (6.12)	53 (23.87)	12 (6.03)	0 (0)	9 (4.57)
Medium	433 (34.45)	32 (17.68)	73 (37.24)	92 (41.44)	71 (35.68)	55 (20.99)	110 (55.84)
High	651 (51.79)	62 (34.25)	111 (56.63)	77 (34.68)	116 (58.29)	207 (79.01)	78 (39.59)
Maternal BMI							
<18	50 (3.92)	2 (1.01)	17 (8.67)	9 (4.04)	2 (1.01)	16 (6.06)	4 (2.04)
18-25	727 (56.93)	58 (29.15)	123 (62.76)	151 (67.71)	56 (28.14)	202 (76.52)	137 (69.9)
25-30	312 (24.43)	72 (36.18)	40 (20.41)	42 (18.83)	83 (41.71)	38 (14.39)	37 (18.88)
>30	188 (14.72)	67 (33.67)	16 (8.16)	21 (9.42)	58 (29.15)	8 (3.03)	18 (9.18)
Outcomes							
z-bmi	0.39 (1.18)	0.22 (1.16)	0.2 (1.11)	0.77 (1.21)	0.5 (1.22)	0.08 (0.89)	0.66 (1.35)
z-fat proportion	-0.05 (0.94)	0.13 (0.93)	-0.07 (0.9)	0.35 (0.95)	-0.03 (0.92)	-0.51 (0.75)	-0.01 (1.01)
z waist circumference	-0.04 (0.97)	-0.23 (0.91)	-0.15 (0.94)	0.23 (1.09)	0.04 (0.99)	-0.32 (0.73)	0.26 (1.01)
z skinfolds	-0.03 (0.96)	-0.05 (0.97)	-0.04 (0.97)	0.25 (1.11)	-0.03 (0.93)	-0.34 (0.65)	0.12 (1.05)

Table 8 Adjusted associations between the prenatal Exposome (90 exposures considered) and Body Mass Index (BMI)-z-scores in childhood, as well as between the postnatal Exposome (109 exposures considered) and Body Mass Index (BMI)-z-scores in childhood. Associations were tested with either an EWAS or a DSA approach (preliminary results based on 1301 Helix subcohort children). Only associations with p-value<0.06 in the adjusted univariate model are shown

Exposure	Family	adjusted model *, **				
		p-value	Beta***	95% CI		FDR corrected p-value
Prenatal exposures (N=90)						
EWAS (significant results)						
Active smoking in pregnancy (vs no active or passive smoking)	Smoking	0.002	0.30	0.11	0.49	0.237
Cotinine category high (vs low)	Smoking	0,011	0.24	0,06	0.43	0.566
Density of facilities within 300 m	Urban env	0.022	-0.07	-0.12	-0.10	0.747
Cadmium	Metals	0.036	0.08	0.006	0.16	0.911
Passive smoking in pregnancy (vs no active or passive)	Smoking	0.059	0.16	-0.006	0.32	0.974
DSA:						
Active smoking in pregnancy (vs no active or passive smoking)	Smoking	0.007	0.26	0.07	0.44	
Passive smoking in pregnancy (vs no active or passive)	Smoking	0.031	0.15	0.01	0.29	
Cotinine	Smoking	0.947	-0.003	-0.09	0.08	
Density of facilities within 300 m	Urban env	0.070	-0.05	-0.10	0.004	
Postnatal exposures (N=109)						
EWAS						
DDE	OCs	0.000	-0.451	-0.540	-0.361	0.000
HCB	OCs	0.000	-0.559	-0.646	-0.471	0.000
PCB138	OCs	0.000	-0.547	-0.648	-0.445	0.000
PCB153	OCs	0.000	-0.585	-0.694	-0.477	0.000
PCB170	OCs	0.000	-0.671	-0.778	-0.563	0.000
PCB180	OCs	0.000	-0.776	-0.895	-0.656	0.000
Sum PCBs	OCs	0.000	-0.653	-0.764	-0.543	0.000
PBDE153	PBDEs	0.000	-0.429	-0.542	-0.316	0.000
PCB118	OCs	0.000	-0.248	-0.332	-0.163	0.000
PFOA	PFAS	0.000	-0.211	-0.295	-0.126	0.000
Cu	Metals	0.000	0.185	0.107	0.263	0.000
DDT	OCs	0.000	-0.234	-0.336	-0.133	0.000
PFNA	PFAS	0.000	-0.185	-0.267	-0.103	0.000
PM indoor	Indoor air	0.000	0.147	0.077	0.217	0.000
Abs indoor	Indoor air	0.000	0.147	0.075	0.219	0.001
PFUNDA	PFAS	0.000	-0.211	-0.319	-0.102	0.001
PFOS	PFAS	0.000	-0.174	-0.267	-0.081	0.002
Cs	Metals	0.001	0.188	0.082	0.294	0.004
Co	Metals	0.001	-0.107	-0.171	-0.044	0.006
Cotinine Dich (binary)	Smoking	0.001	0.291	0.119	0.464	0.006

Mo	Metals	0.001	-0.084	-0.134	-0.033	0.008
Bakery products 3 (high vs low)	Diet	0.002	-0.279	-0.457	-0.101	0.013
Smoke Parents (2 parents vs. none)	Smoking	0.003	0.323	0.113	0.532	0.015
Sleep	Lifestyle	0.005	-0.131	-0.223	-0.039	0.031
Fat consumption 3 (high vs low)	Diet	0.013	-0.225	-0.403	-0.047	0.073
PM10 Year	Outdoor air	0.015	0.279	0.054	0.503	0.078
OXBE	Phenols	0.025	0.093	0.011	0.174	0.125
NO2 Year	Outdoor air	0.026	0.235	0.028	0.442	0.125
Smoke Parents (1 parent vs none)	Smoking	0.028	0.165	0.018	0.311	0.125
ETS 2Cat	Smoking	0.028	0.157	0.017	0.296	0.125
Breakfast cereal 3 (high vs low)	Diet	0.039	-0.162	-0.315	-0.009	0.168
Social participation 1 organisation (vs none)	Social	0.054	-0.142	-0.286	0.002	0.227
Potatoes 2 (medium vs low)	Diet	0.057	0.133	-0.004	0.270	0.233
TrafNear	Traffic	0.060	0.127	-0.005	0.260	0.237
DSA:						
PM indoor tertile 2	Indoor air	-0.046	-0.168	0.076	0.461	
PM indoor tertile 3	Indoor air	0.150	0.017	0.282	0.027	
Copper	metals	0.136	0.074	0.197	0.000	
HCB tertile 2	OCs	-0.537	-0.661	-0.413	0.000	
HCB tertile 3	OCs	-0.752	-0.906	-0.599	0.000	
PBDE153	OCs	-0.234	-0.325	-0.142	0.000	

prenatal: adjusted for cohort, maternal BMI, maternal education, maternal age, ethnicity, parity

** postnatal: adjusted for cohort, maternal BMI, maternal education, maternal age, ethnicity, parity, birth weight

*** for IQR increase in exposure

Table 9 Analysis of the association between the prenatal exposome and FEV1%, through EWAS and through a model adjusting for potential confounding by co-exposures.

Exposure variable	Exposure family	IQR	ExWAS [a]		Model adjusting for potential confounding by co-exposure [ab]	
			Estimate [95% CI][c]	P-value	Estimate [95% CI] [c]	P-value
PFNA in mothers [d]	Perfluoroalkyls (PFA)	0.84 [d]	-1.4[-2.7;-0.1]	0.034	-0.8[-2.8;1.2]	0.425
PFOA in mothers [d]	Perfluoroalkyls (PFA)	0.77 [d]	-1.4[-2.7;-0.1]	0.030	-0.6[-2.6;1.3]	0.520
Inverse distance to nearest road during pregnancy [d]	Traffic	1.15[e]	1.1 [0.1;2.2]	0.030	1.1[0.1;2.2]	0.033

CI: confidence interval of the coefficient estimate; DMTP: Dimethyl thiophosphate; ExWAS: Exposome-wide association study; IQR: Inter-quartile range of the (transformed to approach normality) exposure variable; NO_2: nitrogen dioxide; PFNA: Perfluorononanoate; PFOA: Perfluorooctanoate; T3: trimester 3 of pregnancy.

[a] Results are presented only for exposures with an (uncorrected for multiple hypothesis testing) p-value below 5% in ExWAS.

[b] Results from a multivariate linear regression model including all exposures with a (uncorrected for multiple hypothesis testing) p-value<0.20 in ExWAS. Six additional exposure variables were adjusted for, with an absolute correlation with our exposure variables of interest in the [0.00; 0.42] range. This model had an adjusted R-squared of 0.21.

[c] Coefficient estimates are given for a change in mean FEV1% for an interquartile range change in the given exposure

[d] The exposure variable was log2-transformed before IQR-standardization.

[e] The exposure variable was log-transformed before IQR-standardization.

Table 10 Analysis of the association between the postnatal exposome and FEV1%, through ExWAS and through a model adjusting for potential confounding by co-exposures.

Exposure variable	Exposure family	IQR	ExWAS [a]		Model adjusting for potential confounding by co-exposure [ab]	
			Estimate [95% CI][c]	P-value	Estimate [95% CI] [c]	P-value
Number of bus public transport mode stops in a 300m buffer around school	Built environment	1.32 [d]	-1.2[-2.3;-0.1]	0.027	-1.2[-2.7;0.3]	0.130
Copper	Metals	0.16 [e]	-1.0[-1.9;-0.0]	0.041	-0.9[-1.8;0.1]	0.064

ETPA	Phenols	0.98 [e]	-0.5[-1.0;-0.1]	0.029	-0.6[-1.2;-0.1]	0.024
Sum of DEHP metabolites	Phthalates	0.85 [e]	-1.3[-2.3;-0.3]	0.014	-1.3[-3.1;-0.4]	0.130
MECPP	Phthalates	0.87 [e]	-1.3[-2.3;-0.2]	0.016	[f]	
MEHHP	Phthalates	0.87 [e]	-1.2[-2.2;-0.2]	0.023	[f]	
MEOHP	Phthalates	0.84 [e]	-1.3[-2.3;-0.3]	0.008	[f]	
OXOMINP	Phthalates	1.34 [e]	-0.9[-1.7_0]	0.040	-0.4[-1.6;0.8]	0.539
House crowding	Socio-economic capital	1.00	-1.1[-1.9;-0.2]	0.015	-0.9[-1.7;0.0]	0.039

CI: confidence interval of the coefficient estimate; DEHP: Di-Ethylhexyl Phthalate; ETPA: Ethyl paraben; ExWAS; Exposome-wide association study; IQR: Inter-quartile 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; OXOMINP: Mono-4-methyl-7-oxooctyl phthalate; PFNA: Perfluorononanoate ; PFOA: Perfluorooctanoate; $PM_{2.5}$: particulate matter in the (ambient) air 2.5 micrometres or less in aerodynamical diameter; T3: trimester 3 of pregnancy.

[a] Results are presented only for exposures with an (uncorrected for multiple hypothesis testing) p-value below 5% in ExWAS.

[b] Results from a multivariate linear regression model including all exposures with a (uncorrected for multiple hypothesis testing) p-value<0.20 in ExWAS, except those that were too highly correlated. 23 additional exposure variables were adjusted for, with an absolute correlation with our exposure variables of interest in the [0.00; 0.83] range. This model had an adjusted R-squared of 0.24.

[c] Coefficient estimates are given for a change in mean FEV1% for an interquartile range change in the given exposure.

[d] The exposure variable was log-transformed before IQR-standardization.

[e] The exposure variable was log2-transformed before IQR-standardization.

[f] The exposure variable was removed from the multivariate analyses for it was correlated at >0.9 in absolute value with another exposure.

Exposome database 2.2.

Table 11 Adjusted associations between the prenatal Exposome (92 exposures considered) and the allergy-related outcomes itchy rash, rhinitis, eczema and food allergy. Associations were tested with an EWAS approach (preliminary results based on 1300 Helix subcohort children and V 2.1 of the Exposome database).

	Family	Adjusted model*			
		p-value	Beta**	95% CI	Passes p-value correction?
Prenatal exposures (N=92) (significant results)					0.00101
Itchy rash					
Maternal cotinine level (µg/L)	Smoking	0.029	-0.71	-1.34 -0.07	no
Traffic density on nearest road at pregnancy period (vehicles/day)	Traffic	0.031	0.22	0.02 0.42	no
Rhinitis					
Absorption value during pregnancy (µg/m^3)	Air pollution	0.014	-0.59	-1.06 -0.12	no
Inverse distance to nearest road at pregnancy period (m^{-1})	Traffic	0.039	0.19	0.01 0.37	no
Mono-4-methyl-7-oxooctyl phthalate (OXOMiNP) in mother adjusted for	Phthalates	0.044	0.18	0.01 0.35	no

creatinine (µg/g)

Eczema

No significant results

Food allergy

Traffic density on nearest road at pregnancy period (vehicles/day)	Traffic	0.018	-0.29	-0.53	-0.05	no
Categorized lden (day, evening, night) at pregnancy period dB(A)	Noise	0.037	-0.26	-0.51	-0.02	no
Inverse distance to nearest road at pregnancy period (m^{-1})	Traffic	0.046	0.29	0.01	0.57	no

*prenatal: adjusted for cohort, gender, trimester of conception, parity, maternal BMI, maternal age, maternal education, paternal education, ethnicity

** for IQR increase in exposure

Table 12 Environmental-wide association study between prenatal exposures (n=90) and blood pressure [a].

