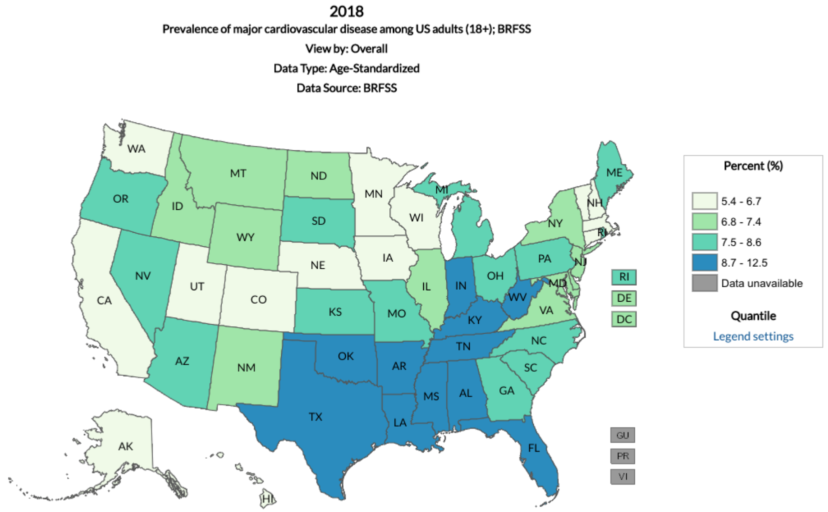
Environmental Health and the HELIX Project

David Conti, PhD

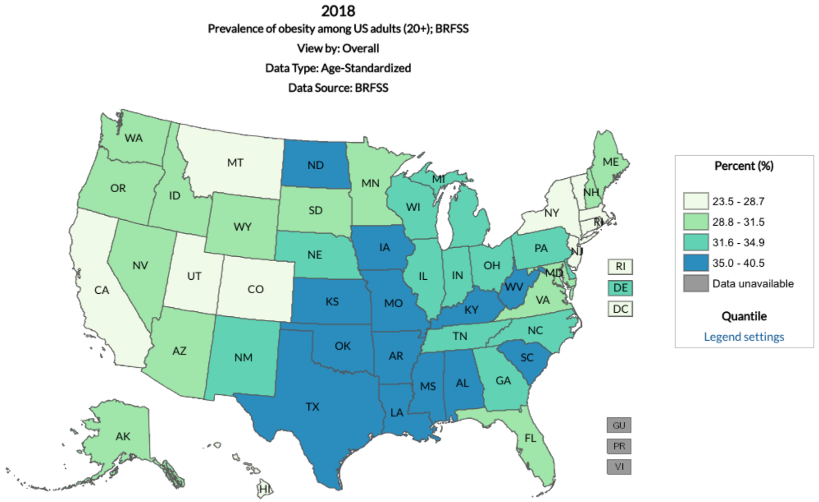
Prevalence of Chronic Cardiometabolic Diseases and Cancer among U.S. Adults

CDC BRFSS, 2018
US Cancer Registry, 2017

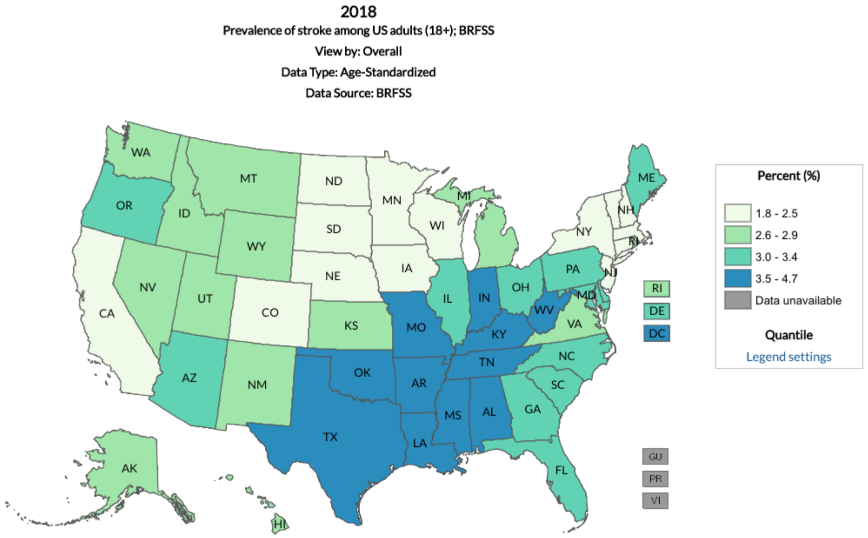
Cardiovascular Disease



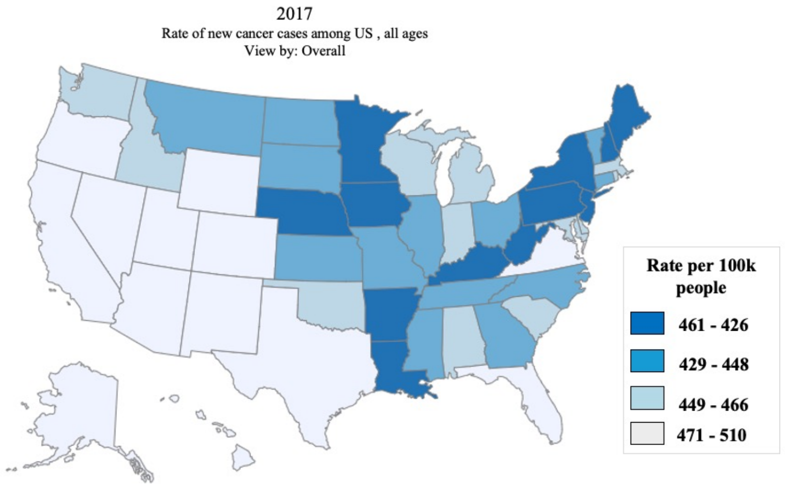
Obesity



Stroke

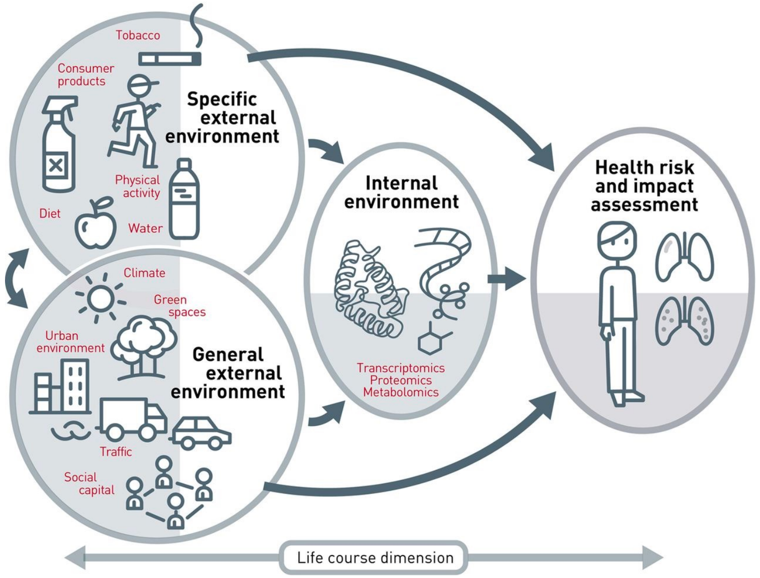


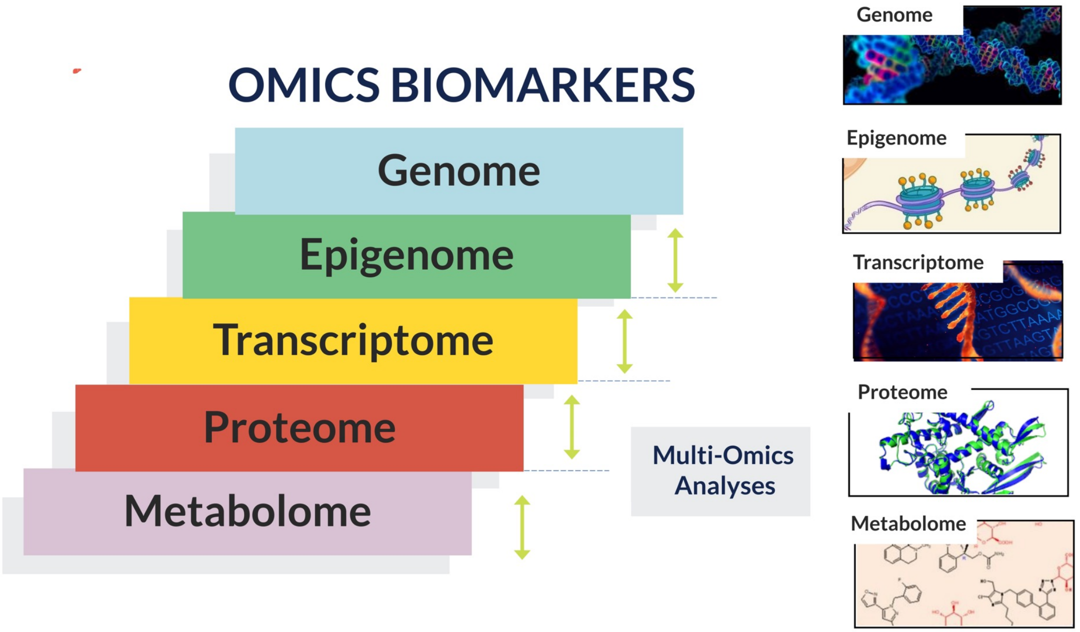
Cancer




THE EXPOSOME:
A New Paradigm for Environmental Health

Features of the Exposome

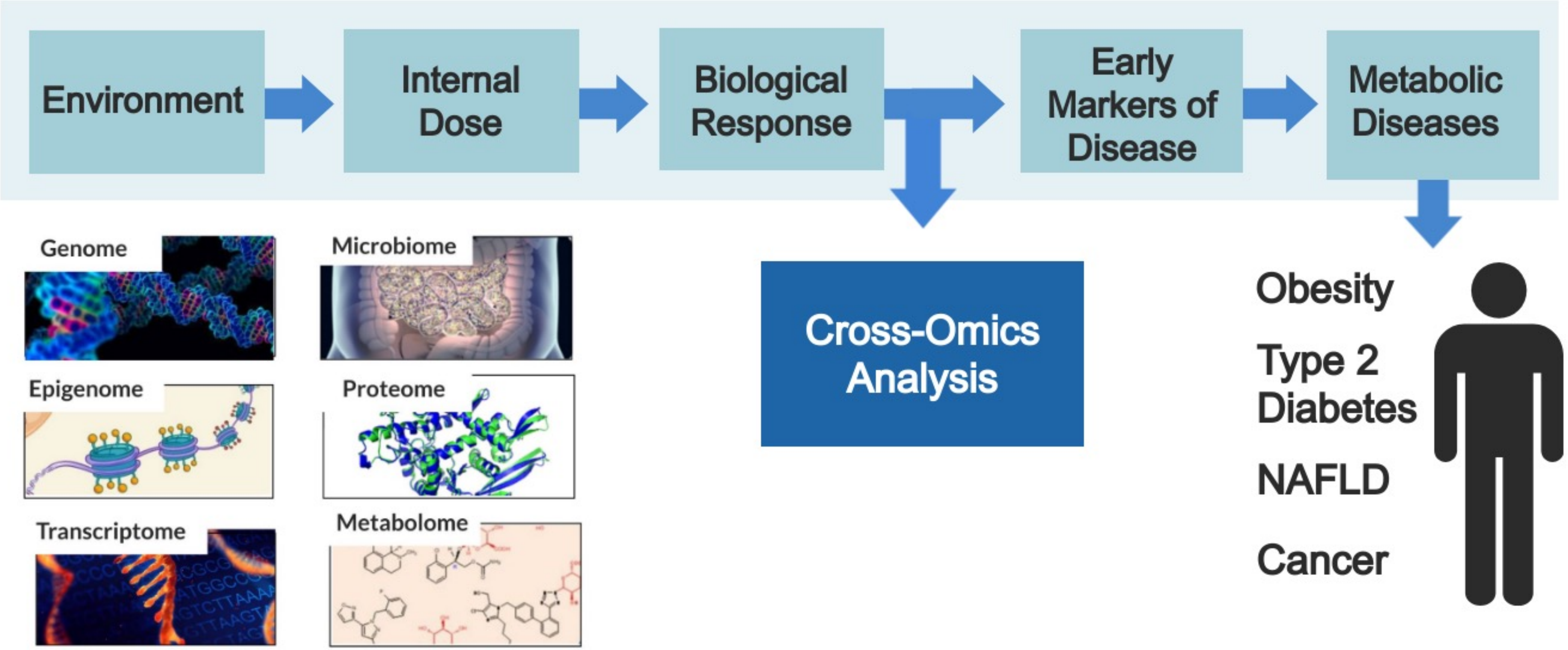




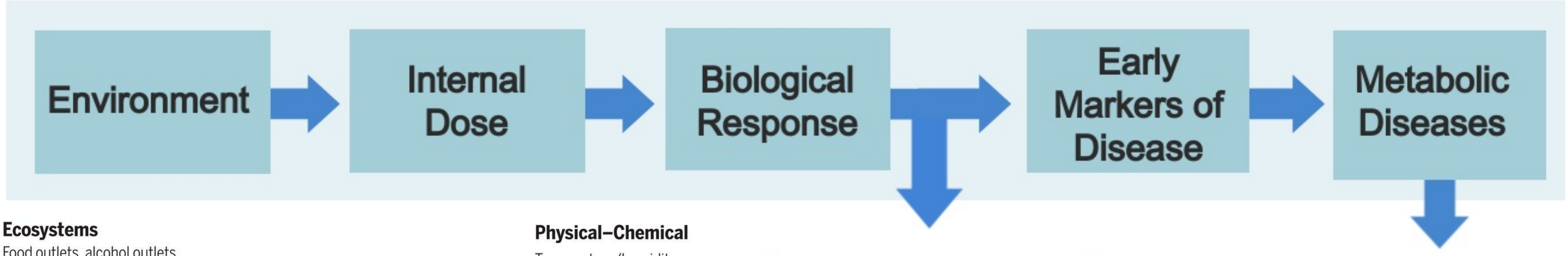
1. **Holistic**
   - Complex system, multiple exposures
2. **Life Course**
   - Temporal sequence
3. **New tools-technologies**
   - Coverage and accuracy of exposures
4. **Cross-Omics analysis**
