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Decoding links between the exposome and health outcomes by multi-omics analysis

Xiaotao Shen PhD

Peng Gao PhD, Allision Zhang PhD

Stanford School of Medicine
Department of Genetics

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shenxt@stanford.edu

@JasperShen1990

shenxt.me

github.com/jaspershen

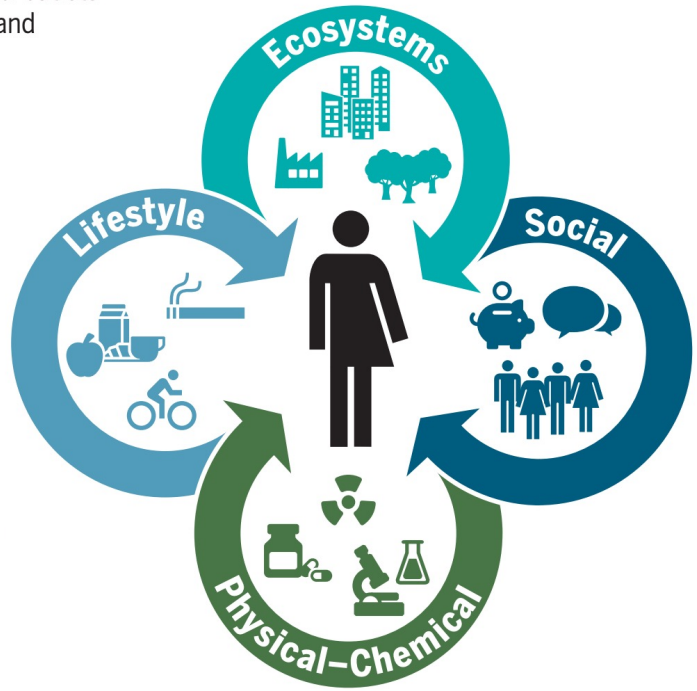
Exposome affects human health outcome

Exposome x Genome = Health outcome (Phenotype)

Ecosystems
Food outlets, alcohol outlets
Built environment and urban land uses
Population density
Walkability
Green/blue space

Lifestyle
Physical activity
Sleep behavior
Diet
Drug use
Smoking
Alcohol use

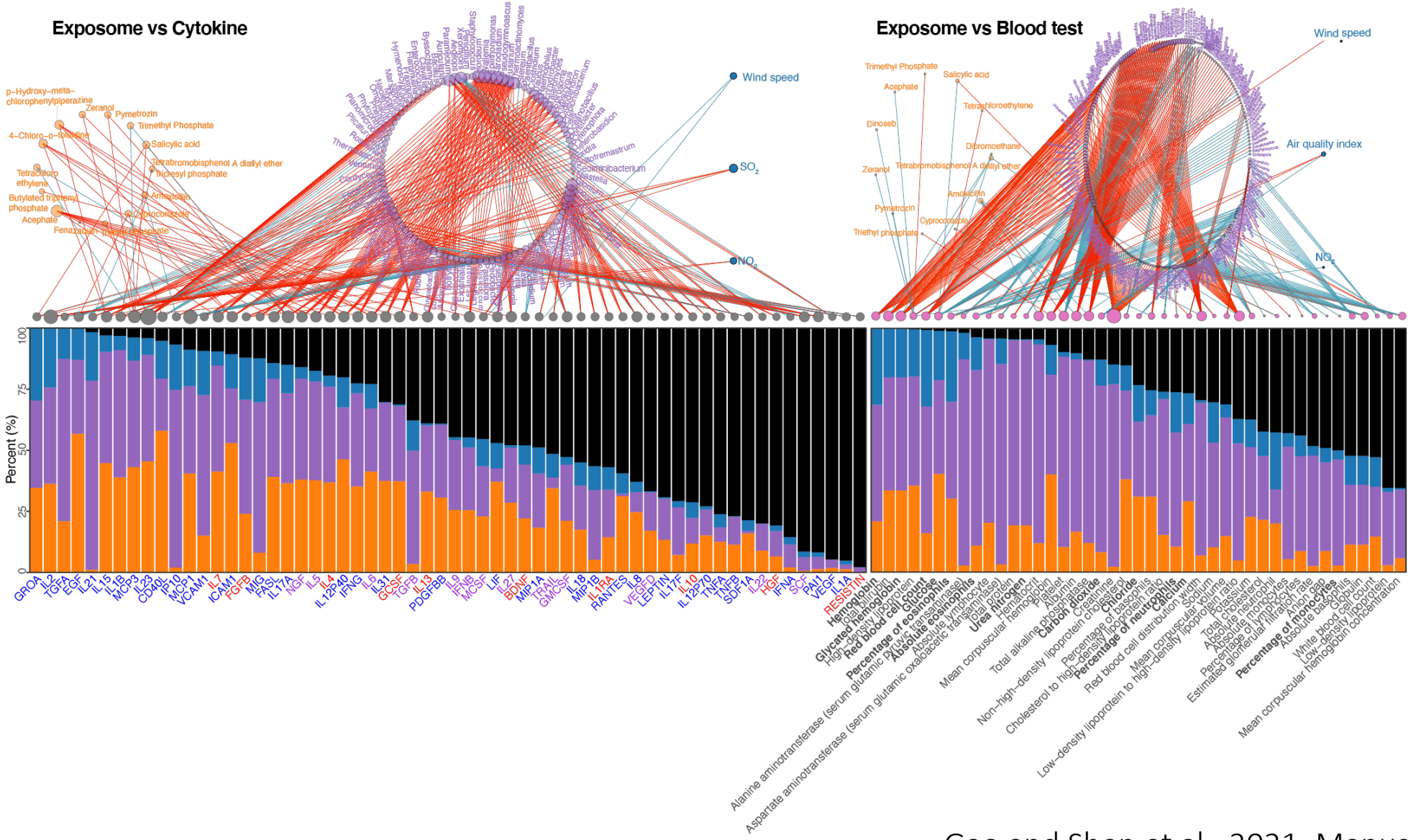
Social
Household income
Inequality
Social capital
Social networks
Cultural norms
Cultural capital
Psychological and mental stress



Physical–Chemical
Temperature/humidity
Electromagnetic fields
Ambient light
Odor and noise
Point, line sources, e.g, factories, ports
Outdoor and indoor air pollution
Agricultural activities, livestock
Pollen/mold/fungus
Pesticides
Fragrance products
Flame retardants (PBDEs)
Persistent organic pollutants
Plastic and plasticizers
Food contaminants
Soil contaminants
Drinking water contamination
Groundwater contamination
Surface water contamination
Occupational exposures

Vermeulen et al., 2020, Science

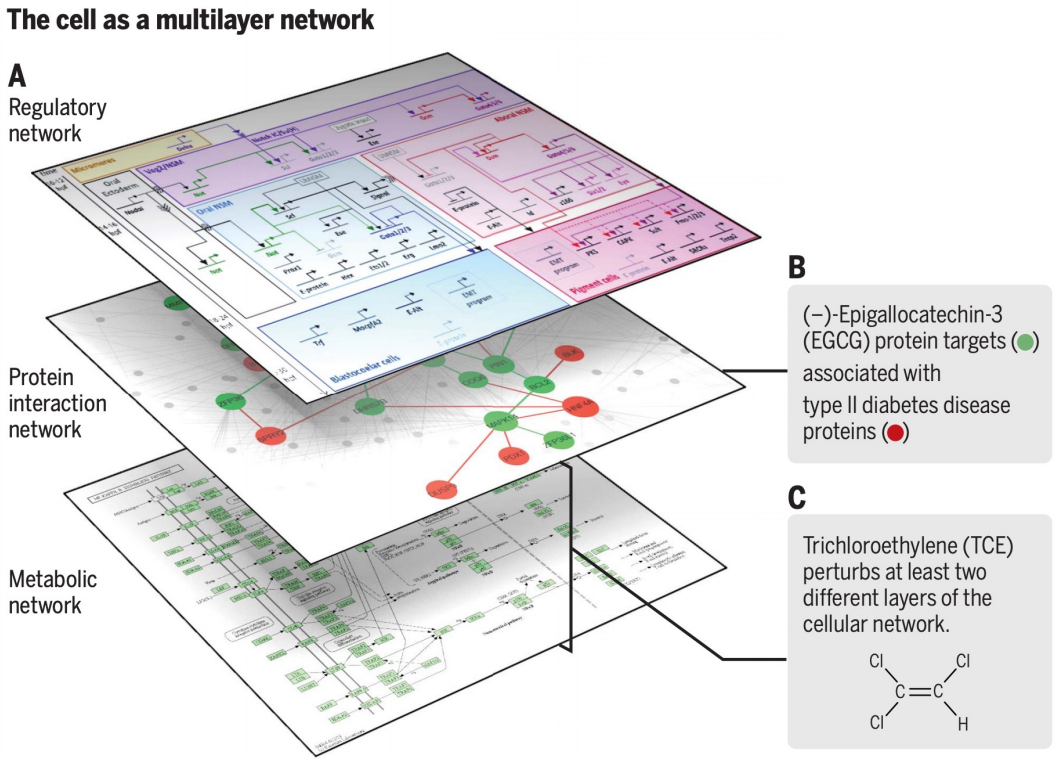
Exposome affect on cytokines and blood tests



Gao and Shen et al., 2021, Manuscript Submitted

Challenges in exposome research

"The challenge in understanding the role of the exposome on our health lies not only in the large number of chemical exposures in our daily lives, but also in the complex ways that they interact with cells (or body)."



Vermeulen et al., 2020, Science

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

https://www.betterplace.org/

Only the childhood data

Motivations and analysis strategy

1. Exposome affect the health outcomes (phenotypes).

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

Exposome
(indoor air, outdoor exposures and chemicals)

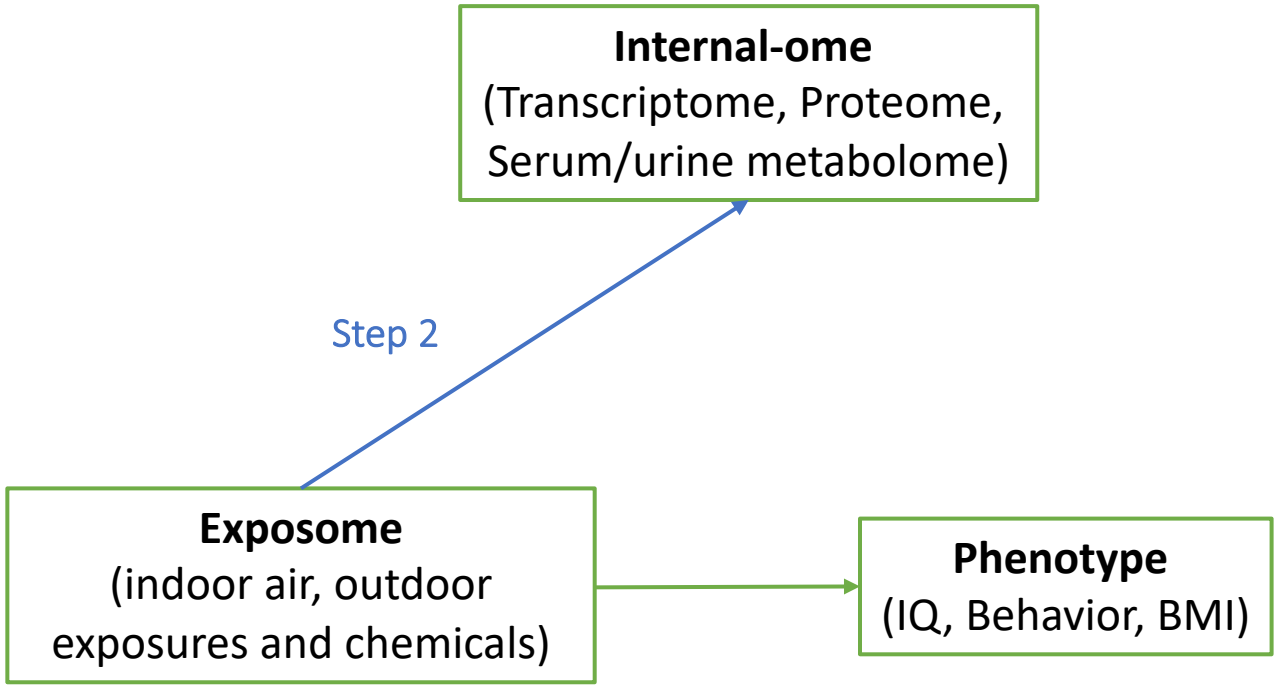
Step 1

Phenotype
(IQ, Behavior, BMI)

https://www.betterplace.org/

Motivations and analysis strategy

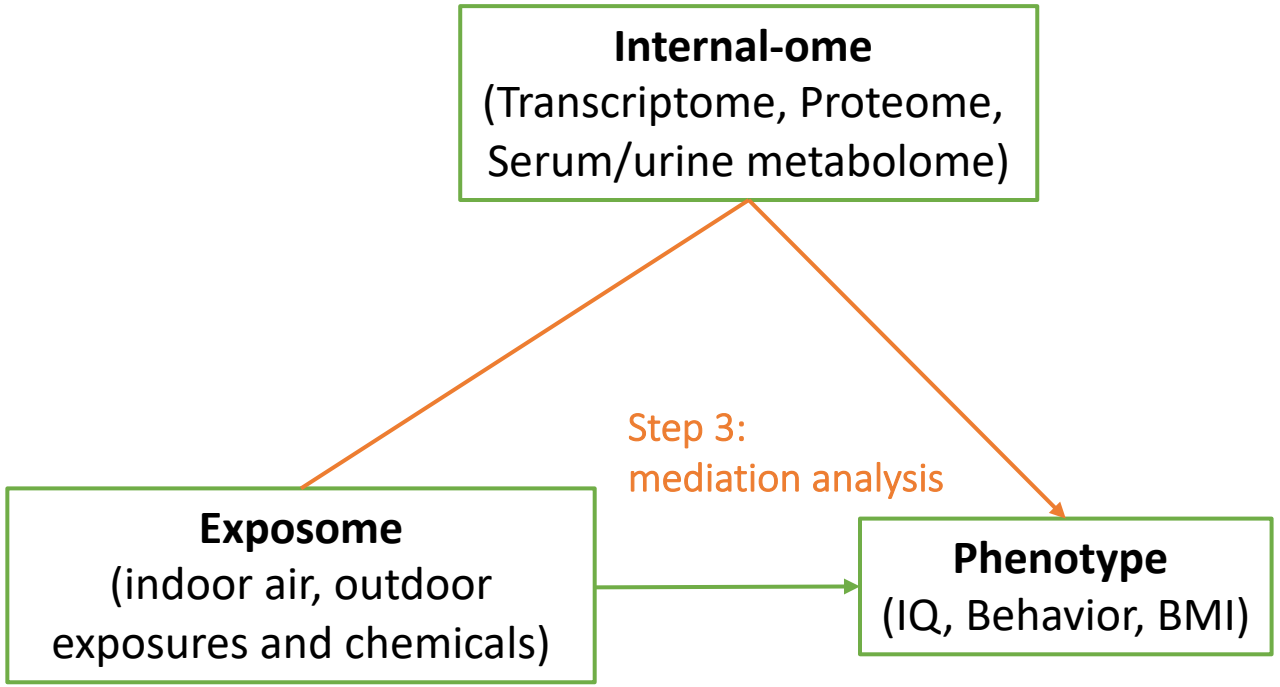
1. **Exposome** affect the **health outcomes (phenotypes).**
2. **Exposome** affect **Internal-ome** (transcriptome, proteome, metabolome).



https://www.betterplace.org/

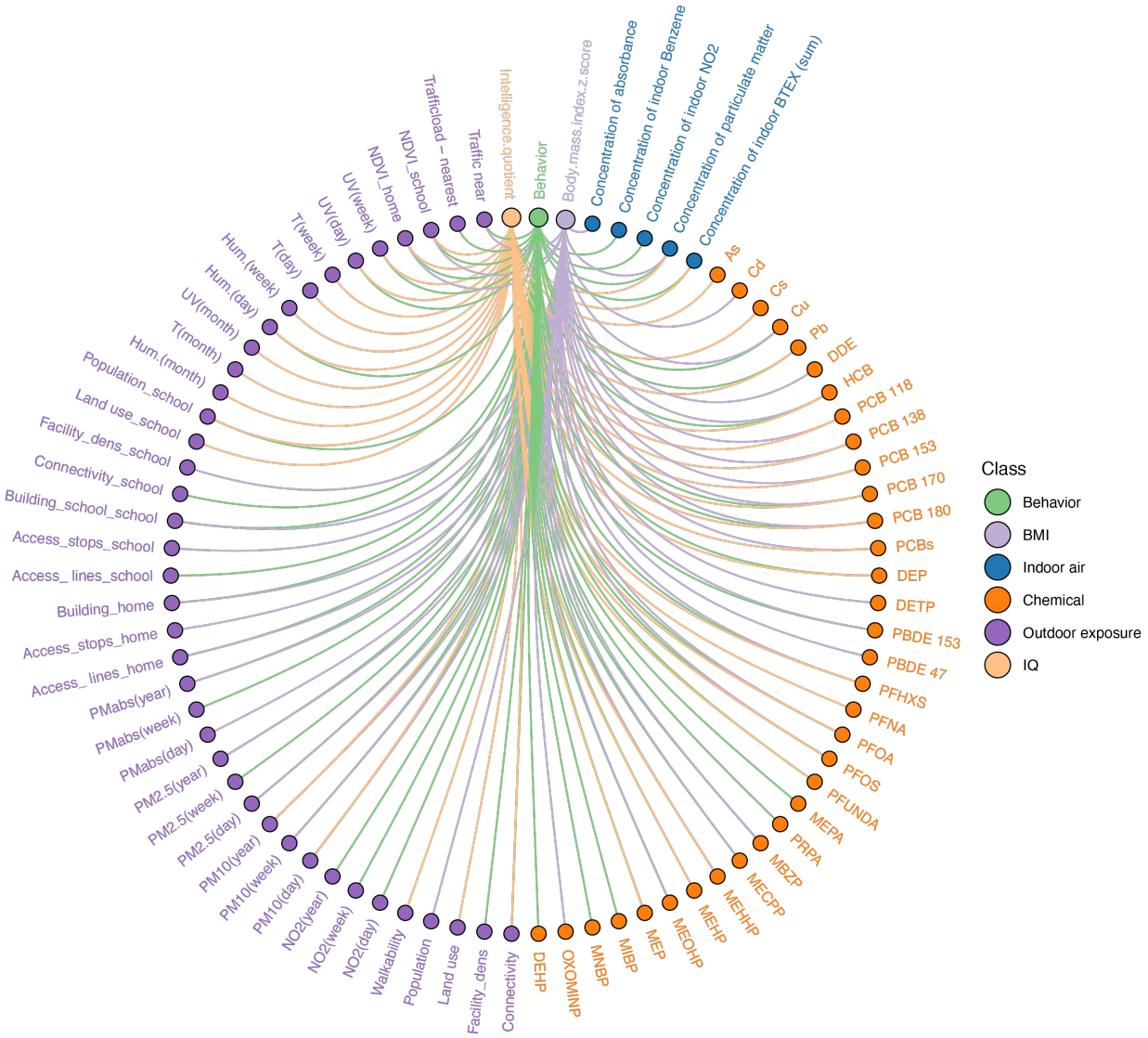
Motivations and analysis strategy

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



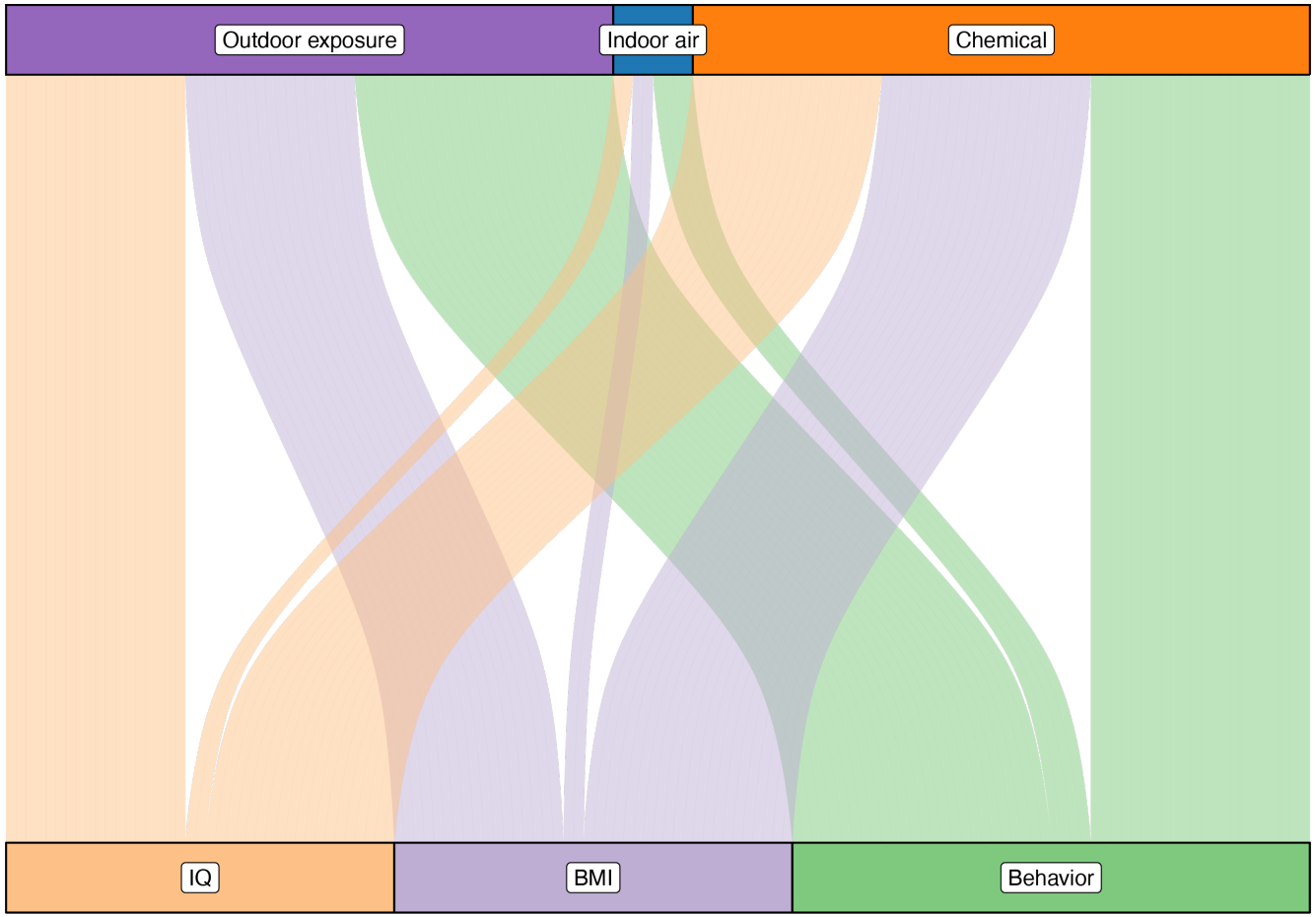
Linear mixed model to find the association between exposome and phenotype
(Child sex, Year of birth, Mother BMI, Gestational age at birth, Maternal age, child height, child weight, birth weight as covariates)