Table 1	p-value	Adjusted beta (95% CI) [b]	Significant after p-value correction? TEF=0.001	Frequency of selection from DSA
Systolic blood pressure				
Facility density (300m)	0.0005	-1.59 (-2.48; -0.70)	Yes	90%
Facility richness (300m)	0.0007	-1.49 (-2.35; -0.63)	Yes	0%
Walkability index	0.0074	-1.40 (-2.43; -0.38)	No	0%
Temperature (av. pregnancy)	0.0229	1.58 (0.22; 2.94)	No	36%
BPA	0.0388	0.80 (0.04; 1.55)	No	2%
PCB 118	0.0405	-1.32 (-2.58; -0.06)	No	54%
PCB 153	0.0434	-1.41 (-2.78; -0.04)	No	0%
Fish and seafood	0.0492	-	No	48%
1st tertile vs 2nd tertile	*0.1924*	*0.99 (-0.50; 2.49)*	-	-
3rd tertile vs. 2nd tertile	*0.0154*	*1.93 (0.37; 3.50)*	-	-
PCBs (sum)	0.0500	-1.32 (-2.64; -0.00)	No	0%
PCB 138	0.0611	-1.12 (-2.30; 0.05)	No	0%
MEOHP	0.0649	-0.57 (-1.18; 0.04)	No	0%
HCB	0.0660	-0.74 (-1.54; 0.05)	No	0%
PCB 180	0.0736	-1.15 (-2.42; 0.11)	No	0%
NDVI (100 m)	0.0871	1.38 (-0.20; 2.95)	No	0%
... continue ...				
Cotinine	0.1380	-	No	6%
2nd tertile vs. 1st tertile	*0.3046*	*-0.90 (-2.63; 0.82)*	-	-
3rd tertile vs. 1st tertile	*0.1647*	*1.16 (-0.45; 2.61)*	-	-
Diastolic blood pressure				
BPA	0.0423	0.72 (0.02; 1.41)	No	0%
Facility density (300m)	0.0437	-0.87 (-1.71; -0.02)	No	0%
Facility richness (300m)	0.0556	-0.80 (-1.61; 0.02)	No	0%
Temperature (av. pregnancy)	0.0631	1.16 (-0.06; 2.38)	No	0%
Fish and seafood	0.0929	-	No	6%
1st tertile vs. 2nd tertile	*0.0643*	*1.37 (-0.08; 2.83)*	-	-
3rd tertile vs. 2nd tertile	*0.0822*	*1.27 (-0.16; 2.71)*	-	-

[a] Only the exposure variables with an uncorrected p-value<0.10 or selected by DSA are reported.

[b] Coefficients for an IQR increase in exposure, models adjusted for cohort (BIB, EDEN, INMA, KANC, MOBA, RHEA), maternal age (continuous), maternal education level (low, middle, high), maternal pre-pregnancy body mass index (continuous), parity (nulliparous, primiparous, multiparous), parental country of birth (none or one parent born in the country of inclusion; both parents), child age (continuous), child sex (boy, girl), child height (continuous).

Exposome database v.2.2

Table 13 Environmental-wide association study between postnatal exposures (n=127) and blood pressure[a].

	p-value	Adjusted beta (95% CI)[b]	Significant after p-value correction? TEF=0.00069	Frequency of selection from DSA
Systolic blood pressure				
DDE	<0.0001	-2.10 (-2.92; -1.28)	Yes	30%
HCB	<0.0001	-2.05 (-2.82; -1.29)	Yes	100%
PCB 153	<0.0001	-1.90 (-2.85; -0.95)	Yes	0%
PCBs (sum)	0.0002	-1.93 (-2.94;-0.92)	Yes	0%
PCB 170	0.0007	-1.73 (-2.73; -0.73)	Yes	0%
PBDE 153	0.0009	-1.66 (-2.64; -0.68)	No	0%
PCB 138	0.0010	-1.54 (-2.46; -0.63)	No	0%
PCB 180	0.0014	-1.77 (-2.86; -0.68)	No	0%
PCB 118	0.0034	-1.07 (-1.78; -0.35)	No	0%
MBZP	0.0107	-0.78 (-1.39; -0.18)	No	0%
MEHP	0.0247	-0.80 (-1.50; -0.10)	No	0%
Indoor benzene	0.0411	0.78 (0.03; 1.53)	No	0%
DMTP	0.0525	-0.66 (-1.33; 0.01)	No	0%
Indoor $PM_{absorbance}$	0.0602	0.60 (-0.03; 1.22)	No	0%
DMDTP	0.0625	1.28 (-0.07; 2.62)	No	0%
BUPA	0.0628	-0.48 (-0.98; 0.03)	No	0%
Copper	0.0638	0.64 (-0.04; 1.31)	No	0%
MECPP	0.0726	-0.70 (-1.47; 0.06)	No	0%
Arsenic	0.0737	-0.86 (-1.80; 0.08)	No	0%
Outdoor NO_2 (av. day)	0.0799	1.01 (-0.12; 2.14)	No	0%
DEHP (sum metabolites)	0.0830	-0.67 (-1.42; 0.09)	No	0%
Sweets intake	0.0959	-	No	0%
2nd tertile vs. 1st tertile	*0.0263*	*-1.38 (-2.65; -0.11)*	-	-
3rd tertile vs. 1st tertile	*0.1320*	*-0.93 (-2.27; 0.41)*	-	-
MEOHP	0.0984	-0.63 (-1.37; 0.12)	No	0%
PFOA	0.2896	0.39 (-0.34; 1.12)	No	2%
Diastolic blood pressure				
Copper	0.0008	1.07 (0.44; 1.69)	No	16%
Temperature (av. day)	0.0023	-1.47 (-2.41; -0.53)	No	38%
BUPA	0.0033	-0.70 (-1.17; -0.23)	No	0%
DDE	0.0047	-1.11 (-1.88; -0.34)	No	4%
PBDE 153	0.0060	-1.29 (-2.21; -0.37)	No	0%
MEP	0.0090	-1.01 (-1.78; -0.25)	No	0%
MBzP	0.0133	-0.71 (-1.27; -0.15)	No	0%
MnBP	0.0196	-0.82 (-1.50; -0.13)	No	0%
HCB	0.0264	-0.82 (-1.54; -0.10)	No	0%
UV (av. day)	0.0310	-0.96 (-1.82; -0.09)	No	0%
MEHP	0.0349	-0.70 (-1.35; -0.05)	No	0%

PCB 170	0.0512	-0.93 (-1.86; 0.00)	No	0%
PCBs (sum)	0.0600	-0.91 (-1.85; 0.04)	No	0%
MECPP	0.0619	-0.68 (-1.40; 0.03)	No	0%
PCB 153	0.0776	-0.81 (-1.70; 0.09)	No	0%
Accessibility (bus lines - school)	0.0812	-1.26 (-2.68; 0.16)	No	0%
PCB 138	0.0959	-0.73 (-1.58; 0.13)	No	0%

[a] Only the exposure variables with an uncorrected p-value<0.10 or selected by DSA are reported.

[b] Coefficients for an IQR increase in exposure, models adjusted for cohort (BIB, EDEN, INMA, KANC, MOBA, RHEA), maternal age (continuous), maternal education level (low, middle, high), maternal pre-pregnancy body mass index (continuous), parity (nulliparous, primiparous, multiparous), parental country of birth (none or one parent born in the country of inclusion; both parents), child age (continuous), child sex (boy, girl), and child height (continuous). Exposome database v.2.2

Table 14 Prenatal and postnatal selected by DSA multi-exposures and blood pressure.

	Time period	Adjusted beta (95% CI) [a]	p-value
Systolic blood pressure			
Facility density (300m)	Pregnancy	**-1.53 (-2.40; -0.66)**	**0.0006**
Temperature (av. pregnancy)	Pregnancy	**1.41 (0.09; 2.73)**	**0.0368**
PCB 118	Pregnancy	**-1.23 (-2.43; -0.03)**	**0.0447**
BPA	Pregnancy	0.70 (-0.03; 1.43)	0.0604
Fish intake	Pregnancy		
1st tertile vs 2nd tertile		1.19 (-0.26; 2.64)	0.1080
3rdtertile vs 2nd tertile		**1.76 (0.24; 3.29)**	**0.0239**
Cotinine	Pregnancy		
2nd tertile vs 1st tertile		-0.89 (-2.57; 0.80)	0.3023
3rd tertile vs 1st tertile		0.91 (-0.59; 2.41)	0.2333
DDE	Postnatal	**-1.42 (-2.37; -0.66)**	**0.0024**
HCB	Postnatal	**-1.52 (-2.37; -0.66)**	**0.0006**
PFOA	Postnatal	**0.82 (0.09; 1.54)**	**0.0282**
Diastolic blood pressure			
Fish intake	Pregnancy		
1st tertile vs. 2nd tertile		1.35 (-0.07; 2.77)	0.0615
3rd tertile vs. 2nd tertile		1.27 (-0.16; 2.70)	0.0820
DDE	Postnatal	**-1.12 (-1.88; -0.35)**	**0.0043**
Copper	Postnatal	**0.91 (0.29; 1.54)**	**0.0041**
Temperature (av. day)	Postnatal	**-1.38 (-2.32; -0.45)**	**0.0038**

[a] Coefficients for an IQR increase in exposure, models adjusted for cohort (BIB, EDEN, INMA, KANC, MOBA, RHEA), maternal age (continuous), maternal education level (low, middle, high), maternal pre-pregnancy body mass index (continuous), parity (nulliparous, primiparous, multiparous), parental country of birth (none or one parent born in the country of inclusion; both parents), child age (continuous), child sex (boy, girl), and child height (continuous). Exposome database v.2.2

Table 15 Result summary: Prenatal Exposome and health. EWAS analyses. All associations with a p-value below 5% (uncorrected p-value) are reported. +/- indicates the sign of regression coefficient.

Exposure family	Exposure	Health outcomes								
		Birth weight	Birth weight, urban Exp.	Lung function	Allergy related diseases	Asthma	BMI	Blood pressure	Cognition	Behavioural problems
Built env.	Walkability							-	+	
	Facility density						-	-		
	Facility richness							-		
Traffic	Inverse distance to nearest road			+	+ (rhinitis, food allergy)					
	Traffic density on nearest road at pregnancy period				+ (itchy rash) - (food allergy)					
Natural spaces										
Atm. pollutants	NO_2 in T3			+						
	$PM_{2.5}$ absorbance in T3	-								
	$PM_{2.5}$ in T3	-								
	NO_2 in T3			+						
	PM absorbance (pregnancy)				- (rhinitis					
Noise					- (food allergy)					
Indoor air										
Organophosphate pesticides	DMTP adjusted for creatinine	+								
Organochlorine compounds	Sum of PCBs	+								
Meteorological variables	Temperature							+		
Metals	Lead	-								
	Cadmium						+			
OCs	PCB 118							-		
	PCB 153							-		
	Sum PCBs							-		

PFAs	PFNA	-			
	PFOA	-			
Tobacco	Maternal cotinine		+ (itchy rash)	+	
	Maternal smoking			+	
Phenols	BPA				+
Phthalates	OXOMiNP in mother		+ (rhinitis)		
Diet	Fish intake				+

Table 16 Result summary: Postnatal Exposome and health, based on ExWAS analyses.

Exposure family	Exposure	Health outcomes						
		Lung function	Allergy related diseases	Asthma	BMI	Blood pressure	Cognition	Behavioural problems
Built env.	Number of bus public transport mode stops in a 300m buffer around school	-						
Atm. pollutants	PM_{10}				+			
Indoor air	Benzene					+		
	PM indoor				+			
Meteorological variables	Temperature					-		
	Vat. D UV dose					-		
Metals	Copper	-			+	+		
	Cs				+			
	Co				-			
	Mo				-			
OCs	DDE				-	-		
	DDT				-			
	HCB				-	-		
	PCB				-	-		
	PCB 138				-	-		
	PCB 153				-	-		
	PCB 170				-	-		
	PCB 180				-	-		
	Sum PCBs				-	-		
	PBDE 153				-	-		
PFAs	PFOA				-			
	PFOS				-			
	PFUNDA				-			
Phenols	BUPA					-		
	Ethyl Paraben (adj. or not for creatinine)	-						
Phthalates	MBzP					-		
	MEP					-		
	MEHP					-		

	MnBP	-
	Sum of DEHP metabolites, MECPP, MEHHP, MEOHP, OXOMINP	-
Socio-economic capital	Family affluence score	+
	House crowding	-

Table 17 Recommendations for authorities. public health practitioners and researchers

	Recommendations
Authorities	Develop evidence-based policies to reduce children exposure to environmental risk factors across Europe; with special attention to major risk factors. as lead and air pollution
Public health practitioners	Create and develop European health databases, with harmonized exposure data for (old and new) environmental risk factors for children. across all European countries
Researchers	Develop epidemiological studies on multiple environmental risk factors; with special attention to provide dose-response functions. with harmonize exposure and outcome definitions

Table 18 HELIX Scientific Publications

2014
The Human Early-Life Exposome (HELIX): Project Rationale and Design Martin Vrijheid et al. Environ Health Perspect. June 2014; 122:6. DOI:10.1289/ehp.1307204
2015
Some challenges of studies aiming to relate the Exposome to human health. (Commentary) Rémy Slama, Martine Vrijheid. Occup Environ Med 2015.
The Pregnancy Exposome: Multiple Environmental Exposures in the INMA-Sabadell Birth Cohort. Oliver Robinson et al. Environmental Science & Technology 49(17) · July 2015. DOI: 10.1021/acs.est.5b01782
2016
The Pregnancy Exposome. Oliver Robinson et al. Current Environmental Health Reports. DOI: 10.1007/s40572-015-0043-2
The exposome concept: a challenge and a potential driver for environmental health research. Siroux V, Agier L, Slama R. Eur Respir Rev 2016;25(140):124-9. DOI:10.1183/16000617.0034-*2016*.
A Systematic Comparison of Linear Regression–Based Statistical Methods to Assess Exposome-Health Associations. Lydiane Agier et al. Environ Health Perspect 124:1848–1856; http://dx.doi. org/10.1289/EHP172
2017
A systematic comparison of statistical methods to detect interactions in exposome-health associations. Barrera-Gómez J et al. Environ Health. 2017 Jul 14;16(1):74. doi: 10.1186/s12940-017-0277-6.
MultiDataSet: an R package for encapsulating multiple data sets with application to omic data integration. Carles Hernandez-Ferrer, Carlos Ruiz-Arenas, Alba Beltran-Gomila, and Juan R. González. BMC Bioinformatics. 2017; 18: 36. doi: 10.1186/s12859-016-1455-1
Assessment of metabolic phenotypic variability in children's urine using 1H NMR spectroscopy. Léa Maitre et al. Nature Scientific Reports 7:46082 | DOI: 10.1038/srep46082

