International Journal of Hygiene and Environmental Health 222 (2019) 864–872

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Socioeconomic position and exposure to multiple environmental chemical contaminants in six European mother-child cohorts

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A B S T R A C T

Background: Human exposure to environmental chemical contaminants at critical periods of development can lead to lifelong health consequences. Traditionally, socioeconomically disadvantaged groups are thought to experience higher contaminant exposures; however, this relationship may not hold for all contaminants.

Methods: Using data from six European birth cohorts (1301 mother-child pairs), we determined biomarkers of exposure to 41 contaminants in biological samples from children (6–12 years) and their mothers during pregnancy, including organochlorine compounds (OCs), polybrominated diphenyl ethers (PBDEs), per- and polyfluoroalkyl substances (PFASs), metals, phthalate metabolites, phenols, and organophosphate (OP) pesticide metabolites. We analyzed these biomarkers with several socioeconomic position (SEP) indicators (maternal education, employment status and family affluence scale).

Results: Higher SEP was associated with higher concentrations of several chemicals during pregnancy, including certain PFASs, mercury, arsenic, several phenols, and OP pesticides. Similarly, childhood concentrations of OCs, PFASs, mercury, arsenic, and bisphenol A were higher in higher SEP groups. Conversely, cadmium exposure during pregnancy and exposure to lead and phthalate metabolites in childhood were higher in lower SEP. Principal components representing multiple pollutant exposures showed similar association with SEP.

Conclusions: This study demonstrates that environmental chemical contaminant exposure during fetal and childhood life is not exclusively associated to lower SEP and that for several contaminants higher SEP groups incur higher exposure levels.

1. Introduction

The development and use of synthetic chemicals has grown immensely over the last century with tens of thousands of chemicals currently in production (Landrigan and Goldman, 2011). These chemicals range in use from plastics for convenience use, pesticides for food production and flame retardants for safety. Recent scientific literature has highlighted widespread human exposure to many of these chemicals (Gore et al 2015). Depending on the chemical, exposure can occur through food, water, air, dust, and/or physical contact with common household items (Landrigan and Goldman, 2011).

Exposures to environmental contaminants are of particular concern in pregnant women and children as many chemicals have been shown to transfer in-utero from the mother to the fetus, and higher levels of certain chemicals have been observed in children due to frequent hand-to-mouth/object activity (Lunder et al 2010; Mamsen et al 2017). The

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https://doi.org/10.1016/j.ijheh.2019.04.002
Received 17 January 2019; Received in revised form 2 April 2019; Accepted 11 April 2019

gestational and childhood period are both critical periods of growth and development that when interrupted by outside sources like environmental contaminants can lead to lifelong health consequences such as, asthma, obesity, neurodevelopmental disabilities and cardiovascular disease (Vrijheid et al 2016).

In environmental health, socioeconomic position (SEP) has long been studied and shown to play a role in a wide variety of health outcomes, including the unequal distribution of environmental risk to exposures (Pampel et al., 2010). This unequal distribution is often related to SEP indicators such as income, social status, employment and education. Depending on the environmental risk and the group(s) being studied, the direction and magnitude of inequality can vary (Hicken et al 2012).

Scientific evidence has reported varying results that both support and contradict the traditional hypothesis of disadvantaged groups as being systematically classified as the "high risk" group. A study in the United States using NHANES data found that individuals with higher SEP had higher burdens of certain metals, per- and polyfluoroalkyl substances (PFASs), phthalates, and oxybenzone (OXBE/BP3), whilst lower SEP was associated with higher levels of bisphenol A (BPA) and three different phthalates (Tyrrell et al 2013). Similarly, a Spanish birth cohort found that polychlorinated biphenyls (PCB), hexachlorobenzene (HCB) and mercury (Hg) were higher in higher social classes (Vrijheid et al 2012). A Korean study examining metals in children found that lead levels where higher in those of lower SEP, while mercury was higher in high socioeconomic position children (Lim et al 2015). This incongruence challenges the traditional hypothesis prompting further exploration.

As outlined in the Sixth Ministerial Conference on Environment and Health in Czech Republic in June 2017, "reducing the exposure of vulnerable groups to hazardous chemicals, particularly during the early stages of human development" is a priority area to better the health of children and future generations. Studying the social determinants of an already vulnerable group like pregnant women and children is of critical importance to minimizing the health burden of chemical contaminants. Our understanding of the role that social determinants play in dictating a person's exposure to environmental contaminants is limited. This study aimed to investigate the associations between indicators of SEP and measured levels of several environmental contaminants in a population of pregnant women and their children (6–12 years old) in six European birth cohorts.

2. Material and methods

2.1. Study population and sample collection

The study population has been previously described in detail (Maitre et al 2018; Vrijheid et al 2014). Briefly, data used was from The Human Early-Life Exposome (HELIX) subcohort which comprises of 1301 mother-child pairs. The participants were recruited from six different European birth cohorts; BiB (Born in Bradford UK (n = 205) (Wright et al 2013), EDEN (Study of determinants of pre- and postnatal developmental, France, n = 198) (Drouillet et al 2009), INMA (Environment and Childhood, Spain, n = 223) (Guxens et al 2012), KANC (Kaunas Cohort, Lithuania n = 204) (Grazuleviciene et al 2009), MoBa (The Norwegian Mother and Child Cohort Study, Norway (Oslo region) n = 272) (Magnus et al 2016) and RHEA (Mother–Child Cohort in Crete, Greece n = 199) (Chatzi et al 2009).

For all cohorts, women were recruited during pregnancy and blood and urine samples were collected (Maitre et al 2018), except for KANC where no urine was collected. As part of the HELIX subcohort follow-up, clinical assessments of their children were carried out between December 2013 and February 2016 and these included blood and urine collection (Maitre et al 2018). These assessments were done in a completely harmonized manner (children only) between the cohorts using the same protocol for sample collection and clinical measures (Maitre et al 2018). All women signed a written consent at initial recruitment during pregnancy, and either the mother and/or father signed a written consent for the participation of their child at the time of clinical assessment. Ethical approval was obtained for this project from the relevant authorities in each of the six participating countries.

