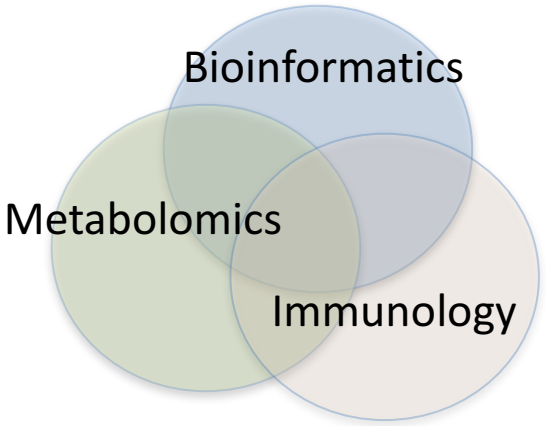
Metabolomics and exposome research



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August 30, 2019

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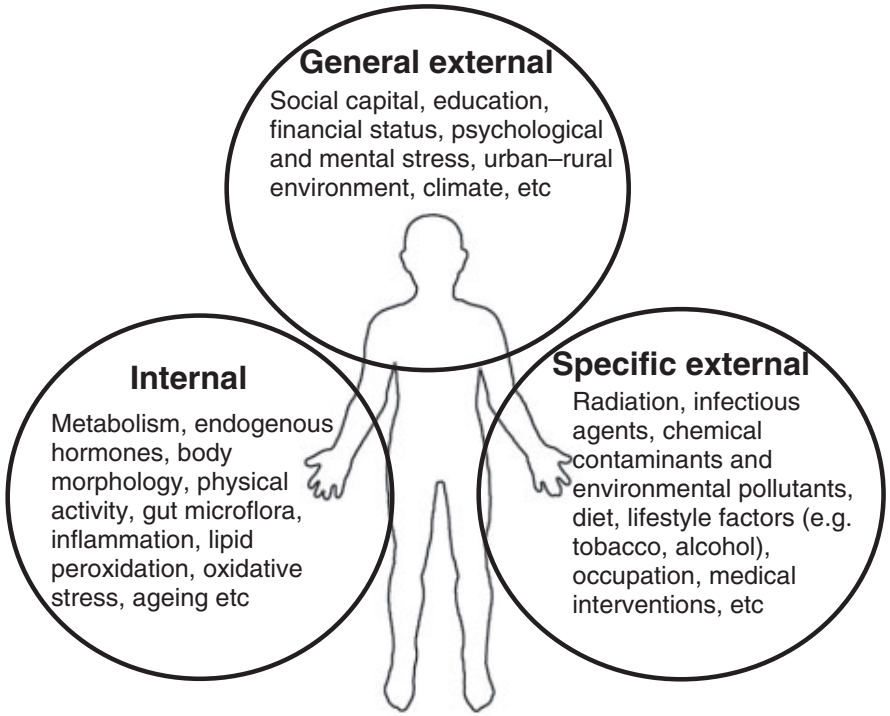
The exposome: from concept to utility

Christopher Paul Wild

International Journal of Epidemiology, 2012, 41:24, https://doi.org/10.1093/ije/dyr236



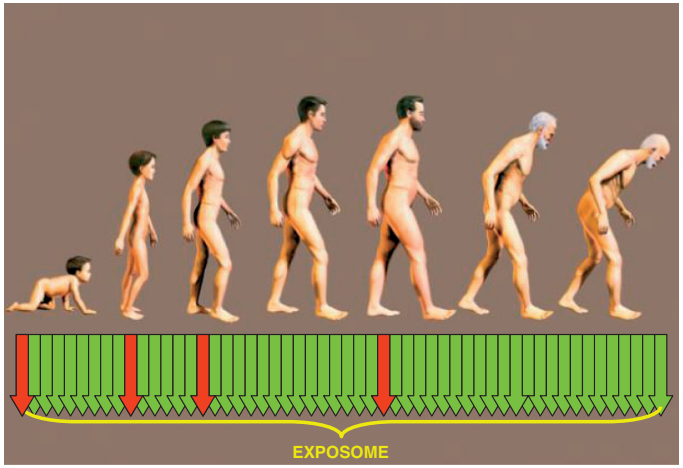
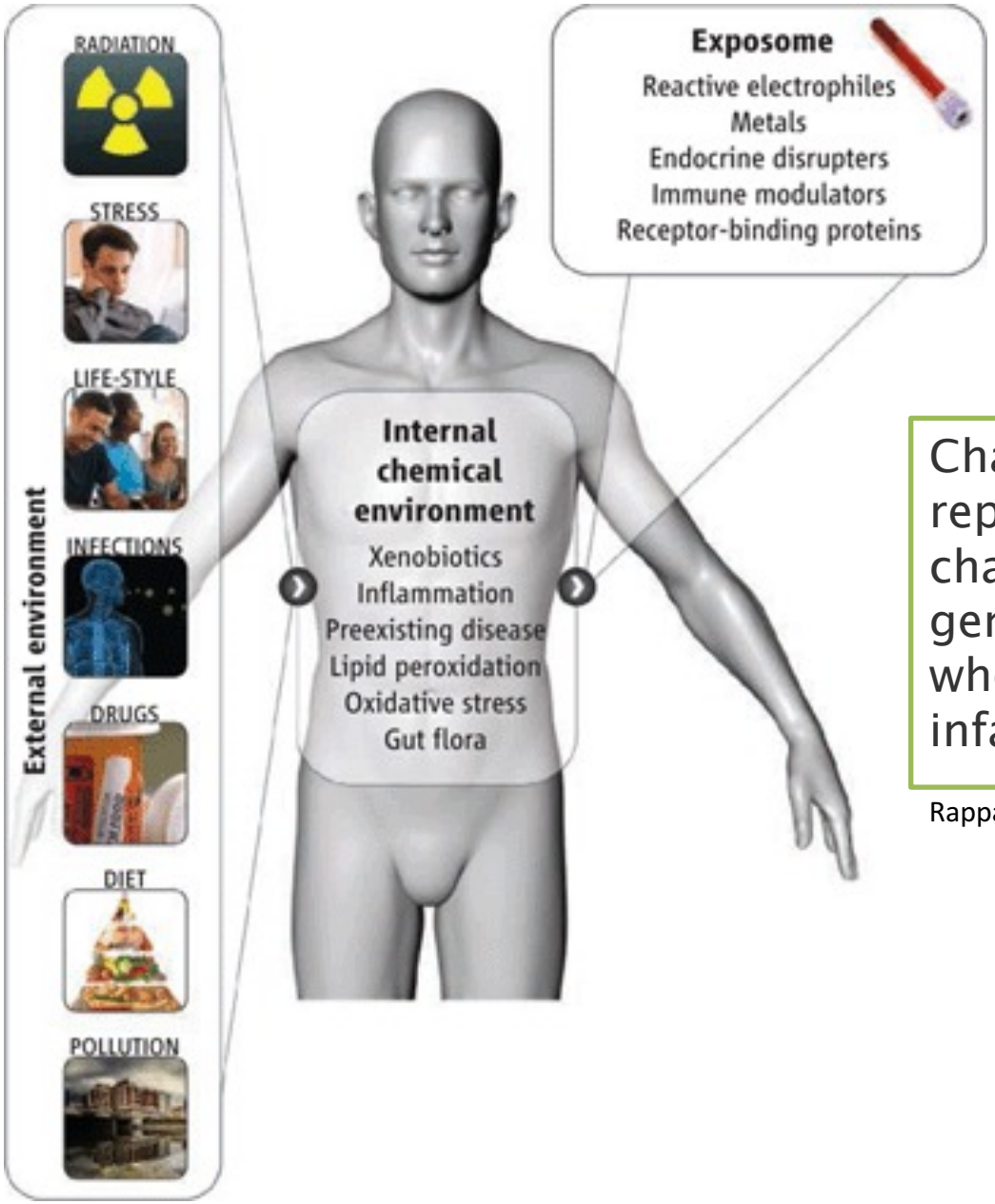


Figure 1 Three different domains of the exposome are presented diagrammatically with non-exhaustive examples for each of these domains

The exposome: from concept to utility

Approach	Tools
Biomarkers (omics)	
General	Genomics, transcriptomics, proteomics, metabolomics, epigenomics
Targeted	Adductomics, lipidomics, immunomics
Sensor technologies (including mobile phones)	Environmental pollutants, physical activity, stress, circadian rhythms, location [global positioning systems (GPS)]
Imaging (including mobile phones, video cameras)	Diet, environment, social interactions
Portable computerized devices (including palmtop computers)	Behaviour and experiences (ecological momentary assessment), stress, diet, physical activity
Improved conventional measurements (combined with environmental measures)	Job-exposure matrices; dietary recall (e.g. EPIC-Soft)

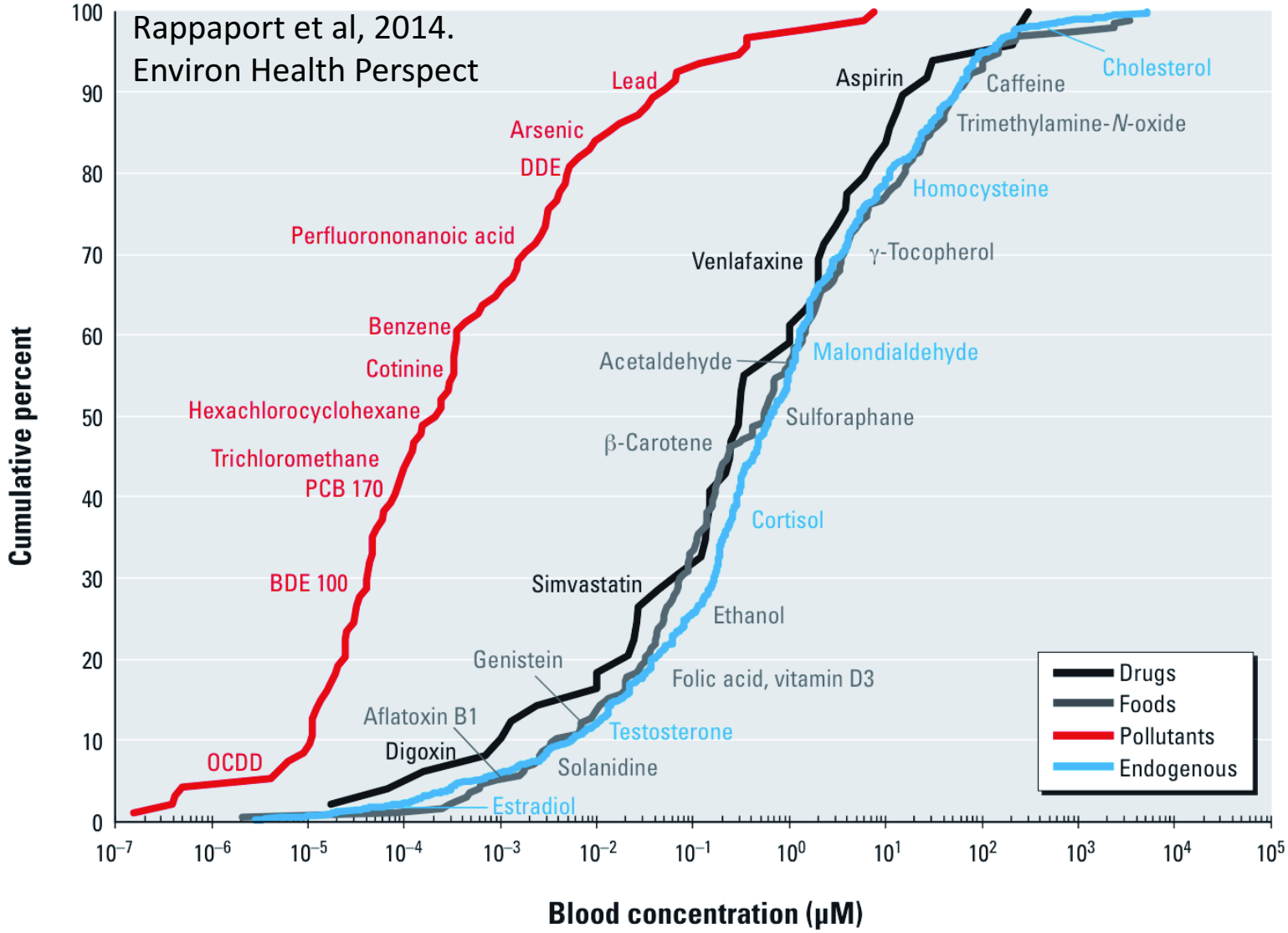


Exposome

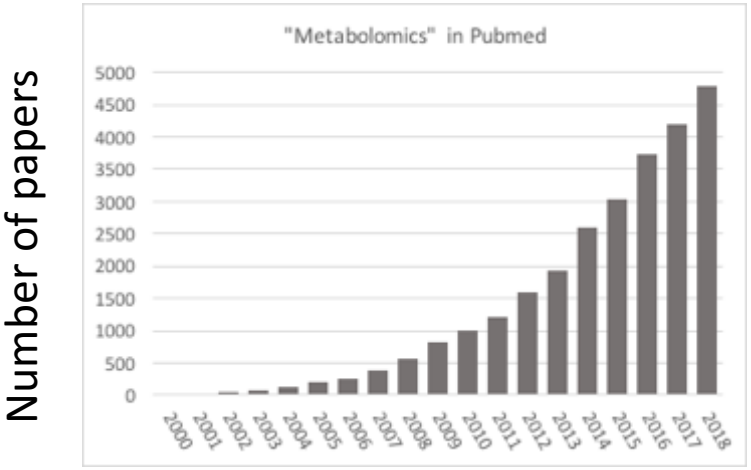
Characterizing the exposome represents a technological challenge like that of the human genome project, which began when DNA sequencing was in its infancy.

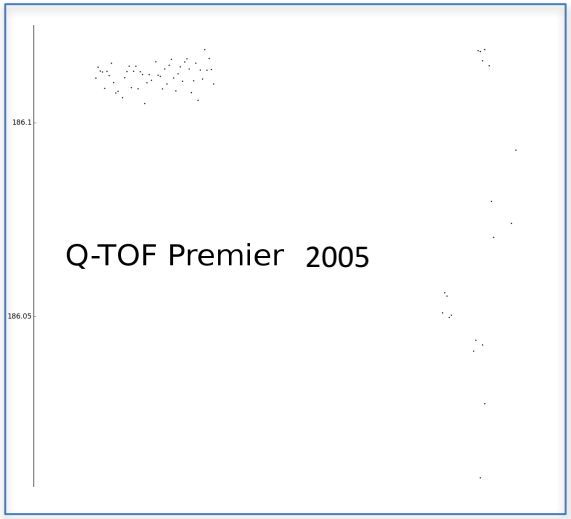
Rappaport and Smith, 2010. Science, 330:460

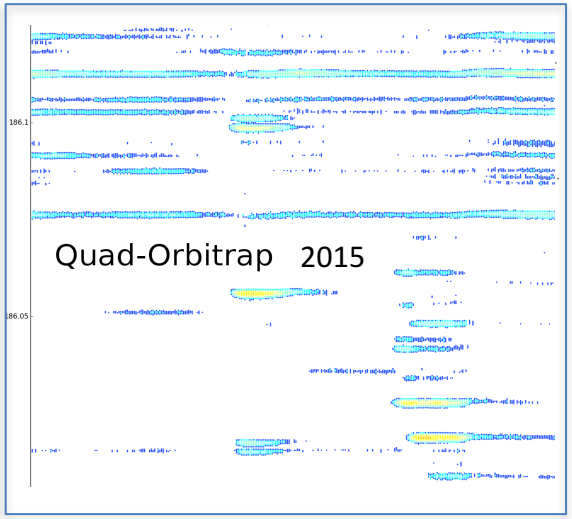
Blood concentration of small molecules

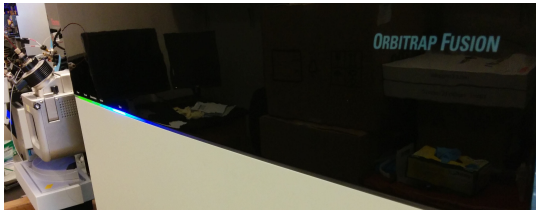


Advance of Metabolomics

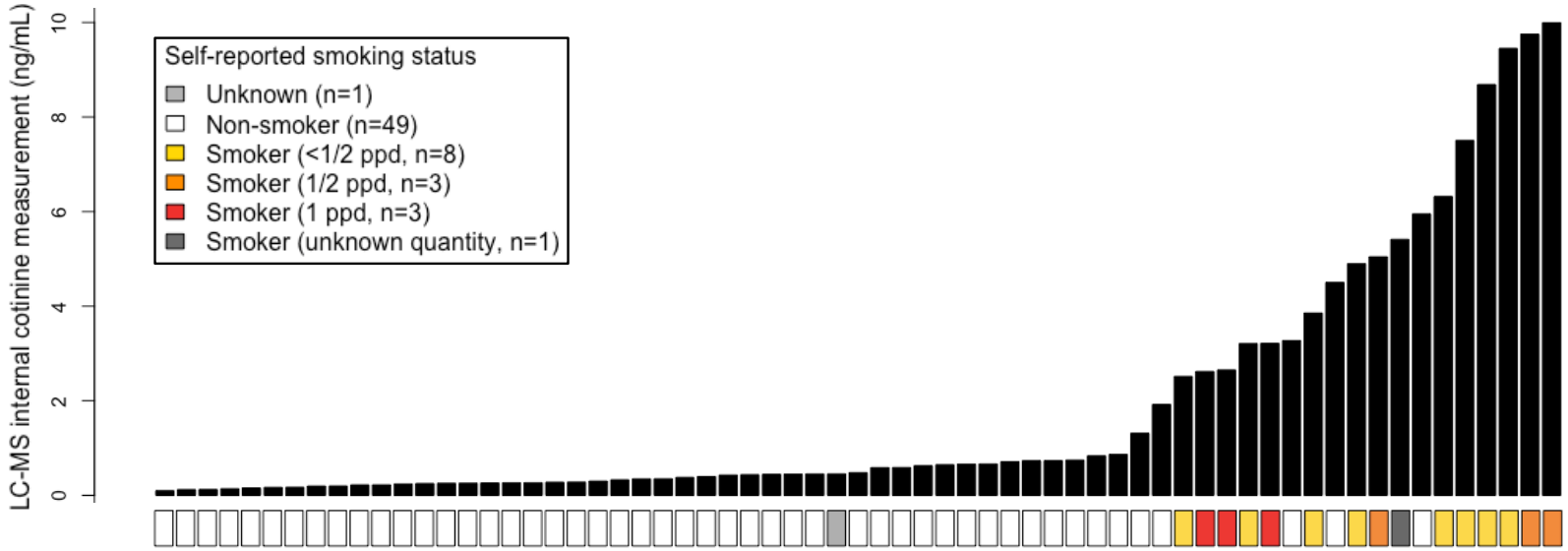






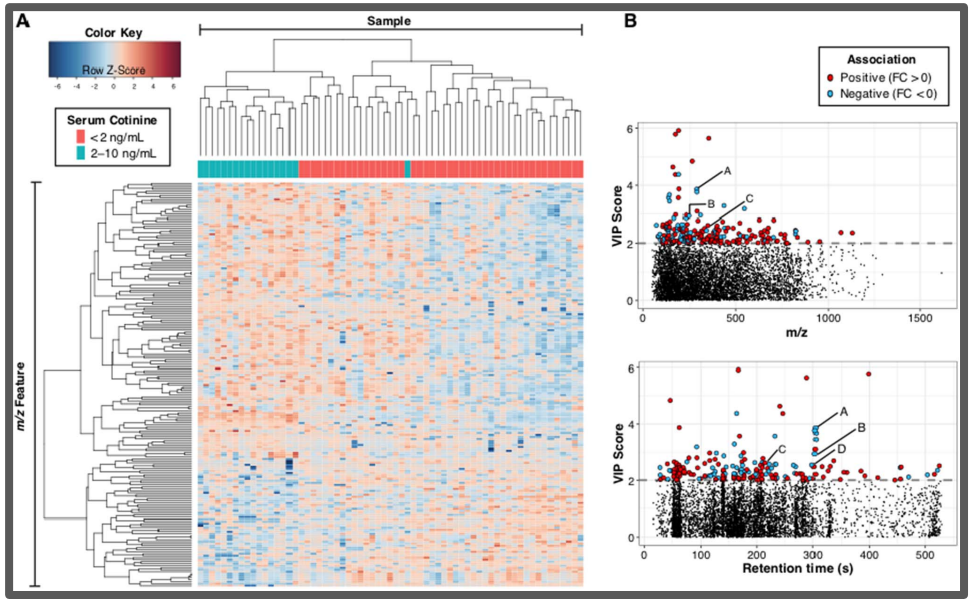


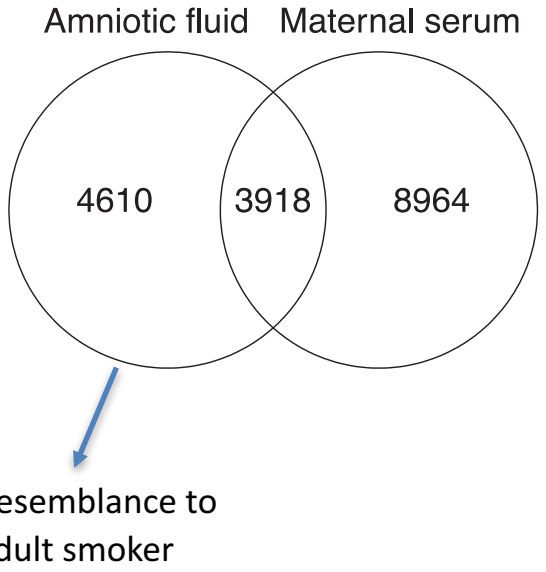
Cotinine level seen directly in metabolomics data



Fischer et al (2017) *Environment International*. 107:227-234.

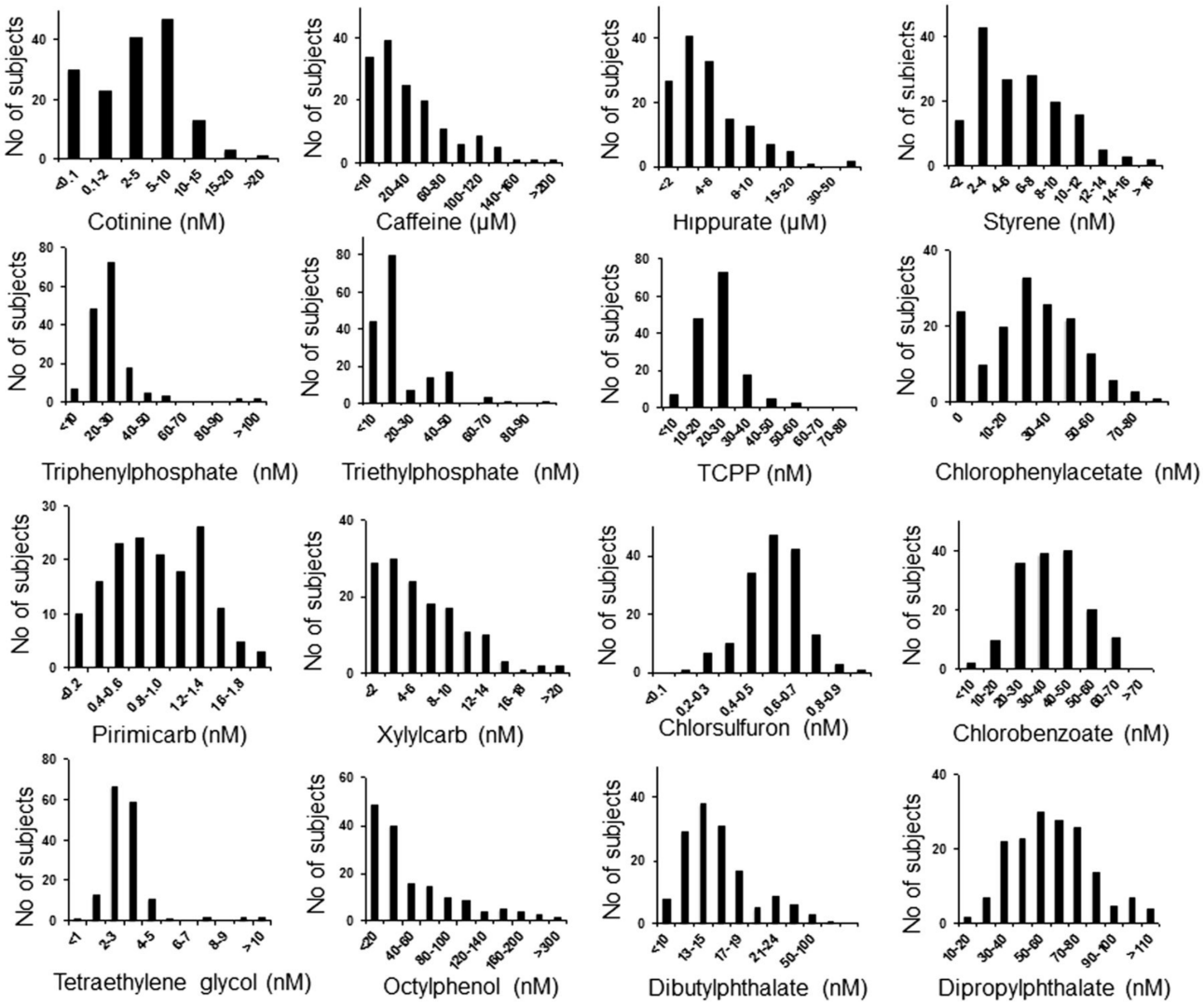
MWAS reveals biological effect of smoking on fetus





Fischer et al (2017) *Environment International*. 107:227-234.

