

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

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Provisional Paper Title: Suicidality/self-harm and psychotic experiences: A test of bi-directionality in a
longitudinal cohort study

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Objective of the study and its significance:

Objectives:

- (i) To conduct the first bi-directional analysis of suicidality/self-harm and psychotic experiences
- (ii) To empirically inform a novel 'suicidal drive' hypothesis for psychosis

Background: The incidence of suicidal ideation and behaviour (SIB) among individuals experiencing psychosis has been well documented [1, 2]. Evidence suggests that SIB is highly prevalent in samples with diagnosed psychotic disorders [3, 4] and in clinically high risk (CHR) and ultra-high risk (UHR) populations [5, 6]. In the general population SIB has also been shown to be highly prevalent among those who report psychotic experiences (PEs) [7, 8]. Recent meta-analysis findings also show that individuals with schizophrenia-spectrum disorder and a history of suicidal ideation are over 6 times more likely to die by suicide [9]. Where associations between both phenomena have been investigated prospectively, psychosis, but not SIB, has been modeled at time one [10, 11]. Moreover, researchers have considered a wide array of factors in attempts to explain SIB among those experiencing psychosis e.g. fear of mental disintegration, depression, hopelessness, auditory hallucinations and substance misuse [12-14].

To date however no known research has considered the possibility that psychosis may be consequential to SIB. While psychosis → SIB directionality certainly seems intuitively plausible, it may also be plausible to suggest that psychosis, for some, may be consequential to SIB. Such a proposal may be considered if psychosis is framed within a context of threat responsiveness i.e. responsiveness to internally generated and self-directed threat*.

*If recognized physiological/psychological trauma reactions ultimately serve to distance or protect an individual from a source of threat or danger, distance and protection from one's self, in the context of SIB, is possibly more likely to be achieved by some psychological process of threat externalization/ attribution. Heightened PE prevalence among those experiencing SIB may reflect such a process.

Recent evidence does seem to show that SIB may be common prior to psychosis. For example, in two samples of individuals at risk of psychosis a high prevalence of suicidal ideation over the preceding two weeks was observed (72.0–76.9%) [15]. Similarly, Welsh and Tiffin [16] reported that 30% of a sample of

adolescents in an 'at-risk mental state' for psychosis had attempted suicide in the past six months. Moreover, a recent study investigating SIB prior to first presentation of psychosis and during a 3-year follow-up in a sample of 397 first-episode psychosis patients found that the greatest suicide risk was evident during the month before and 2 months after first contact with psychiatric services (i.e., 'early' attempts) [17]. Indeed, 15 to 26% of psychosis patients have attempted suicide at least once by their first contact while an additional 2 to 11% make another attempt during the first year of treatment [18-20]. Recently, Granö et al. [21] found that adolescents at heightened risk of psychosis had significantly higher scores of suicidal ideation compared with other help-seeking adolescents, suggesting that the association may be present already before a full-blown psychosis. Furthermore, while monitoring CHR patients enrolled in an early intervention programme for psychosis, Preti et al. [22] found that as psychosis symptom severity decreased, SIB decreased also. Notably however, each of these researchers have adhered to more traditional perspectives regarding psychosis → suicide directionality.

Hypotheses: To initiate empirical testing of a 'suicidal drive' hypothesis therefore the proposed study will attempt to:

- (i) demonstrate that PEs are commonly reported by those who experience SIB
- (ii) demonstrate that SIB can precede/co-occur with PEs
- (iii) demonstrate that SIB → PEs association remains when other risk factors (for both phenomena) have been statistically controlled for
- (iv) demonstrate that the strength of the association between PEs and SIB varies according to SIB severity and recency. It is proposed that if psychosis is responsive to internally generated and self-directed threat then it will not only be preceded by SIB but that PEs will be more strongly associated with SIB at more extreme levels (i.e. ideation – harm – suicidal attempt) and where SIB is most recent and/or sustained (i.e. at age 12 or 18 years, or both).