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

Exposome are associated with phenotypes

Association Distributation

Exposome (Outdoor exposure, indoor air, chemical)



Phenotype (IQ, BMI, Behavior)

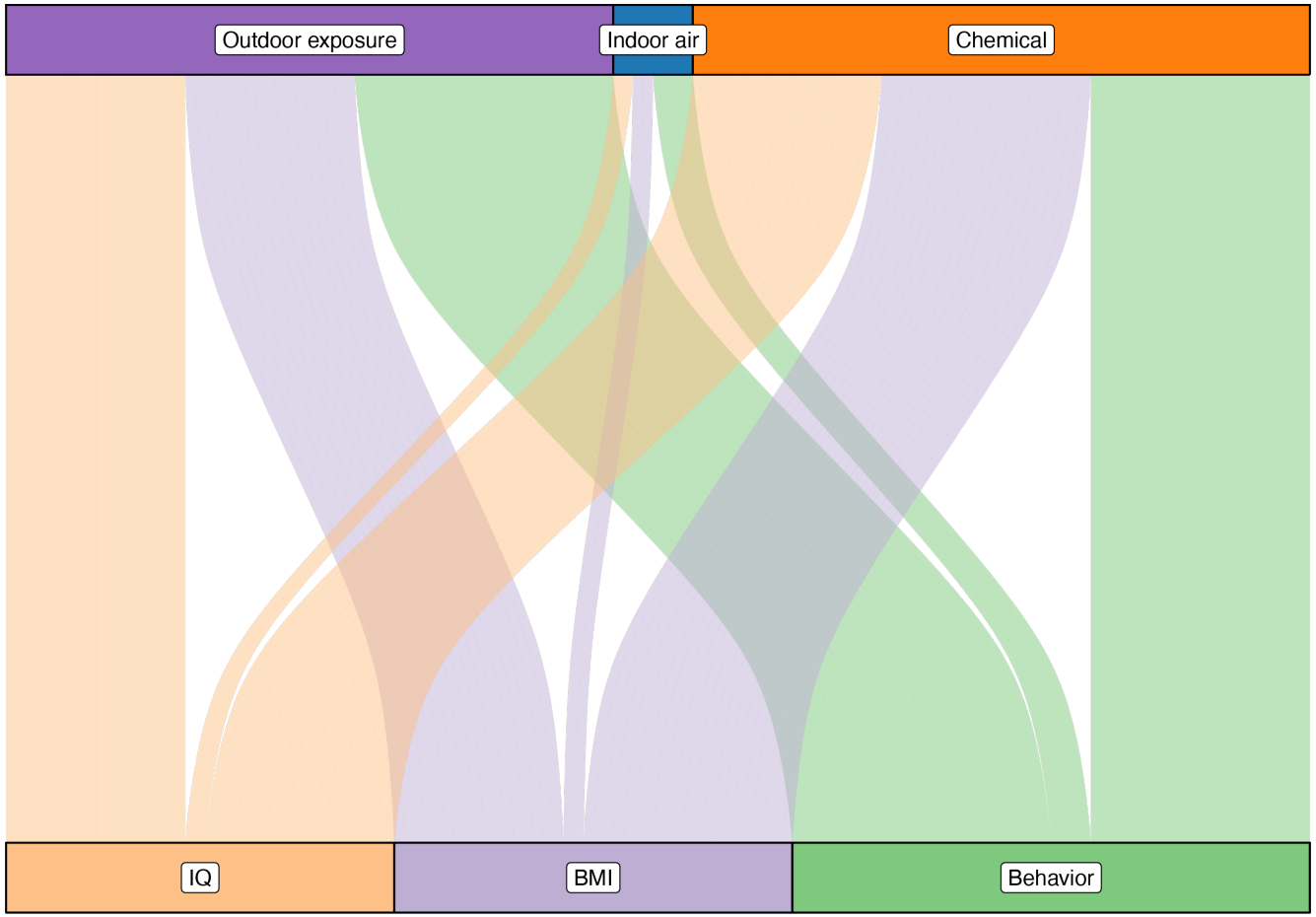
Most of the associations are from outdoor exposures and chemicals.

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

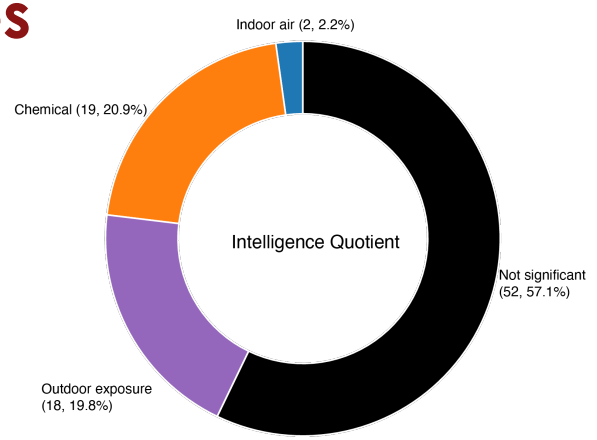
Exposome are associated with phenotypes

Association Distributation

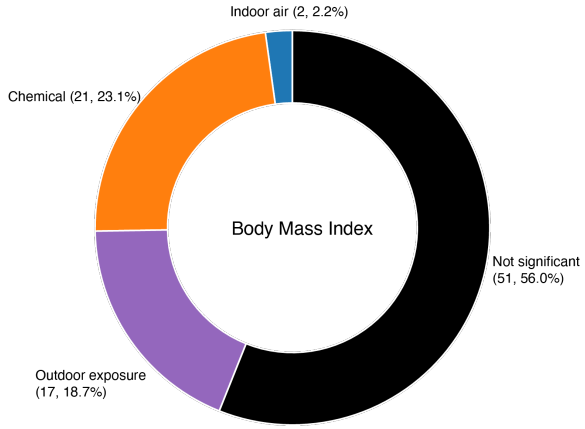
Exposome (Outdoor exposure, indoor air, chemical)



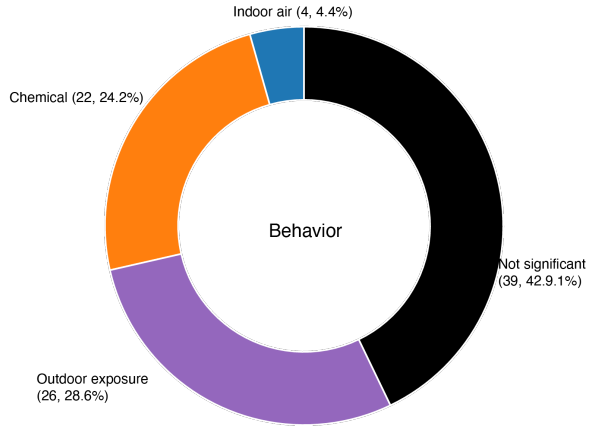
Phenotype (IQ, BMI, Behavior)



Intelligence quotient (IQ):
39 exposome features



Body mass index (BMI):
40 exposome features

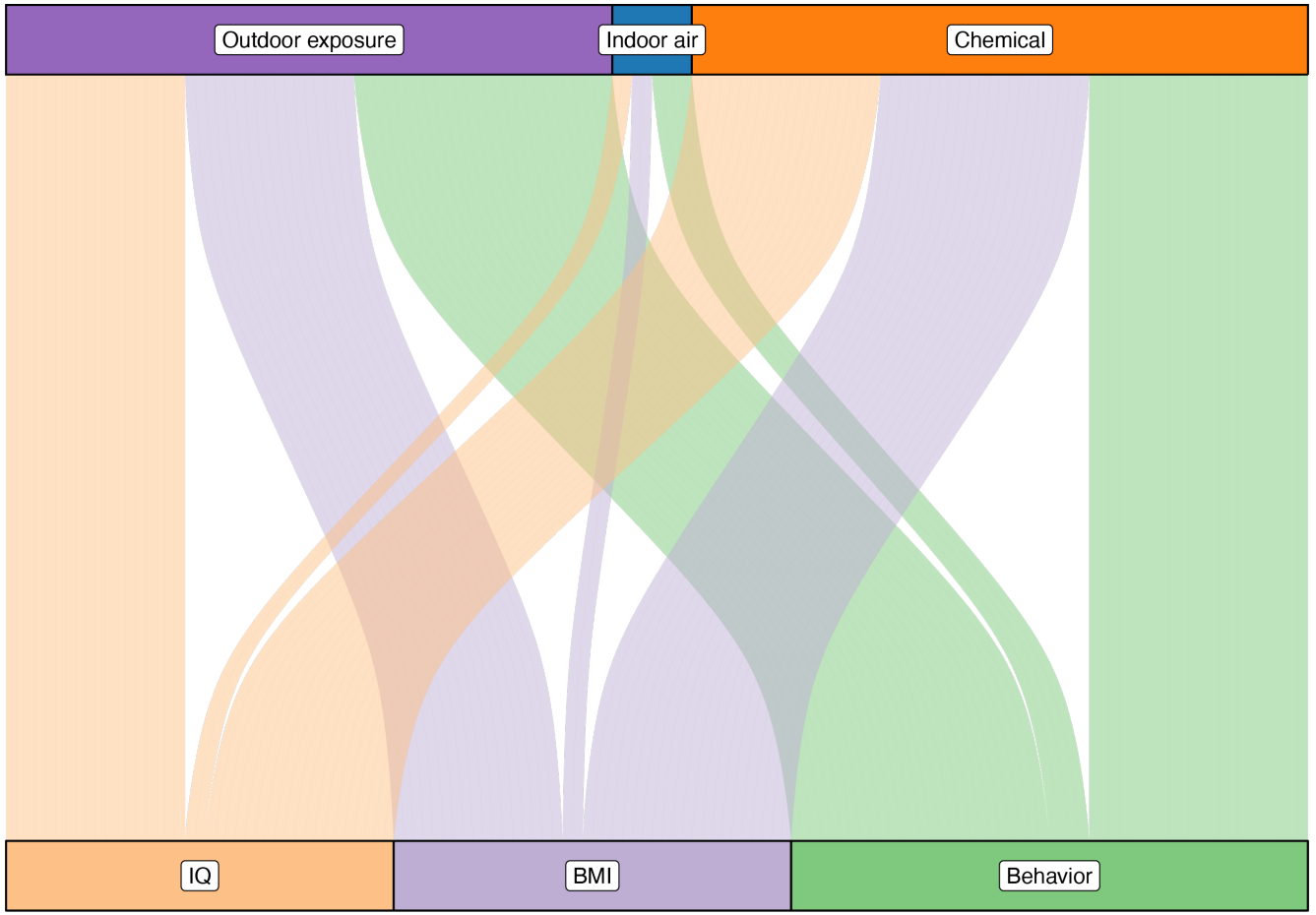


Behavior:
52 exposome features

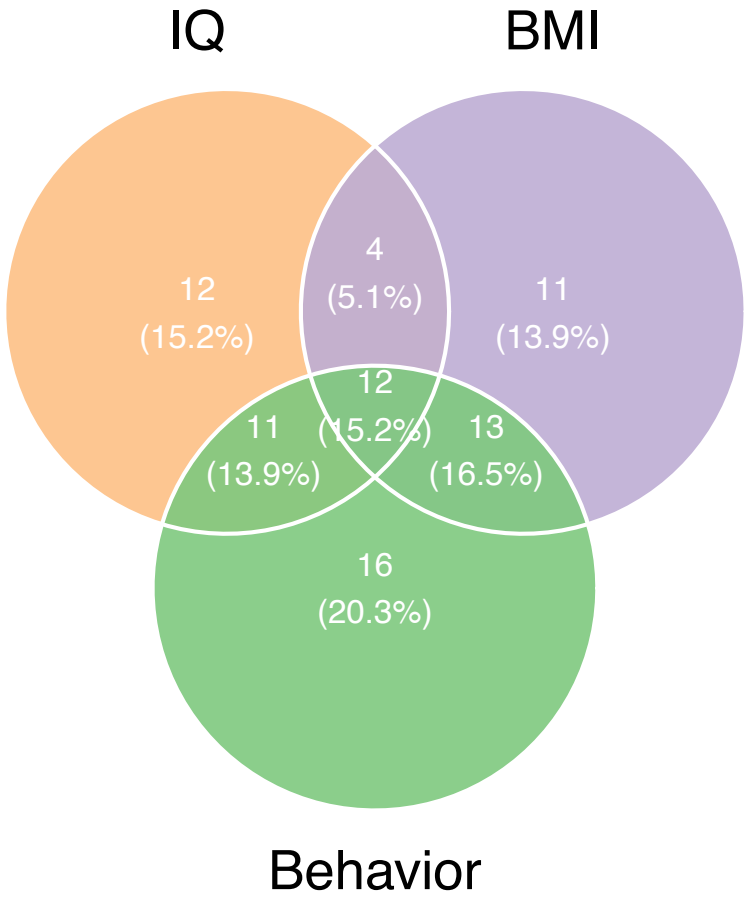
Exposome are associated with phenotypes

Association Distributation

Exposome (Outdoor exposure, indoor air, chemical)

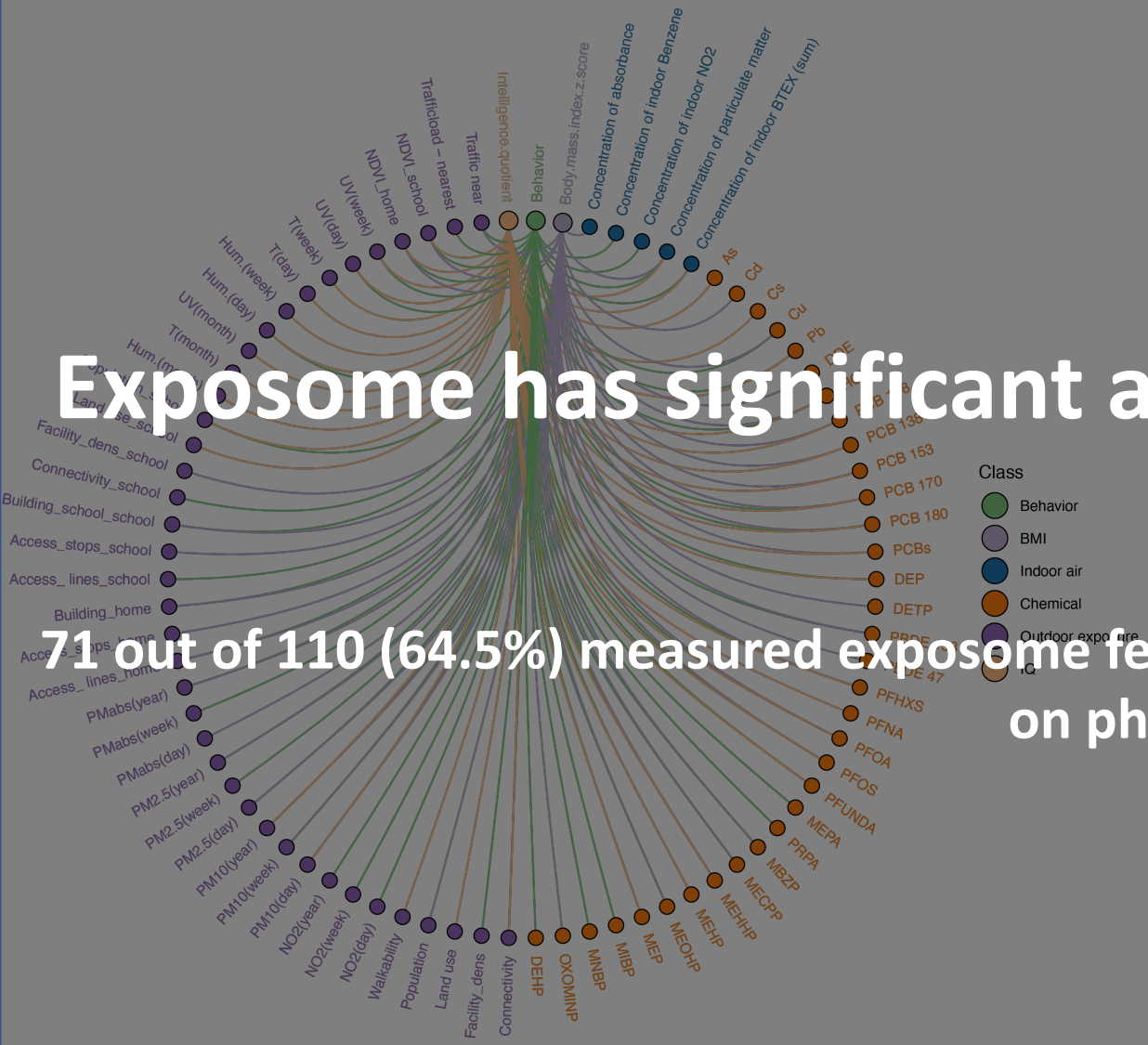


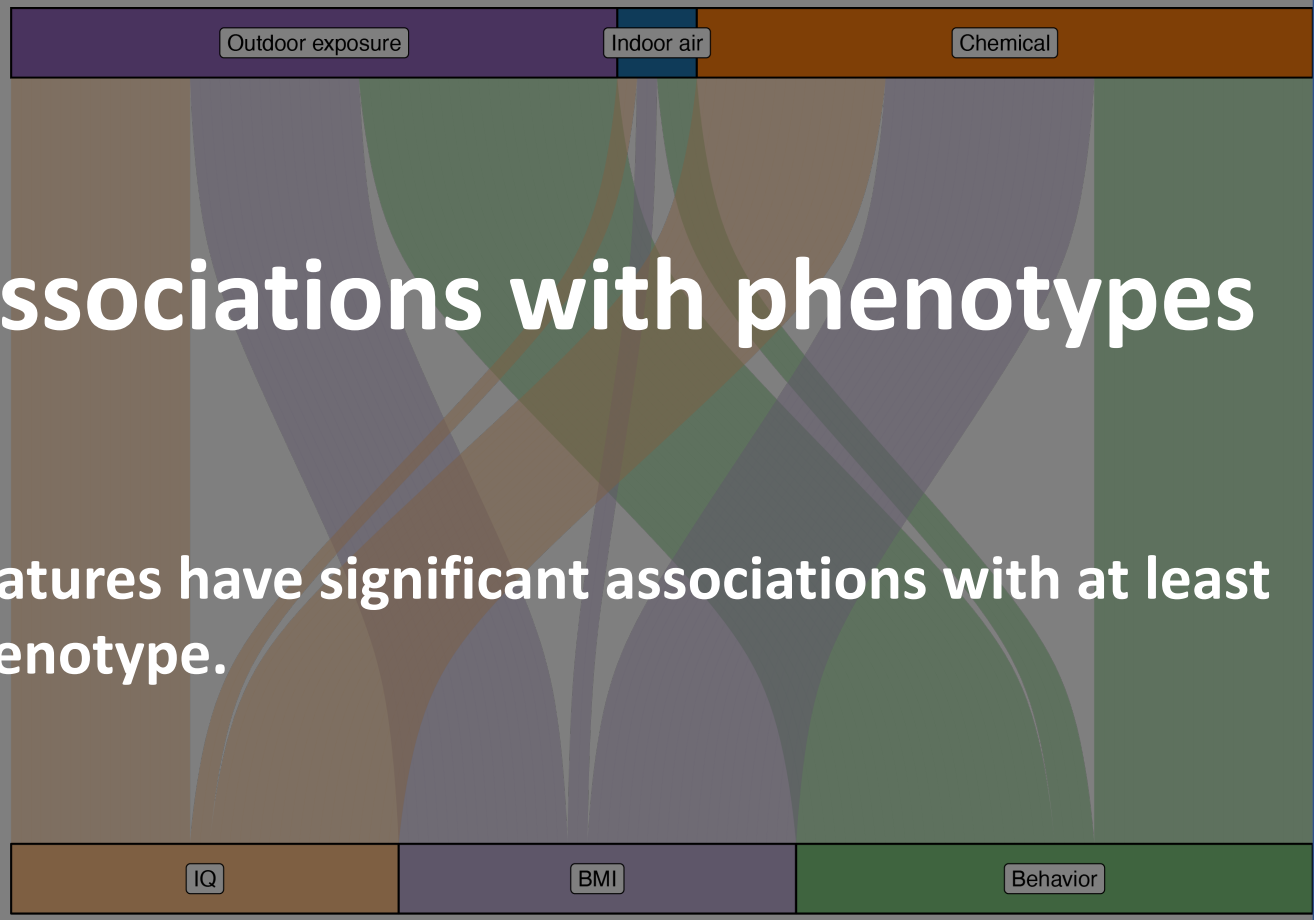
Phenotype (IQ, BMI, Behavior)



