Title

Toward Capturing the Exposome: Exposure Biomarker Variability and Co-Exposure Patterns in the Shared Environment

Running title:

Exposome variability in the household setting

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Abstract

BACKGROUND: Along with time, variation in the exposome is dependent on the location and sex of study participants. One specific factor that may influence exposure co-variations is a shared household environment.

OBJECTIVES: To examine the influence of shared household and partner's sex in relation to the variation in 128 endocrine disrupting chemical (EDC) exposures among couples.

METHODS: In a cohort comprising 501 couples trying for pregnancy, we measured 128 (13 chemical classes) persistent and non-persistent EDCs and estimated 1) sex-specific differences; 2) variance explained by shared household; and 3) Spearman's rank correlation coefficients (r_s) for females, males, and couples' exposures.

RESULTS: Sex was correlated with 8 EDCs including polyfluoroalkyl substances (PFASs) ($p < 0.05$). Shared household explained 43% and 41% of the total variance for PFASs and blood metals, respectively, but less than 20% for the remaining 11 EDC classes. Co-exposure patterns of the exposome were similar between females and males, with within-class r_s higher for persistent and lower for non-persistent chemicals. Median r_ss of polybrominated compounds and urine metalloids were 0.45 and 0.09, respectively, for females (0.41 and 0.08 for males), whereas lower r_ss for these 2 classes were found for couples (0.21 and 0.04).

CONCLUSIONS: Overall, sex did not significantly affect EDC levels in couples. Individual, rather than shared environment, could be a major factor influencing the co-variation of 128 markers of the exposome. Correlations between exposures are lower in couples than in individual partners and have important analytical and sampling implications for epidemiological study.

Keywords: exposome, co-exposures, EDCs, combined exposure, POPs, metals, phthalates, persistent pollutants, mixtures, biomarkers, exposure assessment

Introduction

Variation of environmental exposure levels in the population is a complex phenomenon and is influenced by factors shared by individuals — such as those within a household — and non-shared factors specific to individuals, such as their sex. One could apply the exposome paradigm (Wild 2005), a model to capture the totality of exposures from conception onwards, to comprehensively characterize the individual-level and shared differences of exposure. However, the exposome is a dynamic entity with variations across time (temporal) and place (spatial) (Wild et al. 2013) underscoring the importance of considering variability when assessing human health.

Instead of trying to "capture all" lifetime exposures, investigators can focus on critical and sensitive time windows in human development such as pregnancy, infancy, childhood and adolescence to reduce temporal complexity (Stingone et al. 2017). Furthermore, household-level ascertainments of exposure (i.e., sampling individuals from households) has been posited to be sufficient surrogates for all individuals in the household (Potera 2014). These assumptions may help characterize the exposome and study its time-dependent relationship with health outcomes. For example, the Human Early-Life Exposome (HELIX) project seeks to define the pregnancy and early-life exposomes and health (Vrijheid et al. 2014), while the EXPOsOMICS project has its conceptual framework of a life-course approach to a broader range of exposures (Vineis et al. 2016).

Another challenge includes the difficulty of interpreting exposure-disease associations due to the dense correlations among all exposures (Ioannidis 2016). The dense correlation pattern makes it hard to identify the directionality of the potential causality (Ioannidis et al. 2009). Second, correlations between exposures vary (e.g. absolute median correlation from almost 0 to above 0.5) and, thus, there is no universal scale to assess the biological significance (Patel and Ioannidis 2014). In addition, exposome-wide, or equivalently, environment-wide association studies (EWASs), assess all the associations between exposures and an outcome to identify potential etiologic signals (Manrai et al. 2017). The data-driven approach assumes little

118 to no collinearity between environmental predictors, but it is almost impossible to select any
119 single uncorrelated exposures out from the dense exposome. One strategy for addressing these
120 analytical issues is to characterize the correlations in diverse cohorts to provide reference levels
121 to gauge biological significance of associations.
122
123 We investigated whether cohabiting couples trying for pregnancy would have similar
124 concentrations of endocrine disrupting chemicals (EDCs) given their shared households, and
125 whether concentrations varied across partners in light of their individual exposures arising from
126 other environments such as lifestyle, recreation or occupation. This avenue of study is
127 important given that EDCs have been found to affect human fecundity and fertility (Hauser
128 2006; te Velde et al. 2010), though much of the available evidence relies on research conducted
129 in either men or women but not couples. We utilized the Longitudinal Investigation of Fertility
130 and the Environment (LIFE) Study to empirically assess couples' shared and individual variations
131 in a mixture of EDCs. We selected the LIFE Study because it has 13 classes of EDCs quantified in
132 both partners of the couple in keeping with the couple based nature of human reproduction
133 (Buck Louis et al. 2014, 2016; Patel et al. 2016). To meet our overarching aim, we characterize
134 the dense correlation structure of couples' EDC concentrations and then estimate shared and
135 individual variability. Lastly, we discuss the implications of the findings in designing future
136 exposome-related research.
137

138 ## Methods

139 ### *Study Design and Cohort*

140 Briefly, the LIFE Study enrolled 501 couples planning to discontinue contraception to become
141 pregnant from 16 counties in Michigan and Texas, 2005–2009. Couples were followed daily
142 until pregnant or up to 12 months of trying to become pregnant (infertile). Study participants
143 were screened for eligibility based on a set of criteria and the complete details have been
144 previously published (Buck Louis et al. 2011).
145

146 ### *Data Collection and Toxicologic Analysis*

147 Following enrollment and completion of the baseline interview, couples provided
148 preconception blood (20 mL) and urine (120 mL) samples for the quantification of both man-
149 made and natural EDCs (e.g. phytoestrogens). We also included serum cotinine, a metabolite of
150 nicotine, and have a total of 128 chemicals from 13 different classes (Table 1). Persistent EDCs
151 included 4 classes of serum persistent organic compounds: 36 congeners of polychlorinated
152 biphenyls (PCBs), 9 organochlorine pesticides (OCPs), 11 polybrominated chemicals
153 [polybrominated diphenyl ethers (PBDEs) and 1 polybrominated biphenyl (PBB)], and 7
154 polyfluoroalkyl substances (PFASs), and were quantified by a single laboratory using published
155 standard operating procedures (Kuklenyik et al. 2005; Sjödin et al. 2004).
156
157 Non-persistent ECDs included 5 classes of urinary non-persistent organic compounds: 6
158 phytoestrogens, 14 phthalate metabolites, 6 phenols [bisphenol A (BPA) and benzophenones
159 (BPs)], 12 antimicrobial chemicals [parabens, triclosan (TCS) and triclocarban (TCC)], 2
160 paracetamol & derivatives, and were quantified by another laboratory using published standard
161 operating procedures (Asimakopoulos et al. 2014; Guo et al. 2011; Mumford et al. 2015; Smarr
162 et al. 2016). Other 3 classes of EDCs included 3 blood metals, 17 urinary metals, and 4 urinary
163 metalloids (Bloom et al. 2015a).
164
165 Serum lipids were obtained by measuring total cholesterol, free cholesterol, triglycerides, and
166 phospholipids by an enzymatic method (Akins et al. 1989) and we calculated the total serum
167 lipids as described by Phillips et al. (1989). Creatinine was measured by a Roche/Hitachi Model
168 912 clinical analyzer (Dalla, TX, USA) using the Creatinine Plus Assay (Roche Diagnostics). Serum
169 cotinine, a metabolite of nicotine, was quantified by isotope dilution tandem mass
170 spectrometry (Bernert et al. 1997).
171
172 *Statistical Analysis*
173 Our overall analytical scheme is shown in Figure 1. First, we adjusted each of the indicators of
174 exposures for potential confounders in addition to total lipids (for lipophilic chemicals, n = 56)
175 and creatinine (for urinary chemicals, n = 61) to reduce estimate variability and susceptibility to

