

Supplemental Material

Methods:

Recruitment: Families were contacted via multiple methods including: flyers, advertisements in newspapers, magazines, social media, and websites, recruitment at neighborhood fairs and public places, lab referrals, recruitment via lab website, ResearchMatch, family networks and family support groups. This sample had significant crEA exposure (see sTable 1).

[INSERT sTABLE 1]

All procedures were approved by the university IRB. Parents/legal guardians provided informed consent for themselves and their children, and children provided written or oral assent. Families were provided with a stipend, necessary travel expenses, and small gifts for their participation. Of 1903 study inquiries that were received, 671 families were screened for potential inclusion in the study. 336 families were excluded at this screening stage for the following reasons: not in age range, metal in body, having a mental illness, balancing numbers in crEA/comparison groups, not interested, and personal reasons. A total of 335 children were enrolled: 110 without a history of crEA exposure and 225 with crEA exposure. However, 11 children were excluded at the in-person study visit for the following reasons: no longer interested in participating, family moved out of the U.S. or far away, child diagnosed with mental illness, and child back in foster care. From the 225 children enrolled with crEA exposure, 41 were excluded from the current analysis for missing data. Note the incidence of crEAs in this sample in sTable 2.

[INSERT sTABLE 2]

Aim 1.

Multivariate Models of crEA Heterogeneity: To understand how crEAs co-occur, univariate comparisons of individual variables are not enough. It is essential to understand how they relate to one another from a multivariate perspective, as has been applied previously (Green et al., 2010). Due to their prevalence and differential uses by communities of psychologists, we employed two commonly used approaches towards this aim: Principal component analysis; in the R PCAMix package (PCA; (Chavent et al., 2014)), and Factor Analysis in the R Psych package (FA; (Revelle & Revelle, 2015)). These approaches vary slightly in their formulation, but do so largely independently of our questions of interest, so we tested both to assess the robustness of our understanding of the lower dimensional space that crEAs occur in.

Factor Analysis and Principal Component Analysis: A Pearson correlation matrix was created and FA was applied with a “biquartimin” oblique rotation and a maximum likelihood (ML) estimation method. PCA was used with default values from the PCAMix package. Only complete data were used, and imputation was not applied.

Parallel Analysis Component/Factor Significance Testing: Routinely the creation of a PCA or FA decomposition relies on a selection of a limit to the number of dimensions to extract. Some studies suggest whatever number of components cross some specific threshold of percentage variance-accounted-for, whereas others suggest to do so through visual inspection of the scree-plot, which

is the descending eigenvalue/variance-accounted-for. These approaches can lead to results that are not identical and even highly variable from one another (Zwick & Velicer, 1986). However, Parallel Analysis (Horn, 1965), a non-parametric method of testing for this significance has been developed to use a data driven approach to selecting the number of components (Hayton et al., 2004). Briefly, through repeated permutations of the data and subsequent calculations of the PCA/FA, one can measure the null-distribution of eigenvalues of each component, thereby providing a test for the eigenvalue of each actual component/factor.

Expanding Robustness of the Multivariate Approach: Both FA and PCA, like any statistical model, suffer from sampling induced variability in the estimation of their components/factors. In other words, different samples may yield different underlying structure of the dimensions of ECA exposure profiles and the resulting loadings for each exposure across dimensions. To address this, we extended our multivariate techniques by incorporating bootstrap resampling, which we and others have shown previously to increase the model reproducibility in with high dimensional and noisy data (Nikolaidis et al., 2020). Bootstrap resampling allows us to assess variability in the variable loadings for each dimension, giving us an estimate of which variables reliably contribute to each component/factor. We bootstrapped our sample to generate new samples and ran multivariate decomposition on each bootstrapped sample and extracted 20 components/factors. We repeated this process 1000 times. We then matched the top components for each of these bootstrapped resampled runs, and averaged the absolute value of their variable loadings. For each variable for a given component, we assessed whether the 95% confidence interval of the distribution of loadings cross zero. When the bootstrapped distribution of loadings did not cross zero, variables were labeled ‘stable’ contributors for reliably loading on the component, while the rest were ‘unstable’ contributors. This enabled our dimensional analysis to make interpretable components/factors more easily by dropping out many variables from consideration due to instability.

Aim 2.

Louvain Community Detection Based Subtyping: We use Louvain Community Detection to discover groups of individuals that had similar types of crEA exposures. Louvain Community Detection is a clustering approach that finds robust subtypes of individuals through an iterative modularity-optimizing procedure. Most clustering approaches (K-means, spectral clustering), require the experimenter to choose the resolution of the clustering a priori, which can be problematic and lead to instability across samples. Louvain Community detection on the other hand, chooses the cluster resolution that maximizes the modularity of the network. We have previously demonstrated strengths of this approach for creating highly reproducible subtypes both across samples (Nikolaidis, Paksarian, et al., 2021) and across time (Nikolaidis, DeRosa, et al., 2021).

Aim 3.

Multivariate Predictions of Outcomes: We assessed the extent to which crEA dimensions and crEA subtypes were sensitive to scores on the CBCL, WIAT Reading, and WIAT Numbers. We built machine learning models using conditional random forest (CRF), a robust technique known for its ability to model linear and nonlinear dependencies between predictor variables (Breiman, 1996). Traditional RF models assess the relative importance of each type of crEA variable. Briefly, the RF algorithm creates a series of decision trees for which a random selection of variables is

chosen, and a bootstrapped dataset of the original data is used to train the model. For each iteration of the 1000 runs, the performance on each of these decision trees on the out-of-sample data, roughly $\frac{1}{3}$ of the sample, is aggregated and used to assess the performance of the RF model (for a review of RF, see Friedman et al., 2001). While out-of-sample prediction accuracy is an approximation of model performance in an independent test set, it is not based on an independent sample and therefore it is important to note this when interpreting generalizability to independent data. Random forest variable importance is known to be biased towards continuous variables (Hothorn et al., 2006; Kim & Loh, 2001; Strobl, Boulesteix, & Augustin, 2007; Strobl, Boulesteix, Zeileis, et al., 2007). Given that our models contained both binary (crEAs) and continuous (Factor scores) variables, we addressed this issue through the use of the Conditional Random Forest Party package in R. This approach provides an unbiased tree algorithm with which random forest is calculated. The resulting variable importance measure from this method is unbiased towards binary vs continuous variables, and is also able to assess the relative importance of each variable conditional on all other variables included in the model. This offers us the ability to find unique contributions of each variable to the predictive model.

Results

EFA Model Fit: Parallel analysis suggests 3 factors for the exploratory factor analysis have a significantly higher explanatory variance than what would be expected due to chance. The RMSEA for the 3 factor solution was 0.079 indicating a reasonable approximate fit. TLI was 0.83 for the 3 factor solution, indicating a moderate fit. R-squared between the factors and factor score estimates for each factor were 86.3%, 82.4% and 63.1% for factors 1-3 respectively.

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