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Prenatal and postnatal exposure to PFAS and cardiometabolic factors and inflammation status in children from six European cohorts

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ABSTRACT

Developing children are particularly vulnerable to the effects of exposure to per- and polyfluoroalkyl substances (PFAS), a group of endocrine disrupting chemicals. We hypothesized that early life exposure to PFASs is associated with poor metabolic health in children.

We studied the association between prenatal and postnatal PFASs mixture exposure and cardiometabolic health in children, and the role of inflammatory proteins.

In 1,101 mothers-child pairs from the Human Early Life Exposome project, we measured the concentrations of PFAS in blood collected in pregnancy and at 8 years (range = 6–12 years). We applied Bayesian Kernel Machine regression (BKMR) to estimate the associations between exposure to PFAS mixture and the cardiometabolic factors as age and sex- specific z-scores of waist circumference (WC), systolic and diastolic blood pressures (BP), and concentrations of triglycerides (TG), high-density lipoprotein (HDL-C) and low-density lipoprotein (LDL-C) cholesterol. We measured thirty six inflammatory biomarkers in child plasma and examined the underlying role of inflammatory status for the exposure-outcome association by integrating the three panels into a network.

Exposure to the PFAS mixture was positively associated with HDL-C and systolic BP, and negatively associated with WC, LDL-C and TG. When we examined the independent effects of the individual chemicals in the mixture, prenatal PFHxS was negatively associated with HDL-C and prenatal PFNA was positively associated with WC and these were opposing directions from the overall mixture. Further, the network consisted of five distinct communities connected with positive and negative correlations. The selected inflammatory biomarkers were positively, while the postnatal PFAS were negatively related with the included cardiometabolic factors, and only prenatal PFOA was positively related with the pro-inflammatory cytokine IL-1beta and WC.

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Our study supports that prenatal, rather than postnatal, PFAS exposure might contribute to an unfavorable lipidemic profile and adiposity in childhood.

1. Introduction

Cardiovascular disease (CVD) is the most common cause of death in adults worldwide (GBD 2017 Causes of Death Collaborators, 2018a). At the same time, the main risk factors for CVD, abdominal adiposity, insulin resistance, hypertension and dyslipidemia are manifested at progressively younger ages (GBD 2017 Risk Factor Collaborators, 2018b). In Europe, 6% out of 19,000 2–11 year-olds had metabolic syndrome, a cluster of the CVD risk factors, and more than 30% of 3,500 13–18 year-olds had elevated blood cholesterol, blood glucose or blood pressure (Ahrens et al., 2014; Henriksson et al., 2017). Such unfavorable cardiometabolic status in early life can track through adolescents and adulthood, posing as high as five times increased risk for hypertension, dyslipidemia, diabetes and CVD (Franks et al., 2010; Juonala et al., 2011). As a lifestyle characterized by unhealthy diet, inactivity and a sedentary behavior cannot completely explain the rising prevalence of CVD and its risk factors, emerging experimental and human evidence shows that endocrine disrupting chemicals may play a key role for this epidemic (Barouki et al., 2012; Bhatnagar, 2017; Tang-Péronard et al., 2011).

Per- and polyfluoroalkyl substances (PFAS) are environmentally persistent chemicals, with toxicological properties and potential health concerns, as recently summarized (EFSA et al., 2020). Widespread human exposure through diet along with the persistence and mobility of PFAS led to measurable concentrations in blood and other tissues among general populations worldwide (EFSA et al., 2018; EFSA et al., 2020). Disturbances in lipid metabolism and increased total serum cholesterol levels was identified as the most critical PFAS-induced health effect in humans, while the evidence of effects on other cardiometabolic factors was neither sufficient nor consistent (EFSA et al., 2020). More specifically for early life exposures, prenatal low-dose PFAS exposure have not been consistently linked with obesogenic effects, with positive (Braun et al., 2016; Halldorsson et al., 2012; Høyer et al., 2015; Mora et al., 2017) and null associations (Andersen et al., 2013; Barry et al., 2014). There are few studies exploring child insulin resistance (Fleisch et al., 2017), dyslipidemia (Manzano-Salgado et al., 2017), and the composite metabolic syndrome (Manzano-Salgado et al., 2017), and two studies considered postnatal PFAS exposures, in addition to prenatal (Fleisch et al., 2017; Li et al., 2021). After birth, postnatal PFAS exposure can substantially deviate from the prenatal exposure, with variations in PFAS concentrations between different congeners (Fromme et al., 2010; Kingsley et al., 2018; Papadopoulou et al., 2015; Papadopoulou et al., 2016), and postnatal PFAS exposure might substantially induce toxicity effects revealed later. The epidemiologic evidence of combined prenatal and postnatal PFAS exposure at environmentally relevant concentrations remains inconsistent and with large knowledge gaps (Rappazzo et al., 2017).

Chronic inflammation has been suggested as the underlying mechanism through which PFAS exposure can contribute to the disease exacerbation, especially due to their affinity to the peroxisome proliferator-activated receptors (PPARs), which are responsible for adipocyte differentiation and regulators of lipid and glucose metabolism and inflammation (Behr et al., 2020; Cheng et al., 2019; Mirza et al., 2019). Animal and human evidence supports this biological pathway, for asthma, impaired immune function and liver injury (Deng et al., 2020; Pennings et al., 2016; Tan et al., 2013; Yang et al., 2021). Chronic inflammation has a crucial role to play in the development of metabolic disease, but the extent to which PFAS exposure can contribute to such a process is unknown (Bussler et al., 2017; Rubin et al., 2011).

Our aim was to examine the association between prenatal and postnatal PFAS mixture exposure with cardiometabolic health by Bayesian Kernel Machine Regression, and explore the role of inflammatory biomarkers by constructing an integrated network, in a well-characterized study of 1,101 mother–child pairs.

2. Methods

2.1. Study population

This study is part of the HELIX project (Maitre et al., 2018), a collaboration across six ongoing longitudinal population-based birth cohort studies in Europe: the Born in Bradford (BiB) study in the UK (Wright et al., 2013), the Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant (EDEN) study in France (Heude et al., 2016), the INfancia y Medio Ambiente (INMA) cohort in Spain (Guxens et al., 2012), the Kaunas cohort (KANC) in Lithuania (Grazuleviciene et al., 2009), the Norwegian Mother, Father and Child Cohort Study (MoBa) (Magnus et al., 2016) and the RHEA Mother Child Cohort study in Crete, Greece (Chatzi et al., 2017). Within the larger HELIX (n = 31,472 mother–child pairs), a subcohort of 1,301 children (approximately 200 children in each participating cohort) was selected for detailed characterization of a broad suite of environmental exposures, including several environmental chemicals (Maitre et al., 2018). During 2013–2015, a follow-up of the children was conducted with clinical examinations, computer assisted interviews and biological sample collection by trained personnel. Eligibility criteria for inclusion in the subcohort were: (a) age 6–11 years at the time of the visit, with a preference for ages 7–9 years if possible; (b) sufficient stored pregnancy blood and urine samples available for analysis of prenatal exposure biomarkers; (c) complete address history available from first to last follow-up point; (d) no serious health problems that may affect the performance of the clinical testing or impact the volunteer's safety (e.g., acute respiratory infection). Each cohort selected participants at random from the eligible pool within the entire cohort and invited them to participate in this subcohort until the required number of participants was reached. Our study population consists of 1101 mother–child pairs from the HELIX subcohort, based on availability of information on pre- and postnatal PFAS exposure and complete data on childhood cardiometabolic factors and protein concentrations at follow-up (mean age 8 years; range = 6.0 to 12 years).

All participating families provided written informed consent. Approval for the HELIX project was obtained from the local ethical committees at each site.

2.2. PFAS concentrations in pregnancy and childhood

PFAS concentrations were measured in maternal biological samples collected prenatally or at birth and in children's biological samples collected during the HELIX follow-up (Tamayo-Uria et al., 2019). Maternal samples were collected at mean week of gestation (SD) 27 (1) in BiB, 26 (1) in EDEN, 14 (2) in INMA, 39 (1) in KANC, 19 (1) in MoBa and 14 (4) in Rhea. Child blood samples were collected at mean age (SD) 7 (0.2) years old in BiB, 11 (0.6) in EDEN, 9 (0.6) in INMA, 7 (0.5) in KANC, 9 (0.5) in MoBa and 7 (0.3) in RHEA. Four PFASs were analysed in maternal plasma for the BiB, INMA, MoBa and RHEA cohorts, in maternal serum for the BiB and EDEN cohorts and in maternal whole blood in the KANC cohort and in child plasma for all cohorts: perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorononanoate (PFNA). Perfluoroundecanoate (PFUnDA) was measured in all child samples. From the INMA cohort, only 15 (7%) women had available PFUnDA

concentrations and maternal PFUnDA was not included in our analyses as it would result in the exclusion of a cohort.

All the chemical analyses were performed at the Section for Food Safety at the Norwegian Institute of Public Health (NIPH), Oslo, Norway, except for 208 maternal samples from the INMA cohort which were analyzed at the Institute for Occupational Medicine, RWTH Aachen University, Germany (Manzano-Salgado et al., 2015). PFUnDA concentrations were not available for these samples. Concentrations were determined using column switching liquid chromatography (LC) coupled to a triple quadrupole mass spectrometer in serum or plasma samples and online solid phase extraction with ultra-high performance LC coupled with tandem mass spectrometry in whole blood samples (Haug et al., 2009; Poothong et al., 2017). Maternal PFAS concentrations were measured in serum or plasma in 5 of the 6 participating cohorts and these results were assumed comparable, while for the one cohort with available PFAS concentrations in maternal whole blood, 1:2 ratios were assumed for whole blood:serum/plasma and whole blood concentrations were multiplied by a factor of two to be comparable with the other cohorts.

The limit of detection (LOD) was 0.02 μg/L and the limit of quantification (LOQ) was 0.05 μg/L for samples assessed at NIPH, while for samples assessed at RWTH Aachen University, LODs ranged from 0.05 to 0.1 μg/L. Values below LOQ were replaced with the observed values, whenever available. For non-observed concentrations, singly imputed values were obtained using a quantile regression approach (Haug et al., 2018). A detailed description of the analytical methods, the quality assurance and quality control has been published elsewhere (Haug et al., 2018).

2.3. Child cardiometabolic factors

During the HELIX follow-up, specific training workshops were organized to standardize the clinical assessment between the cohorts (Maitre et al., 2018). In these workshops, all field workers participated and were trained to obtain measurements that were comparable to those measured by an experienced anthropometrist. Waist circumference (WC) was measured to the nearest 0.1 cm, midway between the lowest rib margin and the iliac crest, using a flexible tape and recorded in duplicate. The mean of the measurements was used. Height was measured to the nearest 0.1 cm with a stadiometer (Seca 213, California, USA) and weight to the nearest 0.1 kg with a digital scale, without shoes and with light clothing. Blood pressure was taken in sitting position after 5 min of rest using the OMRON 705-CPII automated oscillometric device. The mean of three consecutive measurements that were taken with 1 min intervals was used. Blood pressure was measured towards the end of the visit to ensure that children had not consumed anything that may affect the results (chocolate, cola drinks) in the previous hour. Systolic and diastolic blood pressures and pulse rate from each measurement were recorded. The concentrations (mg/dL) of HDL and LDL cholesterol (HDL-C and LDL-C) and triglycerides (TG) were measured in child non-fasting serum using homogenous enzymatic colorimetric methods on a Modular Analytics System from Roche Diagnostics GmbH Mannheim and according to the manufacturer's instructions. We constructed age and sex- specific z-scores for child WC, TG, HDL-C, LDL-C. BP z-scores were additionally standardized for child height and TG were log-transformed before standardization, following previous methodology (Ahrens et al., 2014).

2.4. Inflammatory status in children

Child blood samples were collected using standardized protocols during the HELIX follow-up. A set of 43 proteins were *a priori* selected based on the literature and on the commercially available kits from Luminex xMAP multiplex platform (Luminex Corp). We selected three kits for the subsequent analyses, to assess 50 measurements that represented 43 unique proteins: the human cytokines 30plex magnetic panel (Cat #. LHC6003M), the human apoliprotein 5-plex magnetic panel (LHP0001M) and the humam adipokine 15-plex magnetic panel (LHC0017M) **(Supplementary Table S1)**. All the analyses were conducted at the University Pompeu Fabra Centre for Genomic Regulation Proteomics Unit in Barcelona, Spain.

All samples were randomized to ensure a representation of each cohort in each measurement plate (batch) and we made no distinctions by cohort or gender. For protein quantification, an 8-point calibration curve per plate was performed with protein standards provided in the Luminex kit and following the procedures described by the vendor. Commercial heat inactivated, sterile-filtered plasma from human male AB plasma (Sigma Cat #. H3667) was used as constant controls to control for intra- and inter-plate variability. Four control samples were added per plate. No duplicate measurements were done for the HELIX samples. All samples were diluted ½ for the 30-plex kit, ¼ for the 15-plex kit and 1/2500 for the 5-plex kit. The coefficients of variation for each protein estimated by plate and then averaged ranged from 3.42% to 36%. The derived raw intensities were converted to ng/ml (5-plex kit: adiponectine, CRP, APO-A1, APO-B, APO-E) and to pg/ml (15 and 30-plex kits) using the calculated standard curves of each plate and accounting for the dilutions that were made prior to measurement.

Further, we obtained the limit of detection (LOD) as well as the lower and upper quantification limits (LOQ1 and LOQ2, respectively) from the calibration curves for each protein. Seven proteins were excluded from further analysis due to low detection rates (detection frequency $< 30\%$), namely IL7, VEGF, GMCSF, Lipocalin2, RANTES, Resistin and SAA. In addition, seven proteins were measured in two different plex (IL1beta, IL6, IL8, IL10, MCP1, HGF, TNFalfa) and the measure with lower quality was excluded from the analysis. For the included proteins ($n = 36$), data was log transformed to reach normal distribution. Then, we subtracted the difference between the overall protein average minus the plate specific protein average to account for the plate batch effect. All values between LOQ2 and LOQ1 were imputed using a truncated normal distribution implemented in the truncdist R package (Nadarajah and Kotz, 2006). Thirty five proteins were included to describe the inflammatory status of the HELIX children: two adipokines (adiponectin and leptin), three apolipoproteins (apoA1, apoB, apoE), four CC chemokines (monocyte chemoattractant protein 1[MCP-1], Eotaxin, macrophage inflammatory protein 1-alpha [MIP-1α], macrophage inflammatory protein-1β [MIP-1β], three CXC chemokines (Interleukin 8 [IL-8], monokine induced by gamma interferon [MIG], interferon gamma-induced protein 10 [IP10]), two interferons (IFN-α and IFN-γ), ten interleukins (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, IL-15, IL-17), the interleukin-1 receptor antagonist (IL-1RA), the interleukin 2 receptor (IL-2R), epidermal growth factor (EGF), basic fibroblast growth factor (FGF-2), granulocyte colony-stimulating factor (G-CSF), hepatocyte growth factor (HGF), plasminogen activator inhibitor-1 (PAI-1), connecting peptide (C-peptide), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) and the TNF cytokine B cell-activating factor (BAFF).

2.5. Statistical analysis

We examined the association of prenatal and postnatal exposure to the PFAS with the cardiometabolic factors by fitting Bayesian Kernel Machine Regression (BKMR) models. All our models were adjusted for the same set of confounders, identified based on previous knowledge and a directed acyclic graph (DAG) approach (**Supplementary Figure S1**): cohort, maternal age (in years), parity (nulliparous/multiparous), maternal education level (low, middle, high), maternal pre-pregnancy BMI (in kg/m2), child ethnicity (White European, Other), age at examination (in years) and sex (male/female).

BKMR is a non-parametric flexible modeling approach that can accommodate for correlation, non-linearity and interaction effects when estimating the exposure (PFAS mixture)-response associations (Bobb et al., 2015). As the correlations of PFASs within maternal or child

samples are higher than between mother–child pairs (Papadopoulou et al., 2016; Tamayo-Uria et al., 2019; Verner et al., 2016), we conducted a hierarchical variable selection. In the first level, variable selection is done at the group level (i.e. choosing whether the group of all prenatal exposures and the group of all postnatal exposures are useful in predicting the outcome); and at the second level, variable selection is done on the exposures within each group.

The main models are described as:

$$Y_i = h[Group_{1=}(\text{maternal PFOA, PFNA, PFHxS, PFOS}), Group_{2=}(\text{child PFOA, PFNA, PFUnDA, PFHxS, PFOS})] + \beta z_i + e_i$$

where Y_i is each of the cardiometabolic factors for each participant *i*, *h[]* is the high-dimensional exposure–response function which can incorporate both non-linear relationships and interactions among exposures and is estimated using a Gaussian kernel machine representation. Further, z_i is a vector of covariates and β their associated regression coefficients and $e_i \sim N(0,\sigma^2)$. PFAS were log-transformed for the BKMR analyses and BKMR was fitted using the Markov chain Monte Carlo algorithm with 10,000 iterations. Once fitted, BKMR provides a posterior inclusion probability (PIP) for each of the exposures, which constitutes a measure of the relative importance of each exposure within the h function to the overall mixture effects. Since we used a hierarchical variable selection method two sets of PIPs were obtained, the groupPIP representing the probability of inclusion for each of two groups (pre and postnatal PFASs) and the conditional PIPs (condPIP) which represented the probability that a particular chemical within the group was included in the model. Note that group-level or individual PFASs-level PIPs are not constrained to sum to 1. Credible intervals obtained from the BKMR model incorporated the additional uncertainty due to estimation of a high-dimension set of exposures and accounting for multiple-testing penalty. We further estimated the overall joint effect of exposure to the PFAS mixture by providing an estimate of the change in the outcome when the PFAS mixture exposure is increasing up to 95th percentile, compared to holding all PFAS at their 25th percentile (reference level). We also explored the gender differences by stratification in the BKMR analyses, as metabolic effects in children of prenatal PFAS exposure have been previously suggested to differ by sex (Fleisch et al., 2017). The time of collection of the maternal samples varied by cohort, and the PFAS concentrations are expected to be lower by increasing trimester for reasons described by Fisher et al (Fisher et al., 2016), including the increased mother: fetus transfer ratio and maternal blood dilution due to increased weight gain as the gestation progresses (Supplementary Table S3). Therefore, we conducted stratified BKMR analysis, by trimester of maternal sample collection. As secondary analyses, we examined the association of prenatal and postnatal exposure to the PFAS with the cardiometabolic factors by linear regression models by mutually adjusting for all PFASs, among other confounders.

