

Childhood exposure to non-persistent endocrine disrupting chemicals and multi-omic markers in a population-based child cohort

Lorenzo Fabbri 1,2 Ronan Garlantezec 10 Cathrine Thomsen 4 John Wright 5 Remy Slama 6 Barbara Heude 7 Regina Grazuleviciene 8 Leda Chatzi 9 Chung-Ho E Lau 11,12 Alexandros P Siskos 13 Hector Keun 13 Maribel Casas 1,2,3 Martine Vrijheid 1,2,3 Lea Maitre 1,2,3

²Universitat Pompeu Fabra (UPF), Barcelona, Spain ³CIBER Epidemiologia y Salud Pública (CIBERESP), Madrid, Spain ⁴Department of Environmental Health, Norwegian Institute for Health, Norway ⁵Bradford Institute for Health, Norwegian Institute of Public Health, Norway ⁶Team of Environmental Epidemiology applied to Reproduction and Respiratory Health, Institute for Advanced Biosciences (IAB), Inserm, CNRS, Université Grenoble, France ⁹Department of Preventive Medicine, Keck School of Medicine, University of Southern California, France of Preventive Medicine, University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University of Southern California, France of Environmental Sciences, Vytautas Magnus University Of Southern California, France of Environmental Sciences, Vytautas Magnus University Of Southern California, Vytautas Magnus University Of Southern Calif ¹⁰Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé environnement et travail), UMR_ S 1085, Rennes, Encherche en santé environment and Health, School of Public Health, Imperial College, South Kensington, London, UK ¹³Cancer en santé environnement et travail), UMR_ S 1085, Rennes, Encherche en santé environnement and Health, School of Public Health, Imperial College, South Kensington, London, UK ¹³Cancer en santé environnement et travail), UMR_ S 1085, Rennes, Encherche en santé environnement and Health, School of Public Health, Imperial College, South Kensington, London, UK ¹³Cancer en santé environnement et travail), UMR_ S 1085, Rennes, Encherche en santé environnement et travail), UMR_ S 1085, Rennes, Encherche en santé environnement et travail), UMR_ S 1085, Rennes, Encherche en santé environnement et travail), UMR_ S 1085, Rennes, Encherche en santé environnement et travail (Institut de recherche en santé environnement et travail), UMR_ S 1085, Rennes, Encherche en santé environnement et travail (Institut de recherche en santé Metabolism & Systems Toxicology Group, Division of Cancer, Department of Surgery and Cancer & Division of Systems Medicine, Department of Metabolism, Digestion & Reproduction, Imperial College London, Hammersmith Hospital Campus, London, UK **For further information contact: lorenzo.fabbri@isglobal.org

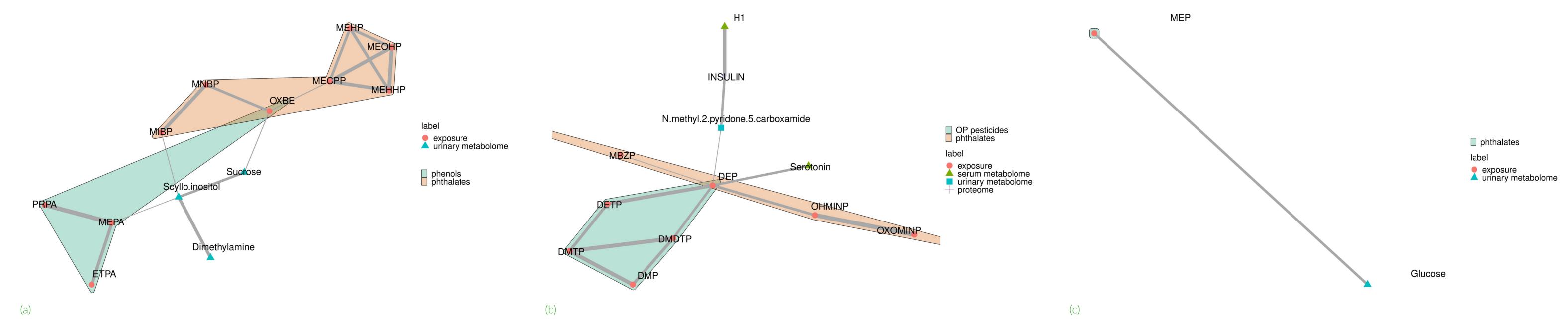
Background & Objectives

- The general population is exposed to a cocktail of chemical exposures
- Non-persistent endocrine disruptors (EDCs) are a class of chemicals that interfere with the endocrine system
- The early stages of life are particularly vulnerable to the effects of EDCs
- Multi-omic signatures might provide mechanistic insights into the effect of EDC exposure, in particular before the onset of clinical symptoms in children
- We aimed to identify multi-omic signatures associated with non-persistent EDCs using an integrative approach based on Partial Correlation Networks

Methods Study design 🚽 Multi-Omics Exposures Exposure assessment Omics 1 networks Week 1 - pool of 15 urines Organophosphate (OP) pesticides (P=7) Phenols (P=10) Phthalates (P=5) $(P_{tot}=22)$ ~6-month interval Blood samples Organophosphate (OP) pesticides (P=7) Phenols (P=10) Phthalates (P=5) Week 2 - pool of 15 urines $(P_{tot}=22)$

Results

- The time-specific networks ($N_{\text{edges}} = 1,064, N_{\text{edges}} = 1,109$) included associations of comparable strength ($\rho = 0.09 \; (-0.09, 0.11)$ for both) and statistical significance ($q = 0.008 \; (0.001, 0.025), \; q = 0.01 \; (0.001, 0.027)$). The significant edges represented less than 3% of the possible connections
- The merged network consisted of $N_{\rm edges} = 229$
- Graph merging led to the exclusion of the majority of exposure-omic connections (Figure 1b). Notably, none of the protein-exposure associations were reproducible
- The merged network consisted of 32 connected components, 3 of which included mixed exposure-omic connections (Figure 2)





(b) Pie chart showing the proportion of edge types for the time-specific and merged

e-e e-ms ms-ms e-mu ms-mu mu-mu p-mu ms-p p-p

Figure 1. Multi-Omics - EDCs association network.

(a) Merged network showing all the connected components.

- We integrated Multi-Omic and exposure data from a child cohort using an integrative approach, and we identified associations reproducible across time points
- networks. e = exposure, ms = serum metabolite, mu = urinary metabolite, mu = urinary metabolite, mu = urinary metabolite, mu = urinary metabolite, p = protein. The association between DEP and Serotonergic system

Conclusions

In future work we plan to include methylation data