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

Exposome are associated with phenotypes

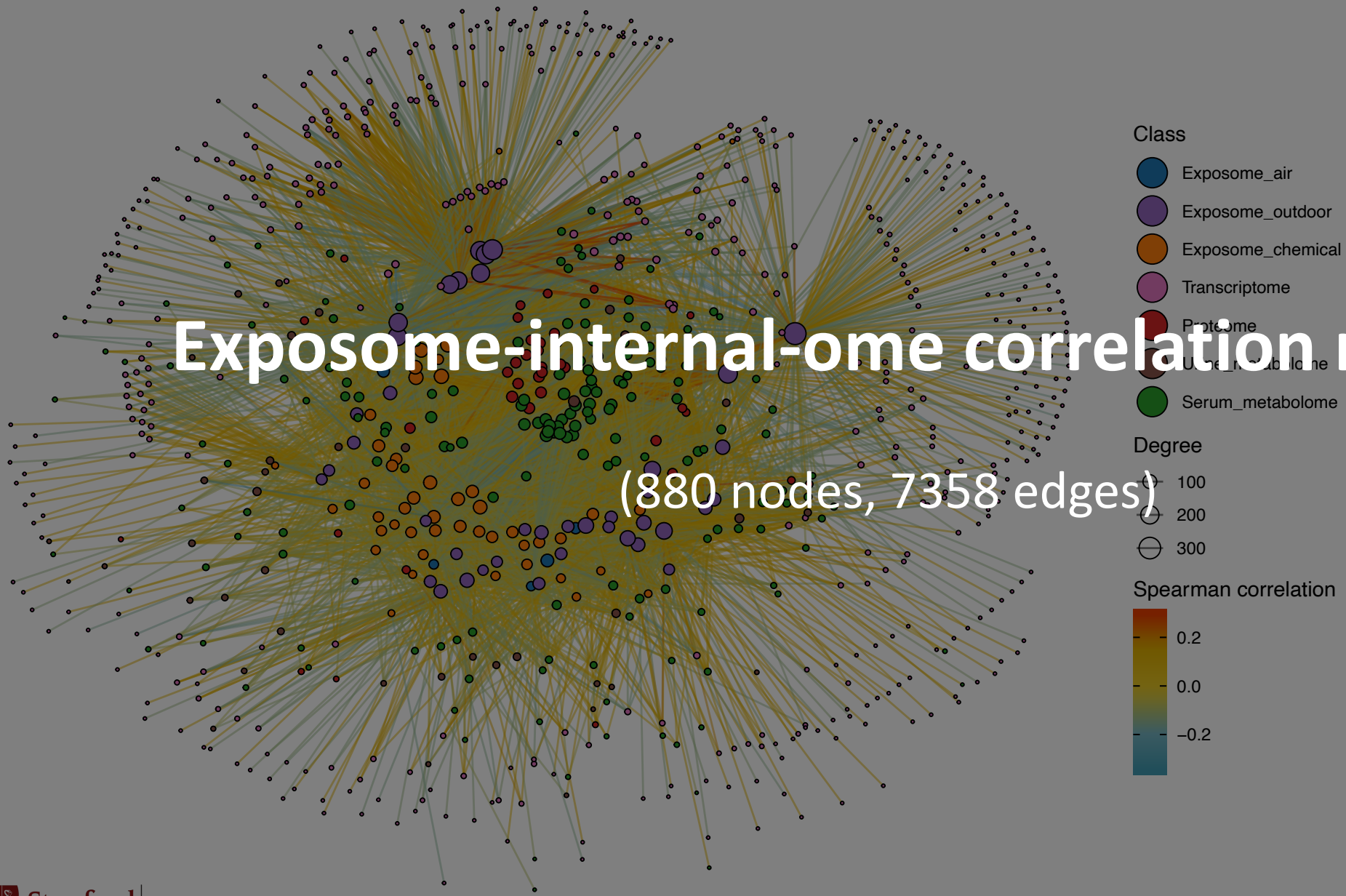




Exposome has significant associations with phenotypes

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

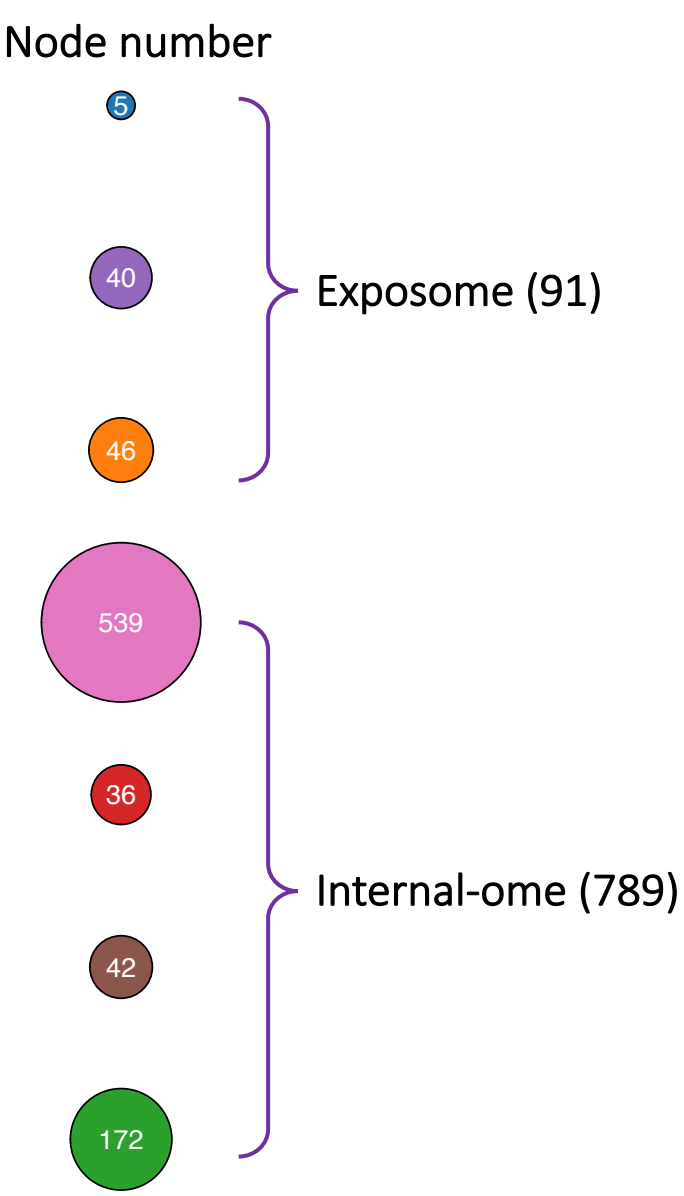
Exposome are associated with internal-omics data

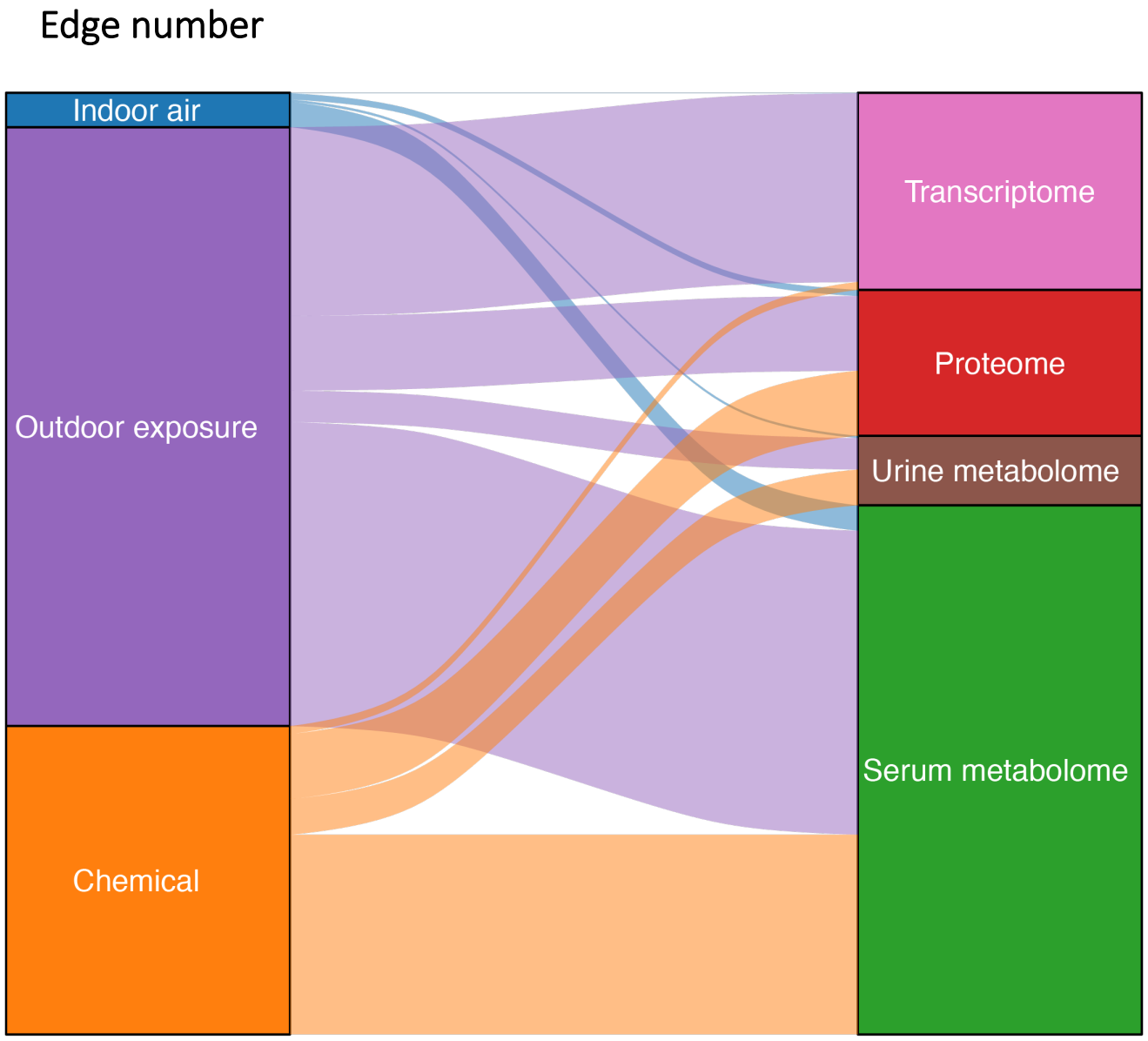


Exposome-internal-ome correlation network

(880 nodes, 7358 edges)

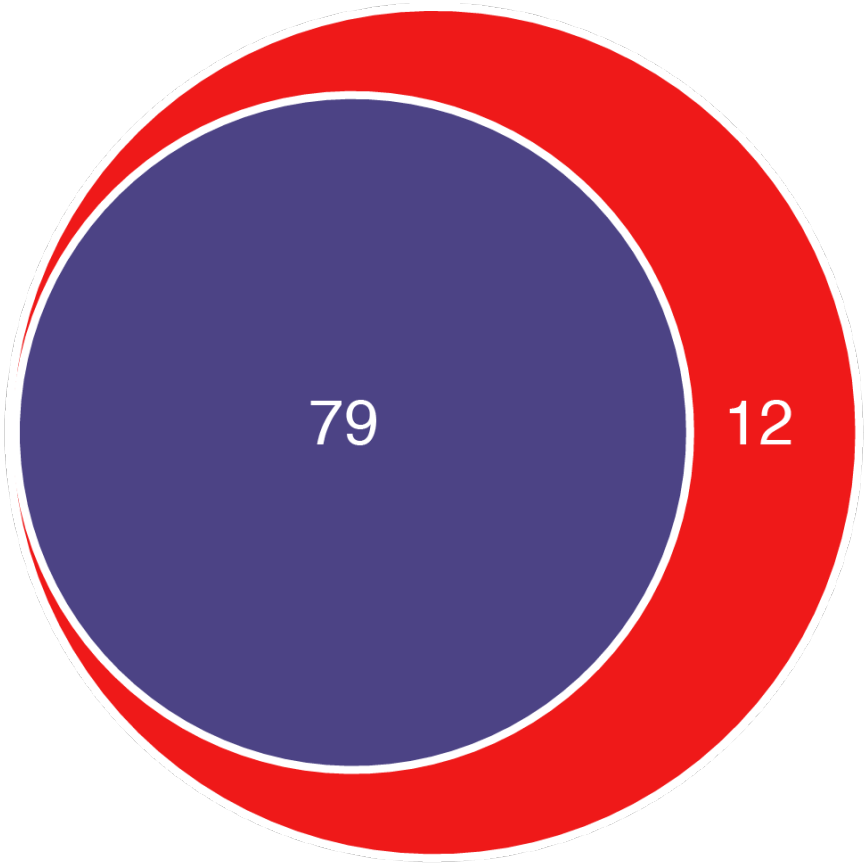
Exposome are associated with internal-omics data





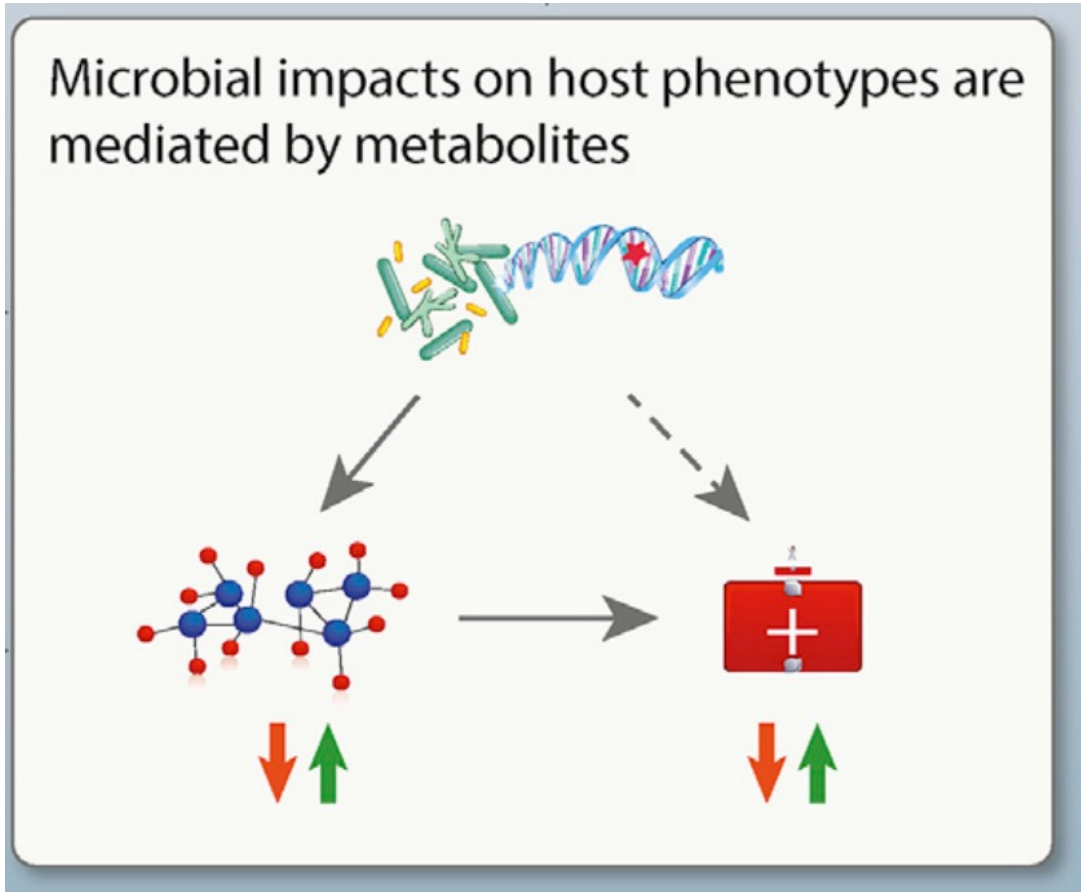
Exposome contributes to phenotypic changes through internal-ome

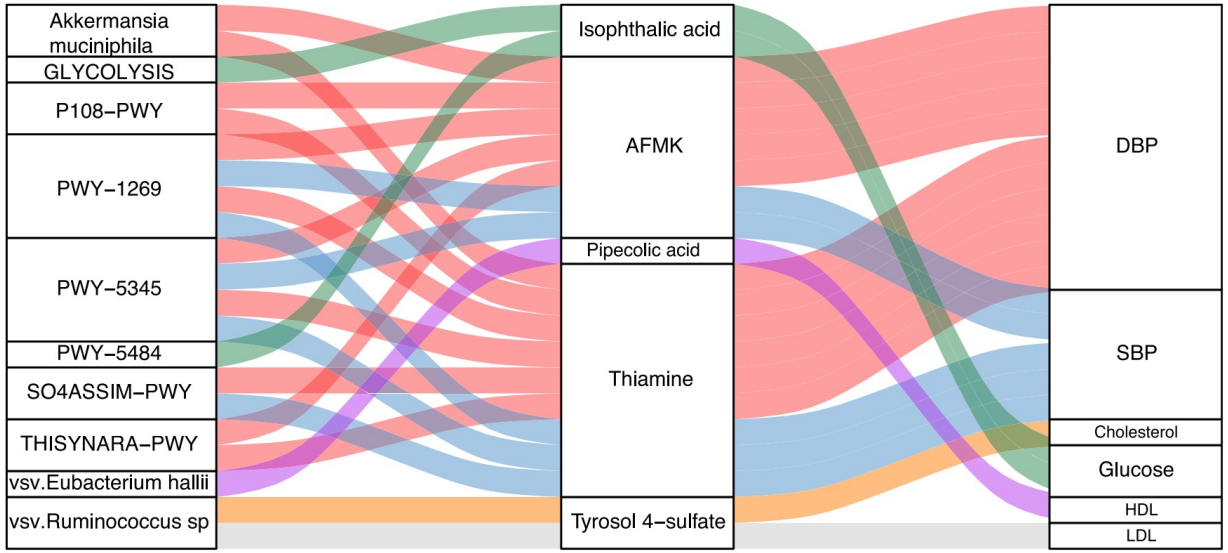
1. 79 out of 110 exposome features are associated with phenotypes.
2. 91 out of 110 exposome features are associated with internal-ome features.



Exposome contributes to phenotypic changes through internal-ome

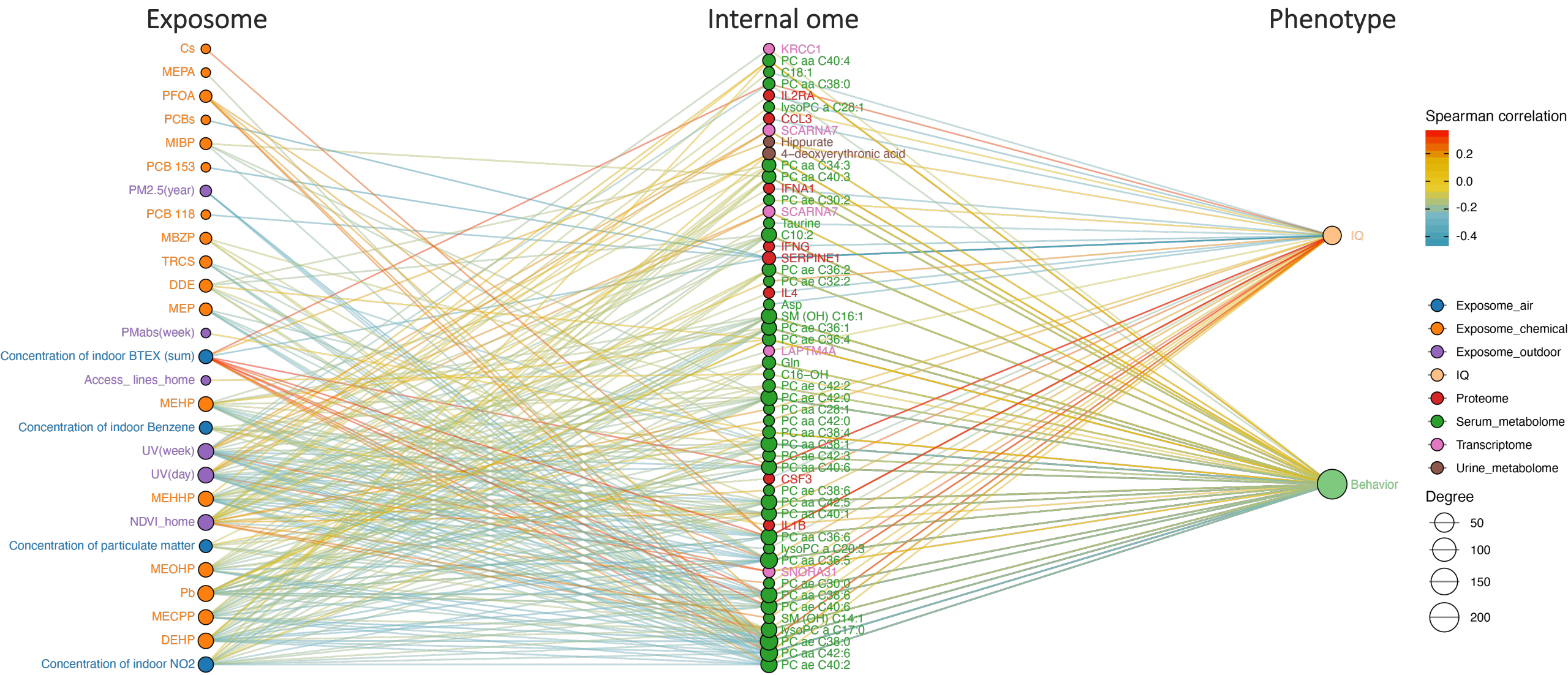
To evaluate whether internal-ome features can mediate the exposome impact on phenotypes, we applied **bi-directional mediation** analysis.