As a second step and in order to examine the role of child inflammatory status in the association between PFAS exposure and cardiometabolic health, we constructed and integrated network by applying the xMWAS method (Uppal et al., 2018). The input data were all the prenatal and postnatal PFAS concentrations (n = 9), the measured concentrations of the proteins (n = 36) and the z-scores of the cardiometabolic factors that had an association with the PFAS mixture as estimated by the previous step. Therefore, z-score of diastolic BP was excluded from the network analysis. The xMWAS provides an automated framework for integrative and differential network analysis through three steps: 1) pairwise data integration; 2) visualization of a multi-data integrative network; and 3) multilevel community detection. For step 1, we applied sparse Partial Least Squares regression (sPLS), a dimension reduction technique, for pairwise data integration and for generating the correlation matrices. sPLS performs simultaneous data integration and variable selection using a LASSO penalty for the loading vectors. For step 3, we used the betweenness centrality measure (BCM) to evaluate the importance of nodes and variables with BCM $\geq$ 0.20 were considered important components of the identified network. Only associations that were significant at $p < 0.05$ were included in network analysis and the correlation threshold was set to 0.6.

All significance levels were set to 0.05 in this study. We used STATA to calculate summary statistics and used R (version R 3.6.2, R Development Core Team) for all other analyses including the BKMR and the xMWAS.

3. Results

Regarding PFAS concentrations in maternal and child blood, PFOS, PFOA, PFNA and PFHxS were detected in more than 97% of the samples, with PFOS and PFOA being the most abundant substances (Table 1). We observed strong positive correlations within mothers and children, with the highest between PFOS and PFHxS in mothers (rho = 0.71) and between PFOS and PFNA in children (rho = 0.64). Moderate positive correlations were found between mother–child pairs, with the strongest between mother–child PFHxS and mother–child PFOS (rho = 0.50 and 0.49, respectively).

3.1. Prenatal and postnatal PFAS exposure and cardiometabolic factors in childhood

By applying BKMR analyses, we observed that pre- and post-natal PFAS mixture exposure was positively associated with HDL-C and Systolic BP, and negatively associated with WC, LDL-C, TG (Fig. 1). Among those, the strongest dose–response associations were found for HDL-C (positive) and WC (negative), while the positive association with Systolic BP was seen in high PFAS mixture exposure levels (>50th percentile). More specifically, when exposure of the PFAS mixture was in the 95th percentile vs 25th percentile, the increase in HDL-C z-score was 0.19 (95% CI = 0.19,0.20) and the decrease in WC z-score was −0.21 (95% CI = -0.21,-0.20) (**Supplementary Table 2**). For all cardiometabolic factors, postnatal PFASs were contributing more to the mixture than prenatal, according to the group posterior inclusion probabilities (PIPs), besides Systolic BP where PIPs were similar (**Supplementary Table 2**). Regarding the contribution of individual PFAS in the identified mixture, prenatal PFHxS and postnatal PFUnDA were the main contributors for HDL-C and TG, and pre- and post-natal PFOA for LDL-C. For both blood pressures, prenatal PFOS and postnatal PFNA, and for WC, prenatal PFNA and postnatal PFOA were identified as the main contributors to the BKMR mixture (**Supplementary Table 2**). As expected, the univariate exposure–response association for the PFAS that was contributing the most to the derived mixture, was in agreement with the observed association of the overall mixture. More specifically, postnatal PFOA was negatively associated with WC and LDL-C, and postnatal PFUnDA with TG and postnatal PFUnDA was positively associated with HDL-C. For systolic BP, this comparison was less straightforward (**Supplementary Figure S2**). However, when all the PFAS in the mixture were held on the 50th percentile, prenatal PFHxS was negatively associated with HDL-C, prenatal PFNA was positively associated with WC, and postnatal PFOS was positively associated with LDL-C, and these were opposing directions from the overall mixture (**Supplementary Figure S2)**.

In stratified analyses, the positive association with HDL-C and the negative association with WC and the specific BKMR derived PFAS mixtures, persisted independently of gender, while for the other cardiometabolic factors associations were attenuated (**Supplementary Table S2 & Supplementary Figure S3**). After stratifying by the trimester of maternal blood sample collection, we obtained similar positive associations with the derived PFAS mixture and HDL-C for all subsamples as for the overall sample, while for the subsample with 2nd trimester measurements the associations were stronger (Supplementary Table S4 and Figure S4). Similarly for LDL-C, TG and Systolic BP, in the 2nd trimester sub-sample the effect estimates were similar to the overall sample, though with wider confidence intervals, while for WC the all

Table 1
PFAS concentration (in μg/L) in maternal samples collected in pregnancy and in child samples in the HELIX subcohort (n = 1,101 mothers-child pairs).

	PFAS concentrations (in μg/L)								
	Maternal samples [a]				Child samples [b]				
	PFOA	PFNA	PFHxS	PFOS	PFOA	PFNA	PFUnDA	PFHxS	PFOS
Samples > LOD (%)	99.6%	97.8%	97.1%	100%	100%	99.5%	66.2%	99.7%	99.7%
10th	0.80	0.23	0.19	2.36	0.95	0.18	0.02	0.10	0.73
25th	1.34	0.42	0.30	3.99	1.17	0.29	0.03	0.18	1.22
50th	2.22	0.69	0.53	6.15	1.53	0.47	0.06	0.34	1.93
75th	3.29	1.10	0.88	9.16	1.96	0.73	0.10	0.56	3.11
90th	4.37	1.58	1.39	14.41	2.43	1.14	0.17	0.82	4.63
Spearman correlation coefficients									
Maternal samples									
PFNA	0.61								
PFHxS	0.65	0.29							
PFOS	0.64	0.46	0.71						
Child samples									
PFOA	0.20	−0.01	0.15	0.14					
PFNA	0.16	0.21	0.20	0.39	0.44				
PFUnDA	0.21	0.14	0.19	0.28	0.25	0.51			
PFHxS	0.26	−0.11	0.50	0.47	0.40	0.39	0.33		
PFOS	0.25	0.20	0.26	0.49	0.43	0.64	0.50	0.58	

[a] PFASs analyzed plasma samples for the BIB, INMA, MoBa and RHEA cohorts, in serum samples for the BIB and EDEN cohorts and in whole blood in the KANC cohort.
[b] PFASs were analyzed in plasma samples collected at 6–12 years.