176 bias (Heavner et al. 2006; Schisterman et al. 2005). Specifically, we adjusted PCBs, OCPs, and
177 polybrominated chemicals for total lipids and all other urinary chemicals for creatinine.
178 Chemicals were log-transformed (x + 1) and continuous covariates were rescaled to have mean
179 zero and unit variance (Figure 1A). After extracting the residuals, we calculated the Spearman's
180 rank correlation (r_s) matrices for EDCs in females, males, and couples.
181
182 Adjusting procedures such as Bonferroni correction assume independence between
183 independent variables. One way to resolve this analytical issue is to account for the correlation.
184 To study the effect of correlations between exposures on the family-wise error rate, we
185 calculated the effective number of variables (M_{eff}) (Nyholt 2004) for estimating the Bonferroni
186 adjusted *p* values with formula 1, where $Var(\lambda_{obs})$ is the eigenvalue variance of the correlation
187 matrix and M is the original number of variables.
188
189 $$\mathrm{M}_{eff} = 1 + (M - 1)\left(1 - \frac{Var(\lambda_{obs})}{M}\right) \text{ ... formula 1}$$
190
191 We estimated the sex-specific difference with a paired t-test (by household) after extracting the
192 residuals from a linear model adjusted for age (Figure 1B). We used a similar approach to
193 estimate the percentage of variance explained by the shared environment. However, sex and
194 age variables were excluded in the adjustment step to isolate their effects (Figure 1C).
195 Afterward, we extracted and regressed the residuals against the household variable to obtain
196 the adjusted coefficient of determination (R^2).
197
198 We computed concordance as the Pearson correlation coefficient (*r*) between the chemical
199 relatedness r_s in this study and that in the 2003–2004 National Health and Nutrition
200 Examination Survey (NHANES) (Patel and Ioannidis 2014) to assess generalizability of the co-
201 exposure patterns. We estimated the concordance based on a total of 101 matched biomarkers
202 between the 2 studies. We chose the 2003–2004 NHANES because 1) many of the chemicals
203 measured in LIFE were also measured in NHANES and 2) by the same laboratory; and 3) the
204 time period (2003–2004) is close to the beginning of recruitment for the LIFE Study.

We used all the instrument derived concentrations for the analyses (Richardson and Ciampi 2003; Schisterman et al. 2006). For missing values, we substituted them by multiple imputation, assuming a missing-at-random scenario (Louis et al. 2013). We conducted imputation based on the information from available demographic, previous history of clinical symptoms and all other chemical variables and created a total of 10 imputed data sets for males and females separately.

We visualized the correlations between exposures as exposome globe using the R package Circlize (Champely 2017). EDCs were sorted from lipophilic to hydrophilic to aid visual interpretation of the patterns. We combined the final estimates from imputations using Rubin's method (Schafer 1999) and calculate the *p* values of correlations by permutation tests. To adjust for multiple testing, we used the false discovery rate (FDR) *q* values unless otherwise specified. We executed all analyses using the computing environment R (v 3.3.1) (R Core Team 2016). For reproducibility purpose, all analytic code is publicly available on GitHub via a MIT license (github.com/jakemkc/exposome_variability).

Results

Important sociodemographic differences were observed between partners (Table 2). Overall, female partners were younger, had a lower body mass index (BMI) (< 25), consumed fewer alcoholic drinks, were less likely to report a hypertension or high cholesterol, and had lower serum cotinine and lipids and creatinine than male partners ($p < 0.01$).

Nine (7%) chemicals were correlated with partner's sex ($p < 0.05$), i.e., cotinine, blood lead, mercury and cadmium; and 5 PFASs: perfluorodecanoate (PFDeA), perfluorononanoate (PFNA), perfluorooctane sulfonamide (PFOSA), perfluorooctane sulfonate (PFOS), and perfluorooctanoate (PFOA). Of note, findings were robust to the FDR with the exception of blood cadmium.

Figure 2 shows the boxplot summary of the variance explained by the shared environment. We estimated that two classes of chemicals, PFASs and blood metals, had higher levels of explained variance (median 0.43 and 0.41 respectively) than the others. For the rest of the 11 classes, median explained variances were ranged from 0.04 (phthalates) to 0.21 (cotinine). A few persistent organic compounds, namely PCB congener 28, PBDE congener 47, and β-hexachlorocyclohexane (β-HCH), had an explained variance over 50%.

The exposome globe (Patel and Manrai 2015) displays the r_ss for females (right-half), for males (left-half), and for couples (across the left-right of the globe) (Figure 3). To assist interpretation, we only presented the r_ss outside the range of −0.25 to 0.25 as lines connecting different parts on the track, and they represent less than 10% of all the r_ss. For females, we observed two larger positively correlated "clusters" across EDC classes: A) a dense cluster with serum persistent organic compounds such as PCBs and OCPs (upper right of Figure 3); B) another loosely packed cluster with urinary EDCs such as phytoestrogens, phthalates, phenols, and antimicrobial compounds (lower right of Figure 3). Correlations between serum and urinary EDCs were mostly small and distributed between −0.25 and 0.25. For males, there were similar co-exposure patterns to females

While we found similar correlations in the population of males and females separately, we found that correlations in couple living in the same household were, in fact, less densely packed and with values attenuated toward the null (Figure 3; see Figure S1).

Summary of the within-class correlations as absolute magnitude is shown in Figure 4. For females (Figure 4A), we found that polybrominated compounds had the highest median correlation (r_s = 0.45) while urine metalloids had the lowest (r_s = 0.09). Across different chemical classes, persistent organic compounds such as polybrominated compounds, PCBs and OCPs had higher median correlations (0.45, 0.38, and 0.34 respectively). For the rest of the classes, the median correlations were all below 0.25. Males (Figure 4B) had similar within-class correlation distributions as were found in females. The class with highest and lowest median correlations were polybrominated compounds (r_s = 0.41) and paracetamols (r_s = 0.02) respectively.

In contrast, we found a strong diminishing effects to the within-class correlations, both in terms of the median and interquartile range (IQR), in couples (Figure 4C). Comparing the couples with females and males, all chemical classes had the median correlations below 0.25 and urine metals were the class with greatest percentage drop (83%). We also observed a substantial reduction in the IQRs of the chemical classes. For example, the IQR of polybrominated compounds was 0.21, which corresponds to an over 35% drop relatively to females and males. We found that urine metals had the largest drop in IQR (over 77%). Looking more closely to the data, correlations between the same chemicals in couples (i.e. the diagonal of the correlation matrix of couples) were generally higher than that among the same class members. Because of the low number of exposure indicators in blood metals (3 chemicals), paracetamols (2 chemicals), and cotinine (1 chemical), the diminishing effect to within-class correlations was countered and thus the drop in medians and IQRs of these classes were not as prominent as others.

282 *P* values obtained from Bonferroni correction with M_{eff} were highly similar between females
283 and males (Table 3). Both groups had similar M_{eff} values with a difference smaller than 1
284 variable, suggesting that the overall degree of correlations was also similar. After adjusting for
285 the correlation, we found the total number of variables decreased from 128 to 112 for females
286 and 113 for males.
287
288 We estimated the concordances between correlations in the LIFE study (as females, males and
289 couples) and the 2003-2004 NHANES in Table 4. Overall, correlations *r* varied greatly between
290 chemical groups, from −0.78 to 0.98. Certain chemical groups had small sample size ($n \leq 6$) and
291 could cause low and inverse correlations. However, correlations *r* were more consistent and
292 comparable when we discarded group information and considered all chemicals as a whole
293 (females: 0.88; males: 0.84; couples: 0.67); therefore, we conclude the exposure correlation
294 patterns captured in LIFE are comparable to that in the U.S. population.
295
296 Discussion
297 *Findings*
298 Understanding the co-exposure patterns is an important step toward investigating the joint
299 health effects of chemical mixtures and for statistical design of exposome-related
300 investigations. We describe our high level findings here. First, exposure levels of one individual
301 in the household were not correlated with another individual in the same household. Second,
302 the percentages of significant r_s ($q < 0.05$) in males and females were 25.3 and 23.1
303 respectively, in contrast to only 9.5% between couples in the same household (Figure 4).
304 Chemical correlations in a household setting were concordant to those in 03–04 NHANES,
305 indicating reproducible co-exposure correlations with respect to the patterns sought in a
306 generalized and non-institutionalized U.S. population.
307
308 Although couples in our study potentially shared a large degree of dietary and indoor
309 environmental factors, their exposures were only modestly correlated (low r_s). We believe that
310 there are two additional factors affecting the familial co-exposure patterns in our investigation.

311 1) The first one is concerned with how long the couples have been living together. In the U.S.,
312 the median age of first marriage is over 24 since 2000 (U.S. Census Bureau 2016), and newly
313 married couples could show a greater discordance in chemical co-exposure relationships due to
314 a different pre-marriage exposures. 2) The second factor is potential physiological dampening
315 of exposure variability related to the half-life of the target chemicals (Makey et al. 2014;
316 Rappaport and Kupper 2008). Polybrominated compounds, PCBs, and OCPs are persistent
317 chemicals with high lipophilicity and longer half-lives (on the order of years). Their serum
318 concentrations are integrated over a period of time and not completely associated with recent
319 exposure (Aylward et al. 2014). Since most of the couples recruited in LIFE Study were living
320 together, we claim this phenomenon can explain the drop in r_s of persistent chemicals relative
321 to the short-lived urinary chemicals (such as phthalate metabolites, whose half-lives are on the
322 order of days) in couples (Figure 4).
323
324 Wu et al. (2015) conducted a household-based study and measured serum PBDE levels in
325 children and parents and reported the r_s between child and parent were in the range of 0.66 to
326 0.74 (median = 0.68, n = 68) for a number of PBDE compounds. The pairs shared a substantial
327 portion of genes, diet, and living environment and they found that for the latter 2 components,
328 measured as floor-wipe PBDEs, canned meat, tuna and whitefish, were predictive of serum
329 PBDEs. Furthermore, they found higher r_s of PBDEs between older couples (age ≥ 55, range =
330 0.45 to 0.78, median = 0.72). These findings are consistent with our claim.
331
332 Persistent organic chemicals are known to cause adverse health effects and are prioritized by
333 the U.S. Centers for Disease Control and Prevention for health monitoring (Li et al. 2006). Many
334 of them had wide applications in electrical/electronic equipment, agricultural chemicals, and
335 furniture (Dodson et al. 2012; Whitehead et al. 2011). Although other emerging EDCs such as
336 BPA and phthalates have short half-lives, they have extensive modern applications in cosmetics
337 and consumer products (Bloom et al. 2015b; Buck Louis et al. 2014; Louis et al. 2014; Smarr et
338 al. 2017). The ubiquity of these chemicals in different microenvironments such as schools and
339 offices suggests that household environment alone is not a major contributor to body burden,

consistent with our results (Figure 2). PFASs and blood metals had higher variance explained by the shared environment than other chemical classes and we believe that this could be related to the lifestyle of the subjects in the LIFE cohort (e.g. PFAS exposures via food items and personal care products).

Strength and Limitations

Our investigation includes 128 chemical biomarkers with diverse physicochemical properties that span from persistent lipophilic to non-persistent hydrophilic chemicals and is one of the first attempts to systematically characterize their correlations in a household setting. However, we do not know how long the couples have been living together at the baseline of the study to quantitatively assess how this factor affects co-exposure patterns. Also, we only collected biological samples at the baseline; thus, it is not possible to study how exposure levels and co-exposure patterns change longitudinally with time, which could be an important piece of information for assessing fecundity outcome and chemical exposures.

Analytical and Sampling Implications for Exposome-Wide Investigations

Our findings have implications for high-throughput association tests between correlated exposures and health outcomes and phenotypes. One of the typical approaches adjusting for multiplicity in EWASs is controlling the family-wise error rate (e.g. Bonferroni correction). However, the tests are assumed to be independent. Nyholt (2004) provided one solution to address correlation in Bonferroni correction by calculating the effective number of variables (M_{eff}, formula 1), which relies on identifying the number of variables, M, and estimating the eigenvalue variance, $Var(\lambda_{obs})$ of the correlation matrix. For example, conducting an EWAS of a response with respect to the chemical class PCBs containing 36 congeners, one can calculate the correlation matrix (M = 36) and estimate the associated $Var(\lambda_{obs})$ to obtain M_{eff} (Table 3). A new significance level for this set of comparisons will be α/Meff, which is less stringent than Bonferroni correction because Meff wil be smaller than M if correlations exist between congeners. Benjamini and Yekutieli (2001) and Fan et al. (2012) documented a procedure that considers the correlation structure for better controlling the FDR.

