

➤ Hypothesis

To further understand the potential mechanisms by which the exposome could affect phenotype, we hypothesized that internal-omes (such as transcriptome, proteome and metabolome) are an important class of molecules that are involved/mediated in the exposome-phenotype interactions.

› Datasets



Exposome

Indoor air, outdoor
exposures and chemicals

Internal-ome

Transcriptome, Proteome,
Serum/urine metabolome

Phenotype

Intelligence quotient,
Neuro behavior, BMI

➤ Motivations and analysis strategy



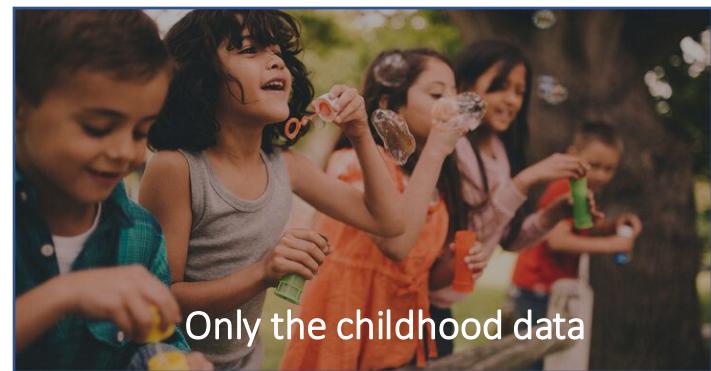
1. Exposome affect the health outcomes (phenotypes).

Internal-ome
(Transcriptome, Proteome,
Serum/urine metabolome)

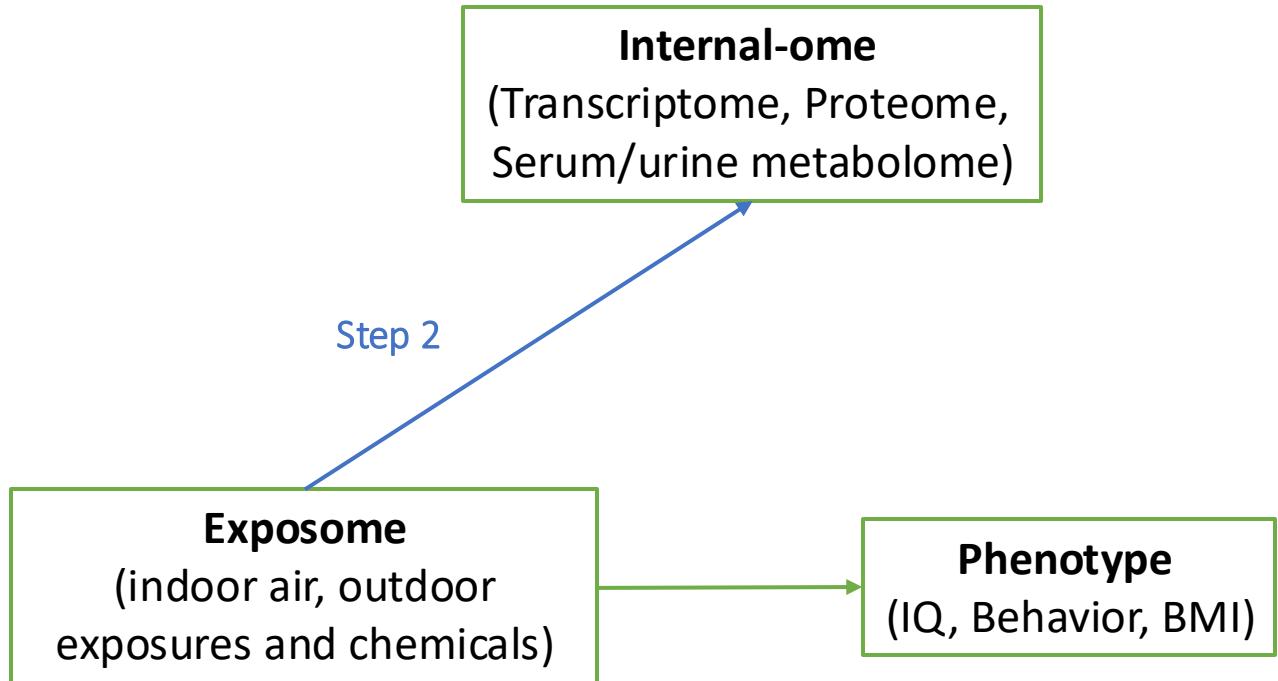


<https://www.betterplace.org/>

› Motivations and analysis strategy

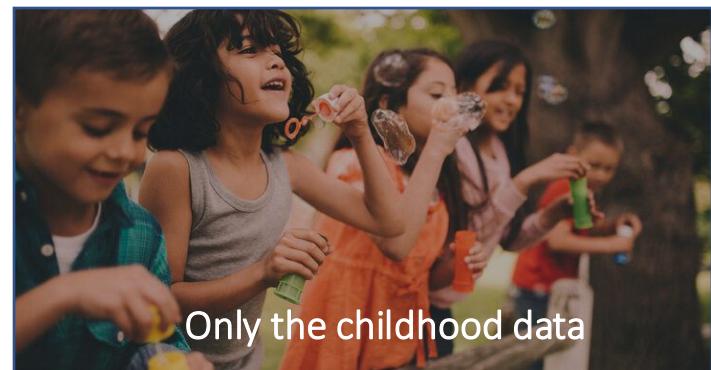


1. Exposome affect the health outcomes (phenotypes).
2. Exposome affect Internal-ome (transcriptome, proteome, metabolome).



