# PFAS and Liver Disease:

## Translating the Knowledge into Humans and Preventive Practices

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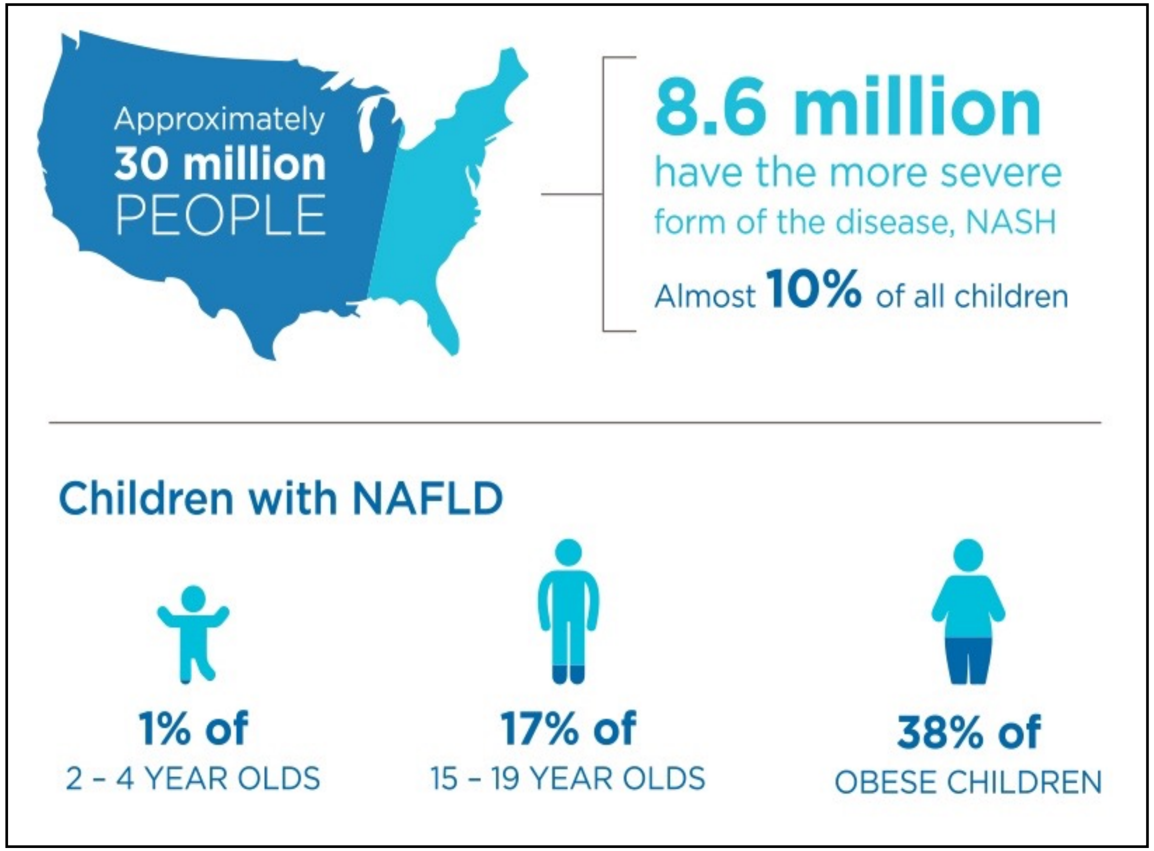
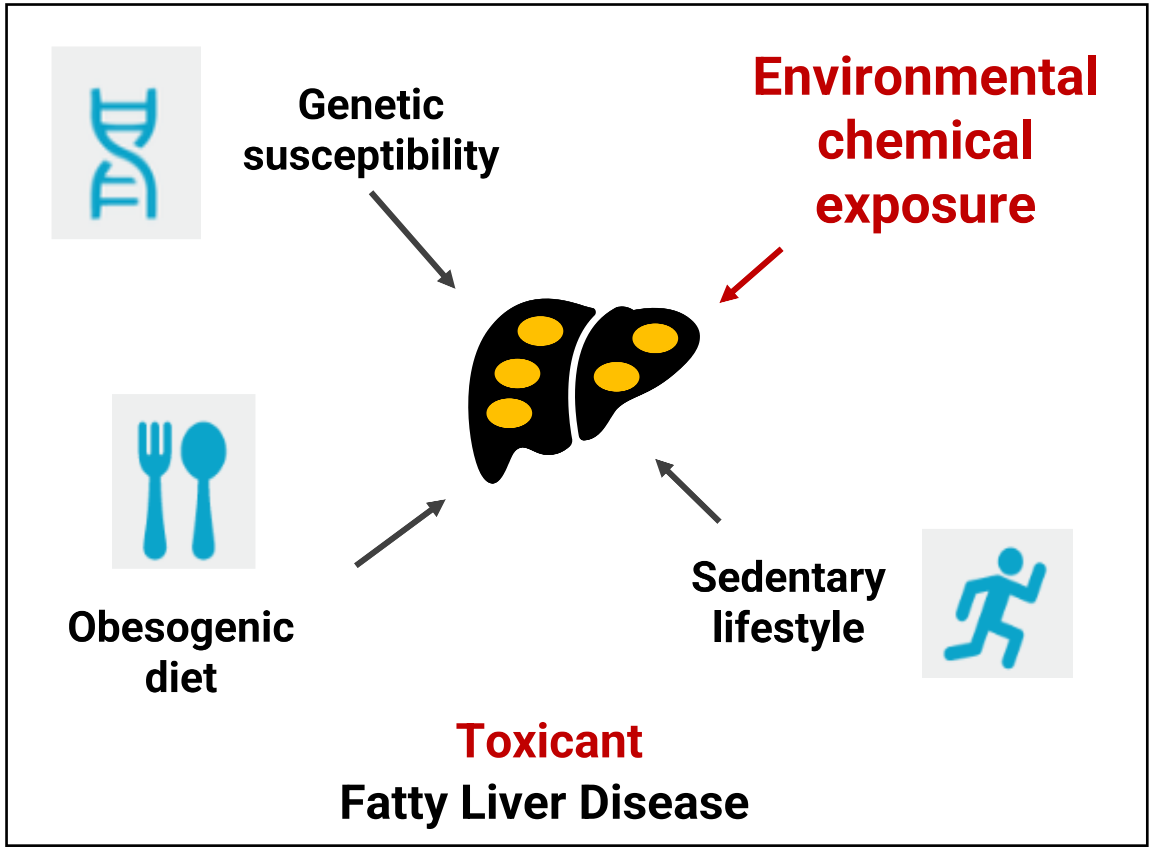
# Non-Alcoholic Fatty Liver Disease (NAFLD): An Epidemic

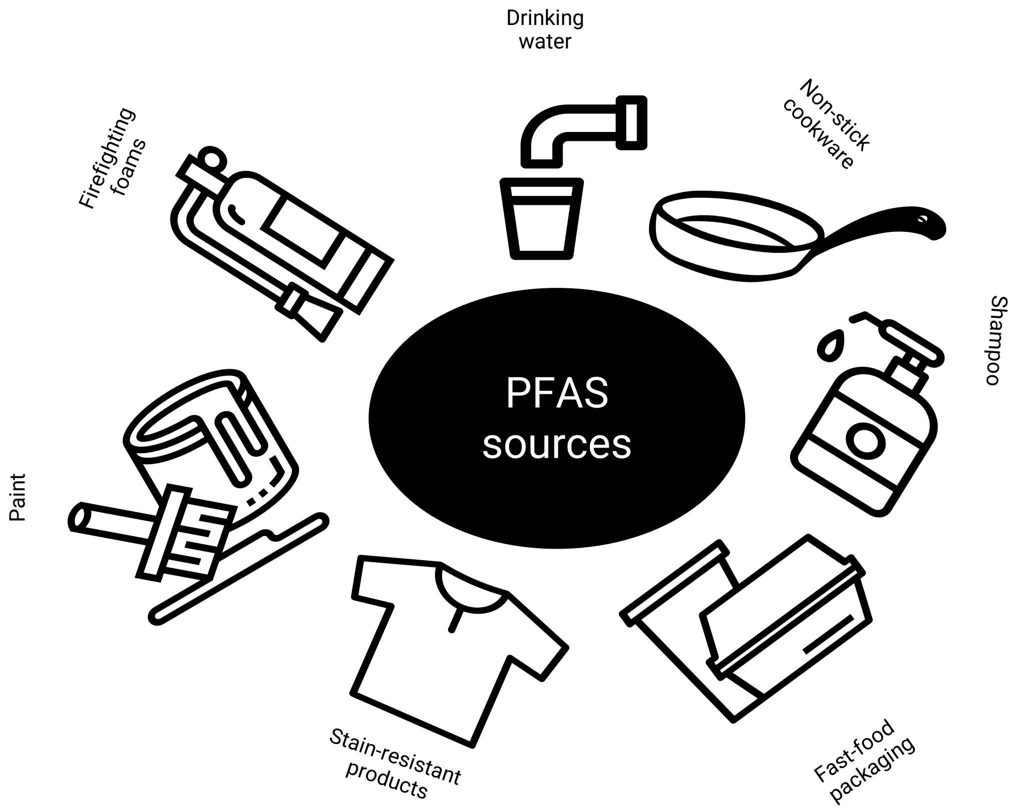
## NAFLD prevalence in the U.S




## *"Metabolism Disrupting Chemical" Hypothesis*



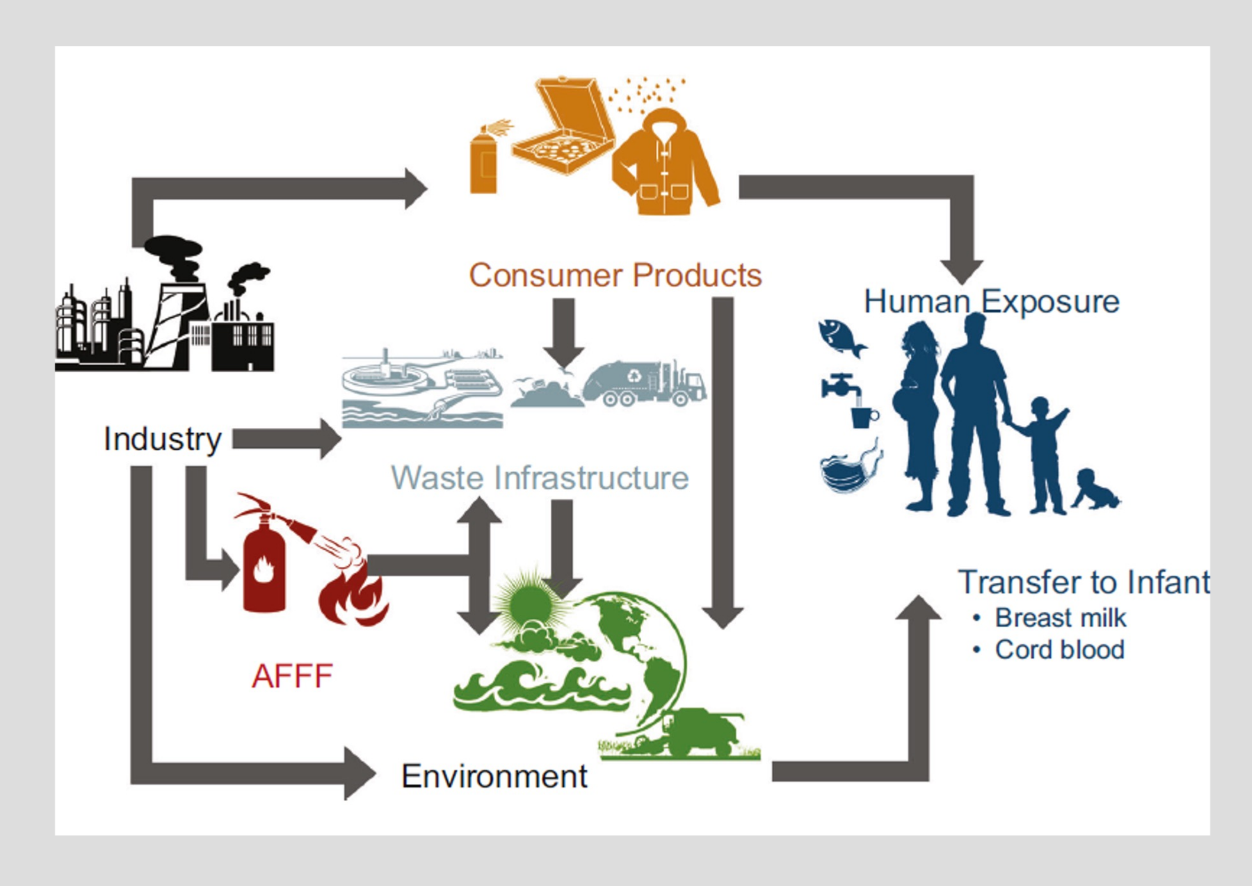
# **Per- and polyfluoroalkyl substances (PFAS):** *The new forever chemicals*



