HELIX BUILDING THE EARLY-LIFE EXPOSOME

Early-life environmental exposures and child respiratory health: the exposome reveals its first results

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UNIVERSITÉ Grenoble Alpes

Early-life exposome and lung function in children in Europe: an analysis of data from the longitudinal, population-based HELIX cohort

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Summary

Background Several single-exposure studies have documented possible effects of environmental factors on lung function, but none has relied on an exposome approach. We aimed to evaluate the association between a broad range of prenatal and postnatal lifestyle and environmental exposures and lung function in children.

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Environmental exposures, lifestyle and Lung function

Smoking

Air Pollution

Diet

Chemical exposures

Greenness

Lung function

- Smoking (Stocks et al, Lancet Resp Med 2013), outdoor air pollution (Gauderman et al, N Engl J Med 2015) are associated with deficits of lung function growth.
- Emerging concerns for other exposures, including chemical exposures (Gascon et al, Epidemiology 2014; Vernet et al, Env Res 2017; Hansen et al, EHP 2014):
  - persistent organochlorine compounds, such as PCBs *(electric insulators)* and DDT *(pesticides)*,
  - Perfluorinated compounds (PFASs) *(non-stick cookware, water-repellent clothing, stain resistant fabrics, carpets)*,
  - phthalate metabolites and phenols *(manufacture of plastics, solvents, personal care products)*

Previous studies focused on single exposure or family of exposures

Issues with single exposure studies

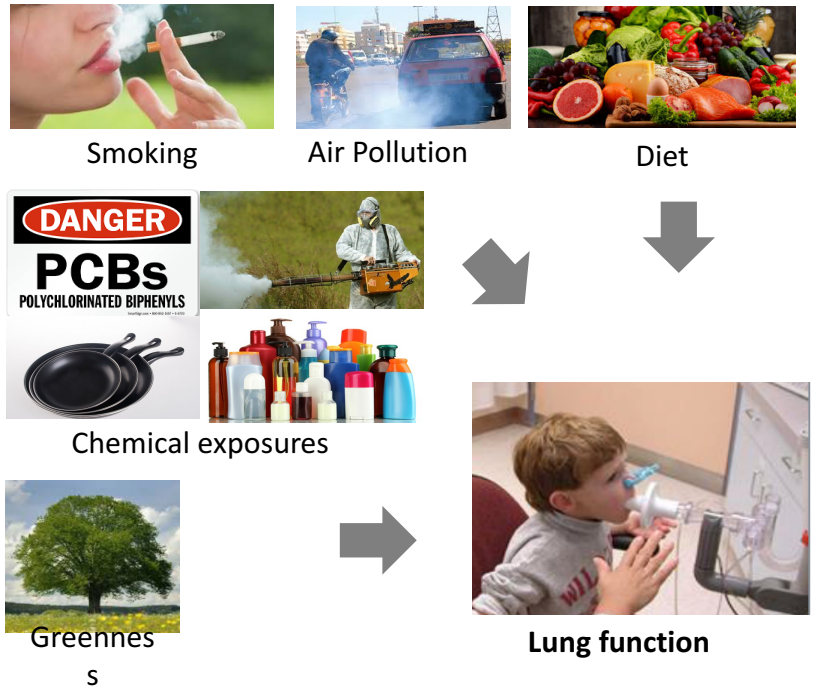
- **Selective reporting of associations** (by authors and journal) ➔ **Publication bias**
- **No correction for multiple testing**
- Cannot take into account **confounding by co-exposures**
- Lack of consideration of **“mixture effects”**

Exposome approach

calls for a holistic view of the effects of environmental exposures on human health by evaluating multiple exposures simultaneously

Aims

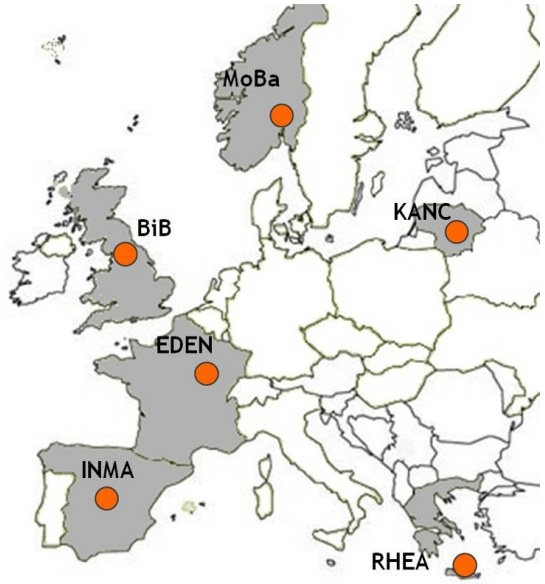
To evaluate the association between prenatal and postnatal environmental exposures and FEV_1 in childhood, in the large European Human Early-life exposome (HELIX) study



Aims

To evaluate the association between prenatal and postnatal environmental exposures and FEV_1 in childhood, in the large European Human Early-life exposome (HELIX) study, using an exposome approach

The Helix population



- 6 cohorts with similar design in 6 EU countries
- Recruitment between 2003 and 2010 according to cohort
- Sample size :
  - Entire cohorts: n=32,000 mother-child pairs
  - Helix subcohort: n=1,200 mother-child pairs from the 6 cohorts
- Neuro-development tests and lung function tests at 6-12 yrs

In utero

Recruitment
(before week 24)

Mid pregnancy:
1 spot urine sample
1 blood sample
(Stored at -80°)

Birth

Weight
Gestational duration
Head circumference

6-12 yrs

Neuro-development tests
Lung function test

Spirometry test

- **By trained research technicians using EasyOne spirometer and a standardised protocol**

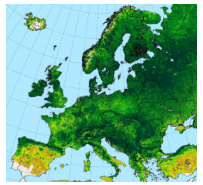
  3 acceptable manoeuvres and reproducible manoeuvres (difference below 200 milliliters between the two highest values for forced vital capacity (FVC) and FEV_1)

- Acceptability and reproducibility criteria **refined using data recorded from the spirometer**
  - BEV/FVC <5%; 1.5s<FET<10s
  - difference below 200 millilitres between the two highest values for forced vital capacity (FVC) and FEV_1
- **Assessment of the curve selection process** on 243 examinations by looking at the shape of the curves:
  - same curve selected for 79% of the examination
  - when a different curve was selected, Pearson correlation between FEV_1 of the two different curves= 0.96

Integrated tools for exposome assessment

17 exposure families: 85 prenatal and 125 postnatal exposure variables

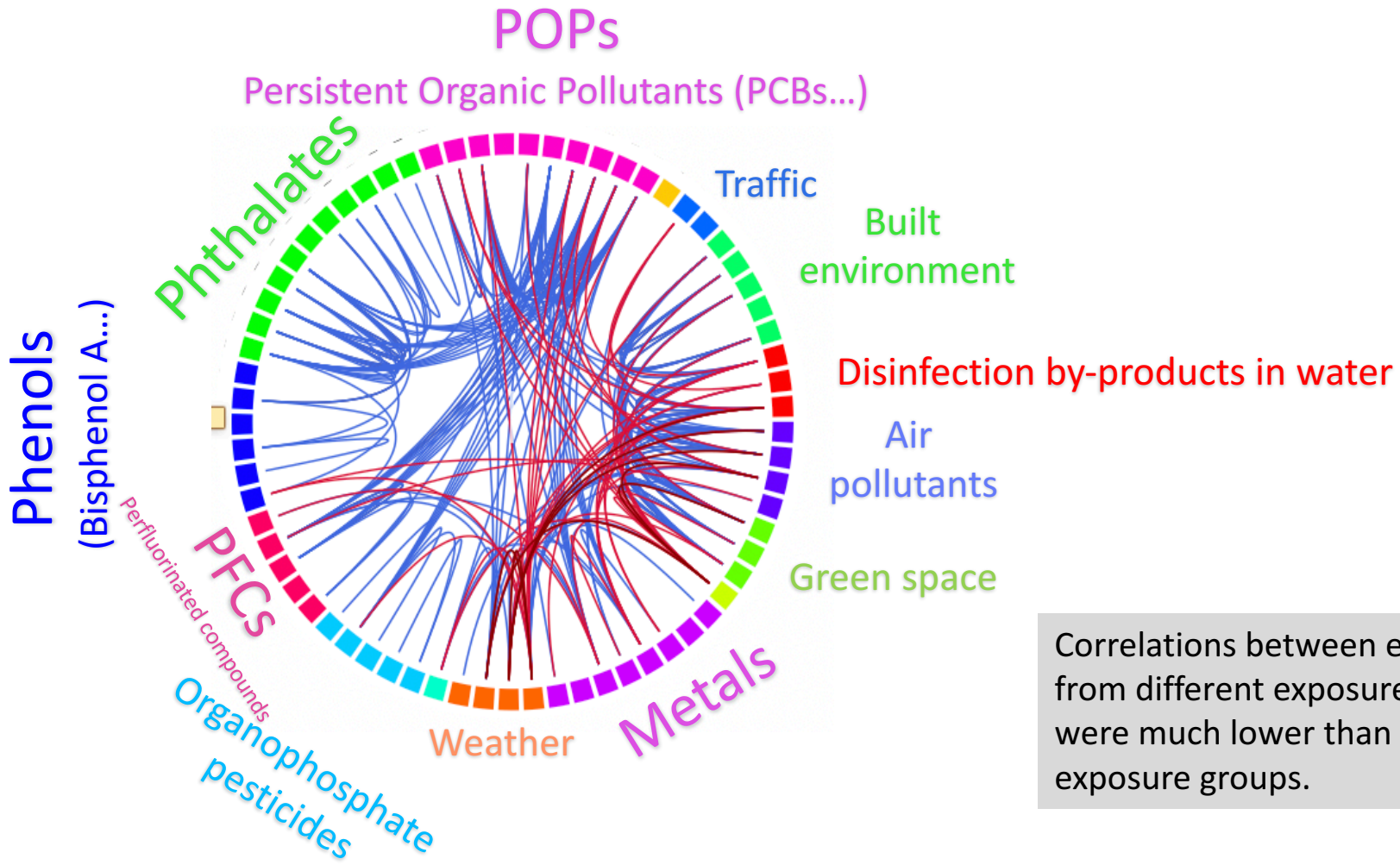
- **Outdoor factors** assessed from monitoring stations, geospatial models, land use databases and satellite data
- **Chemical exposures** measured in plasma, serum, whole blood or urine samples
- **Socio-economic** (Family Affluence Score) **and lifestyle factors** (smoking, diet, breastfeeding, physical activity, alcohol, pets, sleep) assessed by questionnaires



Exposure families
Atmospheric pollutants
UV
Surrounding natural space
Meteorology
Built environment
Traffic
Road traffic noise
Indoor air
Organochlorine compounds
Brominated compounds
Perfluorinated alkylated substances (PFAS)
Metals and essential elements
Phthalate metabolites
Phenols
Organophosphate pesticide metabolites
Water disinfection By-products
Socio-economic and lifestyle

Correlation structure of HELIX full Exposome

(86 exposures from 15 families of factors assessed in 1287 mother-child pairs)



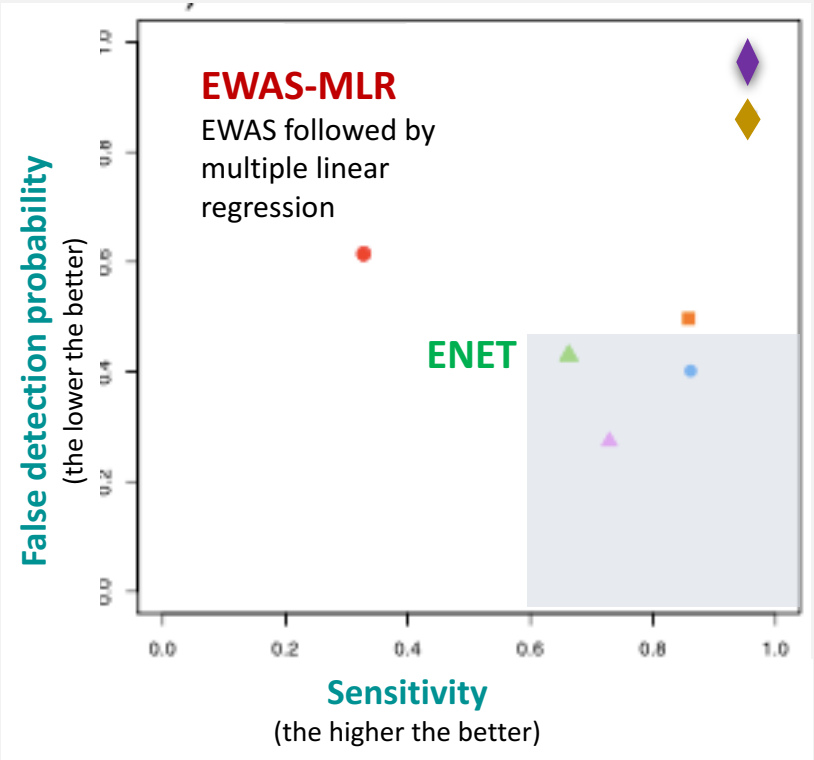
Line colors indicate sign of correlation coefficient (red: $\rho<0$)

Not adjusted for cohort

Correlations between exposures from different exposure groups were much lower than within exposure groups.

(Vrijheid et al, EHP, 2014; Tamayo et al, Env Int 2018)

Statistical analysis



Univariate fishing expedition
(no FDR correction)

EWAS
Exposome wide association study (with FDR correction)

GUESS
(Bayesian variable selection method)

DSA
(Deletion/ Substitution/ Addition Algorithm)

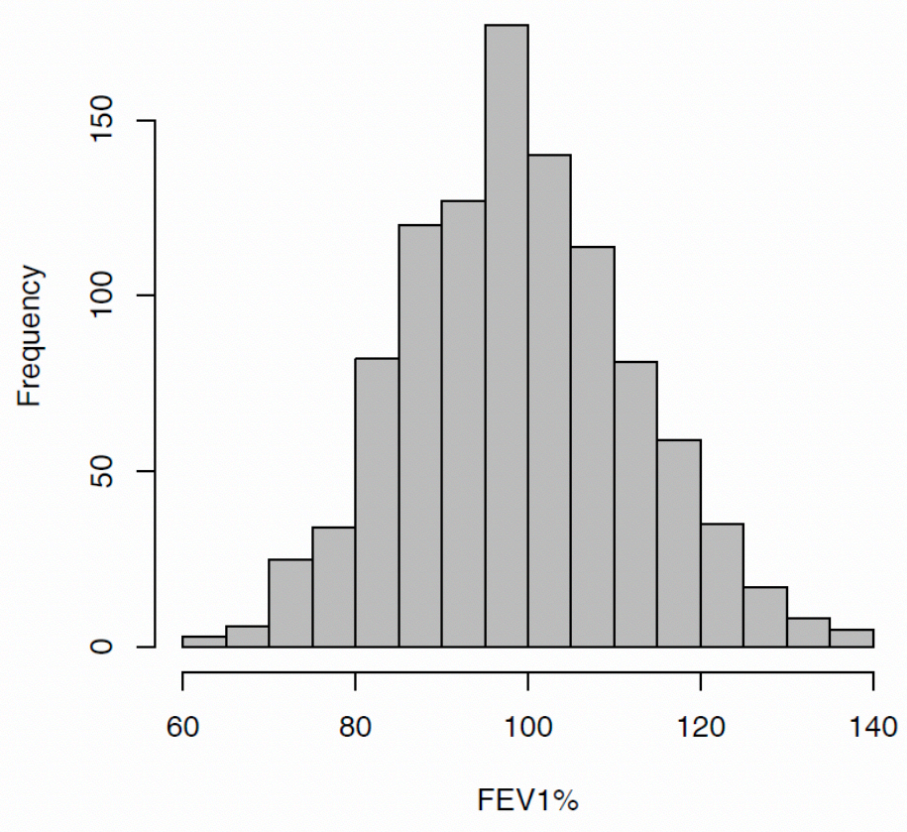
Simulation study aiming at identifying k=1, 2, 10 or 25 real predictors out of 238 exposures (average results)

(Agier et al., *EHP* 2016)

1. **Imputation** of missing values (multiple imputation)(White, *Stat Med* 2011)
2. **Standardization** of exposures (Normalization)
3. **Exposome-Wide Association Study** (ExWAS)(Patel, *PLoSOne* 2010)
   - Considering each exposure in sperate regression models
   - Family-wise error rate **multiple testing correction** method (Li MX, *Hum Genet* 2012)
4. **Deletion-Substitution-Addition (DSA)** algorithm (Sinisi, 2004)
   - Consideration in a single approach all exposures simultaneously (order one terms only)
   - Consideration of all order two exposure-exposure interaction terms (DSA2 model)
5. All analyses were **adjusted for a priori selected factors**
   - Cohort, sex, age, height, parental country of birth, breastfeeding duration, season of conception, presence of older siblings, parental education level, maternal age, maternal BMI, postnatal passive smoking, prenatal active and passive smoking.

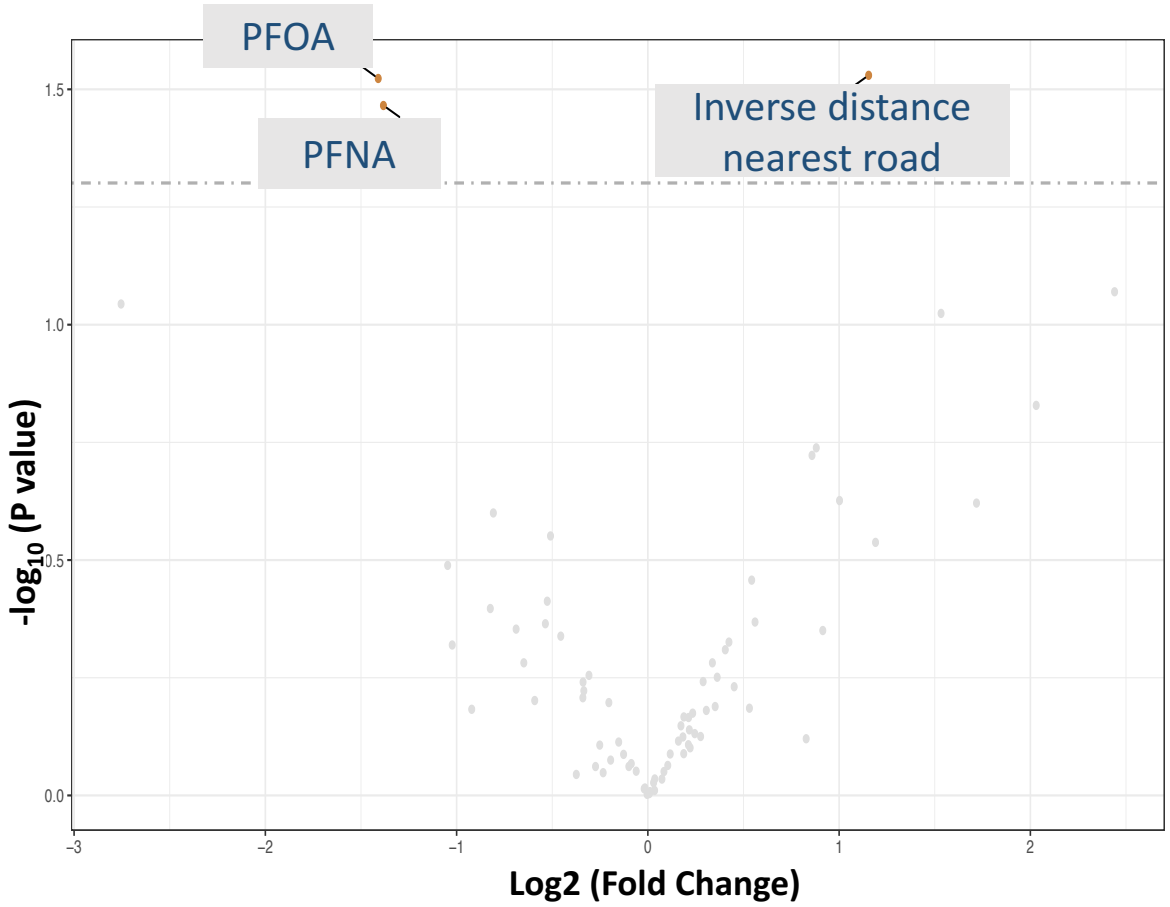
Population description, n=1,033

Factors	Mean (sd) / %
Cohort : BIB, %	14%
EDEN, %	15%
INMA, %	18%
KANC, %	14%
MOBA, %	24%
RHEA, %	15%
Child sex, % males	47%
Child age (years), m(sd)	8.07 (1.58)
Both parents native from the cohort country, %	84%
Highest parental education: High	56%
Middle	40%
Low	4%
Maternal age at pregnancy (years)	30.9 (4.7)
Active smoking during pregnancy, nb cigarettes, m(sd)	0.5 (2.0)
Passive smoking during pregnancy, %	40%
Passive smoking during infancy, %	35%
FEV_1 %pred	98.8 (13.2)



Prenatal Exposome - FEV_1 association

ExWAS results



Exposure variable	Transf. before IQR standard.	IQR	ExWAS		ExWAS-MLR	
			Estimate [95% CI]	P-value	Estimate [95% CI]	P-value
PFNA, µg/L	Log2	0.83	-1.4 [-2.7; -0.1]	0.03	-0.8 [-2.8; 1.2]	0.42
PFOA, µg/L	Log2	0.77	-1.4 [-2.7; -0.1]	0.03	-0.6 [-2.6; 1.3]	0.52
Inverse distance to nearest road, m^{-1}	Log	1.17	1.1 [0.1; 2.2]	0.03	1.1 [0.1; 2.2]	0.03

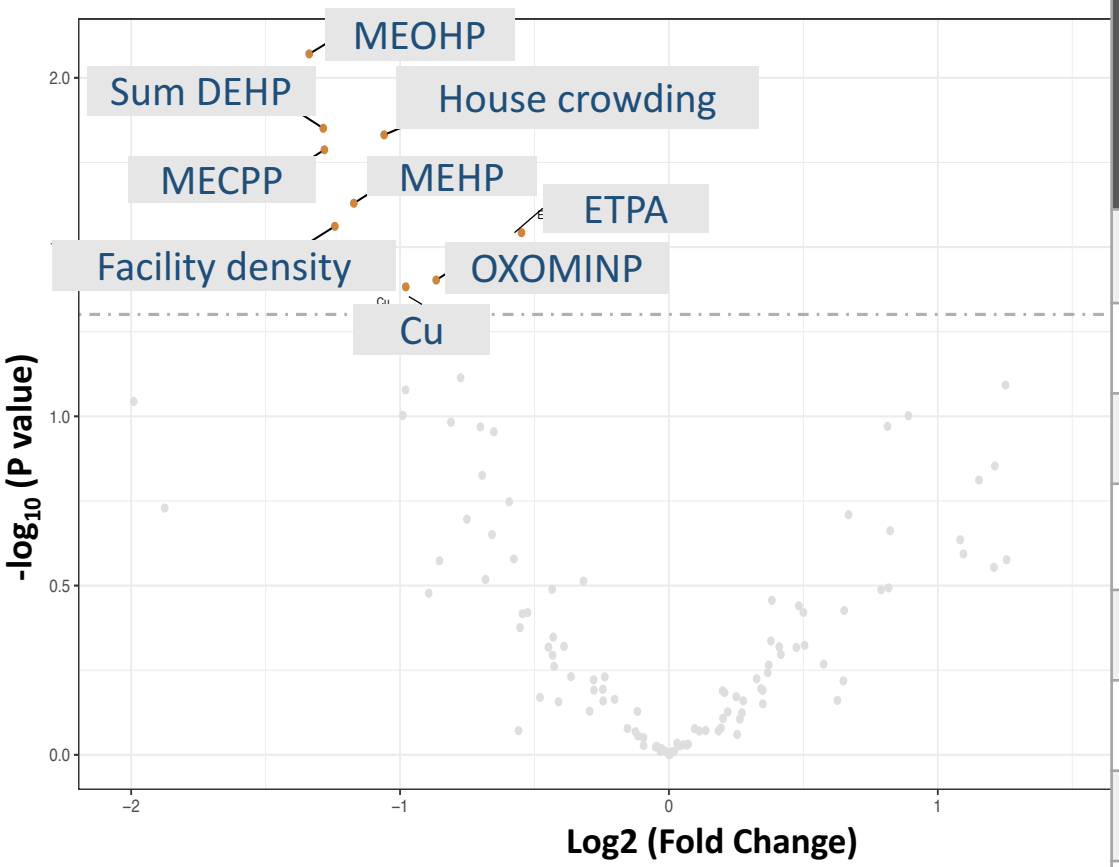
ExWAS-MLR : adjusting for potential confounding by co-exposure

DSA / DSA2

No significant results

Postnatal exposome - FEV_1 association

ExWAS results

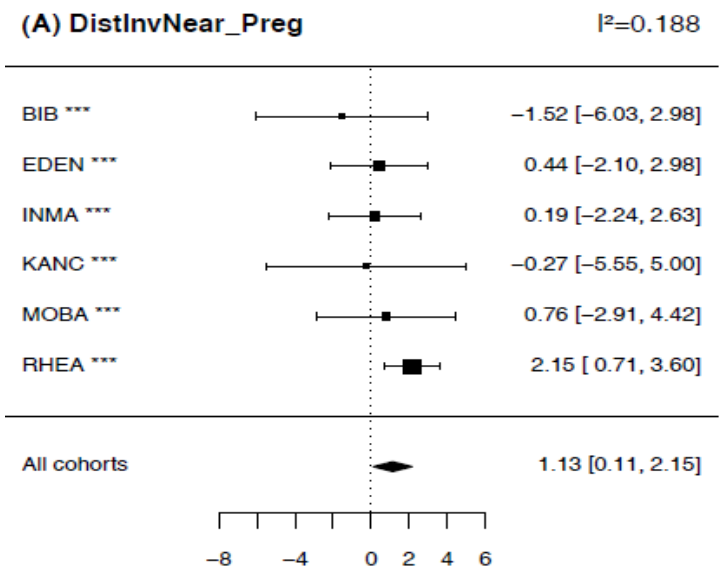


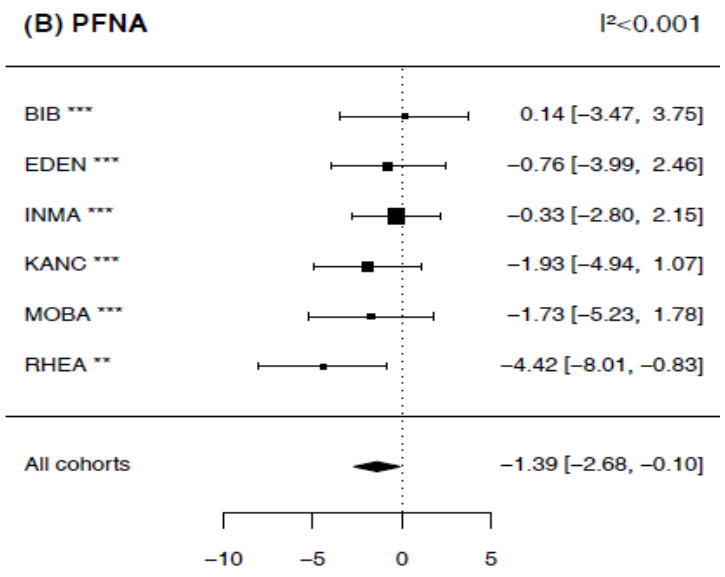
Exposure variable	Transf. before IQR standard	IQR	ExWAS Estimate [95% CI]	ExWAS p-value	ExWAS-MLR Estimate [95% CI]	ExWAS-MLR p-value
Facility density /km²	Log	1.32	-1.2 [-2.3;-0.1]	0.03	-1.2 [-2.7;0.3]	0.13
Copper, µg/L	Log2	0.16	-1.0 [-1.9;-0.0]	0.04	-0.9 [-1.8;0.1]	0.06
Ethyl-paraben, µg/g of creatinine	Log2	0.98	-0.5 [-1.0;-0.1]	0.03	-0.6 [-1.2;-0.1]	0.02
Sum of (DEHP), µg/g of creatinine	Log2	0.85	-1.3 [-2.3;-0.3]	0.01	-1.3 [-3.1;-0.4]	0.13
MECPP, µg/g of creatinine	Log2	0.87	-1.3 [-2.3;-0.2]	0.02	-	
MEHHP, µg/g of creatinine	Log2	0.87	-1.2 [-2.2;-0.2]	0.02	-	
MEOHP, µg/g of creatinine	Log2	0.84	-1.3 [-2.3;-0.3]	0.01	-	
OXOMINP, µg/g of creatinine	Log2	1.34	-0.9 [-1.7;0]	0.04	-0.4 [-1.6;0.8]	0.54
House crowding, nb people	None	1.00	-1.1 [-1.9;-0.2]	0.01	-0.9 [-1.7;0.0]	0.04

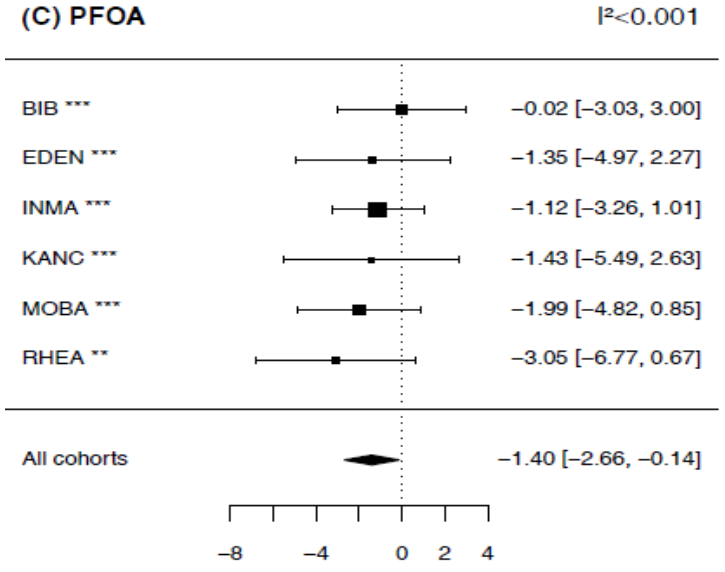
DSA / DSA2

No significant results

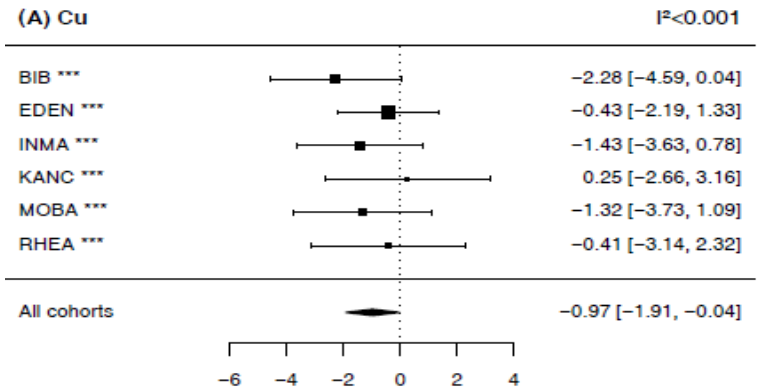
Cohort-by-cohort analysis of the association between **pretanal exposome** and FEV_1%

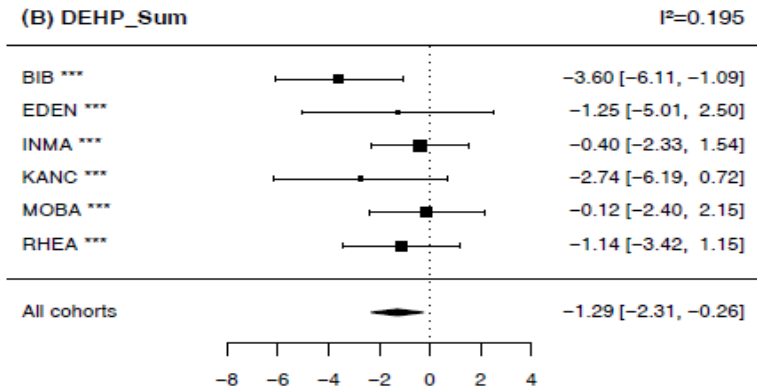


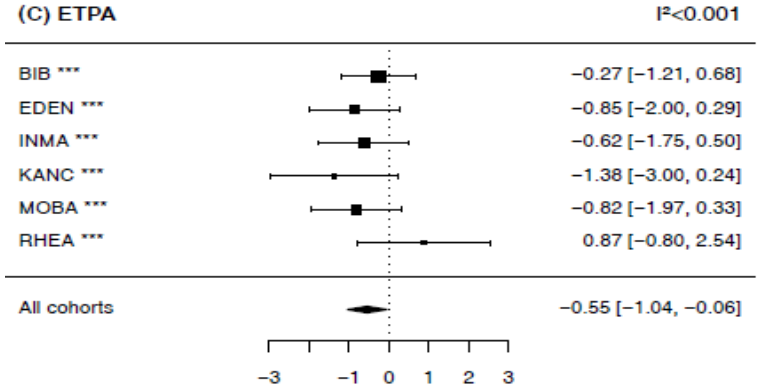


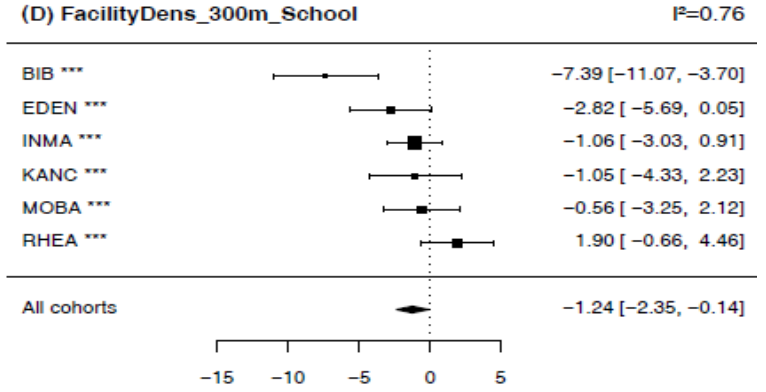


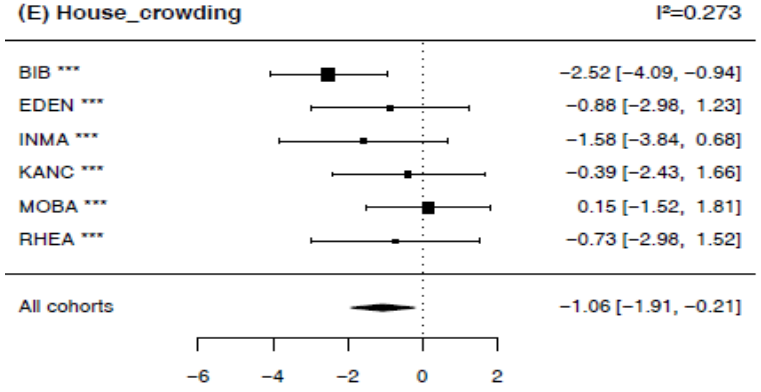
Cohort-by-cohort analysis of the association between **postanal exposome** and FEV_1%

