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

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Provisional Paper Title:
Association of childhood air pollution exposure with adolescent psychopathology.

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Objective of the study and its significance:

Background

Ambient outdoor air pollution is a ubiquitous environmental toxicant estimated to cause 4.2 million premature deaths worldwide each year.[1] Long known to damage the heart and lungs, air pollution exposure is now recognized as capable of causing systemic harm to all organ systems.[2]

Air pollutants may reach the brain directly, through translocation of ultrafine particles (those with diameters <0.1microns) across the nasal olfactory nerve or blood-brain barrier, and indirectly, through inflammatory signaling from other organ systems, particularly the lungs.[3,4] Air pollution exposure has consequently been linked to diverse CNS damage, including chronic neuroinflammation, breakdown of the blood-brain barrier, glial cell dysregulation, cerebral hypoperfusion, abnormal tau and amyloid beta accumulation, widespread vascular damage, and, in children, global impairments to gray and white matter structural integrity, neuron proliferation, and signaling cascades.[5–7]

While the cellular effects of air pollution exposure are well-described, the functional consequences have yet to be fully characterized. In particular, emerging evidence has implicated air pollution exposure in risk for varied developmental and neurobehavioral disorders, including autism, attention deficit hyperactivity disorder, depression, anxiety, bipolar disorder, and schizophrenia.[8–13]

This existing evidence base has limitations. First, most previous studies are cross-sectional, limiting causal inference. Second, most are left-hand censored, having primarily examined disorders among adults, making it difficult to determine what role air pollution may have played in the original development of psychiatric symptoms, which tend to first emerge in childhood and adolescence.[14] Third, they have primarily considered distinct disorder diagnoses, overlooking the dimensional aspect of mental illness and the high likelihood of comorbidity.[15] Fourth, few have attempted to rule-out self-selection into poor-air-neighborhoods by families with liability to mental illness, or, additionally, to rule-out the influence of correlated neighborhood

factors that characterize poor-air-environments (e.g., poverty, crime, dilapidation).[16,17] Fifth, few have evaluated potential moderating factors.

This study seeks to evaluate the association between air pollution exposure in childhood and the development of mental illness in late adolescence, at the transition to adulthood, using 1) longitudinal measures of exposure across childhood and adolescence, 2) a continuous measure of general liability to psychopathology, the p-factor, and the three correlated higher-order factors of internalizing, externalizing, and thought disorder symptoms, 3) high-quality measures of neighborhood characteristics related to socioeconomic disadvantage, including deprivation, dilapidation, disconnection, and dangerousness, and 4) a measure of the potentially moderating factor of residential neighborhood greenery, which alters air pollutant dispersion, particularly from motor vehicles,[18,19] and is believed to modify air-polllution-health associations.[20–22]

Significance

According to the World Health Organization (WHO), 9 out of 10 people currently breathe polluted air.[1] If it indeed causally contributes to psychiatric symptoms, air pollution would represent the most ubiquitous risk factor for mental illness yet discovered. Better evidence about the role that air pollution may play in the development of mental illness will inform future research about the etiology of psychiatric disease, clinical approaches to preventing disease, and public policy regarding transportation, energy production, and sustainable development.

Research questions and statistical analyses

The study analyses will take the following sequence:

1. Description of air pollution exposure in the E-Risk cohort.
    - Two measures of E-Risk Study members' estimated annual exposure to ambient outdoor air pollution will be utilized for this study: 1) annual exposure to nitrogen dioxide (NO_2), which is primarily associated with vehicle emissions, and 2) annual exposure to fine particles with an aerodynamic diameter below 2.5microns ($PM_{2.5}$), which are primarily associated with fuel burning facilities, such as powerplants and waste incinerators. These pollutants were chosen because they are common components of air pollution mixtures, have different aerodynamic properties and emission sources, have well-described cytotoxic properties, have been implicated in CNS pathology in experimental studies, and have existing global WHO guideline health-risk thresholds.
    - Descriptive statistics will be generated for both measures at age 10 and age 17, including the bivariate correlation between the two and their relationship to measures of community urbanicity and family and neighborhood-level SES.

2. Testing associations between air pollution and mental illness.
    - Using Ordinary Least Squares multiple regression, we will test the association of E-Risk Study member annual exposure to ambient outdoor air pollution at age 10 and 17 (averaged together) with overall mental health at age 18, using the continuous general psychopathology "p-factor" as the *primary outcome*.
        - Sensitivity analyses will repeat the primary tests using the two pollution exposure estimates separately at age 10 and 17 to test differential associations by age of exposure.
        - Sensitivity analyses will also repeat the primary tests using a test of "extremes," comparing individuals with the highest quartile of pollution exposure to those in the lowest quartile using logistic regression.

- Secondary analyses will use the continuous correlated psychopathology higher-order factors (internalizing, externalizing, and thought disorder symptoms; *secondary outcomes*) to test for specificity in air-pollution-related mental health differences.
- All associations will be evaluated in: 1) a basic model controlling for sex and ethnicity; 2) a family-covariates-adjusted model controlling for sex, ethnicity, family SES, and family history of mental illness to rule out self-selection into poor-air-quality neighborhoods by families with low socioeconomic status or proxy genetic liability to psychopathology, and 3) a child mental health problems-adjusted model controlling for sex, ethnicity, and age 5-7 measures of mental health problems (internalizing and externalizing scales) to rule out pre-existing symptoms.

2. Ruling out potentially correlated aspects of the neighborhood space.
- In most communities air pollution exposure co-occurs with other disadvantageous characteristics of the neighborhood environment that could account for air pollution-related mental health differences.[18] In this second analytic step, significant associations found in the first step will be subjected to additional stepwise covariate adjustment for the neighborhood variables comprising the Ecological Risk Index (deprivation, dilapidation, disconnection, and dangerousness) separately and then simultaneously via the Ecological Risk Index.

3. Testing potential moderation by residential neighborhood greenery.
- Leafy vegetation has been found to alter transport and dispersion of air pollutants such as NO_2 and $PM_{2.5}$.[18,19,21] This has been proposed as one causal mechanism underlying associations between residential neighborhood greenery and mental health outcomes that have been reported in diverse populations across multiple countries.[22–24] Moderation of the air pollution-mental illness association by ambient green vegetation surrounding the home will be modeled by adding a residential greenery measure (the Normalized Difference Vegetation Index, NDVI, averaged across age 10, 12, and 18) to the covariate-adjusted models built in the first analytic step along with a greenery*air pollution interaction term.

All analyses will be adjusted for the non-independence of twin observations using the Robust Cluster command in Stata to provide robust standard errors adjusted for within-cluster correlated data.

Significant findings may be subjected to additional sensitivity tests restricting the sample to children who did not move prior to age 10, or from age 10 to age 18. If space allows additional sensitivity tests may also investigate air pollution associations with dichotomous mental disorder diagnoses at age 18.

Variables Needed at Which Ages (names and labels):

Study: E-Risk Study & Community Strength Project

Note. Variables highlighted in yellow are in the process of being added to the data dictionary

General Measures:

- familyid — Unique family identifier
- atwinid — Twin A ID (ex chkdg)
- btwinid — Twin B ID (ex chkdg)
- rorderp5 — Random Twin Order
- sampsex — Sex of Twins: In sample
- sethnic — Ethnicity of twin
- nmovel510 — Number of residence changes 5 to 10, LHC

- lc5m12 N changes of address – since age 10
- ph10code_num ONS urbanicity (number code 1-10)
- ph10cat_num ONS urbanicity (categorical least to most urban)
- ph18code_num ONS urbanicity (number code 1-10)
- ph18cat_num ONS urbanicity (categorical least to most urban)
- neigbrhde1218 Neighbourhood address across phases 12 and 18 – Elder

Predictors:

- Location1_NO2_E_P10 NO2 levels at address location 1, age 10
- Location1_PM2_5_E_P10 PM2.5 levels address location 1, age 10
- Location1_NO2_E NO2 levels at address location 1, age 17
- Location1_PM2_5 _E PM2.5 levels address location 1, age 17

Outcomes:

- ph_e P-factor, hierarchical, age 18
- intcf_e Internalizing, 3-factor, age 18
- extcf_e Externalizing, 3-factor, age 18
- thdcf_e Thought disorder, 3-factor, age 18
- dxmdee18 Major depressive episode, age 18
- dxgade18 Gen Anxiety Disorder, age 18
- dxadhd5x_18e DSM-5 ADHD diagnosis, age 18
- dxptsd5lfe18 PTSD lifetime dx, DSM-V, age 18
- dxdrg5e18 Substance use disorder, dsm5

Covariates:

- seswq35 Social class composite
- fhanypm12 Proportion of family members who have any mental disorder, age 12
- totexte5 Total Mum & Teacher Externalising Scale at 5
- totexte7 Total Mum & Teacher Externalising Scale at 7
- totemoe5 Total Mum & Teacher emotional scale (ex somatic) at 5
- totemoe7 Total Mum & Teacher emotional scale (ex somatic) at 7
- zdeprived C-strengths “deprived” neighborhood
- zdirty C-strengths “dilapidated” neighborhood
- zdisorganized C-strengths “disconnected” neighborhood
- zdangerous C-strengths “dangerous” neighborhood
- ecorisk C-strengths Ecological Risk Index

Moderators:

- NDVIhome10 Normalized difference vegetation index (NDVI), age 10
- NDVIhome12 Normalized difference vegetation index (NDVI), age 12
- NDVIhome18 Normalized difference vegetation index (NDVI), age 18

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Data Security Agreement

Provisional Paper Title	Association of childhood air pollution exposure with adolescent psychopathology
Proposing Author	Aaron Reuben
Today's Date	March 30th 2020

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

AR 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/).

AR My project has ethical approval from my institution.

AR 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.

AR 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.

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

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

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

AR 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.

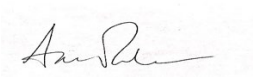
AR Before submitting my paper to a journal, I will submit my draft manuscript and scripts for data checking, and my draft manuscript for co-author mock review, allowing three weeks.

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

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

AR **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)

AR **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:  .....