# What are PFAS?

- > 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.**

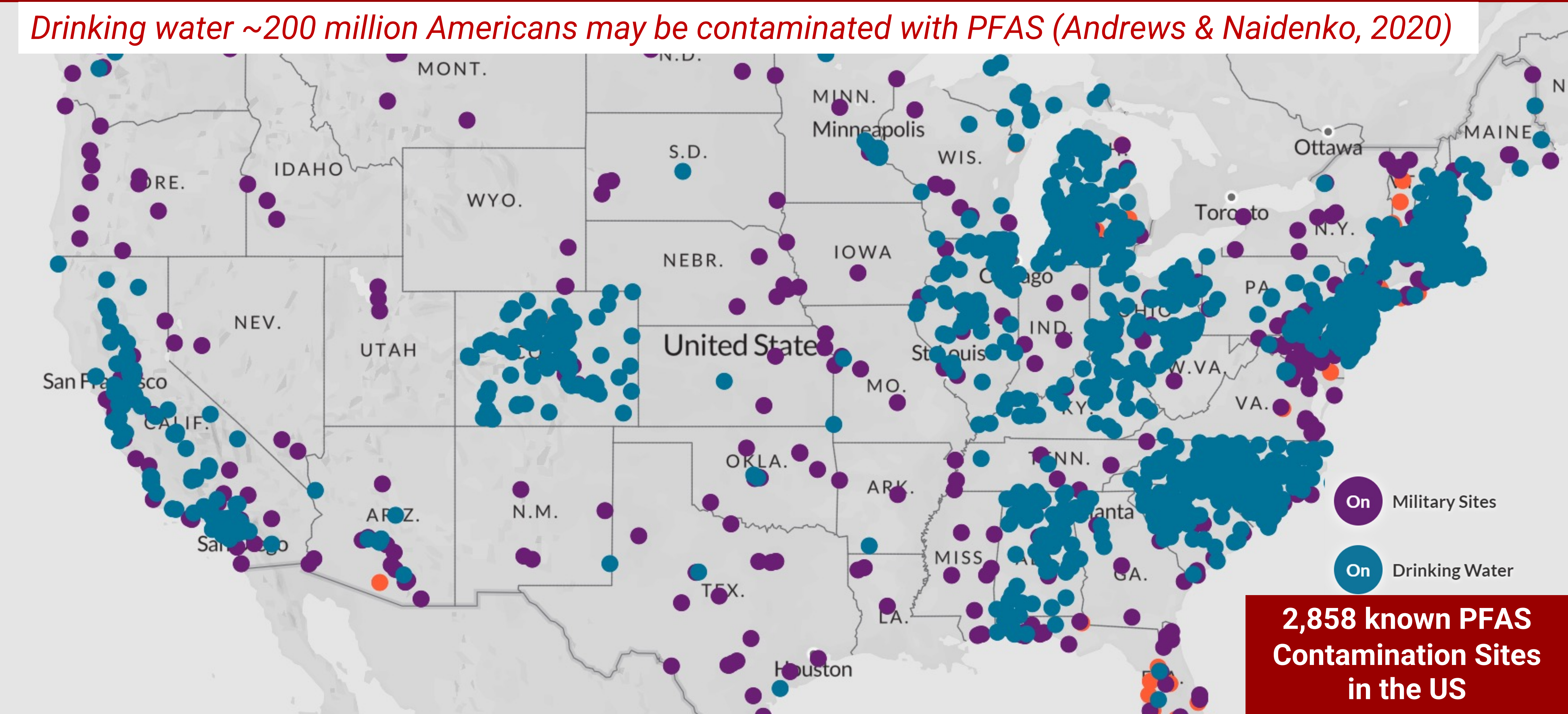
# How are we exposed?




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

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

*Drinking water ~200 million Americans may be contaminated with PFAS (Andrews & Naidenko, 2020)*




**2,858 known PFAS Contamination Sites in the US**

# SUMMARY: PFAS AND LIVER INJURY

HEPATOLOGY AASLD

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

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ELSEVIER

## 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]

JHEP Reports Innovation in Hepatology EASL

RESEARCH ARTICLE | ARTICLES IN PRESS, 100550

## Exposure to perfluoroalkyl substances and risk of hepatocellular carcinoma in a multiethnic cohort

Jesse A. Goodrich • Douglas Walker • Xiangping Lin • Hongxu Wang • Tiffany Lim • Rob McConnell • David V. Conti • Lida Chatzi # • Veronica Wendy Setiawan # • Show less • Show footnotes

Open Access • Published: August 08, 2022 • DOI: https://doi.org/10.1016/j.jhepr.2022.100550

ehp Environmental Health Perspectives

Vol. 130, No. 4 | Review

## Exposure to per- and Polyfluoroalkyl Substances and Markers of Liver Injury: A Systematic Review and Meta-Analysis

is companion of

Invited Perspective: PFAS and Liver Disease: Bringing All the Evidence Together

Elizabeth Costello, Sarah Rock, Nikos Stratakis, Sandrah P. Eckel, Douglas I. Walker, Damaskini Valvi, Dora Cserbik, Todd Jenkins, Stavra A. Xanthakos, Rohit Kohli, Stephanie Sisley, Vasilis Vasiliou, Michele A. La Merrill, Hugo Rosen, David V. Conti, Rob McConnell, and Leda Chatzi

# Emerging Evidence on PFAS and Fatty Liver Disease

## Existing Evidence

Animal studies[1,2]:

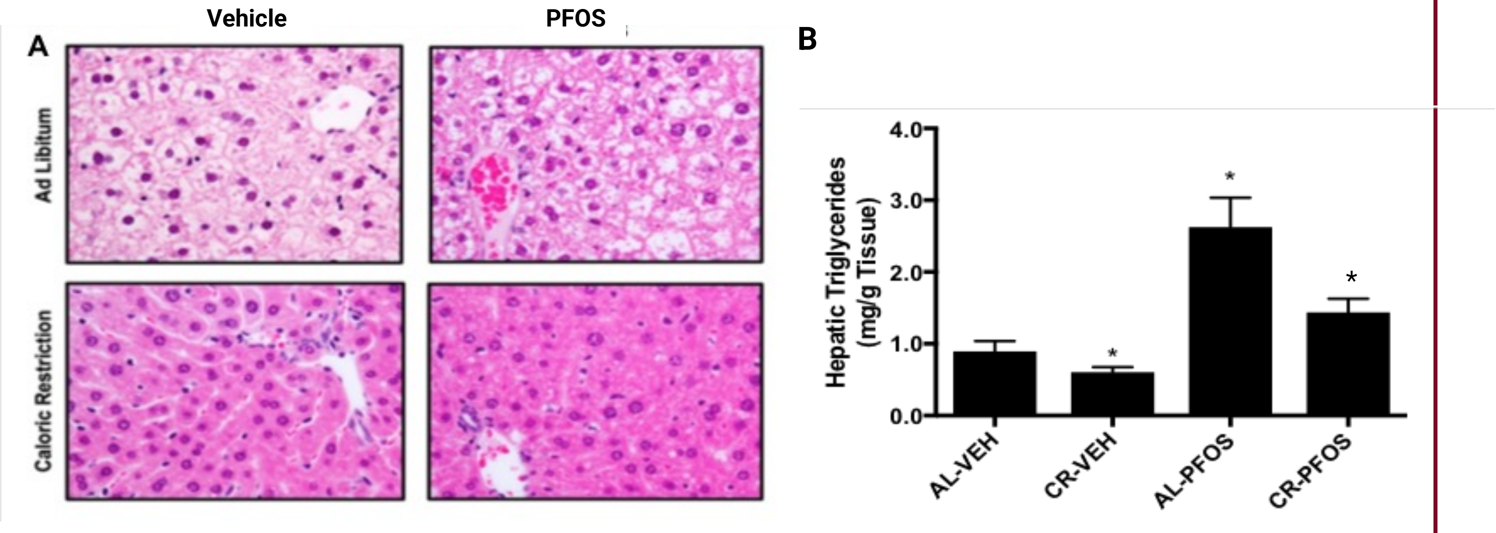
- Liver enlargement
- Hepatic steatosis

General US adults[3,4]:

- Increased levels of alanine aminotransferase (ALT), a surrogate marker for NAFLD screening

## Preliminary Results from Animal Models

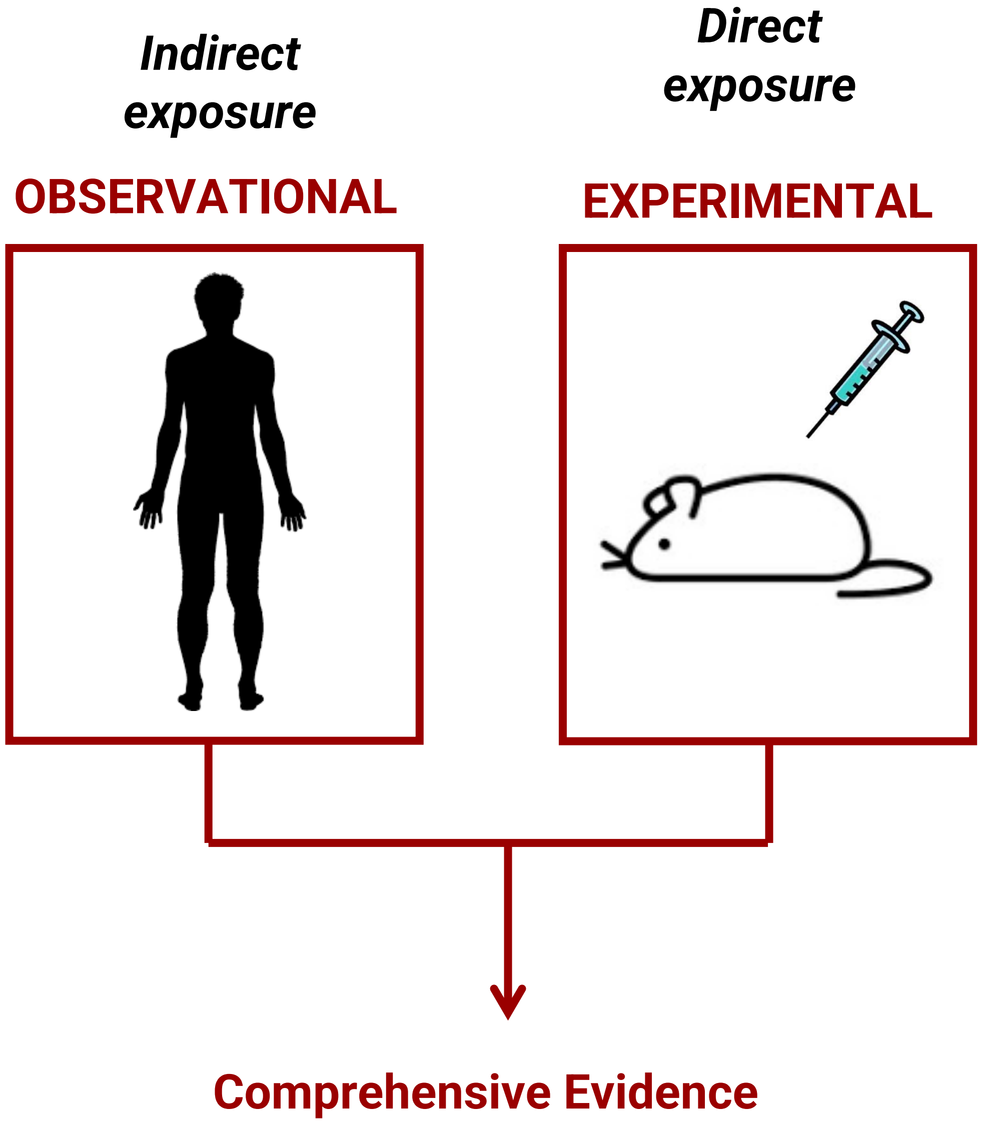
**PFOS** administration increases lipid content in mouse liver (A) and impedes the effect of calorie restriction and increases hepatic triglyceride content (B)




AL, ad libitum; CR, calorie restriction; VEH, vehicle

[1]Das KP et al., 2017; [2]Wu X et al., 2018; [3]Lin CY et al., 2010; [4]Gleason JA et al., 2015

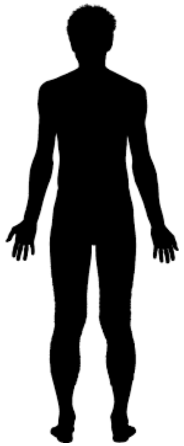
**Exposure to PFAS and Liver Injury:** a systematic review and meta-analysis




*Costello & Rock et al, EHP 2022*

# METHODS

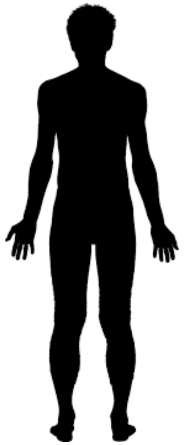
- Systematically review all available **human** and **rodent** studies examining exposure to PFAS and
    - Serum ALT, AST, GGT
    - Liver disease:
        - NAFLD/NASH
        - Steatosis
    - Liver weight (rodents)
    - Histopathological outcomes (rodents)
- Meta-analyzed using a weighted z-score approach