These preliminary hypotheses have been formulated to offer a necessary first investigatory step before exploration of the broader proposed threat response aspects of the 'suicidal drive' hypothesis can be considered.

Statistical analyses:

Step 1: Individuals with PEs (presence of any psychotic experiences) at T2 will be compared to individuals without PEs at T2 (i.e. the age 18 follow-up), across a range of known risk factors for both PEs and SIB ((i) demography, (ii) childhood behavioural and emotional problems, and (iii) childhood victimisation).

Step 1a: Individuals with SIB (presence of suicidal ideation/self-harm/suicide attempt) will be compared to individuals without SIB at Time 2 (i.e. the age 18 follow-up), using the same risk factors (see Tables 1 & 2 below).

Step 2: Associations will be analyzed between psychotic symptoms at T1 (age 12) and SIB at T2 (age 18), and vice versa (see Tables 3 & 4 below).

Step 3: Results will then be adjusted for those risk factors that were found to be associated with the outcomes in steps 1 and 1a (see also Tables 3 & 4 below).

Step 3a. We will repeat these analyses using twins discordant for SIB at age 12 (for associations with age-18 PEs) and then twins discordant for psychotic symptoms at age 12 (for associations with age-18 SIB) in order to more robustly control for unmeasured familial confounders.

Step 4: Interaction contrast ratios (ICRs) will be used to test departure from additivity [40]. Using the odds ratios (OR) derived from the logistic regression models of the dichotomous outcome variables "any follow-up PEs" and "any follow-up SIB". We will calculate ICRs using the formula (i.e. $ICR = OR_{both\ PEs\ and\ SIB} - OR_{PEs,\ no\ SIB} - OR_{no\ PEs,\ SIB} + 1$). Confidence intervals and p-values for ICRs will be generated.

Step 5: A cross-lagged panel model will then estimate all paths between T1 and T2 phenomena simultaneously (where PEs & SIB will continue to be modelled as binary presence/absence variables). Associations will be modelled as logits (ORs) using robust maximum likelihood. This model will also be adjusted incrementally for known risk correlates (see Figure 1 below).

Step 6: A cross-lagged panel model will estimate all paths between T1 and T2 phenomena simultaneously (where PEs & SIB will be modelled as continuous underlying response variables (i.e. SIB severity (ideation – attempt); summed PEs). Polychoric correlations and WLSMV estimation will be used. This model will also be statistically adjusted for risk.

Step 7: A final series of cross-lagged models will estimate temporal paths using alternative coding frames

of each criterion variable, i.e. SIB will be disaggregated into its individual categories and individual PEs will be modelled (dependent on endorsement rates).

Step 8: To further explore associations between SIB at T1 and PEs at T2, notes from the psychosis interviews at ages 12 and 18 will be reviewed by Dr. Fisher to examine the qualitative phenomenological content of reported PEs. Specifically, PEs that co-occur with or have been preceded by SIB are expected to be characterized by threat related content, e.g.

- Paranoia and persecutory delusions characterised by beliefs about personal safety, impending danger or the malevolent intentionality of others to cause harm, injury or death;
- Auditory verbal hallucinations (AVHs) containing and characterised by extreme negative and threatening commentaries, by one or more voices, which instruct or command engagement in suicidal or self-injurious behaviour;
- Passivity experiences and delusions of control, where teens believe that their mind or body is under the influence or control of some kind of external force or agency;
- Threat-based thought insertion and broadcasting/diffusion, which seem to reflect attributions of internal conflict/distress to external agents/sources.

Statistical analyses will be corrected for non-independence of twin observations by using tests based on the sandwich or Huber/White variance estimator (except Step 3a). Also, analyses involving age-18 PEs will be repeated, where possible, with age-18 clinically-verified psychotic symptoms.

The following statistical tables will be populated:

Table 1. Comparison of individuals with any psychotic experiences to individuals with no psychotic experiences at T2 (age 18) follow-up assessment, according to risk factors.

Risk Factor	No Psychotic Experience at T2 (age 18) n(%)	Any Psychotic Experience at T2 (age 18) n(%)	χ^2	p	Cramer's V
Demography					
Childhood behavioural and emotional problems					
Childhood victimisation					

Table 2. Comparison of individuals with any suicidality (SIB) to individuals with no suicidality at T2 (age 18) follow-up assessment, according to risk factors.

Risk Factor	No SIB at T2 (age 18) n(%)	Any SIB at T2 (age 18) n(%)	χ^2	p	Cramer's V
Demography					
Childhood behavioural and emotional problems					
Childhood victimisation					

SIB = suicidal ideation / behaviour

Table 3. Associations between baseline SIB (T1) and presence of any psychotic experience at age 18 (T2) follow-up.

Baseline Status (T1; age 12)		Presence of Psychosis at T2	Logistic Regression			
Categories	n(%)	n(%)	OR (CI)	OR ^a (CI)	OR ^b (CI)	OR ^c (CI)
No psychosis, No SIB						
No Psychosis, SIB						
Psychosis, No SIB						
Both Psychosis & SIB						
Total						

Table 4. Associations between baseline psychotic experiences (T1) and SIB at age 18 (T2) follow-up.

Baseline Status (T1; age 12)		Presence of SIB at T2	Logistic Regression			
Categories	n(%)	n(%)	OR (CI)	OR ^a (CI)	OR ^b (CI)	OR ^c (CI)
No psychosis, No SIB						
No Psychosis, SIB						
Psychosis, No SIB						
Both Psychosis & SIB						
Total						

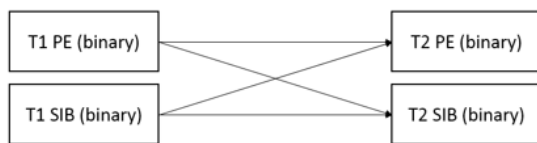
Tables 3 & 4

^a Adjusted for demography

^b Adjusted for demography, childhood behavioural and emotional problems,

^c Adjusted for demography, childhood behavioural and emotional problems, childhood victimisation

Figure 1. Cross lagged panel model with binary coded data



Variables Needed at Which Ages (names and labels):

Study: E-Risk

Age 5

- 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
- SETHNIC Ethnicity of Twins
- IQE5 Childhood IQ

- TOTEXTE5 Total Mum & Teacher Externalising Scale - Elder twin
- TOTEMOE5 Total Mum & Teacher Emotional Scale (Ex Somatic) - Elder twin

Age 12

- PSYSYMP01E12 Psychosis Symptom Count-Verified Coding-Elder - 0, 1+ - Elder
- PSYSYMP01Y12 Psychosis Symptom Count-Verified Coding-Elder - 0, 1+ - Younger
- PSYSYMP012E12 Psychosis Symptom Count - Verified Coding - 0, 1, 2+ - Elder
- PSYHALE12 Psychotic symptoms - Hallucinations - Elder
- PSYDELE12 Psychotic symptoms - Delusions - Elder
- PSYTHE12 Psychotic symptoms - Thought Interference - Elder
- FHANYPM12 Proportion of family members with valid data who have any disorder