2.2. Indicators of socioeconomic position

Women completed questionnaires during pregnancy at the time of recruitment in each cohort. Collected data on maternal characteristics included age, education attained (low = primary school, middle = secondary school, high = university degree or higher), employment status during pregnancy (employed or unemployed), parity (nulliparous = 0 children, primiparous = 1 child, multiparous = 2 or more children), and breastfeeding of any previous children (ever/never and duration). These data were later harmonized between cohorts. At the children's assessments, cohorts used the same study questions for participants. Data on child's age, sex, and breastfeeding (yes/no and duration) were collected. Additionally, family affluence scale (FAS), a four-item measure of family wealth was calculated based on four questions regarding car ownership, bedroom sharing, family travel, and computer ownership. From this a composite FAS score was calculated using a three point ordinal scale; low affluence (FAS low = score of 0,1,2), middle affluence (FAS middle = score of 3,4,5), or high affluence (FAS high = score of 6,7,8,9) (Andersen et al 2008; Boyce et al 2006).

2.3. Environmental contaminants

Concentrations of environmental contaminants were determined in serum, plasma, whole blood, and urine using maternal samples collected during pregnancy or at birth and stored by the cohorts, and in newly collected samples from the children during childhood (Supplementary Material S1-2; Haug et al 2018). Samples were frozen at −80 °C under optimized and standardized procedures (Maitre et al 2018). Environmental contaminants measured (see full names in Table 1) included organochlorine compounds (DDE, DDT, HCB), polychlorinated bisphenyls (PCB-118, -138, −153, −170, −180), polybrominated diphenylethers (PBDE-47, -153), per- and polyfluoroalkyl substances (PFASs) (PFOA, PFNA, PFUnDA, PFHxS, PFOS), and metals and elements (As, Cd, Hg, M, Pb) in blood, and phthalate metabolites (MEP, MiBP, MnBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, oh-MiNP, oxo-MiNP), phenols (MEPA, ETPA, PRPA, BPA, BUPA, OXBE, TCS), and non-specific organophosphate (OP) pesticide metabolites (DMP, DMTP, DMDTP, DEP, DETP, DEDTP) in urine. Lipophilic compounds measured in blood were adjusted by plasma/serum lipids and urine samples were adjusted by creatinine to account for variation in urine dilution, no adjustment was done for PFASs or metals as they are non-lipophilic.

Analyses for archived maternal samples from pregnancy and childhood were performed at one laboratory, the Department of Environmental Exposure and Epidemiology at the Norwegian Institute of Public Health (NIPH) or their contract laboratories, for comparability purposes and to reduce uncertainty. For certain cohorts (EDEN, INMA, and RHEA), maternal samples had been previously analyzed at different laboratories and results were available for select contaminants. To ensure high quality, internal quality control (QC) samples were analyzed with each sample batch and results were plotted in quality control charts by contaminant. The results were found satisfactory and no batch correction was applied. Details regarding laboratories, analytical techniques, quality control measures, inter-laboratory comparison analyses, and limit of detection (LOD) and limit of quantification (LOQ) for each laboratory can be found in Haug et al (2018) and correlations in Supplementary Material S3-4.

Concentrations measured by NIPH or their contract laboratories were reported whenever a signal was observed on the instrument even when below LOQ, these results were used in the statistical calculations.

Table 1
Social Determinants collected during prenatal and postnatal periods of 1301 pregnant women and their children in the HELIX subcohort, original and imputed data sets.

Characteristic	N Missing	Original data set	Imputed data set
		mean ± SD or percent	mean ± SD or percent
Prenatal Characteristics			
Cohort	0		
BiB		15.8(205)	15.8(205)
EDEN		15.2(198)	15.2(198)
INMA		17.1(223)	17.1(223)
KANC		15.7(204)	15.7(204)
MoBa		20.9(272)	20.9(272)
Rhea		15.3(199)	15.3(199)
Maternal Age at delivery (mean ± SD)	16	30.8 ± 4.9	30.8 ± 4.9
Maternal Education	44		
Low (primary)		13.8(173)	14.1
Middle (secondary)		34.4(433)	34.3
High (university or higher)		51.8(651)	51.7
Maternal Working Status	113		
Unemployed		17.4(207)	17.8
Employed		82.6(981)	82.2
Parity	31		
Nulliparous (0)		45.9(583)	45.9
Primiparous (1)		36.2(460)	36.2
Multiparous(> =2)		17.9(227)	17.9
Breastfeeding with previous child	49		
No previous child		46.3(580)	46.3
No		8.9(112)	8.9
Yes		44.7(560)	44.7
Breastfeeding duration with previous child (days) (mean ± SD)	64	104.7 ± 178.8	104.7 ± 178.7
Postnatal Characteristics			
Child's Age (years) (mean ± SD)	0	8.0 ± 1.6	8.0 ± 1.6
Child's Sex	0		
Female		45.3(590)	45.3
Male		54.7(711)	54.7
Family Affluence Scale	8		
Low		10.5(136)	10.5
Middle		38.6(499)	38.7
High		50.9(658)	50.9
Breastfeeding with study child	6		
No		15.4(200)	15.4
Yes		84.6(1095)	84.6
Breastfeeding duration with study child (days) (mean ± SD)	29	217.0 ± 244.6	217.0 ± 244.6

For samples where no concentrations were generated, defined as below LOD, values were singly imputed using a quantile regression approach for the imputation of left-censored missing data implemented in the *imputeLOD* function in the rexposome package in the R software (The R Project (Computing TRPfS, 2016)).

Most contaminants were detected in a high proportion of samples (> 90% quantifiable for 33 contaminants during pregnancy and 32 during childhood). Two contaminants (DMDTP and DEDTP) were not included for analysis due to > 40% of observations being below the LOD, leaving 41 contaminants for the final analysis.

2.4. Statistical analysis

To handle missing values in the SEP and covariate variables, a multiple imputation approach was followed under the assumption of missing at random (van Buuren and Groothuis-Oudshoorn, 2011. In total, 20 imputed data sets were generated using the *ice* command in Stata with imputation models that included additional covariates not included in the analyses models to enhance prediction (Royston and White, 2011).

All environmental contaminants showed non-normal distributions in graphical evaluations and normality tests (qqplot, histogram, Shapiro-Wilk test) and were thus transformed using the base-2 logarithm; the geometric mean (GM), median and interquartile range were used to describe their distributions.

