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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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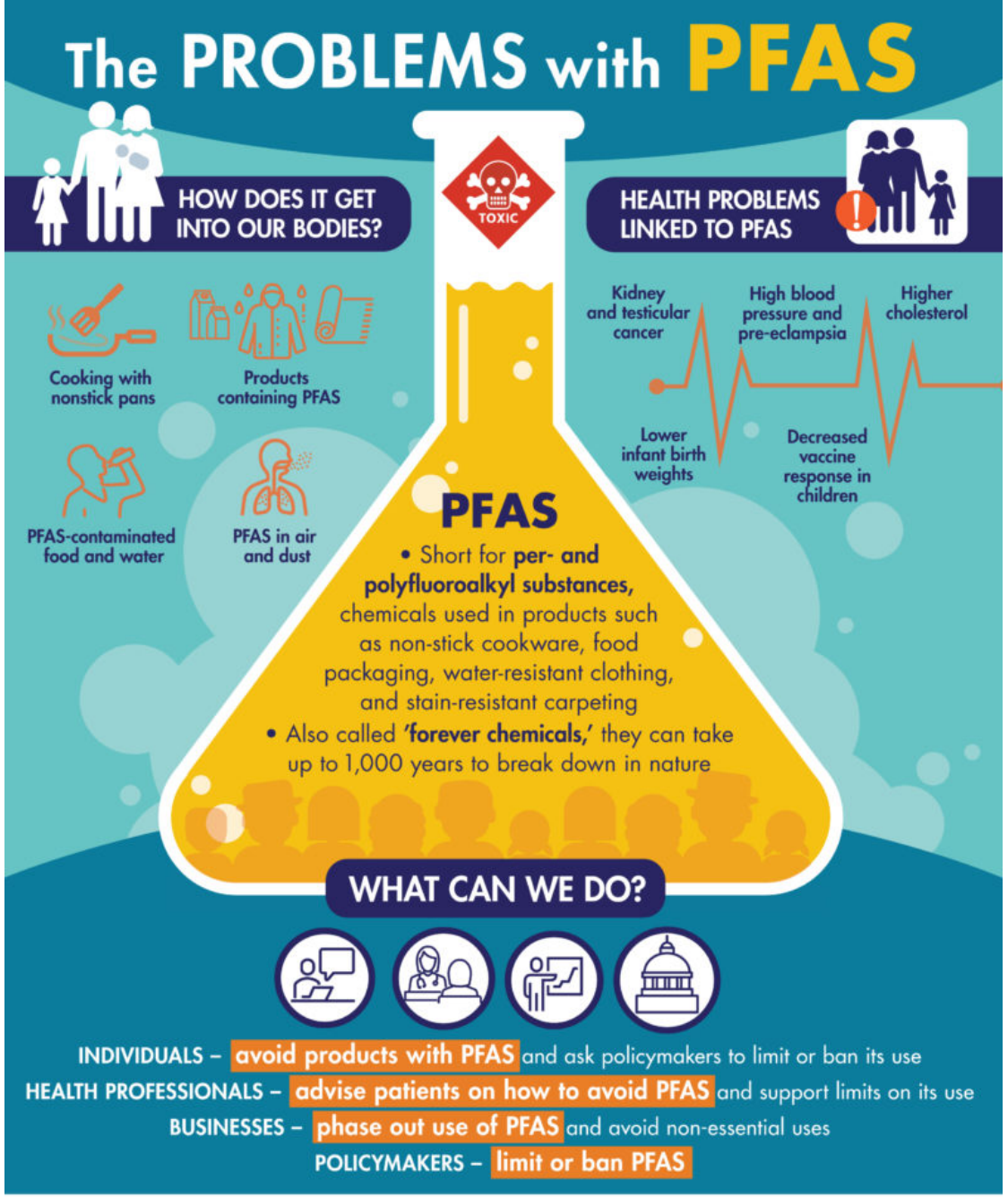

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HELIX BUILDING THE EARLY-LIFE EXPOSOME

