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

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Provisional Paper Title:
Air pollution exposure and mental health outcomes in young adulthood: a genetically-sensitive cohort study.

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Objective of the study and its significance:

Air pollution is a worldwide environmental health issue [1, 2]. Reports have demonstrated that exposure to high levels of pollution is a strong risk factor for poor cardiovascular and respiratory outcomes [3, 4], possibly due to inflammation and oxidative stress [5]. Pollution varies widely across the UK with, for example, long-range transport of $PM_{10/2.5}$ resulting in the largest concentrations in the south-east, reducing north-west. Superimposed on this UK trend is exposure within cities, where vehicles represent the most important local ground-level source of air pollution emissions, and result in large within-city variation in human exposure to $PM_{10/2.5}$, NO_2 and O_3.

Interestingly, reports suggest that pollution may also have an effect on facets of cognitive functioning, behaviour, and mental health outcomes. Studies utilizing spatiotemporal modelling to estimate the effects of specific pollutants on children have implicated exposure as a risk factor in childhood ADHD [6], poor cognitive functioning in both children [7] and adults [8], anxiety [9], depression [10], and suicidality [11, 12]. Studies employing cruder measures of pollution (e.g. traffic density, proximity to roads, comparisons between high and low polluted cities) also produce similar results; school attendance in a high traffic density area was associated with significant reductions in psychomotor functioning and attention even after controlling for a number of socioeconomic factors [13], whilst proximity to a freeway was associated with autism [14]. Moreover, a recent population-based study using a very crude measure of mental health outcome, found increased rates of dispensed psychiatric medication amongst children and adolescents living in areas with higher air pollution concentrations [15]. Identification of such modifiable risk factors is crucial to inform the development of interventions to prevent mental ill-health.

However, few studies have assessed these associations utilising high-resolution measures of air pollution nationally, and using high-quality individual phenotype data collected prospectively. We previously conducted a pilot study in the E-Risk cohort examining the association between annualised estimates of exposure to two pollutants ($PM_{2.5}$ and NO_2) and concurrent and later mental health outcomes (anxiety, depression, ADHD, and conduct disorder). This pilot was restricted to twins residing in the London area at age 12, and air pollution exposure estimates were available for their home address in 2007 (at ~age 12) from concentrations modelled by the MRC-PHE Centre for Environment and Health's London Air Quality Toolkit at a resolution of 20m x 20m. In this subsample, we found preliminary evidence suggestive of an association between exposure to higher air pollution at age 12 and diagnoses of depression and conduct disorder at age 18.

Following ascertainment of a NERC-MRC-CSO grant, air pollution exposure has now been estimated for E-Risk participants' residential addresses (and the two other locations they report spending most of their time) during 2012 for the whole sample (where address data was available). This was achieved by modelling pollution exposure using CMAQ-urban, which is a coupled regional Chemical Transport model and street-scale dispersion model. CMAQ-urban uses a new generation of road traffic emissions inventory in the UK and is able to model air quality from European scale down to individual streets, providing hourly estimates of 4 key pollutants at grid points 20m apart throughout the UK. This model can predict air pollution exposure down to address level. Participants' exposure to each pollutant has been estimated by averaging the levels of the specific pollutant across the year at each of the three locations they reported spending most of their time in, and then averaging this across the three locations. These annualised air pollution estimates have now been combined with the E-Risk phenotypic data thus paving the way for the proposed analysis.

In this study, we plan to investigate the association between these annualised air pollution exposure estimates and mental health problems reported at age 18 in the E-Risk study. Analyses will be adjusted for a range of potential confounders including neighbourhood socioeconomic status (SES) and crime rates at age 18, family SES, family psychiatric history, smoking at age 18, and exposure to victimisation in childhood or adolescence. Significant associations will also be additionally adjusted for the relevant mental health problem at age 12 to ensure that we are not just picking up on mental health problems that were already present in childhood. We will also capitalise upon: (i) the twin design to repeat the analysis in twins who lived apart at age 18 and thus may have recently been exposed to different levels of pollution to control for unmeasured familial confounders; and (ii) the existing pollution data for 2007 to examine longitudinal associations between changes in air pollution exposure and mental health problems in the London sub-sample.

Statistical analyses:

Descriptives
A description of exposure to each pollutant in the sample will be reported. Pollutants included are: NO_x (measure of road transport, with up to 47% thought to be vehicle-based), $PM_{2.5}$ and PM_{10} (particulate matter – all sources, sources related to vehicle exhaust and sources not related to vehicle exhaust considered separately), NO_2 (regulated pollutant), and O_3 (ground level ozone).

Then we will move on to address the following aims:

Research question 1
At age 18, are any measures of annualised air pollution exposure associated with a past-year diagnosis of anxiety, depression, ADHD or conduct disorder?

Logistic regression models will be used to test whether annualised estimates of air pollution exposure are associated with these outcomes at age 18. Each pollutant will be tested separately. All analyses will be adjusted for the non-independence of twin observations. Models will control for potential confounding factors:

Model 1: sex, ethnicity, neighbourhood SES (using the ACORN classification)
Model 2: sex, ethnicity, neighbourhood SES, family SES, family psychiatric history, childhood and adolescent victimization exposure, smoking at 18, and neighbourhood crime rates at 18

Additionally, for any significant associations we will check whether these still hold if we control for the relevant age-12 mental health symptoms/disorder to get a handle on the direction of the association.