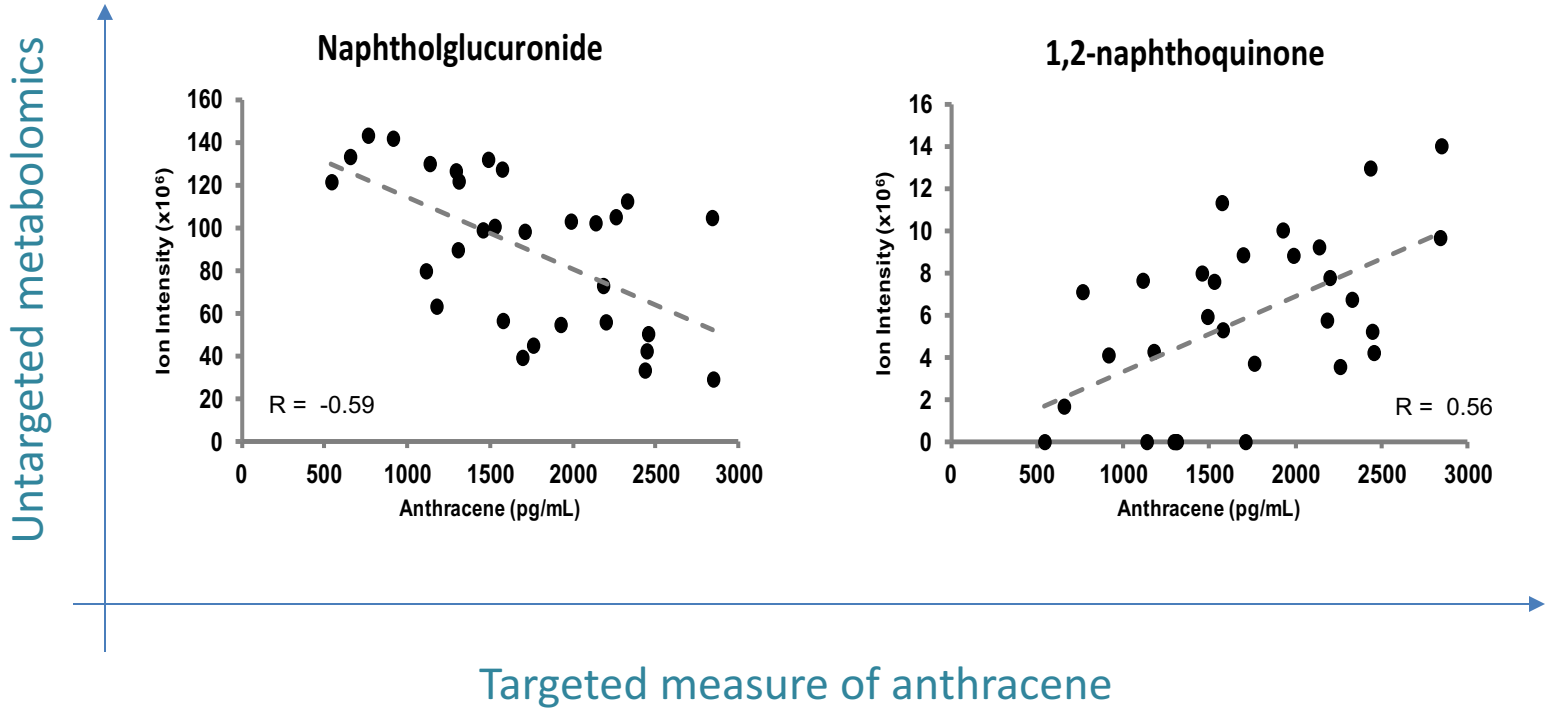
Environmental and dietary chemicals captured in LC-HRMS metabolomics



Histograms of selected environmental and dietary chemicals in 157 healthy adults. Samples were analyzed in triplicate by HRM and quantification was performed using reference standardization.

Go et al, Toxicol Sci. 2015;148(2):531-543. Reference Standardization for Mass Spectrometry and High-resolution Metabolomics Applications to Exposome Research

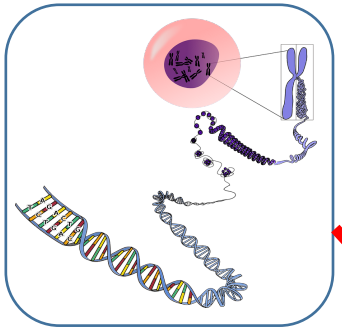
Internal dose or surrogate



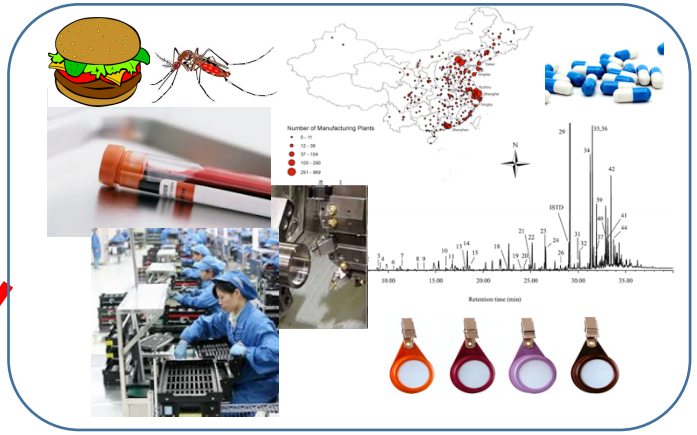
Courtesy: Doug Walker

G × M × E

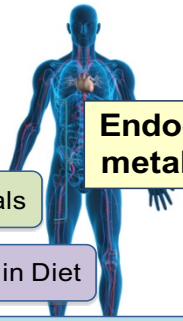
Genome



Environment



Gene function



- Core Biological Metabolome
- Microbiome-related Chemicals
- Non-nutritive Chemicals in Diet
- Supplements and Pharmaceuticals