https://www.projecthelix.eu/

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Aim- Research questions

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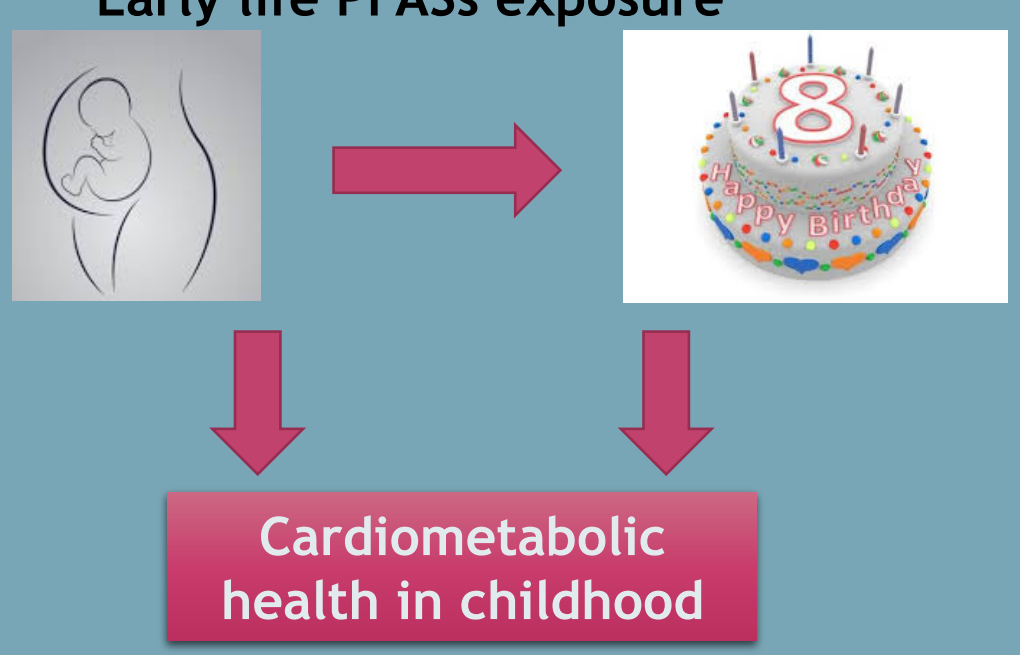
1. What is the associattion between prenatal and postnatal PFAS mixture exposure and cardiometabolic health in young children?

2. What is the role of the inflammatory status?



Methods

HELIX BUILDING THE EARLY-LIFE EXPOSOME

https://www.projecthelix.eu/

Study population:

N=1,101 mother-child pairs from the Helix sub-cohort.

Pre- & Post-natal PFAS measurements

- Pregnancy: PFOA, PFNA, PFOS and PFHxS
- Childhood (mean age 8 years; range = 6 to 12 years): PFOA, PFNA, PFUnDA, PFOS and PFHxS

Child Cardiometabolic health (age and gender z-scores)

Serum Lipids: HDL cholesterol, LDL cholesterol, Triglycerides (TG)

Blood Pressure: Systolic Blood Pressure, Diastolic Blood Pressure

Waist circumference

Maternal characteristics – pregnancy.

	All (n=1101)
	N (%)
Cohort	
BIB	186 (17%)
EDEN	144 (13%)
KANC	188 (17%)
MOBA	209 (19%)
RHEA	166 (15%)
INMA	208 (19%)
Maternal education	
Low	166 (15%)
Medium	377 (34%)
High	558 (51%)
Parity	
Nulliparous	494 (45%)
Multiparous	607 (55%)
	Mean (min-max)
Maternal age (years)	31 (16-44)
Pre-pregnancy BMI (kg/m²)	25.0 (16.2-51.4)

Child characteristics.

	All (n=1101)
	N (%)
Child gender	
Boys	605 (55%)
Girls	496 (45%)
Child ethnicity	
White European	988 (90%)
Other	113 (10%)
	Mean (min-max)
Age at examination (years)	8 (5-12)
BMI (kg/m²)	16.9 (11.7, 29.6)
HDL (mmol/L)	59.4 (27.1,112.1)
LDL (mmol/L)	90.9 (0.7, 205)
TG (mmol/L)	85.1 (24.8, 387.1)
Systolic BP (in mm Hg)	99 (71-159)
Diastolic BP (in mm Hg)	58 (37, 110)
Waist Circumference (cm)	58 (21, 93)

20% OW/OB [1]

3% low [2]

2% high [3]

2% high [3]

29% high [4]

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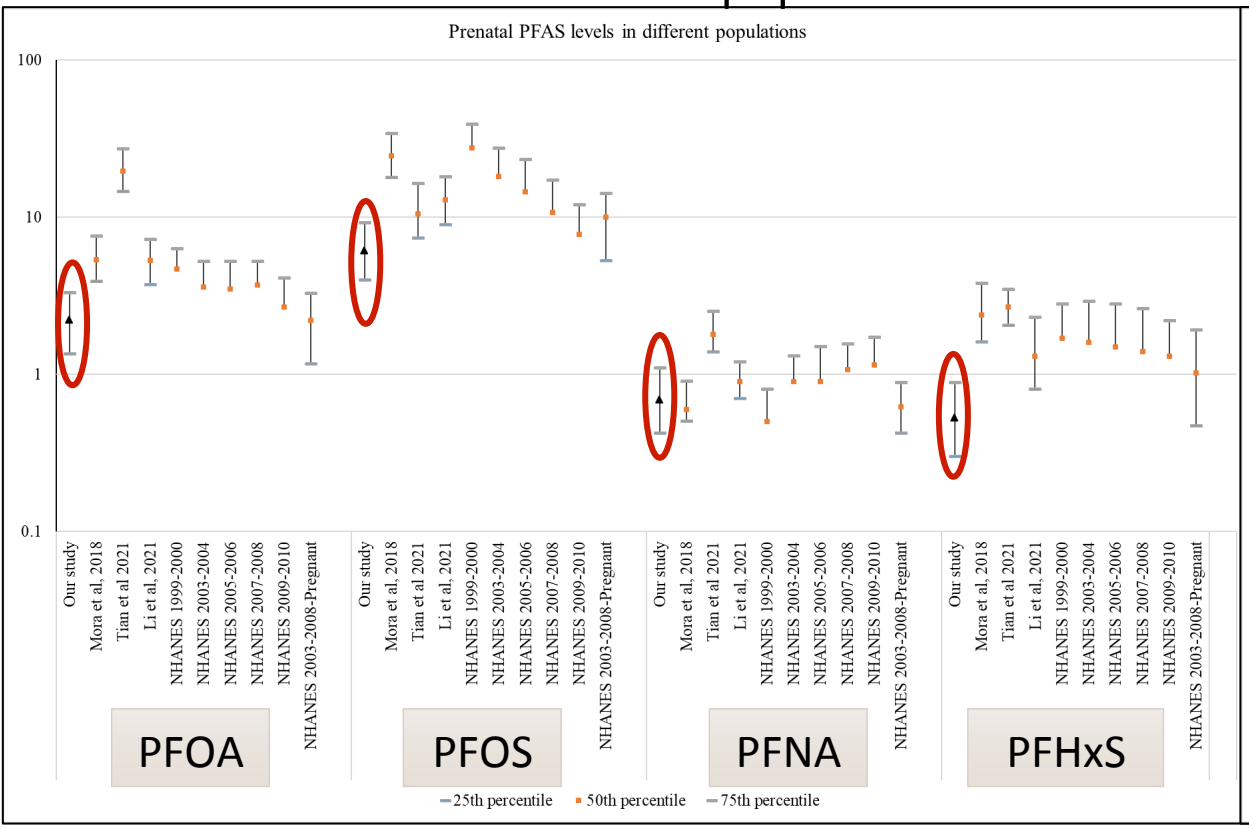
PFASs in maternal and child samples

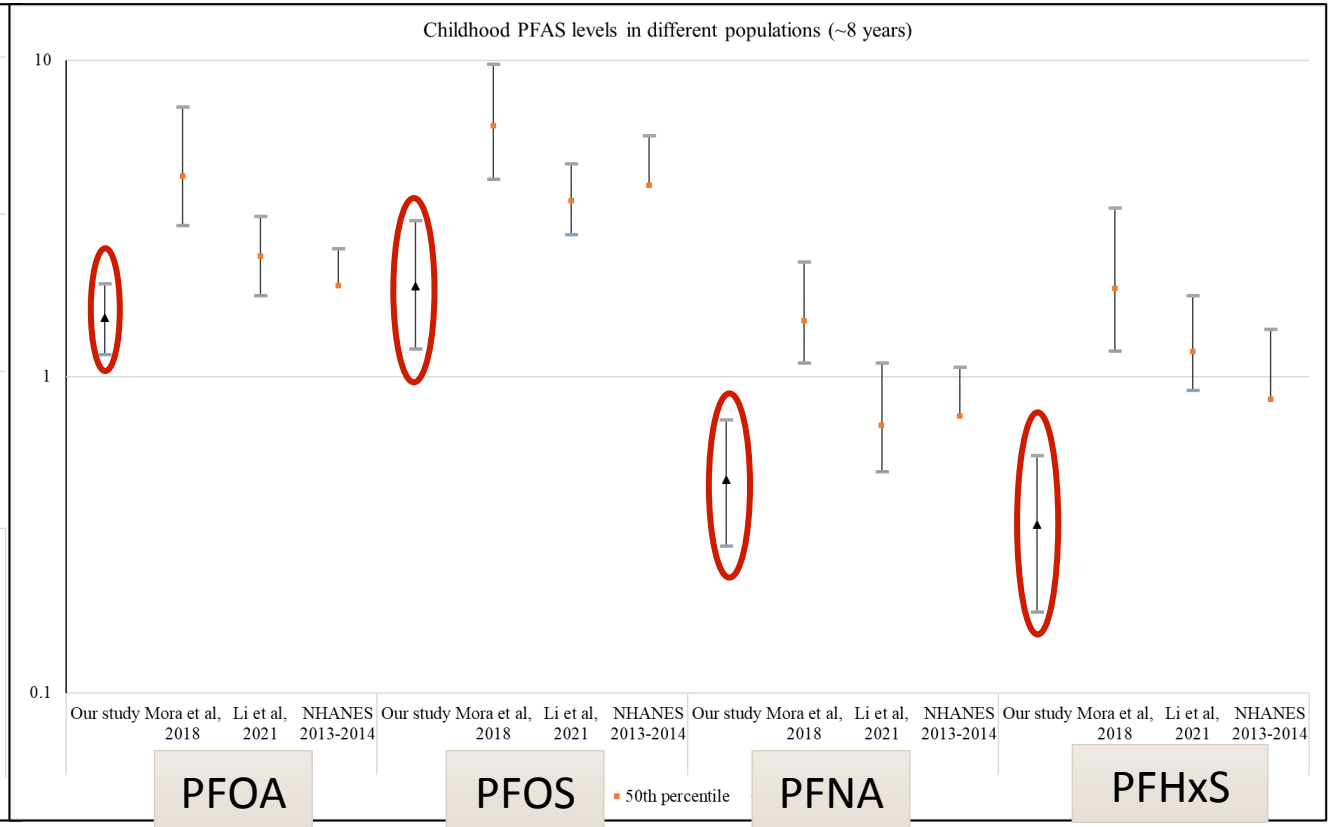
PFAS concentrations (in µg/L)									
	Maternal samples in pregnancy				Child samples (6-12 years)				
	PFOA	PFNA	PFHxS	PFOS	PFOA	PFNA	PFUnDA	PFHxS	PFOS
Samples >LOD (%)	99.6%	97.8%	97.1%	100%	100%	99.5%	66.2%	99.7%	99.7%
10th	0.80	0.23	0.19	2.36	0.95	0.18	0.02	0.10	0.73
25th	1.34	0.42	0.30	3.99	1.17	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	

Relatively low PFAS exposed study groups

Prenatal PFAS levels in different populations



Childhood PFAS levels in different populations (~8 years)



Methods- Statistical plan

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1. **What is the association between prenatal and postnatal PFAS mixture exposure and cardiometabolic health in young children?**

Hierarchical Bayesian kernel machine regression (BKMR):

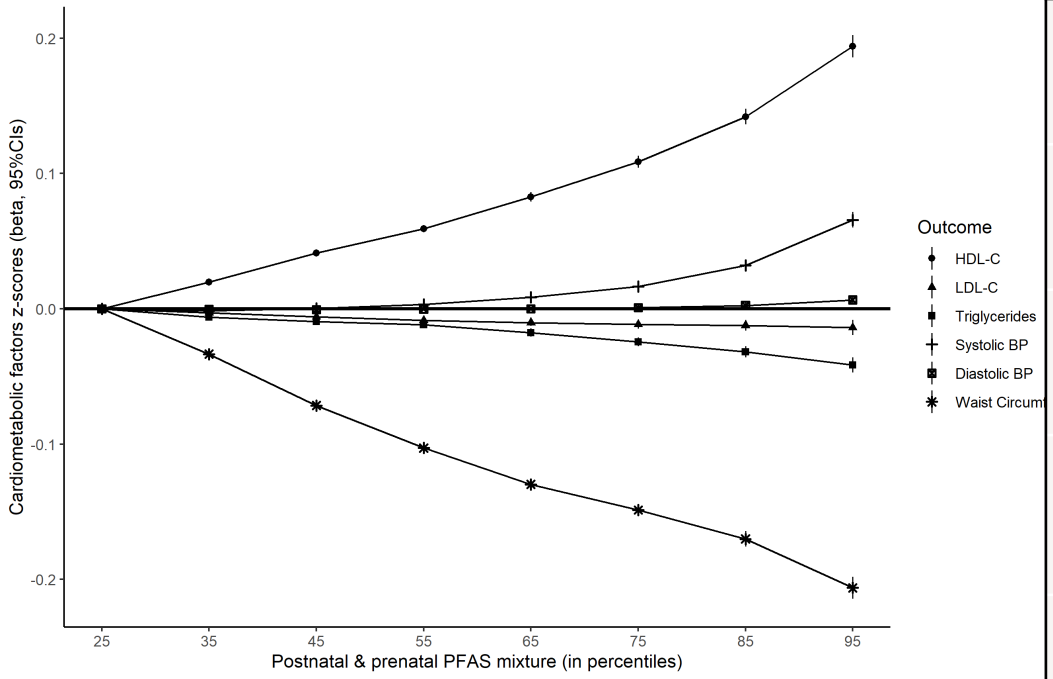
Exposure: log-transformed PFAS in maternal & child blood

Outcome: cardiometabolic factors

Confounders: 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).

