E-Risk Study Concept Paper Form

Response was completed on 11-11-2025 21:38.

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1. Collaborating researchers

Please note:

Once approved, a formal data use agreement will be required between King's College London and the university or research organisation that employs any collaborator having access to the data if they are not a member of staff, a student or affiliate of King's College London. This needs to be signed by both universities/organisations before data access can be granted.

For projects carried out by a student (e.g., MSc/MA, MPhil/PhD, clinical doctorate), the lead applicant should be the student's supervisor at the same university, and the student should be named as the student collaborator requiring access to the data.

If you have additional collaborators, please name them below and indicate whether they need to have access to the data. It would be common, for instance, for other researchers to see summary results of analyses and act as co-authors on your paper without having access to the data. You will not be permitted to share the dataset except with those indicated in the table as requiring access.

Applicable?	**Category**	**Name**	**Email address**	**University/organisation**	**Needs access to data for analysis?**
	Applicant **(lead researcher)**	Dr. Anne-Kathrin Fett	Anne-Kathrin.Fett@city.ac.uk	City St George's, University of London Northampton Square London/ King's College London	(•) Yes ( ) No
( ) Applicable ( ) Not applicable	**Student collaborator** ***(if data is for their dissertation/thesis)***	Dr. Teresa Claudia Pennacchio	terrypennacchio95@gmail.com teresa.pennacchio@c	City St George's, University of London Northampton Square London / University of Bari Aldo Moro	( ) Yes ( ) No
( ) Applicable ( ) Not applicable	**E-Risk Sponsor** ***(if applicant is not an E-Risk investigator)***	Prof. Helen Fisher	helen.2.fisher@kcl.ac.uk	SGDP, King's College London	( ) Yes ( ) No

Are there additional collaborators to add?	( ) Yes ( ) No

If yes, how many additional collaborators would you like to add?	3

Category	Name	Email address	University/organisation	Needs access to data for analysis?
Other collaborator #1	Prof. Linda Antonella Antonucci	linda.antonucci@uniba.it	University of Bari Aldo Moro	○ Yes ◉ No
Other collaborator #2	Dr. Antonella Trotta	Antonella.a.trotta@kcl.ac.uk	King's College London/University of Essex	◉ Yes ○ No
Other collaborator #3	Prof. Danai Dima	Danai.dima@citystgeorges.ac.uk	City St George's, University of London Northampton Square London / King's College London	○ Yes ◉ No

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2. The project proposal

Note: *Please provide sufficient detail to enable the committee to review your proposal. Please be as specific as possible about the project aims and analysis methods as once approved this concept paper will be posted publicly and thus will act as a form of pre-registration of your project. Expand boxes as required.*

Title of project	Toxic Surroundings, Toxic Minds? Cumulative Environmental Risk and Adolescent Psychopathology: A Discordant Twin Design Approach
Background and rationale for project ***(approx. 300 - 1000 words)***	Childhood represents a critical period of vulnerability during which exposure to adverse environmental conditions can significantly affect psychological and behavioral development. A substantial body of research has demonstrated that early negative experiences-such as maltreatment, family conflict, socioeconomic disadvantage, and social isolation-increase the risk of later mental health problems (Evans, Li, & Whipple, 2013; Felitti et al., 1998; Hughes et al., 2017). However, most existing studies are correlational and often unable to disentangle causal environmental effects from shared genetic or familial influences. In this context, the discordant monozygotic (MZ) twin design offers a particularly powerful methodological approach for investigating environmental causality. MZ twins share 100% of their genetic makeup and much of their familial and social environment (e.g., socioeconomic status, schooling, neighborhood), yet they may differ in their exposure to unique environmental experiences such as abuse, peer bullying, or divergent relational dynamics (McGue, Osler, & Christensen, 2010). Studying MZ twin pairs who differ in exposure to environmental risks allows researchers to isolate the impact of