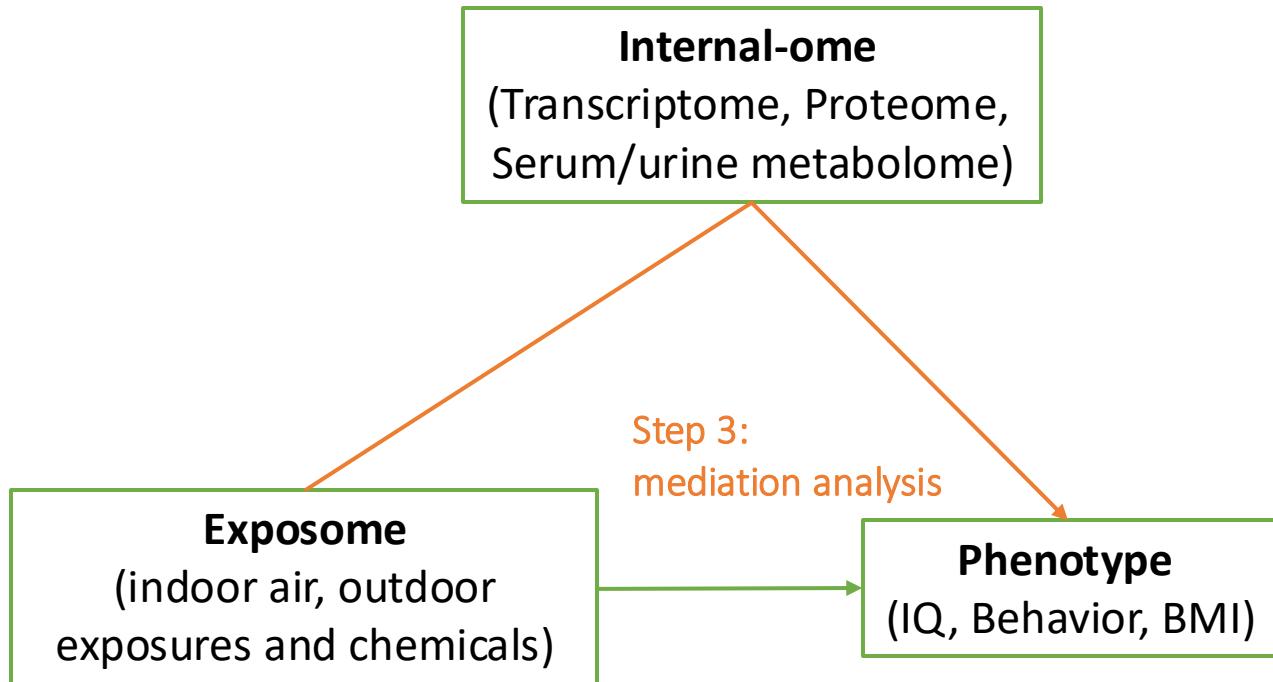
<https://www.betterplace.org/>

› Motivations and analysis strategy



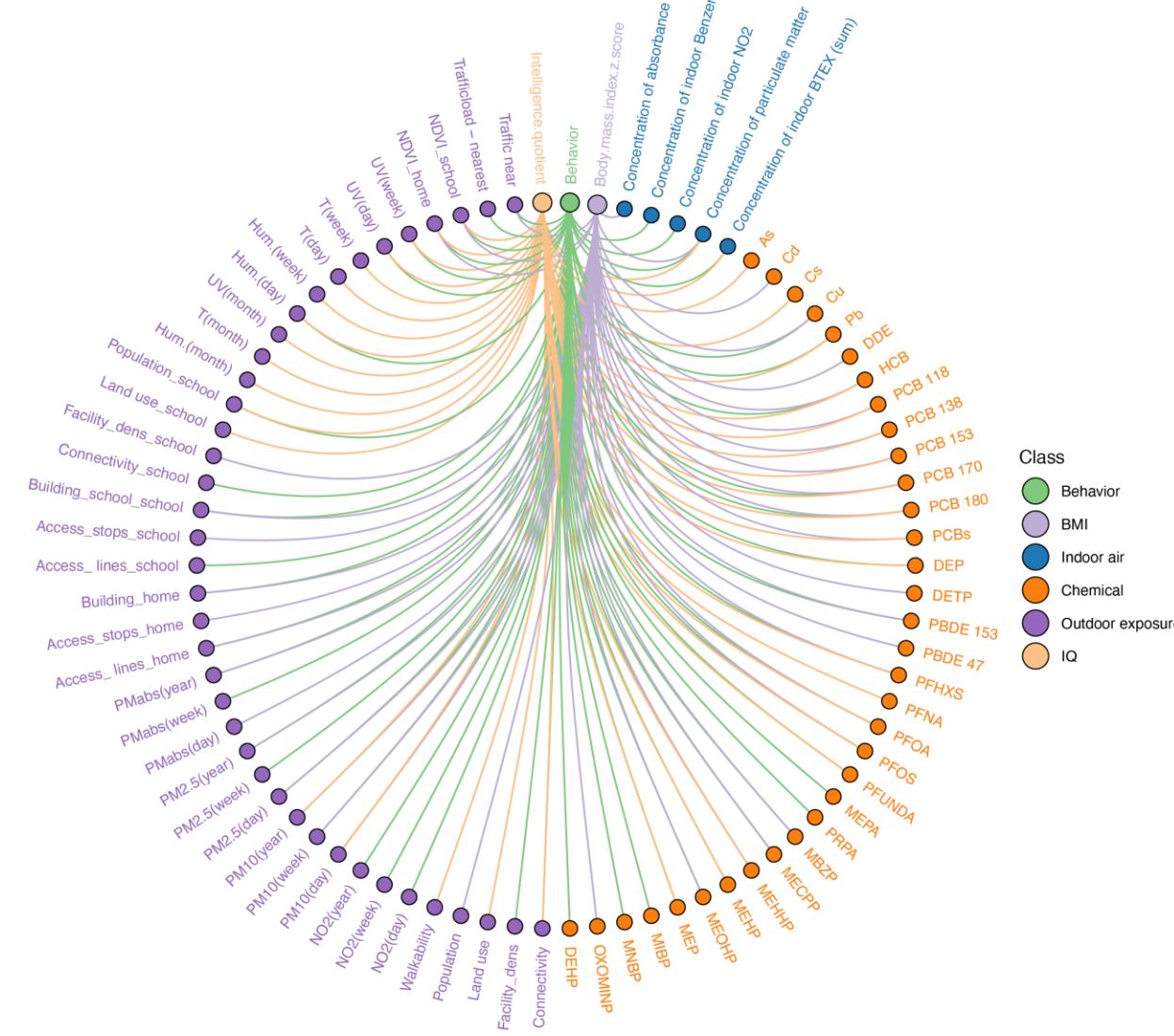
Only the childhood data

1. Exposome affect the health outcomes (phenotypes).
2. Exposome affect Internal-ome (transcriptome, proteome, metabolome).
3. Exposome affect the phenotype via internal-ome (mediation analysis).



<https://www.betterplace.org/>

➤ Exposome are associated with phenotypes



Linear mixed model to find the association between exposome and phenotype
(Child sex, Year of birth, Mother BMI, Gestational age at birth, Maternal age, child height, child weight, birth weight as covariates)

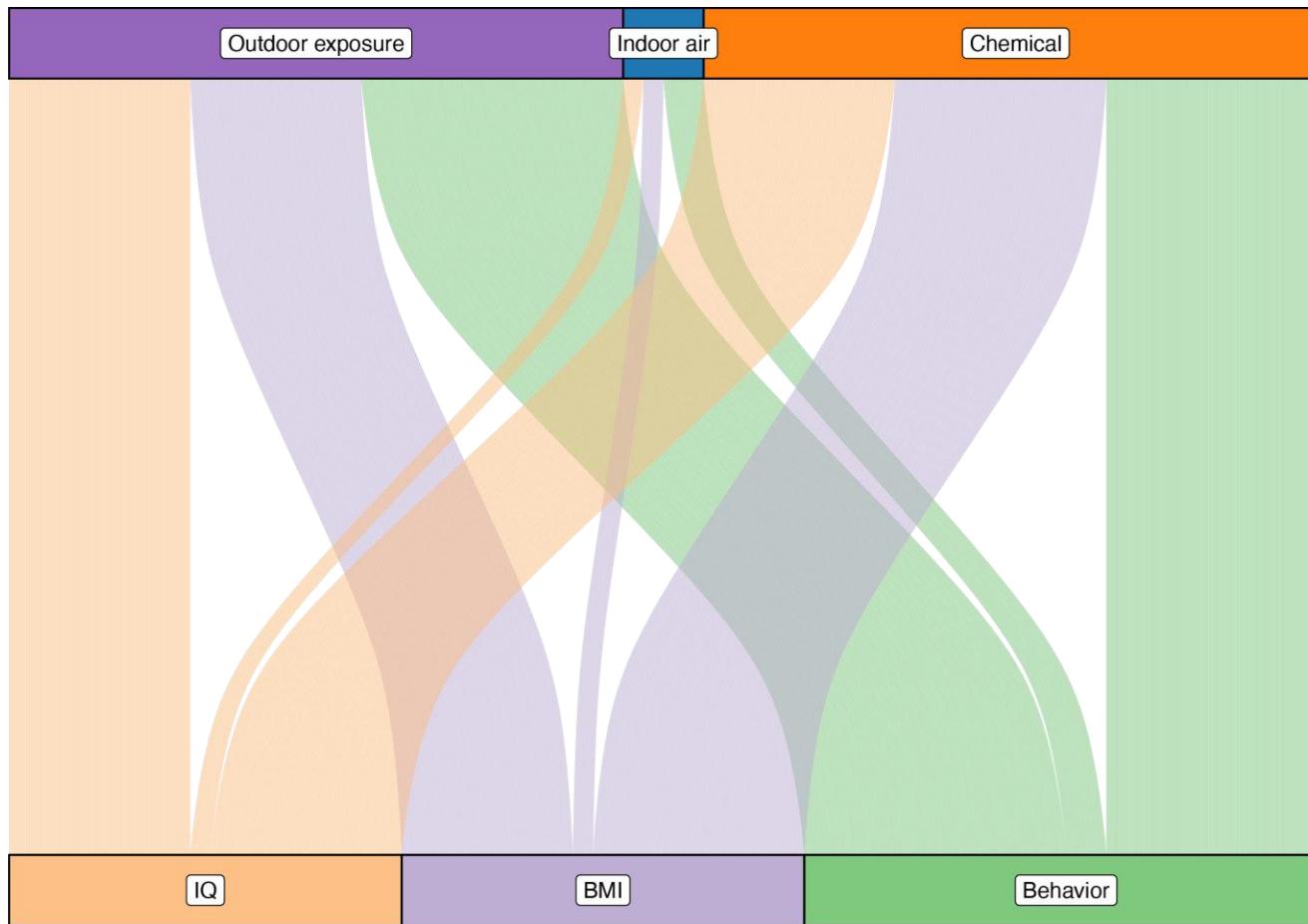
Summary

131 associations in total involving **3 phenotypes** and **79 exposome** features that were significant at $p.\text{adjust} < 0.05$ (BH).