- Sensitivity analyses: child's gender, trimester of maternal sample collection

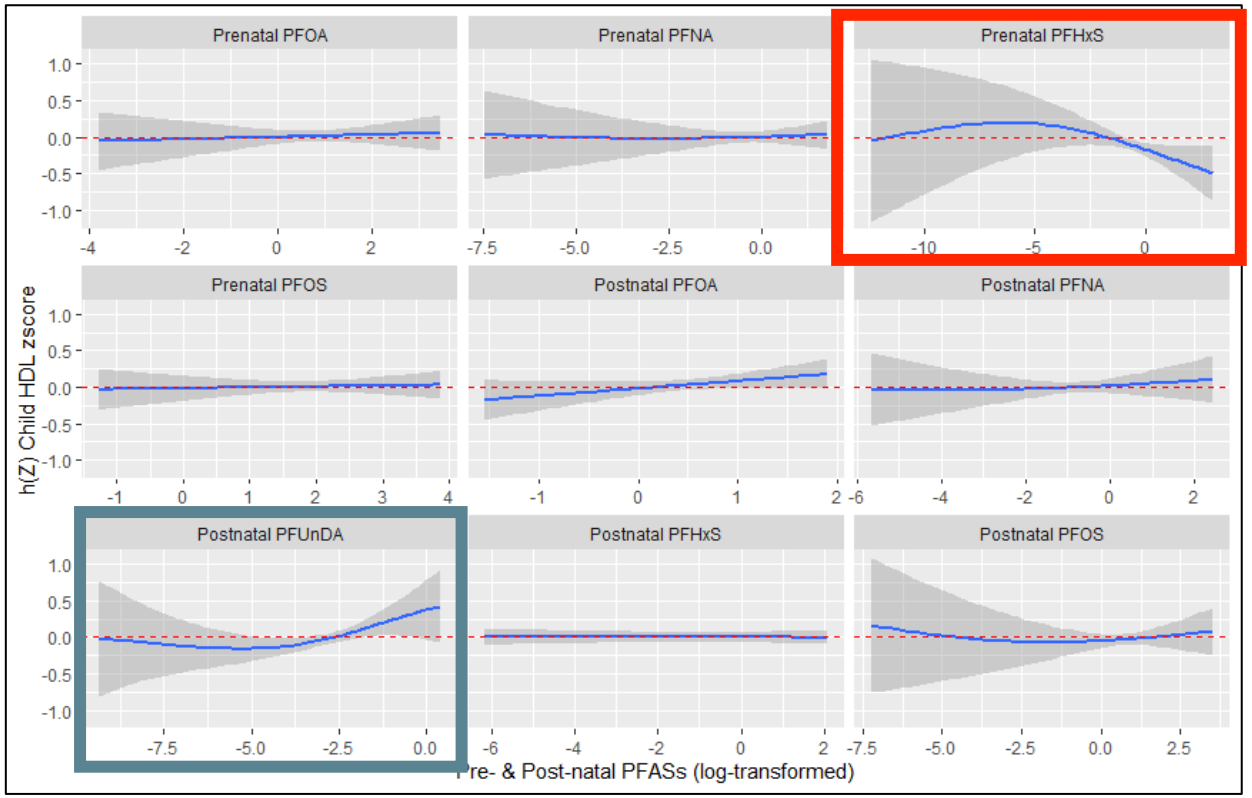
Results – «PFAS mixture effects»



