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

Proposing Author: Joanne Newbury

Author's affiliation, phone, and e-mail address: KCL, 0361, joanne.newbury@kcl.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, Daniel Belsky

Provisional Paper Title: Is genetic risk for schizophrenia associated with urban residency and related risk factors during upbringing? Findings from a longitudinal cohort study.

Date: 20/08/18

Objective of the study and its significance:

Background

Psychotic disorders such as schizophrenia are thought to arise from a combination of genetic and environmental factors. Urban upbringing is one of the most well-established environmental factors implicated in psychosis. A child who is born and raised in an urban (versus rural) setting is around twice as likely to develop a psychotic disorder such as schizophrenia in adulthood (Vassos et al., 2012). Two-thirds of the world's population will be urban by 2050 (Dye, 2008), and there is evidence that the association between urban upbringing and psychosis is becoming progressively stronger over time (Chan et al., 2015, Haukka et al., 2001, Marcelis et al., 1998). It is therefore essential that we uncover the pathways linking the urban environment to psychosis.

A growing body of research now demonstrates that subclinical psychotic symptoms (e.g., hearing voices and extreme paranoia) are also around twice as common among children and adolescents raised in cities (Newbury et al., 2016, Newbury et al., 2017a, Newbury et al., 2017b). These early symptoms are thought to lie on a continuum with adult psychotic disorders (Polanczyk et al., 2010), providing insights into the developmental timing of the association between urbanicity and psychosis. In addition, recent research by this team and others has begun to explore potential components of the urban environment which might comprise the risk. This has highlighted links between psychotic symptoms/disorders and a collection of urbanicity-related risk factors, such as socioeconomic hardship (Polanczyk et al., 2010, Kirkbride et al., 2014), crime victimization (Newbury et al., 2017a, Fisher et al., 2017), residential mobility (Paksarian et al., 2014, Singh et al., 2014), neighbourhood crime (Bhavsar et al., 2014, Newbury et al., 2016), and low social cohesion (Kirkbride et al., 2008, Solmi et al., 2017, Newbury et al., 2016).

The weight of available evidence thus supports a causal role of urbanicity in the aetiology of psychosis – whereby features of the urban environment (e.g., socioeconomic hardship, crime, residential mobility) increase risk for psychosis by increasing developmental exposure to stress (Heinz et al., 2013, March et al., 2008). This mechanism aligns readily with leading aetiological models of psychosis (Garety et al., 2001, Freeman et al., 2002, McGrath et al., 2003, Rapoport et al., 2005).

However, an alternative mechanism remains possible. The social selection model points towards compositional differences between rural and urban residents. Such urban-rural differences could include

social and behavioral factors (e.g., parental age, substance use), although epidemiological research has ruled out confounding by a range of social and behavioural risk factors. Urban and rural residents could also differ in terms of their genetic risk for psychosis. This type of selection could occur, for example, if functional impairment associated with higher genetic risk leads individuals to drift downward in social mobility and migrate into crowded and impoverished areas. This mechanism could mean that the urbanicity-psychosis association is confounded by genes.

This form of genetic confounding has until recently been an intractable question. The advent of the polygenic risk score (PRS) method offers new opportunities to test whether individuals with higher genetic risk for schizophrenia are more likely to live in urban areas. Two recent studies have explored this question, with both identifying significant associations between schizophrenia PRS and urban residency in adulthood (Paksarian et al., 2018, Colodro-Conde et al., 2018). Associations have also been found between schizophrenia PRS and neighbourhood deprivation in adulthood (Sariaslan et al., 2016).

However, no studies have explored whether schizophrenia PRS is associated with urban residency or related risk factors during childhood and adolescence. This is important to establish for several reasons. First, children (versus adults) have comparatively little choice in where they grow up, and therefore genetic selection processes are likely to differ between children and adults. Additionally, it is urban upbringing (rather than adult residency) that is most strongly associated with psychosis risk (Pedersen and Mortensen, 2001). Recent findings on schizophrenia PRS and adult urban residency are therefore consistent with a mechanism whereby adults drift into urban setting after the onset of psychosis symptomology, but to fully understand the role of genetic confounding in the urbanicity-psychosis association we must look at residential environments during upbringing. That is, we do not currently know whether the correlations between schizophrenia PRS and urbanicity indicates (a) confounding (e.g., arising from reverse causation in which psychosis symptomatology leads individuals into more crowded or adverse environments), in which case addressing risks will have little impact on psychosis outcome; or (b) mediating pathways (e.g. in which genetics influence exposure to causal risk factors), in which case addressing risks can break the link between genetics and psychosis. A first set of analyses needed to distinguish confounding from mediation is to understand how genetics relate to the accumulation of psychosis risk factors in children, for whom the onset of subclinical psychotic symptomatology can be observed prospectively and for whom reverse causation can therefore be tested.

Few datasets other than E-Risk have the necessary design – including longitudinal and nationally-representative data, comprehensive phenotypic-, family- and neighbourhood-level measures, and genotyped participants – to test whether genetic risk for schizophrenia is associated with urban residency and 'urban' risk factors during upbringing.

Objectives

This paper has four main goals.

1) We will test whether schizophrenia PRS is associated with degree of urbanicity of the E-Risk participants' home addresses at ages 5, 7, 10, 12 and 18; and whether schizophrenia PRS is associated with degree of urbanicity of the places that participants spend their time at age 18.
    - This will highlight whether youth with higher genetic risk for schizophrenia are more likely to be raised in urban (versus nonurban) settings.
    - This will also highlight whether participants with higher genetic risk for schizophrenia begin to 'select' urban neighbourhoods as they become more independent.

2) We will test correlations between urbanicity and a set of individual-, family-, and neighbourhood-level risk factors which have been linked to psychotic experiences, including family SES, residential mobility, child and adolescent poly-victimisation, conventional crime victimization, and neighbourhood disorder, social cohesion, deprivation, and crime.
    - This will provide a reference point for subsequent analyses by highlighting the urban-rural distribution of this set of risk factors linked to psychotic experiences.

3) We will test whether schizophrenia PRS is associated with these individual-, family-, and neighbourhood-level risk factors.

- This will highlight whether youth with higher genetic risk for schizophrenia are more likely to experience these risk factors.

4) We will test whether the associations between urbanicity/related risk factors and psychotic experiences are attenuated after controlling for schizophrenia PRS.
    - This will give an indication of the extent that the association between the urban environment/related risk factors and psychotic experiences is confounded by genes.

NOTE: Since parental genetics are likely to contribute substantially to a child's environment during upbringing, steps 1-3 will be repeated using the mothers' (instead of participants') polygenic risk scores for schizophrenia. We will also evaluate whether schizophrenia PRS is associated with childhood/adolescent psychotic phenomena in the cohort (although schizophrenia PRS only modestly predicts early psychotic phenomena at present (Pain et al., 2018)).

Significance

This study will be the first to explore whether young urban residents have a higher genetic risk for schizophrenia; and similarly, whether youth with higher genetic risk for schizophrenia are more likely to be exposed to risk factors linked to the urban environment. These questions are important for establishing the causality of the urbanicity-psychosis association. Moreover, mapping the urban-rural distribution of genetic risk for schizophrenia could ultimately help to inform early-intervention efforts.

Statistical analyses

Research questions and statistical analyses

1) Are young people with higher schizophrenia PRS more likely to grow up in urban settings?
    - Using both Pearson's correlation and multinomial logistic regression, we will test whether schizophrenia PRS is associated with the level of urbanicity (three-levels: rural/intermediate/urban, with rural treated as baseline) of the participants' residential neighbourhoods at ages 5, 7, 10, 12, and 18.
    - Using Pearson's correlation and multinomial logistic regression, we will test associations between schizophrenia PRS and the level of urbanicity of the neighbourhoods that participants spent their time in at age 18.

2) Are youth in urban neighbourhoods exposed to more risk factors that have been linked to psychosis?
    - Using Pearson's correlation and linear/logistic regression, we will calculate the associations of urbanicity with family SES, residential mobility, child and adolescent poly-victimisation, conventional crime victimization, and neighbourhood disorder, social cohesion, deprivation, and crime.