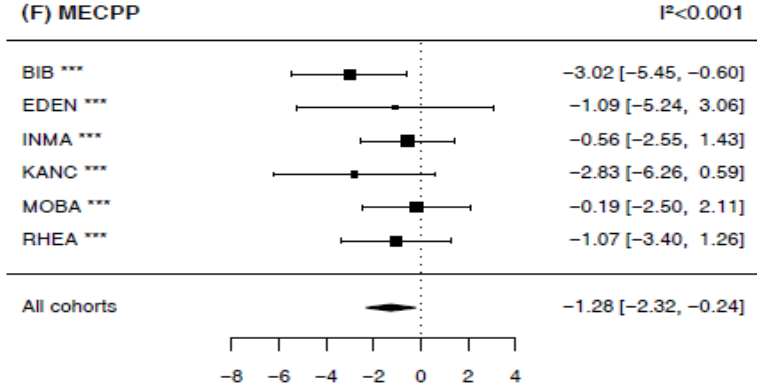




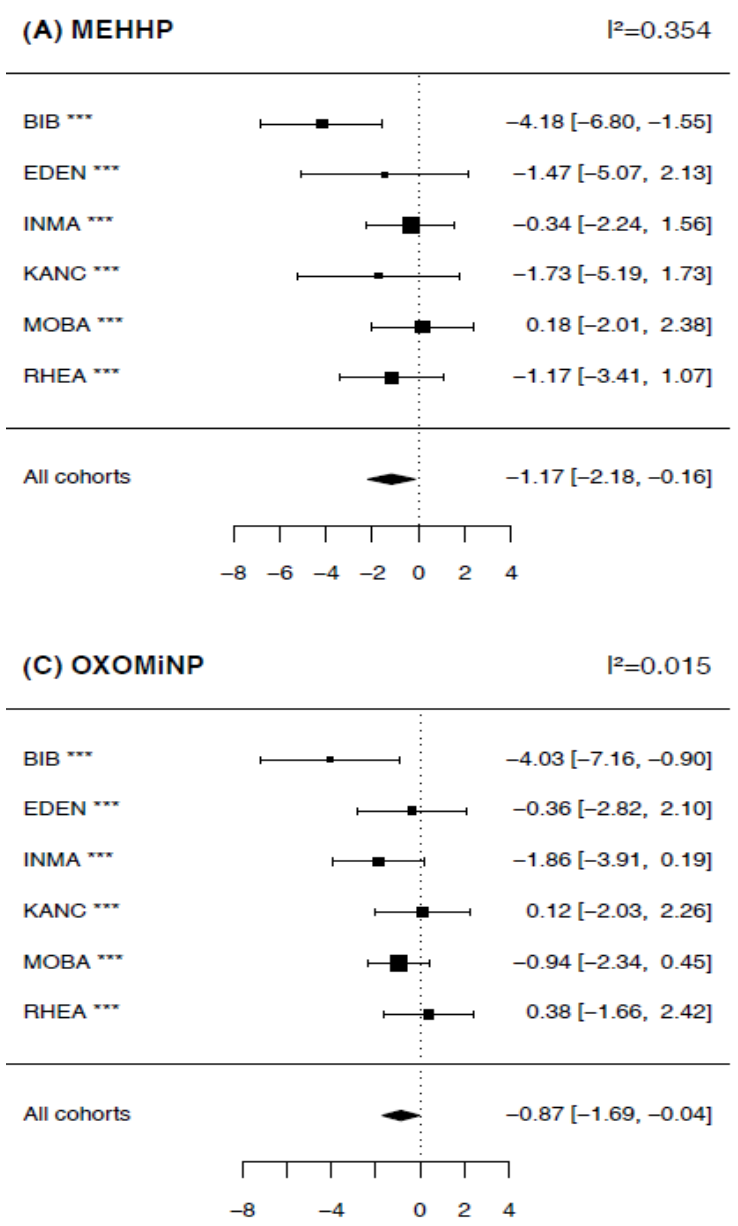








Cohort-by-cohort analysis of the association between **postnatal exposome** and FEV_1%



CONCLUSION

- First study addressing the impact of the exposome on lung function in children by considering a broad spectrum of prenatal and postnatal environmental factors.
- ExWAS was in favor of lower FEV_1 in childhood with
  - prenatal exposure to perfluorinated compounds (PFNA, PFOA)

    Association supported by experimental (deWitt et al Toxicol Pathol 2012) and animal studies (Ryu et al, Am J Physiol Lung Cell Mol Physiol 2014), though data in human are scarce (Impinen et al, Env Res 2018; Qin et al. Env Res 2017).
  - postnatal DEHP and DINP phthalate metabolites

    Convergence with previous findings (Vernet et al EHP 2017; Whyatt et al, EHP 2014; Lin et al, Sci Total Environ 2018).
  - postnatal exposure to phenols (ethyl-paraben)

    Convergence with previous findings (Vernet et al EHP 2017)
  - postnatal exposure to copper (Pearson et al, Eur J Clin Nutr 2005) and house crowding (Cardoso et al., BMC public health 2004).

DISCUSSION

- Limited statistical power due to the multiplicity of the exposures that were tested and the rather small effect on lung function that is expected for these exposures

  No exposure identified by DSA and no two-way interaction between exposures

- Different type and magnitude of misclassification bias between exposures

  Cautious comparison of the exposure-heath association between exposures

- All estimates are available for future meta-analyses
- This exposome approach should be seen as an initial screening step, making it possible to identify questionable exposures for which more specific research is needed.

DISCUSSION

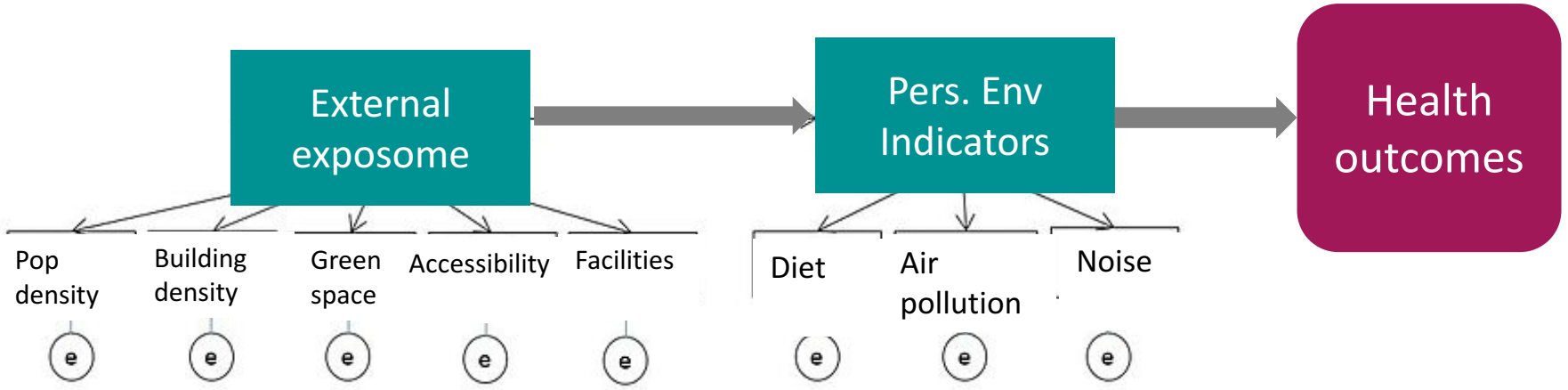
Public health implications

- **Results observed for DINP are of particular public health importance** as the use of DINP is currently increasing in Europe as substitution to DEHP and is now among the most common used plasticizer.
- **The chemical substances identified are ubiquitous**; In helix 9 pregnant women and 9 children over 10 had level above the detection threshold
- **Preventive measures** aimed at lowering exposure to the identified ubiquitous chemicals, through stricter regulation and through informing the public by labelling these chemicals in consumer products, could help to prevent early-life lung function impairment, which in turn might have benefits for long-term health

PERSPECTIVES

To expand the statistical approaches in exposome research in order to:

- **Assess combined effect of exposures** (i.e. clustering approaches)
- **Increase statistical power** by reducing the dimension of the exposome by integrating a-priori knowledge, i.e. from biological pathways
- **Improve causal inference** , i.e. by integrating causal structure within the exposome



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