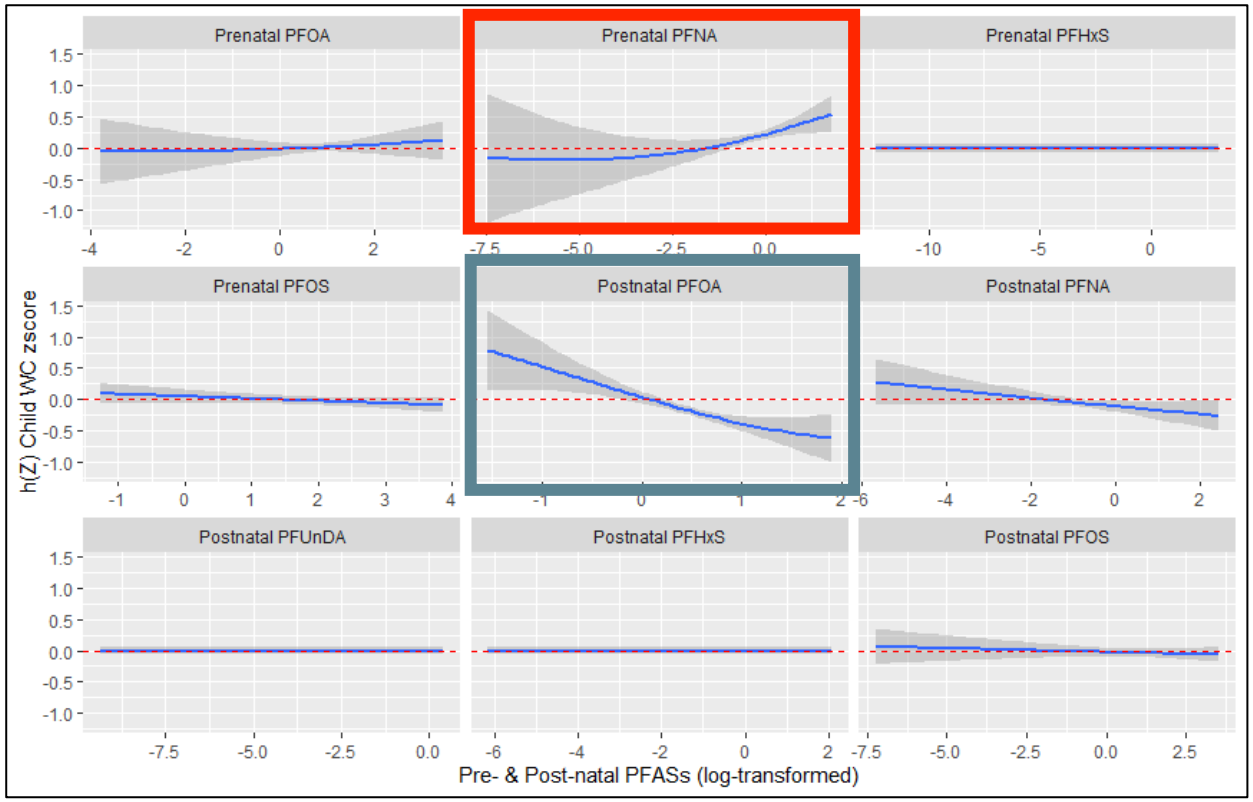
Outcomes	Direction	Dose-response	Contribution to mixture (range: 0 to 1)	
			Prenatal PFAS	Postnatal PFAS
HDL cholesterol	**Positive**	**Yes-strong**	PFHxS (0.55)	PFUnDA (0.57)
LDL cholesterol	Negative	No	PFOA (0.43)	PFOA (0.59)
Triglycerides	**Negative**	**Yes**	PFHxS (0.32)	PFUnDA (0.52)
Systolic Blood Pressure	**Positive (for exposure levels >50th percentile)**	**Yes**	PFOS (0.40)	PFNA (0.42)
Diastolic Blood Pressure	Null	Unsure	PFOS (0.34)	PFNA (0.63)
Waist circumference	**Negative**	**Yes-strong**	PFNA (0.80)	PFOA (0.97)

Results – «individual PFAS effects»