FHSUIREED12	Strong Fam History of suicide, Reeds score >= 80th percentile, Belsky 2012
SHARMSUICE12	Self-Harm/Suicidal Behaviour - P12 – Elder
SHARMSUICY12	Self-Harm/Suicidal Behaviour - P12 – Younger
Tim – please can we also have self-harm and suicide attempt separately for elder twin?	
SCIIurban3	3 category urban vs nonurban vs rural neighborhood
EX_SVE12	Exposed to severe victimization (0/1), 5-12, E-Twin
Age 18	
POLYVCTZCE18	Poly-victimisation 4 cat (0,1,2,3+) - P18 - Elder
PSYSYMPO1E18	Psychosis Symptom Count (0,1+) – P18 – Elder
PSYEXPE18	Psychotic Experiences Scale - P18 - Elder
PSYEXPCE18	Psychotic Experiences (cat) - P18 - Elder
PSYEXPCY18	Psychotic Experiences (cat) - P18 - Younger
PSYHALE18	Psychotic symptoms - Hallucinations - P18 - Elder
PSYDELE18	Psychotic symptoms - Delusions - P18 - Elder
PSYTHE18	Psychotic symptoms - Thought Interference - P18 - Elder
FF1E18FIN	Thoughts can be read by another - P18 - Elder
FF3E18FIN	Sent messages through radio or TV - P18 - Elder
FF5E18FIN	Being followed or spied on - P18 - Elder
FF7E18FIN	Heard voices others cannot hear - P18 - Elder
FF9E18FIN	Felt under the control of special power - P18 - Elder
FF11E18FIN	Read thoughts of another person - P18 - Elder
FF13E18FIN	See something others cannot see - P18 – Elder
FF15E18	I have become more sensitive to lights or sounds – Elder
FF16E18	I feel as though I can't trust anyone – Elder
FF17E18	I worry that my food may be poisoned – Elder
FF18E18	People or places I know seem different – Elder
FF19E18	I believe I have special abilities or powers – Elder
FF20E18	My thinking is unusual or frightening – Elder
SUICATE18	Suicide attempted - P18 - Elder
SHARME18	Self harm - P18 - Elder
SHARMSUICE18	Suicide attempt or self harm (age 18) – Elder
SHARMSUICY18	Suicide attempt or self harm (age 18) – Younger
MDE_A9_E18	MDE - thoughts of death, suicide - P18 - Elder

Notes from psychosis interviews at 12 and 18 (only to be made available to Helen Fisher)

References cited:

1. Radomsky ED, Haas G L, Mann JJ, Sweeney JA (1999) Suicidal behavior in patients with schizophrenia and other psychotic disorders. *Am J Psychiat* 156: 1590-1595.
2. DeVlyder JE, Lukens EP, Link BG, Lieberman JA (2015) Suicidal ideation and suicide attempts among adults with psychotic experiences: data from the Collaborative Psychiatric Epidemiology Surveys. *JAMA Psychiat* 72: 219-225.
3. Harkavy-Friedman JM (2015) Suicide risk and prevention in patients with schizophrenia. *Suicidologi* 14: 2.
4. Palmer BA, Pankratz S, Bostwick JM (2005) The life time risk of suicide in schizophrenia: are examination. *JAMA Psychiat* 62: 247–253.
5. DeVlyder JE, Oh AJ, Ben-David S, Azimov N, Harkavy-Friedman JM, Corcoran CM (2012) Obsessive compulsive symptoms in individuals at clinical risk for psychosis: association with depressive symptoms and suicidal ideation. *Schizophr Res* 140: 110-113.
6. Hutton P, Bowe S, Parker S, Ford S (2011) Prevalence of suicide risk factors in people at ultra-high risk of developing psychosis: a service audit. *Early Interven Psychiat* 5: 375-380.
7. Taylor PJ, Hutton P, Wood L (2015) Are people at risk of psychosis also at risk of suicide and self-harm? A systematic review and meta-analysis. *Psychol Med* 45: 911-926.
8. Koyanagi A, Stickley A, Haro JM (2015) Subclinical psychosis and suicidal behavior in England: Findings from the 2007 Adult Psychiatric Morbidity Survey. *Schizophr Res* 168: 62-67.
9. Chapman CL, Mullin K, Ryan CJ, Kuffel A, Nielsen O, Large MM (2015) Meta-analysis of the association between suicidal ideation and later suicide among patients with either a schizophrenia spectrum psychosis or a mood disorder. *Acta Psychiat Scand* 131: 162-173.
10. Fisher, H. L., Caspi, A., Poulton, R., Meier, M. H., Houts, R., Harrington, H., ... & Moffitt, T. E. (2013) Specificity of childhood psychotic symptoms for predicting schizophrenia by 38 years of age: a birth cohort study. *Psychol Med* 43: 2077-2086.
11. Kelleher, I., Corcoran, P., Keeley, H., Wigman, J. T., Devlin, N., Ramsay, H., ... & Wasserman, D. (2013) Psychotic symptoms and population risk for suicide attempt: a prospective cohort study. *JAMA psychiat* 70: 940-948.
12. Haw C, Hawton K, Sutton L, Sinclair J, Deeks JJ (2005) Schizophrenia and deliberate self-harm: A systematic review of risk factors. *Suicide Life- Threat* 35: 50–62.
13. Hawton K, Sutton L, Haw C, Sinclair J, Deeks JJ (2005) Schizophrenia and suicide: a systematic review of risk factors. *Brit J Psychiat* 187: 9–20.
14. Hor K, Taylor M (2010) Suicide and schizophrenia: a systematic review of rates and risk factors. *J Psychopharmacol* 24: 81–90.
15. Hui C, Morcillo C, Russo DA, Stochl J, Shelley GF, Painter M, Jones P, Perez J (2013) Psychiatric morbidity, functioning and quality of life in young people at clinical high risk for psychosis. *Schizophr Res* 148: 175–180.
16. Welsh P, Tiffin PA (2013) The 'at-risk mental state' for psychosis in adolescents: clinical presentation, transition and remission. *Child Psychiat Hum D* 45: 90–98.
17. Ayesa-Arriola R, Alcaraz EG, Hernández BV, Pérez-Iglesias R, Moríñigo JDL, Duta R, ... & Crespo-Facorro B (2015) Suicidal behaviour in first-episode non-affective psychosis: Specific risk periods and stage-related factors. *Eur Neuropsychopharm*, doi:10.1016/j.euroneuro.2015.09.008.
18. Addington J, Williams J, Young J, Addington D (2004) Suicidal behaviour in early psychosis. *Acta Psychiat Scand* 109: 116-120.
19. Agerbo E, Nordentoft M, Mortensen PB (2002) Familial, psychiatric, and socioeconomic risk factors for suicide in young people: nested case-control study. *Bmj* 325: 74.
20. Verdoux H, Liraud F, Gonzales B, Assens F, Abalan F, Van Os J (2001) Predictors and outcome characteristics associated with suicidal behaviour in early psychosis: a two-year follow-up of first-admitted subjects. *Acta Psychiat Scand* 103: 347-354.
21. Granö N, Karjalainen M, Suominen K, Roine M (2011) Poor functioning ability is associated with high risk of developing psychosis in adolescents. *Nord J Psychiat* 65: 16–21.
22. Preti A, Meneghelli A, Pisano A, Cocchi A (2009) Risk of suicide and suicidal ideation in psychosis: results from an Italian multi-modal pilot program on early intervention in psychosis. *Schizophr Res* 113: 145-150.
23. Polanczyk, G., Moffitt, T. E., Arseneault, L., Cannon, M., Ambler, A., Keefe, R. S., ... & Caspi, A. (2010). Etiological and clinical features of childhood psychotic symptoms: results from a birth cohort. *Archives of general psychiatry*, 67, 328-338.

Data Security Agreement

Provisional Paper Title	Suicidality/self-harm and psychotic experiences: A test of bi-directionality in a longitudinal cohort study
Proposing Author	Jamie Murphy
Today's Date	12/05/2018

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(Please initial your agreement)

- JM 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/>)
- JM My project has ethical approval from my institution.
- JM 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.
- JM I will treat all data as "restricted" and store in a secure fashion.
- JM I will not share the data with anyone, including students or other collaborators not specifically listed on this concept paper.
- JM I will not merge data from different files or sources, except where explicit approval has been given by the PI.
- JM 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.
- JM 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.
- JM 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: Jamie Murphy

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

Provisional Paper Title: Suicidality/self-harm and psychotic experiences: A test of bi-directionality in a longitudinal cohort study

Potential co-authors: Mark Shevlin, Philip Hyland, Richard Bentall, Orla McBride, Louise Arseneault, Andrea Danese, Terrie Moffitt, Avshalom Caspi, Helen Fisher

Potential Journals: Schizophrenia Bulletin

Intended Submission Date (month/year): 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: