Table 1: Description of the overall study population stratified by visit.

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Visit A**, N = 140*1* | **Visit B**, N = 143*1* |
| **Cohort** |  |  |
| BIB | 27 (19%) | 27 (19%) |
| EDEN | 23 (16%) | 23 (16%) |
| KANC | 27 (19%) | 26 (18%) |
| RHEA | 29 (21%) | 29 (20%) |
| SAB | 34 (24%) | 38 (27%) |
| **Sex** |  |  |
| female | 60 (43%) | 61 (43%) |
| male | 80 (57%) | 82 (57%) |
| **Age** | 6.97 (6.44, 8.85) | 7.55 (6.93, 9.62) |
| **Ethnicity** |  |  |
| Caucasian | 129 (92%) | 132 (92%) |
| Pakistani | 10 (7.1%) | 10 (7.0%) |
| other | 1 (0.7%) | 1 (0.7%) |
| **zBMI** | 0.28 (-0.34, 1.09) | 0.26 (-0.34, 1.09) |
| **hs\_dift\_mealblood\_imp** | 3.25 (2.83, 4.09) | 2.17 (1.63, 3.17) |
| **Season** |  |  |
| autumn | 35 (25%) | 38 (27%) |
| spring | 50 (36%) | 49 (34%) |
| summer | 20 (14%) | 8 (5.6%) |
| winter | 35 (25%) | 48 (34%) |
| *1*n (%); Median (IQR) | | |

Table 2: Edge- and node-level description of the visit-specific and merged networks.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Visit A Network** | **Visit B Network** |  | **Merged network** |
| **Diameter** |  | 7 | 7 |  | 19 |
| **Edges** (n) |  | 4,083 | 4,908 |  | 950 |
| density |  | 0.03 | 0.04 |  | 0.01 |
| sign1 | -1 | 1,547 (38%) | 1,956 (40%) |  | 182 (19%) |
| 1 | 2,536 (62%) | 2,952 (60%) | 768 (81%) |
| partial correlations1 |  | 0.05 (-0.06, 0.06) | 0.05 (-0.05, 0.06) | network A | 0.06 (0.05, 0.08) |
| network B | 0.06 (0.05, 0.08) |
| q-values1 |  | 0.024 (0.006, 0.051) | 0.023 (0.005, 0.048) | network A | 0.009 (0.001, 0.032) |
| network B | 0.007 (0.000, 0.03) |
| probability ≥ 0.81 |  | 4,083 (2.7%) | 4,908 (3.3%) |  |  |
| **Nodes** (n) |  | 516 | 514 |  | 462 |
| degree1 |  | 16 (7, 24) | 21 (8, 28) |  | 4.0 (2.0, 6.0) |
| type of node1 | exposure | 22 (4.3%) | 22 (4.3%) |  | 22 (4.8%) |
| methylome | 237 (46%) | 238 (46%) | 193 (42%) |
| serum metabolome | 177 (34%) | 174 (34%) | 169 (37%) |
| urinary metabolome | 44 (8.5%) | 44 (8.6%) | 42 (9.1%) |
| proteome | 36 (7.0%) | 36 (7.0%) | 36 (7.8%) |
| *1*n (%); Median (IQR) | | | |  |  |

~~Table 2: Edge- (top) and node- (bottom) level description of the time-specific networks.~~

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | A | | | B | | |
| **Characteristic** | **Group** | **N** | **N = 4,083***1* | **Group** | **N** | **N = 4,908***1* |
| sign | Edges | 4,083 |  | Edges | 4,908 |  |
| -1 | Edges |  | 1,547 (38%) | Edges |  | 1,956 (40%) |
| 1 | Edges |  | 2,536 (62%) | Edges |  | 2,952 (60%) |
| pcor | Edges | 4,083 | 0.05 (-0.06, 0.06) | Edges | 4,908 | 0.05 (-0.05, 0.06) |
| qval | Edges | 4,083 | 0.024 (0.006, 0.051) | Edges | 4,908 | 0.023 (0.005, 0.048) |
| layer | Nodes | 516 |  | Nodes | 514 |  |
| exposure | Nodes |  | 22 (4.3%) | Nodes |  | 22 (4.3%) |
| methylome | Nodes |  | 237 (46%) | Nodes |  | 238 (46%) |
| serum metabolome | Nodes |  | 177 (34%) | Nodes |  | 174 (34%) |
| urinary metabolome | Nodes |  | 44 (8.5%) | Nodes |  | 44 (8.6%) |
| proteome | Nodes |  | 36 (7.0%) | Nodes |  | 36 (7.0%) |
| degree | Nodes | 516 | 16 (7, 24) | Nodes | 514 | 21 (8, 28) |
| *1*n (%); Median (IQR) | | | | | | |

Table 3: Table listing the number and proportion of the edge types for the merged and visit-specific networks. Reported is also the average percent change, defined as the ratio between the number of edges in the merged network and the average number of edges in the visit-specific networks.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Layer node 1** | **Layer node 2** | **n** | **p** | **nA** | **pA** | **nB** | **pB** | **Average change (%)** |
| exposure | exposure | 38 | 4 | 64 | 2 | 63 | 1 | 59.8 |
| serum metabolite | 3 | 0 | 35 | 1 | 72 | 1 | 5.6 |
| urinary metabolite | 6 | 1 | 58 | 1 | 87 | 2 | 8.3 |
| protein | 3 | 0 | 33 | 1 | 37 | 1 | 8.6 |
| methylome | exposure | 11 | 1 | 197 | 5 | 254 | 5 | 4.9 |
| methylome | 329 | 35 | 1416 | 35 | 1735 | 35 | 20.9 |
| serum metabolite | 40 | 4 | 420 | 10 | 612 | 12 | 7.8 |
| urinary metabolite | 33 | 3 | 495 | 12 | 599 | 12 | 6.0 |
| protein | 14 | 1 | 285 | 7 | 277 | 6 | 5.0 |
| serum metabolite | serum metabolite | 360 | 38 | 522 | 13 | 579 | 12 | 65.4 |
| urinary metabolite | 10 | 1 | 133 | 3 | 166 | 3 | 6.7 |
| urinary metabolite | urinary metabolite | 41 | 4 | 158 | 4 | 154 | 3 | 26.3 |
| protein | serum metabolite | 5 | 1 | 74 | 2 | 90 | 2 | 6.1 |
| urinary metabolite | 1 | 0 | 86 | 2 | 84 | 2 | 1.2 |
| protein | 56 | 6 | 107 | 3 | 99 | 2 | 54.4 |

Table 4: Table listing the five strongest mixed associations in magnitude for the visit-specific networks.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Node 1** | **Layer** | **Degree** | **Node 2** | **Layer** | **Degree** | **pcor** | **qval** | **Visit** |
| BPA | exposure | 24 | FGFBasic | proteome | 20 | -0.156 | 0 | A |
| Trimethylamine oxide | urinary metabolome | 30 | OXOMINP | exposure | 21 | -0.108 | 0 | A |
| MBZP | exposure | 38 | BAFF | proteome | 18 | -0.1 | 0 | A |
| MCP1 | proteome | 29 | MBZP | exposure | 38 | 0.1 | 0 | A |
| cg00766289 | methylome | 25 | MEP | exposure | 30 | -0.094 | 0 | A |
| cg08158662 | methylome | 32 | MEP | exposure | 32 | -0.109 | 0 | B |
| cg22507960 | methylome | 17 | BPA | exposure | 31 | -0.099 | 0 | B |
| cg18628367 | methylome | 20 | DETP | exposure | 38 | -0.096 | 0 | B |
| MBZP | exposure | 39 | Acetate | urinary metabolome | 27 | 0.093 | 0 | B |
| DETP | exposure | 38 | cg26767081 | methylome | 32 | 0.092 | 0 | B |

~~Table 5: Edge- (top) and node- (bottom) level description of the merged network.~~