HDL cholesterol- POSITIVE



Waist circumference - NEGATIVE



Methods- Statistical plan

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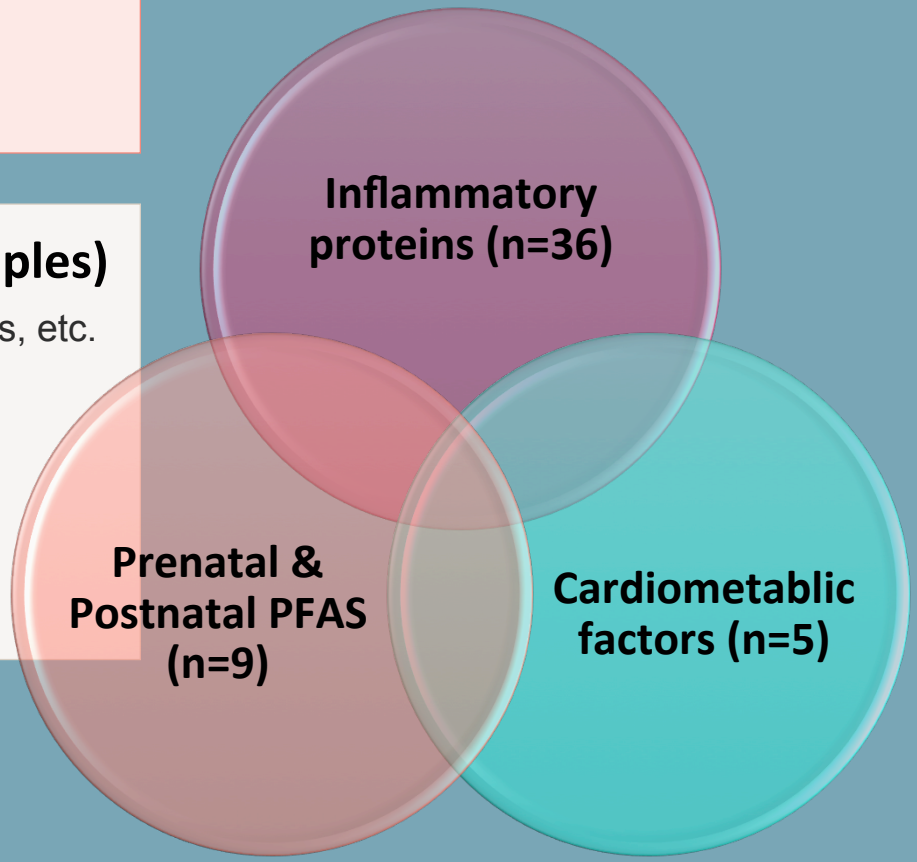
2. What is the role of the child's inflammatory status?

- **N=36 proteins analyzed by three Luminex kits (child blood samples)**

Adipokines, apolipoproteins, CC chemokines, CXC chemokines, interferons, interleukins, etc.

- **Integrated network by applying the xMWAS method:**
  1. pairwise data integration
  2. visualization of a multi-data integrative network
  3. multilevel community detection.



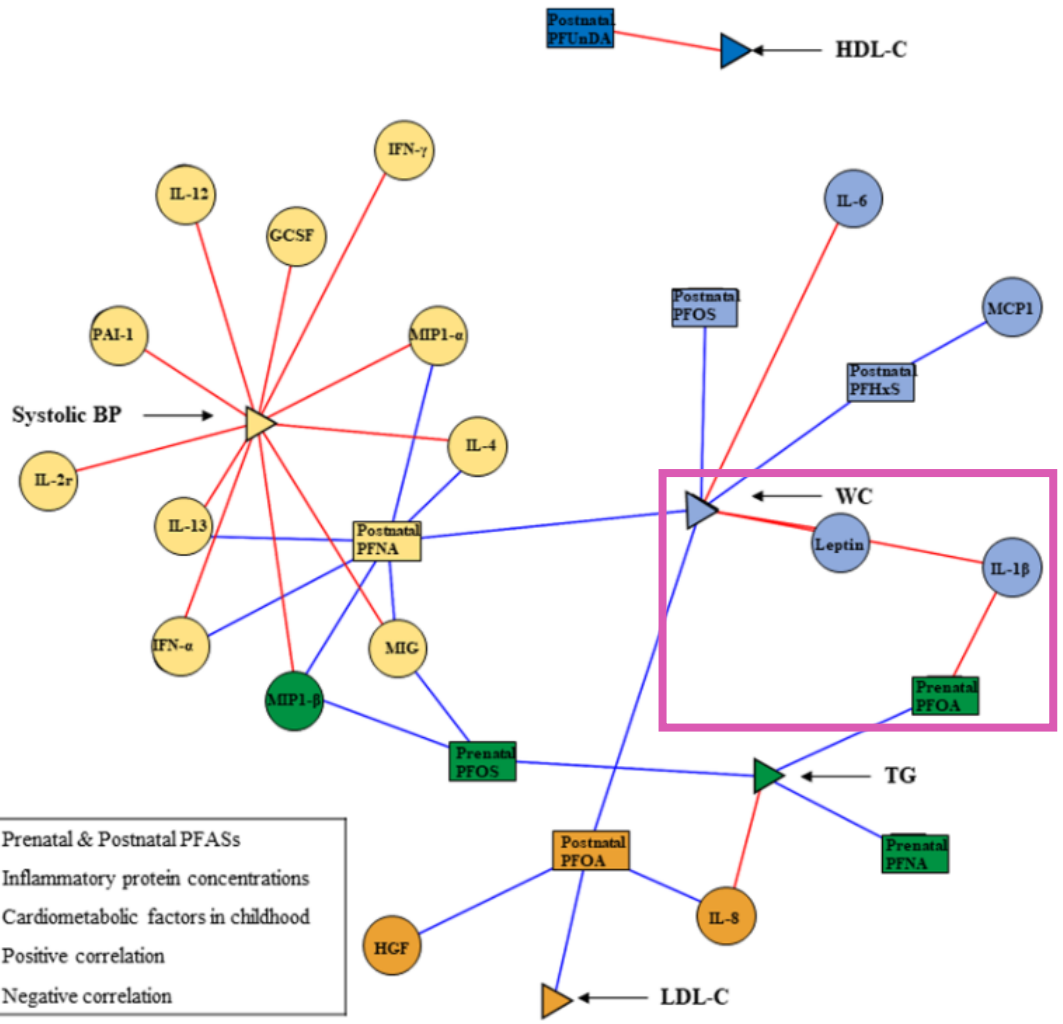


Fig. 2. Graph of the integrative network analysis of prenatal and postnatal PFAS, inflammatory protein concentrations in child's blood and cardiometabolic factors in childhood as derived by the xMWAS. Five communities were detected by the multilevel community detection algorithm, and are represented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

Community 1 (dark blue):
Postnatal PFUnDA, HDL-C

Community 2 (light blue):
Postnatal PFHxS and PFOS, WC, IL-1β, IL-6, leptin and MCP1

Community 3 (green):
Prenatal PFOA, PFNA and PFOS, TG, MIP1-β

Community 4 (orange):
Postnatal PFOA, LDL-C, IL-8 and HGF

Community 5 (yellow):
Postnatal PFNA, Systolic BP, and ten inflammatory proteins

Summary

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- **Pre- and Post-natal PFAS mixture exposure was positively associated with HDL-C and Systolic BP, and negatively associated with WC and TG.**
- **Postnatal PFASs were driving these associations with the PFAS mixture.**
- **Prenatal PFAS were associated with poorer cardiometabolic health (lower HDL-C and higher WC), but these associations were weaker.**
- **Most PFAS were negatively linked with inflammatory proteins→ phenotype:** Low PFAS exposure (pre &post) & obesity-induced inflammation
- *** Prenatal PFAS→ IL1-beta→ adiposity***

Summary-in context of similar studies

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- Our results confirm that gestation is a period of increased susceptibility to the detrimental effects of PFAS.
  - *Health Outcomes and Measures of the Environment (HOME) Study, Cincinnati, Ohio*
- Substantial uncertainty around this health outcome
- PFAS exposure in childhood were mostly negatively linked with the clusters of cardiometabolic factors-inflammatory proteins.
- Confirm the role of PFAS on suppression of inflammatory response
  - *suppressed antibody response to vaccination and increased occurrence of asthma, suggesting reduced immunological response, as well as lower levels of proteomic markers of inflammation*

Zoom out

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- Need to protect vulnerable populations against serious health impacts linked to PFAS exposure. Even at background level exposures.

- The global elimination of PFOS and PFOA, the main PFAS found in biological samples worldwide, has been regulated through the Stockholm Convention (since 2009 for PFOS and since 2020 for PFOA) and this is covered by EU/EEA legislations.
- The restriction of manufacture of more PFASs has been approved and regulated (ECHA) and is to be applied in the EU/EEA.

- Room for more action→ substances are currently being evaluated one at the time (i.e PFOS, PFOA) vs. entire families of chemicals (PFAS)→ loopholes in current chemicals regulations→ "regrettable substitutions".

- Barriers for a common solution[1]: Multiple uses- multiple sources of exposure - variability of this substance group - lack of a complete overview on substances and uses – new patents

1. Nordic Council of Ministers. 2018. Workshop on joint strategies for PFASs

ATHLETE (Advancing Tools for Human Early Lifecourse Exposome Research and Translation)

https://athleteproject.eu/

1. Set up a **prospective Europe-wide exposome cohort** covering the first two decades of the life course, building on 17 existing cohorts across Europe.
2. Measure **numerous environmental exposures** (urban, chemical, lifestyle and social risk factors) during pregnancy, childhood, and adolescence.
3. Link this "early-life exposome" with **children's biological responses and cardiometabolic, respiratory, and mental health.**
4. Estimate the **societal impact** of the exposome by calculating economic costs and impacts for children's health, in order to guide evidence-based policies and administrative decisions.
5. Implement **interventions for reducing exposures** related to the urban and chemical exposome.
6. **Translate acquired knowledge** for policymakers and citizens.
7. Make exposome data, tools and results available to researchers and policy makers in an **online ATHLETE toolbox** for use during and after the project, including an openly accessible exposome data infrastructure.
8. Work together with nine projects as part of the European Human Exposome Network to implement the world's largest network studying the impact of environmental exposure on human health.

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