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

Lorenzo Fabbri (@lorenzoF92SM)

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Outline

- Background & Objectives
- Methods
- Results
- Conclusions and Future Work

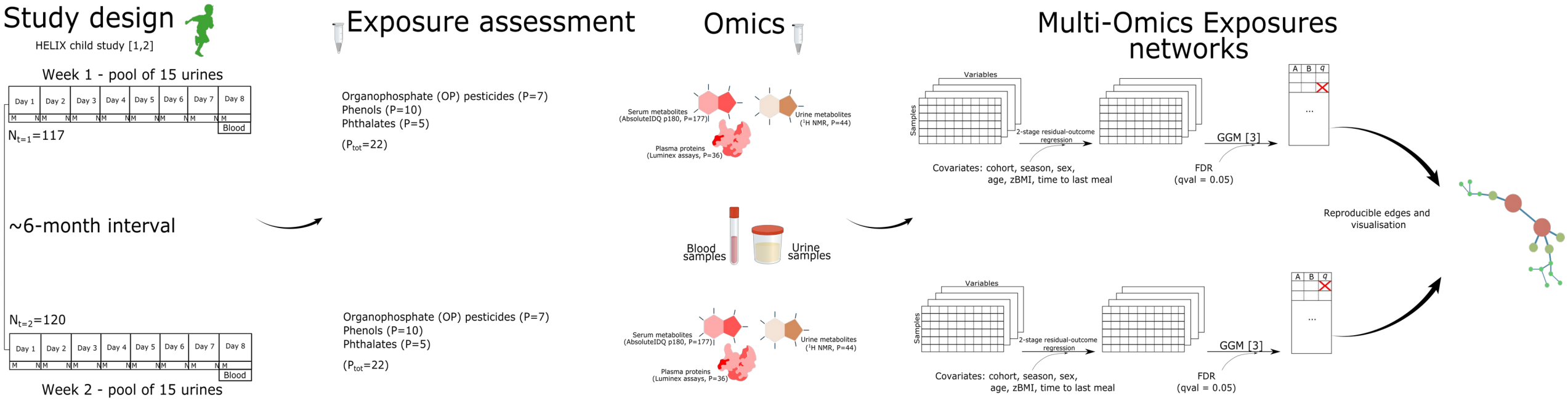
Background & Objectives

- 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
- **Multi-omic** signatures might provide mechanistic insights into the effect of EDC exposure
- We aimed to identify multi-omic signatures associated with non-persistent EDCs using an integrative approach based on **Partial Correlation Networks**

Methods

- Main idea: move from `single biomarker ~ single exposure` to `all biomarkers ~ all exposures` (i.e., *integrative* approach)
- First attempt: **(s)PLS** in regression mode
  - Issues: questionable predictive ability, models explained *little* variation in the Exposome
- Second attempt: regularized partial correlation coefficients and **GGM**s

Methods



[1] Vrijheid M, et al. "The human early-life exposome (HELIX): project rationale and design." (2014)
[2] Casas M, et al. "Variability of urinary concentrations of non-persistent chemicals in pregnant women and school-aged children." (2018)
[3] Schafer J, Strimmer K. "A Shrinkage Approach to Large-Scale Covariance Matrix Estimation and Implications for Functional Genomics." (2005)

Methods

Study design

HELIX child study [1,2]

Week 1 - pool of 15 urines

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
M N	M N	M N	M N	M N	M N	M N	M Blood

$N_{t=1}$=117

~6-month interval

$N_{t=2}$=120

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
M N	M N	M N	M N	M N	M N	M N	M Blood

Week 2 - pool of 15 urines

Exposure assessment

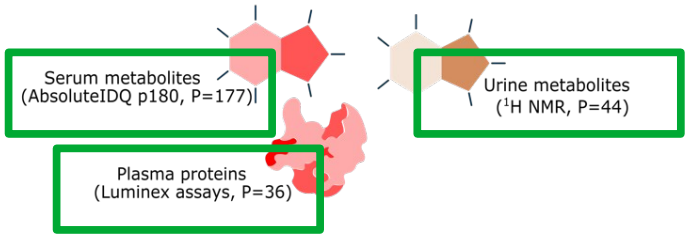
Organophosphate (OP) pesticides (P=7)
Phenols (P=10)
Phthalates (P=5)

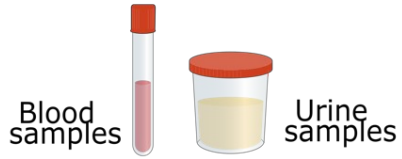
(P_{tot}=22)

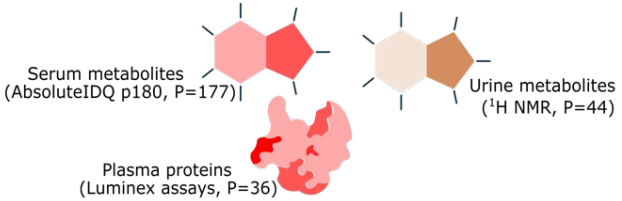
Organophosphate (OP) pesticides (P=7)
Phenols (P=10)
Phthalates (P=5)

(P_{tot}=22)

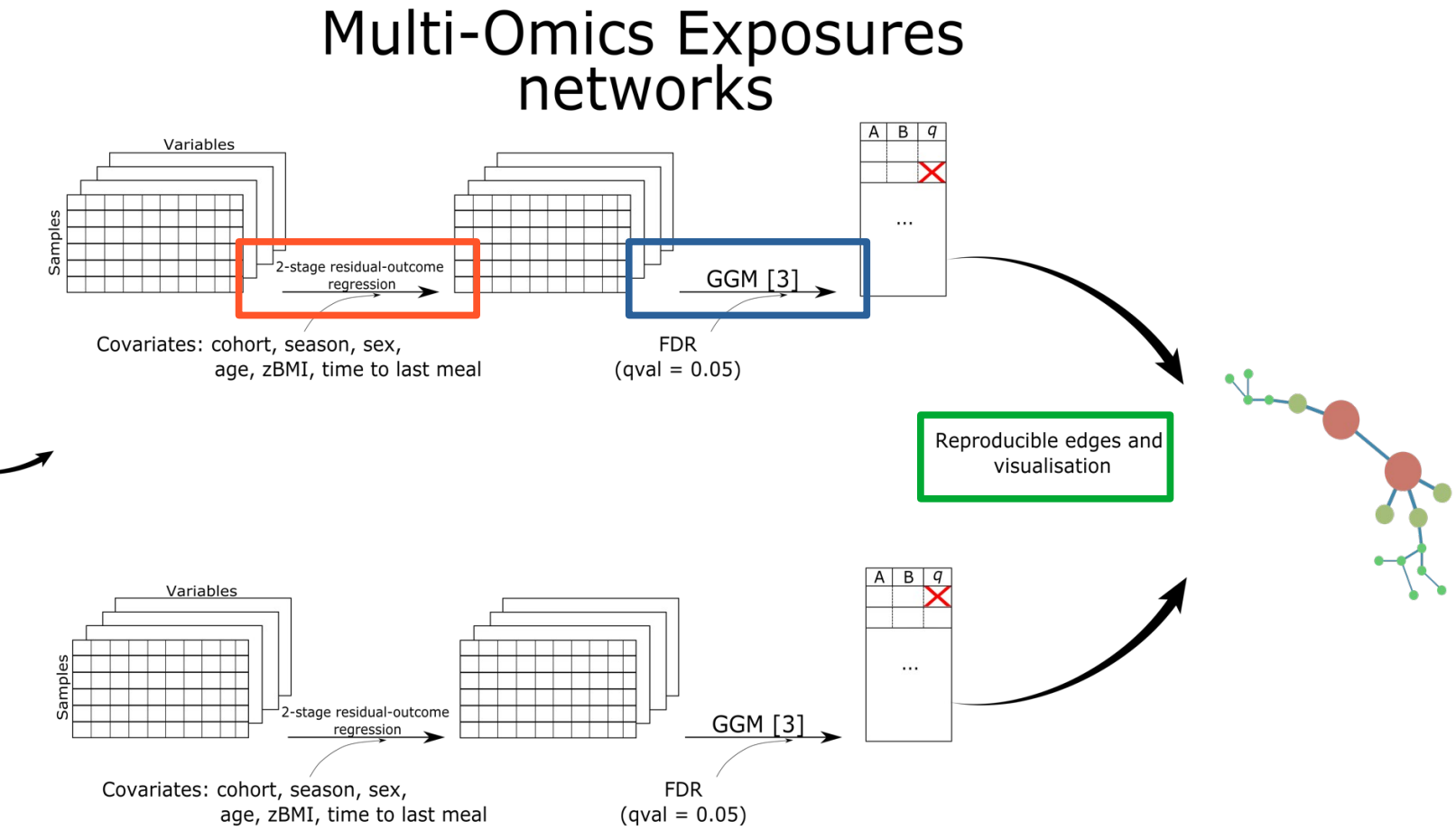
Omics







Methods



Pipeline (for each time point separately):