➤ Exposome are associated with phenotypes

Association Distribution

Exposome (Outdoor exposure, indoor air, chemical)



Phenotype (IQ, BMI, Behavior)

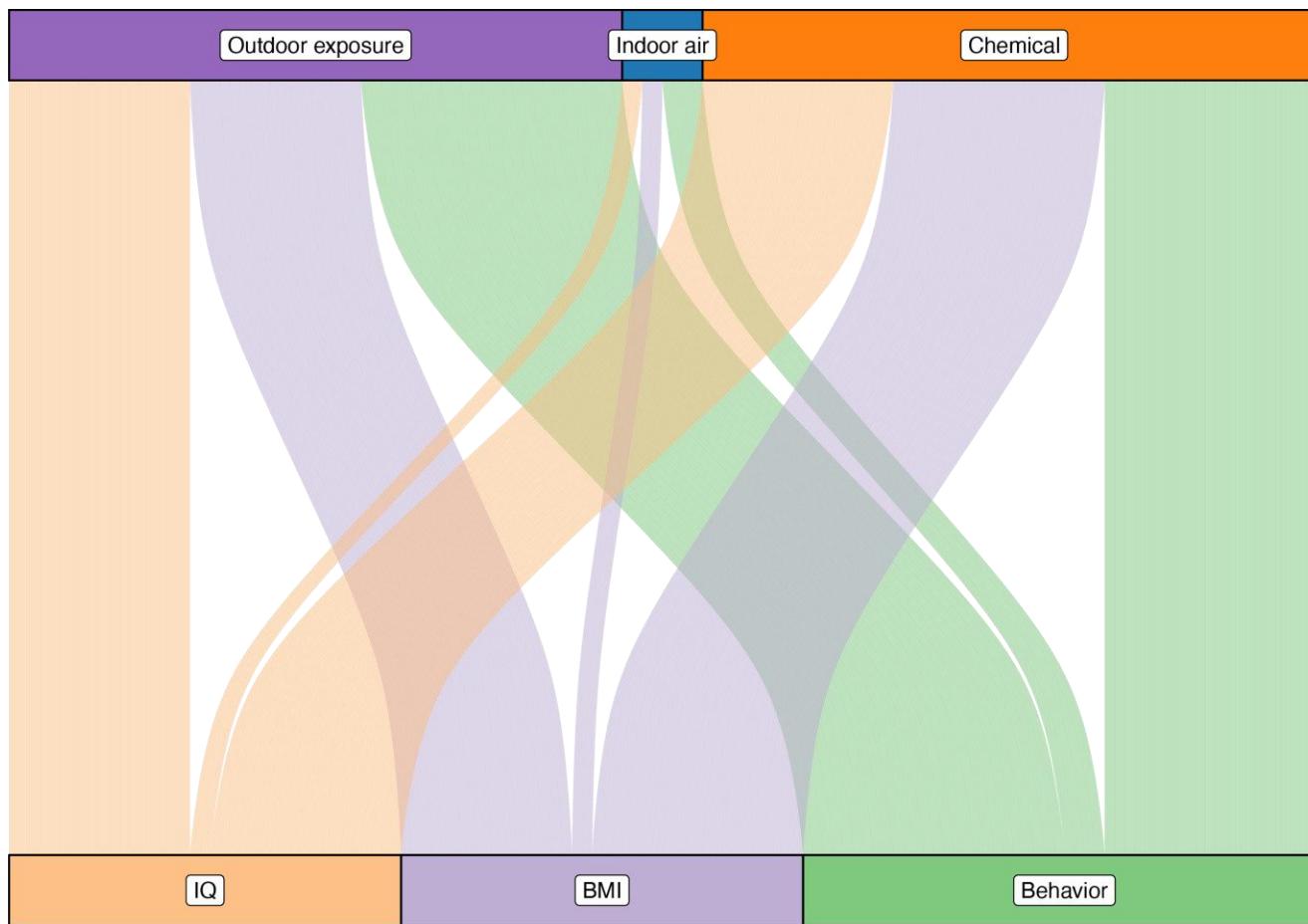
Most of the associations are from **outdoor exposures and chemicals**.

Phenotypes, IQ, BMI and Behavior have very similar number of associations with exposome.

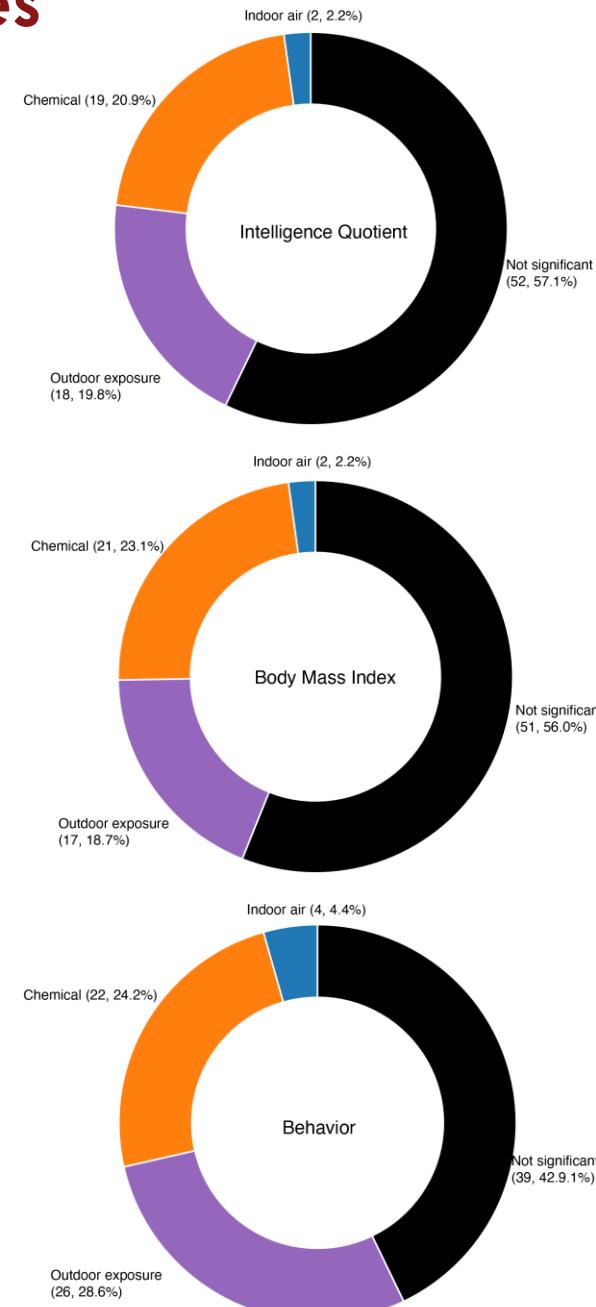
➤ Exposome are associated with phenotypes

Association Distribution

Exposome (Outdoor exposure, indoor air, chemical)



Phenotype (IQ, BMI, Behavior)



Intelligence quotient (IQ):
39 exposome features

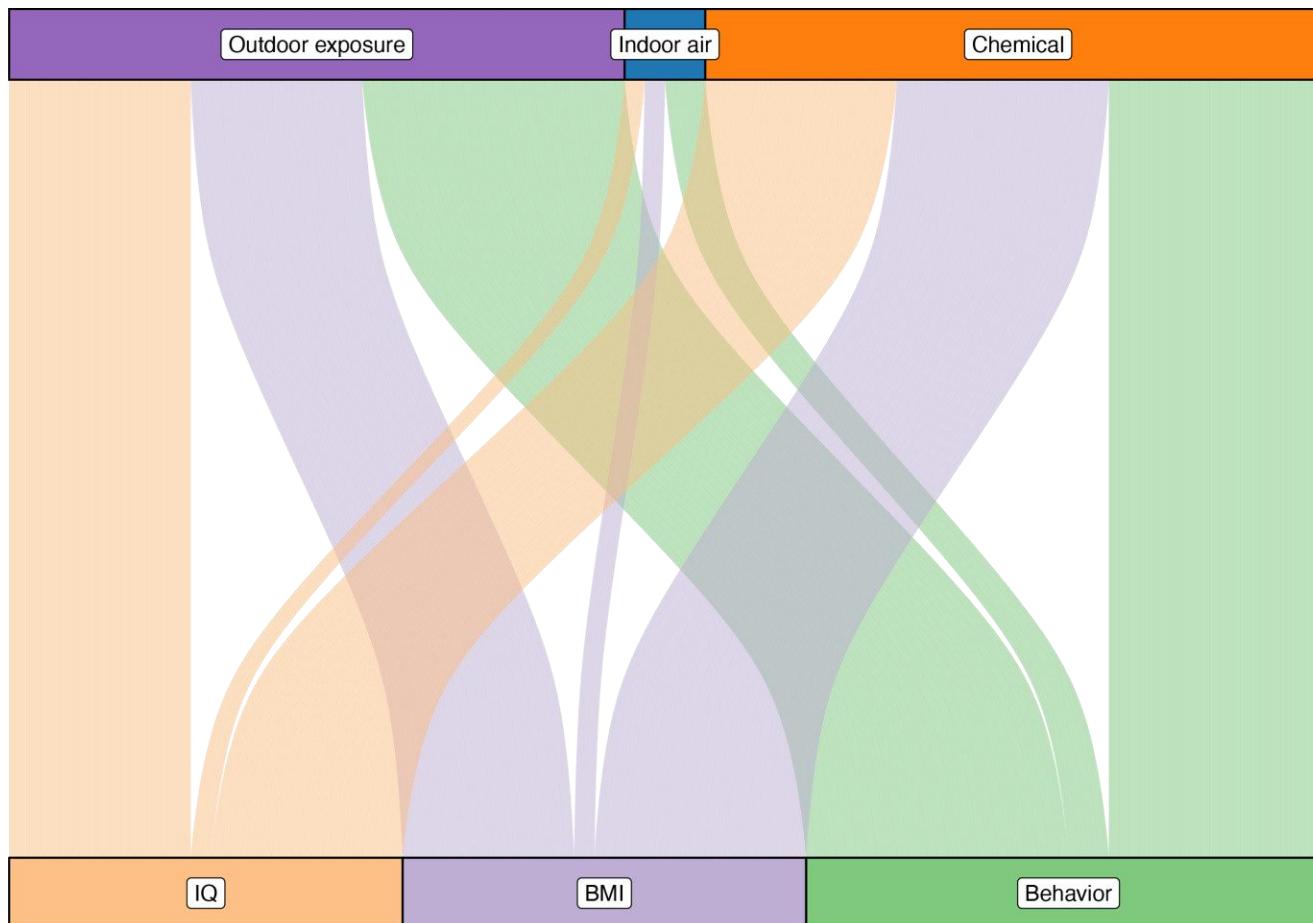
Body mass index (BMI):
40 exposome features

Behavior:
52 exposome features

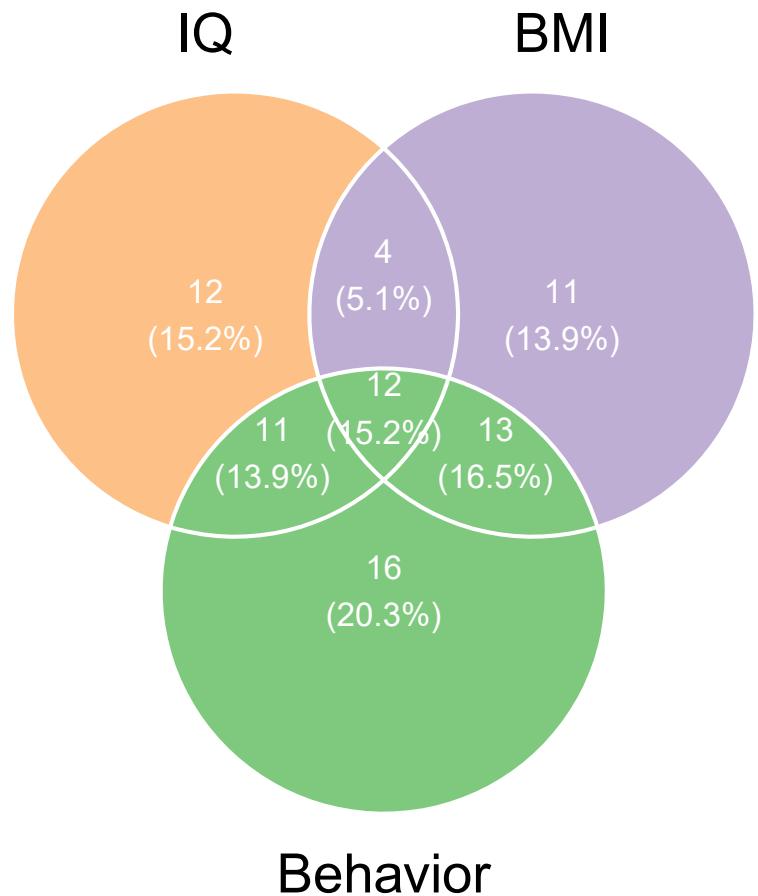
➤ Exposome are associated with phenotypes

Association Distribution

Exposome (Outdoor exposure, indoor air, chemical)



Phenotype (IQ, BMI, Behavior)



Overlap between IQ, BMI and behavior's associations with the exposome **are modest (< 50%)**.

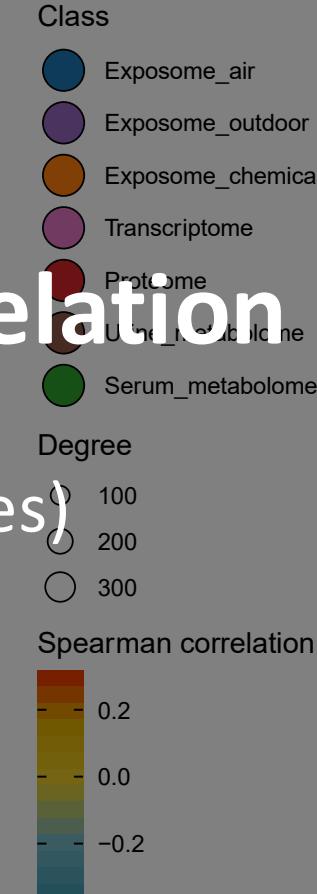
➤ Exposome are associated with phenotypes

Exposome has significant associations with phenotypes

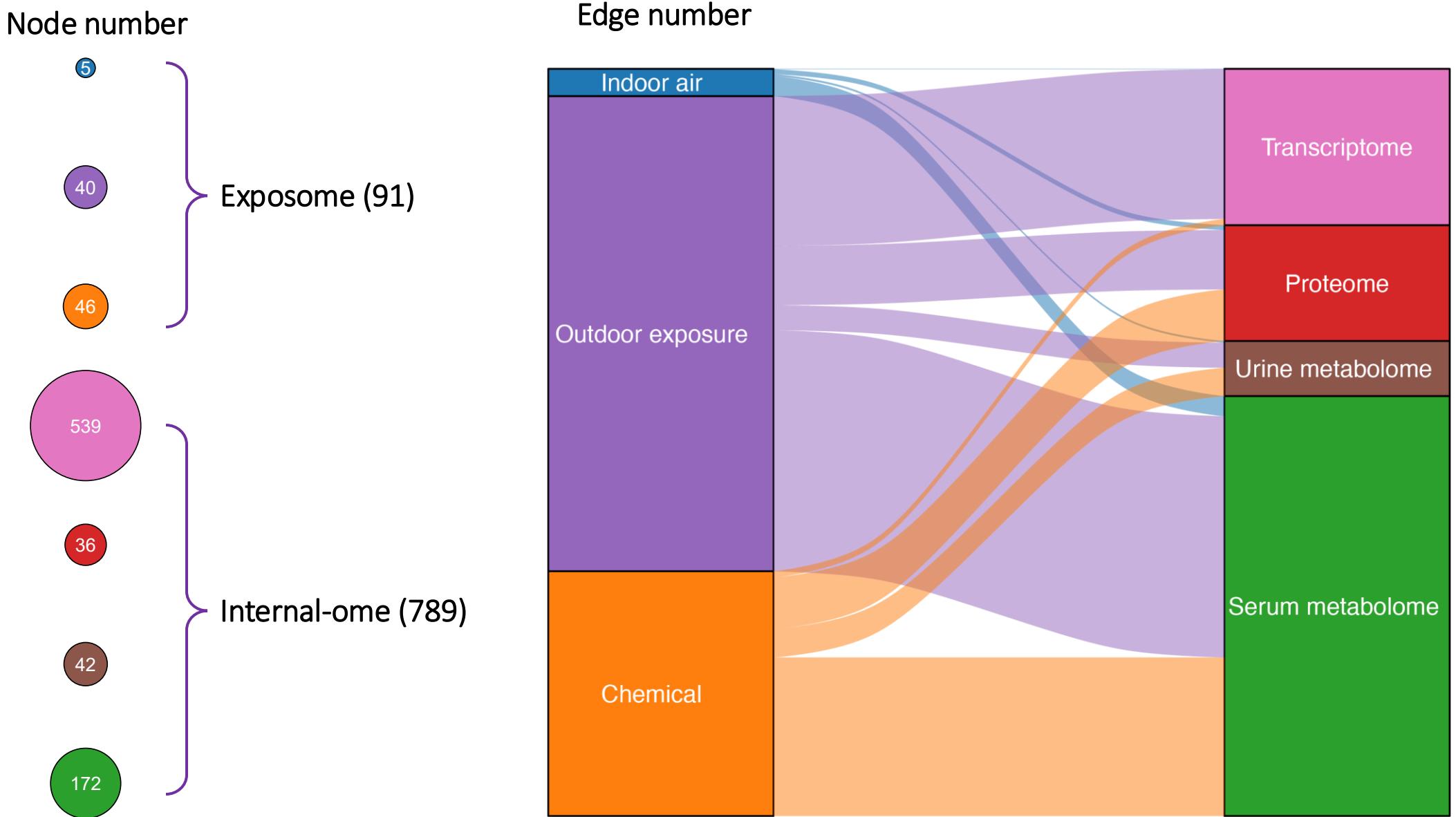
71 out of 110 (64.5%) measured exposome features have significant associations with at least one phenotype.