Firstly, multivariable linear regression models were used to examine how levels of environmental contaminants during pregnancy and childhood varied by selected indicators of SEP, for each of the 41 contaminants separately using both complete-case and imputed data sets. SEP was defined as maternal education and maternal employment status for pregnant women, and maternal education and FAS score for children. In the multivariate adjusted models, covariates included were chosen a-priori as those reported to influence environmental contaminant concentrations in the literature. In order to keep models as parsimonious as possible the same covariates were used across all contaminants. Multivariable adjusted models during pregnancy included cohort, parity, previous breastfeeding, and age of mother at chemical measurement (Caspersen and Ida, 2016; Manzano-Salgado and Cyntia, 2015), while models for childhood were adjusted for cohort, parity (of mother), previous breastfeeding (of mother), breastfeeding, and child age at measurement (Fisher et al 2016; Mondal et al 2014; Morck et al 2015). A sensitivity analysis further adjusting pregnancy models for fish consumption and smoking was carried out (Brandhagen et al 2014; Mondal et al 2014).

Given the large number of environmental contaminants, we conducted principal component analysis (PCA) to reduce the dimensionality of our data. PCA reduces the number of correlated variables into a small number of new variables called components, which capture as much variance of the original variables as possible while still remaining uncorrelated with one another (SAS Institute n.d.). PCA was applied separately to the imputed datasets for mothers and their children using the R function *prcomp*. After examining the scree plot and using Kaiser's rule, all components with an eigenvalue greater than 1 were retained, resulting in 13 components for pregnancy and 12 components for childhood. Next, varimax rotation was applied and after examining the data only those components that accounted for 5% or more of variance in the data were retained for further analysis. This resulted in 5 components for pregnancy and 4 components for childhood. In order to conduct regression analysis with the components, scores were calculated for each subject based on the component weight in conjunction with the original variable values. Finally, multivariate linear regression models were run to investigate the relationship between socioeconomic position and the new components. A sensitivity analysis taking out one cohort at a time was carried out to understand any differences between the cohorts.

Statistical significance was defined as p-value < 0.05. Preliminary and regression analyses were performed using STATA version 12.0 (StataCop, College Station, TX, USA), and principal component analysis was carried out using RStudio version 3.4.1 (The R Foundation for Statistical Computing).

3. Results

In our study population, pregnant women were on average 30.8 years old at delivery, 82.6% were employed during pregnancy and for 45.9% of them this was their first child. About half of pregnant women had a high level of education (51.8%), while 34.4% had a mid level and 13.8% had a low level education. On average children were 8 years old at the time of sample collection (age range: 5.4–12.1), 54.7% were male and 84.6% of them were breastfed. Half (50.9%) of the families were classified as having high affluence, 38.6% as middle and 10.5% as low affluence (Table 1). The mean and frequency of demographic characteristics were generally similar in the original and imputed data sets

Table 2
Median concentrations of biomarkers of 41 chemical contaminants (detailed distributions and percent detected in Supplementary Material Table S6).

Chemical Contaminants	Abbrev.	Unit	Pregnancy			Childhood		
			N	Median (p25-75)	PC	N	Median (p25-75)	PC
Persistent Pesticides:								
4,4′dichlorodiphenyldichloroethylene	DDE	ng/g lipid	1048	52.3 (25.9–110.7)	PC4	1279	21.7 (11.5–45.6)	–
4,4′dichlorodiphenyltrichloroethane	DDT	ng/g lipid	826	1.3 (0.8–3.0)	PC4	1279	0.7 (0.3–1.6)	–
Hexachlorobenzene	HCB	ng/g lipid	1048	8.2 (5.6–12.9)	–	1279	8.2 (6.3–11.4)	–
2,2′,4,4′-Tetrabromodiphenyl Ether	PBDE-47	ng/g lipid	684	0.4 (0.3–0.7)	PC4	1279	0.2 (0.1–0.4)	–
2,2′,4,4′,5,5′-Hexabromodiphenyl ether	PBDE-153	ng/g lipid	648	0.4 (0.03–0.7)	–	1279	0.2 (0.03–0.4)	–
2,3′,4,4′,5-Pentachlorobiphenyl	PCB-118	ng/g lipid	829	2.6 (1.6–4.8)	PC1	1279	2.0 (1.5–2.9)	–
2,2′,3,4,4′,5′-Hexachlorobiphenyl	PCB-138	ng/g lipid	1048	9.1 (5.5–16.1)	PC1	1279	5.4 (3.4–8.7)	PC2
2,2′,4,4′,5,5′-Hexachlorobiphenyl	PCB-153	ng/g lipid	1048	17.6 (10.4–30.5)	PC1	1279	11.6 (7.3–18.6)	PC2
2,2′,3,3′,4,4′,5-Heptachlorobiphenyl	PCB-170	ng/g lipid	826	3.7 (1.8–7.1)	PC1	1279	1.3 (0.6–2.7)	PC2
2,2′,3,4,4′,5,5′-Heptachlorobiphenyl	PCB-180	ng/g lipid	1048	10.4 (5.8–18.5)	PC1	1279	3.7 (1.6–8.0)	PC2
Per- and Polyfluoroalkyl Substances:								
Perfluorooctanoate	PFOA	μg/L	1240	2.3 (1.4–3.3)	–	1301	1.5 (1.2–2.0)	PC3
Perfluorononanoate	PFNA	μg/L	1240	0.7 (0.4–1.1)	PC4	1301	0.5 (0.3–0.7)	PC3
Perfluoroundecanoate	PFUnDA	μg/L	1032	0.2 (0.1–0.3)	PC4	1301	0.03 (0.02–0.1)	PC3
Perfluorohexane sulfonate	PFHxS	μg/L	1240	0.5 (0.3–0.9)	–	1301	0.4 (0.2–0.6)	PC3
Perfluorooctane sulfonate	PFOS	μg/L	1240	6.4 (4.1–9.6)	–	1301	2.0 (1.3–3.2)	PC3
Metals:								
Arsenic	As	μg/L	833	1.2 (0.3–2.3)	–	1298	1.4 (0.3–2.3)	–
Cadmium	Cd	μg/L	833	0.2 (0.1–0.3)	–	1298	0.1 (0.04–0.1)	–
Mercury	Hg	μg/L	1020	1.9 (1.0–3.4)	–	1298	0.9 (0.4–1.7)	–
Manganese	Mn	μg/L	833	11.1 (8.5–14.3)	–	1298	8.6 (7.1–10.5)	–
Lead	Pb	μg/L	833	9.7 (7.1–13.2)	–	1298	8.5 (6.4–11.1)	–
Phthalate Metabolites:								
Monoethyl phthalate	MEP	μg/g crt.	1080	178.9 (72.1–468.4)	–	1301	32.8 (15.0–79.4)	–
Mono-iso-butyl phthalate	MiBP	μg/g crt.	1088	38.7 (23.3–60.6)	–	1301	40.3 (24.6–71.5)	–
Mono-n-butyl phthalate	MnBP	μg/g crt.	1089	29.6 (18.3–47.3)	–	1301	22.7 (14.5–38.8)	–
Mono benzyl phthalate	MBzP	μg/g crt.	1088	7.3 (3.6–15.2)	–	1300	4.8 (2.7–8.7)	–
Mono-2-ethylhexyl phthalate	MEHP	μg/g crt.	1085	8.7 (4.4–15.2)	PC3	1260	2.9 (1.6–5.1)	PC1
Mono-2-ethyl-5-hydroxyhexyl phthalate	MEHHP	μg/g crt.	1089	18.2 (10.5–31.2)	PC3	1298	19.4 (11.4–33.2)	PC1
Mono-2-ethyl-5-oxohexyl phthalate	MEOHP	μg/g crt.	1089	14.1 (8.3–23.7)	PC3	1300	12.3 (7.1–20.5)	PC1
Mono-2-ethyl 5-carboxypentyl phthalate	MECPP	μg/g crt.	913	33.6 (22.4–52.3)	PC3	1300	32.9 (19.9–57.8)	PC1
Mono-4-methyl-7-hydroxyoctyl phthalate	oh-MiNP	μg/g crt.	914	0.9 (0.6–1.5)	–	1301	5.0 (3.1–9.3)	–
Mono-4-methyl-7-oxooctyl phthalate	oxo-MiNP	μg/g crt.	914	1.0 (0.6–1.7)	–	1301	2.7 (1.7–5.0)	–
Phenols:								
Methyl paraben	MEPA	μg/g crt.	815	166.8 (39.5–389.4)	–	1299	6.3 (3.1–24.3)	PC4
Ethyl paraben	ETPA	μg/g crt.	817	6.3 (1.1–26.7)	–	1298	0.7 (0.4–1.2)	PC4
Propyl paraben	PRPA	μg/g crt.	1083	44.2 (8.9–134.2)	–	1284	0.2 (0.02–1.6)	PC4
Bisphenol-A	BPA	μg/g crt.	1084	2.8 (1.6–6.6)	PC2	1289	3.8 (2.3–7.0)	–
N-Butyl paraben	BUPA	μg/g crt.	1083	3.4 (0.4–14.4)	PC2	1296	0.1 (0.05–0.1)	–
Oxybenzone	OXBE	μg/g crt.	1085	4.9 (1.5–27.4)	PC2	1301	2.0 (0.8–6.7)	–
Triclosan	TCS	μg/g crt.	1085	6.9 (1.5–79.7)	–	1301	0.6 (0.3–1.5)	–
OP Pesticide Metabolites:								
Dimethyl phosphate	DMP	μg/g crt.	1080	8.4 (4.1–16.4)	PC5	1295	0.4 (0.3–4.7)	–
Dimethyl thiophosphate	DMTP	μg/g crt.	1084	5.0 (2.0–12.3)	PC5	1300	2.8 (1.2–6.3)	–
Diethyl phosphate	DEP	μg/g crt.	1082	3.3 (1.9–6.4)	PC5	1299	1.8 (0.4–4.7)	–
Diethyl thiophosphate	DETP	μg/g crt.	1037	0.6 (0.1–2.6)	PC5	1280	0.1 (0.1–1.7)	–

Abbreviations: Abbrev. = abbreviation, ng = nanogram, g = gram, μg = microgram, L = liter, crt. = creatinine, PC = principal component.

Detailed SEP indicators by cohort in Supplementary Material S5.

Environmental contaminant distributions are shown in Table 2 and in more detail in Supplementary Material S6. For most contaminants, concentrations were somewhat higher during pregnancy than childhood (Haug et al 2018).

3.1. Socioeconomic position and single environmental contaminants

Fig. 1 shows the associations between SEP indicators and 41 environmental contaminants analyzed during pregnancy and in childhood (see Supplementary Material S7-10 for complete regression output, complete-case and imputed). During pregnancy, concentrations of several contaminants measured were lower in low or middle education groups when compared to the high education group (Fig. 1; Supplementary Material S7). PFUnDA concentrations were 10% lower in the low education group [Geometric Mean Ratio(GMR) = 0.90; 95%CI 0.80, 1.00] and Hg concentrations were 17% lower [GMR = 0.83; 95%CI 0.72, 0.95]. In low educated women, concentrations of several phenols were around half of those in high educated women (GMRs for MEPA, ETPA, PRPA and BUPA between 0.49 and 0.59). BPA concentrations were reduced only in the middle education group [GMR = 0.86; 95%CI 0.74, 0.99] compared to high education. OP pesticide metabolites also showed lower concentrations in pregnant women of lower education with significant differences observed for DMP [GMR = 0.79; 95%CI 0.67, 0.94] and DMTP [GMR = 0.70; 95%CI 0.54, 0.90]. Conversely, Cd concentrations were 30% higher in the low education group [GMR = 1.30; 95%CI 1.12, 1.50] when compared to high education; the sensitivity analysis additionally adjusting for smoking reduced this to 12% higher (no longer statistically significant). Further adjustment for fish consumption did not change the effect estimates (Supplementary Material S19-S20).

