ENVIRONMENTAL-RISK (E-RISK) LONGITUDINAL TWIN STUDY
CONCEPT PAPER FORM

Proposing Author: Simon Riches

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Sponsoring Investigator (if the proposing author is a student, a post-doc or a colleague): Helen Fisher

Proposed co-authors: Raha Bagher-Niakan, Manar Alsultan, Louise Arseneault, Eloise Crush, Helen Fisher [+ any other investigators who are interested]

Provisional Paper Title: Protective factors for early psychotic phenomena among children of mothers with psychosis

Date: 12th April 2018

Note. The proposed analyses will form the basis of two MSc dissertations undertaken by Raha (focusing on childhood psychotic symptoms) and Manar (focusing on adolescent psychotic experiences) supervised by Helen Fisher and Simon Riches, and will then be combined into a single paper by Simon Riches to submit as an invited paper to a special issue in Frontiers in Psychiatry on *Parents with Mental and/or Substance Use Disorders and their Children*.

Objective of the study and its significance:

Psychotic disorders, especially schizophrenia, are responsible for a substantial proportion of disability worldwide, are associated with 10-25 years shorter life expectancy, and place a huge burden on families, health services, and society more broadly. As current treatments are unable to provide a cure, it is crucial to focus on early identification of at-risk individuals to prevent the development of psychosis. Interventions in the prodromal stage have yielded some success but often fail to prevent poorer functional outcomes in the longer-term (Addington et al., 2011). Therefore, intervening even earlier before prodromal symptoms have emerged may be needed (Uher et al., 2014). However, what form these preventive interventions should take is unknown.

One way to inform the content of such interventions is to examine factors that protect 'at-risk' children from developing the early signs of psychosis (e.g., sub-clinical psychotic experiences). One of the most widely replicated risk factors for psychosis is having a family member with the disorder. For instance, having a parent with schizophrenia increases a child's risk of developing schizophrenia themselves by approximately eight-fold (Rasic et al., 2014). A previous analysis of the Environmental Risk (E-Risk) Longitudinal Twin study, a nationally-representative general population sample of twins, has also demonstrated that children were over twice as likely to report psychotic experiences (e.g., hearing voices, having visions, or being extremely paranoid) at age 12 if their mother had experienced a psychosis-spectrum disorder (Polanczyk et al., 2010). In this sample, we have recently shown that having better cognitive functioning, growing up in a

happier and more stimulating family environment, living in a cohesive community, engaging in physical activity, and the presence of a supportive adult can protect children from developing psychotic phenomena (Crush et al., 2018; Crush et al., submitted). Here we propose to investigate whether these factors can also protect children at high risk of psychosis, by virtue of having a mother with a psychotic disorder or psychotic symptoms, from developing sub-clinical psychotic phenomena in childhood and adolescence within the E-Risk cohort. The findings of this study have the potential to inform the focus of interventions to prevent the emergence of early psychotic phenomena and thus ultimately improve the outcomes of high-risk children.

Statistical analyses:

Bivariate and multivariate logistic regression analyses will be conducted to explore the associations between individual, family, and community-level putative protective factors and absence of (i) age-12 psychotic symptoms, and (ii) age-18 psychotic experiences, in the sub-sample of children whose mothers have experienced psychosis. We will conduct analyses defining maternal psychosis as (i) clinical diagnoses of schizophreniform psychosis, and (ii) presence of psychotic symptoms. For the age-18 outcome, we will run sensitivity analyses substituting psychotic experiences with the clinically verified psychotic symptoms.

We will also test in the whole sample for interactions between maternal psychosis status and any factors found to be associated with an absence of psychotic experiences in the sub-group analyses to examine whether these factors were specifically protective in relation to having a mother who has experienced psychotic phenomena.

All analyses will be adjusted for the non-independence of twin observations using the Huber/White variance estimator, child's gender, and family socio-economic status. The age-18 analyses will also be adjusted for age-12 psychotic symptoms and other age-12 mental health problems.

Variables Needed at Which Ages (names and labels):

Study: E-Risk

General Information

FAMILYID	Unique family identifier
ATWINID	Twin A ID (ex chkdg)
BTWINID	Twin B ID (ex chkdg)
RORDERP5	Random Twin Order
RISKS	Sample Groups
COHORT	Cohort
SAMPSEX	Sex of Twins: In sample
ZYGOSITY	Zygosity
SESWQ35	Social Class Composite

Risk variables

PSYSPECM10	Psychosis Spectrum Condition in mother
PSYSYM12	Mother Psychosis - Symptom Count

Putative protective factors

IQE5	Pro-rated IQ score - Elder
ATHOME7	Atmosphere at home - Phase 7

ATHOME10	Atmosphere at home - Phase 10
SCOHM5	Neighbourhood Social Cohesion
S2COHE	Neighborhood Social Cohesion (at 13/14)
SSUPPORTE18	Social Support scale - P18 - Elder
SSFAME18	Social Support Family Subscale - P18 - Elder
SSFRNE18	Social Support Friends Subscale - P18 - Elder
SSOTHE18	Social Support Significant Other Subscale - P18 - Elder
PHYACTE18	Physical activity (overall) - P18 – Elder

