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

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Provisional Paper Title: Is air pollution associated with adolescent psychotic experiences? Findings from a UK cohort study

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Objective of the study and its significance:

Background

An extensive body of research demonstrates that individuals who are born and raised in cities have a two-fold adulthood risk for psychotic disorder (Allardyce et al., 2001, Lewis et al., 1992, Pedersen and Mortensen, 2001, Sundquist et al., 2004, van Os et al., 2001, Vassos et al., 2012). Given that 70% of the world's population will be urban by 2050 (Dye, 2008), understanding the mechanisms linking the urban environment to psychosis is an increasingly urgent public health priority.

Growing evidence from the E-Risk study (Newbury et al., 2016, 2017a, Newbury et al., 2017b) and others (Lundberg et al., 2009, Mimarakis et al., 2018, Singh et al., 2014, Spauwen et al., 2004) has now identified significantly higher rates of early psychotic phenomena among children, adolescents, and young adults living in urban versus rural neighbourhoods. Our research has shown that adverse neighbourhood social conditions including higher levels of disorder and lower levels of social cohesion only partly explain this association (Newbury *et al.*, 2016, 2017a, Newbury *et al.*, 2017b), indicating that other aspects of the neighbourhood (such as pollution) are likely to be involved. These early expressions of psychosis are thought to lie on a phenotypic and aetiological continuum with adult psychotic disorder, making them a prime target for intervention as well as a useful paradigm to investigate the pathogenesis of psychosis.

However, very little is currently known about the potential role of air pollution in early psychotic phenomena. Pollution is a worldwide health issue (Health Effects Institute, 2010,

World Health Organization, 2013), but is a particular problem in highly urban areas such as London where air pollution levels consistently exceed limits set by WHO and the European Union (Beevers *et al.*, 2016). Air pollutants such as nitrogen dioxide (NO_2) and particulate matter ($PM_{2.5}$) are implicated in a range of physical health problems including cardiovascular and respiratory disease (Kelly and Fussell, 2015, Rückerl *et al.*, 2011). Post-mortem studies have also revealed air pollutants in brain tissue (Calderón-Garcidueñas *et al.*, 2008). Once in the brain, air pollutants could increase risk for psychopathology by triggering neuroinflammation and oxidative stress (Block and Calderón-Garcidueñas, 2009), with infants and children potentially being most vulnerable due the young brain's rapid development. Associations have been documented between air pollution and anxiety (Power *et al.*, 2015), depression (Szyszkowicz *et al.*, 2009), and suicidality (Bakian *et al.*, 2015). However, only one study has investigated the association of air pollution with psychotic disorder (Pedersen *et al.*, 2004), and this study used a proxy for air pollution (distance to roads). Research using direct, high resolution measures of pollution is needed.

Recent pilot work by E-Risk investigators has demonstrated associations between air pollution levels at age 12 and depression and conduct disorder at age 18 in a London subsample of E-Risk participants (Roberts et al., under review). In collaboration with the MRC-PHE Centre for Environment and Health and following ascertainment of a NERC-MRC-CSO grant, extremely high resolution annualized estimates of 4 key air pollutants have been linked to the home addresses and two additional addresses of the entire E-Risk sample in 2012, the year prior to the age 18 assessments. Pollution estimates were modelled using CMAQ-urban, which uses a new generation of road traffic emissions inventory to model air quality down to individual streets at 20m grid points throughout the UK. Participants' exposure to pollutants – including NO_x (measure of road traffic), $PM_{2.5}$ and PM_{10} (particulate matter), NO_2 (regulated pollutant), and O_3 (ground level ozone) – has been estimated by averaging the levels of the specific pollutant across the year at each of the three locations participants reported spending most of their time, and then averaging this across the three locations.

Objectives

This study will test the role of air pollution exposure (in the year prior to the age 18 assessment) in the association between urban residency and adolescent psychotic experiences reported at age 18.

1) We will calculate the levels of air pollution in rural, intermediate, and urban settings, to check whether air pollution levels vary by degree of urbanicity in the E-Risk sample.
2) We will then test whether exposure to any of the air pollutants is associated with adolescent psychotic experiences.
3) We will then test the extent that air pollution exposure mediates the association between urban residency at age 12/18 and adolescent psychotic experiences at age 18.

Analyses will be adjusted for key potential confounders, including neighbourhood SES and crime rates, neighbourhood social processes, family SES, family psychiatric history, maternal psychosis, smoking at age 18, cannabis and alcohol use at age 18, and earlier

childhood psychotic symptoms.

Significance

Understanding the mechanisms linking the urban environment to the emergence of psychotic symptoms and disorders is an increasingly urgent public health priority. This study will be the first to use high resolution measures of air pollution to test the role of exposure to pollution in the association between urban upbringing and early psychotic phenomena. This study will therefore provide insights into the basis of previous and future findings on the urbanicity-psychosis association. In addition, given that late adolescence heralds the peak age of risk for a first episode of psychosis, the findings from this study will inform early intervention and urban policy efforts to improve the mental health of youth in cities.

Statistical analyses:

1) Are levels of air pollution higher in urban neighbourhoods?

- Annualized estimates of the four pollutants (NO_x, $PM_{2.5}$/PM_{10}, NO_2, O_3) for the home addresses and the combined exposure (home plus 2 additional addresses) will be stratified by degree of urbanicity (rural/intermediate/urban) at age 18.
- Linear regression will be used to test whether urbanicity is associated with pollution levels.

2) Are any of the four air pollutants associated with adolescent psychotic experiences? Are any of the four air pollutants associated with clinically-verified adolescent psychotic symptoms?

- Ordinal logistic regression will be used to test whether annualized estimates of air pollution (home and combined exposure) are associated with age-18 psychotic experiences.
- To test sensitivity, logistic regression will be used to test whether air pollution is also associated with clinically-verified age-18 psychotic symptoms.
- Analyses will be adjusted for neighbourhood SES and crime rates, neighbourhood social processes, family SES, family psychiatric history, maternal psychosis, smoking at age 18, cannabis and alcohol use at age 18, and earlier childhood psychotic symptoms.

3) Do pollution levels mediate the association between urban residency at age 12/18 and adolescent psychotic experiences.

- KHB pathway decomposition will be used to check the extent that air pollution exposure (home and combined) mediates the association between urban residency at age 12 and psychotic experiences at age 18. In this longitudinal model, analyses

will be restricted to participants who did not move house between ages 12 and 18 (71.4%).

- KHB pathway decomposition will also be used to test in a cross-sectional model whether air pollution levels mediate the association between age-18 urbanicity and adolescent psychotic experiences.
- Analyses will be adjusted for neighbourhood SES and crime rates, neighbourhood social processes, family SES, family psychiatric history, maternal psychosis, smoking at age 18, cannabis and alcohol use at age 18, and earlier childhood psychotic symptoms.

All analyses will account for the nonindependence of twin observations using the CLUSTER command in STATA.

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
- ph5code_num — ONS urbanicity (number code 1-10)
- ph5cat_num — ONS urbanicity (categorical least to most urban)

Age 7

- p7cacorn — Neighbourhood deprivation
- ph7code_num — ONS urbanicity (number code 1-10)
- ph7cat_num — ONS urbanicity (categorical least to most urban)

Age 10

- p10cacor — Neighbourhood deprivation
- 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)
- p12cacor — Neighbourhood deprivation
- 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

- fhanypm12 Family psychiatric history
- psysym12 Mother psychosis – symptom count
- lc5m12 N changes of address – since age 10

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

- smkcnume18 Smoking current (number of cigarettes), elder
- smkcnumy18 Smoking current (number of cigarettes), younger
- smkdlye18 Ever a daily smoker, elder
- smkdlyy18 Ever a daily smoker, younger

- p18cacor Neighbourhood deprivation
- ph18code_num ONS urbanicity (number code 1-10)
- ph18cat_num ONS urbanicity (categorical least to most urban)
- Index of multiple deprivation at age 18

- ttlcrm2011_qrtl Total crime for 2011, quartile
- neigbrhde1218 Neighbourhood address across phases 12 and 18 – Elder
- twin18e18 Live with twin at age 18 – Elder

Pollution data

Primary (home) address

- Location1.PM_{10}
- Location1.$PM_{2.5}$
- Location1.NO_x
- Location1.NO_2
- Location1.O_3

Address 2

- Location2.PM_{10}
- Location2.$PM_{2.5}$
- Location2.NO_x
- Location2.NO_2
- Location2.O_3

Address 3

- Location3.PM_{10}
- Location3.$PM_{2.5}$
- Location3.NO_x
- Location3.NO_2
- Location3.O_3

Address 4

- Location4.PM_{10}
- Location4.$PM_{2.5}$
- Location4.NO_x
- Location4.NO_2
- Location4.O_3

Address 5

- Location5.PM_{10}
- Location5.$PM_{2.5}$
- Location5.NO_x
- Location5.NO_2
- Location5.O_3

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Data Security Agreement

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Proposing Author	Joanne Newbury
Today's Date	18/12/17

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

JN I am current on Human Subjects Training (CITI (www.citiprogram.org) or training in human subject protection through my post or courses.

JN My project is covered by Duke or King's IRB OR I have /will obtain IRB approval from my home institution.

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 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 Terrie or Avshalom 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 manuscript gets accepted for publication.

JN I will return all data files to the Data Manager after the project is complete. Collaborators and graduates of DPPP may not take a data file away from the DPPP office. The data remains the property of the Study and cannot be used for further analyses without express, written permission.

JN 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)

Signature: