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

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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].
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**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>familyid</td>
<td>Unique family identifier</td>
</tr>
<tr>
<td>atwinid</td>
<td>Twin A ID (ex chkdg)</td>
</tr>
<tr>
<td>btwinid</td>
<td>Twin B ID (ex chkdg)</td>
</tr>
<tr>
<td>rorderp5</td>
<td>Random Twin Order</td>
</tr>
<tr>
<td>risks</td>
<td>Sample Groups</td>
</tr>
<tr>
<td>cohort</td>
<td>Cohort</td>
</tr>
<tr>
<td>sampsex</td>
<td>Sex of Twins: In sample</td>
</tr>
<tr>
<td>zygosity</td>
<td>Zygosity</td>
</tr>
</tbody>
</table>

**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**
- psysympe12  Age-12 childhood psychotic symptoms (Elder)
- psysympe12  Psychotic symptom count (Elder)
- IQ12E  Pro-Rated IQ (INF & MR) – Elder
- infes12  Information Scaled Score, 12E
- mrss12  Matrix Reasoning Scaled Score, 12E
- p12cacor  Neighbourhood deprivation at age 12
- ph12cat_num  ONS urbanicity (categorical least to most urban)
- fhanym12  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**
- psysympe18  Age-18 adolescent psychotic symptoms - elder
- psyxppe18  Age-18 adolescent psychotic experiences full count – elder
- psyxpee18  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
- smkdy1e18  Ever a daily smoker, elder
- smkpyr  Smoking, pack years (age12 to 18)
- marjsex18  Marijuana - Symptom scale - P18 - Elder
- dxmarje18  Marijuana dependency, dsm4 - P18 - Elder
- alicxe18  Alcohol - symptom scale - P18 – Elder
- dxalcedepe18  Alcohol dependent, dsm4_based - P18 – Elder
- dxmdee18  Major depression episode, dsm4 - P18 - Elder
- rvpapr1e18  RVP A-prime - P18 – Elder
- rvpmlte18  RVP Mean Latency - P18 – Elder
- rvptfac1e18  RVP Total False Alarms (Categorical) - P18 – Elder
- swmsta18  SWM Strategy - P18 - Elder
- swmteae18  SWM Total errors - P18 - Elder
- ssmmlre18  SWM Mean time to last response - P18 – Elder
- sspsple18  SSP Span length - P18 - Elder
- sspsrsle18  SSP Span length [reverse] - P18 – Elder
Inflammation latent classes based on CRP/IL-6/suPAR

- **LCA_inflam_LJHR2019**
- **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

- **p18cacin** 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:**

7. Newbury, J., et al., *Cumulative effects of neighborhood social adversity and personal*


31. Khandaker, G.M., et al., Association of serum interleukin 6 and C-reactive protein in


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 **never** 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: .................................................................