➤ Exposome are associated with internal-omics data

Exposome-internal-ome correlation network
(880 nodes, 7358 edges)

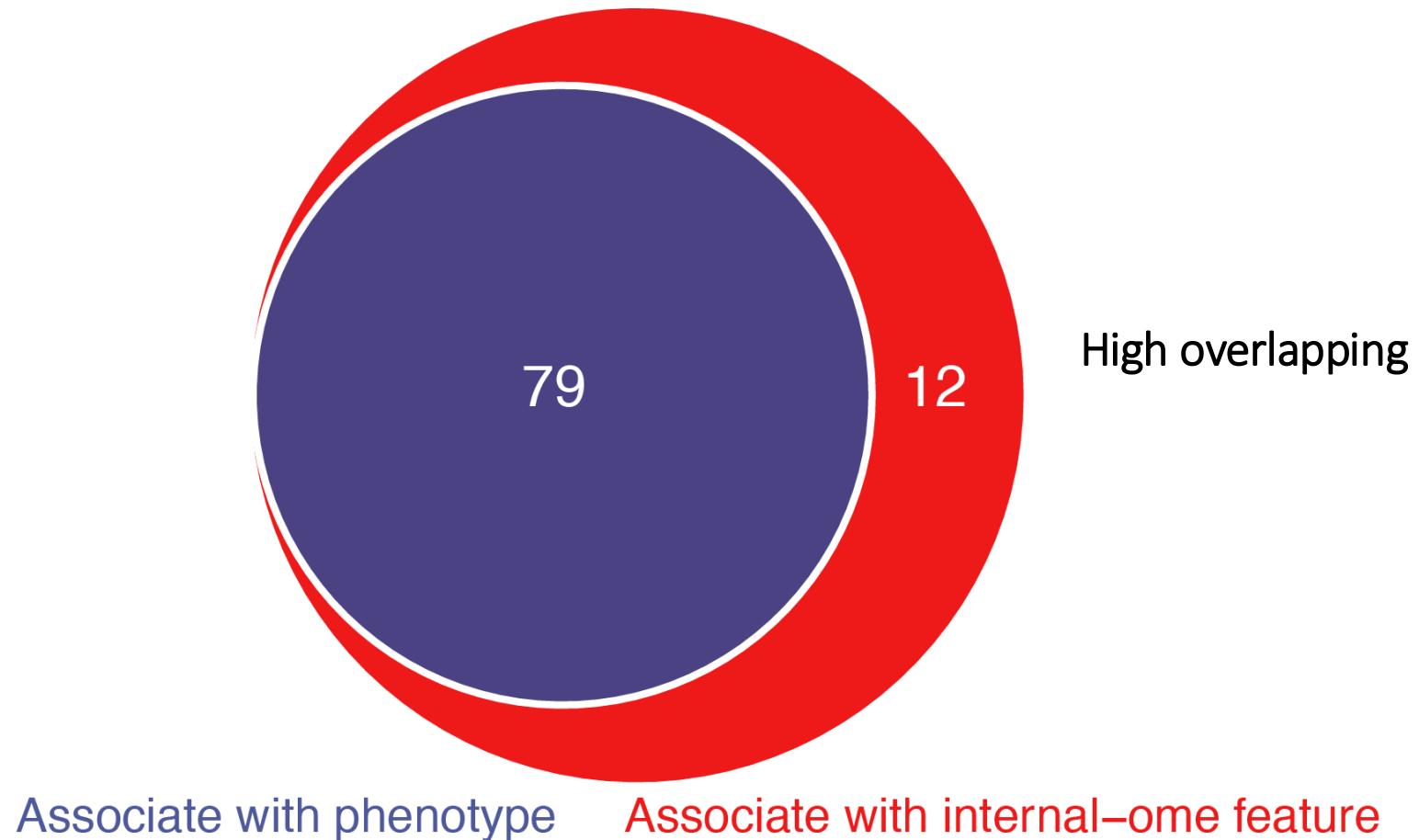


➤ Exposome are associated with internal-omics data



➤ Exposome contributes to phenotypic changes through internal-ome

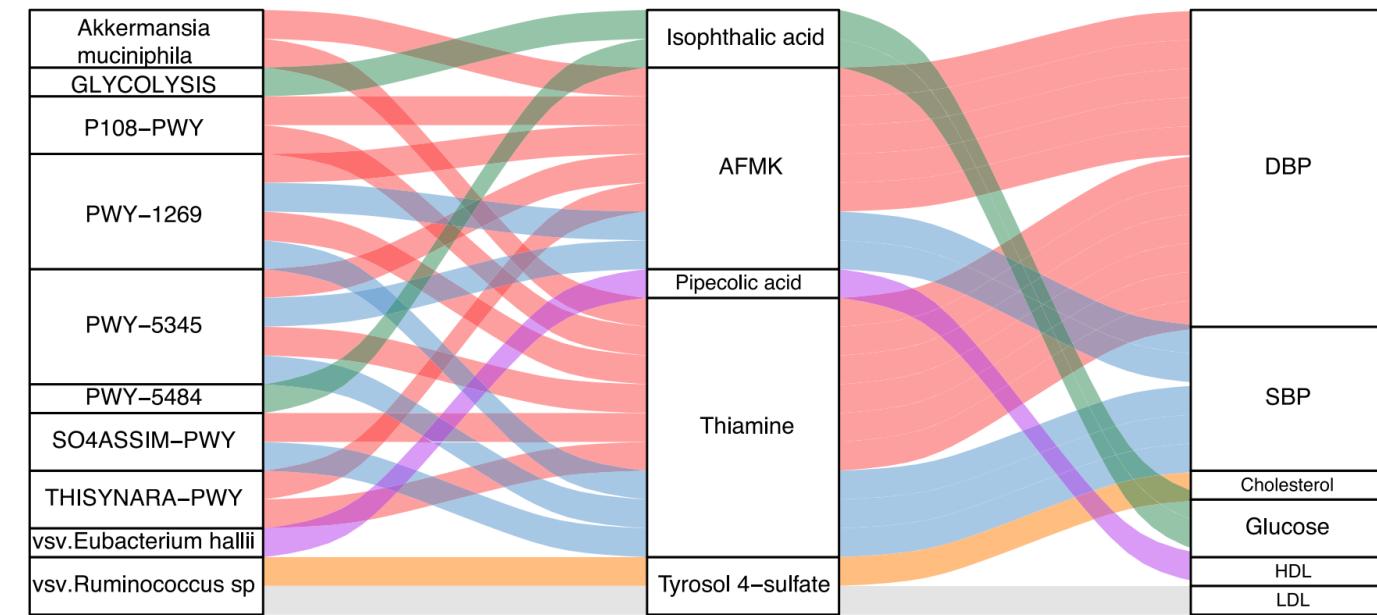
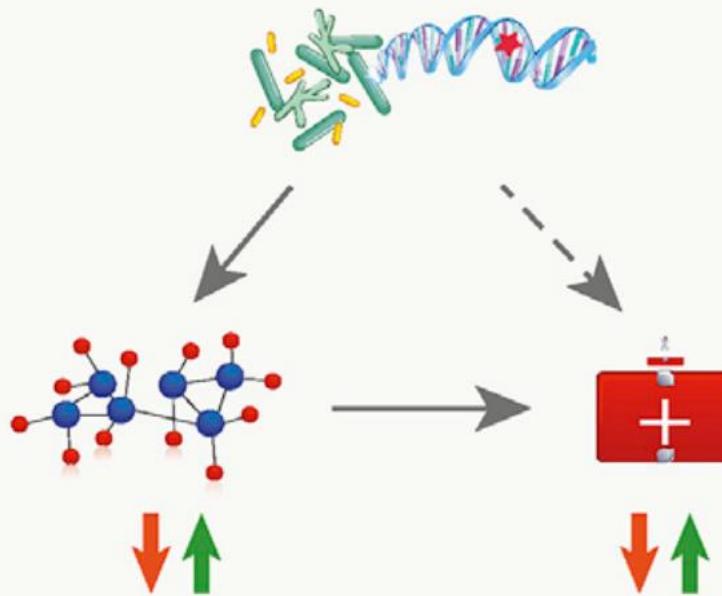
1. 79 out of 110 exposome features are associated with phenotypes.
2. 91 out of 110 exposome features are associated with internal-ome features.