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **N** | **N = 950***1* |
| Edges | | |
| sign | 950 |  |
| -1 |  | 182 (19%) |
| 1 |  | 768 (81%) |
| pcor A | 950 | 0.06 (0.05, 0.08) |
| qval A | 950 | 0.009 (0.001, 0.032) |
| pcor B | 950 | 0.06 (0.05, 0.08) |
| qval B | 950 | 0.007 (0.000, 0.03) |
| Nodes | | |
| layer | 462 |  |
| exposure |  | 22 (4.8%) |
| methylome |  | 193 (42%) |
| serum metabolome |  | 169 (37%) |
| urinary metabolome |  | 42 (9.1%) |
| proteome |  | 36 (7.8%) |
| degree | 462 | 4.00 (2.00, 6.00) |
| *1*n (%); Median (IQR) | | |

~~Table 6: Network-level properties of the merged and time-specific networks.~~

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| network | number of nodes | number of edges | diameter | edge density |
| merged | 462 | 950 | 19 | 0.01 |
| A | 516 | 4083 | 7 | 0.03 |
| B | 514 | 4908 | 7 | 0.04 |

Table 7: Table listing the mixed edges in the merged network, by chemical class and omic layer. Reported are the visit-specific partial correlations and q-values. In the case of CpG sites, the mapped genes are also reported.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Chemical class** | **Chemical** | **Omic layer** | **Omic feature** | **pcorA** | **pcorB** | **qvalA** | **qvalB** | **Genes** |
| OP pesticide metabolites | DEP | Methylome | cg21873275 | 0.076 | 0.053 | 0.001 | 0.047 | - |
| Proteome | GCSF | 0.084 | 0.08 | <0.001 | <0.001 |  |
| Serum metabolome | Serotonin | 0.051 | 0.053 | 0.074 | 0.05 |  |
| Urinary metabolome | N-methylpicolinic acid | 0.062 | 0.083 | 0.017 | <0.001 |  |
| Phenols | ETPA | Methylome | cg04320635 | -0.052 | -0.056 | 0.069 | 0.03 | GSE1;RP11-118F19.1 |
| cg14242246 | 0.06 | 0.056 | 0.021 | 0.033 | C2orf28;SLC5A6 |
| cg24891846 | 0.063 | 0.05 | 0.014 | 0.066 | CACNA1A |
| BUPA | Methylome | cg03060555 | 0.069 | 0.082 | 0.005 | <0.001 | ZBTB38 |
| cg04320635 | -0.052 | -0.066 | 0.069 | 0.006 | GSE1;RP11-118F19.1 |
| cg20320656 | 0.063 | 0.052 | 0.015 | 0.054 | LETMD1 |
| OXBE | Methylome | cg27466129 | -0.089 | -0.051 | <0.001 | 0.062 | KIAA0513 |
| Urinary metabolome | Dimethylamine | -0.071 | -0.074 | 0.003 | 0.001 |  |
| TRCS | Methylome | cg10072921 | 0.072 | 0.089 | 0.003 | <0.001 | - |
| cg25408086 | 0.065 | 0.054 | 0.01 | 0.039 | CCNT1 |
| Proteome | Leptin | -0.072 | -0.059 | 0.003 | 0.02 |  |
| Serum metabolome | Serotonin | -0.055 | -0.054 | 0.049 | 0.042 |  |
| Phthalate metabolites | MBZP | Proteome | EGF | 0.062 | 0.058 | 0.016 | 0.022 |  |
| Urinary metabolome | N-acetyl neuraminic acid | 0.072 | 0.057 | 0.003 | 0.024 |  |
| MEHP | Methylome | cg20080548 | -0.057 | -0.066 | 0.037 | 0.007 | SBSN |
| Urinary metabolome | Acetate | -0.063 | -0.057 | 0.013 | 0.028 |  |
| OHMINP | Serum metabolome | Kynurenine | -0.051 | -0.06 | 0.074 | 0.016 |  |
| OXOMINP | Urinary metabolome | 5-oxoproline | 0.06 | 0.056 | 0.023 | 0.031 |  |
| MIBP | Urinary metabolome | Scyllo-inositol | -0.051 | -0.077 | 0.081 | 0.001 |  |