369

370 In the future, exposome-related investigations, will include many more variables than ever
371 before with the emergence of highly sensitive high-resolution mass spectrometry techniques
372 (Jones 2016) and availability of large data sets from reproducibility initiatives (Manrai et al.
373 2017). Attempts to assess health outcome associated with a number of exposures may increase
374 R^2 and lead to "overfitting" (Hawkins 2004). Additionally, dense correlations among exposures
375 indicate that multicollinearity may also influence the reliability of the association size in
376 multiple regression or even potential confounding. We claim that these analytic challenges
377 could be ameliorated through understanding co-exposure patterns. For example, statistical
378 approaches for evaluating the effects of mixture exposures such as principal component
379 analysis generally involve dimensionality reduction that relies on estimating the correlation
380 structure to reduce the number of exposures being considered prior to analysis but are difficult
381 to interpret (Taylor et al. 2016). Other regression approaches, such as the Elastic Net (Zou and
382 Hastie 2005) can consider highly co-linear exposure variables while giving coefficients that are
383 similar to that delivered from a typical regression model; however, inferential estimates (e.g. *p*
384 values and confidence intervals) are still in development (Taylor and Tibshirani 2015).
385
386
387 Capturing population-level exposure variability — and the demographic variables that are
388 associated with the variation, such as sex, location, and time — is a grand ambition in the
389 exposome concept (Manrai et al. 2017). Given people spend over 90% of their time indoor and
390 more than 12 hours a day at home (bls.gov/tus), household samples (e.g. such as house dust)
391 might be a reasonable surrogate to represent home exposures to family members who share
392 the same living environment. While sampling the household is a tempting approach because of
393 the simplicity and cost-savings over personal measurement, it may fail to catch a significant
394 fraction of exposure variability in the population as we found that shared environment could
395 explain a small percentage of biomarker variance (Figure 2). For epidemiological investigation
396 that sample study participants who are nested in a unit, for example, schools or homes,

397 conducting preliminary measurements to assess the influence of shared environment is one of
398 the ways to justify unit-based measurement.
399
400 Finally, correlations of chemical mixtures can also be an important tool used in exposure
401 science and cumulative risk assessment as groups of correlated chemicals are often released
402 from a single source (e.g. power plant and vehicular exhaust (Ravindra et al. 2008). Thus,
403 studying the co-exposure patterns is the first step to identify the sources prior to more in-depth
404 source apportionment methods such as positive matrix factorization and chemical mass
405 balance receptor models (Rizzo and Scheff 2007). In cumulative risk assessment, dose addition
406 is one of the common approaches to estimate the risks from mixture exposures by assuming a
407 shared toxicity mechanism between chemicals (e.g. binding to the same receptor) (Chen et al.
408 2001). Knowing the co-exposure correlations could be a first step toward identification of
409 exposures with similar physicochemical properties to guide follow-up investigations.

410 ## Conclusions

411 While we observed similar co-exposure patterns between females and males, the correlations
412 were much lower in couples. Our analyses empirically demonstrate that shared environment
413 explains less than 20% of the biomarker variance in 11 out of 13 EDC classes. The influence of
414 shared environment to EDC levels is likely conditional on 1) the duration of residence of the
415 subjects and 2) the lipophilicity and persistency of the chemicals. These factors should be
416 considered when using surrogate measurement to assess the exposures of family members.
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568 Tables

569 Table 1. List of chemical classes and measured chemicals in the current study.

EDC Class	No.	Individual Chemicals	Medium	LOQ
Polychlorinated biphenyls (PCBs)	36	Congeners: 28, 44, 49, 52, 66, 74, 87, 99, 101, 105, 110, 114, 118, 128, 138, 146, 149, 151, 153, 156, 157, 167, 170, 172, 177, 178, 180, 183, 187, 189, 194, 195, 196, 201, 206, 209	Serum	1-3 pg/g, wet weight
Organochlorine pesticides (OCPs)	9	Hexachlorobenzene (HCB), β-hexachlorocyclohexane (β-HCH), γ-hexachlorocyclohexane (γ-HCH), oxychlordane, *trans*-nonachlor, *p,p*'-DDT, *o,p*'-DDT, *p,p*'-DDE, and mirex	Serum	1-3 pg/g, wet weight
Polybrominated chemicals[a]	11	Brominated biphenyl (BB 153); brominated diphenyl ethers (BDEs) congeners: 17, 28, 47, 66, 85, 99, 100, 153, 154, 183	Serum	5 pg/g, wet weight
Polyfluoroalkyl substances (PFASs)	7	2-(*N*-ethyl-perfluorooctane sulfonamido) acetate (Et-PFOSA-AcOH), 2-(*N*-methyl-perfluorooctane sulfonamido) acetate (Me-PFOSA-AcOH), perfluorodecanoate (PFDeA), perfluorononanoate (PFNA), perfluorooctane sulfonamide (PFOSA), perfluorooctane sulfonate (PFOS), and perfluorooctanoate (PFOA)	Serum	0.04-0.1 ng/mL, wet weight
Phytoestrogens	6	Genistein, daidzein, *O*-desmethylangolensin, equol, enterodiol, and enterolactone	Urine	0.2-0.6 ng/mL
Phthalate metabolites	14	Mono (3-carboxypropyl) phthalate (mCPP), monomethyl phthalate (mMP), monoethyl phthalate (mEP), mono (2-isobutyl phthalate) (miBP), mono-n-butyl phthalate (mBP), mono (2-ethyl-5-carboxyphentyl) phthalate (mECPP), mono-[(2-carboxymethyl) hexyl] phthalate (mCMHP), mono (2-ethyl-5-oxohexyl) phthalate (mEOHP), mono (2-ethyl-5-hydroxyhexyl) phthalate (mEHHP), monocyclohexyl phthalate (mCHP), monobenzyl phthalate (mBzP), mono (2-ethylhexyl) phthalate (mEHP), mono-isononyl phthalate (mNP), and monooctyl phthalate (mOP)	Urine	0.2-2 ng/mL
Phenols[b]	6	Total bisphenol A (BPA); benzophenones (BPs): 4-hydroxybenzophenone (4-OH-BP), 2,4-dihydroxybenzophenone (2,4-OH-BP), 2,2′,4,4′-tetrahydroxybenzophenone (2,2′4,4′-OH-BP), 2-hydroxy-4-methoxybenzophenone (2-OH-4-MeO-BP), and 2,2′-dihydroxy-4-methoxybenzophenone (2,2′-OH-4-MeO-BP)	Urine	0.02-0.05 ng/mL
Antimicrobial chemicals[c]	12	Triclosan (TCS) and triclocarban (TCC); parabens: methyl paraben (MP), ethyl paraben (EP), propyl paraben (PP), butyl paraben (BP), benzyl paraben (BzP), heptyl paraben (HP), 4-hydroxy benzoic acid (4-HB), 3,4-dihydroxy benzoic (3,4-DHB), methyl-protocatechuic acid (OH-Me-P), and ethyl-protocatechuic acid (OH-Et-P)	Urine	0.02-0.05 ng/mL
Paracetamol & derivatives	2	Paracetamol and 4-aminophenol	Urine	0.5 ng/mL and 0.25 ng/mL
Blood metals	3	Cadmium (Cd), lead (Pb), and mercury (Hg)		10 ng/L to 10 μg/L
Cotinine[d]	1	Cotinine	Serum	0.01 ng/mL
Urine metals	17	Manganese (Mn), chromium (Cr), beryllium (Be), cobalt (Co), molybdenum (Mo), cadmium (Cd), tin (Sn), caesium (Cs), barium (Ba), nickel (Ni), copper (Cu), zinc (Zn), tungsten (W), platinum (Pt), thallium (Tl), lead (Pb), and uranium (U)	Urine	10 ng/L to 10 μg/L
Urine metalloids	4	Selenium (Se), arsenic (As), antimony (Sb), and tellurium (Te)	Urine	10 ng/L to 10 μg/L

570

571 Note: LOQ, Limits of quantification.

572 [a]Polybrominated chemicals contain mostly PBDEs with one PBB.
573 [b]Phenols contain mostly benzophenones with one BPA.
574 [c]Antimicrobial chemicals contain mostly parabens with TCS and TCC.
575 [d]Serum cotinine is not an EDC but included for comprehensive investigation.
576
577