Table 19 Planning of HELIX manuscripts

Status publication	Proposed title	Study population	First author(s)*
Published EHP 2014	HELIX study design		Martine Vrijheid
Submitted Dec 2017. BMJ Open	Cohort Profile: the Human Early Life Exposome (HELIX) study - A European Population-Based Exposome Cohort		Lea Maitre
1. Describing the Exposome			
Submitted to EPH Sept 2017 **Revision requested**	Describing the outdoor exposome (levels, correlations, PCA, predictors, inequalities) "The Urban Exposome during pregnancy and its socio-economic determinants"	Whole cohorts (10-30,000)	Oliver Robinson
Drafted	Describing the full exposome) "The early life exposome: description and patterns in six European countries"	Subcohort (1200)	Ibon Tamayo
draft January 2018 – addressing comments	Description of chemical exposures "In-utero and early life exposure to a wide range of environmental contaminants across six European cohorts"	Subcohort (1200)	Line Småstuen Haug,
Submitted to EHP January 2018 – rejected. Env Int	Variability in non-persistent chemicals in pregnancy and children "Variability of the Non-Persistent Chemical Exposome in Pregnant Women and School-age Children"	Panels	Maribel Casas
Drafted	Variability in outdoor exposures "Personal continuously monitoring of outdoor exposures in children and pregnant women"	Panels	David Donaire
Drafting	Predicting the prenatal exposure to perfluorinated compounds in a Spanish birth cohort using PBPK modeling	INMA cohort	Céline Brochot
ESD March 2018	Estimating the early-life exposure to two perfluorinated compounds (PFOS and PFOA) using PBPK modeling and biomarker measurements	HELIX cohort	Céline Brochot
ESD April 2018	Assessing the impact of a single biomarker measurement to reconstruct the exposure of pregnant women to Di(2-ethylhexyl) phthalate	Panel of pregnant women	Florence Zeman

2. Full exposome (all subcohort exposures) and health - N=1200			
Drafted	Birth outcomes "Full exposome and birth weight in HELIX children"	Subcohort (n=1200)	Lydiane Agier
Drafted	Obesity "Environment and childhood obesity: an exposome approach"	Subcohort (n=1200)	Martine Vrijheid
Drafting	Cardiometabolic risk markers "Associations between multiple environmental exposures in pregnancy and childhood and cardio-metabolic risk in children"	Subcohort (n=1200)	Marina Vafeiadi
Drafting	Blood pressure "Environmental determinants of blood pressure in children: and exposome approach"	Subcohort (n=1200)	Charline Warembourg
Drafting	Asthma, wheezing, infections, lung function, allergies (more than 1 paper) "Full exposome and allergic diseases in children" "Full exposome and asthma in children" "Full exposome and lung function in HELIX children"	Subcohort (n=1200)	Berit Granum John Wright
Drafted			Lydiane Agier
Drafting	Neurodevelopment –behaviour "Child behavior and the full exposome"	Subcohort (n=1200)	Lea Maitre
Drafting	Neurodevelopment – cognition "Full exposome and Child Cognitive Development"	Subcohort (n=1200)	Jordi Julvez
3. Outdoor exposome			
Drafted	Birth outcomes "Outdoor exposome and pregnancy outcomes"	Whole cohorts (30,000)	Mark Nieuwenhuijsen, Lydiane Agier
Drafting	Obesity Growth?	Whole cohorts (all >20,000)	Serena Fossati
Drafting	Blood pressure	Whole cohorts	Charline Warembourg

Drafting	Asthma, wheezing	Whole cohorts (all: 10-15,000)	Berit Granum
Drafting	lung function	Whole cohorts (Eden, INMA, RHEA, BiB)	Valerie Siroux
Drafting	Association between outdoor exposome during pregnancy and childhood and children's cognitive and psychomotor function between one and five years old	Whole cohorts (all but KANC)	Monica Guxens
Drafting	The association between the urban exposome and child behaviour	Whole cohorts (all)	Oliver Robinson
4. Describing omics data			
Published Nature Scientific Reports, April 2017	Assessment of metabolic phenotypic variability in children's urine using 1H NMR spectroscopy	Panels	Léa Maitre,
Drafting	Determinants of child urinary and serum metabolic phenotypes in HELIX	subcohort	Muireann Coen
Drafting	Seasonal variability metabolomics, methylation, transcriptomics, proteomics	Panels (comparing 2 periods)	Muireann, Hector, IC team, Mariona, Marta Vives, CRG team
5. Exposure-omics			
A. Exposome (all exposures) with each omics platform			
Drafting	"Effect of exposome on molecular phenotypes in children"	Subcohort	Omics working group
B. Specific pollutant groups with each omics platform			
2018	Air pollution (long term only?) Short term? (panels)	Subcohort and panels	INSERM, Solene
2018	POPs (long term)	subcohort	ISGlobal, Charline
2018	ETS "Prenatal and postnatal environmental tobacco smoking and molecular signatures in children"	Subcohort and panels	Marta/Mariona

2018	Metals	subcohort	ICL?
2018-2019	Non-persistent pollutants (short and long-term)	Panels and subcohort	ISGlobal, Lea, Cathrine
Draft nearly ready for circulation – submission to ESD April 2018	Diet-metabolomics Metabolic phenotypes of obesity, dietary habits and cardio-metabolic outcomes in HELIX cohort children	Subcohort	Hector, Muireann Alexandros Siskos
Later	Diet-other omics	Subcohort	Margaretha, Leda
later	Other exposures – urban environment, green spaces, UV, physical activity, etc	Subcohort and panels	?
6. Exposome statistical analysis methods			
Published EHP 2016	GWAS-type and variable selection-type approaches		Lydiane Agier
Published Environ Health, July 2017	A systematic comparison of statistical methods to detect interactions in exposome-health associations.		José Barrera-Gómez,
2018	Measurement error models		Lydiane AGier
Published	MultiDataSet: and R package for encapsulating multiple data sets with application to omic data integration		Carles Hernandez-Ferrer, Juan R. González
7. Burden of disease and impact assessment			
Submitted to EHP Sept 2017 – rejected. Env Int.	Environmental burden of childhood disease in Europe		David Rojas
Drafted	"Health impact assessment of walking to school in Barcelona"		David Rojas

Table 20 Grant proposals based on HELIX work

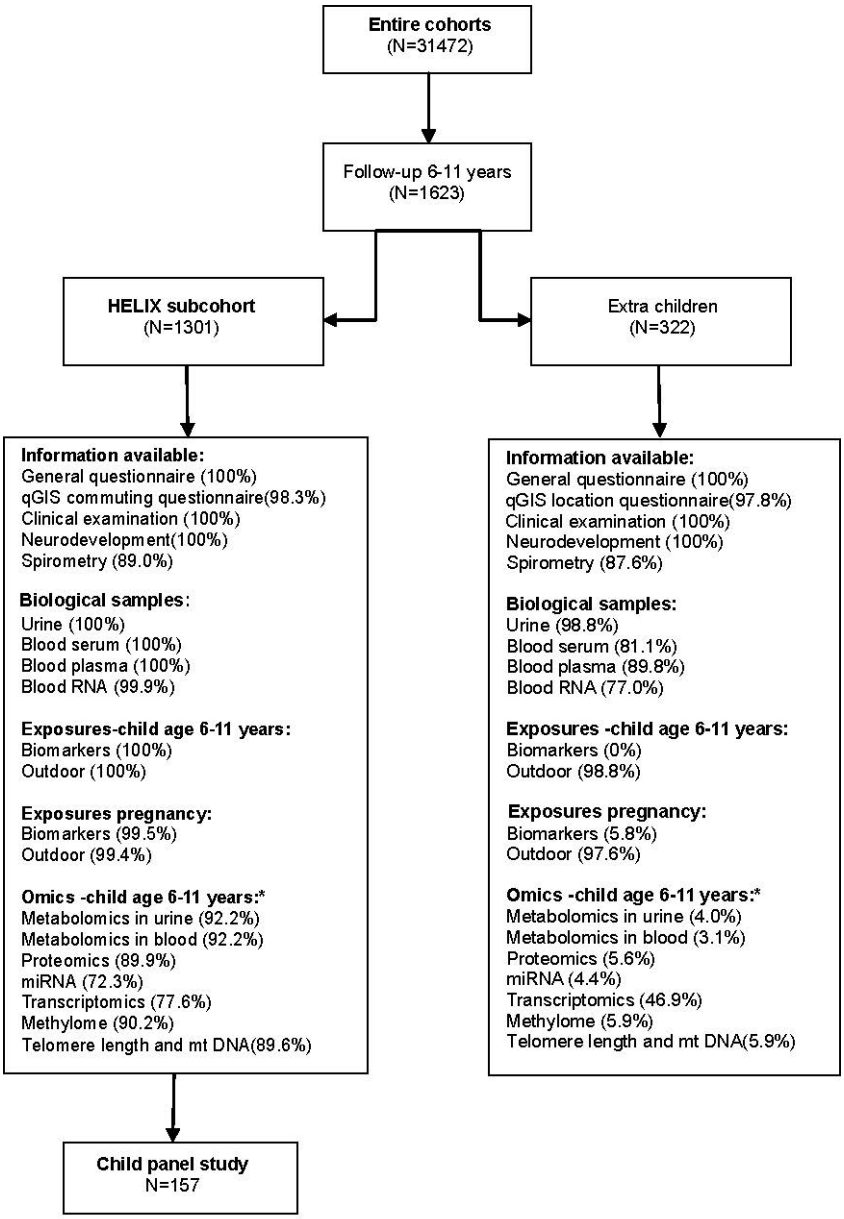
Title	Coordinating PI	Call Institution	Status
Endocrine disruptors and childhood lung function and asthma (ENDOLUNG)	Maribel Casas, ISGlobal		Accepted, ongoing.
Assessing adverse health effects in CHILDhood of Traffic Related Air Pollution, after accounting for correlated confounding or modifying factors (CHILDTRAP)	Mark Nieuwenhuijsen	ISGlobal	Under review
Developmental origins of child liver injury: the effect of early life environmental exposures	Leda Chatzi, USC	University of Southern Californa	Accepted
Health status and lifestyle of the INMA children	Maribel Casas, ISGlobal	ISGlobal	Accepted
Exposome, genetics and molecular endophenotypes in children (Exp-ChildQTL)	Mariona Bustamante, ISGlobal	FIS	Accepted
HBM4EU – Science and policy for a healthy future	Catherine Ganzleben, German Environment Agency	H2020	Accepted, ongoing
The LifeCycle Project	Vincent Jaddoe, Erasmus MC	H2020	Accpted, ongoing
STOP – Science and Technology in childhood Obesity Policy	Franco Sassi, ICL London	H2020	Accepted

Table 21 A short brief on HELIX and the meaning of 'exposome' produced for dissemination purposes.

Humans are exposed to environmental contaminants from the moment of conception until later in life. The totality of environmental exposures from conception until old age is defined as the 'exposome'. In other words: ***the exposome can be defined as the measure of all the exposures of an individual in a lifetime and how those exposures relate to health.*** *It includes exposures from our diets, our lifestyles, and our behaviors. Pregnancy and the early years of life are well recognized to be periods of high susceptibility to environmental damage with lifetime consequences. The HELIX approach involves combining all environmental hazards that mothers and children are exposed to, and linking this to the health, growth and development of children. T****he key focus of the exposome concept is to take a holistic approach using new and emerging technologies to describe 'the totality of human environmental (i.e. non-genetic) exposures from conception onwards.*** *We need to learn more about how the environment influences our health, both in negative and positive ways. With this knowledge we can make better decisions in our personal lives and regulatory agencies can make better decisions about minimizing the adverse effects on populations. We believe this knowledge will help to lead to improved strategies aimed at preventing unfavorable health outcomes in children such as asthma, allergies, neurodevelopment disorders or obesity; and impacts in later life, such as diabetes, heart disease, and Alzheimer's disease.*

Figures

Figure 1: The HELIX multilevel study design, drawing on nested study populations for data collection of different intensities.



**Omics data available after quality control*

Abbreviations: miRNA, micro RNA; mtDNA, mitochondrial DNA

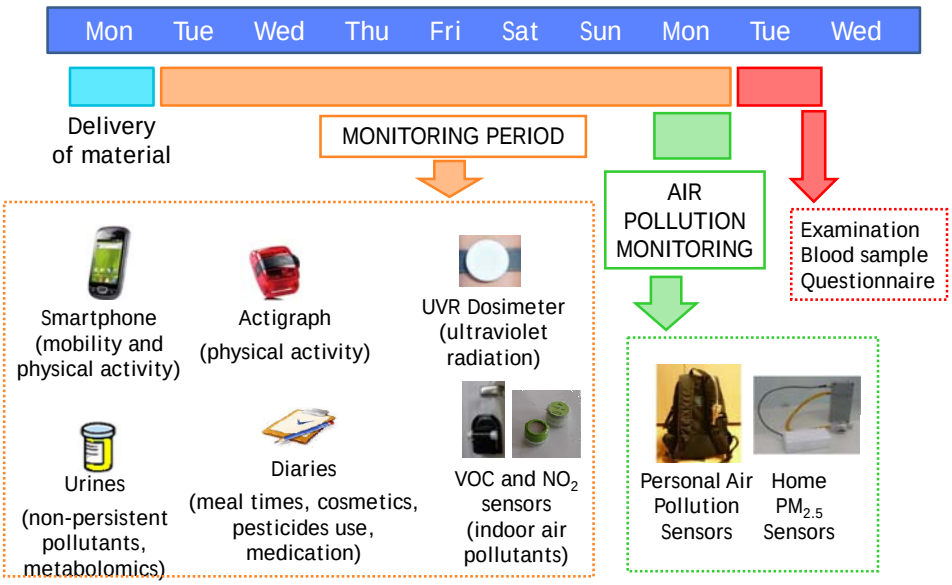


Figure 2 Overview of panel study set up. Each participant repeated the week in a second period. In the child panel the full subcohort follow up protocol was completed at the end of the first week.