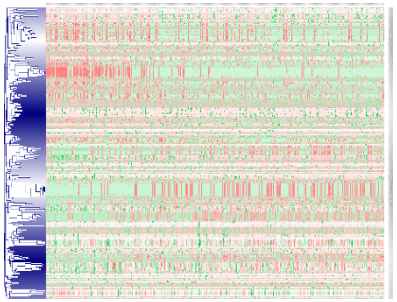
Endogenous metabolome

Environmental metabolome

- Commercial Products
- Environmental Chemicals

Body burden

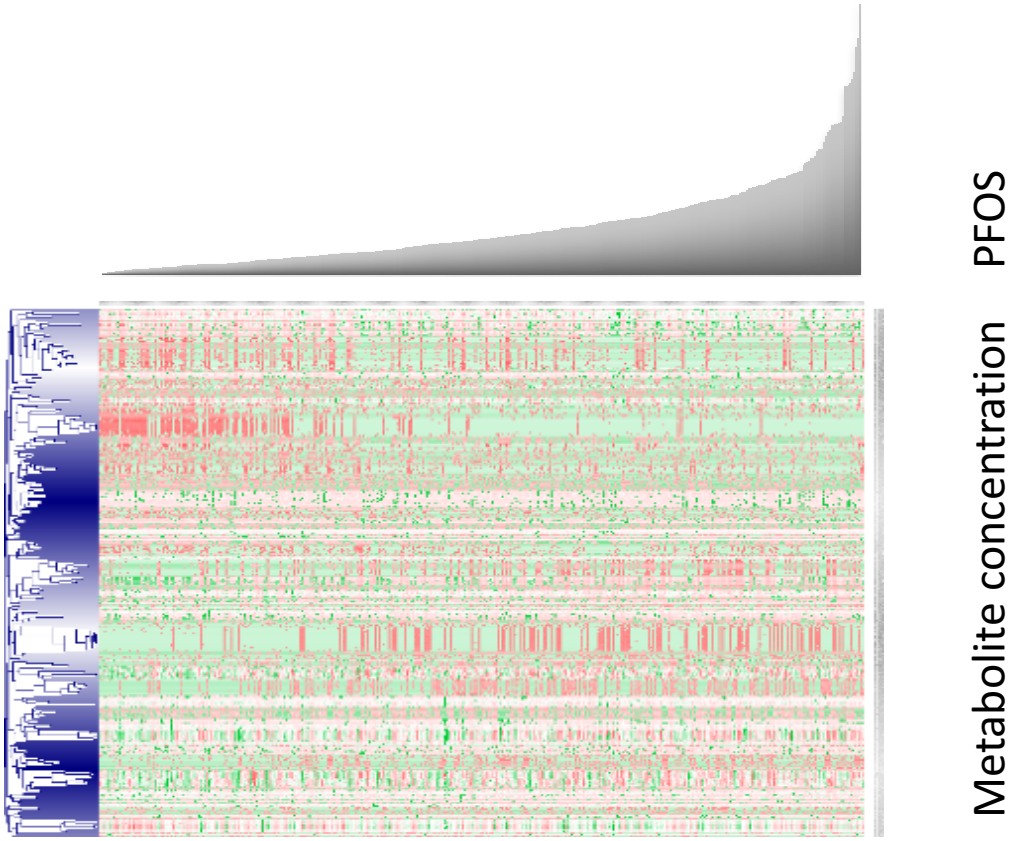
Molecular response



Metabolome

Figure by Doug Walker, Dean Jones & Shuzhao Li

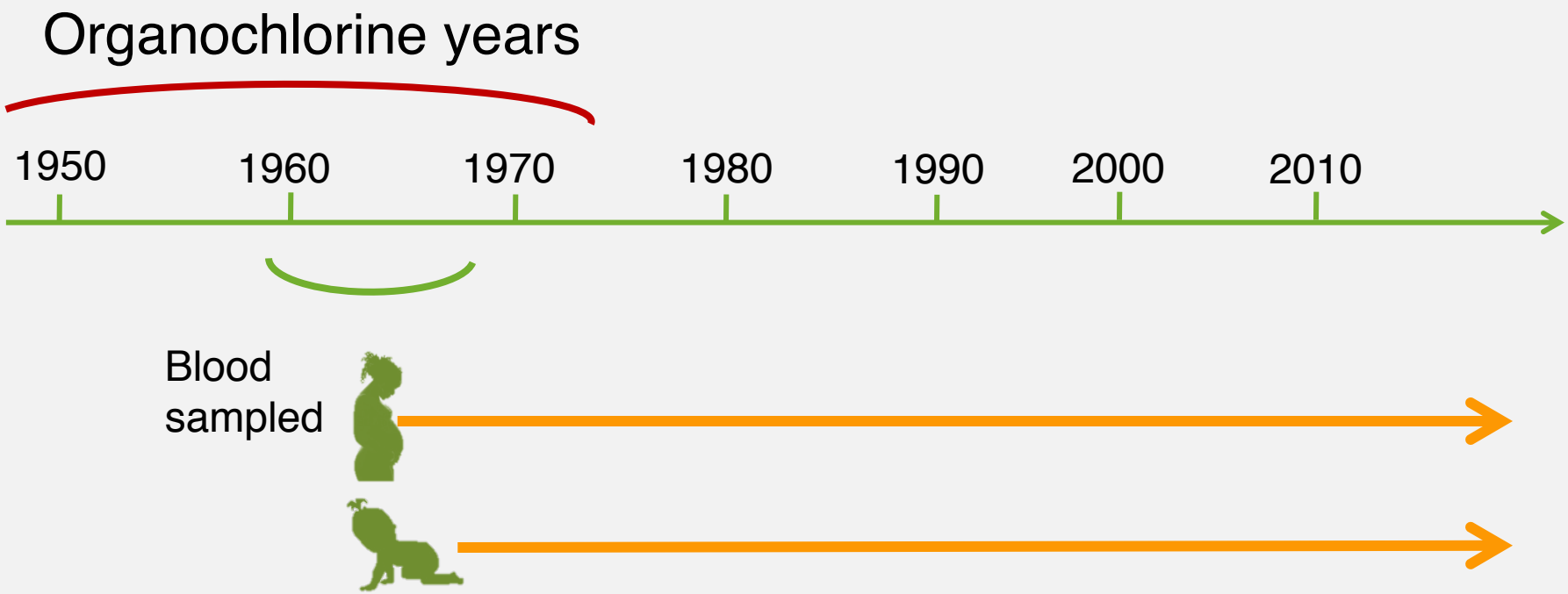
Metabolome wide association study (MWAS) to gauge bioeffect



chds
Child Health and Development Studies

During 1959-1967
over 15,000 pregnant women in the
Kaiser Permanente Health Plan
joined the CHDS.

Child Health and Development Studies



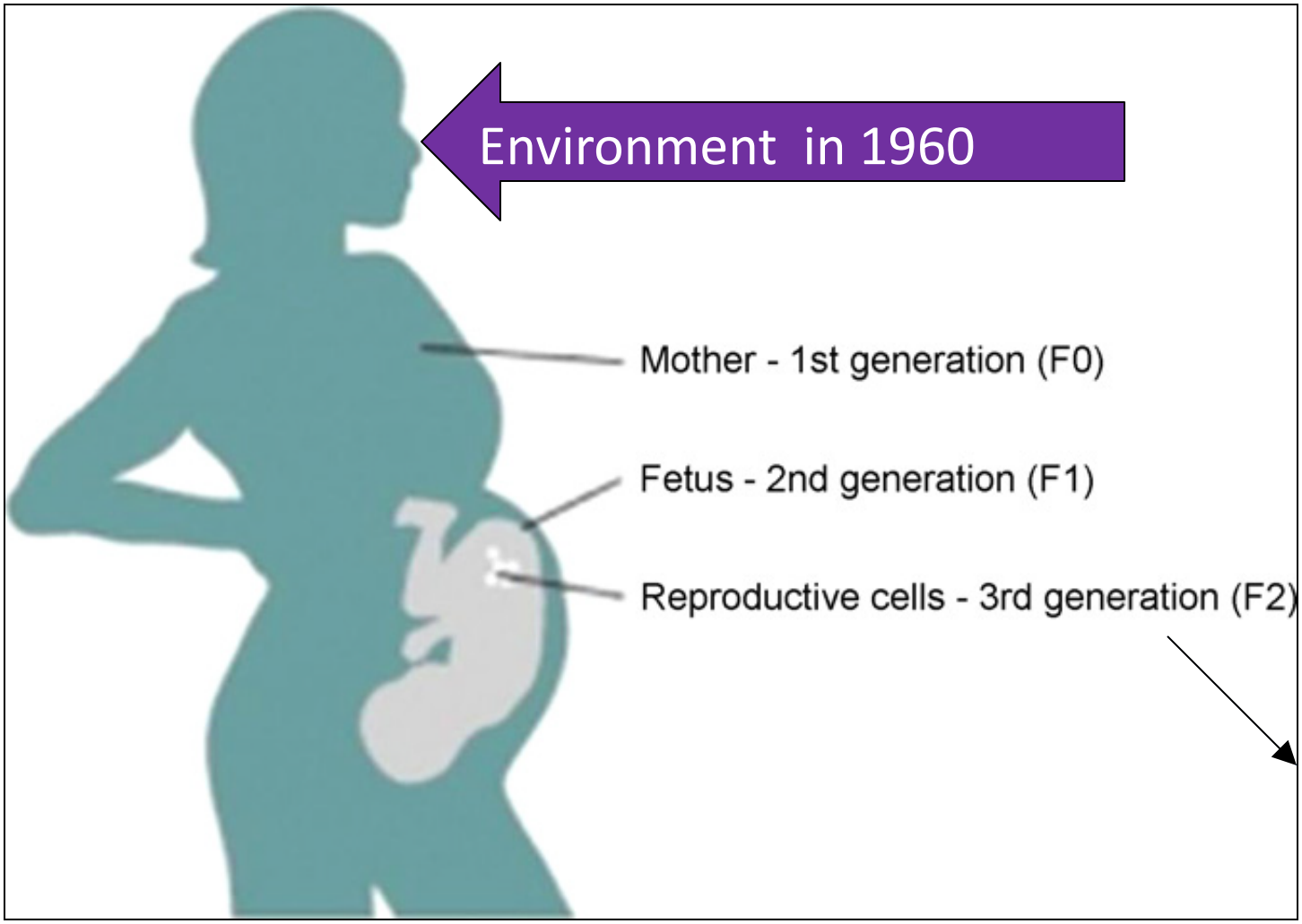
Blood samples from our cohort were taken during the height of organochlorine use and allow us to measure exposure for the mother, fetus and future grandchildren

chds
Child Health and Development Studies

Slide design courtesy of Silent Spring Institute

Vulnerability Differs by Generation

- One exposure can impact three or more generations of women differently



Adapted from Perera F, Herbstman J, Reproductive Toxicology PMID: 21256208

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Metabolome Wide Association Study of serum DDT and DDE in Pregnancy and Early Postpartum

Xin Hu[a], Shuzhao Li[a], Piera Cirillo[b], Nickilou Krigbaum[b], ViLinh Tran[a], Tomoko Ishikawa[c], Michele A. La Merrill[c], Dean P. Jones[a,**], Barbara Cohn[b,*]

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[b] *The Center for Research on Women and Children's Health, Child Health and Development Studies, Public Health Institute, 1683 Shattuck Avenue, Suite B, Berkeley, CA 94709, USA*

[c] *Department of Environmental Toxicology, University of California, Davis, CA 95616, USA*

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Metabolome Wide Association Study of Serum Poly and Perfluoroalkyl Substances (PFASs) in Pregnancy and Early Postpartum

Xin Hu[a], Shuzhao Li[a], Piera M. Cirillo[b], Nickilou Y. Krigbaum[b], ViLinh Tran[a], Dean P. Jones[a,**], Barbara A. Cohn[b,*]

[a] *Department of Medicine, School of Medicine, Emory University, Atlanta, GA 30303, USA*
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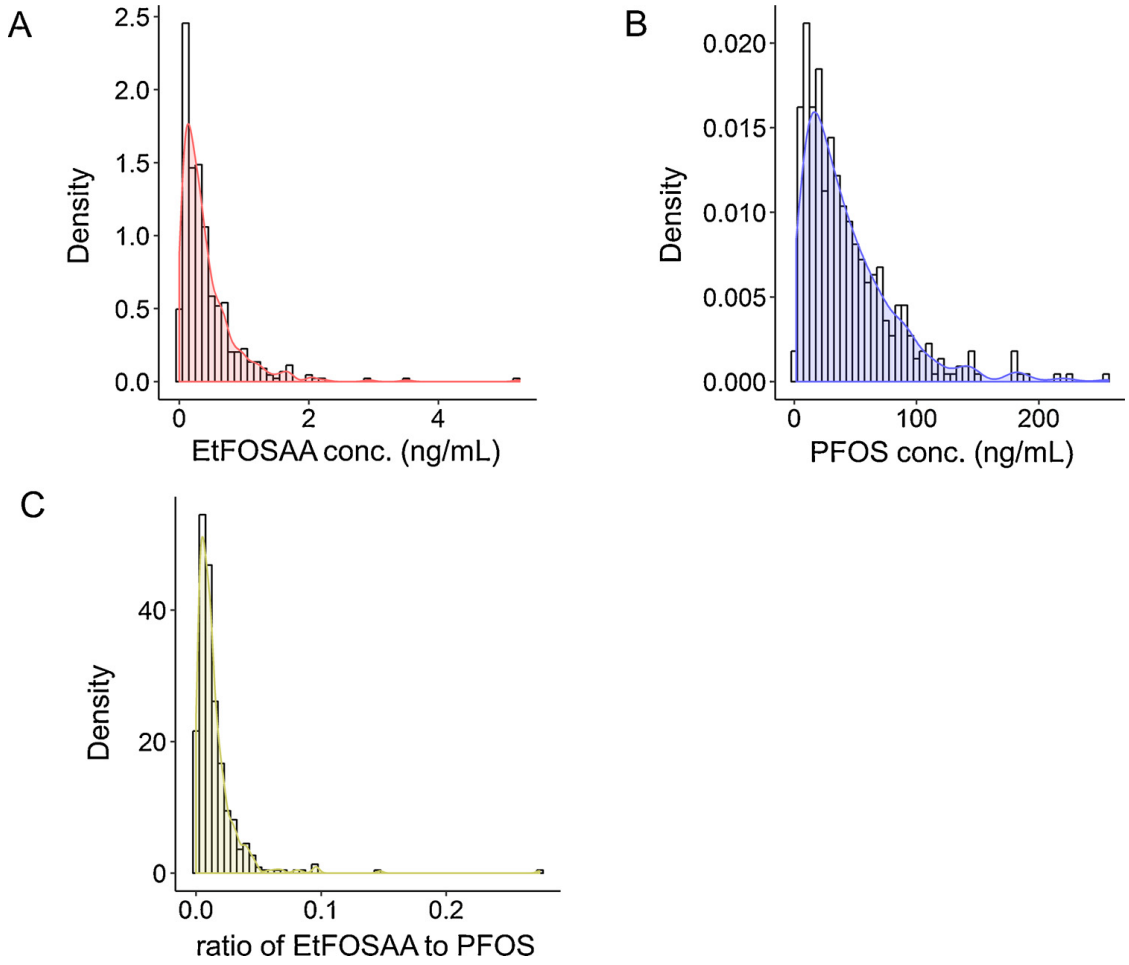


Fig. 1. Distribution of serum EtFOSAA (A), PFOS (B) concentrations and the ratio of EtFOSAA to PFOS (C) in 397 subjects from the Child Health and Development Studies (CHDS) cohort, visualized by histogram and density curves.

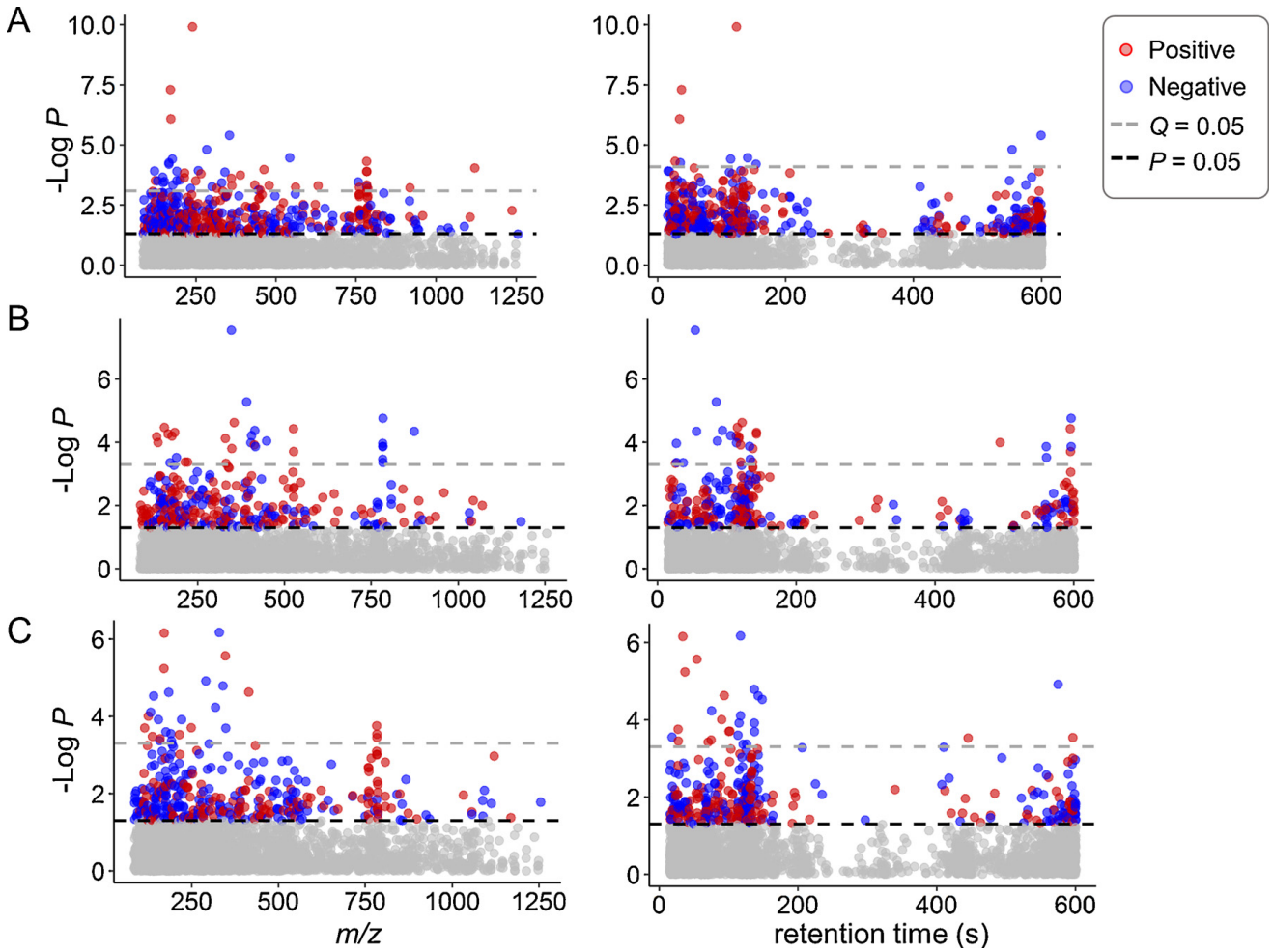


Fig. 2. Metabolome-wide association study (MWAS) of serum EtFOSAA (A), PFOS (B) and the EtFOSAA/PFOS ratio (C) in 397 subjects from the CHDS cohort. Type 1 Manhattan plot for –log P vs m/z features and type 2 Manhattan plot for –log P vs retention time with C18 chromatography separation are presented left and right, respectively. Red indicates positive correlation between significant features ($P < 0.05$) and exposure; blue indicates negative correlation.