578 Table 2. Sociodemographic and lifestyle characteristics of females and males in the LIFE Study.

Characteristics	Females (*n* = 501)	Males (*n* = 501)
Age (year) **	29.99 ± 4.14	31.77 ± 4.92
BMI (kg/m^2) **		
< 25	230 (46)	84 (17)
≥ 25 & < 30	136 (27)	206 (41)
≥ 30	135 (27)	311 (62)
Non-Hispanic White	396 (79)	397 (79)
College graduate or higher *	474 (95)	457 (91)
Yearly income $80,000 or over	297 (59)	298 (59)
Regular vigorous exercise in the past 12 months	200 (40)	211 (42)
Smoke at the time of study		
No	445 (89)	440 (88)
Yes (No. of cigarettes on a typical day)		
1 - 3	19 (4)	26 (5)
4 - 6	8 (2)	11 (2)
7 - 10	15 (3)	8 (2)
11-15	7 (1)	2 (0)
16 - 25	3 (1)	10 (2)
> 25	4 (1)	4 (1)
≥ 12 alcoholic drinks in the past 12 months **	374 (75)	428 (85)
No. of alcoholic drinks on a typical occasion **		
0	128 (26)	73 (15)
1	108 (22)	63 (13)
2	169 (34)	150 (30)
3	68 (14)	99 (20)
4	19 (4)	62 (12)
5	9 (2)	54 (11)
History of diabetes	6 (1)	14 (3)
History of high blood pressure **	20 (4)	52 (10)
History of high cholesterol **	41 (8)	78 (16)
Serum cotinine (ng/mL)[a] **	0.62 ± 0.23	1.24 ± 2.17
Serum total lipids (mg/dL)[a] **	2.00 ± 0.03	6.56 ± 0.26
Urinary creatinine (mg/dL)[a] **	4.22 ± 0.86	4.76 ± 0.73

579

580 Note: BMI, body mass index. Values in mean ± SD or n (%).

581 *$p < 0.05$; **$p < 0.01$.

582 [a]log+1 transformed values.

583

584

585

586 Table 3. Number of effective variables for each chemical class after adjusting for the within-class correlation.

		Females				Males	
Chemical class	M	M_{eff}	M_{diff}	*P* value	M_{eff}	M_{diff}	*P* value
Serum persistent organic compounds							
Polychlorinated biphenyls (PCBs)	36	28.38	7.62	0.002	28.69	7.31	0.002
Organochlorine pesticides (OCPs)	9	7.94	1.06	0.006	8.17	0.83	0.006
Polybrominated chemicals	11	8.22	2.78	0.006	8.38	2.62	0.006
Polyfluoroalkyl substances (PFASs)	7	6.13	0.87	0.008	6.25	0.75	0.008
Urinary non-persistent organic compounds							
Phytoestrogens	6	5.34	0.66	0.009	5.38	0.62	0.009
Phthalate metabolites	14	12.72	1.28	0.004	12.87	1.13	0.004
Phenols	6	5.48	0.52	0.009	5.51	0.49	0.009
Antimicrobial chemicals	12	11.38	0.62	0.004	11.60	0.40	0.004
Paracetamol & derivatives	2	1.99	0.01	0.025	2.00	0.00	0.025
Others							
Blood metals	3	2.91	0.09	0.017	2.91	0.09	0.017
Serum cotinine	1	1.00	0.00	0.050	1.00	0.00	0.050
Urine metals	17	16.13	0.87	0.003	16.22	0.78	0.003
Urine metalloids	4	3.95	0.05	0.013	3.95	0.05	0.013
Total	128	111.57	16.43	0.0004	112.94	15.06	0.0004

587

588 Note: M, number of variables in the corresponding chemical classes; M_{eff}, number of effective variables after taking account of
589 within-class correlation; M_{diff}, the different between M and M_{eff}; *P* value, Bonferroni adjusted *p* values as $0.05/M_{eff}$.

590

591

592

593 Table 4. Correlations of chemical relatedness between 2003–2004 NHANES and current study by different chemical classes.

Chemical class[a]	Females		Males		Couples	
	Pearson *r*	*n*	Pearson *r*	*n*	Pearson *r*	*n*
Blood_metals	0.07	3	0.13	3	-0.04	6
OCPs	0.69	36	0.51	36	0.25	72
PCBs	0.88	561	0.88	561	0.77	1122
PFASs	0.31	21	0.29	21	0.32	42
Phthalates	0.90	78	0.89	78	0.34	156
Phytoestogens	0.98	15	0.97	15	0.86	30
Polybrominated_cpds	0.76	55	0.74	55	0.77	110
Urine_metalloids	0.41	3	-0.78	3	0.34	6
Urine_metals	0.82	55	0.78	55	-0.01	110
Total	0.84	827	0.84	827	0.67	1654

594

595 Note: Pearson *r*, Pearson correlation coefficients of the chemical relatedness (spearman correlations of chemicals) between National
596 Health and Nutrition Examination Survey (NHANES) and this study; *n*, sample size.
597 [a]Only 9 classes are shown because not all chemicals in 13 chemical classes in this study could be matched with NHANES.
598

599 Figure Legends

600 Figure 1. Analytical scheme to investigate the variability and correlations in this study. A) We first extract the residuals from a linear
601 model after adjusting for the base covariates (total lipids or creatinine) to calculate the effective number of variables (M_{eff}) and
602 Spearman's rank correlation (r_s). B) Then, we used another linear model with an additional age variable to obtain residuals and
603 conducted paired t-test to test the difference of biomarkers between females and males living in the same household. C) Afterward,
604 we further adjusted for sex prior to extracting residuals to calculate the percentage of biomarker variance explained by the shared
605 environment.
606
607 Figure 2. Summary of the percentage variance explained by the shared environment. Boxplots of the adjusted coefficient of
608 determination (R^2) within different chemical classes are shown. Interquartile range is not shown for Cotinine class because it
609 contains only 1 compound. For each box, median and interquartile range are drawn and the whiskers are extended to the largest
610 values within 1.5*interquartile range. Black dots denote correlations outside of the range covered by the whiskers.
611
612 Figure 3. Exposome correlation globe showing the relationships between females, males and couples. Right-half represents
613 biomarkers in females; left-half represents biomarkers in males. Only Spearman's rank correlations greater than 0.25 and smaller
614 than −0.25 were shown as connections in the globe. Red line denotes positive correlation and dark green line denotes negative one.
615 Color intensity and line width are proportional to the size of the correlation. Within-class and between-class correlations are shown
616 outside and inside of the track respectively. Correlations in couples are indicated by the lines linking females and males (i.e. crossing
617 the vertical-half of the globe).
618
619 Figure 4. Boxplots of Spearman's rank correlations (r_s) within different chemical classes. A) Females; B) Males; and C) Couples. For
620 couples, summary statistics were estimated with the full 128 x 128 correlation matrix instead of with the half triangle. Certain
621 classes contain only 1 pair of correlation (paracetamols in females, paracetamols in males, and cotinine in couples). "All" represents
622 the grouping by the correlation of all pairs of chemicals available. Horizontal line drawn across the chemical classes is equal to the
623 95th percentile of the null distribution obtained from permuting the concentrations of all chemicals. Definition of whisker and black
624 dot can be referred to the caption in Figure 2.
625

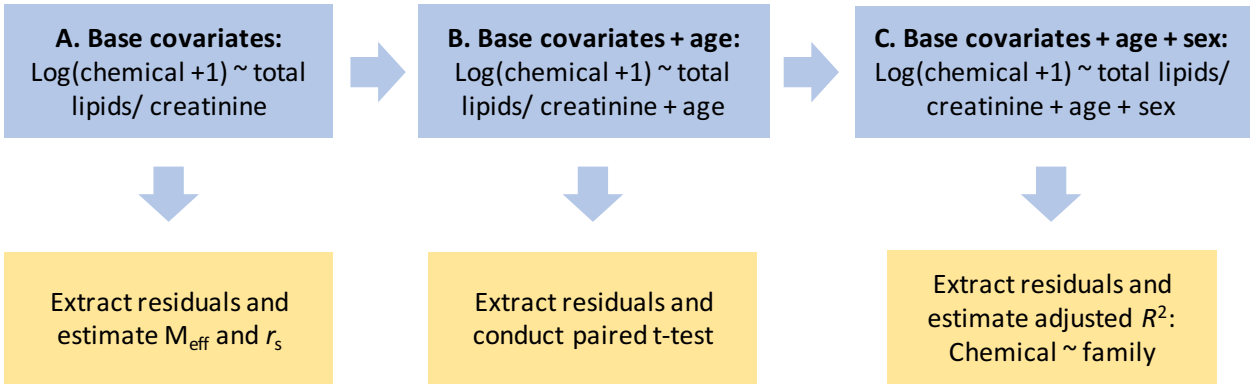

A. Base covariates:
Log(chemical +1) ~ total lipids/ creatinine
B. Base covariates + age:
Log(chemical +1) ~ total lipids/ creatinine + age
C. Base covariates + age + sex:
Log(chemical +1) ~ total lipids/ creatinine + age + sex
Extract residuals and estimate M_{eff} and r_s
Extract residuals and conduct paired t-test
Extract residuals and estimate adjusted R^2: Chemical ~ family

Figure 1

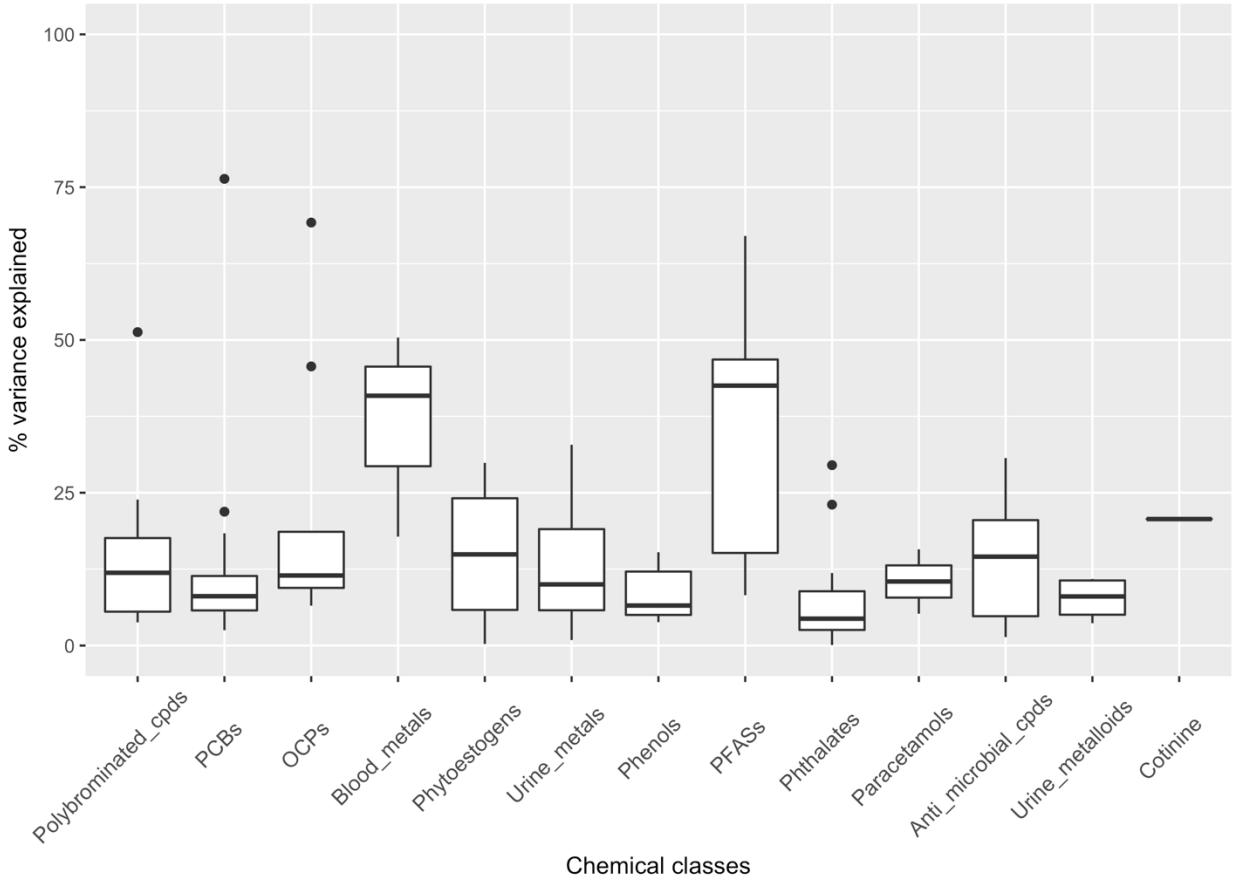
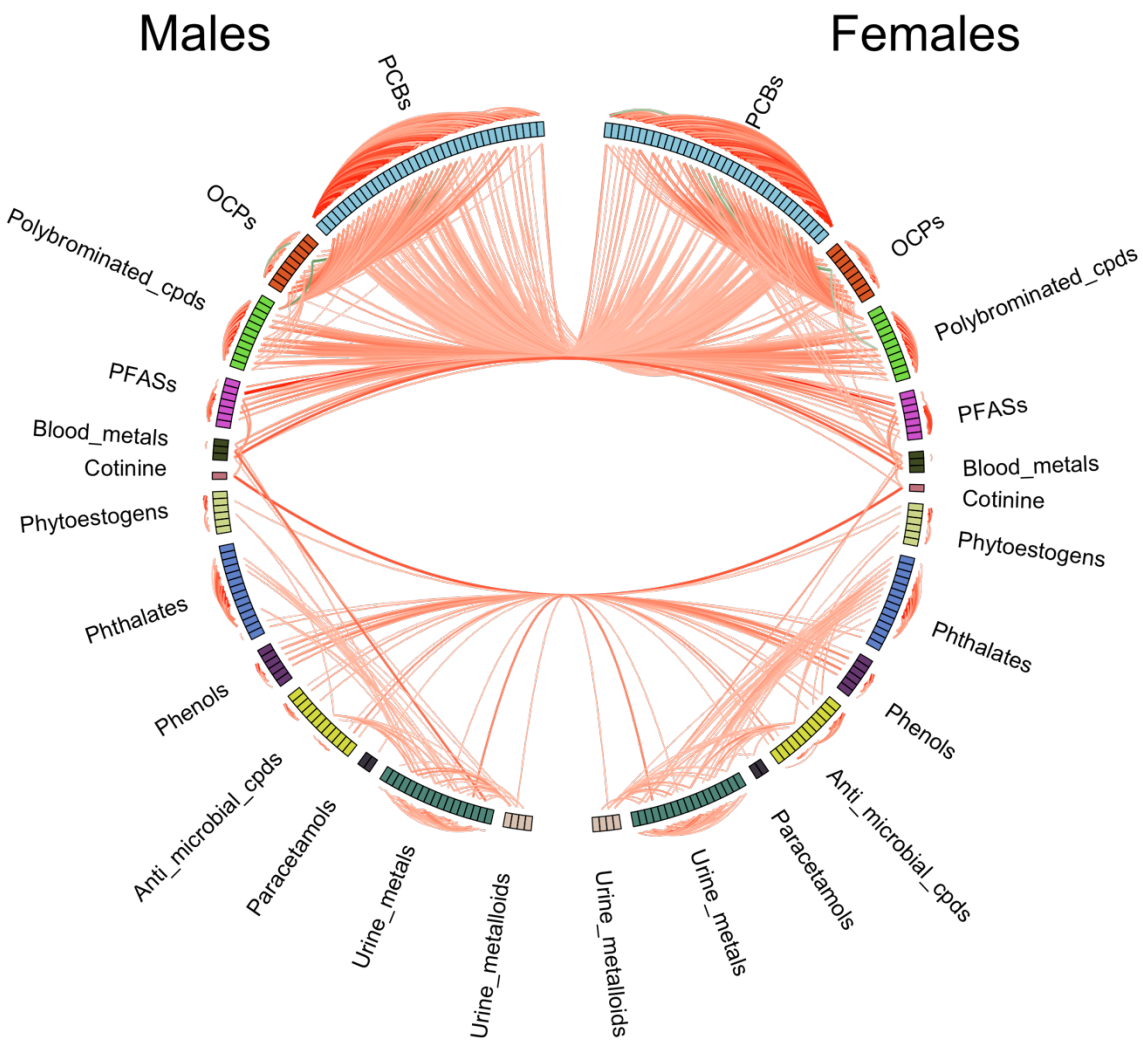

100
75
50
25
0
% variance explained
Polybrominated_cpds
PCBs
OCPs
Blood_metals
Phytoestogens
Urine_metals
Phenols
PFASs
Phthalates
Paracetamols
Anti_microbial_cpds
Urine_metalloids
Cotinine
Chemical classes

Figure 2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Paracetamols
Urine_metals
Urine_metalloids
PCBs
OCPs
Polybrominated_cpds
PFASs
Blood_metals
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Phthalates
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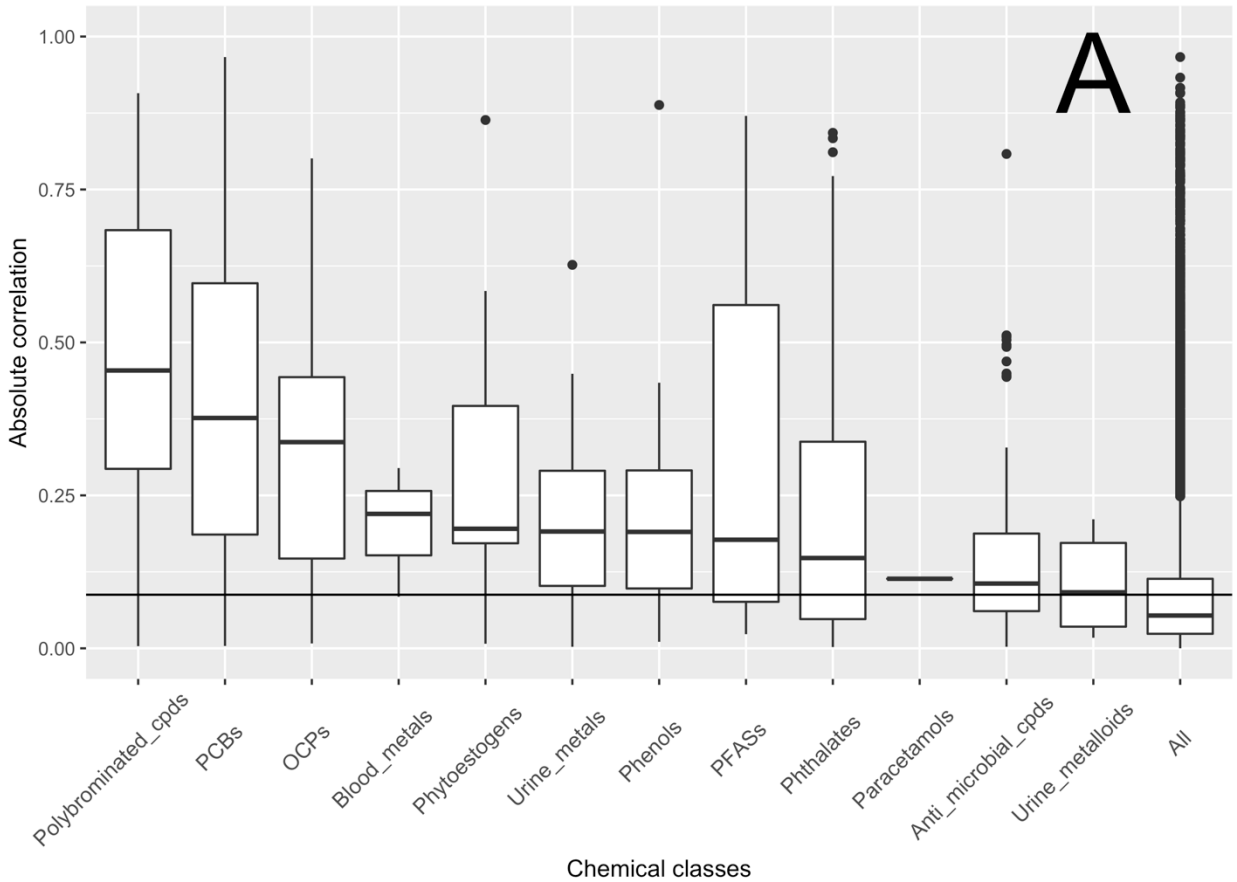
Urine_metals
Urine_metalloids