Table 8: Non-persistent EDCs analyzed in the HELIX project.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Class** | **Compound** | **Abbreviation** | **PubChem CID** | **CTD** |
| OP pesticide metabolites | diethyl dithiophosphate | DEDTP | 9274 | C000654497 |
| diethyl phosphate | DEP | 654 | C034789 |
| diethyl thiophosphate | DETP | 3683036 | C035638 |
| dimethyl dithiophosphate | DMDTP | 36158 | C040339 |
| dimethyl phosphate | DMP | 13134 | C007477 |
| dimethyl thiophosphate | DMTP | 168140 | C040340 |
| Phenols | bisphenol A | BPA | 6623 | C006780 |
| ethyl-paraben | ETPA | 8434 | C012313 |
| methyl-paraben | MEPA | 7456 | C015358 |
| n-butyl-paraben | BUPA | 7184 | C038091 |
| oxybenzone | OXBE | 4632 | C005290 |
| propyl-paraben | PRPA | 7175 | C006068 |
| triclosan | TRCS | 5564 | D014260 |
| Phthalate metabolites | mono benzyl phthalate | MBzP | 31736 | C103325 |
| mono-2-ethyl 5-carboxypentyl phthalate | MECPP | 148386 | C051450 |
| mono-2-ethyl-5-hydroxyhexyl phthalate | MEHHP | 170295 | C479069 |
| mono-2-ethyl-5-oxohexyl phthalate | MEOHP | 119096 | C080276 |
| mono-2-ethylhexyl phthalate | MEHP | 21924291 | C016599 |
| mono-4-methyl-7-hydroxyoctyl phthalate | oh-MiNP | 102401880 | NA |
| mono-4-methyl-7-oxooctyl phthalate | oxo-MiNP | 102401881 | NA |
| mono-iso-butyl phthalate | MiBP | 92272 | C575690 |
| mono-n-butyl phthalate | MnBP | 8575 | C028577 |
| monoethyl phthalate | MEP | 75318 | C581825 |

Table 9: Study population selection for each visit and each data type.

|  |  |  |
| --- | --- | --- |
| **Data type** | **Visit A** (n) | **Visit B** (n) |
| exposure | 152 | 152 |
| methylome | 149 | 149 |
| serum metabolome | 155 | 155 |
| urinary metabolome | 156 | 154 |
| proteome | 150 | 155 |
| intersection | 140 | 143 |

Table 10: Biological interpretation and literature review of the mixed associations for the merged network.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Chemical class** | **Compound** | **Omic layer** | **Omic feature** | **Genes** | **References** |
| OP pesticide metabolites | DEP | Methylome | cg21873275 | - |  |
| Proteome | GCSF |  |  |
| Serum metabolome | Serotonin |  | (Slotkin and Seidler 2008; Judge et al. 2016; Sarrouilhe, Defamie, and Mesnil 2021) |
| Urinary metabolome | N-methylpicolinic acid |  |  |
| Phenols | ETPA | Methylome | cg04320635 | GSE1;RP11-118F19.1 |  |
| cg14242246 | C2orf28;SLC5A6 |  |
| cg24891846 | CACNA1A |  |
| BUPA | Methylome | cg03060555 | ZBTB38 |  |
| cg04320635 | GSE1;RP11-118F19.1 |  |
| cg20320656 | LETMD1 |  |
| OXBE | Methylome | cg27466129 | KIAA0513 |  |
| Urinary metabolome | Dimethylamine |  | (Mitchell, Zhang, and Smith 2008; Gago-Ferrero, Díaz-Cruz, and Barceló 2012) |
| TRCS | Methylome | cg10072921 | - |  |
| cg25408086 | CCNT1 |  |
| Proteome | Leptin |  | (Shapiro et al. 2018) |
| Serum metabolome | Serotonin |  | (Houten et al. 2016) |
| Phthalate metabolites | MBZP | Proteome | EGF |  |  |
| Urinary metabolome | N-acetyl neuraminic acid |  |  |
| MEHP | Methylome | cg20080548 | SBSN |  |
| Urinary metabolome | Acetate |  |  |
| OHMINP | Serum metabolome | Kynurenine |  |  |
| OXOMINP | Urinary metabolome | 5-oxoproline |  |  |
| MIBP | Urinary metabolome | Scyllo-inositol |  |  |