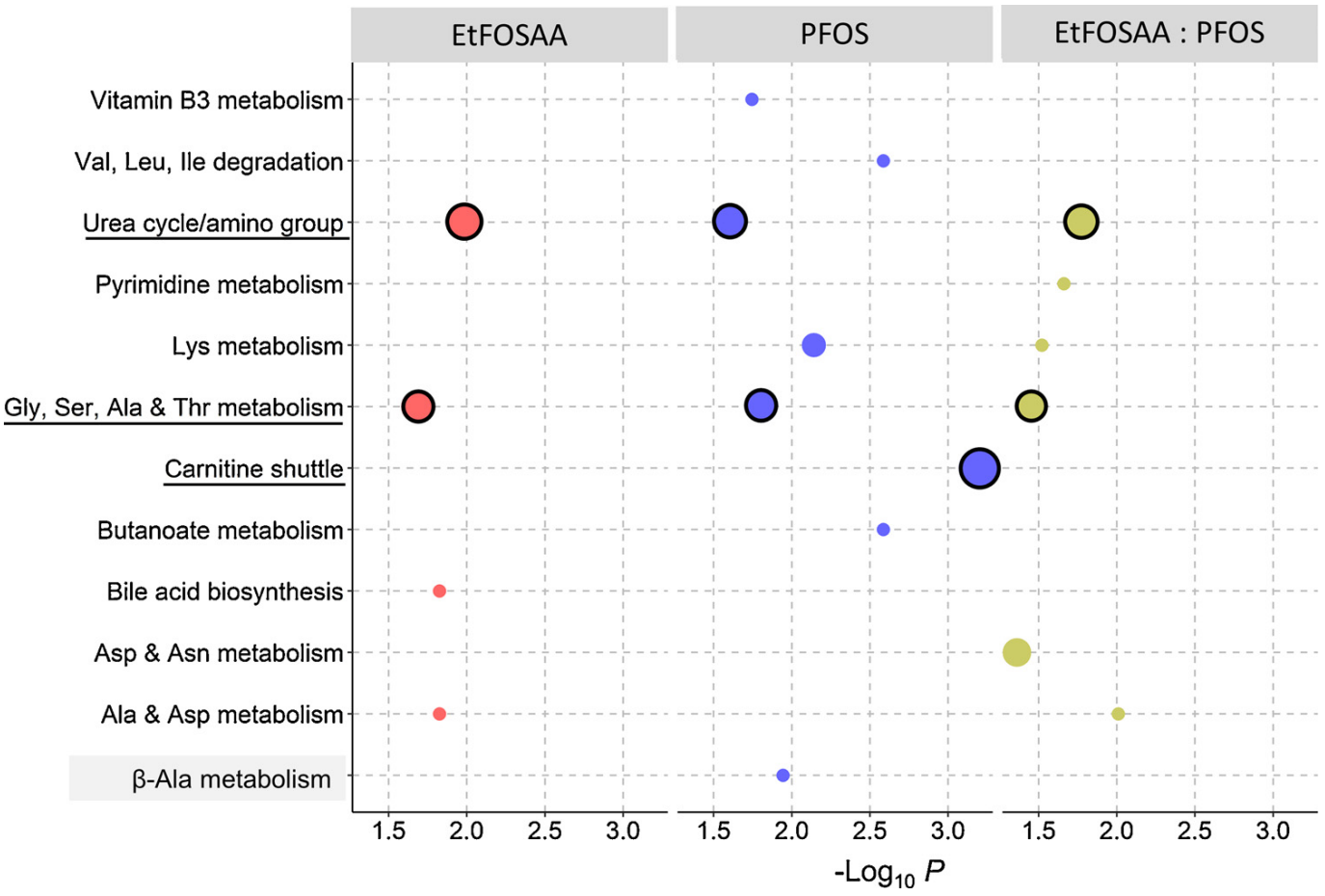


Fig. 3. Metabolic pathways enriched by significant features associated with EtFOSAA, PFOS concentrations and the EtFOSAA/PFOS ratio. Size of circles is proportional to the overlap size (i.e. number of significant metabolites in each pathway). Major pathways (≥ 6 metabolites) are circled in black outline.

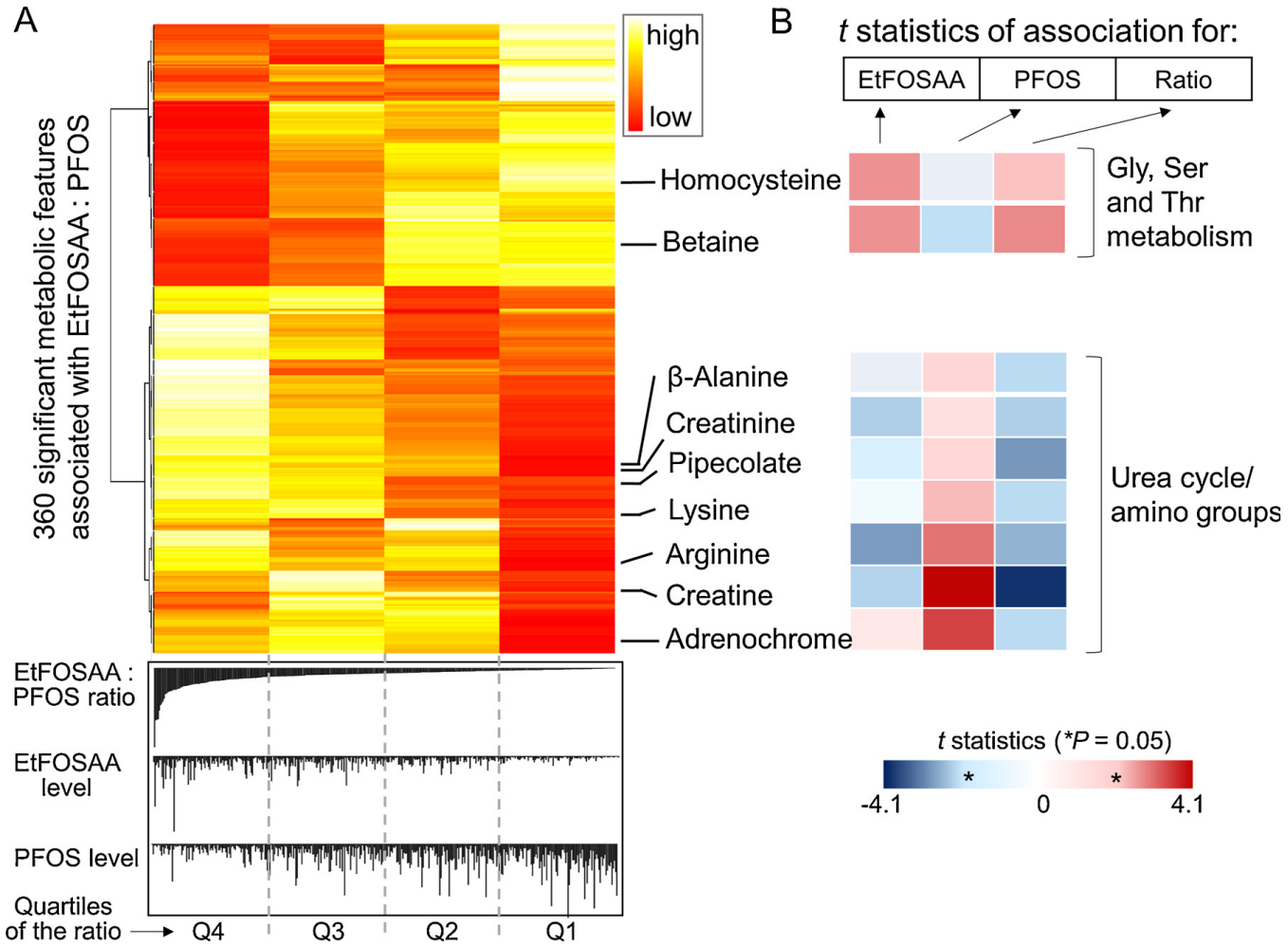
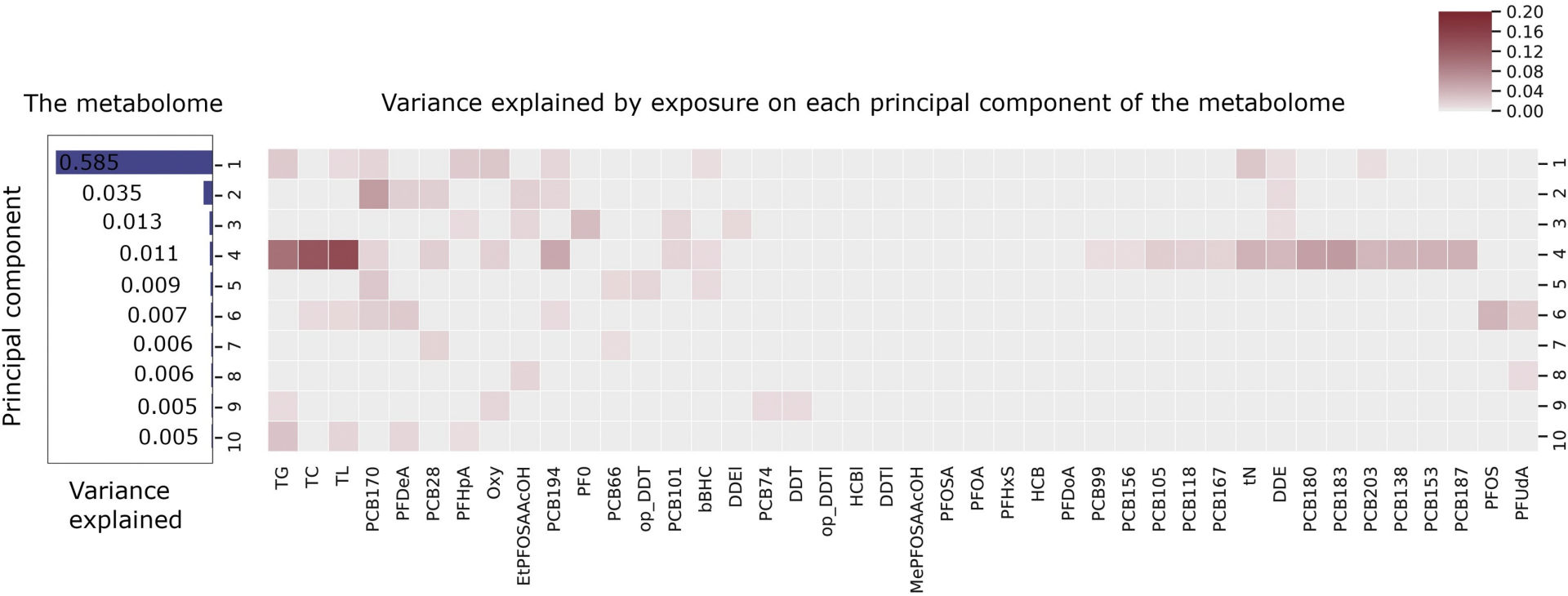


Fig. 4. Key metabolites in two major common pathways associated with EtFOSAA and PFOS exposure. A: Heat map of quartile average abundance of metabolites significantly associated with the EtFOSAA/PFOS ratio. The metabolites here are annotated by accurate mass (5 ppm, details in Supplemental Table S2), and selected metabolites were further confirmed by authentic chemical standards (arginine, lysine, creatine, creatinine, β-alanine).

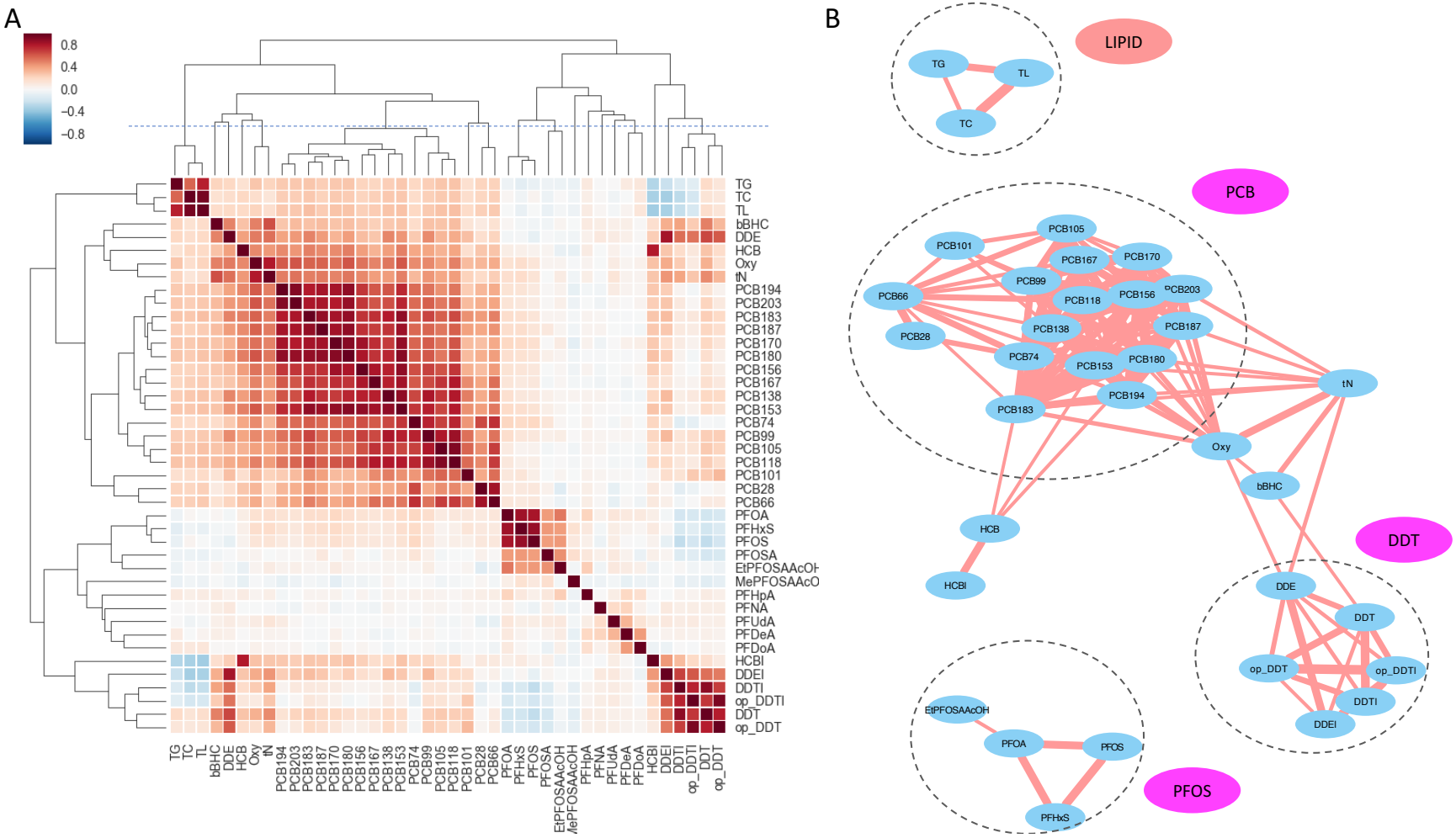
Mixed exposures

Li et al, 2019. https://doi.org/10.1016/j.reprotox.2019.06.013



Variance analysis of the metabolome and environmental exposures.
Principal component analysis was performed on the serum metabolomics data from 397 CHDS participants, and the contribution of top 10 principal components is shown on the left. Corresponding to each of the components, the variance explained by each exposure (R2) is colored coded in the heatmap on the right. Data are only shown for features with $p < 0.05$ in Pearson correlation analysis. The lipid measures, TG, TC and TL, are included as control.

Exposure communities in CHDS data



Acknowledgement

Emory University
Dean P. Jones
Xin Hu
Douglas Walker
ViLinh Tran
Bill Liang
Judy Fridovich-Keil
Taylor Fischer

CHDS
Barbara Cohn
Piera Cirrilo
Nickilou Krigbaum

CHEAR - U2CES026560
Common Fund Metabolomics - U01OD026489, U2COD026485
HERCULES - P30ES019776
Center for Children's Health - P50ES026071, EPA 83615301
NIAID - UH2AI132345, U19AI090023
California Breast Cancer Research Program - 21UB-8002