*Costello & Rock et al, EHP 2022*

# Search Results

| PFAS | |
|---|---|
| PFOA | PFOS |
| PFNA | PFHxS |
| PFDA | PFBA |
| PFDoA | PFBS |
| PFUA | PFHxA |
| GenX | |



25 Human Studies

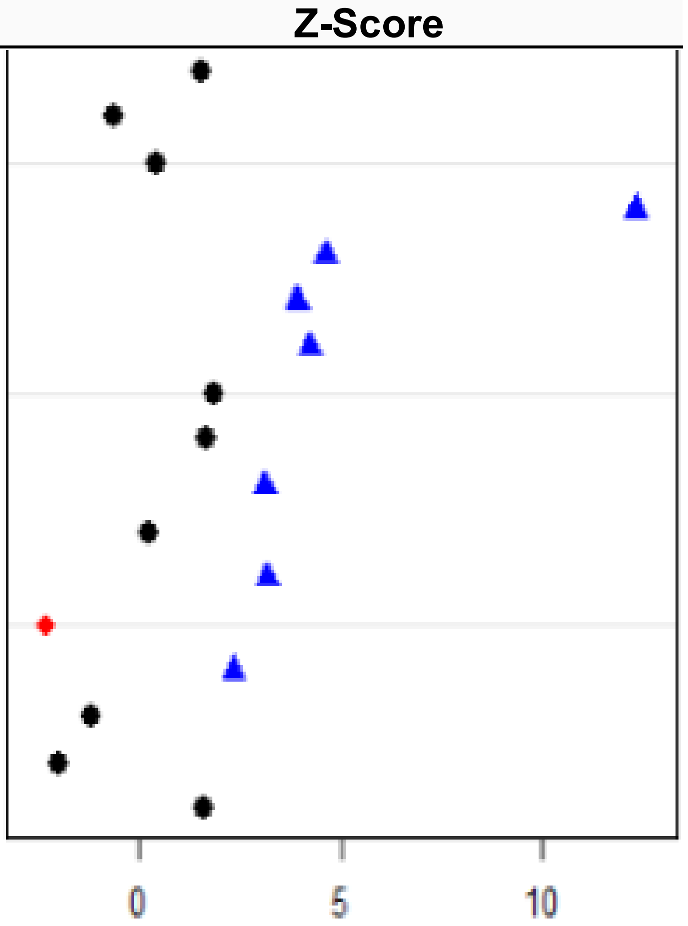
86 Rodent Studies

*Costello & Rock et al, EHP 2022*

# **RESULTS** **Human Studies:** Exposure to PFOA and ALT

**Weighted Z-score: 6.20 ($p < 0.001$)**

| Reference | Population | Age | Sex | N | Exposure | Blood Conc. |
|---|---|---|---|---|---|---|
| Sakr, 07’ | GHS | ≥18 | Overall | 1024 | PFOA | 0.428 ppm[b] |
| Olsen, 07’ | Plant Employees | 21-67 | Male | 506 | PFOA | 2210 ng/mL[b] |
| Emmett, 06’ | Little Hocking, OH | 2-90 | Overall | 371 | PFOA | 354 ng/mL[a] |
| Gallo, 12’ | C8HP | ≥ 18 | Overall | 46452 | PFOA | 28.0 ng/mL[a] |
| Darrow, 16’ | C8HP | > 20 | Male | 12364 | PFOA | 17.1 ng/mL[a] |
| Darrow, 16’ | C8HP | > 20 | Female | 15683 | PFOA | 16.0 ng/mL[a] |
| Nian, 19’ | I C8HP | 22-95 | Overall | 1605 | PFOA | 6.19 ng/mL[a] |
| Lin, 10’ | NHANES 99’ – 03’ | ≥ 20 | Male | 1063 | PFOA | 5.05 ng/mL[b] |
| Lin, 10’ | NHANES 99’ – 03’ | ≥ 20 | Female | 1134 | PFOA | 4.06 ng/mL[b] |
| Gleason, 15’ | NHANES 07’- 10’ | ≥ 12 | Overall | 4333 | PFOA | 3.5 ng/mL[c] |
| Jain, 19’ | NHANES 11-14’ | ≥ 20 | Overall | 1082 | PFOA | 2.2 ng/mL[c] |
| Jain, 19’ | NHANES 11’-14’ | ≥ 20 | Overall | 1801 | PFOA | 2.0 ng/mL[c] |
| Attanasio, 19’ | NHANES 13’-16’ | 12-19 | Male | 354 | PFOA | 1.50 ng/mL[c] |
| Attanasio 19’ | NHANES 13’-16’ | 12-19 | Female | 305 | PFOA | 1.22 ng/mL[c] |
| Mora 18’ | Project Viva | 6-11 | Male | 332 | PFOA | 4.4 ng/mL[a] |
| Mora 18’ | Project Viva | 6-11 | Female | 298 | PFOA | 4.2 ng/mL[a] |
| Khalil 18’ | DCH | 8-12 | Overall | 48 | PFOA | 0.99 ng/mL[a] |



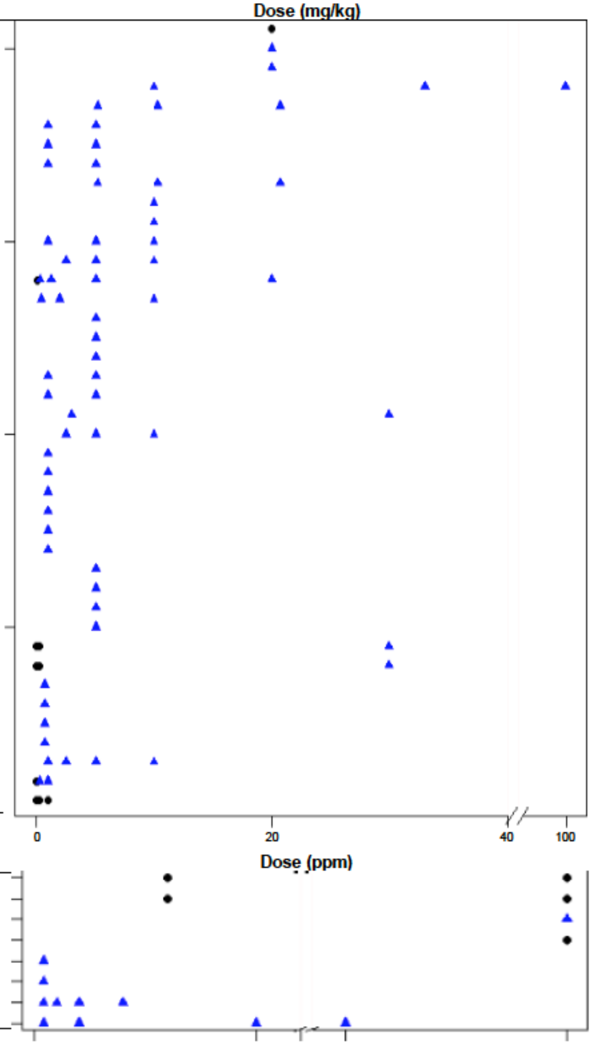

Strip plot for the Z-scores of the cross-sectional analyses of PFOA on ALT. Sex specific results are presented separately where available. The weighted Z-score calculation was performed for ages 12 and older, using the larger of overlapping cohorts. Cohorts: GHS: General Health Survey; C8HP: C8 Health Project; I C8HP: Isomers of C8 Health Project; NHANES: National Health and Nutrition Examination Survey; DCH: Dayton Children’s Hospital. Positive association ( ▲); negative association: (◆); no association: (●). [a]Median; [b]Mean; [c]Geometric Mean.

*Costello & Rock et al, EHP 2022*

# **RESULTS** **Rodent Studies:** Exposure to PFOA and Liver Weight

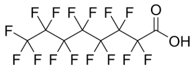
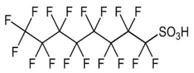
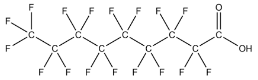
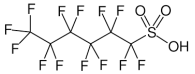
| [1]Reference | Species | Strain (Sex) | Exposure Route | Exposure | Duration | Sample Collection |
|---|---|---|---|---|---|---|
| Martin, 2007 | Rats | SD (M) | Gavage | PFOA | 1D | EOT |
| Martin, 2007 | Rats | SD (M) | Gavage | PFOA | 2D | EOT |
| Martin, 2007 | Rats | SD (M) | Gavage | PFOA | 5D | EOT |
| Rigden, 2015 | Rats | SD (M) | Gavage | PFOA | 3D | 4D Post |
| Minata, 2010 | Mice | 129S4/Svlmj (M) | Gavage | PFOA | 4W | EOT |
| Nakagawa, 2012 | Mice | mPPARα (M) | Gavage | PFOA | 6W | EOT |
| Nakagawa, 2012 | Mice | hPPARα (M) | Gavage | PFOA | 6W | EOT |
| Nakagawa, 2012 | Mice | PPARα-null (M) | Gavage | PFOA | 6W | EOT |
| Minata, 2010 | Mice | PPARα-null (M) | Gavage | PFOA | 4W | EOT |
| Das, 2017 | Mice | PPARα-null (M) | Gavage | PFOA | 7D | EOT |
| Das, 2017 | Mice | SV129 (M) | Gavage | PFOA | 7D | EOT |
| Yahia, 2010 | Mice | ICR (Dams) | Gavage | PFOA | GD0-GD17 | EOT |
| Yang B 2014 | Mice | Kunming (M) | Gavage | PFOA | 14D | EOT |
| Yan, 2014 | Mice | BALB/c (M) | Gavage | PFOA | 28D | EOT |
| Guo, 2019 | Mice | BALB/c (M) | Gavage | PFOA | 28D | EOT |
| Yan, 2015 | Mice | BALB/c (M) | Gavage | PFOA | 28D | EOT |
| Yan, 2015 | Mice | BALB/c (M) | Gavage | PFOA+4-PBA 125 | 28D | EOT |
| Yan, 2015 | Mice | BALB/c (M) | Gavage | PFOA+4-PBA 250 | 28D | EOT |
| Blake, 2020 | Mice | CD-1 (Dams) | Gavage | PFOA | E1.5-11.5 | E17.5 |
| Blake, 2020 | Mice | CD-1 (Dams) | Gavage | PFOA | E1.5-11.5 | EOT |
| Wang G, 2021 | Mice | C57BL/6J (M) | Gavage | PFOA | 15D | EOT |
| Wang G, 2021 | Mice | C57BL/6J (M) | Gavage | PFOA | 30D | EOT |
| Li X, 2019 | Mice | C57BL/6 (M) | Gavage | PFOA+LFD | 16W | EOT |
| Li X, 2019 | Mice | C57BL/6 (M) | Gavage | PFOA+LFD | 8W | EOT |
| Li X, 2019 | Mice | C57BL/6 (M) | Gavage | PFOA+LFD | 2W | EOT |
| Li X, 2019 | Mice | C57BL/6 (M) | Gavage | PFOA+HFD | 16W | EOT |
| Li X, 2019 | Mice | C57BL/6 (M) | Gavage | PFOA+HFD | 8W | EOT |
| Li X, 2019 | Mice | C57BL/6 (M) | Gavage | PFOA+HFD | 2W | EOT |
| Tan, 2013 | Mice | C57BL/6N (M) | Diet | PFOA | 3W | EOT |
| Tan, 2013 | Mice | C57BL/6N (M) | Diet | PFOA+HFD | 3W | EOT |
| Cui, 2019 | Mice | C57BL/6J (M) | Gavage | PFOA | 28D | EOT |
| Cui, 2019 | Mice | miR-34a-/- C57BL/6J (M) | Gavage | PFOA | 28D | EOT |
| Pouwer, 2019 | Mice | APOE*3-Leiden CETP (M) | Diet | PFOA | 6W | EOT |
| Pouwer, 2019 | Mice | APOE*3-Leiden CETP (M) | Diet | PFOA | 4W | EOT |
| Schlezinger, 2020 | Mice | hPPARα (M) | Water | PFOA | 6W | EOT |
| Schlezinger, 2020 | Mice | PPARα-null (M) | Water | PFOA | 6W | EOT |
| Schlezinger, 2020 | Mice | hPPARα (F) | Water | PFOA | 6W | EOT |
| Schlezinger, 2020 | Mice | PPARα-null (F) | Water | PFOA | 6W | EOT |
| Li D, 2019 | Mice | Kunming (F) | Prenatal | PFOA | GD1-17 | PND21 |
| Quist, 2015 | Mice | CD-1 (F) | Prenatal | PFOA | GD1-17 | PND21 |
| Quist, 2015 | Mice | CD-1 (F) | Prenatal | PFOA | GD1-17 | PND91 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Butenhoff, 2012c | Rats | SD (M) | Diet | PFOA | 2Y | EOT |
| Butenhoff, 2012c | Rats | SD (F) | Diet | PFOA | 2Y | EOT |
| Butenhoff, 2012c | Rats | SD (M) | Diet | PFOA | 1Y | EOT |
| Butenhoff, 2012c | Rats | SD (F) | Diet | PFOA | 1Y | EOT |
| Qazi, 2013b | Mice | C57BL/6 (M) | Diet | PFOA | 28D | EOT |
| Qazi, 2013b | Mice | C57BL/6 (M) | Diet | PFOA | 10D | EOT |
| Botelho, 2015 | Mice | C57BL/6 (M) | Diet | PFOA | 10D | EOT |
| Son, 2008 | Mice | ICR (M) | Water | PFOA | 21D | EOT |




Strip plots for PFOA and relative liver weight in animal studies. Blue triangles indicate a significant increase in relative liver weight relative to control. Black dots indicate no significant change in relative liver weight relative to control. Plots are ordered by species and strain. *Abbreviations:* End of treatment (EOT); low fat diet (LFD); high fat diet (HFD); postnatal day (PND); gestational day (GD); embryonic day (E); Sprague Dawley (SD); 4-phenylbutyric acid (4-PBA).