non-shared environmental factors on mental health outcomes while controlling for shared genetic and familial confounders. This project focuses specifically on cumulative environmental risk, defined as an additive index reflecting the total accumulation of exposure to psychosocial adversities-each potentially low in intensity but harmful in the aggregate-across childhood and adolescence. The cumulative risk literature indicates that as the number of contextual risk factors accumulate, child externalizing and internalizing problems increase (Ackerman et al., 1999; Trentacosta et al., 2008). We focus on the developmental window between ages 5 and 12, a sensitive period for the maturation of cognitive, self-regulatory, and socio-emotional systems, in which neurobiological and behavioral compensatory mechanisms emerge. Early-life adversities are thought to exert particularly severe and enduring effects on later mental health and psychosocial functioning, with evidence suggesting that the earlier the exposure, the greater the risk of long-term psychopathology and impaired functioning (Shonkoff et al., 2012). By targeting this age range, the project aims to capture sustained exposure during a developmental stage when adversities may leave lasting imprints on trajectories of general psychopathology, operationalized as the latent p factor, capturing shared variance across externalizing, internalizing, and thought disorder symptoms. By "sustained exposure" we refer to the repeated or prolonged presence of adversity across multiple time points rather than isolated events. Specifically, for the discordant MZ twin design, cumulative environmental risk can be decomposed into shared and non-shared components. The shared risk index captures the total amount of adversities experienced between ages 5 and 12 that are common to both members of a twin pair (e.g., socioeconomic disadvantage, family-level conflict), reflecting exposures that contribute to between-family variation in psychopathology risk. However, the aforementioned adversities also include non-shared experiences, namely traumas and peer-related adversities, that can meaningfully differ between MZ co-twins and thus provides leverage for discordant twin analyses, isolating the effects of individual-specific environments from genetic and familial confounding. Examining both allows us to test complementary hypotheses: whether family-wide cumulative adversity increases general psychopathology risk, and whether twin-specific experiences exert causal effects above and beyond shared genetic and family context. This approach strengthens causal conclusions about environmental effects by effectively accounting for genetic confounding (McGue et al., 2010). Although cumulative environmental risk has been linked to various adverse developmental and mental health outcomes, it has rarely been examined using intra-pair discordance among MZ twins, highlighting a critical gap in the literature. Beyond cumulative environmental risk, additional educational, dispositional and cognitive factors have also been implicated in the etiology of general psychopathology. Educational factors such as academic achievement have been consistently associated with both internalizing and externalizing problems, suggesting that adverse educational experiences may exacerbate the impact of childhood adversity (Masten et al., 2005). Dispositional factors, including personality and temperament, shape coping strategies and socio-emotional development, influencing vulnerability to later psychopathology and interacting with environmental exposures across development (Ormel et al., 2005; McGue & Iacono, 2005). Moreover, cognitive factors, particularly theory of mind (ToM), executive function and general cognitive ability, have been consistently associated with the general psychopathology factor (p-factor). Impaired executive control-such as difficulties in attention, goal-directed behavior, and cognitive regulation-has been linked to elevated p scores (Romer et al., 2021; Adam et al., 2023). Several studies also document that lower overall cognitive performance (e.g., lower IQ) is associated with higher general psychopathology across the lifespan (Caspi et al., 2014). Integrating these individual predictors (educational, dispositional and cognitive factors) into ML models (e.g., Support Vector Machine algorithms) to predict psychopathology at the end of adolescence allows the project to go beyond causal inference at the group level, enhancing the ability to capture complex developmental pathways and improve individual-level prediction of risk for general psychopathology. This dual approach-discordant twin analysis for causal inference and predictive modeling for personalized risk stratification-maximizes both theoretical and translational value. Although cumulative environmental risk has been the primary focus of many prior studies, the integration of additional educational, dispositional and cognitive predictors within ML frameworks offers an

	opportunity to improve prediction accuracy and capture complex, non-linear interactions (Antonucci et al., 2022; Dwyer, Falkai, & Koutsouleris, 2018). Beyond environmental components, it is also essential to consider the genetic dimension of vulnerability to psychopathology. The inclusion of polygenic scores (PGS) allows for the quantification of individual genetic liability associated with specific psychiatric disorders and for the examination of how this liability interacts with exposure to cumulative environmental risks. Specifically, PGS will be used for ADHD (Demontis et al., 2019, Nature Genetics), Major Depressive Disorder (Wray et al., 2018, Nature Genetics), Schizophrenia (Pardiñas et al., 2018, Nature Genetics), Post-Traumatic Stress Disorder (Nievergelt et al., 2019, Nature Communications), Anxiety Disorders (Otowa et al., 2016, Molecular Psychiatry), Autism Spectrum Disorder (Grove et al., 2019), Alcohol Dependence (Walters et al., 2018, Nature Neuroscience), and Cannabis Use Disorder (Johnson et al., 2020, The Lancet). The integration of these genetic indices within the project is not merely intended as a control measure but represents an important analytical extension: it enables a more precise distinction between the causal effects of non-shared environmental factors and those attributable to individual genetic predispositions, thereby increasing the inferential robustness of the discordant MZ twin design. Moreover, the inclusion of PGS makes it possible to explore potential gene × environment (G×E) interactions, evocative and non-evocative correlations, and to assess whether the impact of cumulative environmental risk is moderated by disorder-specific genetic liability across different psychopathological domains. Alternatively, using Structural Equation Modeling, we will assess if cumulative environmental risk may mediate the association between genetic liability and general psychopathology. These PGS will not be included as predictors in the main machine learning models; instead, they will be used in secondary mediation or moderation analyses via Structural Equation Modeling to explore potential gene-environment interactions through algorithmic representations of shared and non-shared environmental variability. We have employed this analytical procedure in previous publications (Antonucci, Raio et al., 2024; Pergola et al., 2019). This way, the secondary genetic analyses will provide an essential complementary perspective, strengthen the interpretation of results and contributing to an integrated understanding of risk pathways underlying general psychopathology. Leveraging the longitudinal design and twin-based structure of the E-Risk cohort, this project aims to generate novel evidence on the causal impact of environmental risk on adolescent psychopathology, ultimately informing early identification strategies and the development of personalized preventive interventions during adolescence.
Project aims / objectives	GENERAL OBJECTIVE To estimate the causal impact of cumulative environmental risk on adolescent general psychopathology using a discordant MZ twin design. The project follows a three-phase sequential strategy: development of a cumulative environmental risk index, including a distinction between shared and non-shared components; prediction of individual-level general psychopathology (p-factor) at age 18 via ML, incorporating both cumulative risk and additional educational, dispositional and cognitive predictors; and intra-pair analyses of discordant MZ twins focused on non-shared risk exposure, which represents the core of the causal investigation. SPECIFIC OBJECTIVES 1. To construct a cumulative environmental risk index capturing environmental adversity across ages 5 to 12 using validated multi-informant indicators from the E-Risk dataset, distinguishing between shared and non-shared environmental exposures. 2. To develop ML models predicting individual-level general psychopathology operationalized as the latent p factor, capturing shared variance across internalizing, externalizing, and thought disorder symptoms, at age 18 based on the cumulative environmental risk index, and to test whether the inclusion of additional educational, dispositional and cognitive predictors measured between ages 5 and 12 increases predictive accuracy by capturing complex, non-linear pathways to psychopathology. 3. To conduct intra-pair analyses of MZ twin pairs discordant for non-shared cumulative environmental risk, estimating the direct effects of individual-specific environmental adversity on general psychopathology, controlling for genetic and familial confounding. 4. To examine whether the potential association between polygenic scores (PGS) for

	multiple major psychiatric disorders, and the observed general psychopathology factor at age 18 is potentially mediated or moderated - alternatively or serially - by algorithmic decisions based on shared and non-shared environmental variability between twins. This approach will be based on a Structural Equation Modeling-based strategy and will allow for testing for gene-environment interplay mechanisms underlying the developmental emergence of general psychopathology (Selzam et al., 2018; Allegrini et al., 2020; Sprooten et al., 2021).
Brief statement of your hypothesis	H1: Higher scores on the cumulative environmental risk index (assessed between ages 5 and 12) will significantly predict higher levels of general psychopathological symptoms at age 18, operationalized as the latent p factor and including internalizing, externalizing, and thought disorder domains. H2: ML models integrating the cumulative environmental risk index with additional educational, dispositional and cognitive predictors measured between ages 5 and 12 will accurately identify adolescents at elevated risk for general psychopathology (p-factor) at age 18, capturing complex and potentially non-linear interactions. H3: In MZ twin pairs discordant for the non-shared components of cumulative environmental risk, the twin with higher exposure will display significantly greater general psychopathology (p-factor) at age 18, providing evidence for a causal role of individual-specific environmental adversity. H4: Higher polygenic scores for multiple major psychiatric disorders, will be significantly associated with higher levels of general psychopathology (p-factor) at age 18. These associations are expected to be partially mediated or moderated, either independently or sequentially, by algorithmic predictions based on shared and non-shared environmental variability, capturing gene-environment interplay mechanisms underlying individual differences in psychopathology risk.
Data analysis methods to be used ***(approx. 100 - 500 words)***	Sample and Dataset This study will use data from the E-Risk cohort. All predictors-used for the cumulative environmental risk index and ML models-will be collected from ages 5 to 12. Participants with more than 30% missing data on critical predictors or outcomes will be excluded. General psychopathological outcomes will be assessed at age 18 to allow predictive modeling. Outcome Variables (Age 18) General psychopathology will be operationalized as the latent p factor, capturing shared variance across internalizing, externalizing, and thought disorder symptoms. The p factor will be derived using a bi-factor confirmatory factor analysis already described in previous publications (Schaefer et al., 2018). Specifically, domains and instruments will include: •Externalizing: alcohol/cannabis dependence (Diagnostic Interview Schedule), tobacco dependence (Fagerstrom Test), conduct disorder (DSM-IV/DSM-5 checklists) at age 18; •Internalizing: depression, generalized anxiety, PTSD (Diagnostic Interview Schedule), eating disorders (Eating disorder symptoms self-report) at age 18; •Thought disorder: delusions, hallucinations, unusual thoughts/feelings (structured interviews, items from PRIME-screen and SIPS) at age 18; These outcomes will serve as dependent variables in ML models for individual-level risk prediction and as endpoints in intra-pair discordant MZ twin analyses to estimate the causal impact of non-shared environmental exposures while controlling for genetic and familial confounds. Predictor Variables (Ages 5-12) Predictors will be drawn from ages 5 to 12 to capture sustained environmental exposures. This time window is chosen to ensure temporal separation from the outcome, which is general psychopathology (p-factor) at age 18. Cumulative Environmental Risk Index A cumulative environmental risk index will be constructed following established cumulative risk models (Rutter, 1979; Sameroff et al., 2004) and more recent weighted approaches (Bouter et al., 2025). Traditionally, such indices are created by summing dichotomized indicators of adversity (0 = absence, 1 = presence), with extensive evidence showing that risk for psychopathology increases as adversities accumulate and co-occur (Ackerman et al., 1999; Appleyard et al., 2005). In line with recent developments, each environmental

indicator will first be dichotomized based on theoretically and empirically justified cut-offs and then assigned a weight corresponding to its relative association with mental health outcomes, derived from the most recent meta-analytic estimates (see Bouter et al., 2025). The weighted indicators will be summed to obtain a composite cumulative environmental risk index, which can be further standardized to facilitate interpretability and comparability across models. This approach retains the simplicity and transparency of traditional cumulative risk scores while improving their sensitivity and theoretical validity by accounting for differential risk magnitudes across environmental exposures. Importantly, to preserve the capacity to test mediating and moderating mechanisms, individual-level educational, dispositional, and cognitive predictors will be considered separately from the cumulative environmental risk index, rather than being included within it (Trentacosta et al., 2008).

The index will include traumatic experiences (abuse, neglect; domestic violence treated as shared), peer adversity (bullying, social exclusion, classroom behavior), family context (harsh parenting, conflict, poor monitoring, sibling's conflicts), socioeconomic disadvantage (poverty, housing instability, material deprivation), and neighborhood adversity (perceived safety, social cohesion). Exposure intensity and duration will be considered. For intra-pair analyses, exposures will be decomposed into:

•Shared: common to both twins (e.g., family-abuse, family-neglect, domestic violence, socioeconomic disadvantage, family conflict, neighborhood adversity, sibling's conflicts);

•Non-shared: differing between twins (e.g., extra-family abuse, traumatic experiences, peer adversity, classroom behavior, social exclusion) used to estimate causal effects.

Prior research has established robust associations between educational, dispositional and cognitive factors and general psychopathology (p-factor) (Caspi et al., 2014; Caspi et al., 2024). The present project extends this literature by leveraging the longitudinal twin design of the E-Risk cohort and applying ML methods to integrate predictors across domains, thus moving from group-level associations to individualized prediction while controlling for genetic and familial confounding.

Additional Predictors for ML Models

Additional variables will not be included in the cumulative environmental risk index. Instead, they will be entered as independent predictors in ML models alongside the cumulative risk index, enabling the examination of their unique effects and interactive contributions to the individual-prediction of general psychopathology (p-factor) at age 18. Specifically, the following domains will be considered:

Educational factors: level of education, academic achievement (Masten et al., 2005);

Dispositional factors: personality and temperament (Ormel et al., 2005; McGue & Iacono, 2005);

Cognitive factors: ToM, executive functioning, overall cognitive performance (IQ) with subdomains of crystallized, fluid, and working memory (Romer et al., 2021; Adam et al., 2023; Caspi et al., 2014);

All predictive models will be controlled for early emotional and behavioural problems and pre-existing psychopathology, to account for baseline individual differences in vulnerability prior to the age-18 outcomes.

PGS for Secondary Genetic Analyses:

PGS will be used for secondary genetic analyses. These PGSs have been previously derived within the E-Risk study and will be requested accordingly (see Objective 4 and variable request section).

