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Supplemental Material

Metabolic Signatures of Youth Exposure to Mixtures of Per- and Polyfluoroalkyl Substances: A Multi-Cohort Study

Jesse A. Goodrich, Douglas I. Walker, Jingxuan He, Xiangping Lin, Brittney O. Baumert, Xin Hu, Tanya L. Alderete, Zhanghua Chen, Damaskini Valvi, Zoe C. Fuentes, Sarah Rock, Hongxu Wang, Kiros Berhane, Frank D. Gilliland, Michael I. Goran, Dean P. Jones, David V. Conti, and Leda Chatzi

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Table S1. PFAS concentrations (µg/L) for the low and high counterfactual exposure profiles used to calculate the overall mixture effect for the metabolome wide association study. The geometric mean and 95% confidence intervals are provided for additional context. In this study, the low exposure profile is defined as setting each log-transformed and standardized PFAS at a z-score of -0.5 ($x^* = -0.5$) and the high exposure profile is defined as setting each log-transformed and standardized PFAS at a z-score of 0.5 (z-score of 0.5; $x^* = 0.5$).

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Table S3. Metabolic pathways associated with exposure to a mixture of six PFAS in adolescents from the SOLAR cohort (n = 312) and young adults from the CHS cohort (n = 137). Meta-analysis p values are provided for pathways associated with PFAS in both cohorts. Pathway enrichment was performed using MetaboAnalyst version 5.0. The number of significant empirical compounds may not match the number of metabolites presented in figures 2-5 (main text) because MetaboAnalyst can annotate individual empirical compounds to multiple pathways and because individual LC-MS features may map to multiple empirical compounds.

Table S4. Effect estimates of individual annotated metabolites associated with exposure to a mixture of six PFAS in overweight and obese adolescents from the SOLAR cohort (n = 312), in young adults from the CHS cohort (n = 137), and in a pooled analysis with both the SOLAR and CHS cohorts. Effect estimates for PFAS mixture (ψ) and the 95% Bayesian credible interval (BCI) estimate the change in metabolite levels (SD of the log transformed feature intensity) when increasing all PFAS in the mixture from the 30th percentile to the 70th percentile. This estimate is also equivalent to a standardized mean difference calculated between a hypothetical group of individuals with all PFAS at the ~70th percentile versus a hypothetical group of individuals with all PFAS at the ~30th percentile.

Table S5. Metabolic pathways associated with exposure to a mixture of six PFAS in the pooled analysis of adolescents from the SOLAR cohort (n = 312) and young adults from the CHS cohort (n = 137). Pathway enrichment was performed using MetaboAnalyst version 5.0.

Figure S1. Directed Acyclic Graph (DAG) showing the covariates included in the models between PFAS exposure and metabolites.

Figure S2. Correlation between plasma PFAS concentrations in A) adolescents from the SOLAR cohort (n = 312) and B) young adults from the CHS cohort (n = 137). The upper triangle shows the pairwise spearman correlation coefficient for all PFAS, the lower triangle shows a scatter plot between each pair of PFAS, and the diagonal shows a density plot of PFAS concentrations in each cohort.

Figure S3. Heatmap showing the posterior inclusion probabilities (PIPs) between individual PFAS and metabolites associated with the metabolism of aromatic amino acids in A) adolescents from the SOLAR cohort (n = 312) and B) young adults from the CHS cohort (n = 137). The PIP is the posterior probability that the coefficient is non-zero, and higher PIPs suggest that the specific PFAS congener is more likely to have a causal effect in the true model. PIPs greater than 1/6 (~0.167) indicate a greater likelihood that the individual PFAS has a non-zero effect on the overall mixture; PIPs > 1/6 are labeled with text. Metabolites are grouped by aromatic amino acid metabolism sub pathways, indicated on the right of the plot.

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Figure S5. Heatmap showing the posterior inclusion probabilities (PIPs) between individual PFAS and metabolites associated with the metabolism of non-aromatic amino acids in A) adolescents from the SOLAR cohort (n = 312) and B) young adults from the CHS cohort (n = 137). The PIP is the posterior probability that the coefficient is non-zero, and higher PIPs suggest that the specific PFAS congener is more likely to have a causal effect in the true model. PIPs greater than 1/6 (~0.167) indicate a greater likelihood that the individual PFAS has a non-zero effect on the overall mixture; PIPs > 1/6 are labeled with text. Metabolites are grouped by non-aromatic amino acid metabolism pathways, indicated on the right of the plot.

Figure S6. Heatmap showing the posterior inclusion probabilities (PIPs) between individual PFAS and metabolites associated with metabolism of cofactors in adolescents from the SOLAR cohort (n = 312). No significant associations were observed in the CHS cohort. The PIP is the posterior probability that the coefficient is non-zero, and higher PIPs suggest that the specific PFAS congener is more likely to have a causal effect in the true model. PIPs greater than 1/6 (~0.167) indicate a greater likelihood that the individual PFAS has a non-zero effect on the overall mixture; PIPs > 1/6 are labeled with text.