➤ Exposome contributes to phenotypic changes through internal-ome

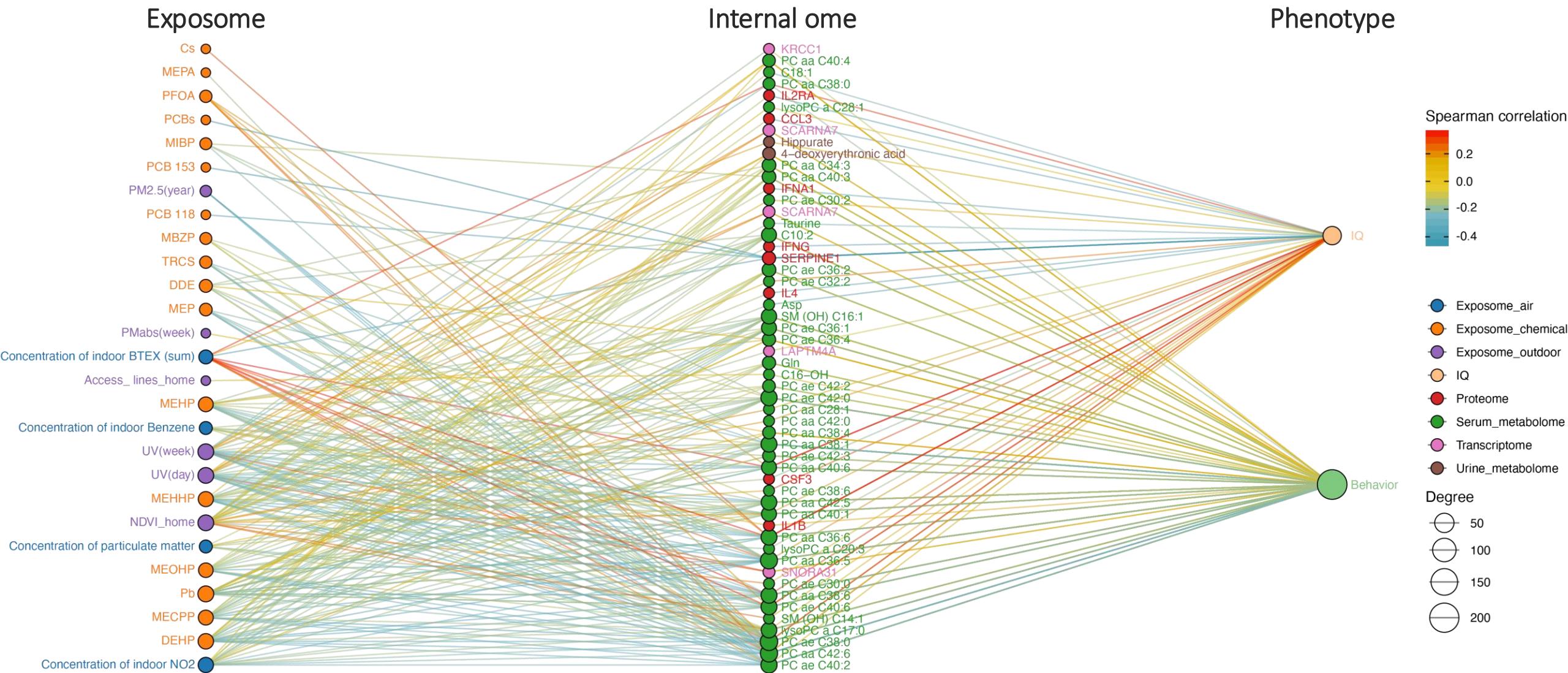
To evaluate whether internal-ome features can mediate the exposome impact on phenotypes, we applied **bi-directional mediation analysis**.