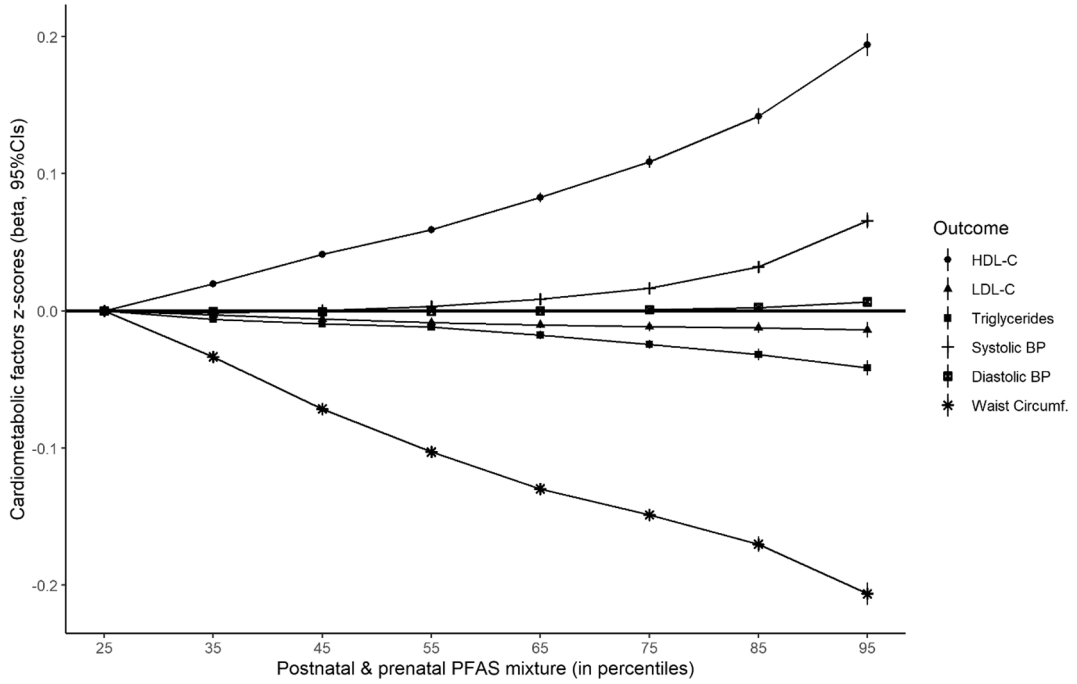

Fig. 1. Joint effect (h(z) , 95 %CIs) of the pre- and post-natal PFASs mixture on the cardiometabolic factors by increasing PFAS mixture levels (from 25th to 95th percentile), compared to low PFASs mixture (reference: 25th percentile), using Bayesian kernel machine regression (BKMR) model, adjusted for maternal age and education, pre-pregnancy BMI, parity, cohort, child ethnicity, age and sex.

subsamples were in line with the overall negative association with the derived PFAS mixture, but this association was significant only among the 3rd trimester sub-sample.

In addition, our findings from the multi-pollutant linear regression models are in agreement with the results from the BKMR analysis (Supplementary Table S3). More specifically, postnatal PFUnDA and PFOS was driving the positive association with HDL-C, while a negative, though weak association was found with prenatal PFHxS. A weak positive association was also found between postnatal PFOS and LDL-C. Postnatal PFOA and postnatal PFUnDA was driving the negative association with WC and TG, respectively, as observed also in the BKMR analyses.

3.2. Integrated network analysis

By applying the xMWAS network analysis we were able to identify and visualize the complex network between prenatal and postnatal PFAS concentrations, inflammatory proteins in child's blood and cardiometabolic factors in childhood. Eight PFAS, 17 proteins and the five cardiometabolic factors were selected and arranged in five communities, one per child outcome, connected through positive and negative correlations (Fig. 2). The derived correlation matrix is presented in Supplementary Table S4 and all the possible connections between the triad, PFAS, inflammatory biomarkers and health outcomes are presented in Supplementary Table S5.

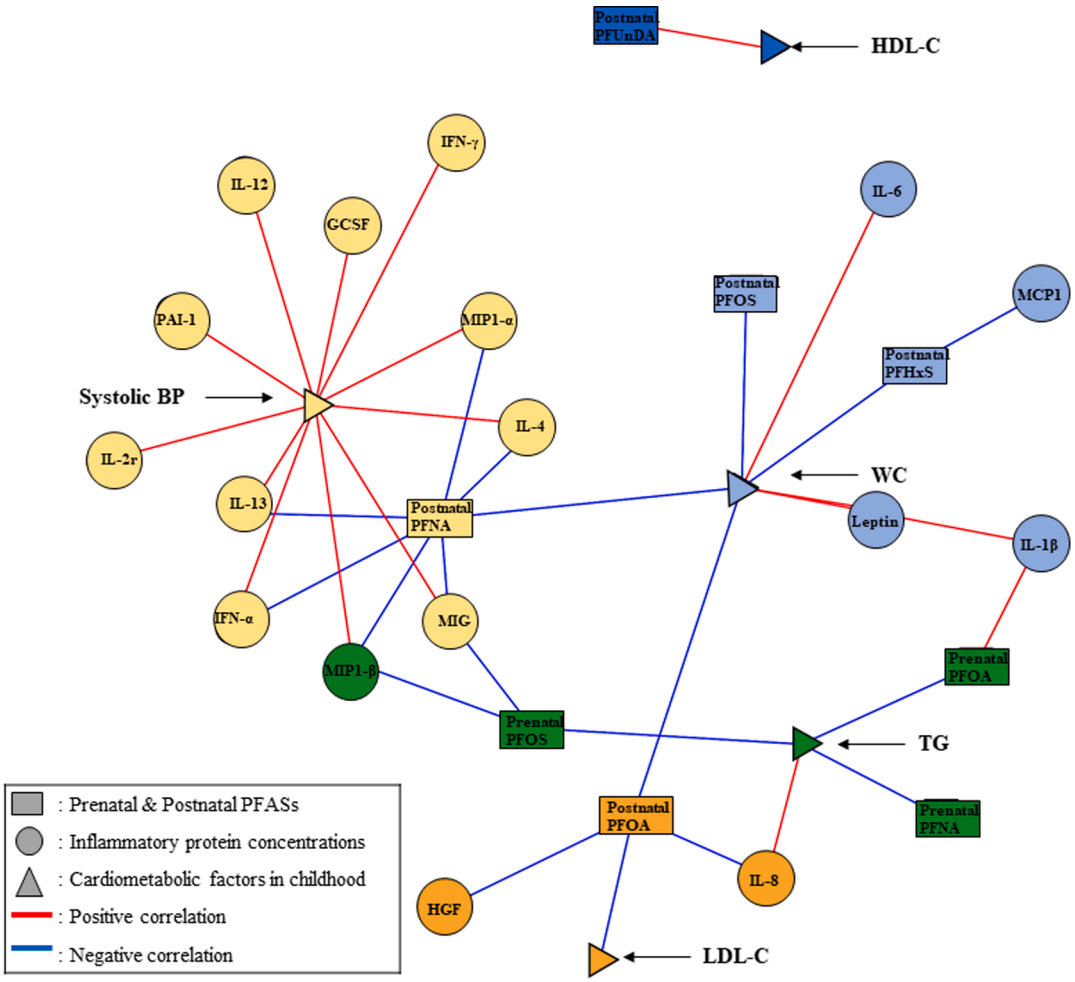

Fig. 2. Graph of the integrative network analysis of prenatal and postnatal PFAS, inflammatory protein concentrations in child's blood and cardiometabolic factors in childhood as derived by the xMWAS. Five communities were detected by the multilevel community detection algorithm, and are represented by different colors.

The smallest community (dark blue color) comprised of postnatal PFUnDA and HDL-C connected by a positive correlation. This is in line with our findings from the BKMR analysis, where postnatal PFUnDA was the main contributor of the derived PFAS mixture that was positively associated with HDL-C. No protein was linked with postnatal PFUnDA and HDL-C. Postnatal PFOA was linked to LDL-C, IL-8 and HGF and they were all assigned in one community, connected by negative correlations (orange color). Postnatal PFOA was an important contributor to the derived BKMR PFAS mixture and was negatively associated with LDL-C. TG was assigned together with prenatal PFOA, PFNA and PFOS and MIP1-β in one community, connected by negative correlations only (green color). The BKMR derived mixture was also negatively associated with TG. After examining all possible connections linking PFAS, and inflammatory biomarkers with TG, between and within communities, an increase in prenatal PFOA, PFOA, PFNA and postnatal PFOA, was linked with lower TG, IL-8, MIG and MIP1-β and higher IL-1β (Supplementary Table S5).

Further, the largest community in the network comprised of Systolic BP, postnatal PFNA and ten inflammatory proteins (yellow color). Postnatal PFNA was also a major contributor to the derived PFAS mixture and was positively associated with Systolic BP in the BKMR analysis. We identified six inflammatory proteins that were linking postnatal PFNA and systolic BP, namely, IL-4, IL-13, MIP1-α, MIP1-β, MIG and IFN-α. Of those biomarkers, MIG and MIP1-β were also negatively correlated with prenatal PFOS.

WC was assigned in one community with postnatal PFHxS and PFOS, together with IL-1β, IL-6, leptin and MCP1 (light blue color). After examining all possible connections linking PFAS and inflammatory biomarkers with WC, between and within communities, we observed that an increase in postnatal PFHxS, PFNA, PFOA and PFOS, was linked with lower WC, leptin, IL-6 and IL-1β, HGF, IL-8, MCP-1, IL-4, IL-13, MIP1-α, MIP1-β, MIG and IFN-α. Interestingly, we identified a positive correlation between prenatal PFOA and WC, through IL-1β.

4. Discussion

In a well-characterized mother–child study, we found that exposure to a mixture of prenatal and postnatal PFAS was associated with an increase in HDL-C and decrease WC in childhood, even in low exposure levels. We also found a positive association between the PFAS mixture and Systolic BP, but for higher exposure levels (>50th percentile). Through the integrative network analysis we identified several inflammatory biomarkers positively and negatively correlated with the PFAS and all the studied cardiometabolic factors, except for HDL-C.

There is limited evidence of the association between early life PFAS exposure and child cardiometabolic health, with examination of both prenatal and postnatal windows of exposure. We found that exposure to a PFAS mixture, mostly reflecting childhood exposures, was associated with higher HDL-C at 8 years. This is in line with a study among US mother–child pairs that reported a positive cross-sectional association between PFAS exposure and HDL-C at 8 years (Mora et al., 2018). In the same study, mutually adjusted models for pre- and post-natal exposures were not presented and null associations were found for prenatal exposures (Mora et al., 2018). Null associations between prenatal PFAS