3) Are young people with higher schizophrenia PRS more likely to be exposed to risk factors linked to urbanicity?
    - Pearson's correlations/spearman's correlation/linear regression/logistic regression will be used to test associations between schizophrenia PRS and family SES, residential mobility, child and adolescent poly-victimisation, conventional crime victimization, and neighbourhood disorder, social cohesion, deprivation, and crime.

4) Is the association between urbanicity/related risk factors and psychotic phenomena confounded by genes?
    - Multiple ordinal logistic regression models will be fitted for psychotic phenomena (dependent variable) and urbanicity/related risk factors (independent variable). Schizophrenia PRS will be added as an additional independent variable to estimate confounding by this measure of genetic risk.

NOTE: Analytic steps 1-3 will be repeated using the mothers' polygenic risk scores for schizophrenia. We will also use Pearson's correlation and binary/ordinal logistic regression to test whether schizophrenia PRS predicts early psychotic phenomena.

All analyses will control for the non-independence of twin observations using the CLUSTER method in STATA. To check the sensitivity of effect sizes and directions, analyses will be repeated at the family-level by randomly dropping one twin in each pair.

Variables Needed at Which Ages (names and labels):

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

Study: E-Risk

- 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

- seswq35 — Social class composite
- p5cacorn — Neighbourhood deprivation at age 5
- IMDscore5 — Index of multiple deprivation at age 5
- ph5code_num — ONS urbanicity (number code 1-10)
- ph5cat_num — ONS urbanicity (categorical least to most urban)

Age 7

- p7cacorn — Neighbourhood deprivation at age 7
- IMDscore7 — Index of multiple 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
- IMDscore10 — Index of multiple 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

Age 12

- psysymp01e12 — Age-12 childhood psychotic symptoms (Elder)
- psysympe12 — Psychotic symptom count (Elder)
- p12cacor — Neighbourhood deprivation at age 12
- IMDscore12 — Index of multiple deprivation at age 12
- ph12code_num — ONS urbanicity (number code 1-10)
- ph12cat_num — ONS urbanicity (categorical least to most urban)
- 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
- p18cacor Neighbourhood deprivation at age 12
- IMDscore18 Index of multiple deprivation at age 12
- ph18code_num ONS urbanicity (number code 1-10)
- ph18cat_num ONS urbanicity (categorical least to most urban)
- ttlcrm2011 Monthly average # of all crimes in 2011
- ttlcrm2011_qrtl Monthly average # of all crimes in 2011 – quartile
- violent2011 Monthly average # violent crimes in 2011
- violent2011_qrtl Monthly average # violent crimes in 2011 – quartile
- vctzdiconce18 JVQ conventional crime victimization 2-cat – elder
- polyvctzce18 Polyvictimisation 4 cat (0,1,2,3+) - P18 - Elder
- Location1_Type Type of primary address provided at age 18
- Location2_Type Type of second address provided at age 18
- Location3_Type Type of third address provided at age 18
- ph18code_num_L2 ONS urbanicity (number code 1-10) – Location 2
- ph18cat_num_L2 ONS urbanicity (categorical least to most urban) – Location 2
- ph18code_num_L3 ONS urbanicity (number code 1-10) – Location 3
- ph18cat_num_L3 ONS urbanicity (categorical least to most urban) – Location 3
- neigbrhde1218 Neighbourhood address across phases 12 and 18 – Elder
- cohabe18 Twins living together at age 18 – Elder
- zrpgsSCZ participant polygenic risk scores for schizophrenia
- zrpgsSCZmat mother polygenic risk scores for schizophrenia

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Data Security Agreement

Provisional Paper Title	Is genetic risk for schizophrenia associated with urban residency and related risk factors during upbringing? Findings from a longitudinal cohort study.
Proposing Author	Joanne Newbury
Today's Date	20/08/2018

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: Is genetic risk for schizophrenia associated with urban residency and related risk factors during upbringing? Findings from a longitudinal cohort study.

Potential co-authors: Helen Fisher, Louise Arseneault, Terrie Moffitt, Avshalom Caspi, Candice Odgers, Daniel Belsky

Potential Journals:

Intended Submission Date (month/year): 02/19

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: .....