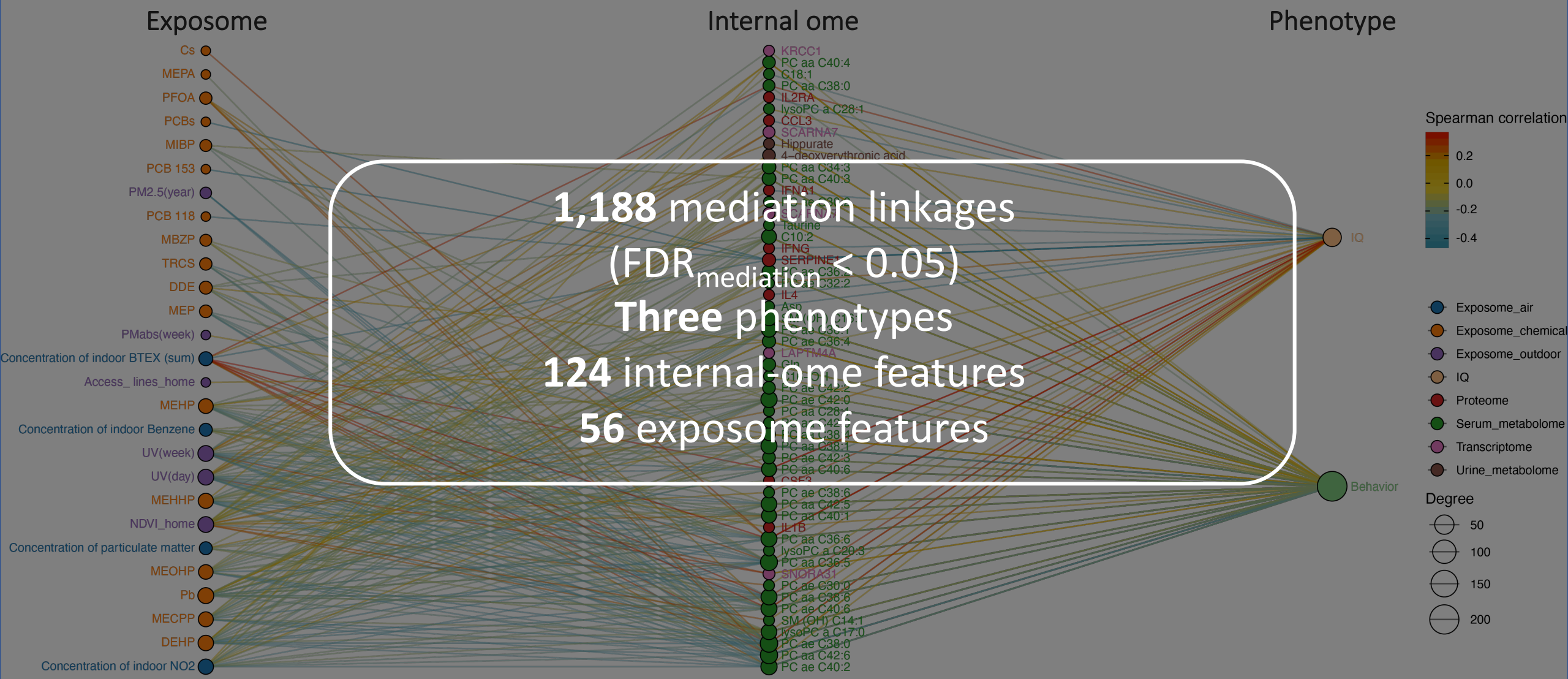
Chen et al., 2021, Cell 184, 1–14

Exposome contributes to phenotypic changes through internal-ome



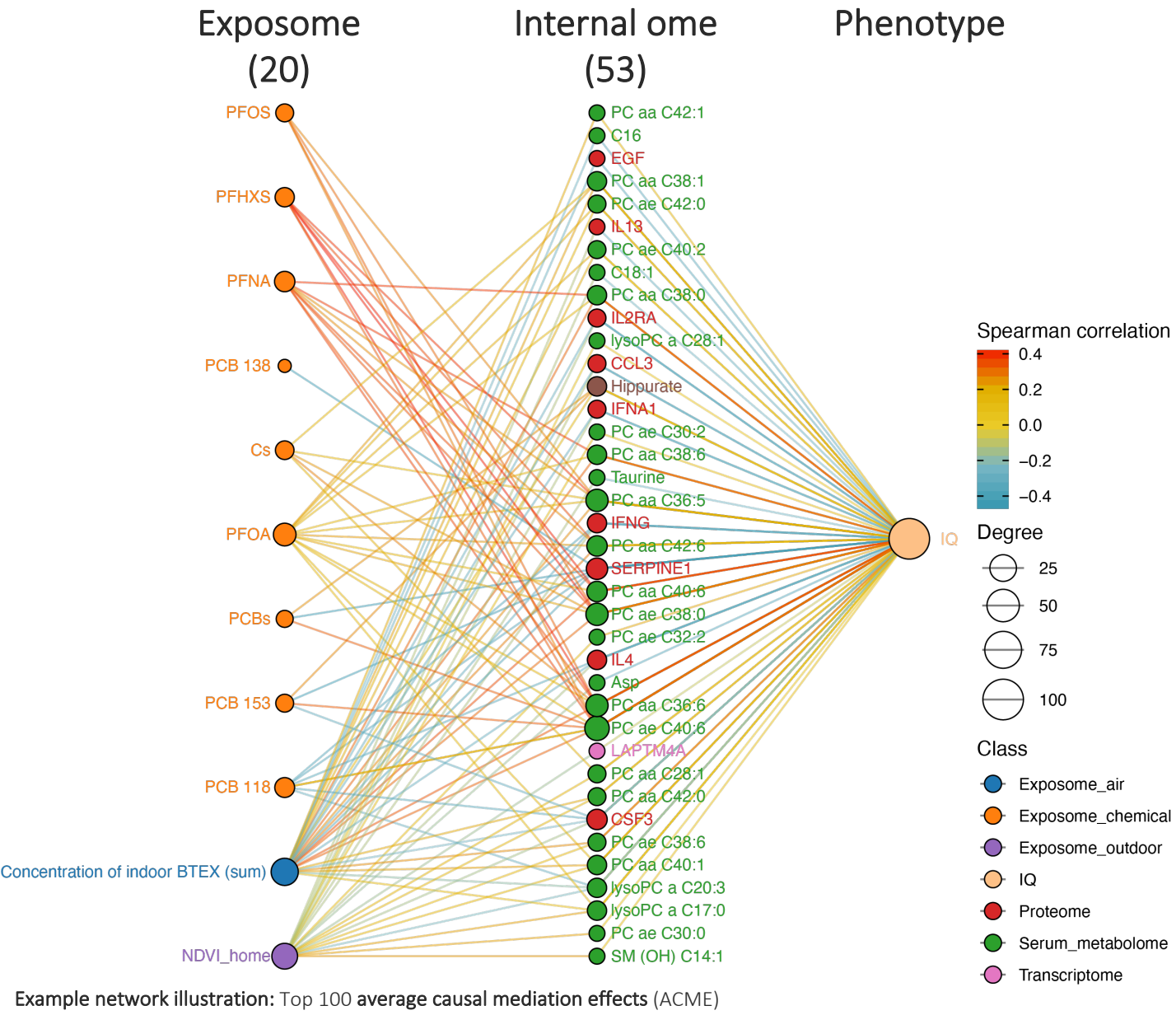
Example network illustration: Top 250 average causal mediation effects (ACME)

