E-Risk Study Concept Paper Form

Response was completed on 27-09-2025 18:37.

Record ID	65

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)**	Abanish Singh, PhD	abanish.singh@duke.edu	Duke University School of Medicine, Durham, NC, USA	◉ Yes ○ No
○ Applicable ◉ Not applicable	**Student collaborator** ***(if data is for their dissertation/thesis)***				
◉ Applicable ○ Not applicable	**E-Risk Sponsor** ***(if applicant is not an E-Risk investigator)***	Avshalom Caspi, PhD Terrie Moffitt, PhD	avshalom.caspi@duke.edu terrie.moffitt@duke.e	Duke University School of Medicine, Durham, NC, USA	◉ Yes ○ No

Are there additional collaborators to add?	◉ Yes ○ No
If yes, how many additional collaborators would you like to add?	4 ⌄

Category	Name	Email address	University/organisation	Needs access to data for analysis?
Other collaborator #1	Jonathan Posner, MD	jonathan.posner@duke.edu	Duke University School of Medicine, Durham, NC, USA	(●) Yes ( ) No
Other collaborator #2	Helen Fisher, PhD	helen.2.fisher@kcl.ac.uk	King's College London, UK	( ) Yes (●) No
Other collaborator #3	Louise Arseneault, PhD	louise.arseneault@kcl.ac.uk	King's College London, UK	( ) Yes (●) No
Other collaborator #4	Karen Sugden, PhD	karen.sugden@duke.edu	Duke University, Durham, NC, USA	(●) 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	Gene by ACE Genome-wide Interaction Analysis of CBCL Anxious/Depressed Syndrome Scale
Background and rationale for project ***(approx. 300 - 1000 words)***	Research consistently demonstrates a strong association between depressive symptoms in children and adolescents and adverse childhood experiences (ACEs). Distinct ACE patterns have been identified, with the "Child Maltreatment" class exhibiting the highest risk for depressive symptoms compared to other groups (Kim, Lee et al. 2022). A dose-response relationship is evident, where higher ACE scores correspond to increased risk and severity of depressive symptoms (Tsehay, Necho et al. 2020, Abbott and Slack 2021). Children exposed to four or more adverse childhood experiences (ACEs) have significantly higher odds of anxiety and depression {Elmore, 2020 #859}. Longitudinal studies further reveal that ACEs predict both concurrent and future depressive symptoms in adolescents, with the CBCL Anxious/Depressed Syndrome Scale symptoms mediating the link between recent ACEs and later somatic complaints (Lee, Oxford et al. 2022). These findings highlight the enduring impact of childhood adversity on mental health, including CBCL Anxious/Depressed Syndrome Scale, underscoring the importance of early intervention

	and prevention strategies potentially informed by genetic analysis. However, the precise identification of genes and genetic variants influencing Anxious/Depressed Syndrome Scale in youth exposed to ACEs remains unresolved. Genetic influences underlying childhood psychopathology show correlations with common psychiatric disorders, including Anxious/Depressed Syndrome Scale (Neumann, Nolte et al. 2022). While these insights are valuable, further research is needed to elucidate specific gene-environment interactions in anxious/depressed symptoms, particularly involving ACEs in adolescent populations.
Project aims / objectives	The objectives of this study are: 1) To perform ancestry-stratified gene-by-environment (GxE) genome-wide association study (GWAS) of CBCL Anxious/Depressed Syndrome Scale in a discovery dataset comprising adolescent participants, 2) To evaluate the cross-ancestry replication of SNP associations resulted from the preceding analysis, 3) To evaluate pathway enrichment scoring analysis using the GWAS outcomes, and 4) To replicate SNP associations in an independent dataset comprising adolescent participants.
Brief statement of your hypothesis	We hypothesized that evaluating single nucleotide polymorphism (SNP) associations with CBCL Anxious/Depressed Syndrome Scale in the presence of adverse childhood experiences (ACEs) within an adolescent population dataset will identify genetic risk factors whose relationships with CBCL Anxious/Depressed Syndrome Scale vary depending on ACE exposure.
Data analysis methods to be used ***(approx. 100 - 500 words)***	Discovery Dataset: We will use phenotypic and genetic data from the Adolescent Brain and Cognitive Development (ABCD) Study. Launched in 2016, ABCD follows over 11,000 children across the U.S., beginning at ages 9-10, to track their development into young adulthood. The study employs neuroimaging, behavioural assessments, and biospecimen analyses to explore the influence of genetic, environmental, and lifestyle factors on the developing brain to understand adolescent brain maturation and mental health trajectories (Casey, Cannonier et al. 2018, Volkow, Koob et al. 2018). While the study population comprised mostly White participants, there were also participants from other self-declared racial/ethnic groups, including Blacks, Natives and Islanders (Native American, Alaska Native, Native Hawaiian, Guamanian, Samoan, and Other Pacific Islander), and Asians and Other Races (Chinese, Japanese, Korean, Filipino, Vietnamese, Other Asian, Asian Indians, and Other Races). Replication Dataset: For the replication dataset, we will use the Environmental Risk (E-Risk) Longitudinal Twin Study, which was initiated in 1998 by Professors Terrie E. Moffitt and Avshalom Caspi and funded by the UK Medical Research Council until 2027 to investigate the roles of genetic, epigenetic, and environmental factors in the development of behaviours and mental health problems from childhood to adulthood (Caspi, Moffitt et al. 2004, Wong, Caspi et al. 2010, Fisher, Caspi et al. 2015, Wertz, Caspi et al. 2018). The study recruited a nationally representative cohort of 2,232 same-sex twins born in England and Wales in 1994-1995, ensuring representation across the UK's socioeconomic spectrum. Longitudinal assessments were conducted at ages 5, 7, 10, 12, and 18 with retention rates exceeding 90%. Study Variables: In addition to genome-wide imputed SNP data, the study will include the phenotypic variables CBCL Anxious/Depressed Syndrome Scale and ACE, as well as the demographic variables, age and sex (M/F), from the ABCD dataset. In case the same variables are unavailable in replication dataset (i.e., E-Risk), we will identify proxy variables that match the item or question-level data for each variable. For example, ASEBA Anxious/Depressed Subscale is not available for participants at age 18, therefore, we will use depression diagnosis at age 18. Similarly, if the same SNPs that resulted from the discovery analysis are unavailable in the E-Risk dataset, we will identify proxy SNPs (i.e., those in strong linkage disequilibrium) from the GWAS array of the E-Risk dataset. Statistical Analysis: Discovery Analysis: We will perform a discovery GxE GWAS analysis to evaluate the SNP associations with CBCL Anxious/Depressed Syndrome Scale in the presence of ACE (i.e., SNPxACE term) using non-White participants and White participants. We will model these