Outcome Variables

PSYSYMP01E12	Psychosis Symptom Count-Verified Coding-Elder - 0, 1+ - Elder
PSYSYMP01E18	Age-18 adolescent psychotic symptoms – elder
PSYEXPCE18	Age-18 adolescent psychotic experiences categorical – elder

Additional confounders

anyCDdx_emt512	Any CD dx from 5 to 12, mum/tchr, Elder
adhdanye512	Any ADHD dx [incl meds] - P5-12 - Elder
cdicate12	Clinically significant depression (CDI >= 20) - P12 - Elder
masccate12	Extreme anxiety (>= 95th percentile) - P12 - Elder

References cited:

Addington J, Cornblatt BA, Cadenhead KS, Cannon TD, McGlashan TH, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Woods SW, Heinssen R: At clinical high risk for psychosis: outcome for nonconverters. Am J Psychiatry. 2011, 168: 800-805.

Crush E, Arseneault L, Jaffee SR, Danese A, Fisher HL., 2018. Protective Factors for Psychotic Symptoms Among Poly-victimized Children. Schizophr Bull. 44 (3), 691–700.

Crush E, Arseneault L, Moffitt TE, Danese A, Caspi A, Jaffee SR, Matthews T, Fisher HL, submitted. Protective factors for psychotic experiences amongst adolescents exposed to multiple forms of victimization.

Polanczyk, G., Moffitt, T., Arseneault, L., Cannon, M., Ambler, A., Keefe, R.S., Houts, R., Odgers, C.L., Caspi, A., 2010. Etiological and clinical features of childhood psychotic symptoms. Arch. Gen. Psychiatry 67, 328-338.

Rasic D, Hajek T, Alda M, Uher R, 2014. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder and major depressive disorder: a meta-analysis of family high-risk studies. Schizophr Bull. 40, 28-38.

Uher R, Cumby J, MacKenzie LE, Morash-Conway J, Glover JM, Aylott A, Propper L, Abidi S, Bagnell A, Pavlova B, Hajek T, Lovas D, Pajer K, Gardner W, Levy A, Alda M., 2014. A familial risk enriched cohort as a platform for testing early interventions to prevent severe mental illness. BMC Psychiatry, 14, 344.

Data Security Agreement

Provisional Paper Title	Protective factors for early psychotic phenomena among children of mothers with psychosis
Proposing Author	Simon Riches
Today's Date	12th April 2018

Please keep one copy for your records
(Please initial your agreement)

SR I am familiar with the King's College London research ethics guidelines (https://www.kcl.ac.uk/innovation/research/support/ethics/about/index.aspx) and the MRC good research practice guidelines (https://www.mrc.ac.uk/research/policies-and-guidance-for-researchers/good-research-practice/)

SR My project has ethical approval from my institution.

SR My computer is (a) encrypted at the hard drive level, (b) password-protected, (c) configured to lock after 15 minutes of inactivity, AND (d) has an antivirus client which is updated regularly.

SR I will treat all data as "restricted" and store in a secure fashion.

SR I will not share the data with anyone, including students or other collaborators not specifically listed on this concept paper.

SR I will not merge data from different files or sources, except where explicit approval has been given by the PI.

SR I will not post data online or submit the data file to a journal for them to post.
Some journals are now requesting the data file as part of the manuscript submission process. The E-Risk Study cannot be shared because the Study Members have not given informed consent for unrestricted open access. Speak to the study PI for strategies for dealing with data sharing requests from Journals.

SR Before submitting my paper to a journal, I will submit my draft manuscript and scripts for data checking, and my draft manuscript for co-author mock review, allowing three weeks.

SR I will submit analysis scripts and new variable documentation to project data manager after the manuscript gets accepted for publication.

N/A **For projects using location data:** I will ensure geographical location information, including postcodes or geographical coordinates for the E-Risk study member's homes or schools, is never combined or stored with any other E-Risk data (family or twin-level data)

N/A **For projects using genomic data:** I will only use the SNP and/or 450K data in conjunction with the phenotypes that have been approved for use in this project at the concept paper stage.

Signature: .....  .....

CONCEPT PAPER RESPONSE FORM

A. To be completed by the proposing author

Proposing Author: Dr Simon Riches

X I have read the E-Risk data-sharing policy guidelines and agree to follow them

Provisional Paper Title: Protective factors for early psychotic phenomena among children of mothers with psychosis

Potential co-authors: Raha Bagher-Niakan, Manar Alsultan, Louise Arseneault, Eloise Crush, Helen Fisher
[+ any other investigators who are interested]

Potential Journals:
Intended Submission Date (month/year): 31st August 2018

Please keep one copy for your records and return one to Louise (louise.arseneault@kcl.ac.uk)

B. To be completed by potential co-authors:

☐ Approved ☐ Not Approved ☐ Let's discuss, I have concerns

Comments:

Please check your contribution(s) for authorship:

☐ Conceptualizing and designing the longitudinal study

☐ Conceptualizing and collecting one or more variables

☐ Data collection

☐ Conceptualizing and designing this specific paper project

☐ Statistical analyses

☐ Writing

☐ Reviewing manuscript drafts

☐ Final approval before submission for publication

☐ Acknowledgment only, I will not be a co-author

Signature: .....