Associations between maternal employment status and environmental contaminant exposures were generally weaker than those for maternal education, with GMRs closer to 1 and fewer statistically significant associations (Fig. 1; Supplementary Material S8). We observed lower exposure to all measured PFASs in unemployed pregnant women compared to employed, with GMRs between 0.97 and 0.92 (for example PFOA [GMR = 0.89; 95%CI 0.83, 0.96]). Conversely, DDE

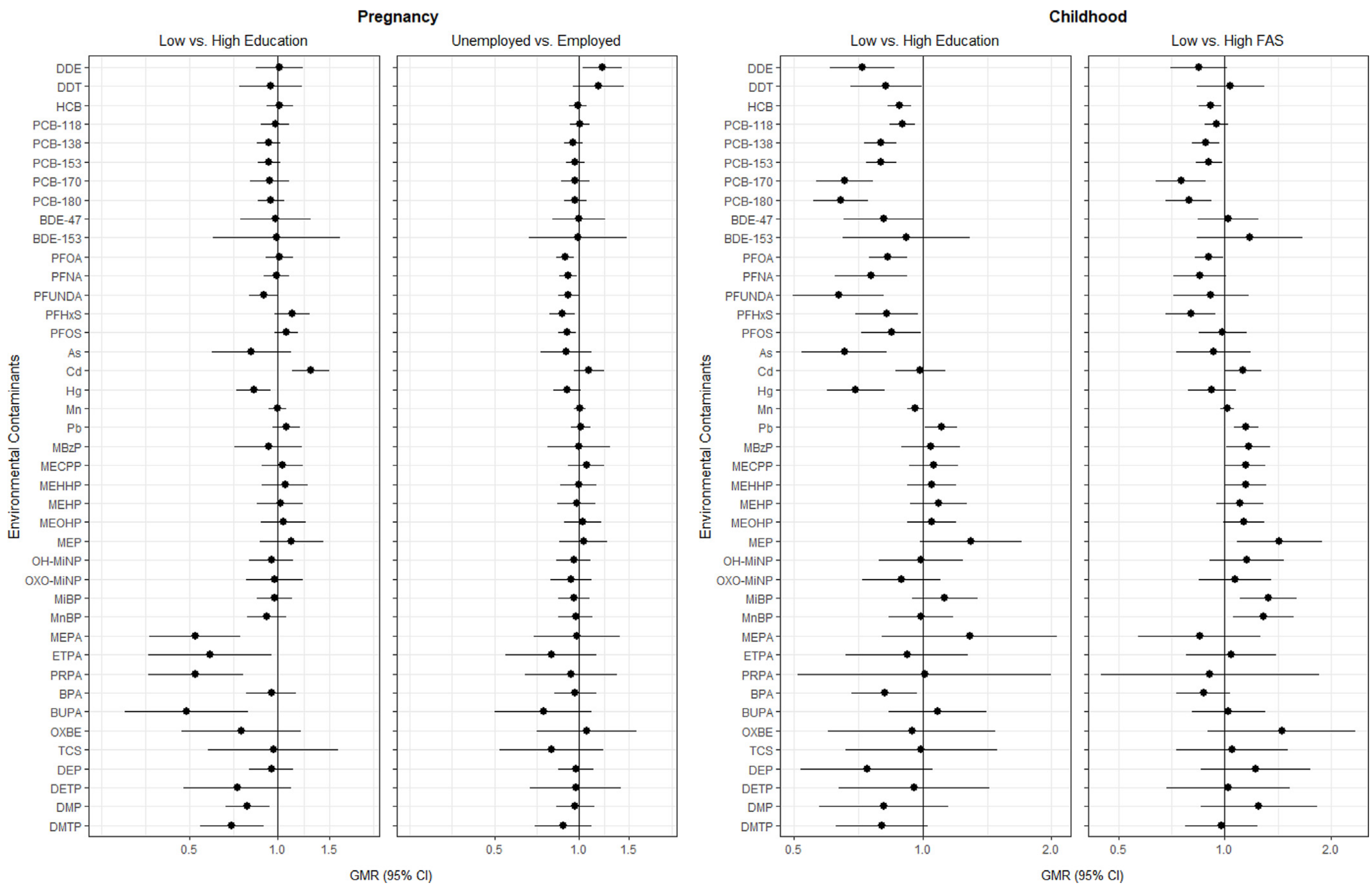

Fig. 1. Adjusted associations (Geometric Mean Ratio (95% CI) between maternal education and employment status and concentrations of chemicals in pregnant women (Pregnancy) and between maternal education and family affluence scale (FAS) and concentrations of chemicals in children (Childhood), ages 6–12 years during childhood, imputed data (n = 1301). Pregnancy models were adjusted for cohort, parity, previous breastfeeding, and age at chemical measurement. Childhood models were adjusted for cohort, parity, previous breastfeeding, breastfeeding of study child, and child age at chemical measurement (years). For interpretation: GMR values < 1 signify lower exposure and GMR values > 1 signify higher exposure in comparison to the reference category.

concentrations were 21% higher in unemployed pregnant women compared to those who were employed [GMR = 1.21; 95%CI 1.03, 1.42]. Sensitivity analysis adjusting pregnancy models for fish consumption or smoking did not change associations for employment status.

In children, lower maternal education was associated with lower concentrations of several groups of contaminants. All organochlorine compounds (DDE, DDT, HCB, and PCBs) showed lower concentrations in children of mothers with low education compared to those whose mothers with a high education, with GMRs between 0.64 and 0.90 (Fig. 1; Supplementary Material S9. For example, DDE concentrations were 28% lower [GMR = 0.72; 95%CI 0.61, 0.86]. PFASs also showed lower childhood concentrations in the low education group (GMRs between 0.64 and 0.84), as did As [GMR = 0.66; 95%CI 0.52, 0.82], Hg [GMR = 0.70; 95%CI 0.60, 0.81], and BPA [GMR = 0.81; 95%CI 0.68, 0.97]. On the other hand, Pb concentrations were 10% higher [GMR = 1.10; 95%CI 1.01, 1.20] in children with mothers with low education.

Significant associations with FAS score indicating lower exposure in children with families in the lower FAS score groups were observed, although less pronounced than with maternal education (Fig. 1; Supplementary Material S10). For example, HCB concentrations were 9% lower in the FAS low group when compared to high. A similar trend was observed for several PCBs (for example PCB-170 [GMR = 0.75; 95%CI 0.64, 0.89]), and certain PFASs (for example PFOA [GMR = 0.90; 95%CI 0.82, 0.99]). Low FAS was associated with higher concentrations of phthalates with GMRs between 1.15 and 1.43 (for example MiBP [GMR = 1.33; 95%CI 1.11, 1.60]) and heavy metals with GMRs between 1.03 and 1.15 (for example Pb [GMR = 1.15; 95%CI 1.06, 1.24]).

3.2. Socioeconomic position and components combining environmental contaminants

In pregnant women, the five components retained for regression analysis accounted for 42.8% of the total variance of the data. After varimax rotation the components were defined by the following contaminants and loadings; component 1 was highly loaded with PCBs: PCB-118 (0.34), PCB-138 (0.45), PCB-153 (0.43), PCB-170 (0.42), PCB-180 (0.42); component 2 was highly loaded with phenols: OXBE (0.51), BPA (0.49), BUPA (0.39); component 3 was highly loaded with DEHP metabolites: MECPP (0.52), MEOHP (0.51), MEHHP (0.49), MEHP (0.45); component 4 was highly loaded with persistent organic pollutants (POPs mixture): DDE (0.50), DDT (0.34), PBDE-47 (0.40), PFNA (0.38), PFUNDA (0.37); and component 5 was highly loaded with pesticide metabolites: DMTP (0.52), DEP (0.49), DMP (0.49), DETP (0.48) (Supplementary Material S11-12 for detailed loadings).

In pregnancy, linear regression models showed a significant negative association between middle level maternal education and PCB exposure when compared to the high education group (component 1) [β = −0.15; 95%CI -0.30, 0.00] (Table 3). Similarly, significant negative associations were observed between both low and middle level maternal education and phenols (component 2) [low vs high (β = −0.25; 95%CI -0.44, −0.05); middle vs high (β = −0.14; 95%CI -0.27, −0.01)] and OP pesticide metabolites (component 5) [low vs high (β = −0.40; 95%CI -0.66, −0.14); middle vs high (β = −0.30;

Table 3
Association between components from principal-component analysis and selected social determinants for pregnant women (Pregnancy). Adjusted models shown (imputed data, n = 1301).

Pregnancy					
Component		Maternal Education		Maternal Employment Status	
		Cat.	Beta (95%CI)	Cat.	Beta (95%CI)
PC1[a]	: PCBs	low	−0.19 (−0.42, 0.03)	unemployed	−0.10 (−0.28, 0.08)
		middle	−0.15 (−0.30, −0.00)*	employed	reference
		high	reference	–	–
PC2[b]	: phenols	low	−0.25 (−0.44, −0.05)*	unemployed	−0.12 (−0.28, 0.04)
		middle	−0.14 (−0.27, −0.01)*	employed	reference
		high	reference	–	–
PC3[c]	: DEHP metabolites	low	0.13 (−0.21, 0.46)	unemployed	0.10 (−0.17, 0.37)
		middle	0.10 (−0.12, 0.32)	employed	reference
		high	reference	–	–
PC4[d]	: POPs	low	−0.11 (−0.29, 0.06)	unemployed	0.07 (−0.08, 0.21)
		middle	−0.07 (−0.19, 0.05)	employed	reference
		high	reference	–	–
PC5[e]	: OP pesticide metabolites	low	−0.40 (−0.66, −0.14)*	unemployed	−0.11 (−0.33, 0.10)
		middle	−0.30 (−0.48, −0.12)*	employed	reference
		high	reference	–	–

Abbreviations: PC = principal component, Cat. = category of independent variable, CI = confidence interval.
Pregnancy models were adjusted for cohort, parity, previous breastfeeding, and age at chemical measurement.
* indicates p-value significant at < 0.05.
[a] PC1 loaded with PCBs: PCB-118, PCB-138, PCB-153, PCB-170, PCB-180.
[b] PC2 loaded with phenols: OXBE, BPA, BUPA.
[c] PC3 loaded with DEHP metabolites: MECPP, MEOHP, MEHHP, MEHP.
[d] PC4 loaded with a mixture of POPs: DDE, DDT, PBDE-47, PFUNDA, PFNA.
[e] PC5 loaded with OP pesticide metabolites: DMTP, DMP, DETP, DEP.

95%CI -0.48, −0.12)] (Table 3). The observed directions were similar to associations found in the single contaminant models. No significant associations were observed between maternal employment and the components (Table 3).

In sensitivity analysis the observed associations were generally similar between the cohorts and went in the same direction. We observed some heterogeneity (i.e. $I^2 > 25\%$ and p-value < 0.00.5) with maternal education and PC2 (low vs. high: $I^2 = 59\%$) and PC5 (middle vs. high $I^2 = 60.6\%$) (Supplementary Material S15-16).

In children, the four components retained for further analysis accounted for 40.3% of the total variance of the data. The components and their loadings were as follows; component 1 was highly loaded with DEHP metabolites: MEHHP (0.50), MEOHP (0.50), MECPP (0.48), MEHP (0.47); component 2 was highly loaded with PCBs: PCB-138 (0.42), PCB-153 (0.46), PCB-170 (0.44), PCB-180 (0.45), component 3 was highly loaded with PFASs: PFOS (0.51), PFOA (0.48), PFNA (0.45), PFUnDA (0.38), PFHxS (0.34); and component 4 loaded highly with parabens: MEPA (0.60), PRPA (0.52), ETPA (0.43) (Supplementary Material S13-14 for detailed loadings).

In children, a significant negative relationship was found for both low and middle maternal education when compared to high and PCBs (component 2) [low (β = −0.90; 95%CI -1.20, −0.59); middle (β = −0.74; 95%CI -0.95, −0.54)], and PFASs (component 3) [low (β = −0.64; 95%CI -0.90, −0.37); middle (β = −0.44; 95%CI -0.62, −0.26)]. Similar trends were observed with FAS score and PCBs (component 2) [low (β = −0.53; 95%CI -0.86, −0.20)], and PFASs (component 3) [middle (β = −0.21; 95% −0.39, −0.03)]. On the contrary, low FAS score was found to have a positive association with DEHP metabolites (component 1) [low (β = 0.35; 95%CI 0.02, 0.67)] (Table 4). These associations are consistent with findings from single contaminant models.

In sensitivity analysis the observed estimates and directionality were similar to all cohort models. We observed some heterogeneity with maternal education and PC2 (middle vs. high: $I^2 = 66.3\%$) and PC3 (low vs. high: $I^2 = 62.5\%$), and with FAS and PC3 (middle vs. high: $I^2 = 71.3\%$) (Supplementary Material S17-18). Given the low frequency of families for low FAS in MoBa and EDEN cohorts, we removed these cohorts for sensitivity analysis. We observed a loss of significance with PC1 however the coefficient remained similar, and stronger associations for PC2 and PC3 (Supplementary Material S18.1).

4. Discussion

In this large study of a wide variety of environmental chemical contaminants measured during pregnancy and childhood, higher SEP was associated with higher levels of several groups of contaminants, including substances banned decades ago (such as PCBs) and contaminants currently or recently in production (such as PFASs, parabens, pesticides). Of the 41 analyzed contaminants, 29% showed higher concentrations in higher SEP group compared to lower during pregnancy, and this number increased to 39% during childhood. Fewer environmental contaminants (5% in pregnant women and 22% in children) showed higher concentrations in the lower SEP groups, most notably Cd in pregnant women, and phthalates and metals (Cd, Pb) in children.

4.1. Persistent pesticides (DDE, DDT, HCB, PCBs, PBDEs)

In pregnancy and childhood a clear tendency indicating higher concentrations of persistent pesticides with higher SEP was seen. These findings are broadly consistent with existing literature. Two studies on pregnant women reported higher PCB concentrations with higher education levels in Canada (Fisher et al 2016) and higher social class in Spain (Vrijheid et al 2012). A study on adolescents in Belgium found that the mean exposure of PCBs significantly increased with increasing SEP (Morrens et al 2012). On the other hand, a study on African-American women found that higher income was associated with an increase in PCB concentrations, while education was not, and they observed no associations with education or income and DDE concentrations (Borrell, 2004). A study on pregnant women in Canada found similar differences by education for several persistent pesticides including DDE (Fisher et al 2016). Associations in this study were

Table 4
Association between components from principal-component analysis and selected social determinants for children (6–12 years) (Childhood). Adjusted models shown (imputed data, n = 1301).

Childhood					
Component		Maternal Education		Family Affluence Scale (FAS)	
		Cat.	Beta (95%CI)	Cat.	Beta (95%CI)
PC1[a]	: DEHP metabolites	low	0.16 (−0.15, 0.46)	low	0.35 (0.02, 0.67)*
		middle	0.15 (−0.05, 0.36)	middle	0.11 (−0.10, 0.31)
		high	reference	high	reference
PC2[b]	: PCBs	low	−0.90 (−1.20, −0.59)*	low	−0.53 (−0.86, −0.20)*
		middle	−0.74 (−0.95, −0.54)*	middle	−0.05 (−0.25, 0.16)
		high	reference	high	reference
PC3[c]	: PFASs	low	−0.64 (−0.90, −0.37)*	low	−0.27 (−0.55, 0.02)
		middle	−0.44 (−0.62, −0.26)*	middle	−0.21 (−0.39, −0.03)*
		high	reference	high	reference
PC4[d]	: parabens	low	0.01 (−0.25, 0.26)	low	−0.07 (−0.34, 0.20)
		middle	−0.09 (−0.26, 0.08)	middle	−0.10 (−0.26, 0.07)
		high	reference	high	reference

Abbreviations PC = principal component, Cat. = category of independent variable, CI = confidence interval.
Childhood models were adjusted for cohort, parity, previous breastfeeding, breastfeeding of study child, and child age at chemical measurement (years).
* indicates p-value significant at < 0.05.
[a] PC1 loaded with DEHP metabolites: MEHHP, MEOHP, MECPP, MEHP.
[b] PC2 loaded with PCBs: PCB-153, PCB-180, PCB-170, PCB-138.
[c] PC3 loaded with PFASs: PFOS, PFOA, PFNA, PFUnDA, PFHxS.
[d] PC4 loaded with parabens: MEPA, PRPA, ETPA.

stronger for children than pregnant women. Breastfeeding and dietary intake of dairy, meat, and fish affect concentration levels of several persistent pollutants and are also related to SEP. Our analyses adjusted for breastfeeding and fish consumption so these are unlikely to explain the observed SEP gradients, and they may be explained by other dietary or indoor factors. However, it is possible that our breastfeeding and fish measurements may not have been precise enough to capture the difference.

4.2. Per- and polyfluoroalkyl substances (PFASs: PFOA, PFNA, PFUnDA, PFHxS, PFOS)

No associations were observed in principal component models that included PFASs for pregnant women. However in single models we observed higher concentrations of PFUnDA in pregnant women with high education status, and with employed women and all PFASs. One explanation may be higher concentrations of PFASs in offices as found in one study (Fraser et al 2013); however another study found higher levels in household and personal air (Padilla-Sánchez et al 2017). Both studies had low sample sizes and the study by Fraser sampled new and renovated buildings which may increase PFASs levels. Two studies on pregnant women found that PFASs concentrations increased with maternal education (Fisher et al 2016) and household income (Brantsæter et al 2013). However, a Spanish study on pregnant women did not find any association with social class or education (Manzano-Salgado and Cyntia, 2016). In childhood we observed a significant negative association between PFASs concentrations in childhood and level of maternal education in both component and single contaminant models. We did not identify any studies on the social determinants of PFASs in children, however PFASs have been shown to transfer in-utero through the placenta and through breastfeeding (Manzano-Salgado and Cyntia, 2015; Mondal et al 2014). Levels of PFASs have also been found to vary by breastfeeding and diet, most notably higher levels with higher fish and shellfish intake (Brandhagen et al 2014; Manzano-Salgado and Cyntia, 2016), however in this study adjustment for breastfeeding and fish consumption did not alter results. In the US, national biomonitoring data from the National Health and Nutrition Examination Survey (NHANES) indicates that exposure to PFASs is positively associated with family income (Nelson et al 2012), and higher burdens of PFASs with increased SES (Tyrrell et al 2013).

4.3. Metals (As, Cd, Hg, Mn, Pb)

We observed higher concentrations of Hg in mothers and children of higher maternal education, and As for children only. Conversely we observed higher concentrations of Cd in mothers of lower education and children with middle FAS. In children we also found higher Pb concentrations with decreasing maternal education and FAS score. Diet (fish, seafood, cereal-based products) and/or lifestyle factors (smoking) are likely to be the main routes of exposure (Castaño et al 2015; EFSA, 2014; EFSA CONTAM Panel, 2015). These behaviors are also highly related to social status as a systematic review concluded that Pb is higher in children with lower SEP (Bolte et al., 2010). Hg has been more related to fish and seafood consumption, with higher consumption associated with higher education (Schober et al 2003) and social class (Vrijheid et al 2012). In this study, adjusting for fish consumption did not alter the findings, however adjusting for smoking explained part of the association with Cd in pregnant women.