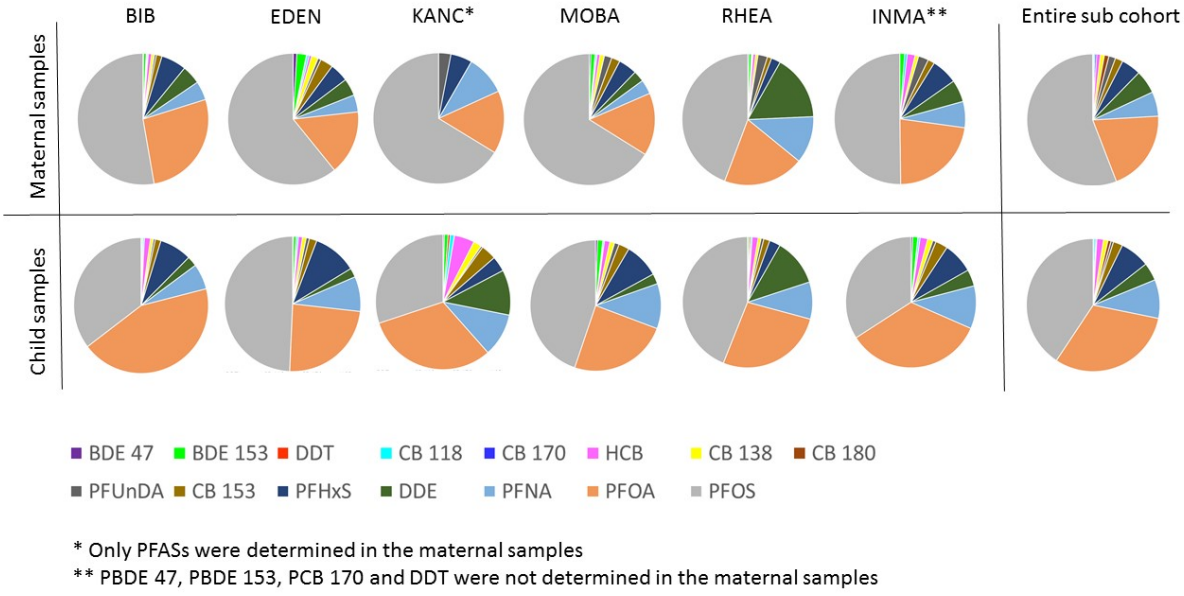


Figure 3 The "chemical exposome" for the persistent organic pollutants (the POPs exposome) measured in blood in children and mothers in the six cohorts.

A. Pregnant women

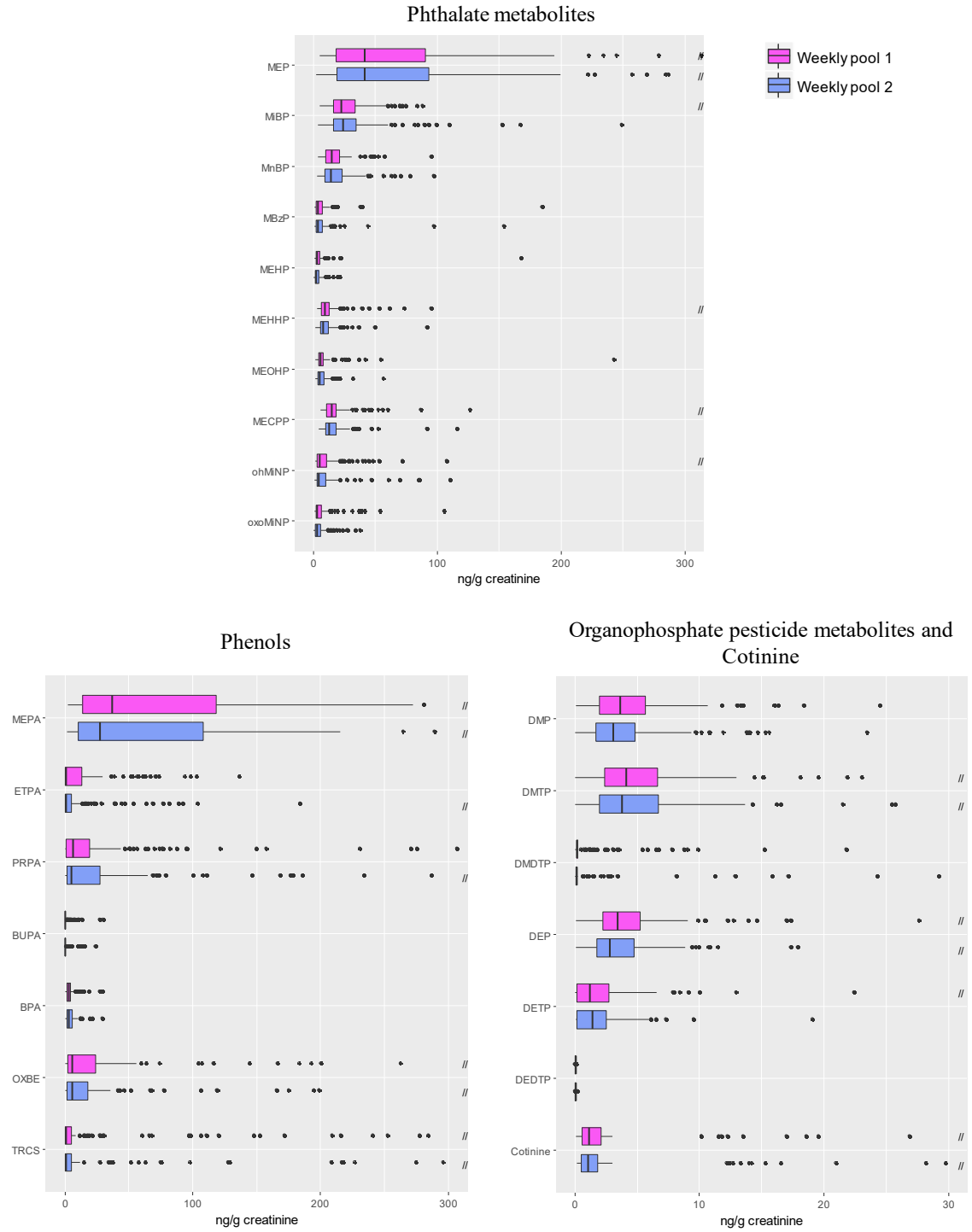
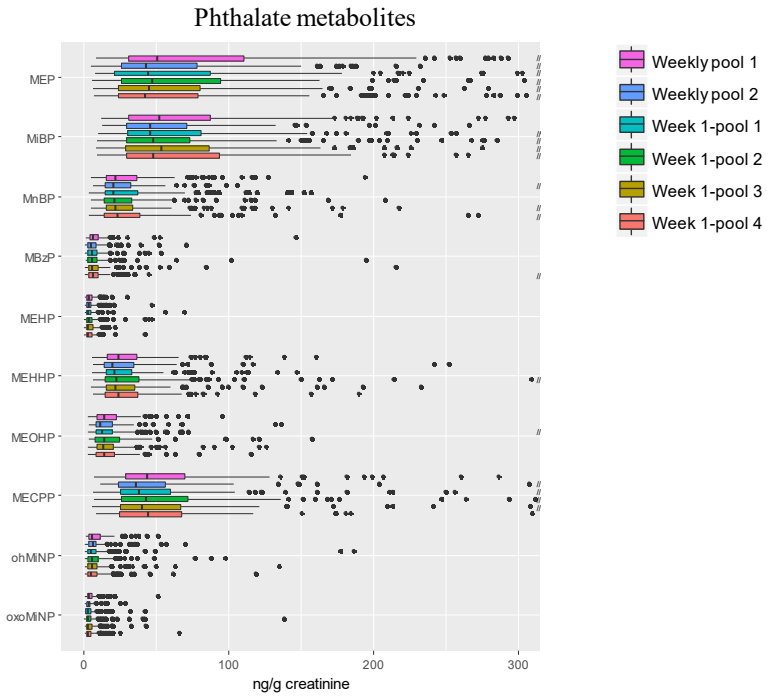
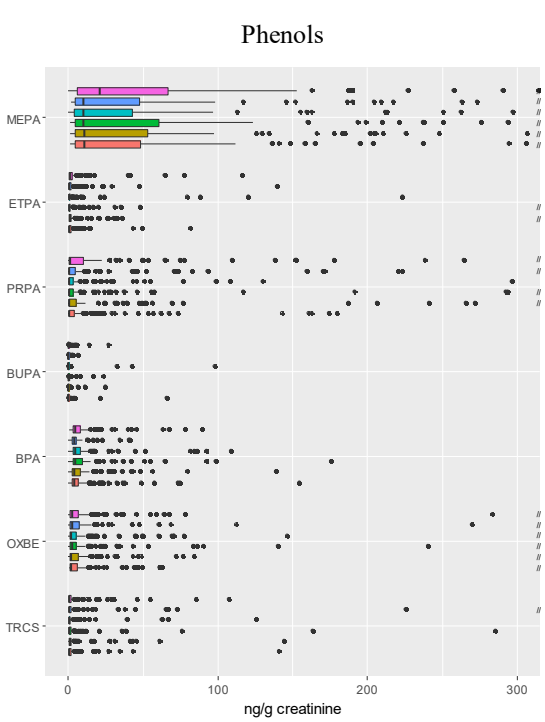


Figure 4 Urinary concentrations a (µg/g creatinine)[a] of phthalate metabolites, phenols, OP pesticide metabolites, and cotinine in pregnant women (A) and children (B)

B. Children





[a] Concentrations below the LOD have been imputed.

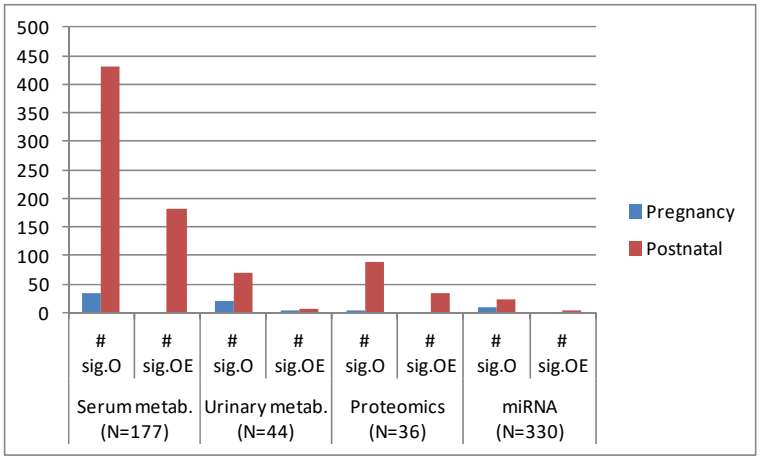


Figure 5 Numbers of significantly associated –omics feature/exposure pairs in global ExWAS analysis.

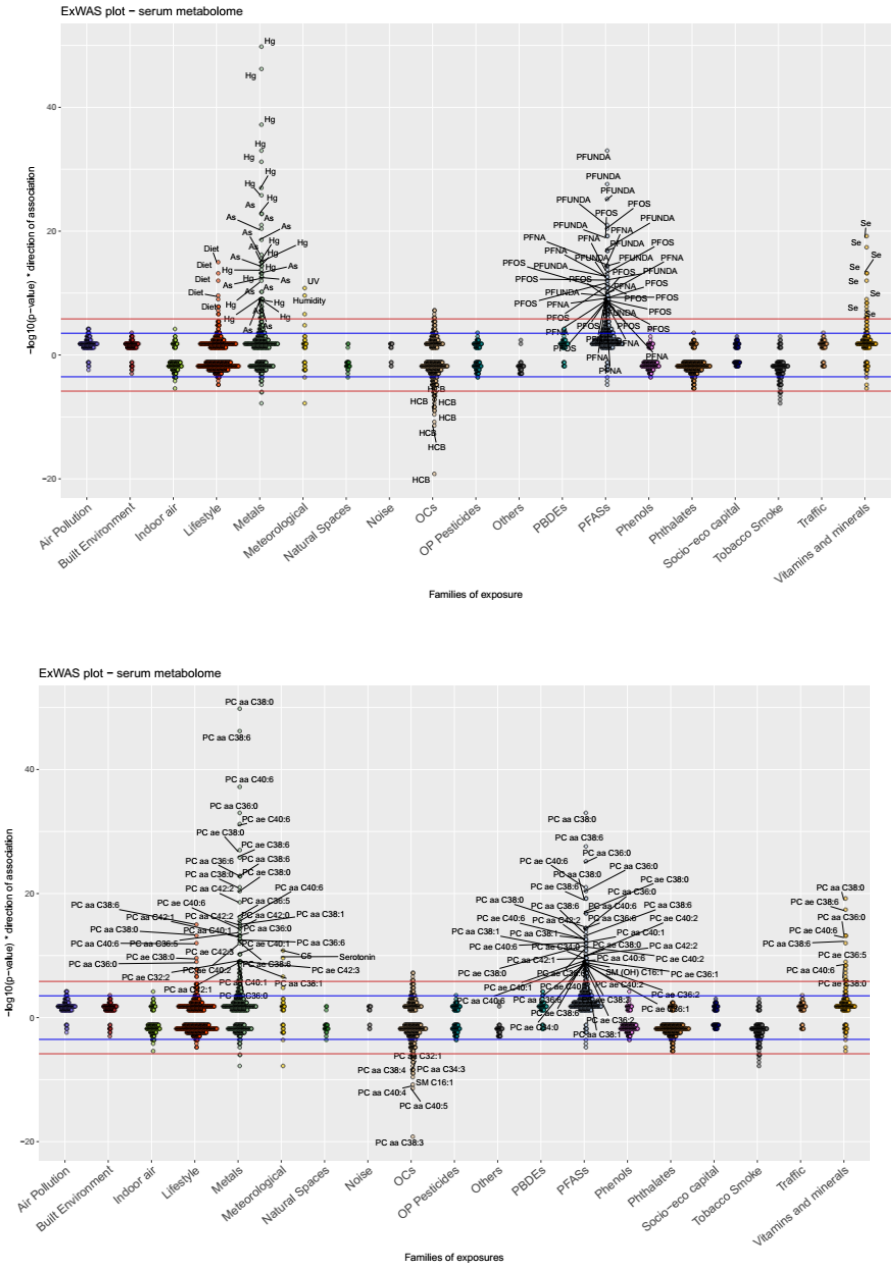


Figure 6 Results of ExWas analysis for the serum metabolome (above: labelled by exposure; below: labelled by metabolite). The lines indicates signficance above Bonferonni threshold (red – OE ; blue – O).