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



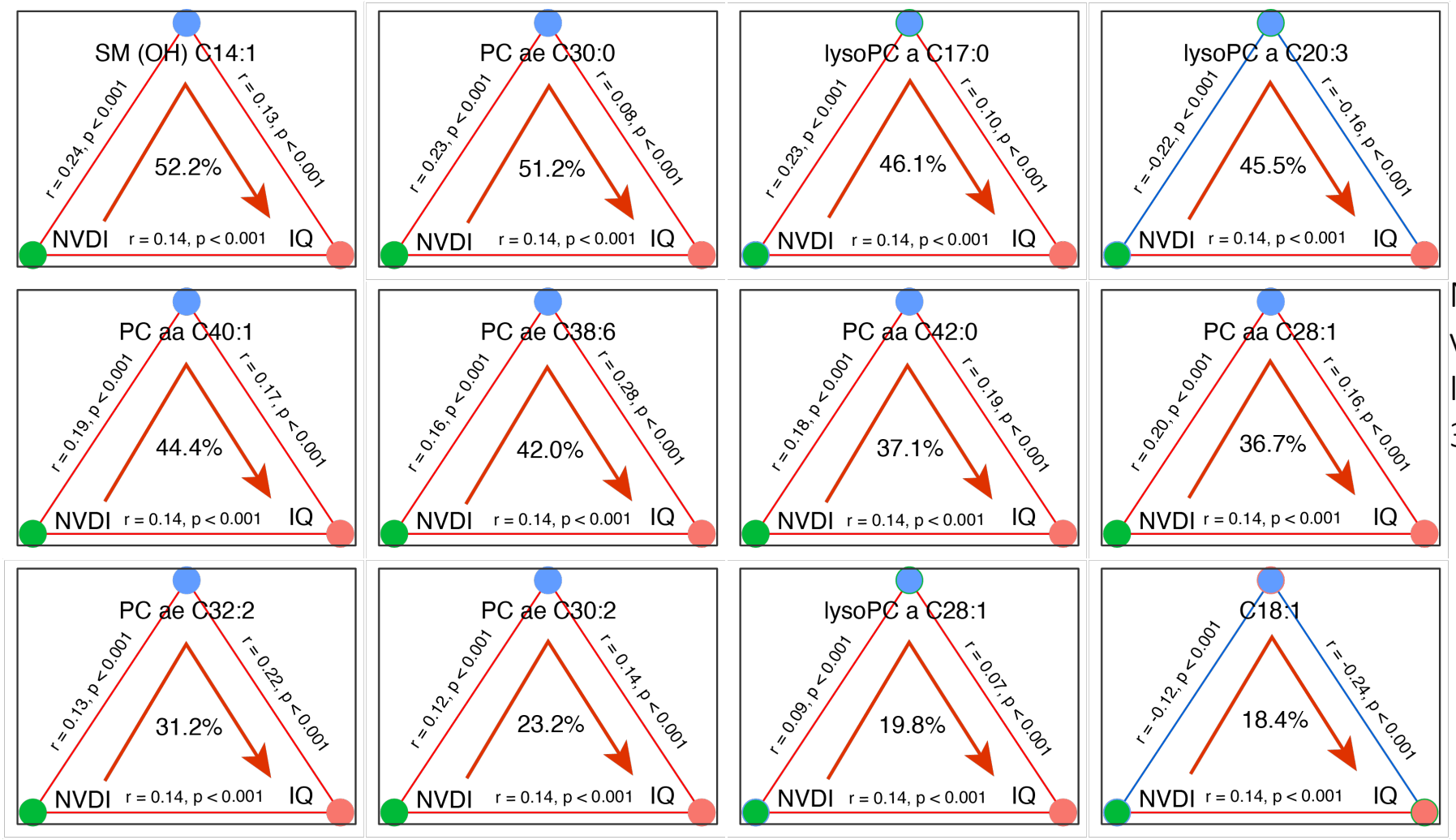
Example network illustration: Top 100 **average causal mediation effects** (ACME)

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.

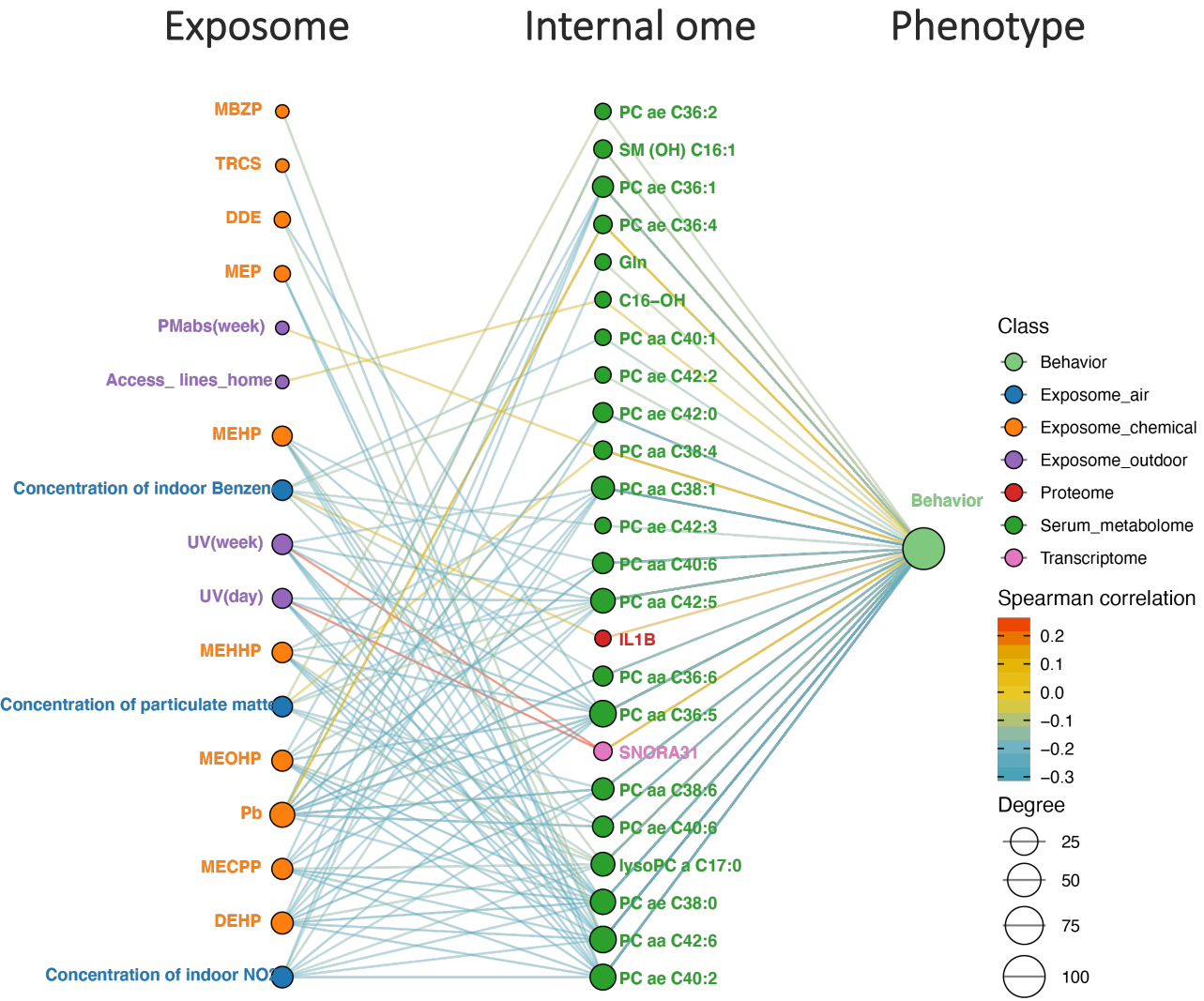
Uauy et al. 2003, JN.
Bijnens et al., 2020, PLOS Medcine.

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



Example network illustration: Top 100 average causal mediation effects (ACME)

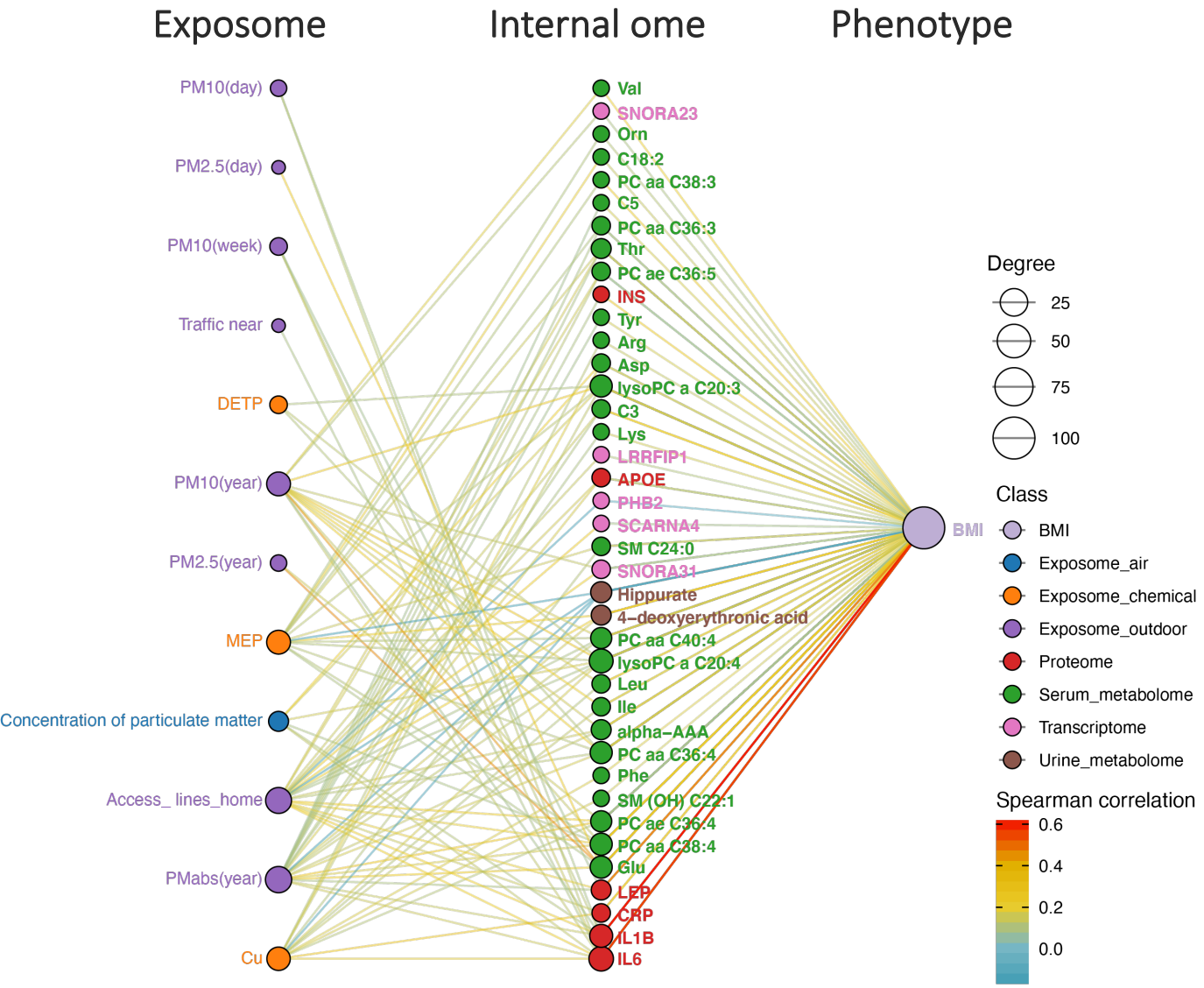
Blood Pb concentrations, even at mean levels of 6.4 µg/dL, were associated with increased risk of behavioral problems in preschool children, including internalizing and pervasive developmental problems.

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



Example network illustration: Top 100 **average causal mediation effects** (ACME)

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 (OR = 9.27, 95% CI: 5.43, 15.82, pfor trend < 0.001) and cholesterol (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

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Our team

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Allision Zhang, PhD

Supervisor:
Michael Snyder, PhD


Stanford
MEDICINE
Thanks for your attention!
Q&A
Xiaotao Shen PhD
Stanford School of Medicine
Department of Genetics
shenxt@stanford.edu
@JasperShen1990
shenxt.me
github.com/jaspershen
27