and HDL-C at 4 years were also reported in a Spanish cohort (Manzano-Salgado et al., 2017). Overall, the epidemiological evidence for a positive association between PFAS exposure and HDL-C is largely consistent, in cross-sectional studies of background and high exposed populations and for several age groups (Canova et al., 2020; Château-Degat et al., 2010; Dalla Zuanna et al., 2021; Frisbee et al., 2010; Geiger et al., 2014; Li et al., 2020; Lin et al., 2020; Liu et al., 2018; Starling et al., 2014), but the longitudinal association is inconsistent. When we examined every PFAS individually while other PFASs in the mixture were held at their median levels, we found that prenatal PFHxS was associated with a reduction in HDL-C; suggesting that when postnatal exposures are moderate, prenatal PFAS exposures can have a detrimental effect on child's HDL-C profile. In approximately 200 mother–child pairs from the HOME study, in the Cincinnati, Ohio area, prenatal and cord blood PFAS were associated with a reduction in HDL-C at 12 years, but when exposure occurred in childhood the association changed direction, in models adjusting for longitudinal exposures (Li et al., 2021). In another recent study of 306 pregnant women, Tian et al., reported that all prenatal PFASs were associated with a reduction in HDL-C in cord blood, when postnatal exposure has not occurred yet (Tian et al., 2021). Through the network analysis, we were not able to report a connection between the "HDL-C—postnatal PFUnDA" component with one of the studied inflammatory proteins, suggesting that higher PFUnDA exposure in healthy children was associated with higher HDL-C, also confirmed by the BKMR analyses, but did not modify the levels of the inflammatory biomarkers under study. Most children in our study had normal high levels of HDL-C, by comparison to the references curves produced by the IDEFICS consortium for European children (De Henauw et al., 2014). Other components that have been found to promote or obstruct the anti-inflammatory properties of HDL-C include high fat diet, *trans*-fatty acid consumption, dietary flavonoids, and the history of metabolic disorders or cardiovascular disease, while evidence of such effects in health young populations are scarce (Desgagné et al., 2016; Millar et al., 2017; Sadana et al., 2020; Su et al., 2021).

Similarly to HDL-C, we found a negative association between the derived PFAS mixture, mostly driven by postnatal PFOA, and WC at 12 years; but when keeping all PFAS in their median, prenatal PFNA was positively associated with WC. Similar opposing directions of the association between PFAS and WC at 12 years, for different windows of PFAS exposure were reported in the mother–child pairs from the HOME study (Li et al., 2021). Thus, our study adds to the evidence that prenatal PFAS exposure, rather than childhood, are more strongly associated with an unfavorable cardiometabolic profile in childhood. Nevertheless, our reported associations were weaker than those reported previously, and this could be attributed to the lower exposure levels. More specifically, maternal blood concentrations of PFAS in our study were lower than those reported in the populations of the studies with similar findings as ours from USA and Shanghai, and the median PFOA, PFOS and PFHxS levels reported for female population and pregnant population (mainly PFOS and PFHxS) in the U.S. National Health and Nutrition Examination Survey (NHANES 1999–2010 and NHANES 2003–2008-Pregnant, respectively) were higher than the 75th percentile of our study population (CDC, 2021b; Jain, 2013; Li et al., 2021; Mora et al., 2018; Tian et al., 2021) (Supplementary Figure S5, panel A). Similarly, children PFAS levels were relatively low compared to American populations (CDC, 2021a; Li et al., 2021; Mora et al., 2018) (Supplementary Figure S5, panel B).

In the same study population, using an exposome approach to study a wide range of prenatal and postnatal exposures and blood pressure (BP), authors reported a positive association between maternal fish consumption and childhood PFOA with systolic BP (Warembourg et al., 2019). Fish consumption is a determinant of PFAS levels in maternal blood along with other contaminants, as reported previously (Papadopoulou et al., 2019). Using the BKMR methodology, we also found a positive association between exposure to PFAS mixture and systolic BP, but for levels of exposure above the 50th percentile. This might be explained by the U-shaped association with postnatal PFNA, one of the main contributors to the derived mixture. Our results, are in line with the HOME study, in terms of the positive association with BP, while they identified PFHxS exposure as the driver of this association (Li et al., 2021). In our study, PFAS exposure in early life was not associated with diastolic BP. The association between PFAS exposure and BP is more complex and an area in need of further investigation.

Through our network analysis, we identified a cluster of positive relationships between WC and the upregulation of pro-inflammatory adipokine, leptin, and the pro-inflammatory cytokines, IL-6and IL-1β. This is in line with the known role of leptin in obesity-induced inflammation, characterized by elevated release of pro-inflammatory cytokines (Kwaifa et al., 2020). In our study, postnatal PFAS were negatively linked to WC and to additional inflammatory biomarkers including HGF, IL-8, MCP-1, IL-4, IL-13, MIP1-α, MIP1-β, MIG and IFN-α, comprising a phenotype of low postnatal PFAS exposure and obesity-induced inflammation. We cannot exclude the possibility that low PFAS exposure might be explained by dilution effects of larger body mass.

Postnatal PFNA and prenatal PFOS were negatively linked with systolic BP and IL-4, IL-13, MIP1-α, MIP1-β, MIG and IFN-α. Inflammation is a key component in the pathophysiology of hypertensive disorders, and a marker of disease development and progression (Tanase et al., 2019). Our results suggest a negative link between PFAS exposure and this inflammatory response accompanied by high BP.

Additionally, postnatal PFOA was negatively linked to LDL-C, TG, HGF and IL-8, and prenatal PFOA, PFNA and PFOS were negatively linked with TG, and through that with IL-8, MIG and MIP1-β. Increased levels of MIP-1beta and interleukin (IL)-8 have been observed in patients with familial hypercholesterolaemia and are suggested to promote an atherosclerotic inflammatory process that are involved in early atherosclerosis (Holven et al., 2003). The hepatocyte growth factor (HGF) is a marker of endothelial damage and an interaction with serum lipids has been reported, towards an unfavorable disease prognosis for patients with dyslipidemia and high HGF levels (Bell et al., 2016; Zhu et al., 2020).

Overall PFAS exposure in childhood were mostly negatively linked with the clusters of cardiometabolic factors-inflammatory proteins and this is in line with the previous evidence on their role on suppression of inflammatory response. More specifically, from previous epidemiological evidence, PFAS exposure has been associated with suppressed antibody response to vaccination and increased occurrence of asthma, suggesting reduced immunological response, as well as lower levels of proteomic markers of inflammation (Chang et al., 2016; Pennings et al., 2016; Rappazzo et al., 2017; Salihovic et al., 2020).

Nevertheless, we found a positive relationship between prenatal PFOA and IL-1beta concentrations and WC and negative relationship with TG. PFOA-induced pro-inflammatory cytokine production, including IL-1beta, has been demonstrated in human lung and liver cells, supporting the concern that PFAS exposure may increase the risk of acute lung toxicity and hepatotoxicity (Sørli et al., 2020; Zhang et al., 2021). Other experimental evidence supports the role of PFOA as potent immunotoxicant, acting by inducing the activation of NF-kB pathway and altering the IL-1β expression in zebrafish spleen (Zhang et al., 2014). Our findings are in line with the experimental evidence but there is a need of additional epidemiological evidence for further interpretation.