	GWAS analyses under an additive model using linear regression, adjusting for age, sex, ACE, and ancestry PCs to control for population structure within each ancestry group. Cross-Ancestry Replication of GxE GWAS Associations: We will examine cross-ancestry replication within the ABCD dataset for each significant SNP association identified in the previous step. Replication of GxE GWAS Associations in Independent Dataset (i.e., E-Risk): We will evaluate the replication in E-Risk dataset for each significant SNP association identified in the discovery step. We will evaluate the aforesaid regression models, additionally accounting for the non-independence of twin observations using the Huber-White/sandwich robust variance estimator clustered on family (twin-pair) ID, or alternatively by fitting mixed-effects models with a random intercept for family ID. While E-RISK participants at age 10 and/or 12 will provide a strong replication strategy for the ABCD findings, as ABCD participants are 9-10 years old, data at a later age, such as 18, could be advantageous because it could highlight the importance of longitudinal follow-up and age-dependent penetrance. Gene Pathway Scoring Analysis: We will use the association results (i.e., p-values) from the discovery GxE GWAS to perform pathway enrichment scoring, a computational approach used to evaluate how groups of genes-organized into biological pathways-are associated with a phenotype or disease. We will conduct this work using predefined pathways from the KEGG, BioCarta, and Reactome databases, as implemented in the Pathway Scoring Algorithm (Marbach, Lamparter et al. 2016).
Significance for theory, research methods, or clinical practice	The significance of our research involves the identification of SNPs, genes, and biological pathways involved in psychiatric illness among individuals exposed to adverse childhood experiences (ACEs), elucidating the complex interplay between genetic vulnerability and environmental stressors in mental health outcomes. Our work would help establish that while ACEs increase risk for disorders like depression and anxiety, part of this risk may stem from pre-existing genetic liabilities that can influence susceptibility to psychopathology. Furthermore, studying these mechanisms may reveal biological pathways for novel therapeutic targets, thus advancing personalized medicine approaches in psychiatry.
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Are there any files you would like to upload to support your concept paper?	○ Yes ◉ No

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3. Expected project outcomes

Please note:

The stated end date must be within 24 months of the date when this form is submitted. This end date will form part of the formal data use agreement and on this date you should delete the dataset. Therefore, it must be a realistic date for completion of the project including all analysis, writing a manuscript, review of the manuscript by all collaborators, submission, revisions, and acceptance of a paper for publication.

If you require an extension to the end date of the project, then you should contact Prof Fisher (helen.2.fisher@kcl.ac.uk) to discuss this. If you have signed a formal data use agreement, you will need to complete a form to request a licence extension. In some cases, we may also ask you to complete a new concept paper form if there have been substantial changes to the project or a long period of time has elapsed (e.g., greater than a year since the end date of the original project).

If the objective of the project is not a journal publication, please suggest an end date within 12 months instead of 24 months, and state a measurable, concrete outcome. If the objective of the project is a student dissertation, then the