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

Proposing Author: Joanne Newbury

Author's affiliation, phone, and e-mail address: University of Bristol, 01275 265801, joanne.newbury@bristol.ac.uk

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

Proposed co-authors: Louise Arseneault, Terrie Moffitt, Avshalom Caspi, Candice Odgers, Laura Howe, Ioannis Bakolis, Aaron Reuben, Andrea Danese, Line Rasmussen, Antonella Trotta, Antony Ambler

Provisional Paper Title: Socioenvironmental risks for adolescent psychotic experiences: exploring biomechanisms in a UK longitudinal cohort.

Date: 12/05/21

Objective of the study and its significance:

Background

Over the past three decades, socioenvironmental factors such as overcrowding, poverty, pollution and disorder [1-5] have been repeatedly associated with psychotic disorders like schizophrenia. More recently these associations have been replicated for subclinical psychotic experiences among children and teenagers [6-11], such as hearing voices that others cannot hear (hallucinations) and extreme feelings of paranoia (delusions). Psychotic experiences signal elevated risk for later mental health problems including psychotic disorders, making them a useful research paradigm and an important target for intervention. However, very little is currently known about how socioenvironmental exposures might increase risk for psychosis. Improving our understanding of the biological mechanisms could ultimately inform preventative interventions. This study will investigate the roles that cognitive function and inflammation play in the association between socioenvironmental exposures in childhood and psychotic experiences in adolescence.

Cognition and inflammation are useful starting points because they provide markers of dynamic processes in the body and brain. Individual differences in cognitive ability are associated with differences in brain structure and function [12-14]. For instance, fMRI and lesion studies implicate connectivity within the frontoparietal network in fluid intelligence and cognitive control [15]. As such, tests of cognitive ability, usually obtained via pen and paper or computer tasks, provide non-invasive proxy measures of neurological functioning. Furthermore, peripheral inflammatory markers obtained from blood samples provide a snapshot of inflammatory and disease processes. Inflammation forms part of a complex arsenal used by the immune system to protect the body from infection and malignancy [16], but chronic inflammation is toxic and, contrary to historical opinion, is now known to damage the blood-brain barrier and adversely affect the brain [16].

Example of one mediation model that will be tested
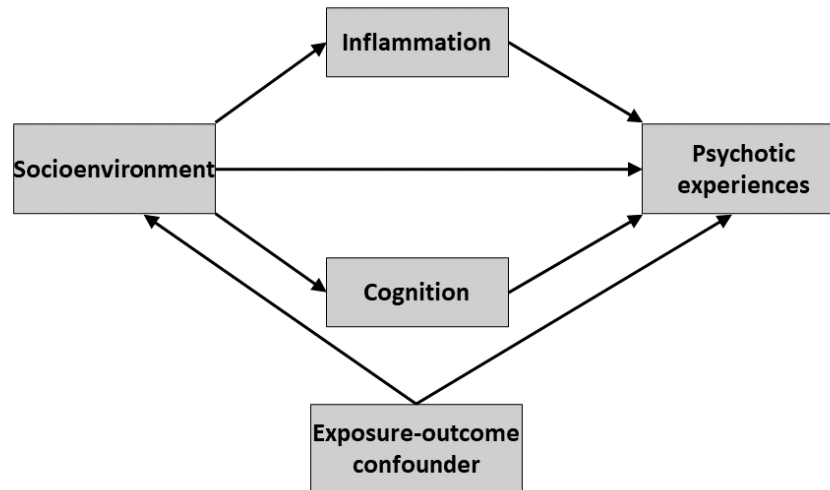
On one side of the mediation model, socioenvironmental exposures such as overcrowding, poverty, and pollution could influence cognitive function and inflammatory processes via both direct, physical pathways, as well as indirect, psychosocial pathways. Physically, inhaled air pollutants may enter the bloodstream and cross the blood-brain barrier [17, 18], where they may then promote inflammatory processes in the body and brain [19]. Air pollution exposure could therefore stunt and alter the developing brain, with downstream effects on cognition and psychopathology. In addition, the psychosocial aspects of overcrowding, poverty, and disorder, could indirectly influence cognition and inflammation by promoting stress. Chronic stress can lead to lasting disruption of the HPA axis [20], the peripheral limb of the body's stress system, and lead to neuroinflammation and neuronal death [21, 22] as well as aberrant interactions with neurotransmitters. [23]. Thus, by increasing stress, adverse neighbourhood social conditions could influence inflammation and cognition.