One strength of this study is the use of a mixture approach to explore the association between the prenatal and postnatal PFAS exposure with child metabolic health. The BKMR methodology allowed us to examine the overall mixture effect, the independent effects of the individual chemicals in the mixture as well as interactions between them. The BKMR does not require the effects of all mixture members to be in the same direction, as other methodologies (i.e. WQS). Given the inconsistent findings from cross- sectional and prospective studies examining the associations of PFAS exposure and cardiometabolic factors, we could not assume the direction of the association. In addition, given the large cross-sectional nature of our data (postnatal PFAS, cardiometabolic

factors and inflammatory biomarkers) we considered the xMWAS network analysis as an appropriate methodology to describe some of the complex relationships between the three panels of information, even without being able to discuss causal inferences. This method did not allow adjustment for confounders and our results are prone to confounding by measured or unmeasured factors and should be interpreted with caution. Nevertheless, the molecular exacerbations underlying the association between early life PFAS exposure and cardiometabolic factors is under current investigation.

The PFAS exposure profile in childhood can substantially divert from the gestational exposure profile, due to the effect of key factors, such as transplacental transfer, early –life exposure through breastfeeding and later dietary exposures, while there are large variations by congener. Mutually adjusted models for pre- and post-natal exposures would most probably provide a less biased effect estimate. Especially for prenatal PFAS exposures, adjusting for postnatal levels is not expected to produce a large bias amplification due to co-exposure because of the relatively weak correlations between maternal and child PFAS concentrations (Weisskopf et al., 2018).

Longitudinal birth cohorts, from which our study draws resources, are exposed to the risk of loss of subjects to follow-up and possible selection bias. Maitre et al., reported that the distribution of family characteristics in the HELIX subcohort, is somewhat different than the entire HELIX cohort, which consist of 31,472 mother–child pairs from the six source birth cohorts (Maitre et al., 2018). More specifically, children of low educated mothers (entire cohort vs. subcohort: 23% vs. 7%), children of parents foreign to the country of the cohort (21% vs. 11%) and firstborns (nulliparous women: 51% vs. 46%) were less likely to participate in the HELIX follow-up examination. We previously found that low maternal education is associated with lower maternal and child PFAS levels, meaning that mother–child pairs with high prenatal and postnatal PFAS exposure are more likely included in our analysis (Montazeri et al., 2019). On the other hand, the inclusion of less firstborn children could mean lower prenatal PFAS exposure in our study, since parity is a strong determinant of maternal PFAS concentrations, but this can vary substantially by the inter-pregnancy interval (Brantsæter et al., 2013; Papadopoulou et al., 2015). Regarding the outcome, overweight and obesity in the HELIX subcohort was similar to what has been reported in cohort or country-specific reports (de Bont et al., 2020; Harskamp-van Ginkel et al., 2020; Kadawathagedara et al., 2018). Overall selection and self-reporting bias is probable in birth cohorts based on voluntary enrolment and face-to-face interviews, while exposure assessment based on biomarkers and a thorough examination of the outcome by trained research assistants might reduce this bias in our study. Finally, non-fasting insulin levels were also assessed in children samples. However, given the moderate correlation between fasting and non-fasting insulin it was not that this will provide an adequate measure of glucose-insulin homeostasis (Hancox and Landhuis, 2011) and we have decided not to include it in our analysis. Therefore, the absence of this measure is a limitation of our study.

5. Conclusion

In this large mother–child study, we found that exposure to a mixture of prenatal and postnatal PFAS was associated with higher HDL-C and lower adiposity at 8 years, and postnatal PFAS were the main contributors to the derived BKMR mixtures. Postnatal PFAS exposure was also linked to lower levels of inflammatory biomarkers in child's blood. Nevertheless, when we examined individual PFAS while other PFASs in the mixture were held at their median levels, we found that prenatal PFAS exposures were associated with an unfavorable cardiometabolic profile of lower HDL-C and increased adiposity, but these associations were weak. We found a positive relationship between prenatal PFOA and concentrations of the pro-inflammatory cytokine, IL-1beta, which was itself linked with larger WC, suggesting increased inflammation but more studies are needed to confirm this association.

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7. Data statement

The HELIX data warehouse has been established as an accessible resource for collaborative research involving researchers external to the project. Access to HELIX data is based on approval by the HELIX Project Executive Committee and by the individual cohorts. Further details on the content of the data warehouse (data catalog) and procedures for external access are described on the project website (http://www.projecthelix.eu/index.php/en/data-inventory).

CRediT authorship contribution statement

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Methodology, Writing – review & editing, Funding acquisition. **Maribel Casas:** Methodology, Investigation, Writing – review & editing. **Serena Fossati:** Methodology, Investigation, Writing – review & editing. **Regina Gražulevičienė:** Methodology, Investigation, Writing – review & editing. **Line Småstuen Haug:** Methodology, Investigation, Writing – review & editing. **Barbara Heude:** Methodology, Investigation, Writing – review & editing. **Léa Maitre:** Methodology, Investigation, Writing – review & editing. **Rosemary R.C. McEachan:** Methodology, Investigation, Writing – review & editing. **Oliver Robinson:** Methodology, Investigation, Writing – review & editing. **Theano Roumeliotaki:** Methodology, Investigation, Writing – review & editing. **Eduard Sabidó:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Eva Borràs:** Investigation. **Jose Urquiza:** Methodology, Investigation, Writing – review & editing. **Marina Vafeiadi:** Methodology, Investigation, Writing – review & editing. **Yinqi Zhao:** Methodology, Investigation, Writing – review & editing, Formal analysis. **Remy Slama:** Conceptualization, Writing – review & editing. **John Wright:** Conceptualization, Writing – review & editing. **David V. Conti:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Martine Vrijheid:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition. **Lida Chatzi:** Conceptualization, Methodology, Investigation, Writing – review & editing, Funding acquisition, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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