*Costello & Rock et al, EHP 2022*

| | | Human | Animal | Conclusions |
|---|---|---|---|---|
| **PFOA** |  | **↑ ALT, GGT, AST**<br>*(Longitudinal and cross-sectional studies)* | **↑ ALT**<br>**Steatosis**<br>**Histopathological alterations** | **Likely relationship between PFOA and liver injury** |
| **PFOS** |  | **↑ ALT**<br>*(Primarily cross-sectional studies)* | **↑ ALT**<br>**Steatosis**<br>**Histopathological alterations** | **Likely relationship between PFOS and liver injury** |
| **PFNA** |  | **↑ ALT**<br>(Cross-sectional studies) | **↑ ALT**<br>**Steatosis**<br>**Histopathological alterations** | **PFNA may be related to liver injury** |
| **PFHxS** |  | No relationship<br>*(Cross-sectional studies)* | **Steatosis**<br>**Histopathological alterations**<br>*(high doses)* | **PFHxS may be related to liver injury.**<br>**(The evidence is limited)** |
| **Other PFAS** | | Limited evidence, more information is needed. | | |
| **PFAS Mixtures** | | **Limited number of studies, but suggests a relationship.** More information is needed. | | |

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

Environmental Factor
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JANUARY 2021

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## 2020 Papers of the Year

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*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**

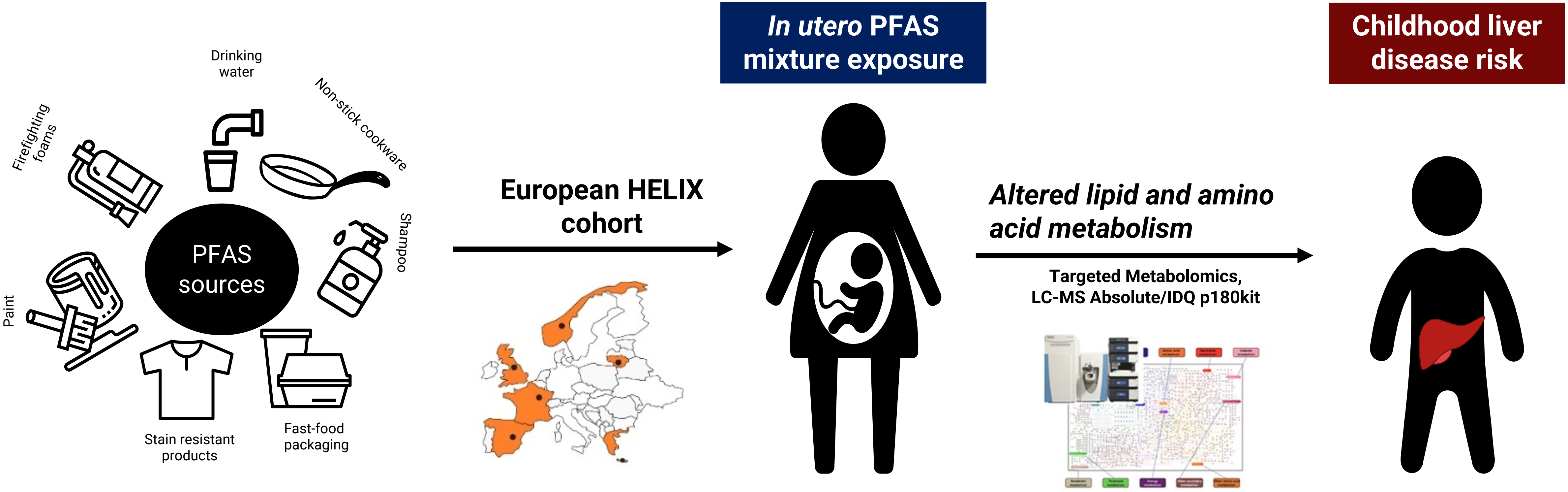
Exposure to per- and polyfluoroalkyl substances (PFAS) in the womb may increase liver injury risk in children, according to NIEHS-funded researchers. This study is the first to examine the impact of early life exposures to a PFAS mixture on child liver injury. PFAS, a large group of synthetic chemicals 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 HYPOTHESIS

## Prenatal PFAS and risk of NAFLD in children




R21ES029681

# STUDY DESIGN

HELIX BUILDING THE EARLY-LIFE EXPOSOME


## 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

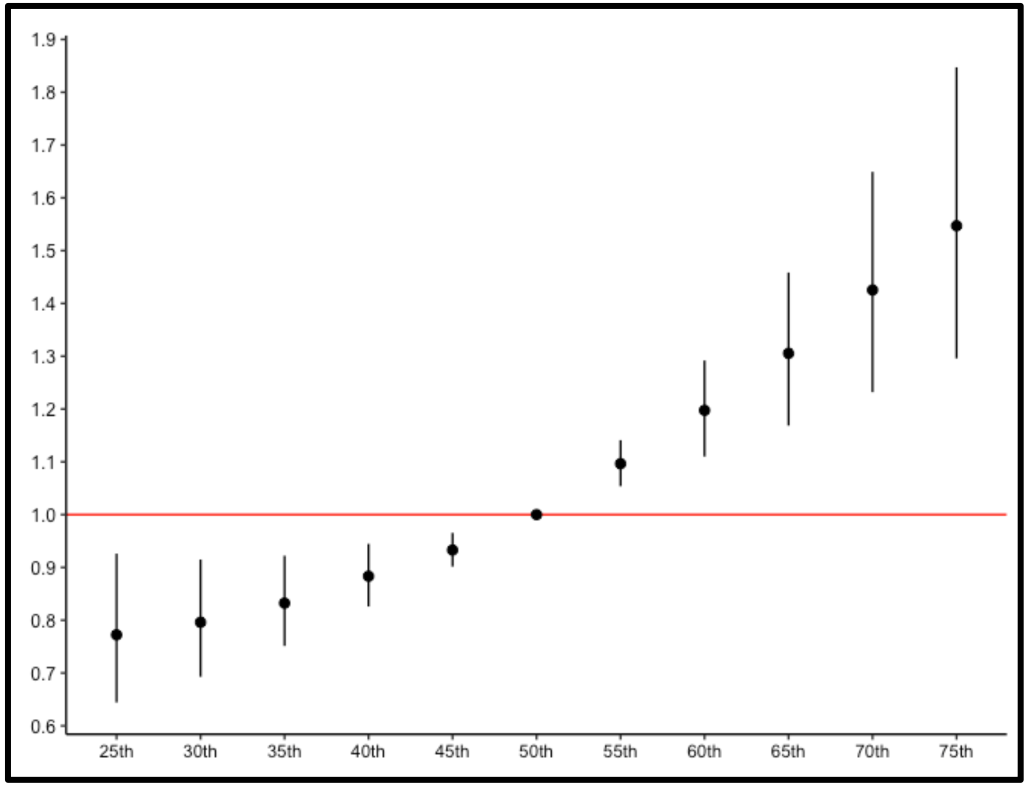
- Urinary metabolomics
- Serum metabolomics
- Proteomics
- Methylation
- Transcriptomics
- MicroRNA (miRNA)
- Mitochondrial DNA content

NIEHS R21 ES029681

# RESULTS

## PFAS Mixture During Pregnancy on Child Liver Injury Risk: BKMR

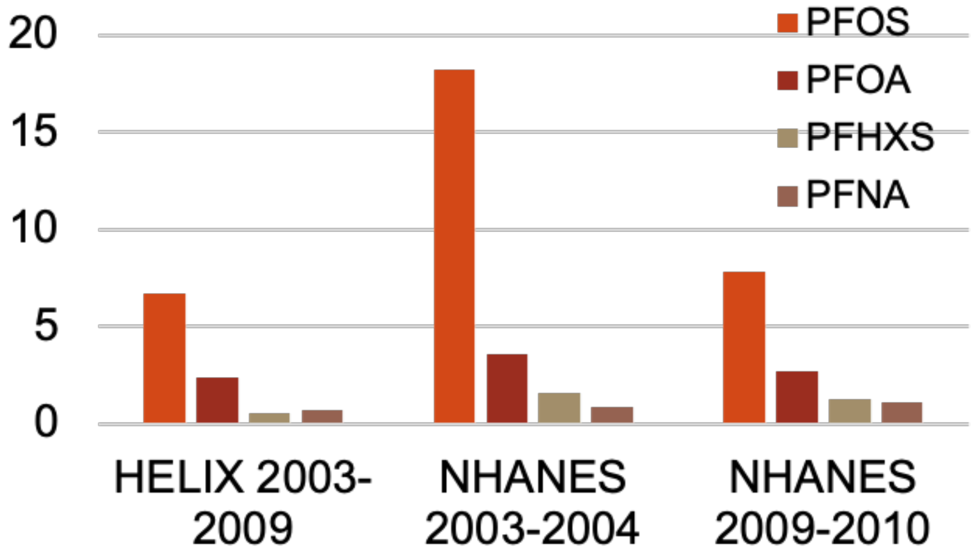
**Joint effect of prenatal PFAS mixture on risk of pediatric liver injury (OR, 95% CI)**




**Maternal PFAS mixture (in percentiles)**

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

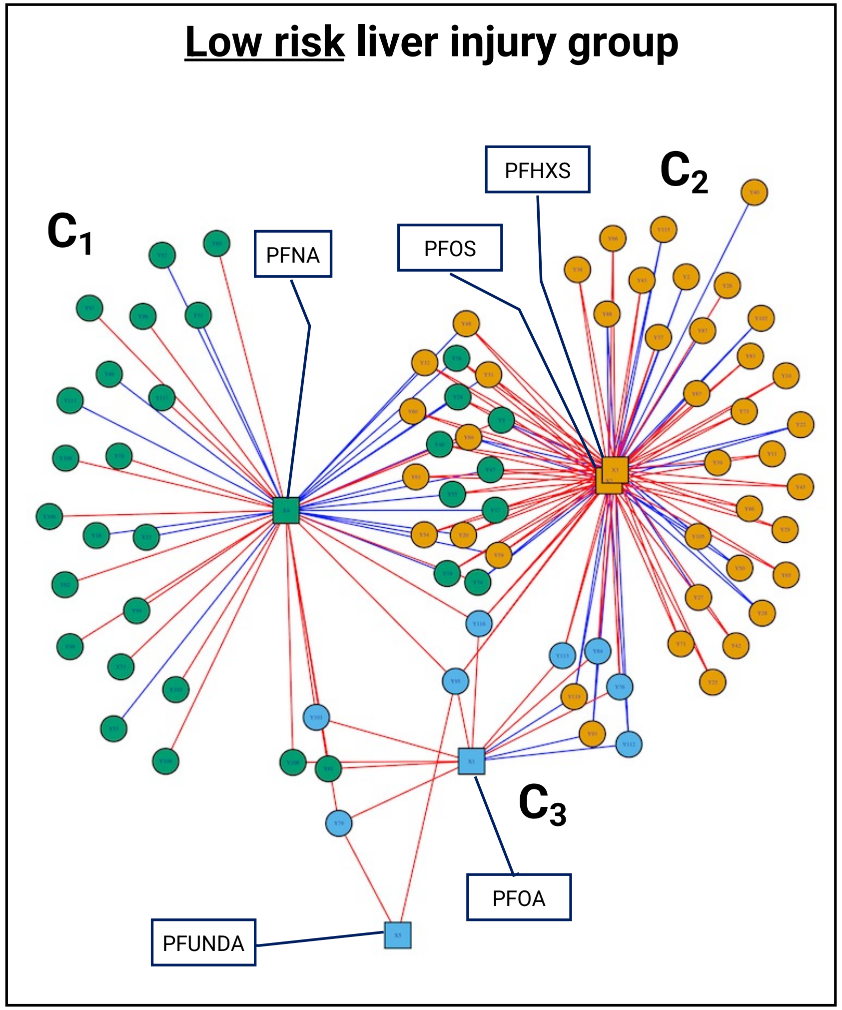
**Median maternal PFAS concentration (ng/ml) in HELIX and female NHANES population**