Research question 2
At age 18, are any measures of annualised air pollution exposure associated with past-year symptoms of anxiety, depression, ADHD or conduct disorder?

Linear regression models will be used to test whether annualised estimates of air pollution exposure are associated with these symptoms at age 18. Each pollutant will be tested separately, and models will control for potential confounding factors as above.

Research question 3
Analyses will be repeated in the 150 twin pairs that were living apart at age 18 and thus may have been exposed to different levels of pollutants. Models will be used to correlate differences in air pollution exposure estimates with differences in mental health diagnoses and symptoms between twins, controlling for the confounding factors noted above where appropriate (e.g., smoking and victimisation). This will provide a more stringent control for unmeasured earlier familial (both genetic and environmental) confounding factors.

Exploratory analyses
Numbers permitting, a subsample of participants with air pollution exposure data available for 2007 and 2012 will be identified, and exploratory longitudinal analyses will investigate the association between changes in air pollution exposure estimates and changes in mental health problems over this time-period.

Variables Needed at Which Ages (names and labels):

Study: E-Risk

General variables
familyid (ID Family)
atwinid
btwinid
risks
cohort
sampsex
zygosity
sethnic - Ethnicity of Twins
seswq35 – social class composite

live with twin at age 12
twin18e18 – Live with twin at age 18, elder
neigbrhde1218 - Home address at phases 12 and 18 - Elder (same or different)
cohabe18 - Twins living together at age 18 - Elder *** (No YT)

Pollution variables
NO_x (year averages 2012)
$PM_{2.5}$ (year averages 2012)
PM_{10} (year averages 2012)
NO_2 (year averages 2012)
O_3 (year averages 2012)

Model fit information

variables received from CMAQ-Urban data for each location

Mental health variables at age 18

Age 18

Diagnoses
dxmdee18 – Major depressive episode, dsm 4, elder
dxmdey18 – Major depressive episode, dsm 4, younger
dxgade18 – Gen Anxiety Disorder, dsm4 based, elder
dxgady18 – Gen Anxiety Disorder, dsm4 based, younger
dxadhd5x_18e - DSM-5 ADHD Dx (based on >=5 Symp) [incl 4 NEET & meds], elder
dxadhd5x_18y - DSM-5 ADHD Dx (based on >=5 Symp) [incl 4 NEET & meds], younger
cdmode18 - Moderate Conduct Disorder (>=5 count), elder
cdmody18 - Moderate Conduct Disorder (>=5 count), younger

Symptoms
gadsxe18 – GAD symptom scale, elder
gadsxy18 – GAD symptom scale, younger
mdesxe18 – Major depressive episode symptom scale, elder
mdesxy18 – Major depressive episode symptom scale, younger
inf_adhd18e - Any informant ADHD symptoms, Max = 8, elder
inf_adhd18y - Any informant ADHD symptoms, Max = 8, younger
cdsxe18 – Conduct disorder – symptoms scale, elder
cdsxy18 – Conduct disorder – symptoms scale, younger

Confounders

Age 12

fhanypm12 – Family psychiatric history
ex_sve12 – Childhood exposure to severe victimization

cdie12 – Depression scale - CDI, elder
masce12 – Anxiety scale – MASC, elder
tadhdem12 - Total Inattentive/Hyperactive/Impulsive - 2 Count - elder
cdtotcrit_esr12 - Tot CD criteria met p12_self-rpt, elder

cdicate12 - Clinically significant depression (CDI >= 20), elder
masccate12 - Extreme anxiety (>= 95th percentile), elder
dxcd_esr12 - CD dx @12, 5+ crit, self-rpt, elder
adhdd3xe12 - ADHD diagnosis - New Criteria [incl meds], elder

Age 18

polyvctzce18 - Poly-victimisation 4 cat (0,1,2,3+) - P18 - Elder

ttlcrm2011_qrtl - total crime for 2011, quartile

ACORN at age 18 – Tim is this available from Candice yet?

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

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Data Security Agreement

Provisional Paper Title	Air pollution exposure and mental health outcomes in young adulthood: a genetically-sensitive cohort study.
Proposing Author	Susanna Roberts
Today's Date	10th November 2017

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

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

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

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

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

SR__ 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., so we have a managed-access process. Speak to Terrie or Avshalom for strategies for achieving compliance with data-sharing policies of journals.

SR__ 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.

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

SR__ 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.

SR__ 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)

Signature: .... Susanna Roberts .....

CONCEPT PAPER RESPONSE FORM

A. To be completed by the proposing author

Proposing Author: Susanna Roberts

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

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Potential co-authors: Helen Fisher, Sean Beevers, Louise Arseneault, Nutthida Kitwiroon, Terrie Moffitt, Avshalom Caspi, Candice Odgers, Aaron Reuben, Frank Kelly

Potential Journals:

Intended Submission Date (month/year): February 2018

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: .....