Supplemental Code. R code used to generate the function for the Bayesian Hierarchical Regression Model with g-computation (BHRM-g). The complete code for this analysis can be found at github.com/chatzilab/PFAS_metabolomics_EHP_2022.

Additional File- Excel Document

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PFAS	SOLAR (n=312)			CHS (n = 137)		
	Low ($x^* = -0.5$)	High ($x^* = 0.5$)	Geometric Mean [95% CI]	Low ($x^* = -0.5$)	High ($x^* = 0.5$)	Geometric Mean [95% CI]
PFOS	7.91	17.7	11.8 [10.8, 12.9]	2.64	4.16	3.31 [3.06, 3.58]
PFHxS	1.02	2.04	1.44 [1.34, 1.56]	0.72	1.51	1.05 [0.922, 1.19]
PFHpS	0.280	0.490	0.373 [0.35, 0.397]	0.15	0.22	0.178 [0.167, 0.19]
PFOA	2.49	4.35	3.29 [3.09, 3.5]	1.12	1.60	1.34 [1.26, 1.42]
PFNA	0.500	0.700	0.589 [0.567, 0.612]	0.42	0.55	0.476 [0.455, 0.499]
PFDA	0.180	0.290	0.231 [0.219, 0.243]	0.14	0.26	0.191 [0.173, 0.211]

Table S2. Geometric mean and 95% confidence intervals of PFAS concentrations (µg/L) in overweight and obese adolescents from the SOLAR cohort, young adults from the CHS cohort, compared to PFAS levels in young persons aged 12-19 years old from the National Health and Nutrition Examination Survey (NHANES) years 2007-2008 and 2017-2018.

PFAS Name	SOLAR (n = 312) 2001-2012	CHS (n = 137) 2014-2018	NHANES Serum PFAS concentrations, Age 12-19 years	
			Survey (Years): 07-08	Survey (Years): 17-18
PFOS	11.8 [10.8, 12.9]	3.31 [3.06, 3.58]	11.3 (10.3-12.3)	2.68 (2.31-3.12)
PFHxS	1.44 [1.34, 1.56]	1.05 [0.922, 1.19]	2.40 (2.09-2.75)	.866 (.732-1.02)
PFHpS	0.373 [0.35, 0.397]	0.178 [0.167, 0.19]	N.R.	.154 (.118-.200)
PFOA	3.29 [3.09, 3.5]	1.34 [1.26, 1.42]	3.91 (3.71-4.12)	1.42 (1.33-1.52)
PFNA	0.589 [0.567, 0.612]	0.476 [0.455, 0.499]	1.16 (1.04-1.30)	.348 (.286-.424)
PFDA	0.231 [0.219, 0.243]	0.191 [0.173, 0.211]	.231 (.214-.248)	.193 (.178-.209)

N.R.: Not Reported.

Table S3. Metabolic pathways associated with exposure to a mixture of six PFAS in adolescents from the SOLAR cohort (n = 312) and young adults from the CHS cohort (n = 137). Meta-analysis p values are provided for pathways associated with PFAS in both cohorts. Pathway enrichment was performed using MetaboAnalyst version 5.0. The number of significant empirical compounds may not match the number of metabolites presented in figures 2-5 (main text) because MetaboAnalyst can annotate individual empirical compounds to multiple pathways and because individual LC-MS features may map to multiple empirical compounds.

| Super Pathway | Pathway Name | SOLAR (n=312) | | CHS (n=137) | | Meta-analysis p-value |
		Significant Compounds (number)	p-value	Significant Compounds (number)	p-value	
Amino acid metabolism (Aromatic Amino Acids)	Tyrosine metabolism	24	0.00019	8	0.022	0.000023
	Tryptophan metabolism	9	0.47	4	0.89	0.73
Amino acid metabolism (Branched-chain)	Valine, leucine and isoleucine degradation	5	0.14	1	0.25	0.11
Amino acid metabolism	Glutathione Metabolism	4	0.0095	1	0.27	0.011
	Urea cycle/amino group metabolism	10	0.096	4	0.088	0.033
	Arginine and Proline Metabolism	9	0.1	4	0.1	0.04
	Lysine metabolism	8	0.056	2	0.24	0.043
	Aspartate and asparagine metabolism	13	0.085	4	0.32	0.08
	Glutamate metabolism	4	0.37	1	0.3	0.29
	Methionine and cysteine metabolism	5	0.61	3	0.094	0.31
	Glycine, serine, alanine and threonine metabolism	7	0.61	3	0.17	0.38
	Beta-Alanine metabolism	5	0.12			
	Alanine and Aspartate Metabolism	5	0.25			
Lipid metabolism	De novo fatty acid biosynthesis	5	0.024	2	0.38	0.034
	Bile acid biosynthesis	4	0.33	5	0.061	0.11
	Prostaglandin formation from arachidonate	6	0.032	1	0.9	0.2