These PGS will not be included as predictors in the main machine learning models; instead, they will be used in secondary mediation or moderation analyses via Structural Equation Modeling to explore potential gene-environment interactions through algorithmic representations of shared and non-shared environmental variability. We have employed this analytical procedure in previous publications (Antonucci, Raio et al., 2024; Pergola et al., 2019). This way, the secondary genetic analyses will provide an essential complementary perspective, strengthen the interpretation of results and contributing to an integrated understanding of risk pathways underlying general psychopathology.

Objective 1: Cumulative Environmental Risk Index

A composite cumulative environmental risk index will be constructed to capture exposure to psychosocial adversities between ages 5 and 12. Following established cumulative risk

	approaches (Rutter, 1979; Sameroff et al., 2004) and more recent refinements introduced by Bouter et al. (2025), individual risk indicators will be standardized and combined into a single continuous score representing cumulative exposure. This method allows for the inclusion of multiple risk domains (e.g., family, peer, and contextual factors) and for the weighting of indicators based on their empirical relevance to adolescent psychopathology, rather than assuming equal contribution of each risk. The final index will be decomposed into shared and non-shared components to enable intra-pair analyses in MZ twins, isolating family-wide from individual-specific environmental effects. Objective 2: Predictive Models of General Psychopathology ML models will predict individual-level general psychopathology at age 18 using the cumulative environmental risk index and additional educational, dispositional, and cognitive predictors measured between ages 5 and 12. This approach allows modelling of complex, non-linear interactions across multiple risk domains, complementing causal inference by providing individualized risk profiles. To address the non-independence of twin observations in the main ML analyses, appropriate strategies will be applied to ensure model validity and generalizability. Specifically, the sample will be structured to account for the twin-pair design-for example, by randomly assigning one twin from each pair to the training set and the co-twin to the validation set, or by using cross-validation methods that cluster individuals based on family. These approaches will minimize bias due to within-pair dependencies while preserving statistical power. Objective 3: Discordant Twin Analysis Intra-pair comparisons of MZ twins discordant for non-shared cumulative risk will estimate the causal impact of individual-specific adversity. Paired t-tests and fixed-effects regression models will control for genetic and shared environmental confounds. Objective 4: Secondary Genetic Analyses Using Polygenic Risk Scores Secondary analyses will employ PGS indexing genetic liability to major psychiatric disorders. One exploratory analysis will be conducted for PGS of major disorders: • ADHDPGS_Twins_Feb2020_Clumped - ADHD (Demontis et al 2019 Nat Genetics) • MDDPGS_Twins_Feb2020_Clumped - Major Depressive Disorder (Wray et al 2018 Nature Genetics) • SchzPGS2018_Twins_Feb2020_Clumped - Schizophrenia (Pardinas et al 2018 Nature Genetics) • PTSD_Twins_Apr2020_Clumped - PTSD (Nievergelt et al 2019 Nature Communications) • AnxCC_Twins_Sept2020_Clumped - Anxiety Disorder Case Control (Otowa et al 2016 Mol Psychiatry) • ASD_Twins_Sept2020_Clumped - autism spectrum disorder (Grove et al 2019) • AlcPGS_twins_Feb2020_Clumped - Alcohol Dependence (Walters et al. 2018 Nature Neuroscience) • CUD_Twins_Nov2020_Clumped - Cannabis Use Disorder (Johnson et al 2020 Lancet) These PGS will not be included in the main ML models. Instead, they will be examined to test associations with levels of general psychopathology (p-factor) at age 18, and to explore whether these genetic liabilities are mediated or moderated-alternatively or sequentially-by algorithmic representations of shared and non-shared environmental variability captured in the ML models. The specific PGSs that we aim to request are listed in the dedicated section detailing the variable requests by age range.
Significance for theory, research methods, or clinical practice	This project combines the methodological rigor of the discordant MZ twin design with predictive modeling to advance understanding of the causal impact of non-shared cumulative environmental adversity on adolescent mental health. By comparing exposure differences within genetically identical twin pairs, the study disentangles environmental effects from genetic and familial confounds, providing robust evidence for causal inference in developmental psychopathology. Simultaneously, integrating ML models allows for individualized prediction of general psychopathology (p-factor) at age 18, capturing complex, non-linear interactions across educational, dispositional and cognitive factors. These complementary approaches have both theoretical and translational significance. The findings will clarify the role of cumulative and domain-specific adversities in shaping the p

	factor of psychopathology, while also identifying adolescents at elevated individual risk. Clinically, this dual strategy can inform early identification frameworks and support the design of targeted, personalized interventions. While based on a UK sample, the methodological framework is broadly applicable and can inform cross-cultural validation efforts. If successful, the findings may support scalable models for personalized prevention and early mental health screening in adolescence.
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