3. Describing the exposome: Variability, determinants, and patterns across the population

3.1. Correlation structure of the exposome

One of the outstanding challenges of interpreting exposure-disease associations is unravelling the dense correlations between all exposures. According to the third Bradford Hill criteria (1965):

> We must not […] over-emphasize the importance of the characteristic. […] One-to-one relationships are not frequent. Indeed, I believe that multicausation is generally more likely than single causation though possibly if we knew all the answer we might get back to a single factor.

The exposome framework allows the specificity of exposure-health associations to be examined. Indeed, the dense correlation pattern between exposures makes it hard to identify the directionality of the potential causal relation between exposures and outcome. The data-driven approach assumes little to no collinearity between environmental predictors, but it is almost impossible to select any single uncorrelated exposures from the dense exposome. One strategy for addressing these analytical issues is to characterise the correlations in diverse cohorts to provide reference levels, within and between families of exposures or "fields", to gauge the biological significance of associations.

The HELIX Project describes the correlation structure of the exposome based on the assessment of over 100 environmental exposures in 1,301 pregnant women and their children across six European birth cohorts (Tamayo-Uria et al., 2019). This exercise constituted an initial step towards identifying the mixture of exposures occurring simultaneously as a result of common routes of exposure, e.g. to arsenic, mercury, and perfluorinated compounds related to fish intake, or arising from common participant behaviour. The correlation structure was

further exemplified in an exposome-metabolome wide association study in pregnant women, in which cotinine levels were strongly associated with urinary coffee metabolites (Maitre et al., 2018). Another potential source of variation may be due to the nature of the measurement or exposure characteristics, e.g. lipophilic persistent pollutants measured in blood are associated with blood lipids and fat mass and are, therefore, highly inter-correlated (Maitre et al., 2022). Temporal, behavioural, and geographical variations can also be interpreted with this type of exercise. For example, in the LIFE study, it was suggested that the individual (see Figure 7) rather than the shared environment of a household could be a major factor influencing the covariation of the exposome (Chung et al., 2018). Clearly, understanding exposure correlations has important analytical and sampling implications for research in exposomics.

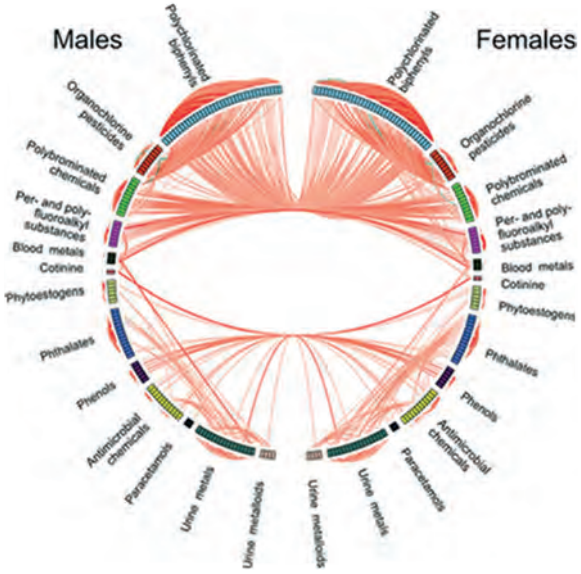

FIGURE 7. Exposome (128 endocrine disrupting chemicals) correlation globe showing the relationships of biomarkers between females, males, and couples.
SOURCE: M. K. Chung et al. (2018), Toward Capturing the Exposome: Exposure Biomarker Variability and Coexposure Patterns in the Shared Environment, *Environmental Science & Technology*, *52*(15) (4 July), 8801-8810, https://pubs.acs.org/doi/10.1021/acs.est.8b01467 (requests for further permissions related to this image should be addressed to the ACS).