	Glycerophospholipid metabolism	8	0.5	2	0.56	0.53
	Glycosphingolipid metabolism	4	0.57	1	0.48	0.54
	Putative anti-Inflammatory metabolites formation from EPA	4	0.0032			
	Fatty Acid Metabolism	5	0.0051			
	Linoleate metabolism	8	0.0063			
	Arachidonic acid metabolism	5	0.057			
	Leukotriene metabolism	5	0.072			
Carbohydrate metabolism	Butanoate metabolism	5	0.36	2	0.23	0.24
	Aminosugars metabolism	4	0.41	1	0.7	0.54
	Ascorbate (Vitamin C) and Aldarate Metabolism	5	0.27			
Energy metabolism	Nitrogen metabolism	4	0.041			
Metabolism of cofactors and vitamins	Porphyrin metabolism	6	0.0032	1	0.49	0.011
	Vitamin B6 (pyridoxine) metabolism	4	0.0051			
	Vitamin B3 (nicotinate and nicotinamide) metabolism	4	0.28			
Nucleotide metabolism	Purine metabolism	8	0.25	4	0.12	0.11
	Pyrimidine metabolism	10	0.15	1	0.59	0.23
Xenobiotics biodegradation and metabolism	Drug metabolism - cytochrome P450	4	0.041			

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Cohort	Super pathway	Metabolite Name	ψ (95% BCI)	P-value	Q-value
SOLAR	Aromatic Amino Acid Metabolism	Hippuric acid	1.40 (0.72, 2.00)	5.10E-05	0.0065
		Phenylacetaldehyde	1.20 (0.81, 1.60)	4.10E-10	2.00E-07
		Ascorbate	1.00 (0.58, 1.40)	1.50E-06	0.00032
		Metanephrine	0.99 (0.35, 1.50)	0.002	0.14
		Norepinephrine sulfate	0.78 (0.35, 1.20)	0.0002	0.02
		Norepinephrine	0.74 (0.37, 1.10)	0.00011	0.012
		Thyroxine	0.72 (0.00, 1.20)	0.0065	0.39
		Tyramine-O-sulfate	0.72 (0.12, 1.40)	0.037	>0.99
		Phenylacetylglutamine	0.71 (0.26, 1.20)	0.002	0.14
		3-Methoxytyramine	0.66 (0.37, 0.96)	8.50E-06	0.0015
		3-O-methyldopa	0.63 (0.19, 1.00)	0.0014	0.1
		L-Glutamic acid	0.50 (0.11, 1.00)	0.024	>0.99
		Pyruvic acid	-0.53 (-0.91, 0.00)	0.022	>0.99
		4-Hydroxyphenylacetaldehyde	-0.54 (-1.10, 0.00)	0.046	>0.99
		Acetoacetic acid	-0.60 (-1.00, 0.00)	0.041	>0.99
		1,2-dehydrosalsolinol	-0.76 (-1.30, 0.00)	0.027	>0.99
		Vanylglycol	-0.92 (-1.50, -0.46)	0.00095	0.075
		Homovanillin	-1.10 (-1.60, -0.55)	7.60E-05	0.0089
	Lipid Metabolism	15-Keto-prostaglandin E2	1.20 (0.75, 1.70)	2.60E-07	7.00E-05
		Dodecanoic acid	1.20 (0.68, 1.70)	5.70E-06	0.001
		Prostaglandin E2	1.10 (0.35, 1.70)	0.0022	0.15

		Glycerol	1.00 (0.60, 1.50)	1.70E-05	0.0025
		Arachidonic acid	0.81 (0.37, 1.30)	0.001	0.081
		Linoleic acid	0.78 (0.19, 1.20)	0.0022	0.15
		13-OxoODE	0.77 (0.31, 1.20)	0.001	0.081
		Elaidic acid	0.64 (0.00, 1.10)	0.034	>0.99
		13(S)-HPOT	0.64 (0.06, 1.00)	0.0043	0.27
		Pelargonic acid	0.63 (0.00, 1.20)	0.027	>0.99
		LysoPC(18:1(9Z))	0.61 (0.00, 1.00)	0.016	0.82
		Leukotriene C5	0.59 (0.00, 1.00)	0.012	0.65
		12,13-epoxy-9-alkoxy-10E-octadecenoate	-0.47 (-0.93, 0.00)	0.091	>0.99
		(E)-4-hydroxynon-2-enal	-0.55 (-0.96, 0.00)	0.019	0.95
	Non-aromatic Amino Acid Metabolism	N-Acetylornithine	1.40 (0.90, 1.80)	1.60E-09	7.10E-07
		N-Acetylputrescine	1.20 (0.70, 1.70)	1.50E-05	0.0023
		6-Amino-2-oxohexanoate	0.93 (0.53, 1.40)	1.90E-05	0.0027
		Aminoadipic acid	0.70 (0.20, 1.20)	0.0057	0.34
		Citrulline	0.54 (0.02, 1.20)	0.075	>0.99
		5-Amino-2-oxopentanoic acid	-0.59 (-1.00, 0.00)	0.02	0.98
		L-Carnitine	-0.73 (-1.20, -0.25)	0.0019	0.13
		Aspartic acid	-0.87 (-1.30, -0.35)	0.00034	0.031
	Other met. pathways	Bilirubin	1.20 (0.63, 1.80)	0.0002	0.02
		Pyridoxamine	1.10 (0.62, 1.60)	1.60E-05	0.0023
		Biliverdin	0.78 (0.30, 1.30)	0.0027	0.18
		4-Pyridoxic acid	0.61 (0.20, 1.00)	0.0045	0.28
CHS	Aromatic Amino Acid Metabolism	Thyroxine	1.60 (0.39, 2.80)	0.023	>0.99
		Hippuric acid	1.30 (0.76, 1.90)	4.40E-06	0.0027
		Dopaquinone	1.30 (0.58, 2.00)	0.00035	0.094
		Homovanillic acid	1.10 (0.16, 1.80)	0.0072	0.97
		Acetoacetic acid	1.00 (0.06, 1.80)	0.012	>0.99
		L-Glutamic acid	0.87 (0.00, 1.70)	0.088	>0.99
		Vanylglycol	0.84 (0.08, 1.40)	0.0066	0.91

	Lipid Metabolism	11-hydroxyeicosatetraenoate glyceryl ester	1.60 (0.96, 2.30)	2.20E-06	0.0014
		Behenic acid	1.40 (0.61, 2.10)	0.00014	0.046
		Docosahexaenoic acid	1.40 (0.35, 2.30)	0.0059	0.81
		Arachidonic acid	0.67 (0.00, 1.50)	0.15	>0.99
	Non-aromatic Amino Acid Metabolism	Aminoadipic acid	1.30 (0.59, 2.30)	0.0016	0.31
		5'-Methylthioadenosine	1.00 (0.00, 1.90)	0.02	>0.99
		3-Dehydroxycarnitine	0.84 (0.00, 1.50)	0.046	>0.99
Pooled	Aromatic Amino Acid Metabolism	Thyroxine	1.40 (0.94, 2.00)	1.70E-07	4.40E-05
		Hippuric acid	1.10 (0.58, 1.40)	1.10E-06	0.00024
		Noradrenochrome	1.10 (0.46, 1.60)	0.00052	0.048
	Lipid Metabolism	Glycerol	2.30 (1.40, 2.90)	6.60E-10	3.20E-07
		Prostaglandin E2	1.30 (0.66, 1.80)	1.20E-05	0.002
	Non-aromatic Amino Acid Metabolism	N-Acetylornithine	1.10 (0.82, 1.30)	1.60E-18	2.70E-15
		Aminoadipic acid	0.67 (0.31, 1.10)	0.00075	0.065
	Other met. pathways	Bilirubin	1.90 (1.30, 2.50)	1.20E-10	6.80E-08
		Pyridoxamine	1.40 (0.71, 2.10)	5.60E-05	0.0074

Table S5. Metabolic pathways associated with exposure to a mixture of six PFAS in the pooled analysis of adolescents from the SOLAR cohort (n = 312) and young adults from the CHS cohort (n = 137). Pathway enrichment was performed using MetaboAnalyst version 5.0.

Super Pathway	Pathway	Significant Compounds (number)	Enrichment *p*-value
Amino acid metabolism (Aromatic Amino Acids)	Tyrosine metabolism	14	0.016
Amino acid metabolism	Urea cycle/amino group metabolism	6	0.042
	Aspartate and asparagine metabolism	5	0.359

Figure S1. Directed Acyclic Graph (DAG) showing the covariates included in the models between PFAS exposure and metabolites.

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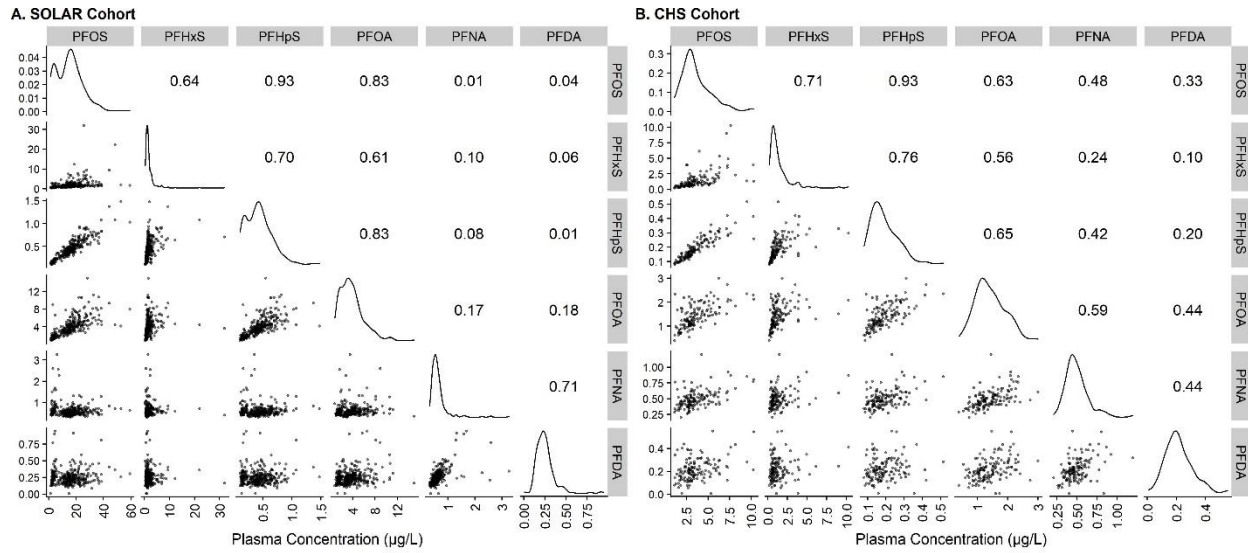
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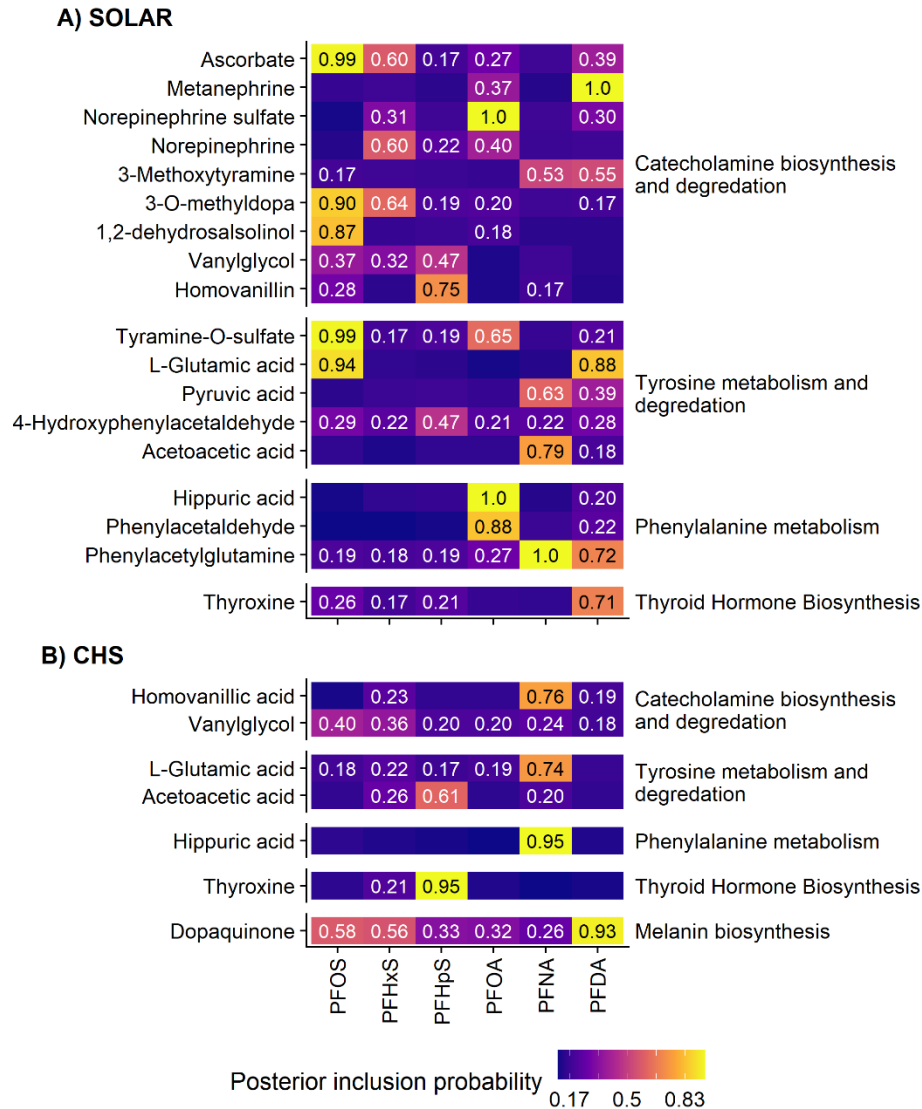
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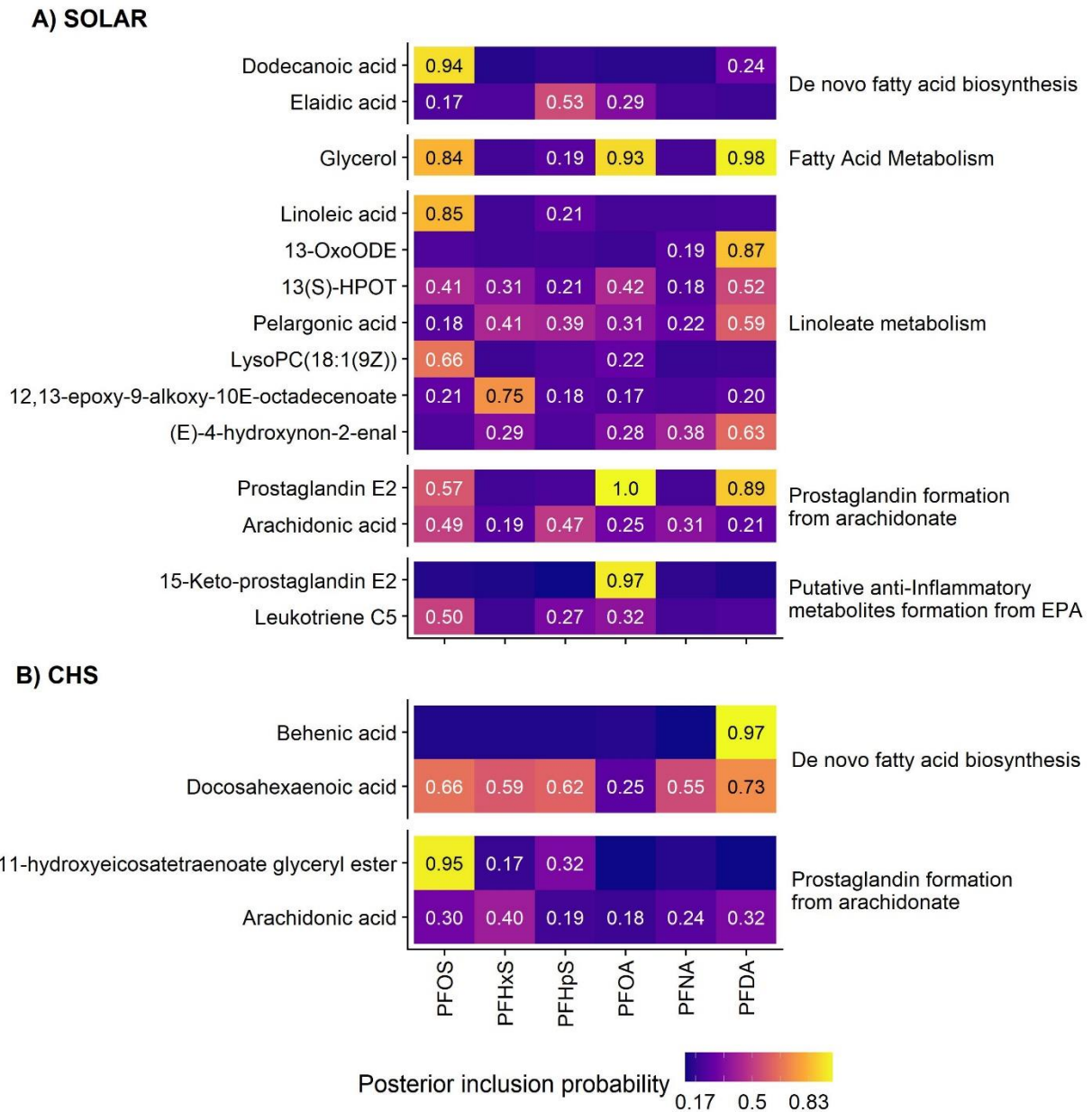
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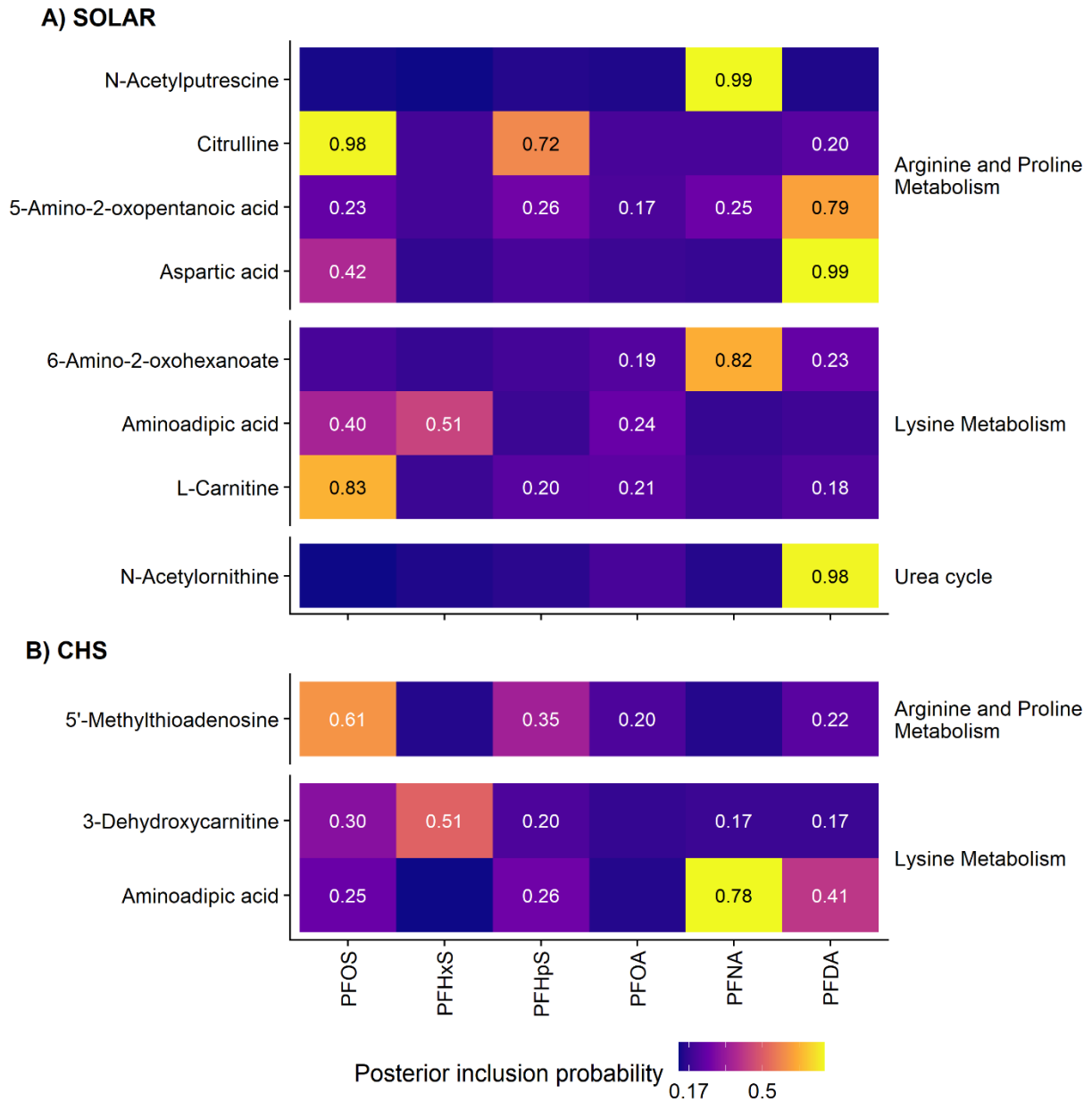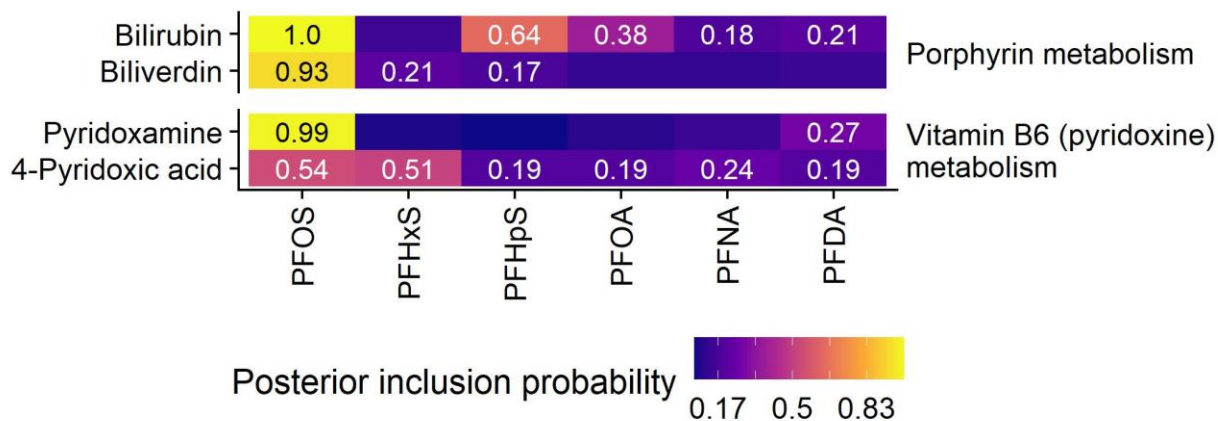
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Supplemental Code. R code used to generate the function for the Bayesian Hierarchical Regression Model with g-computation (BHRM-g). The complete code for this analysis can be found at github.com/chatzilab/PFAS_metabolomics_EHP_2022.

```r
# Description
# input variables
# X: A NxP matrix of exposures for mixture analysis (on the original scale
#    with NA's for individuals with BLD)
# Y: A N-length vector for a continuous outcome
# U: A NxQ matrix of covariates (variables included in the regression
#    model but not included in the g-estimation)
# LOD: A P-length vector of LODs for each exposure. Individuals with missing
#    data will have data imputed below this level of detection
# profiles: A 2xP matrix of two counterfactual profiles of exposures for
#    which a potential outcomes risk difference is calculated (as the
#    exposures are standardized within the function, these profiles should
#    be on the standard normal scale)

library(R2jags)
library(tidyverse)

# Create Function ----------------------------------------------
BHRMA.g <- function(X=NULL, Y=NULL, U=NULL, LOD=NULL, profiles=NULL) {

  # JAGS model
  ridge.BDL.model <-
    "model {
  for(i in 1:N) {
    Y[i] ~ dnorm(mu[i], prec.sigma.Y)
    mu[i] <- alpha +
             inprod(beta[1:P], X.s[i,1:P]) +
             inprod(delta[1:Q], U[i,1:Q])

    # imputation BDL
    for(p in 1:P) {
      X[i,p] ~ dnorm(X.true[i,p],prec.X[p])
      X.true[i,p] <- X.notmiss[i,p]*(1-R[i,p]) + X.miss[i,p]*R[i,p]
      X.notmiss[i,p] ~ dnorm(mu.X[p], tau.X[p])T(LOD[p], )
      X.miss[i,p] ~ dnorm(mu.X[p], tau.X[p])T( , LOD[p])
      X.s[i,p] <- (X.true[i,p] - mu.X[p])/sigma.X[p]
    }
  }
  # prior on outcome variance
  prec.sigma.Y <- 1/(sigma.Y*sigma.Y)
  sigma.Y ~ dunif(0,3)

  # prior on covariate effects
  for(q in 1:Q) { delta[q] ~ dnorm(0, 1.0E-06) }

  # prior on intercept
  alpha ~ dnorm(0, 1.0E-06)

  # prior on exposure effects
  beta[1:P] ~ dmnorm(mu.beta[1:P], T[1:P, 1:P])
  for(j in 1:P) {
    mu.beta[j] <- (1-gamma[j])*prop.mu.beta[j]
```

```r
    b[j] <- beta[j]*gamma[j]
    gamma[j] ~ dbern(pi)
    for(k in 1:P) {
      T[j,k] <- gamma[j]*gamma[k]*XtX[j,k]/(G) +
                (1-gamma[j]*gamma[k])*equals(j,k)*pow(prop.sd.beta[j],-2)
    }
    tau.X[j] <- 1/(sigma.X[j]*sigma.X[j])
    sigma.X[j] ~ dunif(0,5)
    mu.X[j] ~ dnorm(0, 1.0E-06)
    prec.X[j] <- 10000
  }
  pi ~ dbeta(1,P)

  # Hyper-g prior (following Perrakis 2018, note that this is on
  # the G^-1 so the Beta distribution is switchd in terms of a and
  # b from Li and Clyde 2019 equation 34)
  a <- 3
  bw <- a/2 - 1
  w~dbeta(1,bw)
  G <- w/(1-w)


  # g-estimation
  eta.low <- inprod(b[1:P], profiles[1,1:P])
  eta.high <- inprod(b[1:P], profiles[2,1:P])
  psi <- eta.high-eta.low

}"

  # Set N,P,Q,R, and exposure names
  N <- length(Y)
  P <- ncol(X)
  Q <- ncol(U)
  R <- ifelse(is.na(X), 1,0)
  exposure.Names <- colnames(X)

  ### get the univariate result
  univariate.results <- t(sapply(1:P, FUN=function(p) {
    x <- as.matrix(X[,p])
    reg <- glm(Y~x, family=gaussian) # perform logistic regression
    s.reg <- summary(reg)      # get the summary for the regression
    c.reg <- s.reg$coef["x",] # select the coefficients for the exposure
    return(c.reg)
  }, simplify=T))
  univariate.results <- data.frame(exposure.Names,univariate.results)

  ### g prior model result
  prop.mu.beta <- rep(0, P)
  prop.sd.beta <- univariate.results$Std..Error