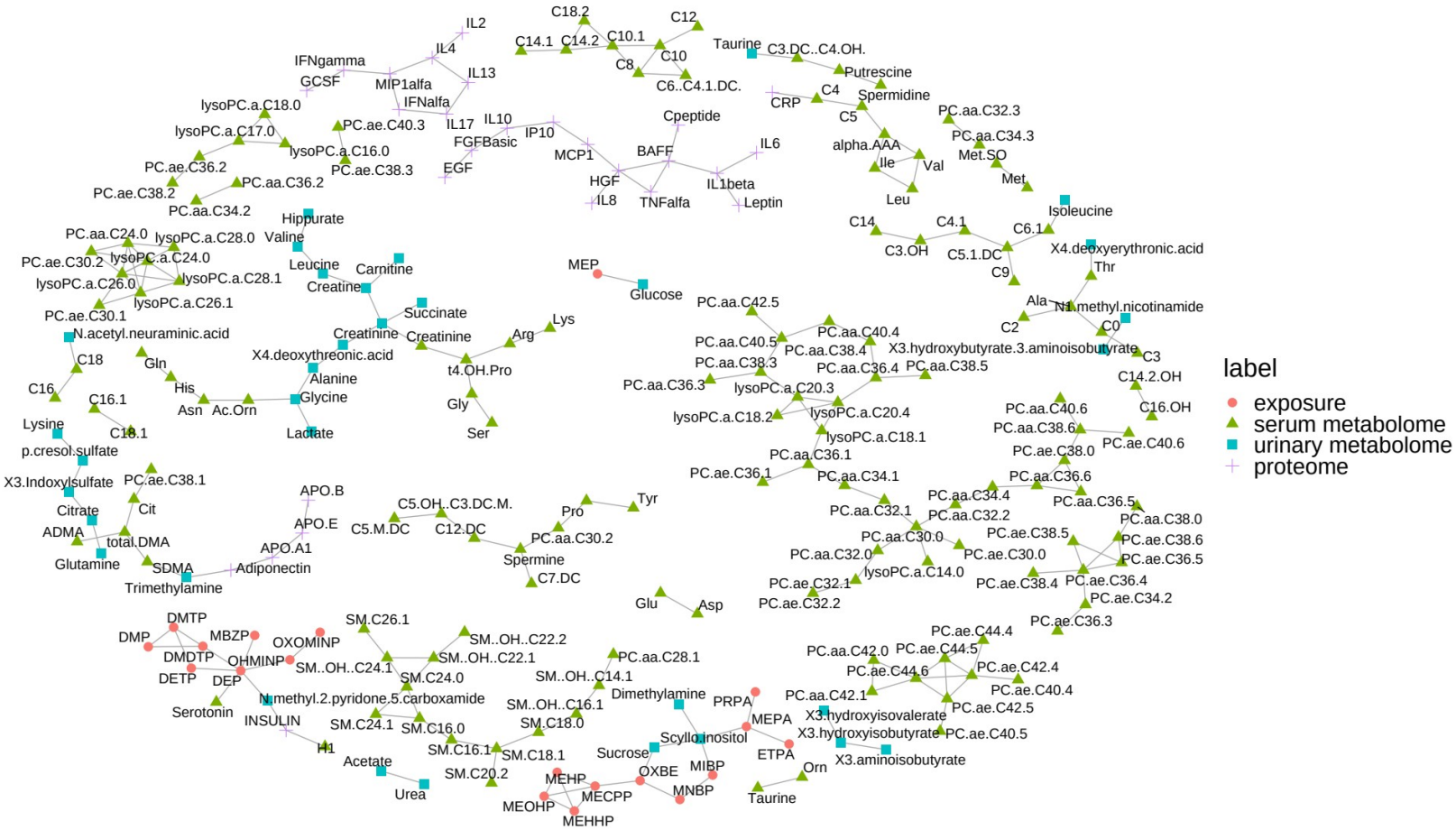
1) Adjustment for covariates (-omics) using 2-stage residual-outcome regression (e.g., `residual(biomarkers ~ covariates)`)
2) Data transformation: auto-scaling
3) Merging exposures and -omics into single matrix
4) Computing correlations using `corpcor` R package (`pcor.shrink` function)
5) Processing: FDR at 0.05 significance level

Network **merging**:

6) Merge by node A, node B and direction (i.e., sign(rho))
7) Focus on Ccs with exposures and -omics

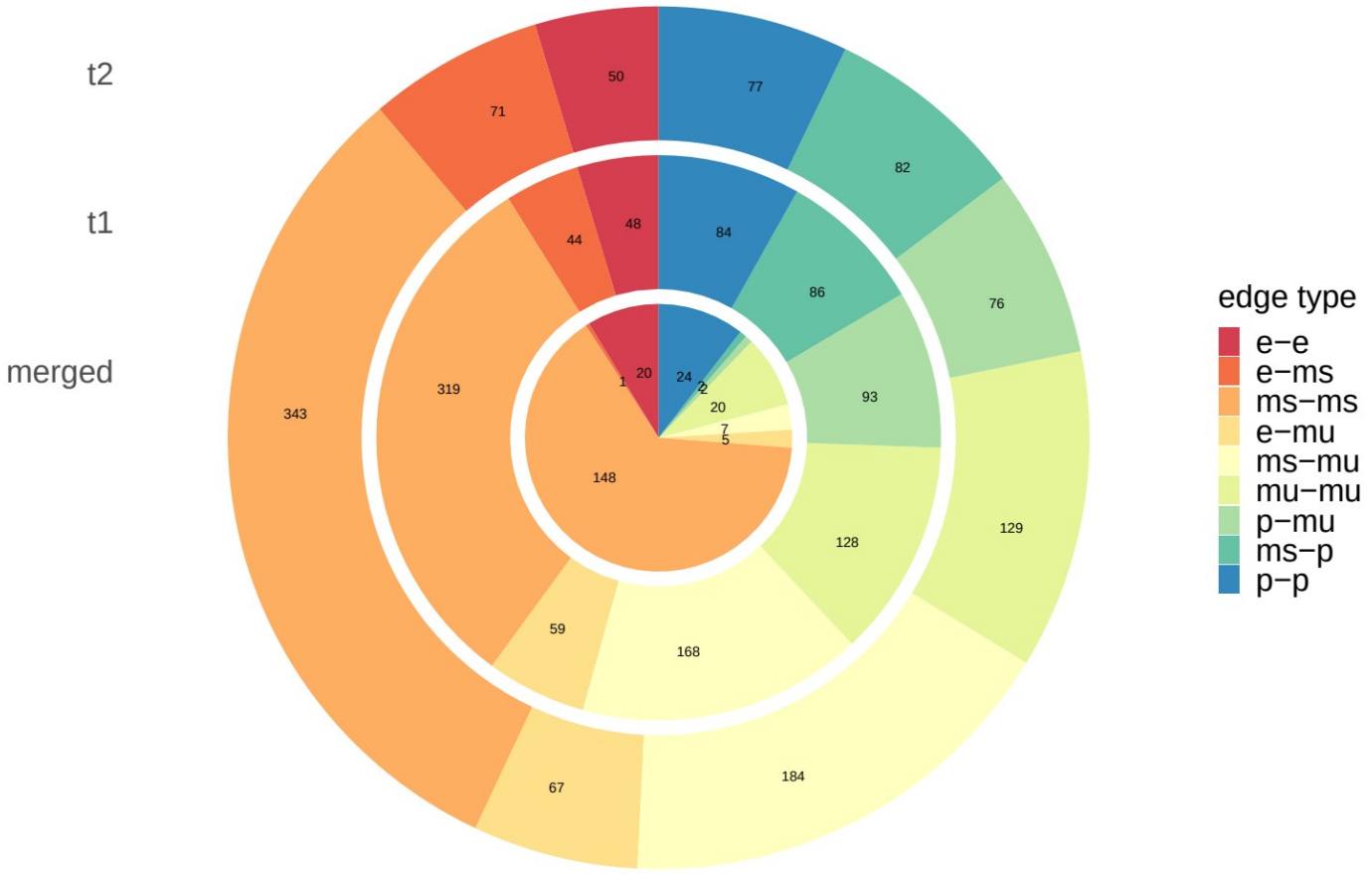
Results

- The time-specific networks (N_{edges}=1,064, N_{edges}=1,109) included associations of comparable strength (ρ=0.09 (-0.09, 0.11)) 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_{edges}=229