4.4. Phthalate metabolites (MEP, MiBP, MnBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, oh-MiNP, oxo-MiNP)

In single contaminant and component analysis we observed higher levels of DEHP metabolites with lower FAS in children. Other studies report similar positive relationships as well as negative relationships depending on the phthalate analyzed (Casas et al 2011; Tyrrell et al 2013). DEHP levels, like other phthalates have been found to decrease with age. This may explain in part why we only observe this association in children. Children may have higher burdens due to their smaller size and increased play activity, putting them into contact with flooring, wall-coverings, and toys (Becker et al 2004). Additionally, phthalates have a short half-life and are eliminated from the body in a few hours or days; thus it is difficult to accurately characterize exposure. A biomarker measurement at one point in time only provides very recent exposure making misclassification more likely.

4.5. Phenols (MEPA, ETPA, PRPA, BPA, BUPA, OXBE, TCS)

We reported a negative association between levels of phenols and maternal education for pregnant women in component and single models. The phenols component was loaded most highly with OXBE (BP3), an environmental contaminant commonly found in sunscreen and cosmetics, both of which are more likely to be used by those of higher social status (Park et al 2018). In children we observed lower concentrations of OXBE with middle FAS. We also observed lower concentrations of BPA in middle level education in pregnancy and low education in childhood. This is contrary to other studies that have reported a relationship between higher BPA concentrations and lower education (Casas et al 2013; Covaci et al 2015), or income groups (Geens et al 2014). Phenols have been associated with a greater cosmetic and personal care product use (Larsson et al 2014), which may in part explain the observed difference. Another explanation could be misclassification as phenols have short half-lives, similar to phthalates (Larsson et al 2014).

4.6. OP pesticide metabolites (DMP, DMTP, DEP, DETP)

In pregnant women we observed higher concentrations of OP pesticide metabolites with higher education in component models, consistent with the single contaminant models for both pregnant women and children. Similar to other non-persistent compounds, OP pesticide metabolites have a short half-life thus making it difficult to accurately measure exposure and in using dialkylphosphates (DAPs) as biomarkers the levels shown may also reflect preformed DAPs further clouding exposure assessment (Lu et al 2011; Weerasekera et al 2009). However, similar findings have been reported in pregnant women in Canada (Sokoloff et al 2016) and the Netherlands (van den Dries et al 2018). Recent studies have cited higher fruit and vegetable consumption, associated with high social position, as a key for increasing exposure (van den Dries et al 2018; Lewis et al 2015; Llop et al 2017).

4.6.1. Strengths and limitations

Major strengths of this study include the prospective cohort design consisting of 1301 mother-child pairs and the harmonized sample collection and analysis across six cohorts for the childhood samples. Also, we defined SEP in this study according to several indicators rather than just one. Especially unique is the use of the family affluence measure, which does not take into account education or occupation. Although the four item FAS score has been indicated not to be discriminatory within very rich or poor countries, we found a good distribution overall in our population. Additionally, our results with this measure and education were similar, further strengthening our associations. Although we were not able to study further SEP indicators like occupation or income, our analysis showed that maternal education gave the strongest social gradients, both during pregnancy and in childhood, thus it seems to be a good predictor of environmental contaminants. Lastly, the use of PCA enabled us to evaluate the combined effect of SEP on many environmental contaminants by creating components that represent a weighted combination of the individual contaminants in its group. In this analysis we used PCA to complement the single contaminant models, as PCA reduces the dimensionality and takes into account correlations between the contaminants. As such, our conclusions are based on the consistency of the results between single contaminant and component models.

In this study, urine and blood collection of the maternal samples were not collected nor stored in a harmonized manner, nor were they analyzed at the same lab. This between-laboratory variability can later cause problems with result interpretation. To reduce this variability samples were chosen at random and sent to the different labs to evaluate any differences, of which results were positive (Supplementary Material S3-4). Further, we cannot completely exclude the possibility of residual confounding by factors such as diet and breastfeeding as it is possible that the included measures are too crude to capture all confounding. Although we analyzed 41 environmental contaminants, we are exposed to many more in our environment and may have missed major environmental contaminants. Additionally, there were missing values for several environmental contaminants. To deal with this issue we used single imputation, which provides valid results under the MAR assumption (Bernhardt et al., 2015). To support the results from the imputed data set we fit the single contaminant models using the original data set and found few differences in significant estimates (Supplementary Material S7-10). Finally, although the study sample is population-based, it is likely to under represent families of lower SEP and rural areas. This is unlikely to have led to false associations, but may have diminished contrast between low and high SEP groups. Future studies should consider including those from non-urban settings and lower SEP. This would also be an opportunity to include area-level SEP indicators, as this study focused on individual indicators, and relationships may differ.

5. Conclusions

Overall these findings provide one of the most comprehensive overviews of the burden of exposure to environmental chemical contaminants by SEP indicators in pregnant women and their children from six different European countries. In this mostly urban European population, among the compounds tested, we more frequently observed families of higher social position to be at higher risk to be exposed to persistent pesticides, PFASs, phenols, OP pesticides, BPA, Hg and As whereas families of lower social position were at risk of higher exposures to Cd, Pb, and phthalates, particularly DEHP metabolites. Many of the contaminants studied are suspected of negatively impacting child health and have been linked to adverse health outcomes in later life (Gore et al 2015). These same health outcomes have also been independently linked to social disparity (Marmot et al 2008). Thus, in future work it is important that researchers looking into health effects of environmental contaminants not only adjust for SEP but rather examine modification to better understand the role of socioeconomic position within health effects.

Declarations of interest

None.

Funding

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement no 308333 – the HELIX project. Dr. Maribel Casas received funding from Instituto de Salud Carlos III (Ministry of Economy and Competitiveness) (MS16/00128). The INMA (Environment and Childhood) Sabadell cohort and biomarker measurements were funded by grants from Instituto de Salud Carlos III (Red INMA G03/176; CB06/02/0041; PI041436; PI081151 incl. FEDER funds; PI12/01890 incl. FEDER funds; CP13/00054 incl. FEDER-funds), CIBERESP, Generalitat de Catalunya-CIRIT 1999SGR 00241, Generalitat de Catalunya-AGAUR (2009 SGR 501, 2014 SGR 822), Fundació La marató de TV3 (090430), Spanish Ministry of Economy and Competitiveness (SAF2012-32991 incl. FEDER funds).

Acknowledgements

We are grateful to all the participating children, parents, practitioners and researchers in the six cohorts who took part in this study, especially to those families in addition donated blood and urine to this specific HELIX study. More details can be found in Supplementary Material S21.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2019.04.002.

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