   - Omics, early biological responses
5. **Untargeted discovery**
   - Unknown exposures

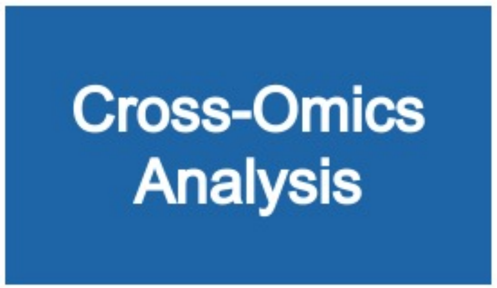
Wild C P Int. J. Epidemiol. 2012
Vermuelen, Science 2020

Environmental determinants of disease: from single exposure to cross-omics approaches



Environmental determinants of disease: from single exposure to cross-omics approaches

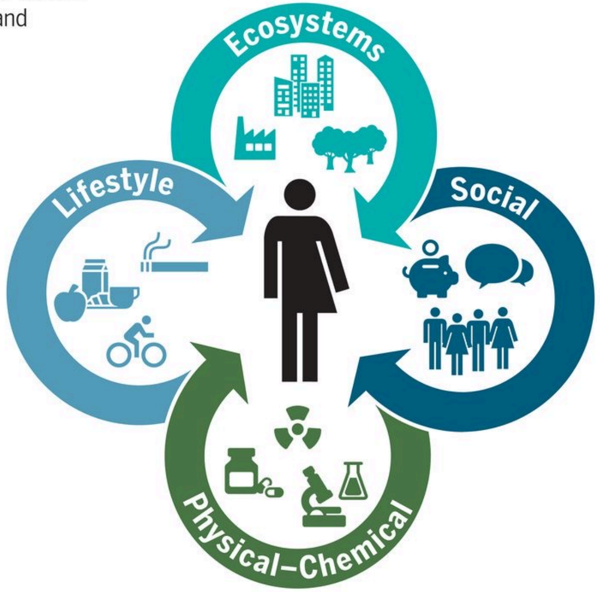




Ecosystems
Food outlets, alcohol outlets
Built environment and urban land uses
Population density
Walkability
Green/blue space

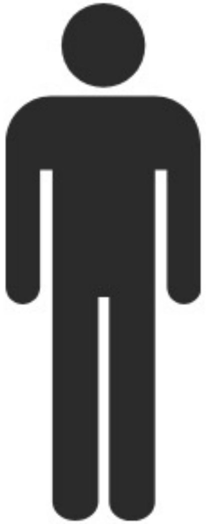
Lifestyle
Physical activity
Sleep behavior
Diet
Drug use
Smoking
Alcohol use

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

Obesity
Type 2 Diabetes
NAFLD
Cancer



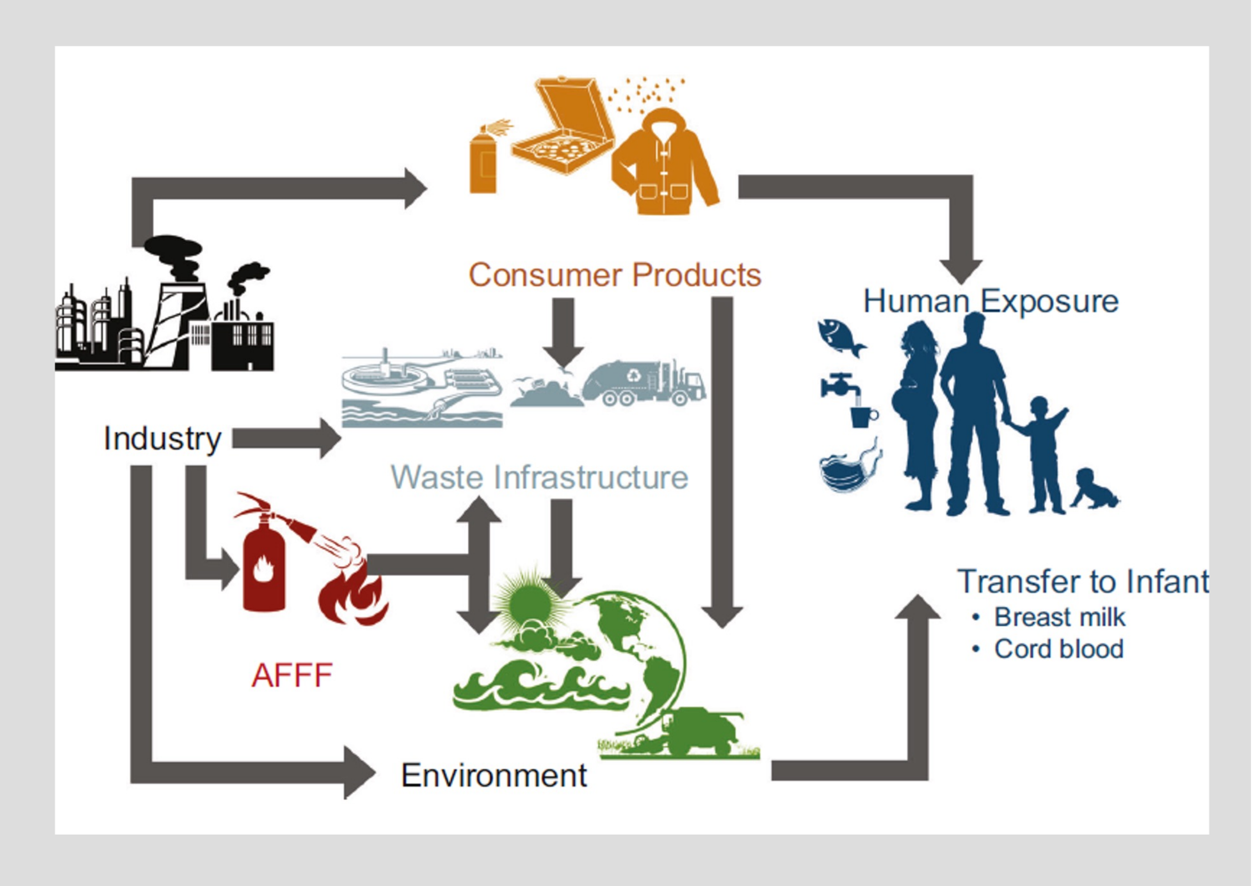
EXAMPLE: PFAS

Per- and polyfluoroalkyl substances (PFAS) – The new *forever* chemicals

What are PFAS?

How are we exposed?

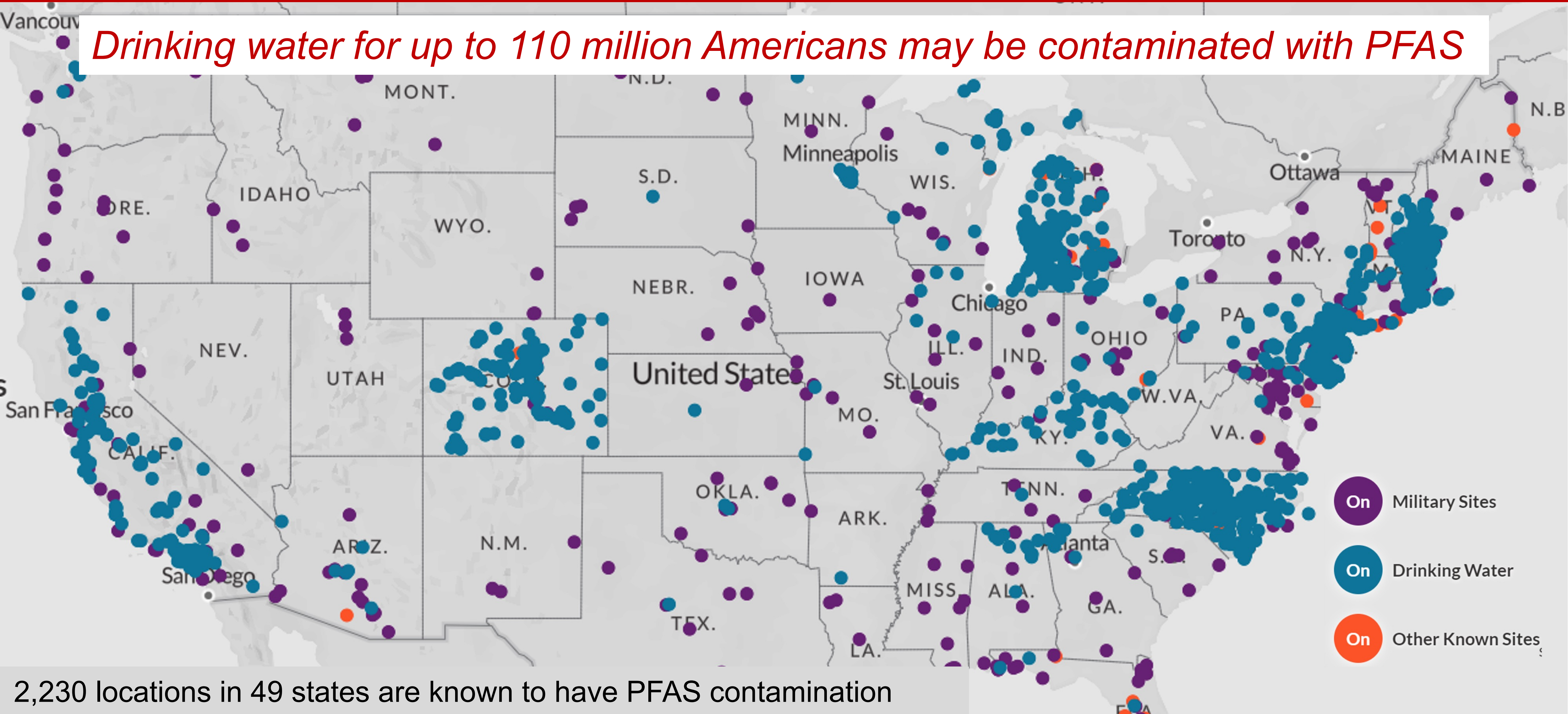
- > 7,000 chemicals
- **PFAS** have been widely used in **industrial applications** and **consumer products**
- **Resistant to degradation**
- **Detected in blood of almost everyone in the U.S.**



Sunderland et al., J Expos Sci & Epidemiol, 2019

PFAS Water Contamination in the United States
July 8, 2022 (EWG)

Drinking water for up to 110 million Americans may be contaminated with PFAS



2,230 locations in 49 states are known to have PFAS contamination

Contents lists available at ScienceDirect

Environment International

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

Perfluoroalkyl substances, metabolomic profiling, and alterations in glucose homeostasis among overweight and obese Hispanic children: A proof-of-concept analysis

Tanya L. Alderete[a,1], Ran Jin[b,1], Douglas I. Walker[c,1], Damaskini Valvi[d], Zhanghua Chen[b], Dean P. Jones[e], Cheng Peng[b], Frank D. Gilliland[b], Kiros Berhane[b], David V. Conti[b], Michael I. Goran[f], Lida Chatzi[b,*]

Contents lists available at ScienceDirect

Environment International

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

Perfluoroalkyl substances and severity of nonalcoholic fatty liver in Children: An untargeted metabolomics approach

Ran Jin[a], Rob McConnell[a], Cioffi Catherine[b], Shujing Xu[a], Douglas I. Walker[c,d,1], Nikos Stratakis[a], Dean P. Jones[c], Gary W. Miller[d,2], Cheng Peng[a], David V. Conti[a], Miriam B. Vos[b,e,3], Leda Chatzi[a,*,3]

PFAS and Metabolic Diseases

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

ORIGINAL

Prenatal Exposure to Perfluoroalkyl Substances Associated with Increased Susceptibility to Liver Injury in Children