  XtX <- t(as.matrix(X))%*%as.matrix(X)

  # run jags
  jdata <- list(N=N, Y=Y, X=X, R=R, U=U, P=P, Q=Q,
                profiles=profiles, LOD=LOD,XtX=XtX,
                prop.mu.beta=prop.mu.beta,
                prop.sd.beta=prop.sd.beta)
```

```r
    var.s <- c("beta", "gamma", "eta.low", "eta.high",  "psi")
    model.fit <- jags.model(file=textConnection(ridge.BDL.model),
                            data=jdata, n.chains=1, n.adapt=4000, quiet=T)
    update(model.fit, n.iter=1000, progress.bar="none")
    model.fit <- coda.samples(model=model.fit,
                              variable.names=var.s,
                              n.iter=5000,
                              thin=1,
                              progress.bar="none")

    # summarize results
    r <- summary(model.fit)
    var.names <- c(paste(exposure.Names, "beta", sep="."),
                   "eta.high",
                   "eta.low",
                   paste(exposure.Names, "gamma", sep="."),
                   "psi")
    ridge.BDL.results <- data.frame(var.names,
                                    r$statistics[,1:2],
                                    r$quantiles[,c(1,5)])
    wald = abs(ridge.BDL.results[,"Mean"]/ridge.BDL.results[,"SD"])
    ridge.BDL.results$p.val = (2*(1-pnorm(wald,0,1)))
    return(ridge.BDL.results)
}
```