Microbial impacts on host phenotypes are mediated by metabolites



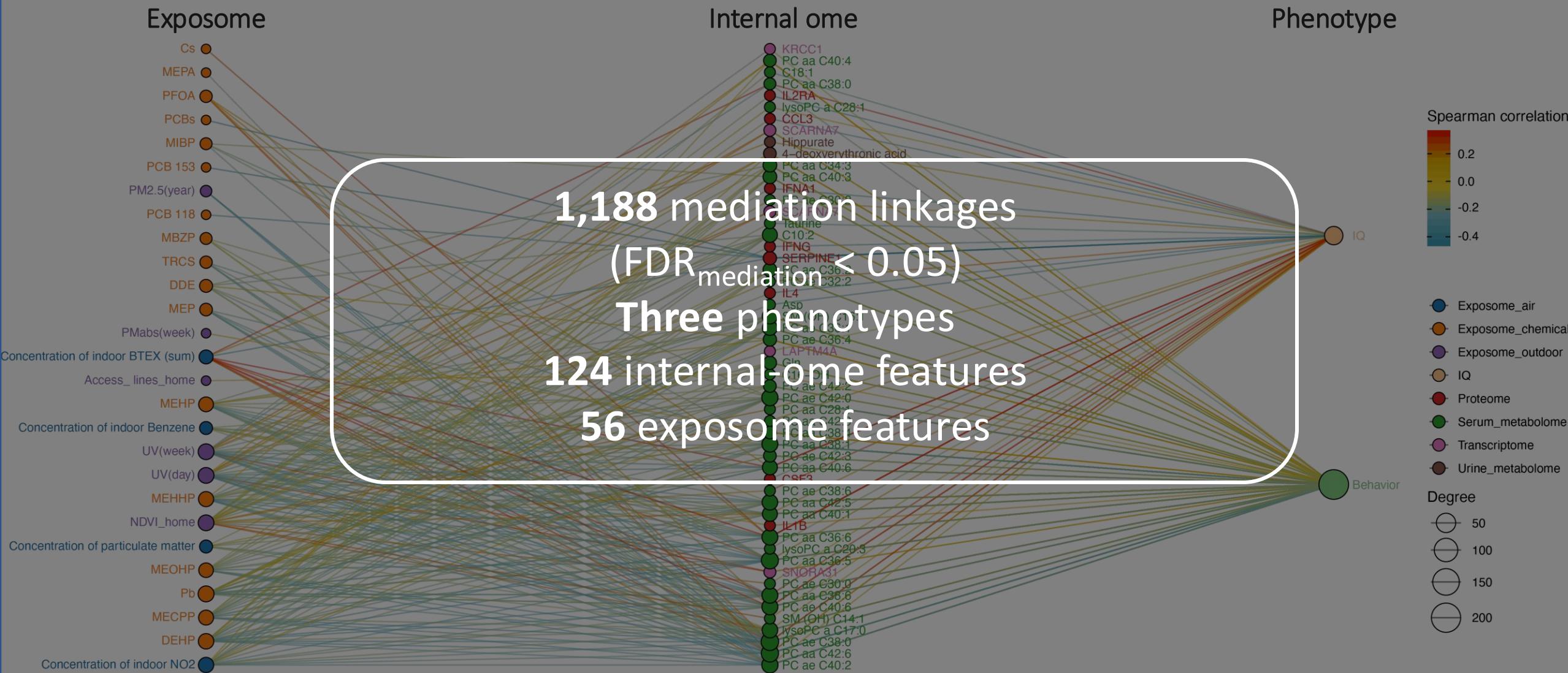
Chen et al., 2021, Cell 184, 1–14

➤ Exposome contributes to phenotypic changes through internal-ome



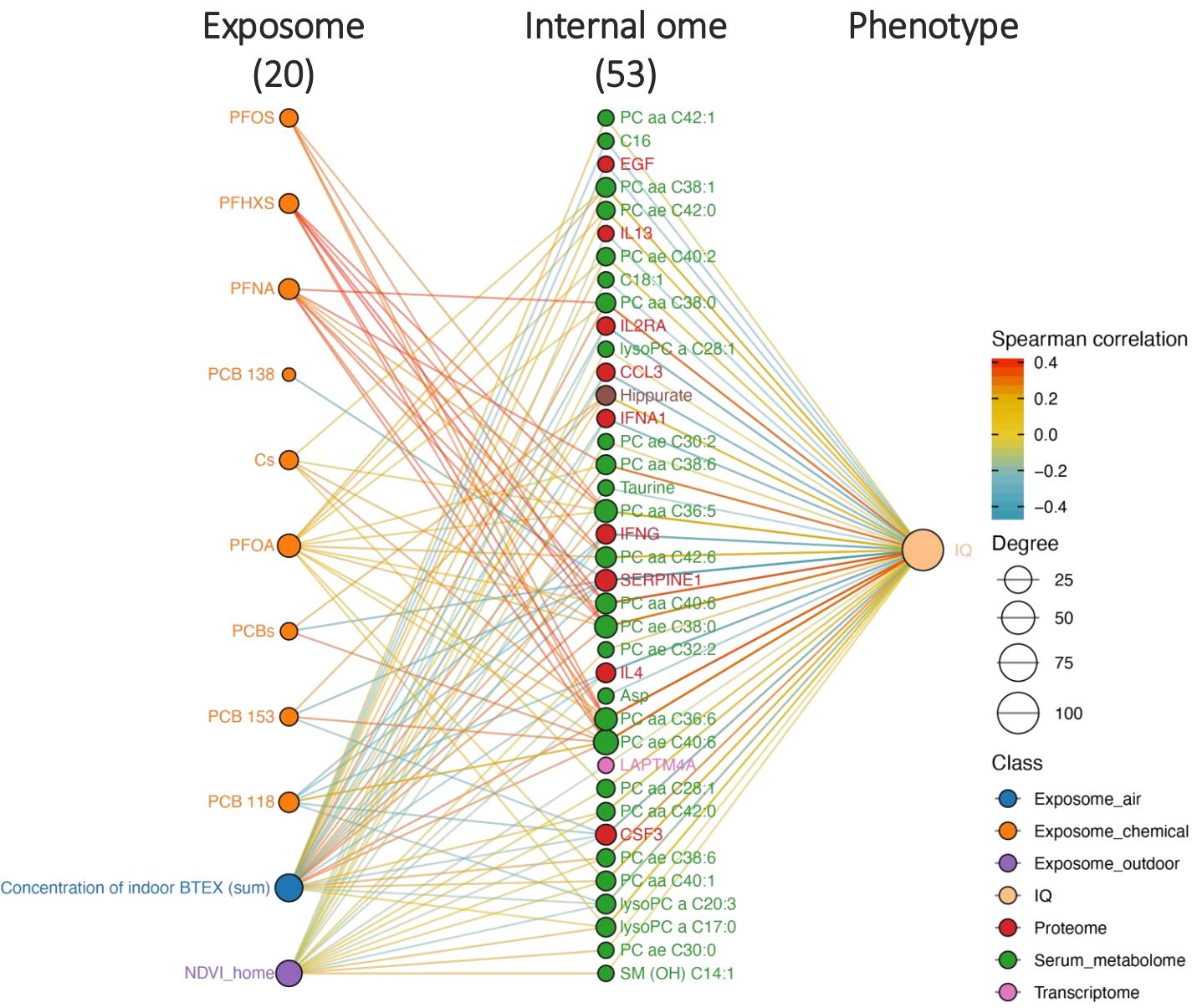
Example network illustration: Top 250 average causal mediation effects (ACME)

➤ Exposome contributes to phenotypic changes through internal-ome



Example network illustration: Top 250 average causal mediation effects (ACME)

➤ Exposome contributes to IQ changes through internal-ome

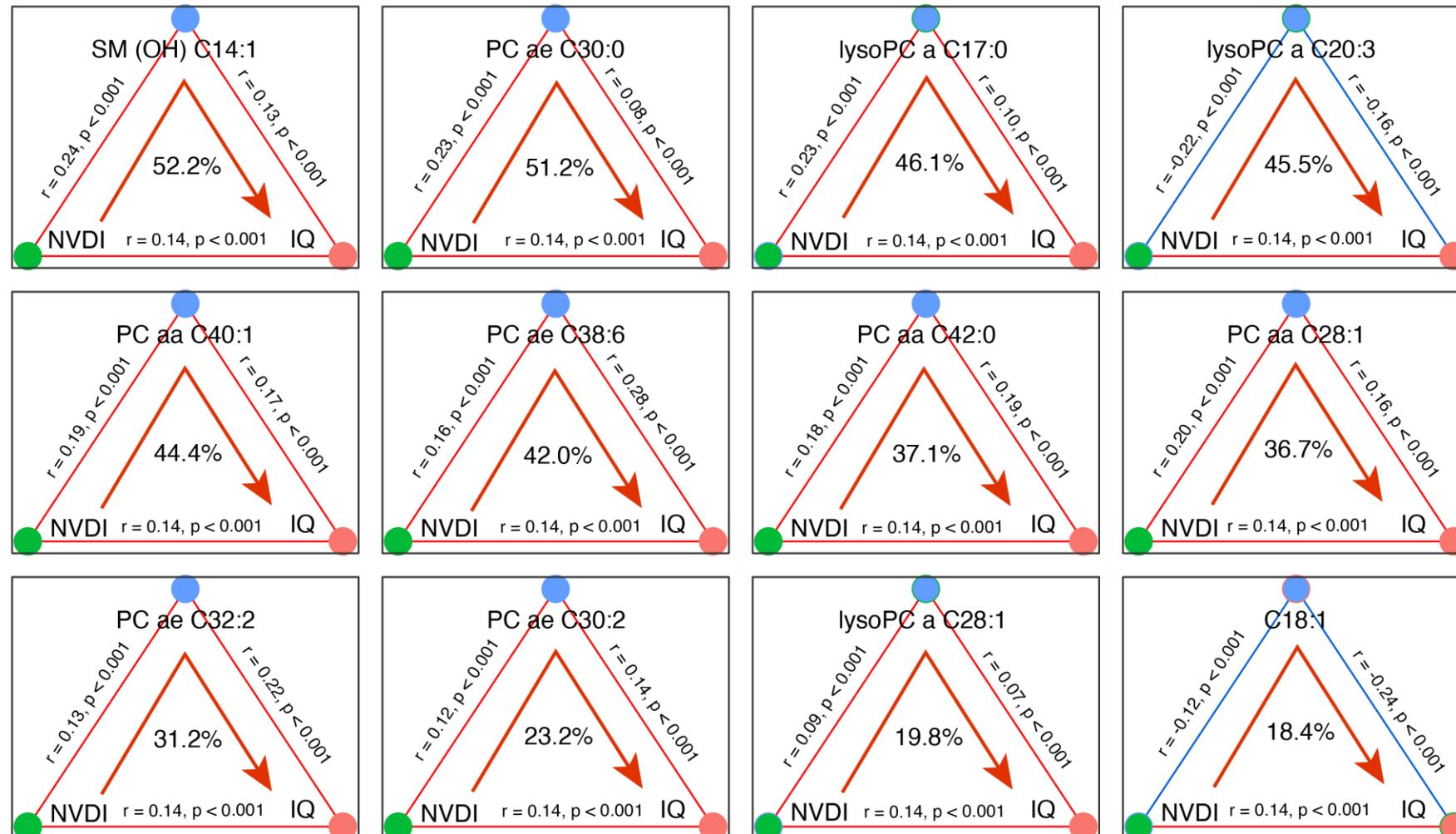


Almost of 25 out of 26 lipids from serum are positively associated with children IQ which has been well documented.

NVDI (normalized difference vegetation index) is positively associated with IQ for urban kids. But the mechanism is not clear.

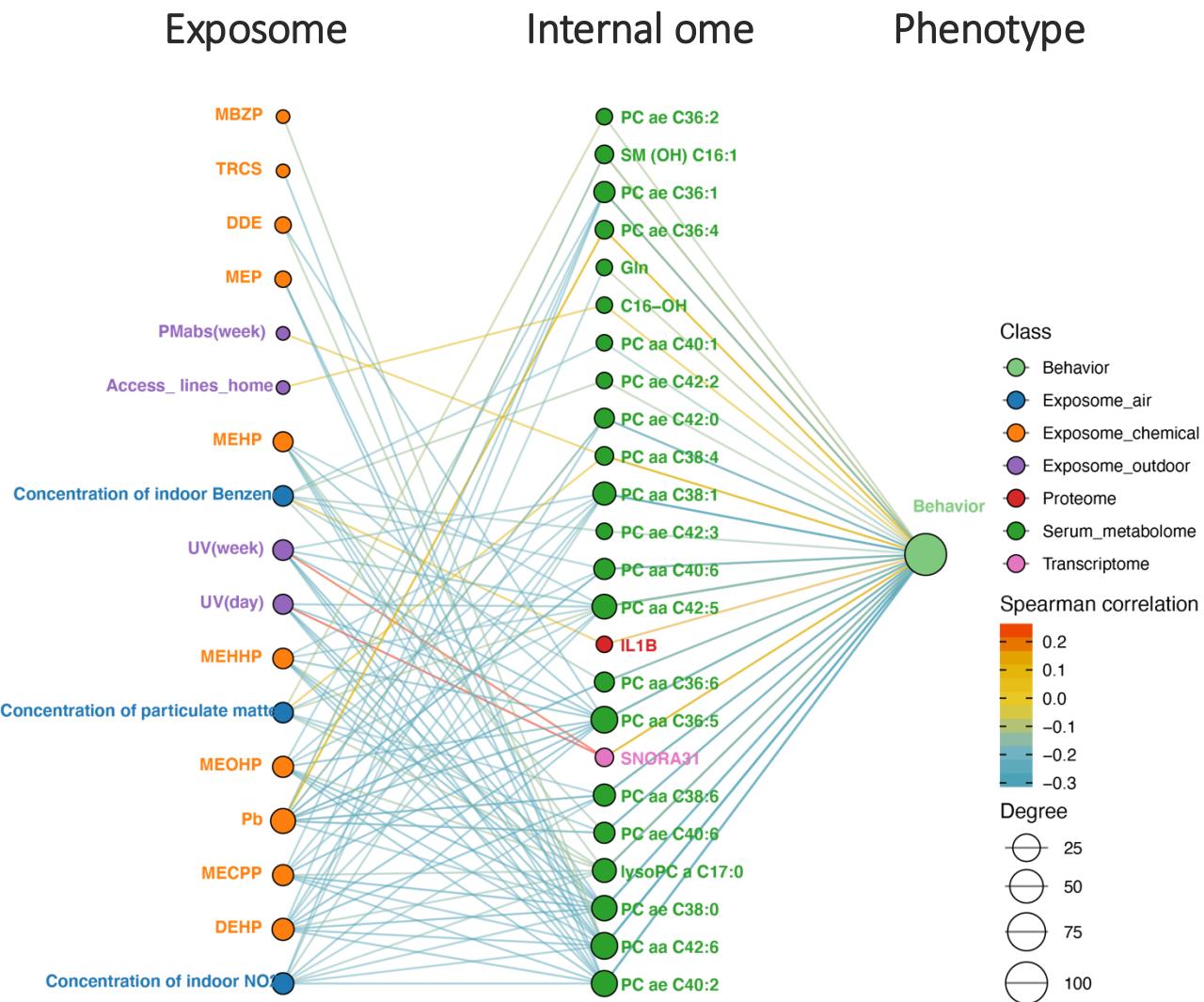
Uauy et al. 2003, JN.
Bijnens et al., 2020, PLOS Medicine.

➤ Exposome contributes to IQ changes through internal-ome



NVDI (normalized difference vegetation index) positively affect IQ via lipids (PC, lysoPC and SM. 34%).

➤ Exposome contributes to Behavior changes through internal-ome



Blood Pb concentrations, even at mean levels of 6.4 µg/dL, were associated with increased risk of behavioral problems in preschool children, including internalizing and pervasive developmental problems.

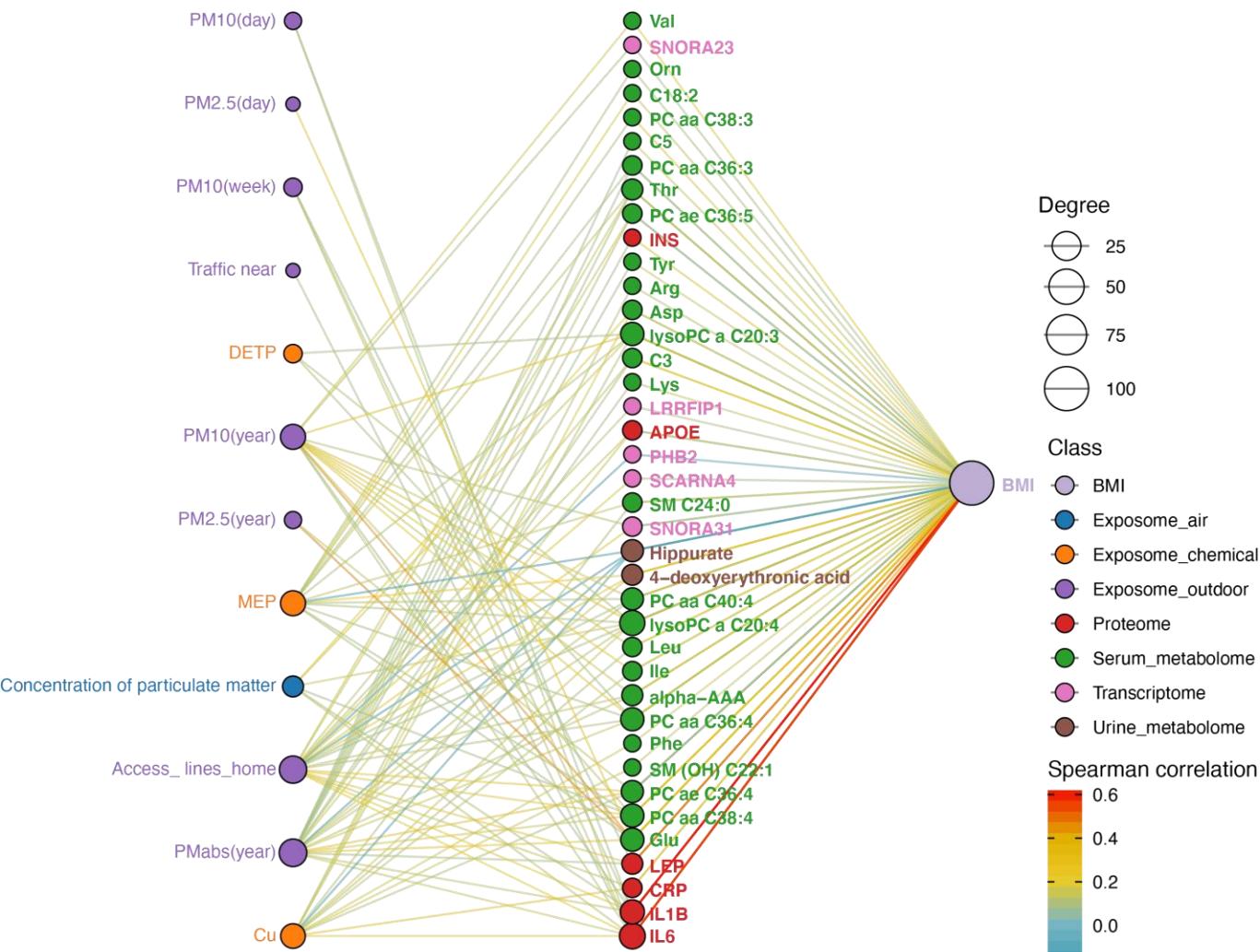
Liu et al., 2014

Several studies suggested that phthalate exposure may increase behavioral problems in childhood.

Braun et al., 2014

➤ Exposome contributes to BMI changes through internal-ome

Exposome Internal ome Phenotype



A study found an inverse association between the daily PM_{10} exposure and the DNA methylation of inflammatory genes, measured in peripheral blood of healthy overweight/obese subjects.

Cantone et al., 2017

Significant associations were found between the highest quartile of copper concentrations in blood with obesity status ($\text{OR} = 9.27$, 95% CI: 5.43, 15.82, pfor trend < 0.001) and cholesterol ($\text{OR} = 3.08$, 95% CI: 1.43, 6.63, pfor trend < 0.001).

Fan et al., 2017

➤ Summary

- ❖ The exposome is associated with internal –omes and further associated with phenotypes
- ❖ Internal –omes mediated the interactions of exposome and phenotypes