Nikos Stratakis, David V Conti, Ran Jin, Katerina Margetaki, Damaskini Valvi, Alexandros P. Siskos, Léa Maitre, Erika Garcia, Nerea Varo, Yinqi Zhao, Theano Roumeliotaki, Marina Vafeiadi, Jose Urquiza, Silvia Fernández-Barrés, Barbara Heude, Xavier Basagana, Maribel Casas, Serena Fossati, Regina Gražulevičienė, Sandra Andrušaitytė, Karan Uppal, Rosemary RC. McEachan, Eleni Papadopoulou, Oliver Robinson, Line Småstuen Haug, John Wright, Miriam B. Vos, Hector C. Keun, Martine Vrijheid, Kiros T. Berhane, Rob McConnell, Lidada Chatzi ... See fewer authors

First published: 01 August 2020 | https://doi.org/10.1002/hep.31483

Contents lists available at ScienceDirect

Environment International

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

Dysregulated lipid and fatty acid metabolism link perfluoroalkyl substances exposure and impaired glucose metabolism in young adults

Zhanghua Chen[a,*], Tingyu Yang[a], Douglas I. Walker[b], Duncan C. Thomas[c], Chenyu Qiu[a], Leda Chatzi[a], Tanya L. Alderete[d], Jeniffer S. Kim[e], David V. Conti[c], Carrie V. Breton[a], Donghai Liang[f], Elizabeth R. Hauser[g], Dean P. Jones[h], Frank D. Gilliland[a]

Prenatal exposure to PFAS and Increased Susceptibility to Liver Injury in Children

Environmental Factor
Your Online Source for NIEHS News
JANUARY 2021
NIH National Institute of Environmental Health Sciences

2020 Papers of the Year

From the nearly 3,500 publications by NIEHS researchers and grantees in 2020, the institute's leaders selected 27 for special recognition as Papers of the Year.

BY ROBIN ARNETTE

Research funded by grants

PFAS linked with liver injury in children

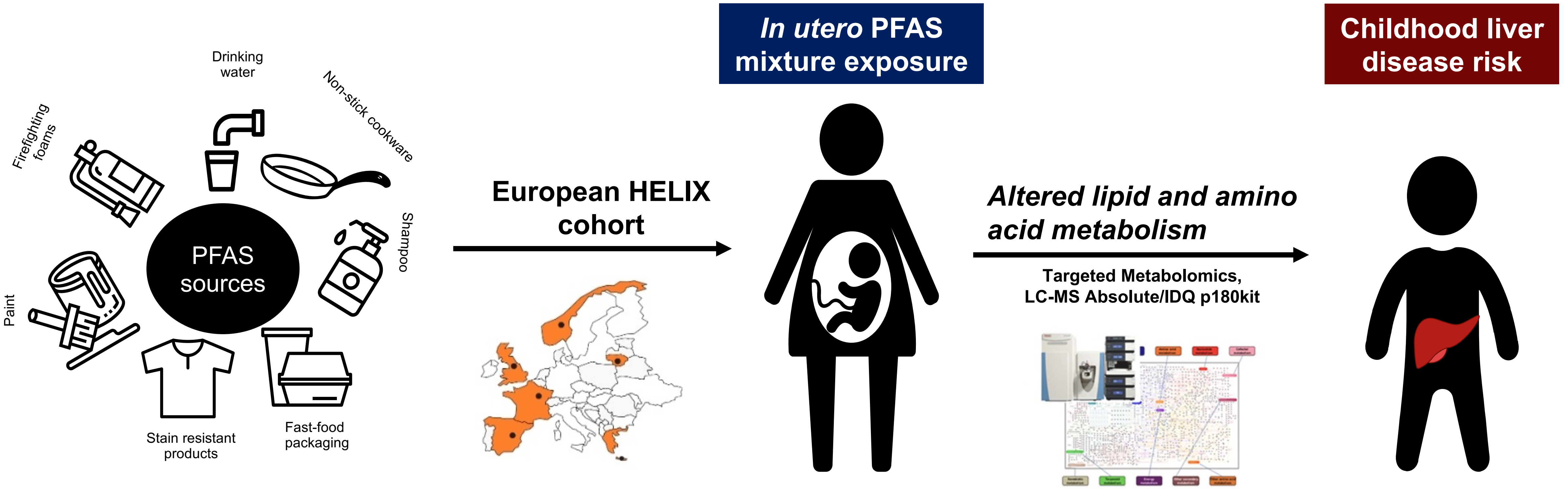
Exposure to per- and polyfluoroalkyl substances (PFAS) in the womb may increase liver injury risk in children, according to NIEHS-funded researchers. This study is the first to examine the impact of early life exposures to a PFAS mixture on child liver injury. PFAS, a large group of synthetic chemicals found in a variety of consumer products, have been linked to immune dysfunction, altered metabolism, brain development, and certain cancers.

- Evaluation of **PFAS mixture**
- Integration of **metabolomics**
- Prospective follow-up design

Stratakis et al, Hepatology 2020

Guided Hypotheses

Prenatal exposure to **PFAS** (perfluoroalkyl and polyfluoroalkyl substances) and risk of non-alcoholic fatty liver disease (**NAFLD**) in childhood



R21ES029681, 5P30ES007048-23

HELIX

Human Early Life Exposome

[1] Pregnancy

[2] Birth/Infancy

[3] Childhood 6-10 years

Maternal biomarker-based EDC exposures
(DDE, PCB-153, PFOA, PFOS, BPA, PBDE, Phthalates, heavy metals)

Pregnancy trimester-specific air pollution
(PM, NO2, traffic load)

CHILD LIVER INJURY
-Liver Enzymes
-CK-18
-Cytokines and Adipokines

Omics Data

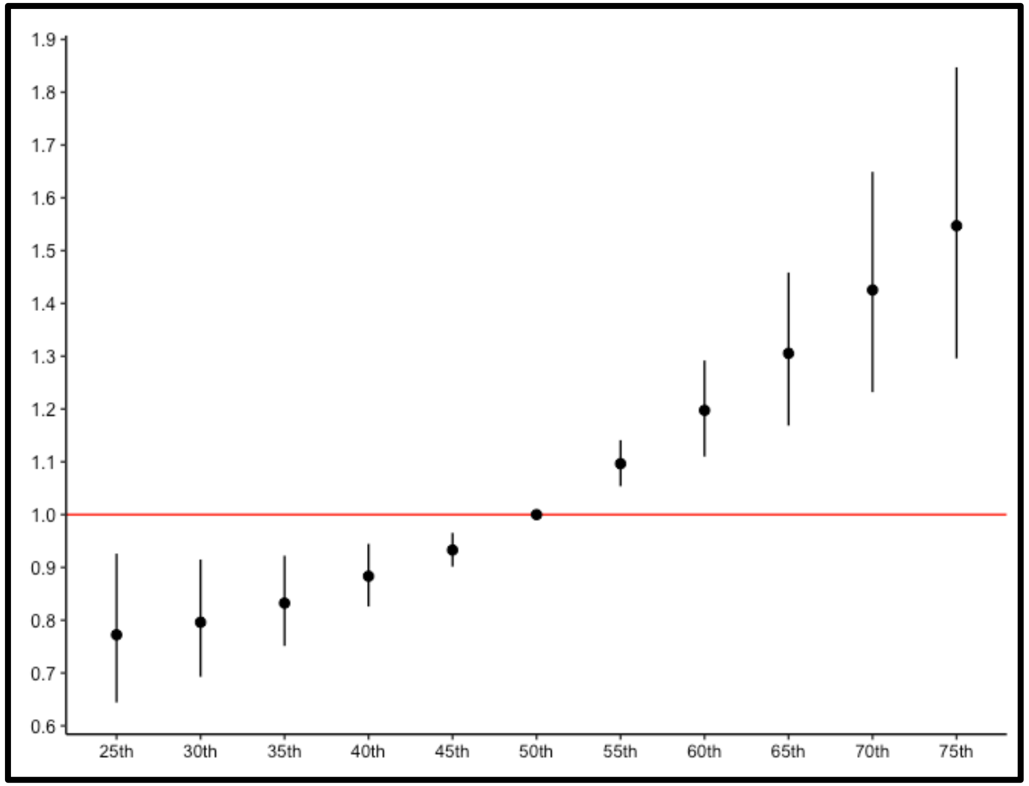
- Urinary metabolomics
- Serum metabolomics
- Proteomics
- Methylation
- Transcriptomics
- MicroRNA (miRNA)
- Mitochondrial DNA content

NIEHS R21 ES029681

HELIX BUILDING THE EARLY-LIFE EXPOSOME

Effect of PFAS Mixture During Pregnancy on Child Liver Injury Risk: BKMR Models

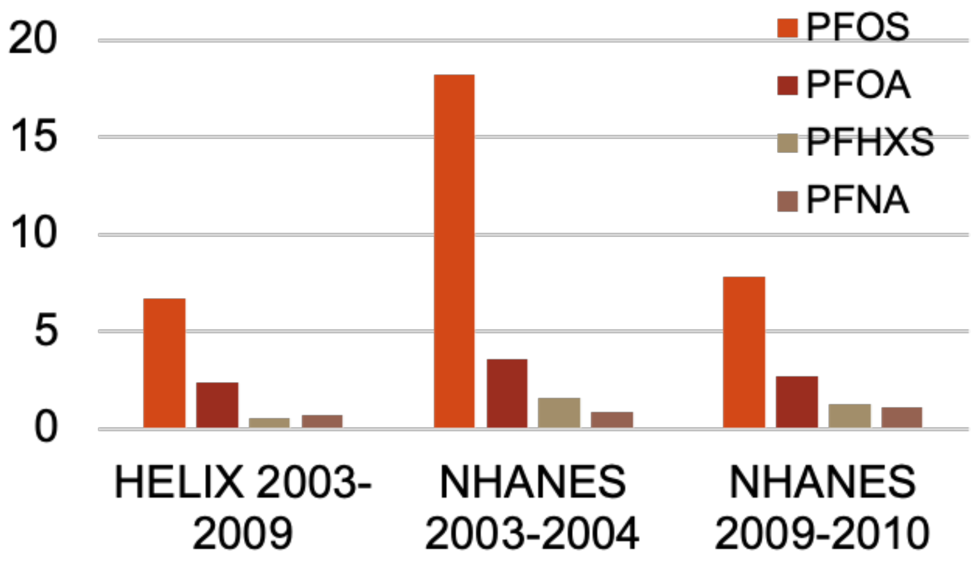
Joint effect of prenatal PFAS mixture on risk of pediatric liver injury (OR, 95% CI)



Maternal PFAS mixture (in percentiles)

Liver injury risk: Any liver enzyme serum concentrations >90th percentile

Median maternal PFAS concentration (ng/ml) in HELIX and female NHANES population



Stratakis et al, Hepatology 2020

Participating Cohorts

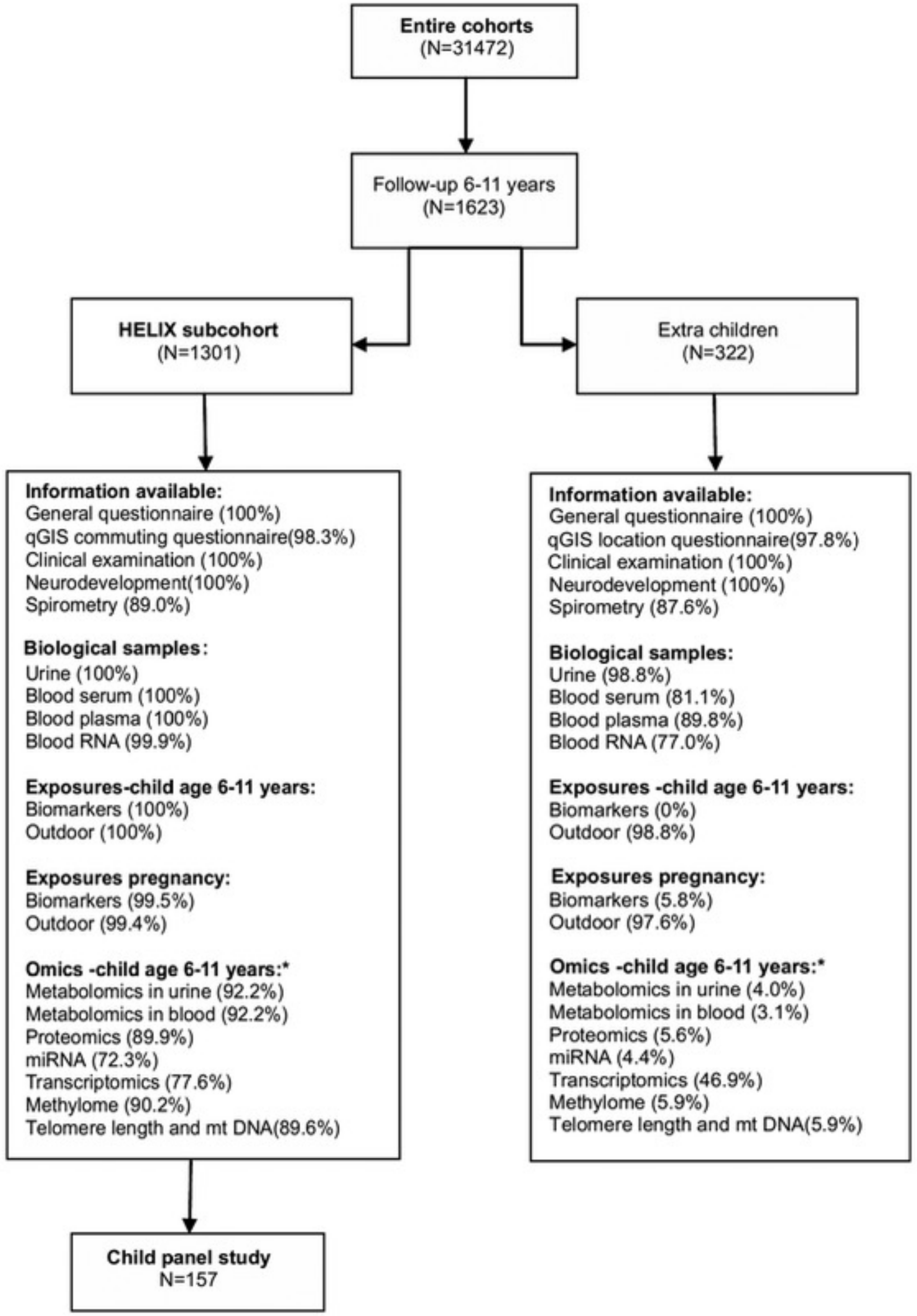
Table 1 Characteristics of the cohorts contributing to the HELIX cohort