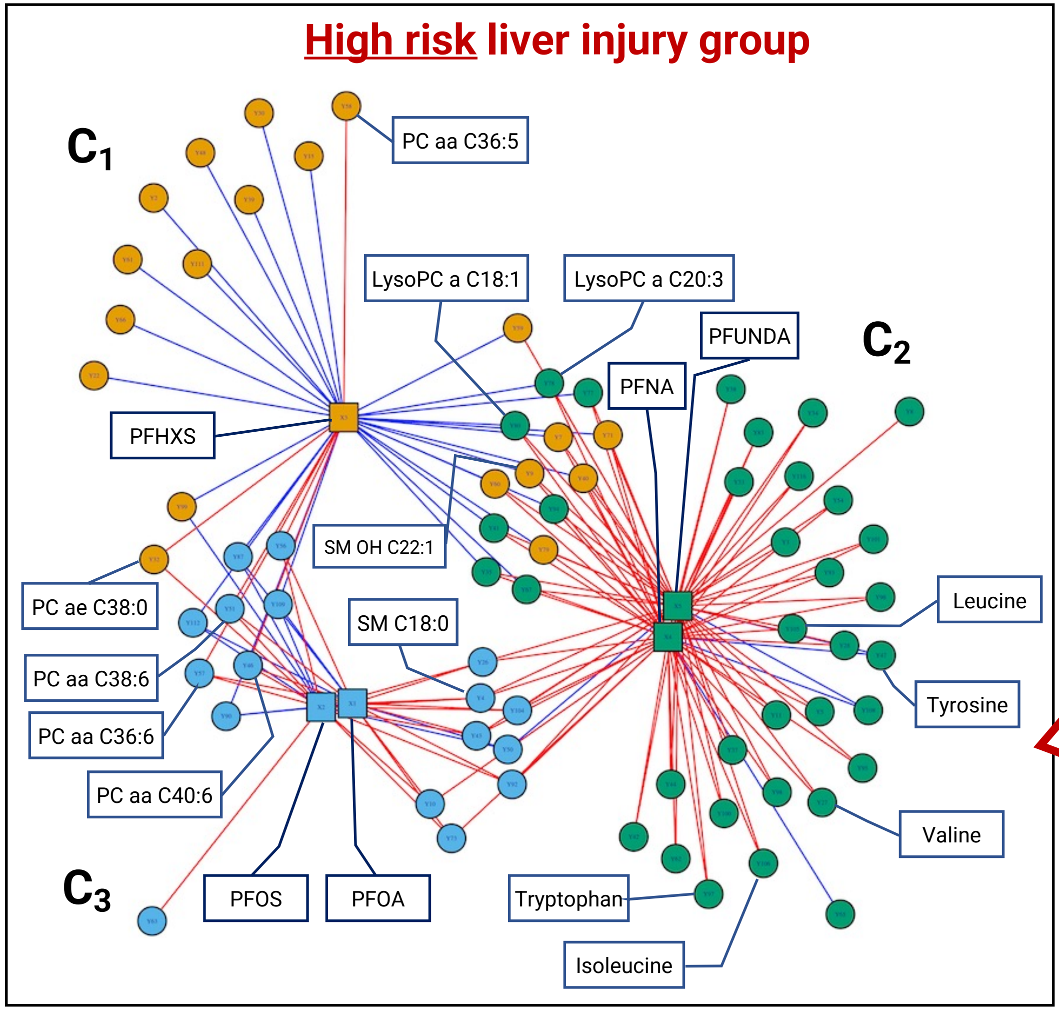



Stratakis et al, Hepatology 2020

# RESULTS Metabolite features are associated with prenatal PFAS and liver injury

### *Network Analysis (xMWAS)*




**42 metabolites with significant network changes between groups as measured by the eigenvector centrality**

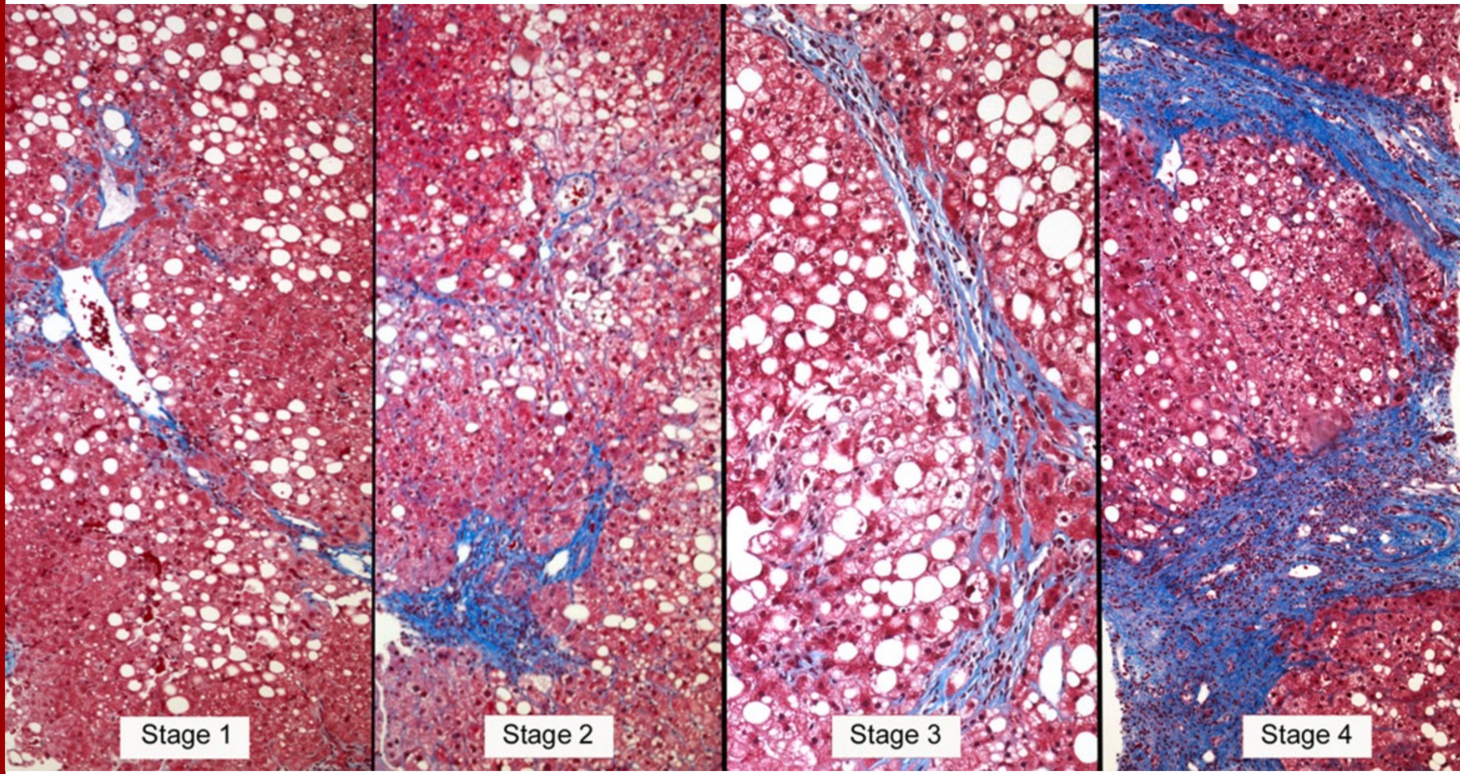
PFAS / Metabolites
*Positive correlation*
*Negative correlation*

Communities ($C_1$...$C_3$)

Higher PFAS are associated with higher levels of branched chain and aromatic amino acids

Stratakis et al, Hepatology 2020

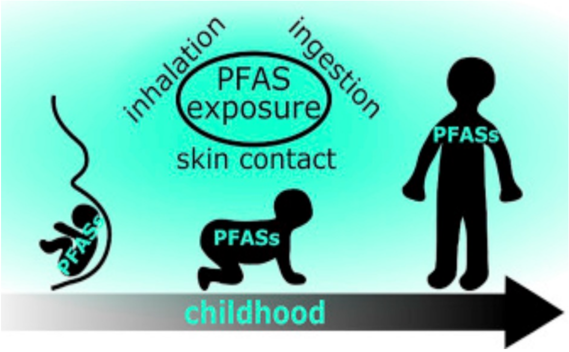
**PFAS and Severity of NAFLD in children:**
An untargeted metabolomics approach




*Jin R et al, Environ Int. 2020*

# **QUESTION** Does PFAS Exposure Exacerbate NAFLD Progression?

*Children have **increased exposure** relative to their body size and **more progressive** form of the disease*



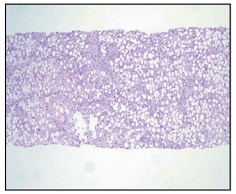
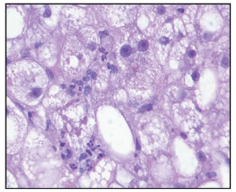
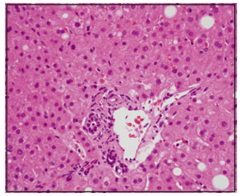
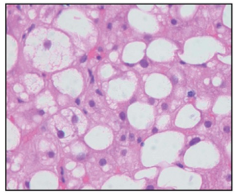
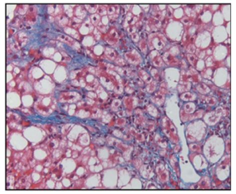

**Aim 1:** To examine associations between blood concentrations of PFAS and NAFLD severity in children, assessed liver histological features under biopsy ("gold standard")

**Aim 2:** To explore metabolic perturbations in associations with PFAS that could possibly contribute to disease progression in NAFLD children

*Jin R et al, Environ Int. 2020*

**RESULTS**

# Liver Histological Features Under Biopsy

| Variables | N (%) |
|---|---|
| **Grade of Steatosis** | |
| **1 (5-33%)** | 27 (36.5) |
| **2 (34-66%)** | 13 (17.6) |
| **3 (>66%)** | 34 (45.9)) |
| **Lobular inflammation** | |
| **0 (no foci)** | 24 (32.4) |
| **1 (<2 foci per 200x field)** | 43 (58.1) |
| **2 (2-4 foci per 200x field)** | 7 (9.5) |
| **3 (>4 foci per 200x field)** | 0 (0) |
| **Portal inflammation** | |
| **0 (none)** | 42 (56.8) |
| **1 (mild)** | 24 (32.4) |
| **2 (moderate to severe)** | 8 (10.8) |
| **Hepatocellular Ballooning** | |
| **0 (none)** | 44 (59.5) |
| **1 (few balloon cells)** | 25 (33.8) |
| **2 (many cells/prominent ballooning)** | 5 (6.76) |
| **Fibrosis stage** | |
| **0 (none)** | 22 (29.7) |
| **1 (Perisinusoidal or periportal)** | 38 (51.4) |
| **2 (Perisinusoidal and portal/periportal)** | 8 (10.8) |
| **3 (Bridging)** | 6 (8.1) |
| **4 (Cirrhosis)** | 0 (0) |

*Jin R et al, Environ Int. 2020*

**RESULTS**

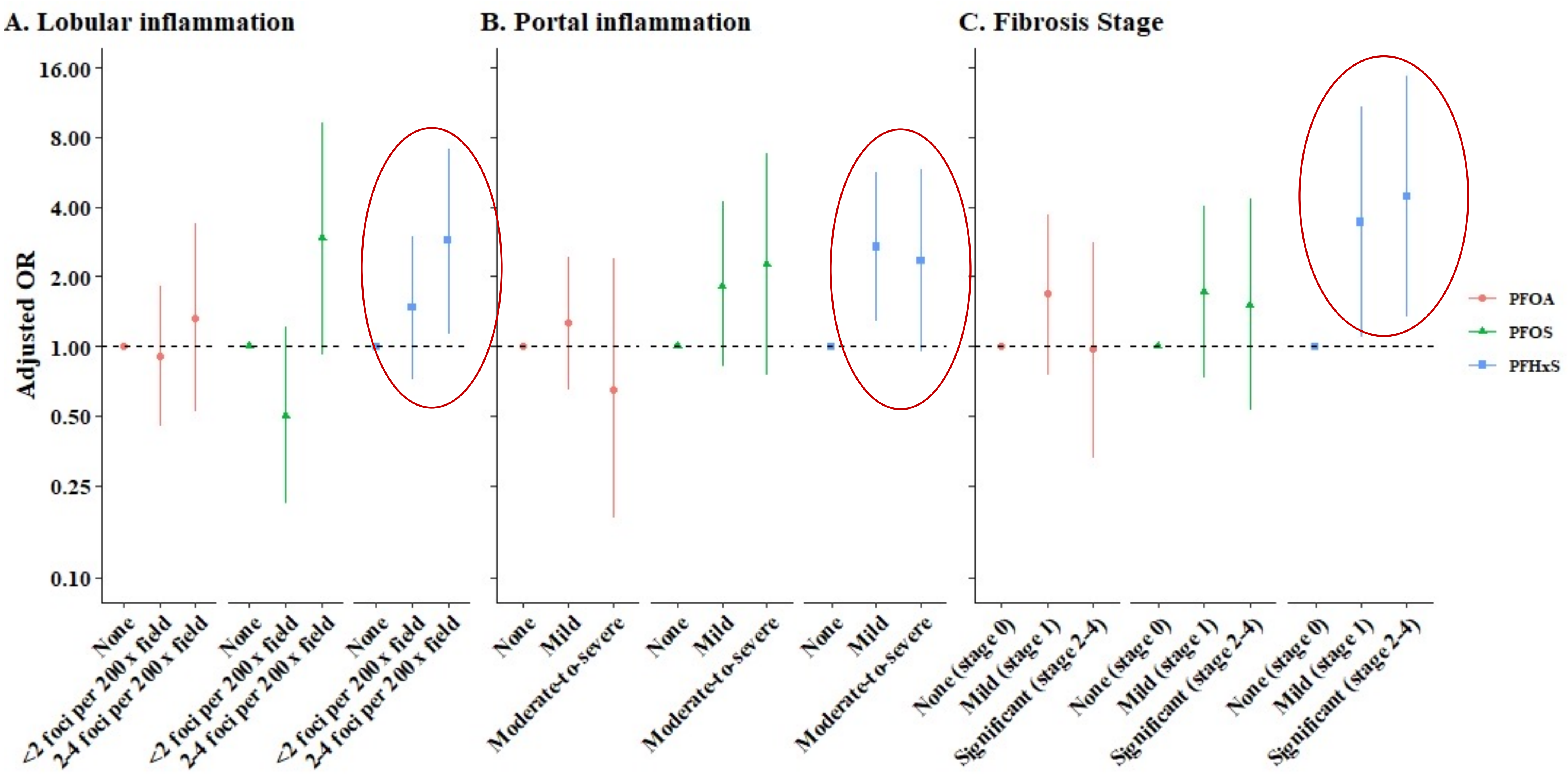
# Clinical Features of Study Population

- **CHEAR Project:**
  - N=74 children
  - 7-19 years
  - Physician-diagnosed NAFLD
- **Characteristics**
  - Highly obese
  - Most Hispanics
  - Most Male
  - Elevated ALT levels (> 25.8 U/L for boys, > 22.1 U/L for girls)

| Variables | Mean (SD) or N (%) |
|---|---|
| **Age (years)** | 14.0 (2.81) |
| **Male, n (%)** | 52 (70.3) |
| **Hispanics, n (%)** | 39 (52.7) |
| **BMI percentile** | 98.4 (2.30)* |
| **Normal weight (n, %)** | 4 (5.4) |
| **Overweight (n, %)** | 7 (9.5) |
| **Obesity (n, %)** | 63 (85.1) |
| **ALT (U/L)** | 90.0 (75.0)* |

*Jin R et al, Environ Int. 2020*

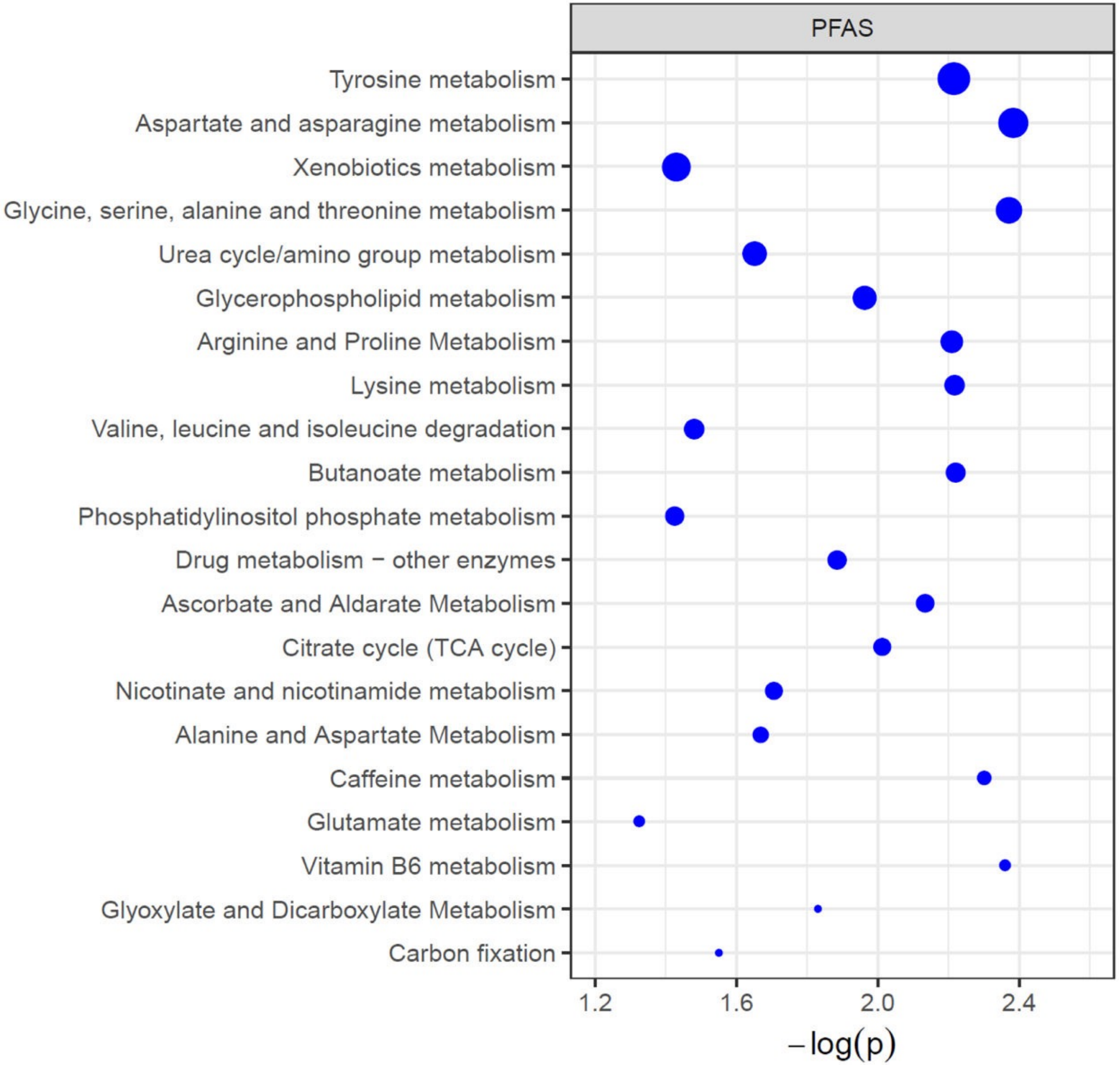
# RESULTS




*Jin R et al, Environ Int. 2020*

**RESULTS**

# Metabolic Disturbance Associated With PFAS




- **Amino acid metabolism**
  - Tyrosine metabolism
  - Aspartate, asparagine metabolism
  - Branch chain amino acid metabolism
- **Lipid metabolism**
  - Glycerophospholipid metabolism
- **Urea cycle metabolism**

*Jin R et al, Environ Int. 2020*

# CONCLUSION

- First study examining PFAS blood concentrations in relation to histopathological staging of NAFLD in children
- NAFLD children with higher blood PFHxS concentrations had increased odds of presenting lobular/portal inflammation and more advanced stage of fibrosis
- Blood concentrations of PFAS were associated with metabolic perturbation in numerous amino acids and phospholipids, key metabolic pathways previously found also to be altered in NAFLD/NASH

*Jin R et al, Environ Int. 2020*

# PFAS and Liver Cancer

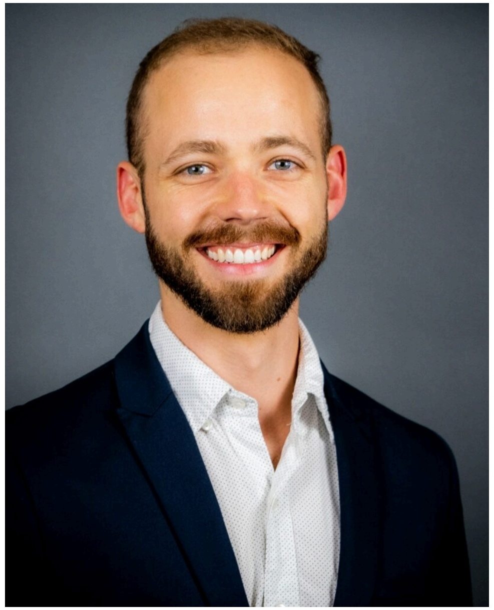
JHEP|Reports
Innovation in Hepatology
EASL

RESEARCH ARTICLE | ARTICLES IN PRESS, 100550

## Exposure to perfluoroalkyl substances and risk of hepatocellular carcinoma in a multiethnic cohort

Jesse A. Goodrich • Douglas Walker • Xiangping Lin • ... David V. Conti • Lida Chatzi # • Veronica Wendy Setiawan # • Show all authors • Show footnotes

Open Access • Published: August 08, 2022 • DOI: https://doi.org/10.1016/j.jhepr.2022.100550



THE HILL

EQUILIBRIUM & SUSTAINABILITY

**Scientists link ‘forever chemical’ exposure to development of liver cancer**

BY SHARON UDASIN - 08/08/22 6:00 PM ET

SHARE TWEET

Medscape

News > Medscape Medical News

**Pervasive 'Forever Chemical' Linked to Liver Cancer**

*J Goodrich et al. JHEP Reports 2022*

# STUDY DESIGN

- Multiethnic Cohort (MEC) Study
  - 50 non-viral incident cases of HCC and 50 matched controls

- Exposures:
  - **Pre-diagnostic** plasma PFAS (PFOS, PFOA, PFHxS, PFDA, PFNA) concentrations
  - Untargeted plasma metabolomics

| | HCC (n=50) | Control (n=50) |
|---|---|---|
| **Age @ blood collection** | 69.7 | 69.2 |
| **Race/ethnicity** | | |
| Afr Amer | 6% | 6% |
| Japn Amer | 38% | 38% |
| Latino | 24% | 24% |
| Native Haw | 14% | 14% |
| White | 18% | 18% |
| **Female** | 38% | 38% |
| **Study area** | | |
| CA | 36% | 36% |
| HI | 64% | 64% |
| **BMI** | | |
| <25 | 18% | 38% |
| 25-<30 | 36% | 46% |
| 30+ | 46% | 16% |
| **T2D** | 38% | 8% |
| **Ever smokers** | 74% | 62% |
| **Alcohol 12+ g/day** | 22% | 16% |

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## RESULTS Associations Between Plasma PFAS Concentrations and HCC Risk

| PFAS | µg/L | OR* (95% CI) | p-value |
|---|---|---|---|
| PFOS | >54.9 | 4.50 (1.20, 16.00) | 0.02 |
| PFHxS | >4.28 | 1.10 (0.56, 2.30) | 0.72 |
| PFOA | >8.6 | 1.20 (0.52, 2.80) | 0.67 |
| PFDA | >0.79 | 0.80 (0.31, 2.00) | 0.64 |
| PFNA | >1.47 | 1.20 (0.49, 3.20) | 0.64 |
| PFUnDA | >1.22 | 2.20 (0.92, 5.50) | 0.07 |
| PFAS Mixture | | 9.9 (1.05, 14.30) | 0.04 |

*High level was based on the 90$^{th}$ percentile in NHANES 1999-2000
OR was adjusted for matching factors
PFAS Mixture effect calculated using quantile g-computation, and represents the odds ratio when increasing all PFAS in the mixture from Low (<90$^{th}$ percentile) to High (>90$^{th}$ percentile).

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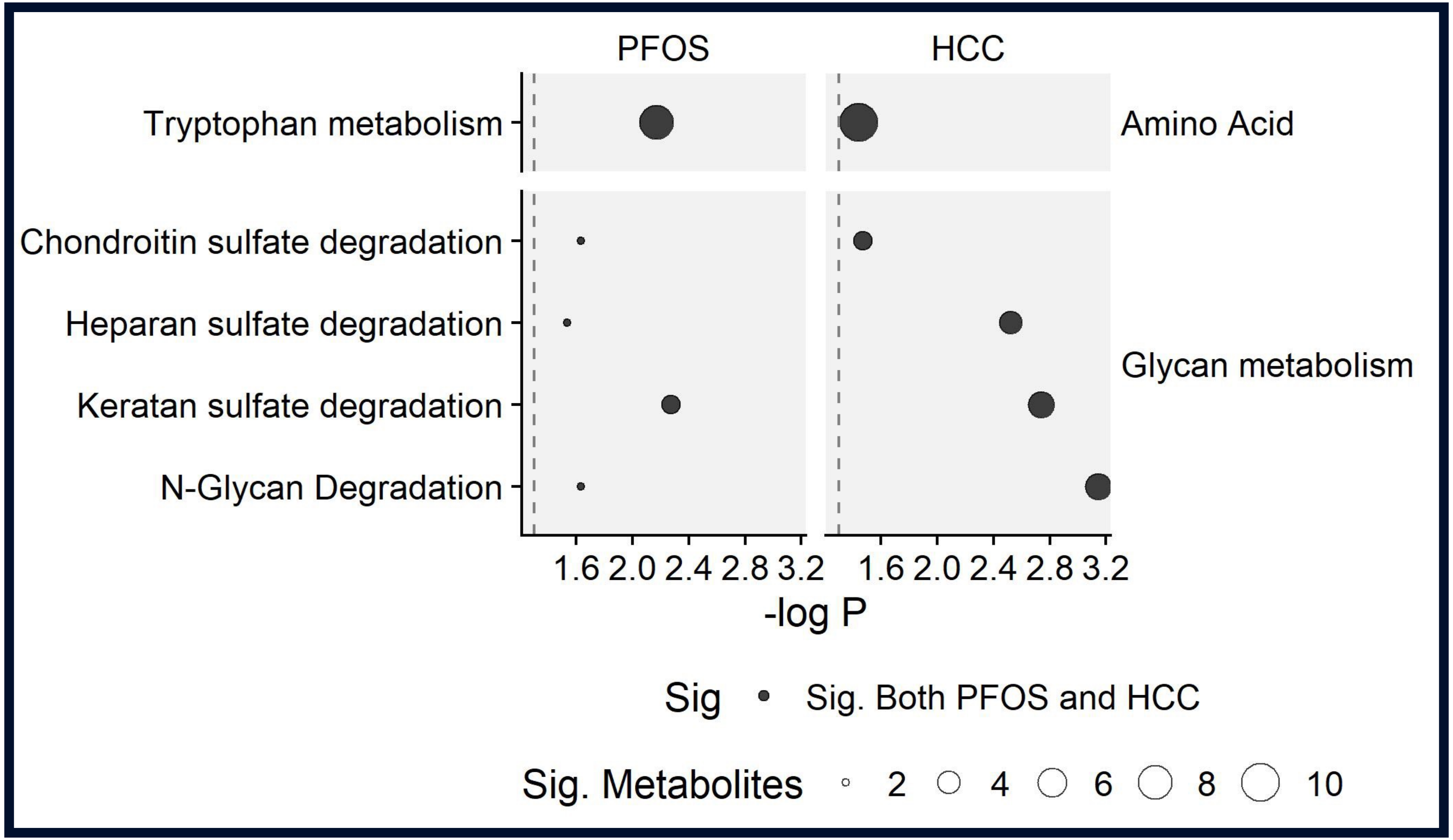
# RESULTS Metabolic Pathways Associated with High PFOS Levels or HCC

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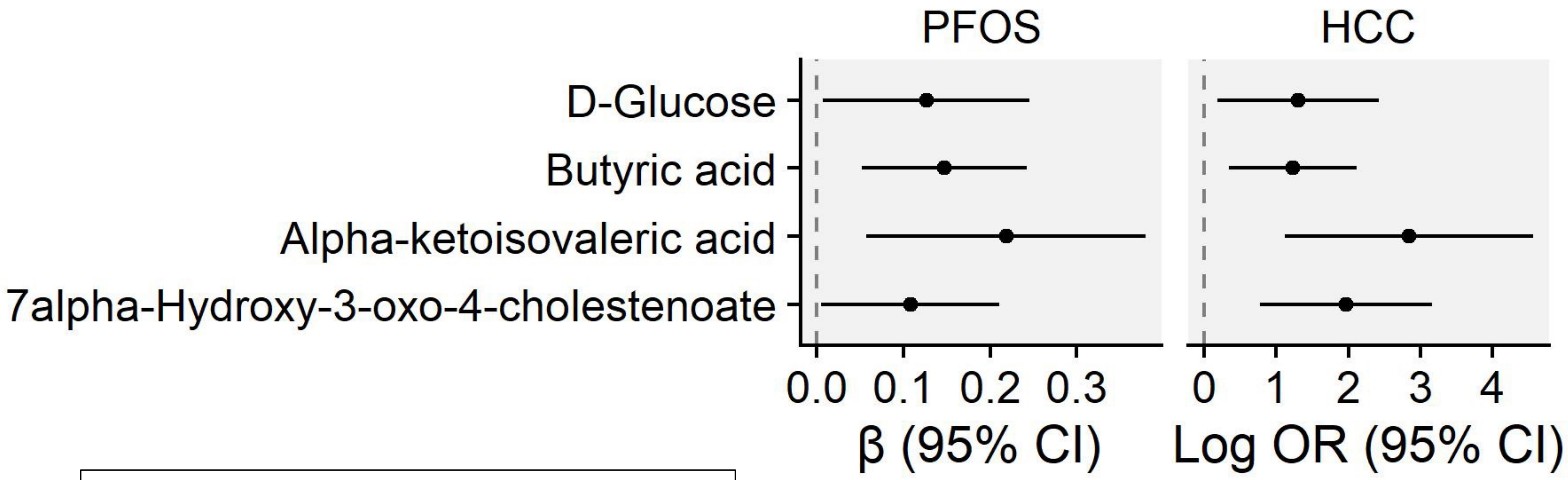
**RESULTS** Metabolites Positively Associated PFOS and HCC Risk




Butyric acid: short chain fatty acid
α-Ketoisovaleric acid: branched-chain α-keto acid
7α-Hydroxy-3-oxo-4-cholestenoate: bile acid

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# CONCLUSION

- High levels of PFOS in pre-diagnostic plasma samples are associated with increased risk of HCC
- Glucose and cholestanol metabolites were positively associated with PFOS exposure and with risk of HCC
- PFOS may increase risk of HCC via effects on glucose metabolism and bile acid biosynthesis

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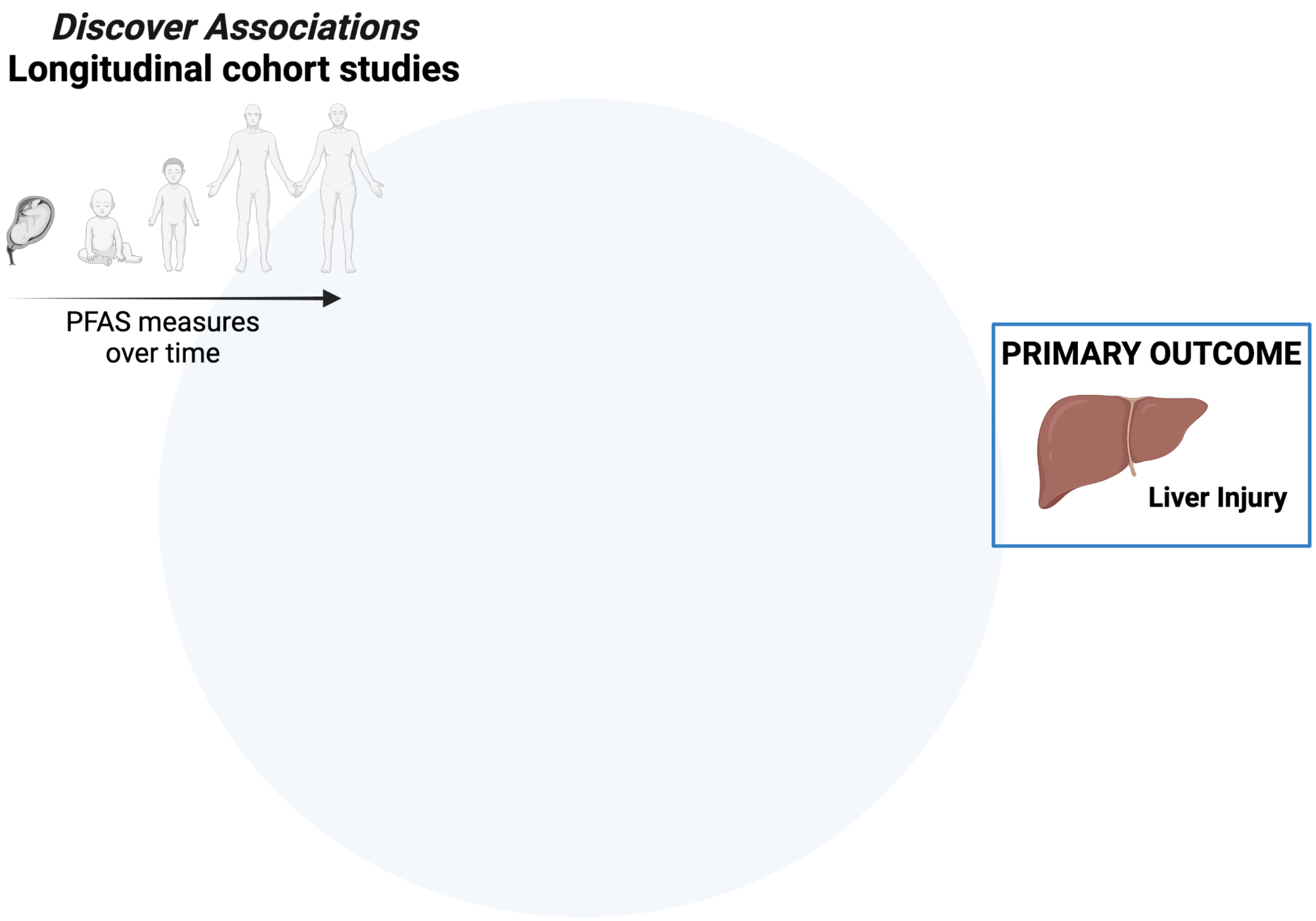
# Translational Framework

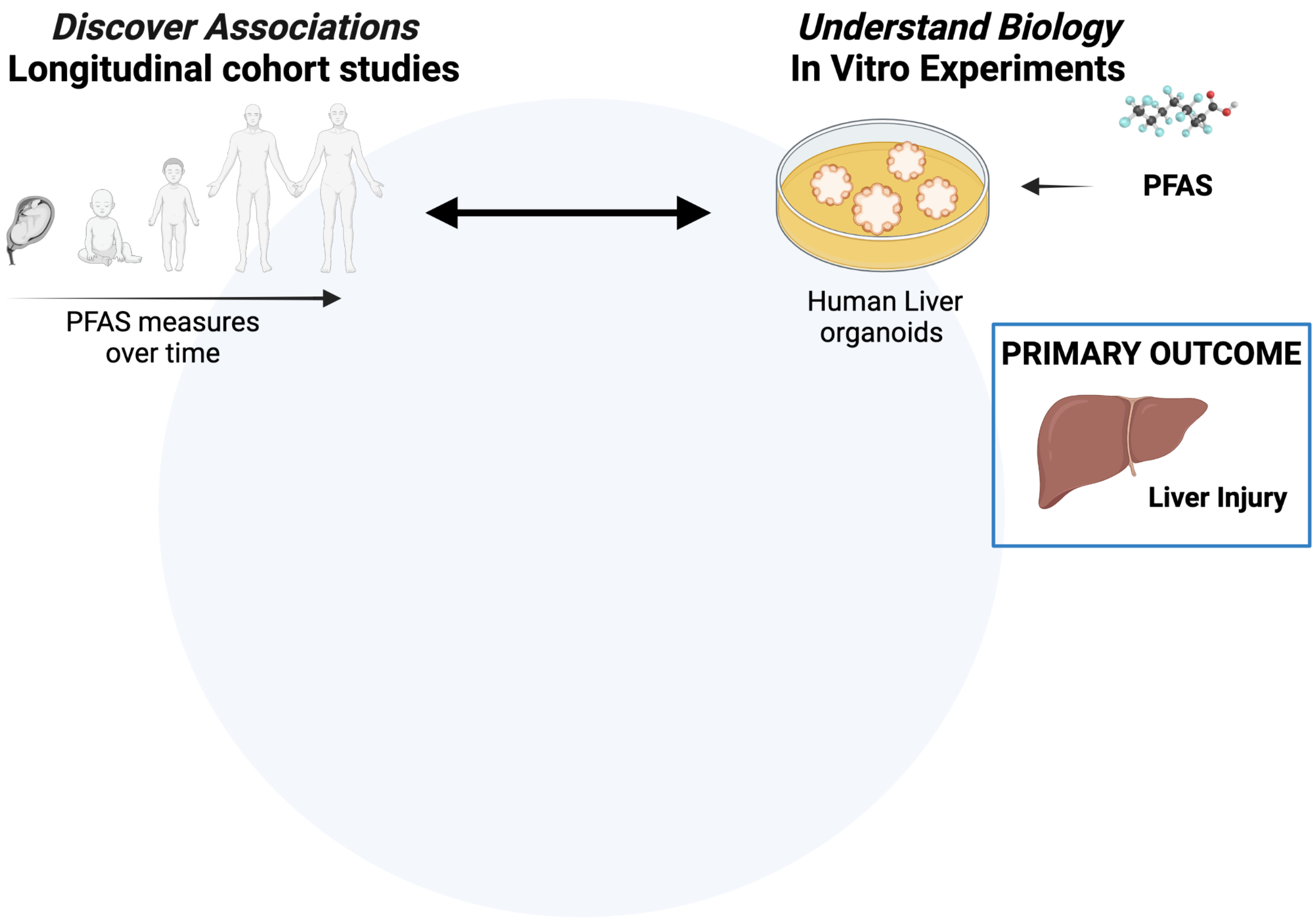
1. Discover Associations



# Translational Framework

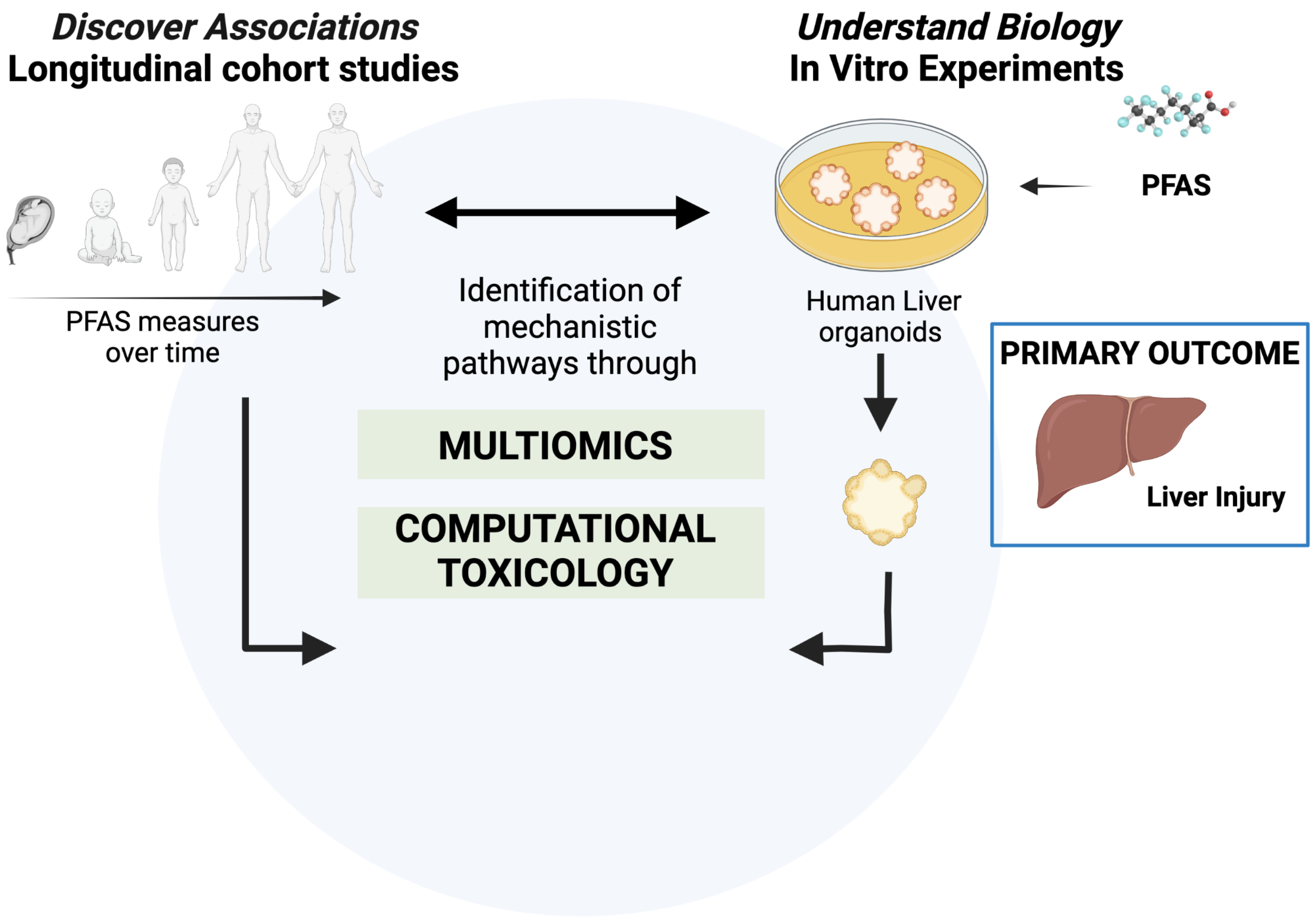
1. Discover Associations

2. Understand Biology



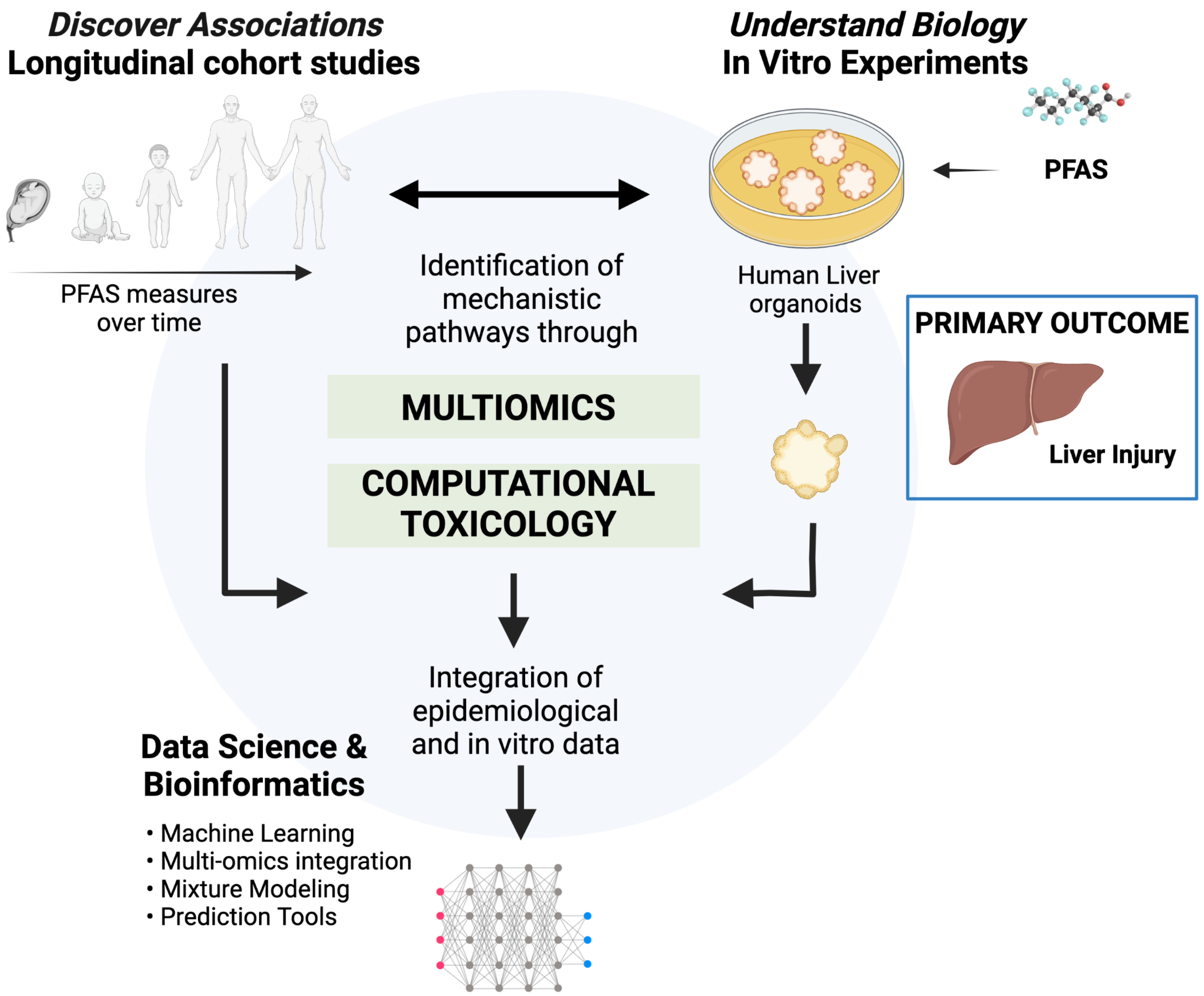
# Translational Framework

1. Discover Associations
2. Understand Biology
3. Integrate Multiomics & Computational Toxicology



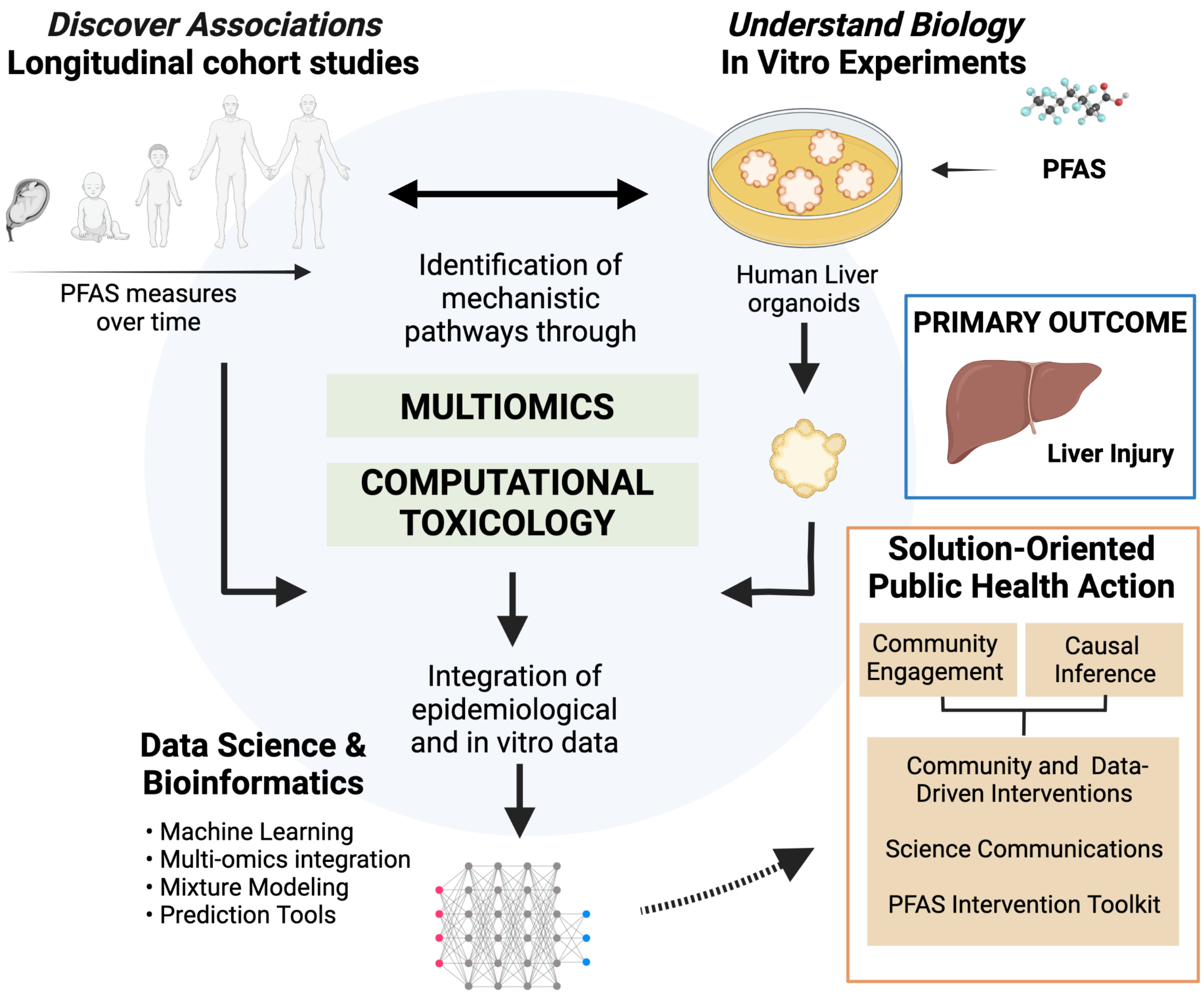
# Translational Framework

1. Discover Associations
2. Understand Biology
3. Integrate Multiomics & Computational Toxicology
4. Data Science and Bioinformatics



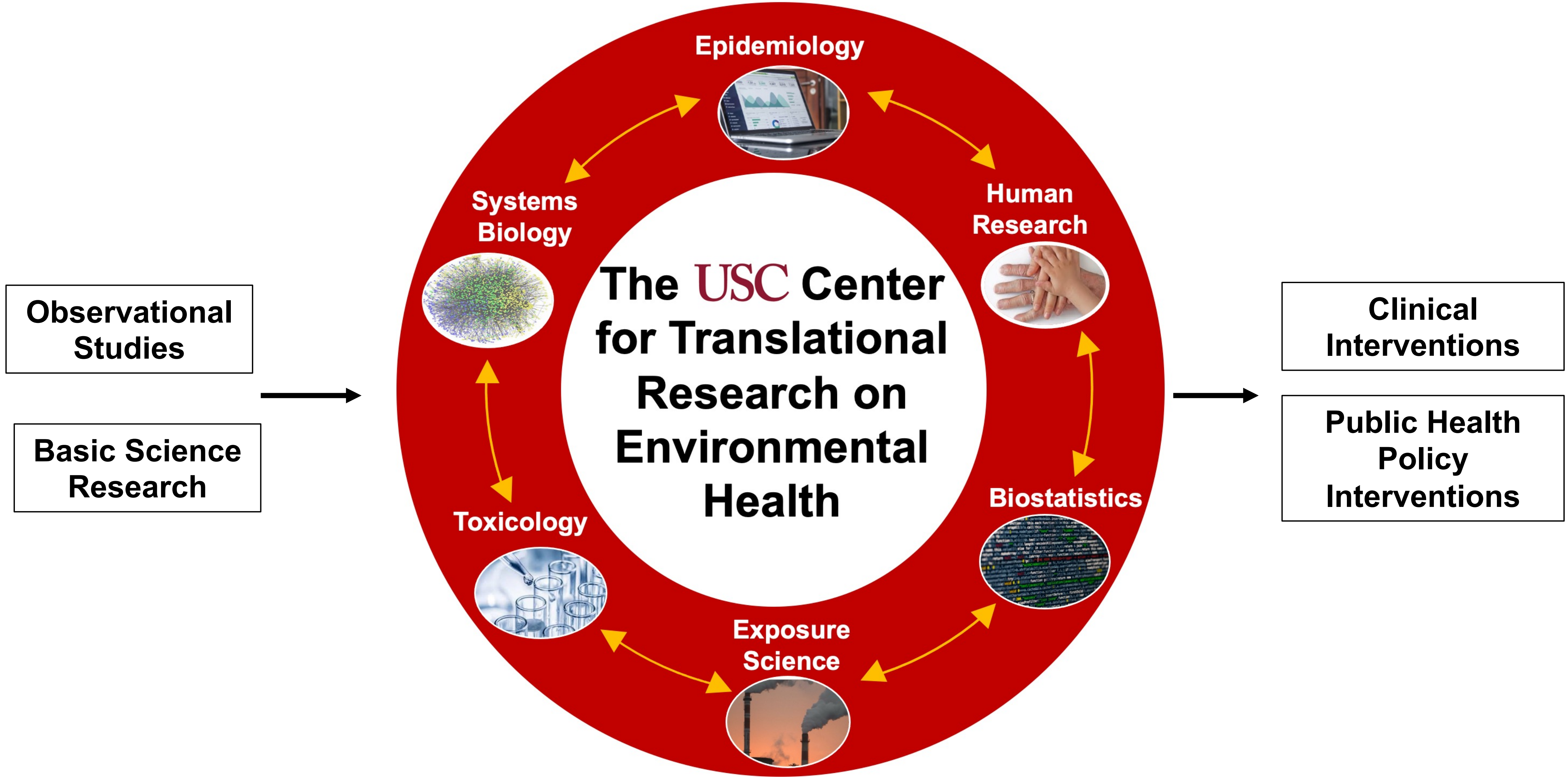
# Translational Framework

1. Discover Associations
2. Understand Biology
3. Integrate Multiomics & Computational Toxicology
4. Data Science and Bioinformatics
5. Solution-Oriented Public Health Action




R35 ES035051-Under review

# USC Center for Translational Research on Environmental Health and Chronic Diseases



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