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

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Provisional Paper Title: Long-term exposure to traffic-related air pollution and Attention Deficit Hyperactivity Disorder

Date: 22/03/2021

Objective of the study and its significance:

Air pollution exposure can harmfully affect neural structures through processes such as neural inflammation and central nervous system oxidative stress (Block & Calderón-Garcidueñas, 2009; Lucchini et al., 2012). Furthermore, air pollution has been linked to the presence and increased severity of several mental illnesses, including depression and anxiety (Braithwaite et al., 2019). However, there have been mixed results amongst studies focusing on the relationship between air pollution and Attention Deficit Hyperactivity Disorder (ADHD; Aghaei et al., 2019). Given the recent findings in birth cohort studies of a group of individuals that experience ADHD despite symptom-onset after the 12 years diagnostic cut-off, and the conceptualization of the persistent, remitted and late-onset ADHD groups in the E-Risk cohort, we wanted to examine how air pollution is related to these ADHD groupings (Agnew-Blais et al., 2016a; Agnew-Blais et al., 2016b; Agnew-Blais et al., 2018; Moffitt et al., 2015).

The objective will be as follows: the study will examine the relationship between air pollution exposure and ADHD trajectory (including membership in persistent, remitted, or late-onset ADHD groups) across childhood and early adulthood. We hypothesize that greater exposure to air pollution will be associated with increased risk of having ADHD and that higher exposure to air pollution will be associated with greater relative risk of being in late-onset and persistent, as compared to remitted, ADHD groups.

There is a possibility that changes in ADHD diagnosis between ages 10 to 18 is reflective of changes in some specific symptoms that can then alter diagnoses in borderline cases but that may not be reflected in all diagnoses. For instance, air pollution exposure has been specifically linked to reduced attention processes in primary school children, adolescents and even adults (Chen & Schwartz, 2009; Kicinski et al., 2015; Sunyer et al., 2017). For this reason, we will also examine whether changes in the severity and presence of symptoms in each factor (hyperactive/impulsive and inattentive), between childhood and early adulthood, are correlated with air pollution exposure.

Finally, neighborhood socioeconomic disadvantage has been associated with increased prescribing of ADHD medication and deterioration in inattention symptoms (Jablonska et al., 2020; Sharp et al., 2019). Previous research has also shown socioeconomic status (SES) to be an effect modifier for the relationship between air pollution and mortality (Ou et al., 2008). In terms of mental health, in adults (age 57-85), the association between air pollution and depression is also greater for those with a lower SES (Pun, Manjourides, & Suh, 2017). This study will thus also examine whether the association between air pollution exposure and ADHD differs according to neighborhood SES.

This study will add to the current literature by investigating whether longer-term exposure to air pollution exposure is a risk factor for ADHD and, if so, how it continues to affect ADHD presentation across childhood and early adulthood. The outcomes of this research will also contribute to our understanding of

the environmental risk factors for ADHD and could help ascertain if there are distinct risk profiles for different trajectories of ADHD. This would add not only to our understanding of the harmful effects of elevated air pollution exposure but could also have potential implications for public health interventions.

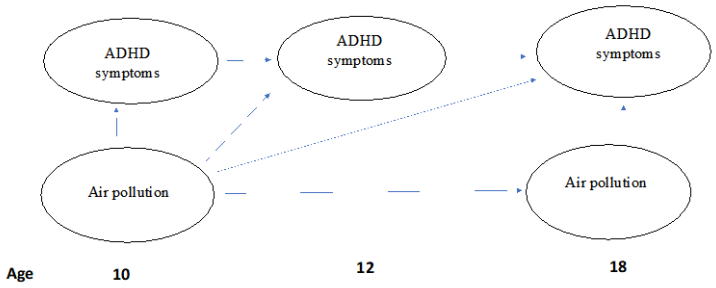
Statistical analyses

All analyses will be conducted with Stata/SE software version 16.0.

1. Descriptive analyses will be conducted to determine the distribution of ADHD groups across the sample with air pollution data available, and the distribution of the variables characterizing the sample and air pollution exposure for ages 10 and 18, across ADHD types.

2. Prospective and cross-sectional associations between air pollution exposure (age 10 and age 18) and ADHD and non-ADHD group membership at age 18 will be examined using multinomial regression models with the use of the cluster command to take into account clustering at the twin level.

3. Longitudinal associations between air pollution and ADHD symptom severity scores in the two dimensions, hyperactivity/impulsivity and inattention, will be examined with the use of 3-level random intercept Poisson or negative binomial models, taking into account twin membership as well as the repeated measures in the study. (Air pollution at ages 10 and 18, and ADHD symptoms at ages 10, 12 and 18). The relevant flow diagram is shown below.



4. Effect modification by neighborhood SES: In the fully-adjusted model, we will include an interaction term between the pollutants and neighborhood SES to examine whether SES modifies the relationship between air pollution and ADHD groups in a multilevel model.

We will control our analysis for the following a-priori confounders: First we will use an unadjusted model (taking into account clustering within families) to look at the associations between each of the pollutants and the ADHD types at both time points (model 1). We will then adjust our models for individual level factors: sex, family SES, family psychiatric history, smoking status, IQ at age 5, and externalizing and internalizing scores at age 5 (model 2). For the final analysis we will further adjust for neighborhood level factors, namely, urbanicity and neighborhood deprivation at age 10 (in addition to the individual factors).

Sensitivity analyses

Non-movers: A sensitivity analysis will be done with the fully adjusted model, excluding all the participants who had moved residences between the ages of 10 and 18, in order to ensure air pollution exposure is consistent over time (insofar as we can estimate it).

Variables Needed at Which Ages (names and labels):

Study: E-Risk
Sex *sampsex*

Family ID *familyid*

Age 5:
ADHD Diagnosis - New Criteria - P5 - Elder *ADHDD3E5*
Prorated IQ - measured using the WPPSI Revised *iqe5*
Family socioeconomic status (SES) *seswq35*
Internalizing symptoms (emotionality) *totemoe5*
Externalizing symptoms *totexte5*

Age 7:
ADHD Diagnosis - New Criteria - P7 – Elder A*DHDD3E7*

Age 10:
ADHD Diagnosis *adhdd3xe10*
Inattention 2 Count – Elder *INET10*
Hyperactive/Impulsive - 2 Count – Elder *HYET10*
Urbanicity *ph10urb_cat3*
Neighborhood deprivation- using ACORN *P10CACORNCategory*
Air Pollution Exposure- NO2, NOx, PM2.5, PM10 measured in 2004, modeled using CMAQ-urban, based on the twins' residential addresses. *Loc1_NO2_P10 Loc1_NOX_P10 Loc1_PM10_P10 Loc1_PM25_P10*

Age 12:
ADHD Diagnosis *adhdd3xe12*
Family psychiatric history- *fhanypm12*
Inattention 2 Count – Elder *INET12*
Hyperactive/Impulsive - 2 Count – Elder *HYET12*
Change in address between ages 10-12 *lc5m12*

Age 18:
ADHD Diagnosis *dxadhd5x_18e*
ADHD Dimension Symptom Scores (scored out of 9): For inattention *SR_INSUM18E* and hyperactivity/impulsiveness *SR_HYSUM18E*
ADHD Groups- Derived from the studies done by Agnew-Blais et al. (2016a; 2016b). *adhd4cate18*
Adolescent tobacco smoking: determined based on whether the participant reported ever having been a daily smoker (yes/no) *smkdlye18*
Change in address between ages 12-18 *neigbrhde1218*
Air Pollution Exposure- NO2, NOx, PM2.5, PM10 measured 2012, modeled using CMAQ-urban. *Loc1_NO2_E18 Loc1_NOx_E18 Loc1_PM2_5_E18 Loc1_PM10_E18 Loc2_NO2_E18 Loc2_NOx_E18 Loc2_PM2_5_E18 Loc2_PM10_E18 Loc3_NO2_E18 Loc3_NOx_E18 Loc3_PM2_5_E18 Loc3_PM10_E18*

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Data Security Agreement

Provisional Paper Title	Long-term exposure to traffic-related air pollution and Attention Deficit Hyperactivity Disorder
Proposing Author	Inika Sharma
Today's Date	26/01/2021

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

__IS__ 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/).

__IS__ My project has ethical approval from my institution.

__IS__ 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.

__IS__ 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.

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

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

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

__IS__ 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.

__IS__ 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.

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

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

__IS__ **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)

____ **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: ....Inika Sharma.....

CONCEPT PAPER RESPONSE FORM

A. To be completed by the proposing author

Proposing Author: Inika Sharma

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

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Potential Journals:

Intended Submission Date (month/year): September 2021.

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: .....