Cohort	Recruitment in original cohort	Exclusions made during recruitment	Years of birth	Region covered by HELIX	No. of births in HELIX entire cohort
BiB, UK[5]	All pregnant women who attended the oral glucose tolerance test clinic at Bradford Royal Infirmary in weeks 26–28 of pregnancy.	Women who planned to move away from Bradford before birth were excluded.	2007–2010	Bradford	10 849
EDEN, France[6]	Pregnant women who attended prenatal care at the University hospitals of Nancy and Poitiers recruited before 24 weeks of amenorrhoea.	Twin pregnancies, women with known diabetes before pregnancy, insufficient French language skills and intention to move away from the recruitment area were excluded.	2003–2006	Nancy and Poitiers, urban areas	1900
INMA, Spain[7]	Pregnant women who attended a prenatal care centre in the study region during weeks 6–10 of pregnancy.	Women who resided or intended to deliver outside the study area, who were aged under 16 years, who had twin or multiple pregnancies, who had assisted reproduction or who had communication problems were excluded.	2003–2008	Gipuzkoa Sabadell Valencia	2063
KANC, Lithuania[8]	Pregnant women who attended one of four prenatal care clinics affiliated to the hospitals of the Kaunas University of Medicine during first trimester of pregnancy.	Women who lived outside Kaunas municipality, had medical records of pregnancy induced hypertension and/or diabetes were excluded.	2007–2008	Kaunas	4107
MoBa, Norway[9]	Recruitment at the first ultrasound (US) scan, ie, during the 17–18 weeks of gestation. All women who gave singleton births in the participating maternity units.	None	1999–2008	Oslo	11 095
RHEA, Greece[10]	Pregnant women who attended US examination before 15 week of pregnancy with residence in and near Heraklion at Crete.	Women who were aged under 16 years or who had communication problems were excluded.	2007–2008	Heraklion	1458
Total					31 472

BiB, Born in Bradford; EDEN, Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant; INMA, INfancia y Medio Ambiente; KANC, Kaunus cohort; MoBa, Norwegian Mother and Child Cohort Study.

Maitre et al. 2018

HELIX BUILDING THE EARLY-LIFE EXPOSOME



Maitre et al. 2018

Figure 1 Flow chart describing design and available data. GIS, Geographic Intelligent Software; HELIX, Human Early Life Exposome; miRNA, microRNA; mtDNA, mitochondrial DNA. *Omics data available after quality control

HELIX BUILDING THE EARLY-LIFE EXPOSOME

Table 2 Health outcomes harmonised across the entire cohort between birth and 5 years of age

Health/development outcomes	Methods	BiB	EDEN	INMA	KANC	MoBa	RHEA	Total number of subjects in the harmonised dataset
Birth								
Birth weight	Measurements	√	√	√	√	√	√	31 472
Gestational duration	Medical records/ ultrasound	√	√	√	√	√	√	31 472
0–5 years								
Repeated weight, height, BMI	Measurements and records	√	√	√	√	√	√	28 305
Waist circumference	Measurements							
1–2 years		√	√	√			√	4598
4–5 years		√	√	√			√	4275
Skinfolds	Measurements							
1–2 years		√	√				√	3364
4–5 years		√	√				√	2774
Blood pressure (4–5 years)	Measurements	√	√	√			√	5182
Cognition	Psychologist-administered tests and parental questionnaires		√	√			√	3470
Motor skills, language	Psychologist-administered tests and parental questionnaires	√	√	√		√	√	10 245
Behaviour	Questionnaires	√	√	√	√	√	√	12 644
Asthma, wheeze	Questionnaires	√	√	√	√	√	√	12 068
Lung function (4–5 years)	Spirometry	√	√	√			√	2719

BiB, Born in Bradford; BMI, body mass index; EDEN, Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant; INMA, INfancia y Medio Ambiente; KANC, Kaunus cohort; MoBa, Norwegian Mother and Child Cohort Study.

Maitre et al. 2

BUILDING THE EARLY-LIFE EXPOSOME

Table 3 Exposure estimates available in the HELIX entire cohort and subcohort

Exposure group	Description*	Pregnancy (and specific trimesters)*	Postnatal 0–5 years	Subcohort 6–11 years
Outdoor and urban exposure estimates available in the entire cohort and in the subcohort				
Atmospheric pollutants	NO_2, $PM_{2.5}$, PM_{10}, $PM_{2.5}$ (absorbance ratio)	√ *	√	√
Ultraviolet (UV)	Ambient UV radiation levels	√	√	√
Surrounding natural space	Average normalised difference vegetation index within buffers of 100, 300 and 500 m Size of and distance to nearest major green or blue space (>5000 m^2) Presence of a major green or blue space in a distance of 300 m	√	√	√
Meteorology	Land surface temperature average in a buffer of 50 m Temperature from meteorological stations (mean, minimum and maximum) Humidity percentage from meteorological stations Atmospheric pressure data from the ESCAPE project	√ *	√	√
Built environment	Population density: inhabitants per km^2 Building density: built area in m^2 per km^2 within 100 and 300 m buffers Street connectivity: number of road intersections per km^2 within 100 and 300 m buffers Accessibility: metres of bus public transport lines and number of bus public transport stops per km^2 within 100, 300 and 500 m buffers Facilities: facility richness index and facility density index in a 300 m buffer Land use evenness index Walkability index in 300 m buffer*	√	√	√
Traffic	Total traffic load of major roads in a 100 m buffer, total traffic load in a 100 m buffer, traffic density on nearest road and inverse distance to nearest road	√	√	√
Road traffic noise	Day and night time road noise levels	√	√	√

Table 3 Exposure estimates available in the HELIX entire cohort and subcohort

Exposure group	Description*	Pregnancy (and specific trimesters)*	Postnatal 0–5 years	Subcohort 6–11 years
Contaminant exposure estimates available in the HELIX subcohort				
Organochlorine compounds	Blood concentrations of dichlorodiphenyldichloroethylene, dichlorodiphenyltrichloroethane, hexachlorobenzene and polychlorinated biphenyl—118, 68, 153, 170, 180. With and without lipid adjustment.	√	–	√
Brominated compounds	Blood concentrations of polybrominated diphenyl ether—47, 153. With and without lipid adjustment.	√	–	√
Perfluorinated alkylated substances	Blood concentrations of perfluorooctanoate, perfluorononanoate, perfluoroundecanoate, perfluorohexane sulfonate, perfluorooctane sulfonate	√	–	√
Metals and essential elements	Whole blood concentrations of arsenic, cadmium, cesium, cobalt, copper, lead, manganese, mercury, molybdenum, thallium, potassium, magnesium, sodium, selenium and zinc	√	–	√
Phthalate metabolites	Urine concentrations of monoethyl phthalate, mono-iso-butyl phthalate, mono-n-butyl phthalate, mono benzyl phthalate, mono-2-ethylhexyl phthalate, mono-2-ethyl-5-hydroxyhexyl phthalate, mono-2-ethyl-5-oxohexyl phthalate, mono-2-ethyl 5-carboxypentyl phthalate, mono-4-methyl-7-hydroxyoctyl phthalate, mono-4-methyl-7-oxooctyl phthalate. With and without creatinine adjustment.	√	–	√

Maitre et al. 2018

HELIX BUILDING THE EARLY-LIFE EXPOSOME

Table 3 Exposure estimates available in the HELIX entire cohort and subcohort

Exposure group	Description*	Pregnancy (and specific trimesters)*	Postnatal 0–5 years	Subcohort 6–11 years
Phenols	Urine concentrations of methyl paraben, ethyl paraben , bisphenol A, propyl paraben, N-butyl paraben, oxybenzone, triclosan. With and without creatinine adjustment.	√	–	√
Organophosphate pesticide metabolites	Urine concentrations of dimethyl phosphate, dimethyl thiophosphate, dimethyl dithiophosphate, diethyl phosphate, diethyl thiophosphate, diethyl dithiophosphate. With and without creatinine adjustment.	√	–	√
Tobacco smoking	Urine levels of cotinine. Questionnaire on active and passive smoking.	√	–	√
Water disinfection by-products	Total concentration of total trihalomethanes (THMs), chloroform and total brominated THMs estimated in tap water from water company concentration and distribution data.	√	–	–
Indoor air	Prediction models for indoor air concentrations of NO_2, $PM_{2.5}$, PM_{abs}, benzene and toluene, ethylbenzene, xylene using panel study data from indoor air samplers.	–	–	√

Maitre et al. 2018

HELIX BUILDING THE EARLY-LIFE EXPOSOME

Table 5 Measurements performed in the child and pregnancy panel studies

Measurement	No. of subjects in child panel study*	No. of subjects in pregnancy panel study*	Description	Measurement point/ period
Geolocation and mobility	146	126	Smartphone GPS with ExpoApp application installed	7 days in each study period
Physical activity	145	148	Smartphone and Actigraph accelerometer	7 days in each study period
NO_2	154	158	Passive samplers for NO_2 installed in the home	7 days in each study period
BTEX	154	158	Passive samplers for BTEX installed in the home	7 days in each study period
$PM_{2.5}$	92	90	Active $PM_{2.5}$ Cyclone pumps (BGI-400–4), carried by participants in backpack and installed in the home	Last 24 hours of each of the two study periods
Black carbon	89	66	MicroAthelometer (AE51) for continuous monitoring	Last 24 hours of each of the two study periods
UV	69	141	Electronic wrist band UV dosimeters[47]	7 days in each study period
Phthalates, phenols, organophosphate pesticides	152	–	Pool of bedtime and first morning urine	4 separate days in one study period
Phthalates, phenols, organophosphate pesticides, cotinine	152	154	Pool of daily urine samples (2 or 3 per day) during 1 week	One pool in each of the two study periods
Phthalates	–	44	All morning and bed time urines during 1 week	7 days in one study period
^{1}H NMR metabolomics	22	–	All morning and bed time urines during 1 week	7 days in one study period
Lung function	62	–	Spirometry	Last day of period 1 and 2
Blood pressure	157	154	OMRON 705-CPII automated oscillometric device	Last day of period 1 and 2
Height and weight	157	145		Last day of period 1 and 2

*With data in both periods.
BTEX, benzene, toluene, ethylene and meta-xylene, para-xylene and ortho-xylene; ^{1}H NMR, proton nuclear magnetic resonance; NO_2, nitrogen dioxide; $PM_{2.5}$, mass concentration of particles <2.5 μm in aerodynamical diameter; UV, ultraviolet.

Maitre et al. 2018

ACKNOWLEDGEMENTS

University of Southern California/CHLA

- Lida Chatzi, PhD
- Rob McConnell, MD
- Jesse Goodrich, PhD
- Wendy Setiawan, PhD
- Max Aung, PhD
- Michael Goran, PhD
- Lucy Golden, PhD
- Sarah Rock, MPH
- Rohit Kohli, MD, PhD
- Sandy Eckel, PhD

Funding Sources

R01ES029944; R01ES030364; R01ES030691
R21 ES028903;
5P30ES007048-23; 5P30DK048522-24,
USC Dean's Pilot Award
USC Center for Liver Disease Research Pilot Award

Emory University

- Douglas Walker, PhD
- Dean Jones, PhD

Columbia University

- Andrea Baccarelli, MD, PhD

NIEHS

- Sue Fenton, PhD

Mount Sinai

- Damaskini Valvi , MD, PhD

Harvard

- Philippe Grandjean, PhD
- Emily Oken, MD, PhD

UC Davis

- Michele La Merrill, PhD

ISGlobal, Barcelona

- Martine Vrijheid, PhD

University of Colorado

- Peter Bjornstad, PhD
- Anne Sterling, PhD