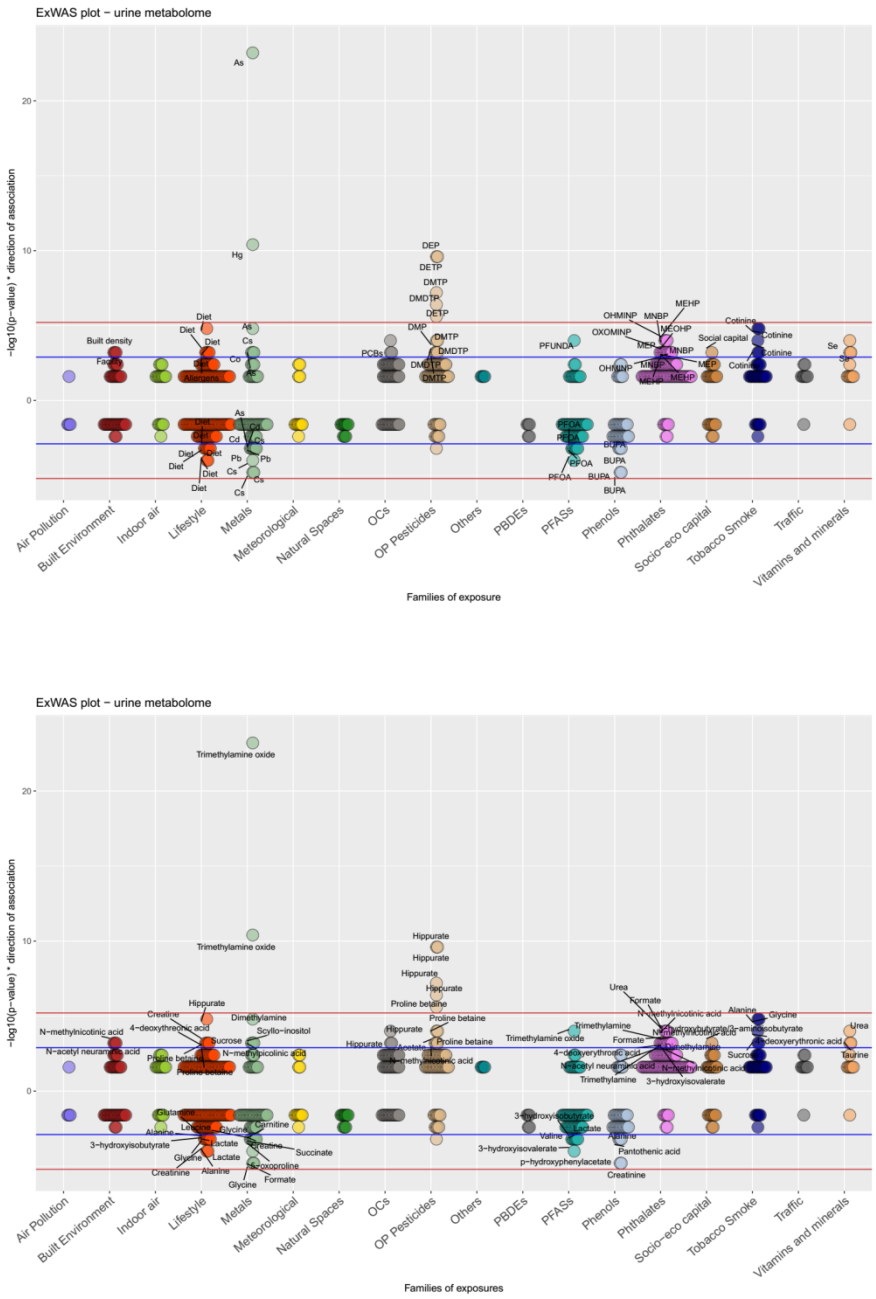


Figure 7 Results of ExWas analysis for the urinary metabolome (above: labelled by exposure; below: labelled by metabolite). The lines indicates signficance above Bonferonni threshold (red – OE ; blue – O).

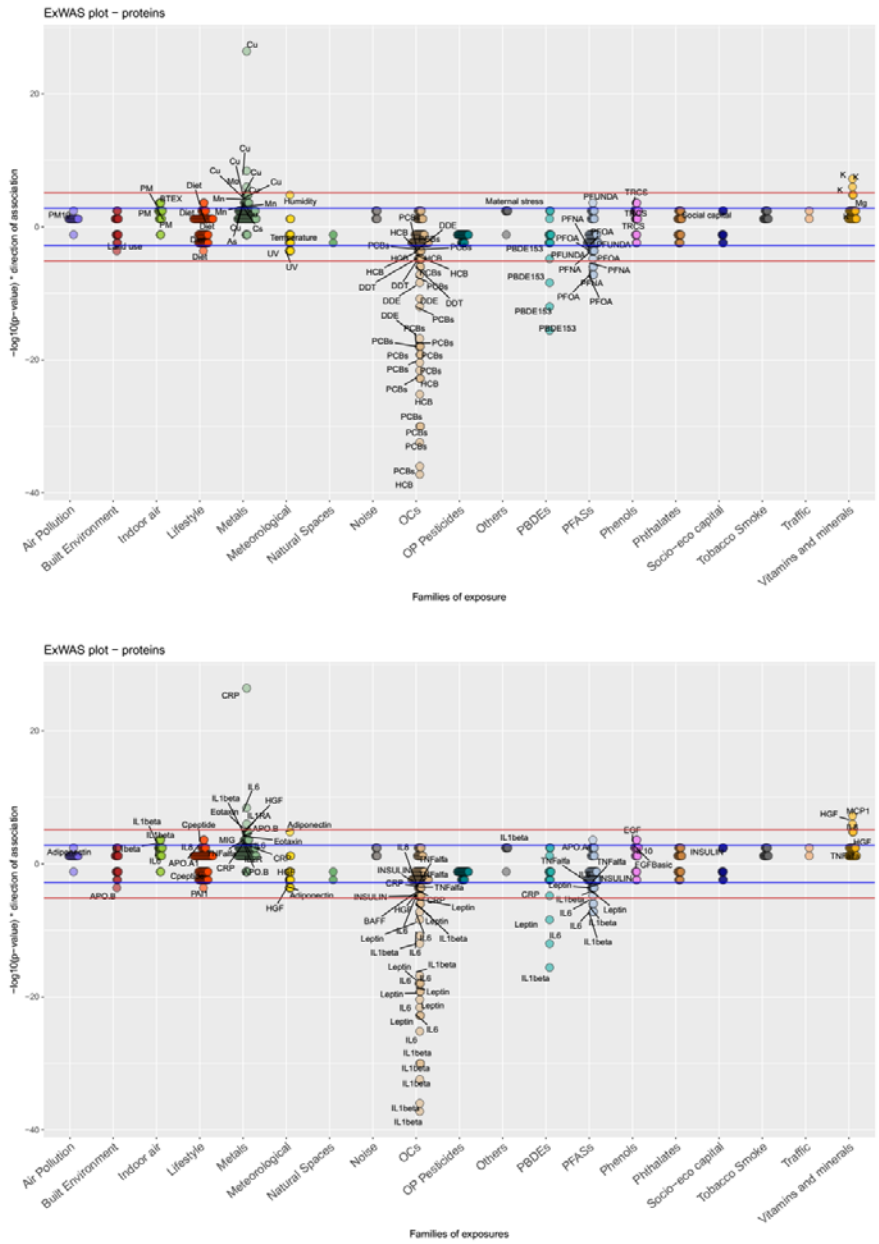


Figure 8 Results of ExWas analysis for the plasma proteome (above: labelled by exposure; below: labelled by protein). The lines indicates signficance above Bonferonni threshold (red – OE ; blue – O).

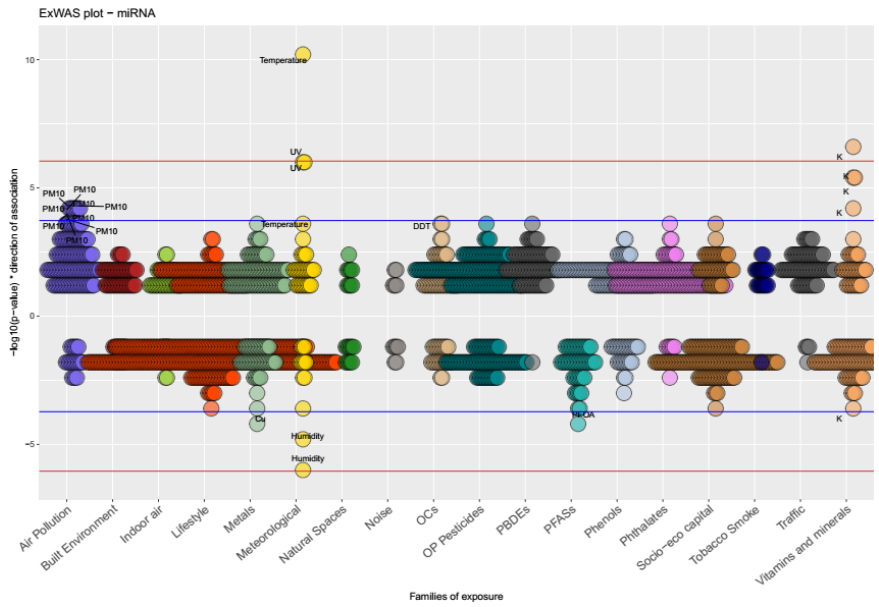


Figure 9 Results of ExWas analysis for the blood miRNA (left: labelled by exposure; right: labelled by protein). The lines indicates signficance above Bonferonni threshold (red – OE ; blue – O).

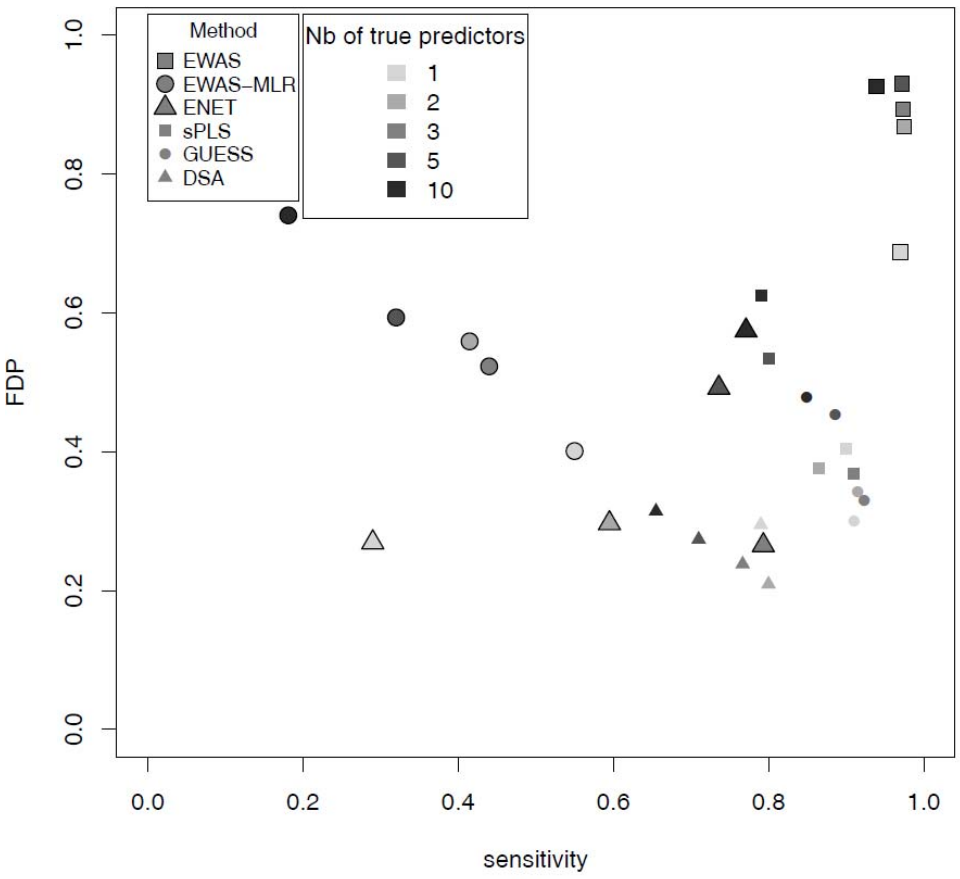


Figure 10 Sensitivity and FDP of each statistical method for 1 to 10 true predictors. For each simulated dataset, the true predictors were randomly selected. Model performances are summarized by the mean value (over the 100 independent simulations) per scenario and statistical method. DSA:

Deletion/substitution/addition; ENET: Elastic net; EWAS: Environment-wide association study; EWAS-MLR: EWAS-Multiple Linear Regression; GUESS: Graphical Unit Evolutionary Stochastic Search; sPLS: Sparse partial least-squares.

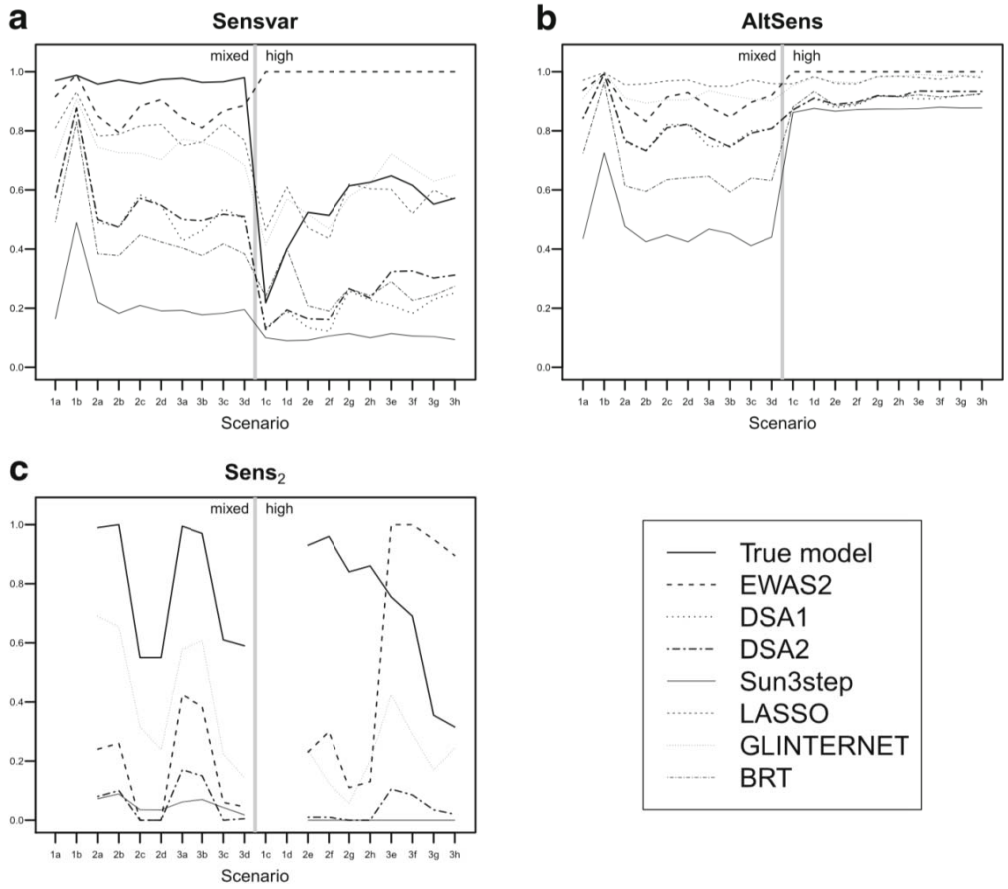


Figure 11 Performance of the compared methods in terms of sensitivity. **a** Sensitivity for variables (Sensvar), **b** Alternative sensitivity (AltSens), and **c** Sensitivity for interactions terms ($Sens_2$). Mean values based on 100 simulations. The vertical line separates scenarios according to the pairwise correlation between the true predictors as "mixed" (any exposure can be selected as a true predictor regardless of correlation), or "high" (exposures are chosen so that all their pairwise correlations are above 0.6). Scenarios 1, 2 and 3 involve no interactions, one two-way interaction, and two two-way interactions, respectively

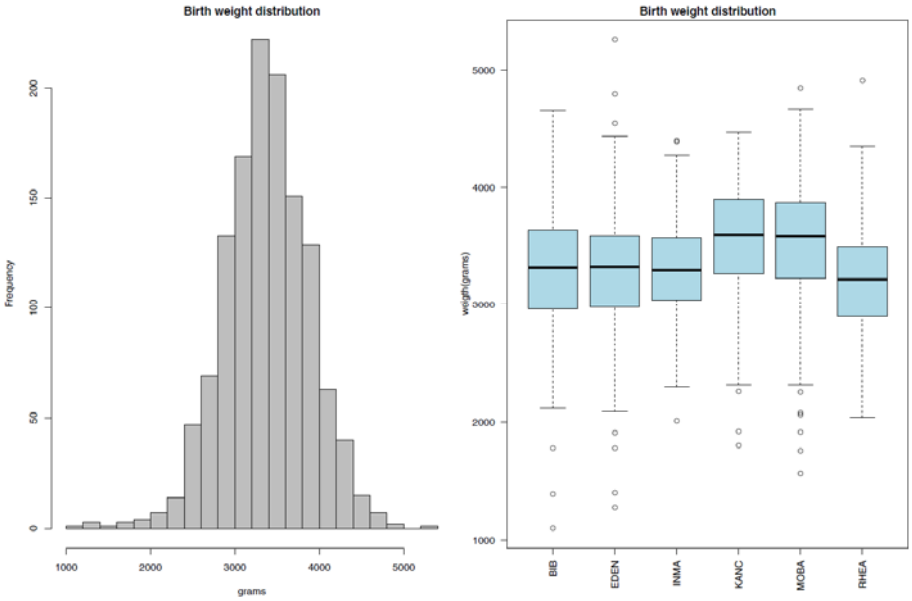


Figure 12 Birth weight distribution (A), and boxplot per subcohort (B).

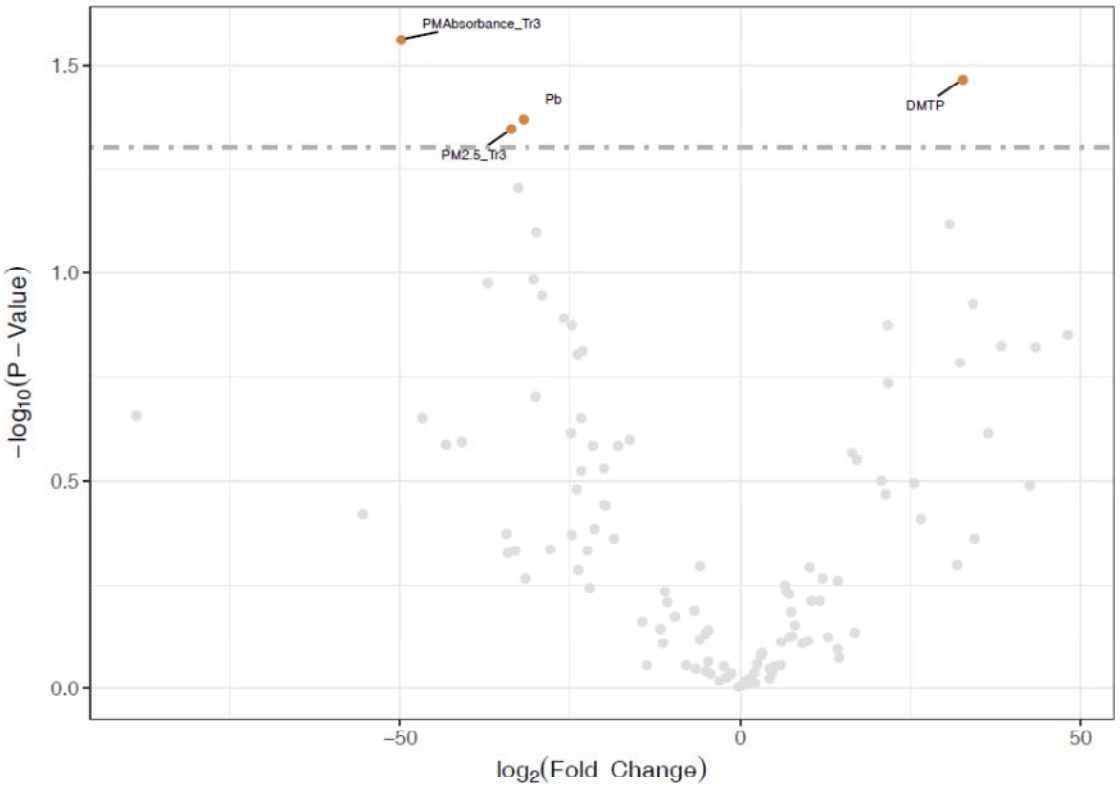


Figure 13 ***Volcano plot of exposure variables coefficient estimate vs. p-value (uncorrected for multiple hypothesis testing) obtained with the EWAS analysis testing the association of the Exposome with birth weight****. Coefficient estimates are given in birth weight fold change for an IQR change in the given exposure. The grey dot-dashed line corresponds to the 0.05 threshold for p-values. Exposome database v.2.2.*

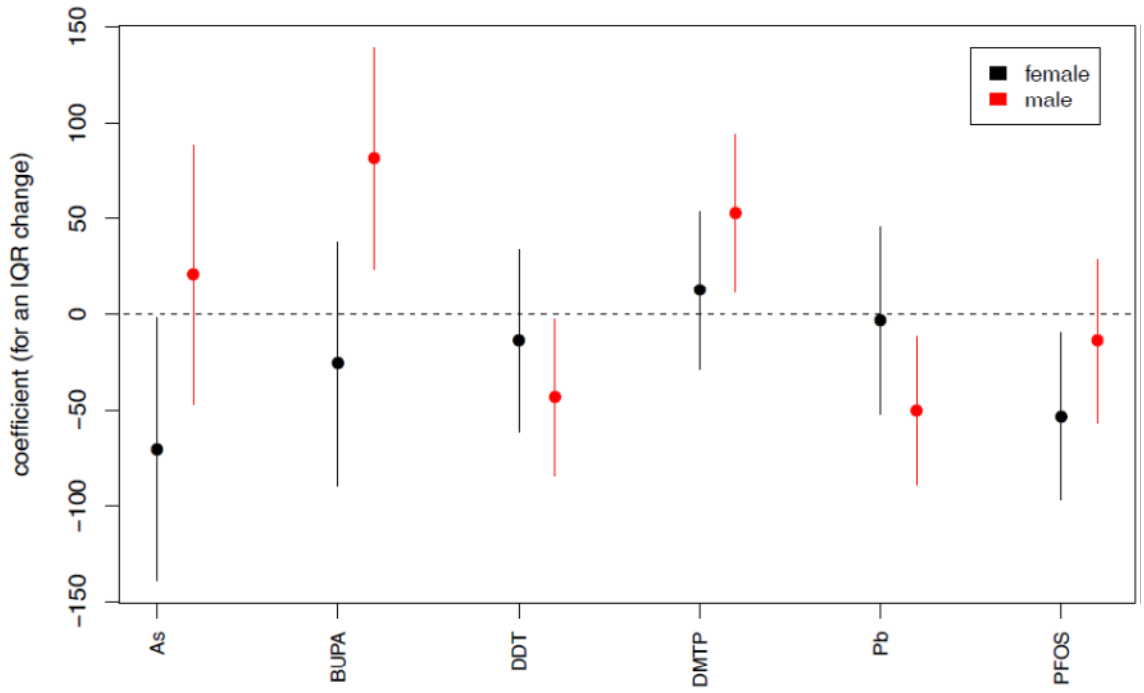


Figure 14 Birth weight change (in grams) for an inter-quartile range change in the given exposure, obtained with the ExWAS analysis testing the sex-specific associations between biomarkers and birth weight, adjusting for potential confounders. Only biomarkers with an (uncorrected) p-value lower than 5% for either sex are presented. The dot displays the coefficient estimate, and the vertical line its 95% confidence interval.

As: arsenic; BUPA: N-Butyl paraben; DDT: dichlorodiphenyltrichloroethane; DMTP: dimethyl thiophosphate; ExWAS: exposome-wide association study; Pb: lead; PFOS: perfluorooctane sulfonate.

Exposome database v.2.2.

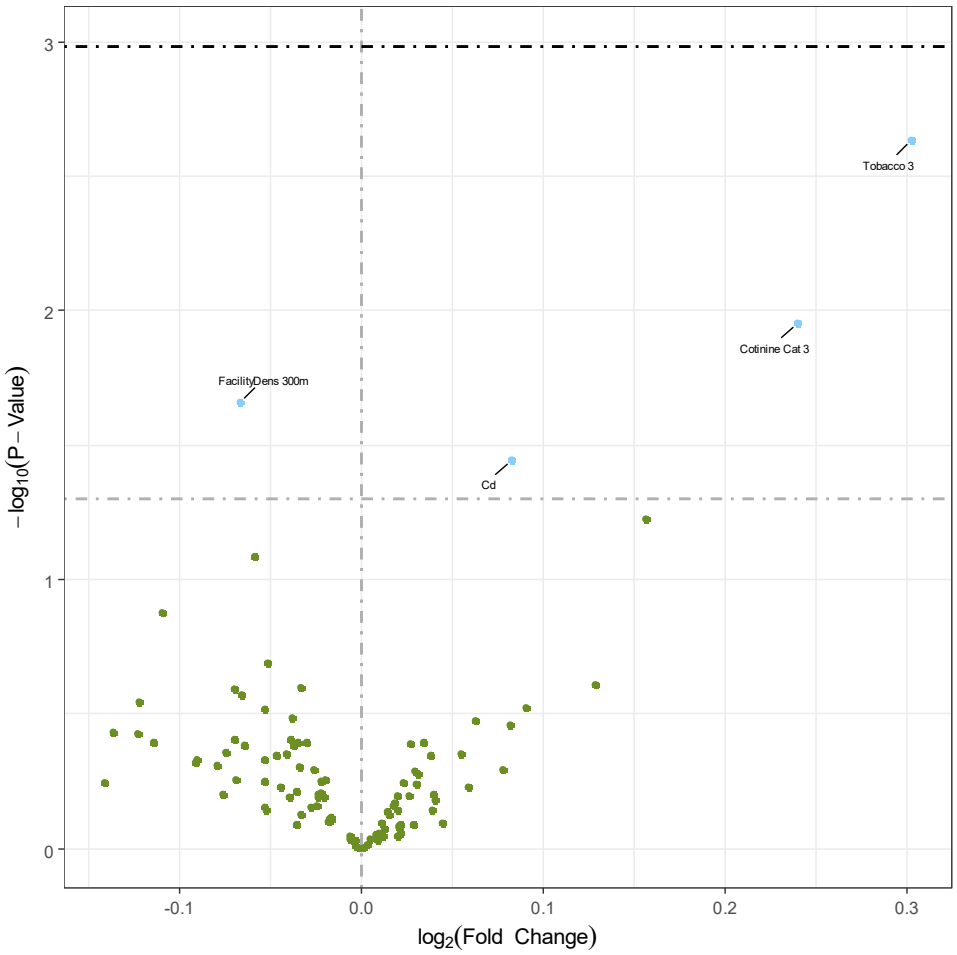


Figure 15 Prenatal Exposome and BMI (Volcano plot).

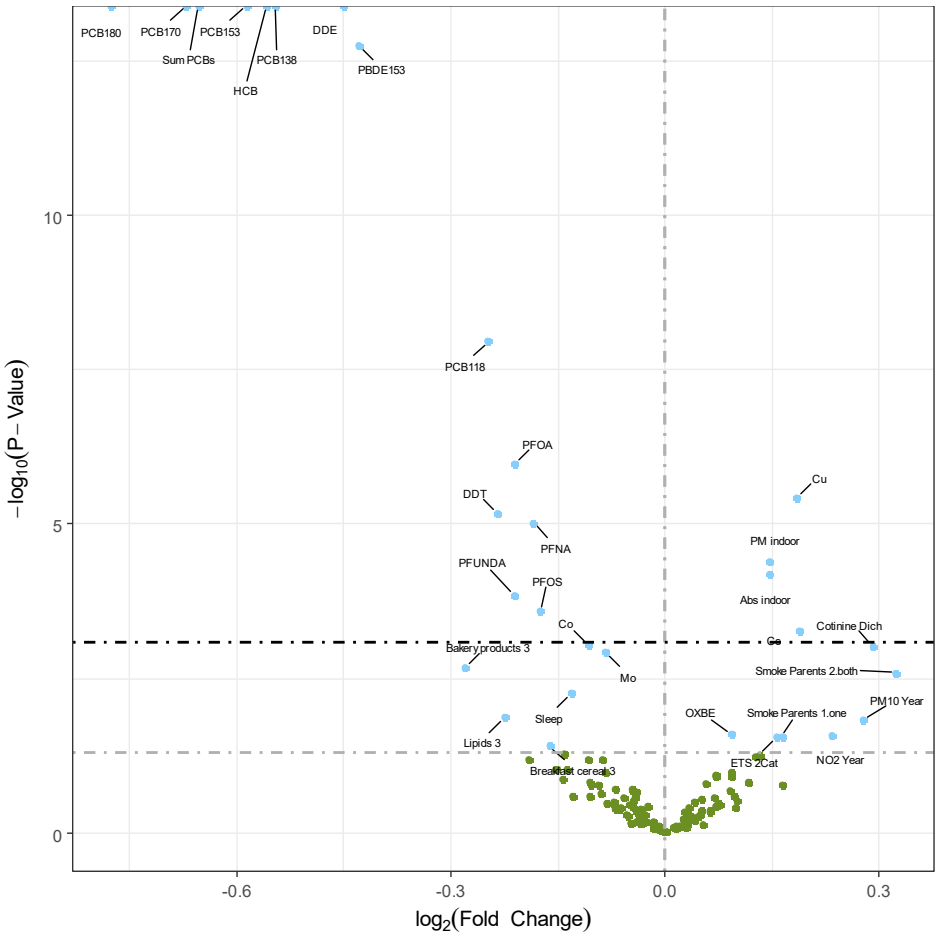


Figure 16 Postnatal Exposome and BMI (Volcano plot).

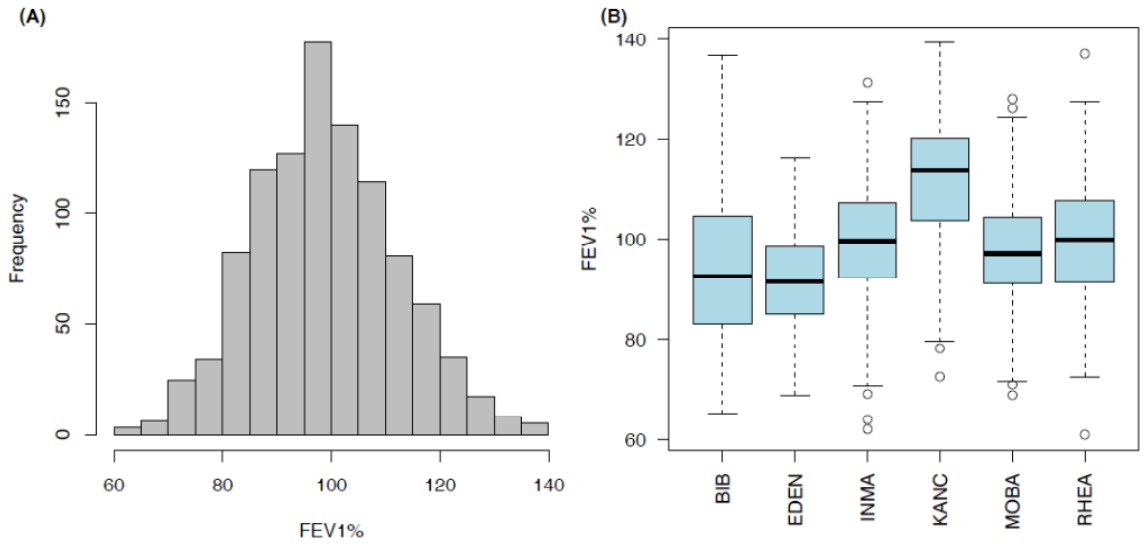


Figure 17 FEV1% distribution given as a histogram (A), and as boxplot per cohort (B).

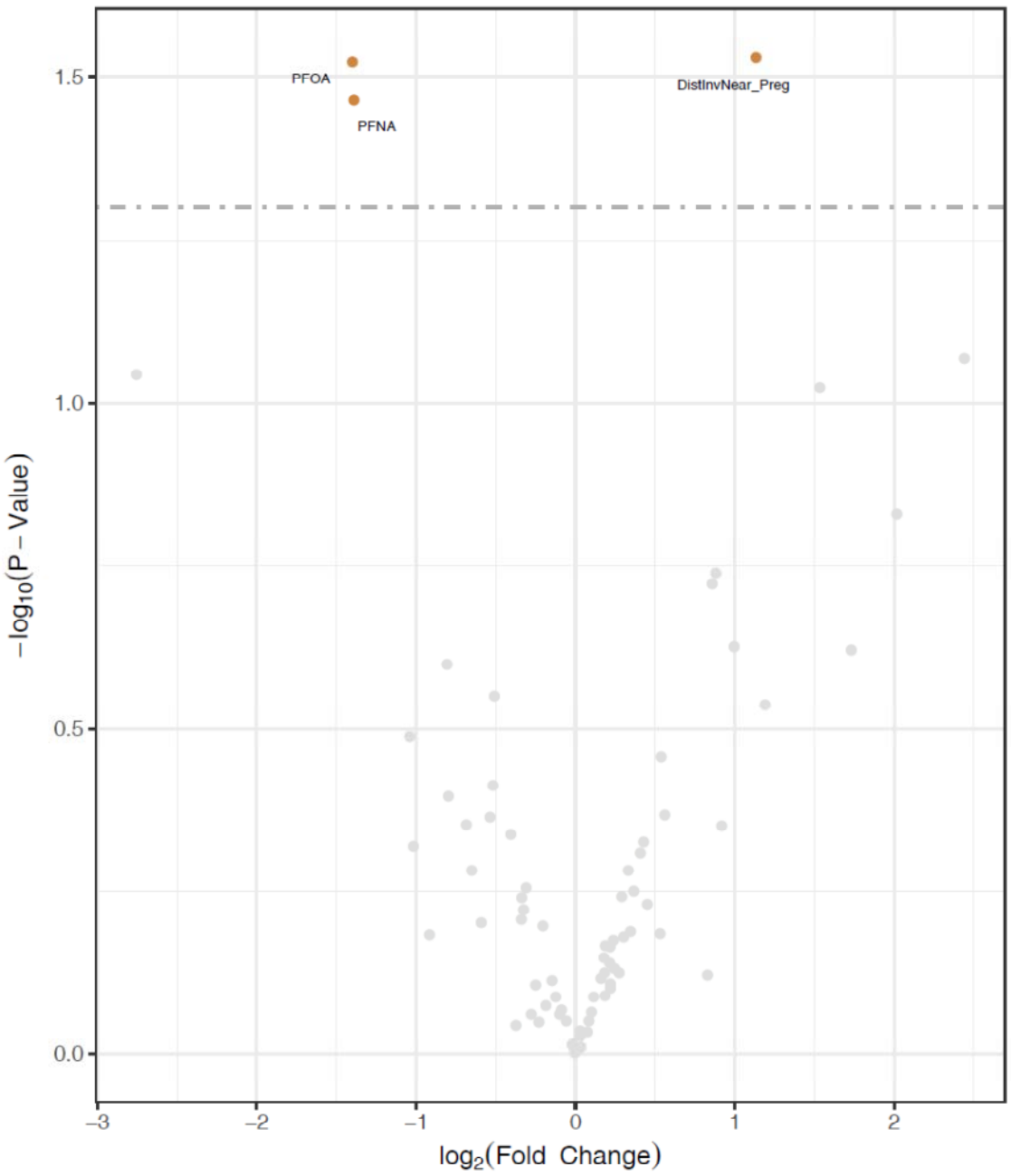


Figure 18 Volcano plot of prenatal exposome coefficient estimate vs. p-value (uncorrected for multiple hypothesis testing) obtained with the EWAS analysis testing the association with FEV1%.
Coefficient estimates are given in log fold change in outcome for an IQR change in the given exposure. The grey dot-dashed line corresponds to the 0.05 threshold for p-values. DistInvNear_Preg: Inverse distance to nearest road during pregnancy; ExWAS= Exposome-wide association study; IQR: Inter-quartile range; PFNA: Perfluorononanoate exposure; PFOA: Perfluorooctanoate exposure. Exposome database 2.2.

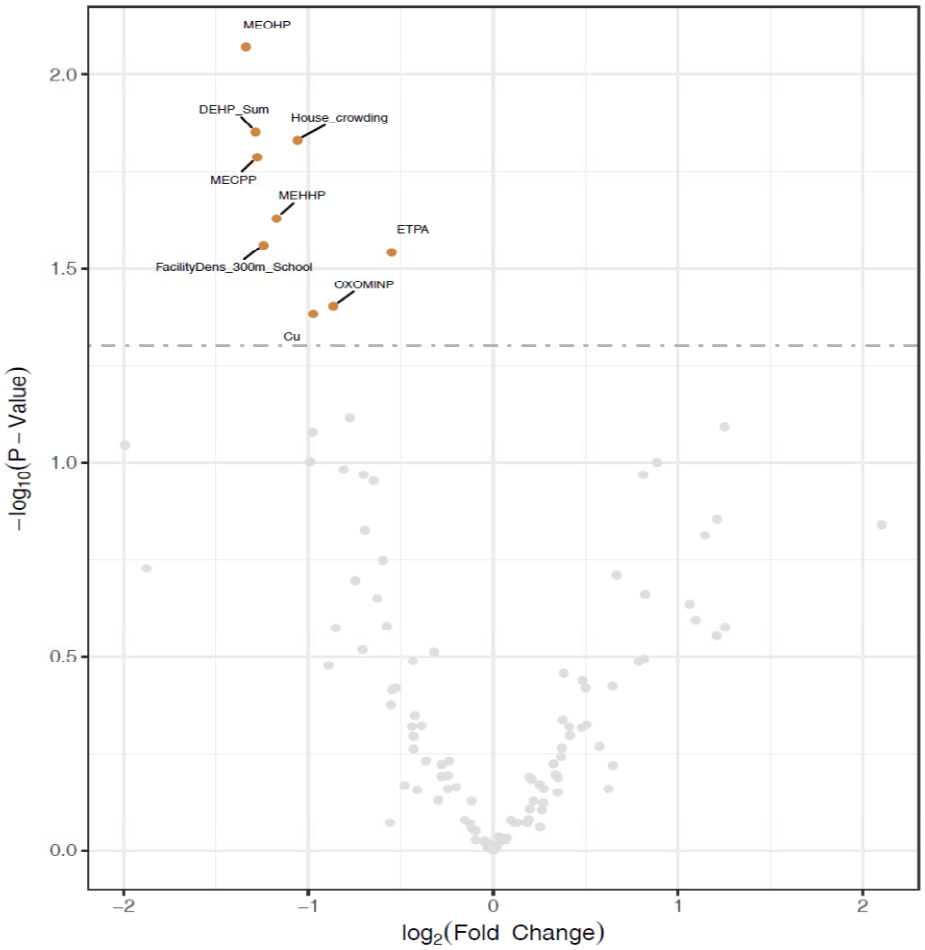
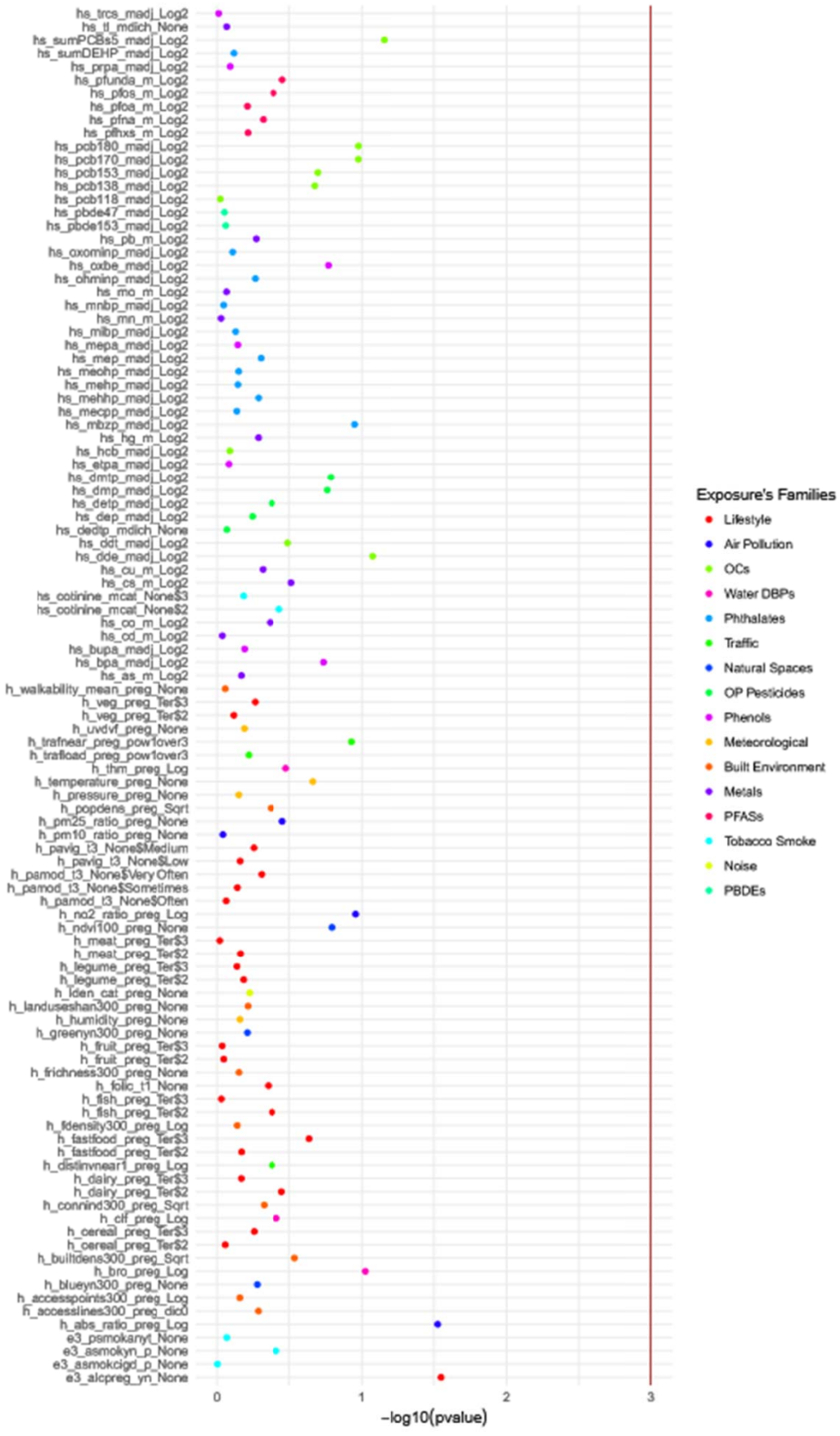


Figure 19 Volcano plot of prenatal exposure variables coefficient estimate vs. p-value (uncorrected for multiple hypothesis testing) obtained with the ExWAS analysis testing the association with FEV1%. Coefficient estimates are given in FEV1% fold change for an IQR change in the given exposure. The grey dot-dashed line corresponds to the 0.05 threshold for p-values.

Cu = copper; DEHP_Sum = sum of DEHP metabolites; ETPA: Ethyl paraben; ExWAS: Exposome-wide association study; FacilityDens_300m_School= Number of bus public transport mode stops in a 300m buffer around school; IQR: Inter-quartile 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 in children; OXOMINP: Mono-4-methyl-7-oxooctyl phthalate.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hs_tl_mdich_None
hs_sumPCBs5_madj_Log2
hs_sumDEHP_madj_Log2
hs_prpa_madj_Log2
hs_pfunda_m_Log2
hs_pfos_m_Log2
hs_pfoa_m_Log2
hs_pfna_m_Log2
hs_pfhxs_m_Log2
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hs_pcb153_madj_Log2
hs_pcb138_madj_Log2
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hs_ohminp_madj_Log2
hs_mo_m_Log2
hs_mnbp_madj_Log2
hs_mn_m_Log2
hs_mibp_madj_Log2
hs_mepa_madj_Log2
hs_mep_madj_Log2
hs_mecpp_madj_Log2
hs_mehp_madj_Log2
hs_mehhp_madj_Log2
hs_mecpp_madj_Log2
hs_mbzp_madj_Log2
hs_hg_m_Log2
hs_hcb_madj_Log2
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hs_detp_madj_Log2
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hs_dde_madj_Log2
hs_cu_m_Log2
hs_cs_m_Log2
hs_cotinine_mcat_None$3
hs_cotinine_mcat_None$2
hs_co_m_Log2
hs_cd_m_Log2
hs_bupa_madj_Log2
hs_bpa_madj_Log2
hs_as_m_Log2
h_walkability_mean_preg_None
h_veg_preg_Ter$3
h_veg_preg_Ter$2
h_uvdvf_preg_None
h_trafnear_preg_pow1over3
h_trafload_preg_pow1over3
h_thm_preg_Log
h_temperature_preg_None
h_pressure_preg_None
h_popdens_preg_Sqrt
h_pm25_ratio_preg_None
h_pm10_ratio_preg_None
h_pavig_t3_None$Medium
h_pavig_t3_None$Low
h_pamod_t3_None$Very Often
h_pamod_t3_None$Sometimes
h_pamod_t3_None$Often
h_no2_ratio_preg_Log
h_ndvi100_preg_None
h_meat_preg_Ter$3
h_meat_preg_Ter$2
h_legume_preg_Ter$3
h_legume_preg_Ter$2
h_lden_cat_preg_None
h_landuseshan300_preg_None
h_humidity_preg_None
h_greenyn300_preg_None
h_fruit_preg_Ter$3
h_fruit_preg_Ter$2
h_frichness300_preg_None
h_folic_t1_None
h_fish_preg_Ter$3
h_fish_preg_Ter$2
h_fdensity300_preg_Log
h_fastfood_preg_Ter$3
h_fastfood_preg_Ter$2
h_distinvnear1_preg_Log
h_dairy_preg_Ter$3
h_dairy_preg_Ter$2
h_connind300_preg_Sqrt
h_clf_preg_Log
h_cereal_preg_Ter$3
h_cereal_preg_Ter$2
h_builtdens300_preg_Sqrt
h_bro_preg_Log
h_blueyn300_preg_None
h_accesspoints300_preg_Log
h_accesslines300_preg_dic0
h_abs_ratio_preg_Log
e3_psmokanyt_None
e3_asmokyn_p_None
e3_asmokcigd_p_None
e3_alcpreg_yn_None
0
1
2
3
−log10(pvalue)
Exposure's Families
Lifestyle
Air Pollution
OCs
Water DBPs
Phthalates
Traffic
Natural Spaces
OP Pesticides
Phenols
Meteorological
Built Environment
Metals
PFASs
Tobacco Smoke
Noise
PBDEs

Figure 20 Adjusted associations between the prenatal Exposome and parent-reported ever asthma. Associations were tested with an EWAS approach (preliminary results based on 1300 HELIX subcohort children and V 2.1 of the Exposome database.

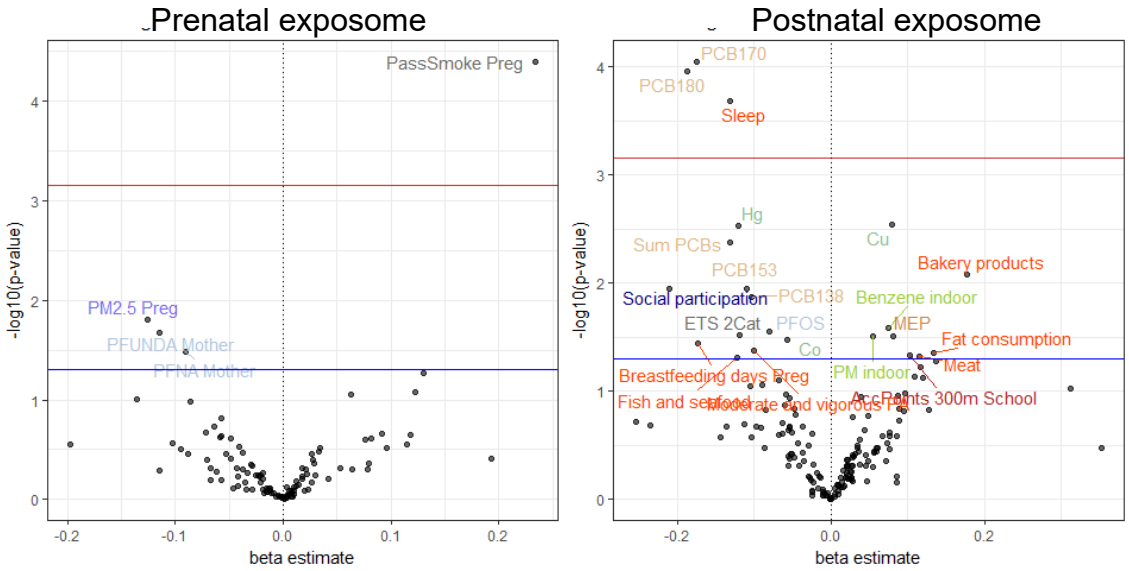

Figure 21 Internalizing Problems (Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints scores) in relation with the prenatal (left panel) and postnatal exposomes (right panel).

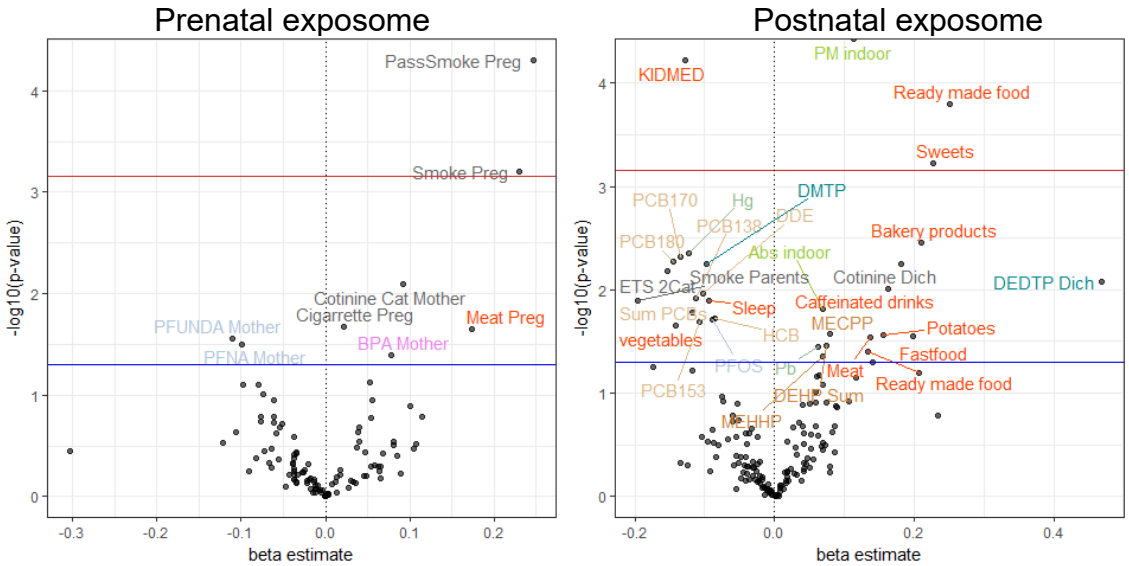

Figure 22 Externalizing Problems (Rule-Breaking Behaviour and Aggressive Behaviour scores) in relation with the prenatal (left panel) and postnatal exposomes (right panel).

Exposome database 2.1.

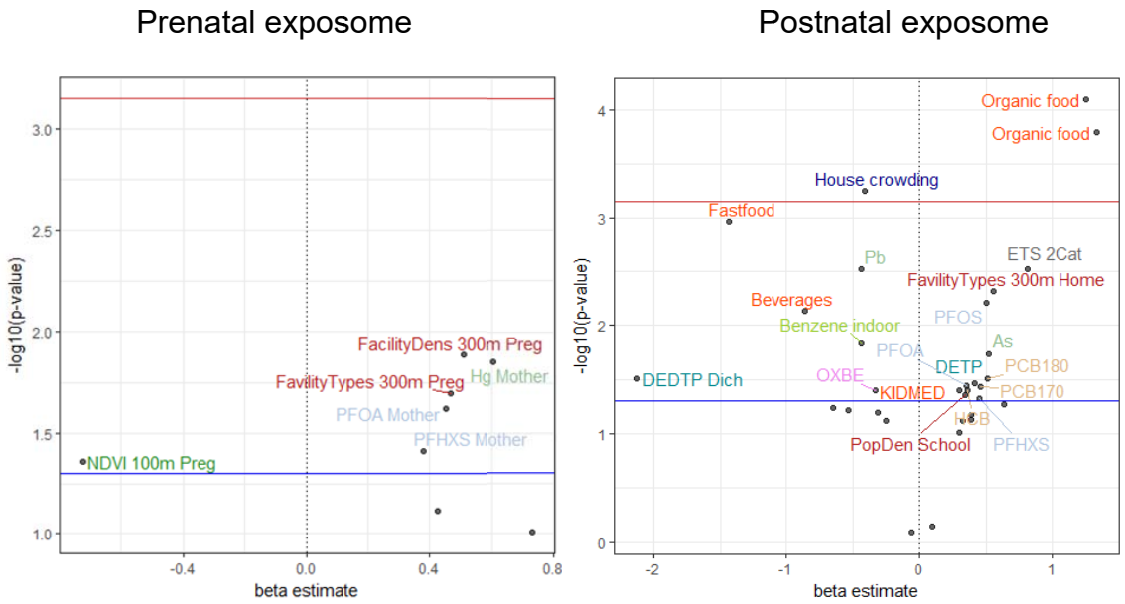

Figure 23 Raven Test score (Fluid Intelligence)

Exposome database 2.1.

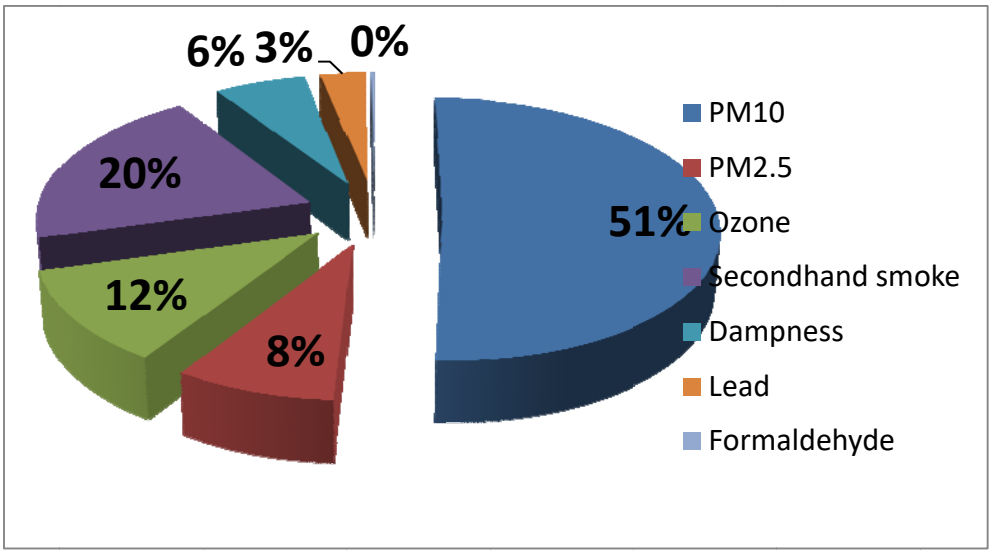

Figure 24 Percentage of exposures studied that contribute to the Environmental burden of disease in EU28, in the population less than 18 years old.

PM10: Particulate matter less than 10 micrometers of diameter; PM25: Particulate matter less than 25 micrometers of diameter

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Beneficiaries

1. ISGlobal, Barcelona Institute for Global Health (former CREAL) Spain (Coordinator) – Martine Vrijheid
2. Nasjonalt Folkehelseinstitutt (NIPH), Norway – Cathrine Thomsen
3. University of Crete (UoC), Greece – Leda Chatzi
4. Institut National de la Santé et de la Recherche Medicale (Inserm), France – Rémy Slama
5. Bradford Teaching Hospitals NHS Foundation Trust (BTHFT), United Kingdom – John Wright
6. Vytauto Didziojo Universitetas (VDU), Lithuania – Regina Gražulevičienė
7. Imperial College of Science, Technology and Medicine (ICL), United Kingdom – Hector Keun, Muireann Coen
8. Fundacío Privada Centre de Regulacío Genomica (CRG), Spain – Eulalia Martí
9. Veiligheids- en Gezondheidsregio Gelderland-Midden (VGGM), Netherlands – Peter van den Hazel
10. Hylobates Consulting S.R.L. (HYLO), Italy – Luca Bucchini
11. Sensing & Control Systems S.L. (S&C), Spain – Alberto Fernandez
12. Institut National de l'Environnement et des risques (INIRIS), France – Céline Brochot
13. Universidade de Santiago de Compostela (USC-CEGEN), Spain – Angel Carracedo