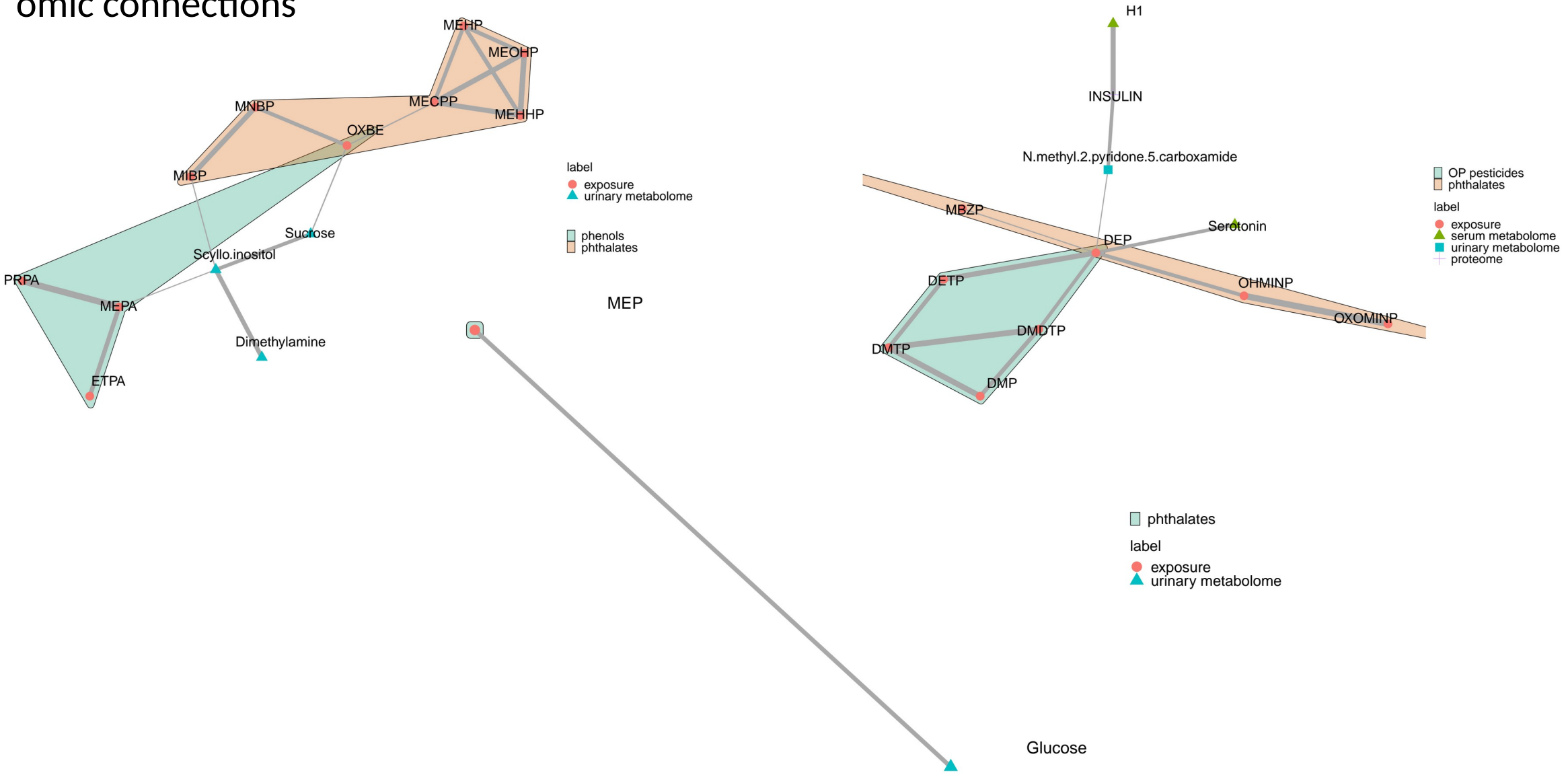
Results

- Graph merging led to the exclusion of the majority of exposure-omic connections. Notably, none of the protein-exposure associations were reproducible



Results

- The merged network consisted of 32 connected components, 3 of which included mixed exposure-omic connections



Conclusions

- We integrated Multi-Omic and exposure data from a child cohort using an integrative approach, and we identified associations reproducible across time points
- The association between **DEP** and **Serotonin** (ρ=0.09 for both time points) was reproducible. Exposure to Organophosphate pesticides has been linked to a variety of brain disorders [4], potentially through the serotonergic system

[4] Sarrouilhe D, Defamie N, Mesnil M. "Is the Exposome Involved in Brain Disorders through the Serotoninergic System?" (2021)

Conclusions

- In future work we plan to include **methylation** data
  - Large number of variables (also compared to dimension of other -omic layers)
    - Filtering CpG sites using agnostic **EWAS**: `beta_i ~ exposure_j + covariates` for all i's and j's (computationally expensive)
    - Controlling for multiple testing
    - Select *top* features
    - Perform analysis (i.e., GGMs) again
    - Interpretation of results