Figure 3


A
Absolute correlation
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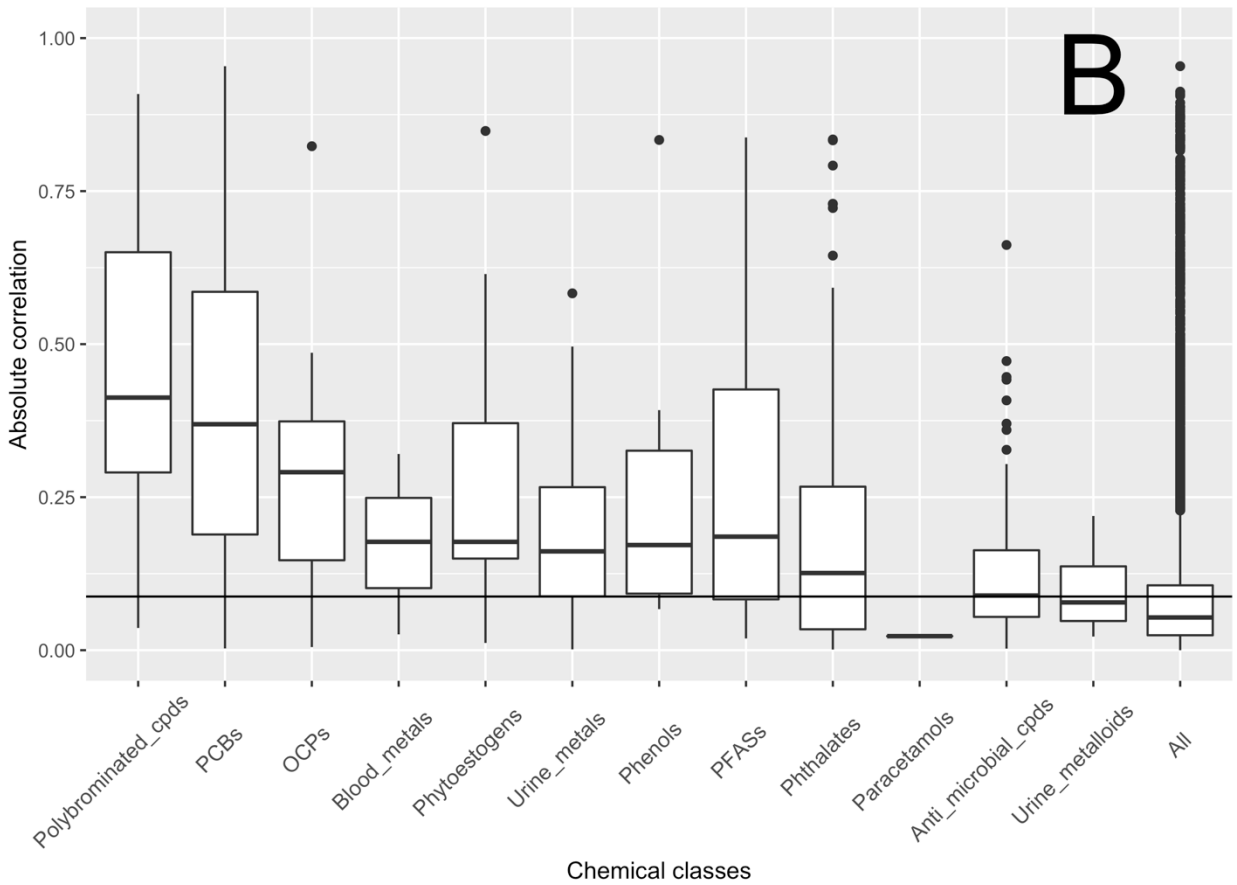
All
Chemical classes


B
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Absolute correlation
Polybrominated_cpds
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Phytoestogens
Urine_metals
Phenols
PFASs
Phthalates
Paracetamols
Anti_microbial_cpds
Urine_metalloids
All
Chemical classes

637
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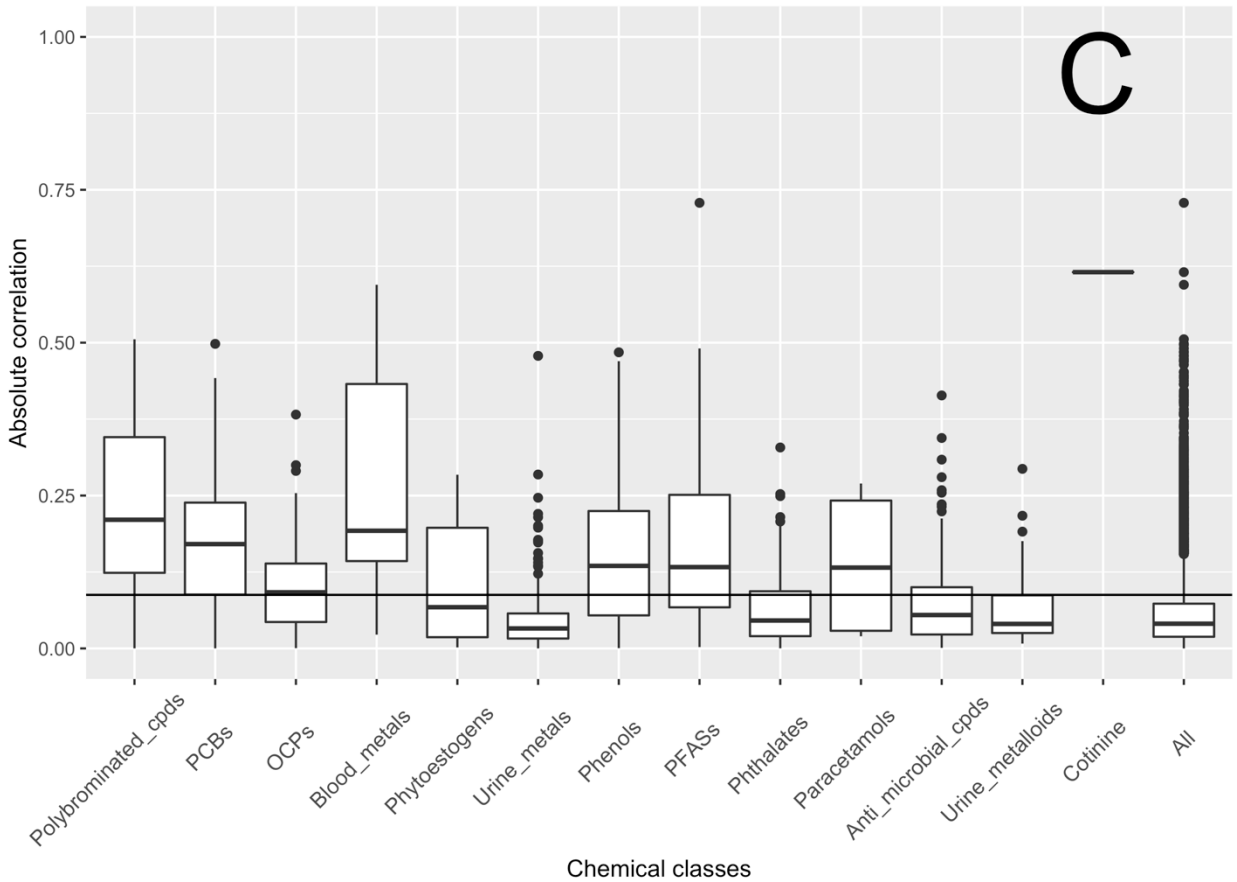
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1.00
0.75
0.50
0.25
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Absolute correlation
Polybrominated_cpds
PCBs
OCPs
Blood_metals
Phytoestogens
Urine_metals
Phenols
PFASs
Phthalates
Paracetamols
Anti_microbial_cpds
Urine_metalloids
Cotinine
All
Chemical classes

Figure 4