On the other side of our mediation model, impaired cognitive function is recognized as a core feature of psychosis [24]. Longitudinal research shows that children with deficits in cognitive ability are more likely to subsequently develop subclinical psychotic phenomena [25] and psychotic disorders [26], which highlights that cognitive problems precede the onset of psychosis and are not just a byproduct of the illness. The process(es) by which cognitive problems might lead to increased risk for psychosis is not fully known. However, shared neural underpinnings including smaller brain structure volumes (e.g., the hippocampus) and abnormal synaptic development and pruning are plausible [27-29]. Likewise, growing evidence suggests a role of inflammation in the aetiology of psychotic disorders [16, 30]. In relation to subclinical psychotic experiences, reports from the ALSPAC study show that children with higher serum concentrations of interleukin-6 (IL-6), a key inflammatory cytokine, have twice the risk for psychotic experiences and disorders by age 18 [31]. In the E-Risk cohort, inflammation levels are significantly higher among victimized children with psychotic symptoms compared to victimized children without psychotic symptoms [32]. Again, the process(es) by which circulating inflammatory markers might increase risk for psychosis is unconfirmed, but might plausibly include neuroinflammation, neurodegeneration, and interactions with neurotransmitters [16].

Notably, it is likely that infants and youth are most vulnerable to adverse socioenvironmental exposures because their brains and immune systems are still developing [33]. However, no studies have combined high-resolution data on socioenvironmental exposures with high-quality data on cognition and inflammation in a longitudinal cohort of children and adolescents to test whether these processes mediate the relationship between socioenvironmental risks and psychotic experiences.

Objectives

This study aims to test the mediatory roles of cognition and inflammation in the association between the socioenvironmental risks and adolescent psychotic experiences. The specific objectives are:

1) To test the longitudinal association of socioenvironmental exposures with cognitive ability and inflammatory markers.
2) To test the longitudinal association of cognitive ability with adolescent psychotic experiences (note: associations between inflammation and psychotic phenomena have previously been tested by Trotta et al., in prep [32]).
3) To test whether cognitive ability and inflammatory markers mediate the relationship between the urban environment and early psychotic phenomena.

***** Notes about data on socioenvironmental conditions, cognition, and inflammation *****

Socioenvironmental conditions: Detailed data on socioenvironmental conditions across upbringing have been collected from multiple sources at several timepoints. Based on our previous work, variables will include urbanicity, air pollution, deprivation, neighbourhood social characteristics, residential mobility, and family disadvantage, and thereby span area-, neighbourhood-, and family-level markers of socioenvironmental disadvantage. These data will also be combined to create a cumulative socioenvironmental risk scale.

Cognition: Overall cognitive ability was measured via tests of general intelligence (IQ) at ages 5, 12, and 18, using a short version of the Wechsler Preschool and Primary Scale of Intelligence-Revised (age 5), a short version of the Wechsler Intelligence Scale for Children-Revised (age 12), and a short version of Wechsler Adult Intelligence Scale-IV (age 18). Subcomponents of IQ, assessing fluid and crystalized cognitive ability, will also be used. In addition, sensitivity analyses will examine associations with specific cognitive domains, including working memory, executive function, and attention, which were measured via neurological testing at age 18 (CANTAB: Cambridge Neuropsychological Test Automated Battery; www.cantab.com; CANTAB Eclipse Test Administration Guide, 2006, Cambridge Cognition, Cambridge, UK).

Inflammation: Peripheral inflammation was measured from blood serum obtained at age 18. Inflammatory markers will include C-reactive protein (CRP), interleukin-6 (IL-6), and soluble urokinase plasminogen activator receptor (suPAR). CRP is a sensitive but non-specific marker of acute inflammation that responds rapidly to underlying disease and infection [34]. IL-6 is a key cytokine involved in regulating inflammation and protecting against infection, and it is linked to chronically high inflammation due to its regulatory role [35]. suPAR is a protein that is severed from cell membranes during inflammatory conditions, and provides an overall marker of immune activity and chronic inflammation [36].

Research questions and statistical analyses

1) Are socioenvironmental risks associated with cognitive function and inflammatory markers?

   - Test the association between childhood socioenvironmental exposures and cognitive ability at ages 12 and 18 using linear regression.
   - Test the association between childhood socioenvironmental exposures and inflammation at age 18 using multinomial logistic regression.

2) Are cognition and inflammation associated with early psychotic experiences?

   - Test the association between cognitive ability (overall IQ and subcomponents) at age 12 and psychotic experiences at age 18 using ordinal logistic regression.
   - Cross-lag models will be used to infer the directionality of associations, additionally using cognitive ability at age 18 and psychotic symptoms at age 12.
   - Sensitivity analyses will be conducted to test the cross-sectional associations of the specific cognitive domains at age 18 with psychotic experiences at age 18.
   - Note: Trotta et al (in prep) [19] have previously tested associations of inflammation with psychotic phenomena in E-Risk. This bivariate analysis will therefore not be required, but

associations will be reported.

3) Do cognition and inflammation mediate the relationship between socioenvironmental exposures and early psychotic phenomena?

- Mediation models will be informed by findings in Steps 1 and 2. Causal mediation modelling (supervised by Laura Howe) and/or structural equation modelling (supervised by Ioannis Bakolis) will both be applied to decompose the effects of socioenvironmental exposures on adolescent psychotic experiences into direct (unmediated) effects, and indirect (mediated) effects via cognitive ability at age 12 and inflammation at age 18.

Note: All analyses will control for the non-independence of twin observations. Main confounders (confounders of the exposure-outcome relationships) will include parent educational attainment, family psychiatric history, polygenic risks scores for schizophrenia, polygenic risk for education and polygenic risk for cognitive performance. Confounders for specific models (e.g., E-M confounders) will additionally include, where appropriate, body mass index, waist-to-hip ratio, body temperature, adolescent smoking and substance problems and child/adolescent victimization. Finally, specificity analyses will be conducted by repeating main analyses with age 18 depression as the outcome.

Variables Needed at Which Ages (names and labels):

NB. highlighted in yellow are those which may not currently be in the data dictionary

Study: E-Risk & SCOPIC

- 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

Age 5
- IQE5   Pro-rated IQ score – Elder
- VERBALE5   Twin's age adjusted vocabulary score – Elder
- PERFE5   Twin's age adjusted block design score - Elder
- seswq35   Social class composite
- HIEDM5   Highest educational qualification (mother)
- HIEDPM5   Highest educational qualification (partner)
- HOHSCM5   HoH Social Class (highest mum/dad)
- ED56M5   Total HHold Income (all sources - before Tax)
- NBENSM5   No. Benefits (ex sickness)
- HTENM5   Housing Tenure
- ED61M5   Household own or have access to a car or van?
- p5cacorn   Neighbourhood deprivation at age 5
- ph5code_num   ONS urbanicity (number code 1-10)
- ph5cat_num   ONS urbanicity (categorical least to most urban)
- nprobm5   Perception of local environment
- ncrimm5   Neighbourhood Personal Victimisation
- ncrim2m5   Individual Reports score 2+ on Crime measure
- scohm5   Neighbourhood Social Cohesion

Age 7
- p7cacorn   Neighbourhood deprivation at age 7
- ph7code_num   ONS urbanicity (number code 1-10)

- ph7cat_num   ONS urbanicity (categorical least to most urban)

Age 10
- p10cacor   Neighbourhood deprivation at age 10
- ph10code_num   ONS urbanicity (number code 1-10)
- ph10cat_num   ONS urbanicity (categorical least to most urban)
- nmovel510   Number of residence changes 5 to 10, LHC
- Loc1_NO2_P10   NO2 levels at address location 1
- Loc1_NOx_P10   NOx levels at address location 1
- Loc1_PM2_5_P10   PM2.5 levels address location 1
- Loc1_PM10_ P10   PM10 levels at address location 1

Age 12
- psysymp01e12   Age-12 childhood psychotic symptoms (Elder)
- psysympe12   Psychotic symptom count (Elder)
- IQ12E   Pro-Rated IQ (INF & MR) – Elder
- infe_ss12   Information Scaled Score, 12E
- mre_ss12   Matrix Reasoning Scaled Score, 12E
- p12cacor   Neighbourhood deprivation at age 12
- ph12code_num   ONS urbanicity (number code 1-10)
- ph12cat_num   ONS urbanicity (categorical least to most urban)
- fhanypm12   Family psychiatric history
- s2cohe   SCOPIC 2 social cohesion
- s2ndsrdr   SCOPIC 2 disorder
- lc5m12   N changes of address – since age 10
- polyve512c   Extent of Polyvictim (Truncated @3), 5-12, E-Twin

Age 18
- psysymp01e18   Age-18 adolescent psychotic symptoms - elder
- psyexpe18   Age-18 adolescent psychotic experiences full count – elder
- psyexpce18   Age-18 adolescent psychotic experiences categorical – elder
- IQ18E   Pro-Rated IQ, (MR, & INF) – Elder
- INFE_SS18   Information Scaled Score, 18E
- MRE_SS18   Matrix Reasoning Scaled Score, 18E
- smkcnume18   Smoking current (number of cigarettes), elder
- smkdlye18   Ever a daily smoker, elder
- smkpkyr   Smoking, pack years (age12 to 18)
- marjsxe18   Marijuana - Symptom scale - P18 - Elder
- dxmarje18   Marijuana dependency, dsm4 - P18 - Elder
- alcsxe18   Alcohol - symptom scale - P18 – Elder
- dxalcdepe18   Alcohol dependent, dsm4_based - P18 – Elder
- dxmdee18   Major depression episode, dsm4 - P18 - Elder

- rvpapre18   RVP A-prime - P18 – Elder
- rvpmlte18   RVP Mean Latency - P18 – Elder
- rvptface18   RVP Total False Alarms (Categorical) - P18 – Elder
- swmstae18   SWM Strategy - P18 - Elder
- swmteae18   SWM Total errors - P18 - Elder
- swmmlre18   SWM Mean time to last response - P18 – Elder
- sspsple18   SSP Span length - P18 - Elder
- ssprsle18   SSP Span length [reverse] - P18 – Elder

- LCA_inflam_LJHR2019   Inflammation latent classes based on CRP/IL-6/suPAR
- CRP_suPAR   Categorical variable stratifying by CRP/suPAR
- IL6_suPAR   Categorical variable stratifying by IL-6/suPAR
- CRP_IL6   Categorical variable stratifying by CRP/suPAR
- CRPE18_4SD   CRP concentration (mg/L) with outliers removed - P18 – Elder
- lnCRP_E18_4SD   Log-transformed CRP with outliers removed – P18 – Elder
- CRP_high   Categorical variable stratifying by high or low CRP
- IL6_E18_4SD   Plasma IL-6 with outliers removed – P18 – Elder
- lnIL6_E18_4SD   Log-transformed IL-6 with outliers removed – P18 – Elder
- IL6_high   Categorical variable stratifying by high or low IL-6
- suPAR_E18_4SD   Plasma suPAR with outliers removed – P18 – Elder
- suPAR_high   Categorical variable stratifying by high or low suPAR

- waisthipe18   Waist Hip Ratio - P18 – Elder
- bmie18   BMI - P18 – Elder
- btempe18   Body temperature, Celsius - P18 – Elder

- p18cacor   Neighbourhood deprivation at age 18
- ph18code_num   ONS urbanicity (number code 1-10)
- ph18cat_num   ONS urbanicity (categorical least to most urban)
- Location1_NO2_E   NO2 levels at address location 1
- Location1_NOx_E   NOx levels at address location 1
- Location1_PM2_5_E   PM2.5 levels address location 1
- Location1_PM10_E   PM10 levels at address location 1
- polyvctzce18   Polyvictimisation 4 cat (0,1,2,3+) - P18 - Elder
- neigbrhde1218   Neighbourhood address across phases 12 and 18 – Elder
- cohabe18   Twins living together at age 18 – Elder

PRS data
- SchzPGS2018_Twins_Feb2020_Clumpe   participant polygenic risk scores for schizophrenia using new Pardinas et al 2018 score
- zr_PGI_CPsingle_twins   Cognitive Performance, SSGAC 2020 (twins)
- zr_PGI_EAsingle_twins   Educational Attainment, SSGAC 2020 (twins)
- zr_PGI_CPsingle_mum   Cognitive Performance, SSGAC 2020 (mums)
- zr_PGI_EAsingle_mum   Educational Attainment, SSGAC 2020 (mums)

References cited:

- 1.   Pedersen, C.B. and P.B. Mortensen, *Urbanization and traffic related exposures as risk factors for schizophrenia.* BMC Psychiatry, 2006. **6**: p. 2.
- 2.   Pedersen, C.B., et al., *Air pollution from traffic and schizophrenia risk.* Schizophrenia Research, 2004. **66**(1): p. 83-85.
- 3.   Vassos, E., et al., *Meta-analysis of the association of urbanicity with schizophrenia.* Schizophrenia Bulletin, 2012. **38**(6): p. 1118-1123.
- 4.   Veling, W., et al., *Social disorganization of neighborhoods and incidence of psychotic disorders: A 7-year first-contact incidence study.* Psychological Medicine, 2015. **45**(9): p. 1789-1798.
- 5.   Kirkbride, J.B., et al., *Social Deprivation, Inequality, and the Neighborhood-Level Incidence of Psychotic Syndromes in East London.* Schizophrenia Bulletin, 2012. **40**(1): p. 169-180.
- 6.   Newbury, J., et al., *Why are children in urban neighborhoods at increased risk for psychotic symptoms? Findings from a UK longitudinal cohort study.* Schizophrenia Bulletin, 2016. **42**(6): p. 1372-1383.
- 7.   Newbury, J., et al., *Cumulative effects of neighborhood social adversity and personal*

crime victimization on adolescent psychotic experiences. Schizophrenia Bulletin, 2018. **44**(2): p. 348-358.

- 8.   Newbury, J.B., et al., *Association of air pollution exposure with psychotic experiences during adolescence.* JAMA Psychiatry, 2019. **76**(6): p. 614-623.
- 9.   Newbury, J.B., et al., *In the eye of the beholder: Perceptions of neighborhood adversity and psychotic experiences in adolescence.* Development and Psychopathology, 2017. **29**(5): p. 1823-1837.
- 10.   Solmi, F., et al., *Trajectories of Neighborhood Cohesion in Childhood, and Psychotic and Depressive Symptoms at Age 13 and 18 Years.* Journal of the American Academy of Child & Adolescent Psychiatry, 2017. **56**(7): p. 570-577.
- 11.   Solmi, F., et al., *Neighbourhood characteristics at birth and positive and negative psychotic symptoms in adolescence: findings from the ALSPAC birth cohort.* Schizophrenia Bulletin, 2019.
- 12.   Rosenberg, M.D., et al., *A neuromarker of sustained attention from whole-brain functional connectivity.* Nature Neuroscience, 2016. **19**(1): p. 165.
- 13.   Smith, S.M., et al., *Functional connectomics from resting-state fMRI.* Trends in Cognitive Sciences, 2013. **17**(12): p. 666-682.
- 14.   Buckner, R.L., *The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging.* Neuron, 2013. **80**(3): p. 807-815.
- 15.   Barbey, A.K., *Network neuroscience theory of human intelligence.* Trends in Cognitive Sciences, 2018. **22**(1): p. 8-20.
- 16.   Khandaker, G.M., et al., *Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment.* The Lancet Psychiatry, 2015. **2**(3): p. 258-270.
- 17.   Brunekreef, B. and S.T. Holgate, *Air pollution and health.* The Lancet, 2002. **360**(9341): p. 1233-1242.
- 18.   Calderón-Garcidueñas, L., et al., *Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid β-42 and α-synuclein in children and young adults.* Toxicologic Pathology, 2008. **36**(2): p. 289-310.
- 19.   Block, M.L. and L. Calderón-Garcidueñas, *Air pollution: Mechanisms of neuroinflammation and CNS disease.* Trends in Neurosciences, 2009. **32**(9): p. 506-516.
- 20.   Herman, J.P. and W.E. Cullinan, *Neurocircuitry of stress: central control of the hypothalamo–pituitary–adrenocortical axis.* Trends in Neurosciences, 1997. **20**(2): p. 78-84.
- 21.   Sorrells, S.F., et al., *The stressed CNS: when glucocorticoids aggravate inflammation.* Neuron, 2009. **64**(1): p. 33-39.
- 22.   Chrousos, G.P., *The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation.* New England Journal of Medicine, 1995. **332**(20): p. 1351-1363.
- 23.   Gray, J.D., et al., *Genomic and epigenomic mechanisms of glucocorticoids in the brain.* Nature Reviews Endocrinology, 2017. **13**(11): p. 661.
- 24.   Green, M.F., et al., *Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria.* Biological psychiatry, 2004. **56**(5): p. 301-307.
- 25.   Niarchou, M., et al., *Defective processing speed and nonclinical psychotic experiences in children: longitudinal analyses in a large birth cohort.* American Journal of Psychiatry, 2013. **170**(5): p. 550-557.
- 26.   Cannon, M., et al., *Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort.* Archives of General Psychiatry, 2002. **59**(5): p. 449-456.
- 27.   McGlashan, T.H. and R.E. Hoffman, *Schizophrenia as a disorder of developmentally reduced synaptic connectivity.* Archives of General Psychiatry, 2000. **57**(7): p. 637-648.
- 28.   van Erp, T.G., et al., *Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium.* Molecular Psychiatry, 2016. **21**(4): p. 547-553.
- 29.   Jirsaraie, R.J., J.M. Sheffield, and D.M. Barch, *Neural correlates of global and specific cognitive deficits in schizophrenia.* Schizophrenia Research, 2018. **201**: p. 237-242.
- 30.   Danese, A. and J.R. Baldwin, *Hidden wounds? Inflammatory links between childhood trauma and psychopathology.* Annual Review of Psychology, 2017. **68**(1): p. 517-544.
- 31.   Khandaker, G.M., et al., *Association of serum interleukin 6 and C-reactive protein in*

childhood with depression and psychosis in young adult life: a population-based longitudinal study. JAMA Psychiatry, 2014. **71**(10): p. 1121-1128.

- 32. Trotta, A., et al. *Associations between Childhood Adversity, C-Reactive Protein levels, and Psychotic Symptoms in Childhood: a Longitudinal Twin Cohort Study*. in *Early Intervention in Psychiatry*. 2018. Wiley.
- 33. UNICEF *Danger in the air: How air pollution can affect brain development in young children*. 2017.
- 34. Rhodes, B., B.G. Fürnrohr, and T.J. Vyse, *C-reactive protein in rheumatology: biology and genetics.* Nature Reviews Rheumatology, 2011. **7**(5): p. 282.
- 35. Hunter, C.A. and S.A. Jones, *IL-6 as a keystone cytokine in health and disease.* Nature Immunology, 2015. **16**(5): p. 448.
- 36. Rasmussen, L.J.H., et al., *Cumulative childhood risk is associated with a new measure of chronic inflammation in adulthood.* Journal of Child Psychology and Psychiatry, 2019. **60**(2): p. 199-208.

Data Security Agreement

Provisional Paper Title	Socioenvironmental risks for adolescent psychotic experiences: exploring biomechanisms in a UK longitudinal cohort
Proposing Author	Joanne Newbury
Today's Date	12/05/21

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

JN 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/).

JN My project has ethical approval from my institution.

JN I am familiar with the EU General Data Protection Regulation (https://mrc.ukri.org/documents/pdf/gdpr-guidance-note-3-consent-in-research-and-confidentiality/), and will use the data in a manner compliant with its requirements.

JN 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.

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

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

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

JN 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.

JN 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.

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

JN I will delete the data after the project is complete.

JN **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 <u>never</u> combined or stored with any other E-Risk data (family or twin-level data)

JN **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:

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

Provisional Paper Title: Socioenvironmental risks for adolescent psychotic experiences: exploring biomechanisms in a UK longitudinal cohort

Potential co-authors: Louise Arseneault, Terrie Moffitt, Avshalom Caspi, Candice Odgers, Laura Howe, Ioannis Bakolis, Aaron Reuben, Andrea Danese, Line Rasmussen, Antonella Trotta, Antony Ambler

Potential Journals:

Intended Submission Date (month/year):   10/21

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: ....