E-Risk Study Concept Paper template

Provisional Paper Title: Air pollution exposure in childhood and mental health disorders in early adulthood: exploring mediation via cognition in a UK longitudinal cohort study
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Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Background & objective of the study:

Air pollution is the largest environmental health priority and one of the most prominent risk factors for ill-health worldwide.[1] Outdoor air pollution research has tended to examine associations with either gaseous (e.g., Nitrogen oxides – NO_x) or particulate matter, defined by the size of material (e.g., $PM_{2.5}$ - particulate matter smaller than 2.5μm). Exposure to a variety of pollutants such as these have been associated with a host of physical health problems, such as cardiovascular or respiratory ill-health.[2,3] There is also a growing evidence base for associations with poorer mental health.[4–6]

Addressing mental ill-health is key global health priority as it is one of the leading causes of disability worldwide.[7] As between half to three-quarters of individuals with mental disorders have an age of onset by 18 years of age[8,9] it is crucial to identify risk factors in early life to guide preventive interventions. Exposure to higher levels of air pollution in childhood is one modifiable potential risk factor.[10]

However, substantial questions remain in the literature regarding air pollution exposure and development of mental health disorders[11] especially around the mechanistic pathways underlying these associations.[4] In prior E-Risk work on this topic, there has been examination of associations between air pollution exposure and psychotic experiences[12] and psychopathology as a continuous measure[13] but only two studies that focused on mental health disorders – one in a small London sub-sample of the E-Risk Study[14] and one in a highly selective risk subsample.[15] Such diagnostic categories can help inform policy action, as despite the commonalities across disorders seen in the general psychopathology factor 'p', services and systems are often designed around categories, which may mean that more effective communication and action with policymakers and clinicians may be possible utilising categorical outcomes. Therefore, this study aims to explore associations between childhood air pollution exposure and diagnosed mental health disorders in the full E-Risk cohort.

We will focus on specific mental health disorders over larger groupings, such as internalising disorders, which may obscure specific effects. Specifically, we will examine longitudinal associations between air pollution at age 10 and major depressive disorder, generalised anxiety disorder, attention-deficit hyperactivity disorder and conduct disorder at age 18. These disorders are prevalent in E-Risk,[16] and have a high impact in terms of years' lived with disability worldwide,[7]

and for which evidence after air pollution exposure is currently more consistent, such as depression or anxiety, though with some uncertainty remaining.[4,5] This will also reduce multiple testing that would occur utilising all available outcome categories.

Though putative mediators exist, such as neuroinflammation[4] there is limited evidence for any particular mechanism of action for how air pollution exposure could lead to the development of mental health disorders in humans. Cognition is one potential mediatory pathway as it is both associated with prior air pollution exposure,[17–19] and with subsequent poorer mental health in early life,[20–25] though there is mixed evidence for these associations.[26–28]

Exposure to air pollution has several proposed mechanisms of action in the brain.[4,17,29] Particulate matter may cross directly via the olfactory nerve or indirectly via pulmonary pathways to the brain.[17] Both PM and gaseous pollutants such as NO_2 may also trigger systemic inflammatory processes.[17] Secondary processes, like neurodegeneration, oxidative stress or disruption to cortical networks[30] may lead to changes in cognition.[4,17] However putative physical mechanisms manifest, these could lead to cognitive outcome changes, such as poorer IQ and working memory. Deficiencies in these may then lead to increased risk for externalising disorders such as conduct disorder[31] and ADHD,[32] possibly through poorer emotional control and increased aggression in social situations,[33] or poorer educational performance.[34] For internalising disorders such as depression and anxiety, similar pathways may exist, such as through poorer academic achievement.[34]

A previous study utilising E-Risk data[35] found that cognitive ability partly mediated the association between childhood socioenvironmental adversity (which included air pollution exposure) and subclinical psychotic phenomena in adolescence. However, no studies to date have explored whether general and specific aspects of cognition might mediate associations between exposure to different air pollutants during childhood and a range of mental disorders in early adulthood.

Therefore, our objectives are:

1) To investigate associations between exposure to different air pollutants at age 10 (NO_2, NO_x, $PM_{2.5}$, PM_{10}) and four common mental health disorders at age 18 (major depressive disorder, generalised anxiety disorder, ADHD, conduct disorder).
2) To explore whether overall cognitive ability at age 12 mediates the association between exposure to each air pollutant at age 10 and each mental health disorder at age 18.
3) To explore whether specific cognitive domains of crystallised ability, fluid ability, and working memory at age 12 mediate the association between exposure to each air pollutant at age 10 and each mental health disorder at age 18.

Significance of the study (for theory, research methods or clinical practice):

It is hoped that understanding associations between air pollution and mental health disorders can help policy makers and health service providers make informed decisions on air pollution reduction plans and subsequent expected improvements in mental health for young people. Further assessment of mediatory pathways could provide understanding on how reduction in air pollution might have an ongoing benefit, where reduction in exposure could improve mental health disorders and IQ / working memory in this age range. It may also indicate potential targets for preventive interventions where exposure to high levels of air pollution cannot be avoided.

Data analysis methods:

We will utilise STATA 18.0 MP. We will consider the level of missingness in the data. If missing data can be predicted by observed data and it is likely missing at random, we will utilise multiple imputation through chained equations to impute missing data for covariates only. Analyses will initially be conducted without any covariates and then re-run including assigned sex at birth, family socioeconomic status (SES) (assessed at age 5), neighbourhood deprivation (averaged across ages 5–10), family psychiatric history (assessed at age 12) and tobacco smoking up to 18 years of

age. Note, prior to analysis, the air pollutants will be rescaled to interquartile range increments, to facilitate comparison of statistical effect sizes across air pollutants with different absolute concentration ranges.

Our main analyses will assess:

1) That higher air pollution exposure at age 10 is associated with higher odds of mental health disorders at age 18

We will separately test the associations between NO_2, NO_x, $PM_{2.5}$ and PM_{10} at age 10 with each diagnostic outcome of generalised anxiety disorder, major depressive disorder, conduct disorder, and attention-deficit hyperactivity disorder at age 18 using binary logistic regression and taking into account the non-independence of data obtained from twins by use of the CLUSTER command. We will report associated odds ratios (OR) and 95% confidence intervals (CIs), representing the increased odds for a disorder per IQR increase in exposure.

2) That statistically significant adjusted associations between higher air pollution exposure at age 10 and mental health disorders at age 18 ($p<0.05$) are partially mediated by cognitive ability total score at age 12

Statistically significant adjusted associations (at $p<0.05$) between each pollutant and mental health disorder (generalised anxiety disorder, major depressive disorder, conduct disorder, and attention-deficit hyperactivity disorder) will be taken forward to the mediation analysis. We will test the associations between each pollutant at age 10 and mental disorders at age 18 with overall cognitive ability scores (IQ) at age 12 as a single mediator (Figure 1).

We will utilise a generalised parametric structural equation modelling approach, which is a statistical technique to test different pathways of the effect of pollutants' exposure on mental health disorders (gsem package in Stata version 18.0 MP), and will allow for us to account for the non-independence of data obtained from twins.

We will use *gsem* to partition the total effect (TE) of each relevant pollutant at age 10 on each relevant mental health disorder at age 18 into the natural direct effect (NDE) (the effects not mediated via overall cognitive ability score) and the natural indirect effect (NIE) (the effects mediated via overall cognitive ability score). We will report the proportion of the effect mediated by overall cognitive ability (NIE/[NDE + NIE]). We will estimate these using bootstrapping (with 500 replications) to recover the correct SEs for direct and indirect effects. We will report associated odds ratios (OR) and 95% confidence intervals (CIs), representing the increased odds for a disorder per IQR increase in exposure. Statistical significance will be set *a priori* at $p < 0.05$.

3) That statistically significant adjusted associations between higher air pollution exposure at age 10 and mental health disorders at age 18 ($p<0.05$) are partially mediated by cognitive ability sub-domains (crystallised ability, fluid ability, and working memory) at age 12

We will use a multiple mediator model following a two-step procedure (Figure 2):

a) First step: We will first test the associations between each pollutant at age 10 and multiple continuous mediators of cognitive ability subdomains (crystallised ability, fluid ability, and working memory) at age 12 with the use of linear regression models. We *a priori* define a p-value lower than 0.15 to select appropriate mediators to include in our final mediation analyses.[36] Multiple mediators require independence from each other, so we will test independence by examining partial correlations between our mediators after accounting for the non-independence of data obtained from twins.

b) Second step: We will assess correlation between the subdomains of cognition included from the first step. If there is a correlation coefficient of 0.7 or greater between any two subdomains, then we will examine each subdomain as mediators in step three in independent models. If all

coefficients are below 0.7, we will proceed as follows, with an additional sensitivity analysis to examine each subdomain as a separate mediator.

c) Third step: We will use a generalised parametric structural equation modelling approach. We will estimate the total effect through estimating the NIE and NDE of the effect of pollutant exposure on generalised anxiety disorder, major depressive disorder, conduct disorder, and attention-deficit hyperactivity disorder. The NDE represents the effect of pollutant exposure on mental health disorders that was independent of crystallised ability, fluid ability, and working memory. The NIE represents the proportion of the pollutant exposure that could be explained by its effect with changes in crystallised ability, fluid ability, and working memory.

As above, to quantify the magnitude of mediation, we will report the proportion of the total effect (TE) mediated by crystallised ability, fluid ability, and working memory (NIE/[NDE + NIE]). We will estimate using bootstrapping (500 replications) to recover the correct SEs for direct and indirect effects. We will report associated odds ratios (OR) and 95% confidence intervals (CIs), representing the increased odds for a disorder per IQR increase in exposure. Statistical significance will be set *a priori* at $p < 0.05$ with no adjustment for multiple testing.

Sensitivity analyses:

Following prior E-Risk air pollution analyses, we will conduct four sensitivity analyses.[12,13] To address the high correlation between pollutants, we will re-run full model analyses utilising one gaseous and one particulate exposure. To assess the role of the highest levels of exposure, we will re-run full model analyses after dichotomising air pollution exposure into the top quartile vs the bottom three quartiles. To assess the role that moving address can have on air pollution exposure, we will repeat analysis after removing participants who moved before age 10, or between age 10 and 18. Lastly, to assess unmeasured confounding for the main association (objective 1), we will calculate and report the E-value, a statistical reporting of the strength of any unmeasured confounding.[37]

We will, conditional on step two of hypothesis 3, conduct an additional sensitivity analysis reporting the magnitude of mediation using each cognitive subdomain as a mediator in its own model, with the same reporting as in step three of hypothesis 3.

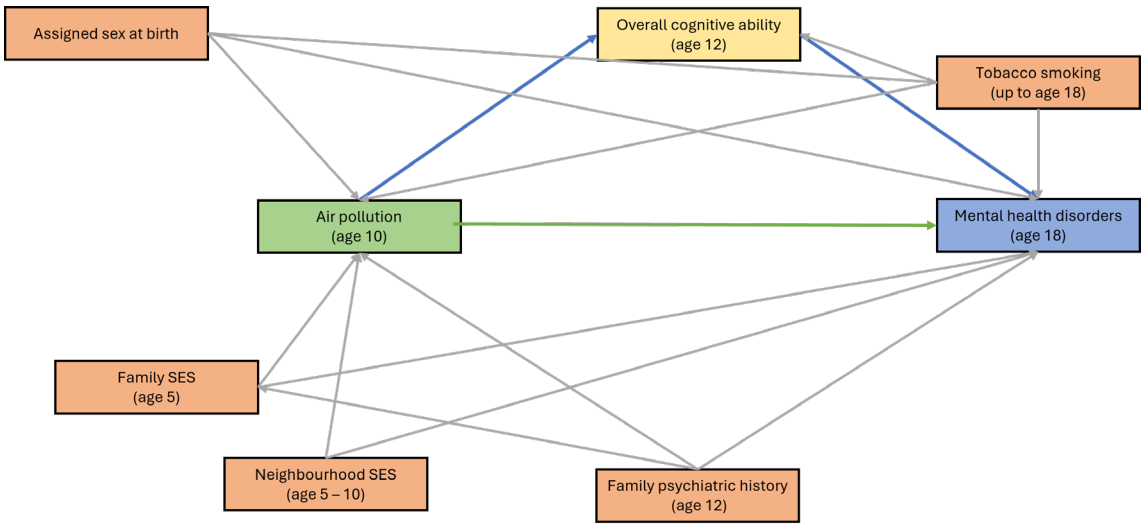

Figure 1 Directed Acyclic Graph for exposure, outcome, mediators and confounders proposed in this study for objective 2.. Green square = exposure, blue square = outcome, yellow square = mediator and red square = confounding variables. Blue lines represent the natural indirect effect, and green line represents the natural direct effect of air pollution exposure on mental health disorders. Grey lines represent confounding associations. SES = Socio-economic status

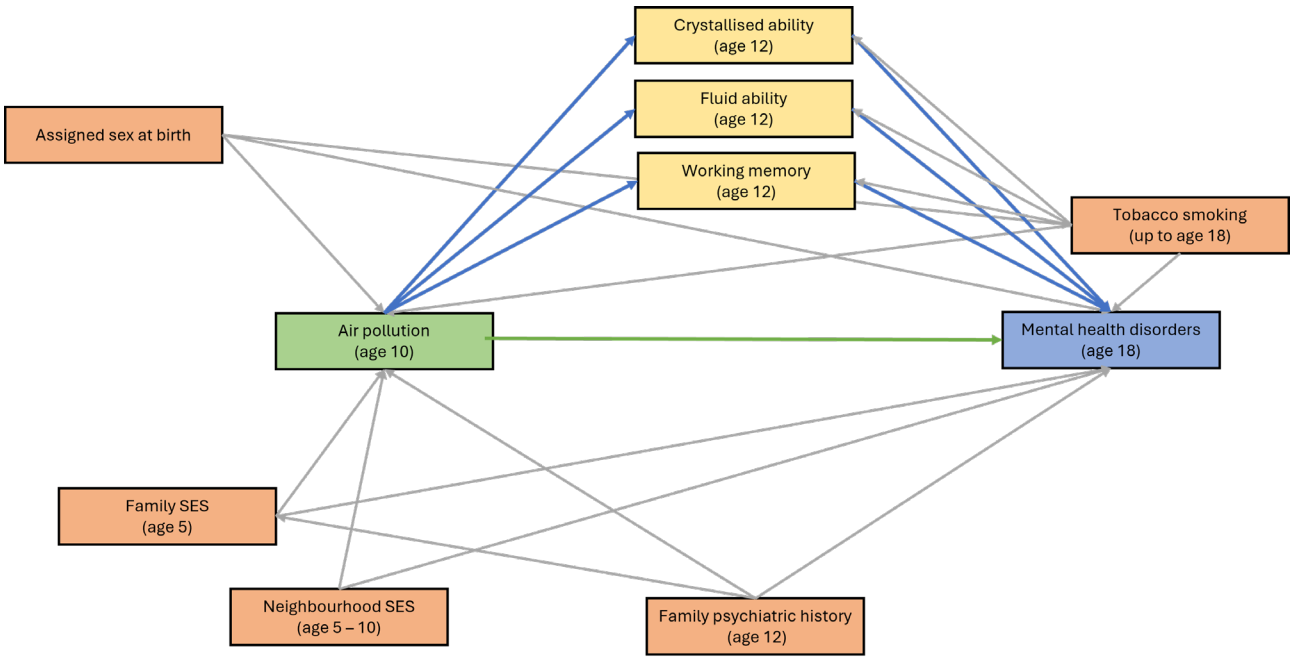

Figure 2 Directed Acyclic Graph for exposure, outcome, mediators and confounders proposed in this study for objective 3. Green square = exposure, blue square = outcome, yellow square = mediator and red square = confounding variables. Blue lines represent the natural indirect effect, and green line represents the natural direct effect of air pollution exposure on mental health disorders. Grey lines represent confounding associations. SES = Socio-economic status.

Variables needed and at which ages:

Age 5

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
SESWQ35	Social Class Composite
P5CACORNCategory	Acorn Category at Age 5 based on 2001 CENSUS

Age 7

P7CACORNCategory	Acorn Category at Age 7 based on 2001 CENSUS

Age 10

Home_NO2_P10	Nitrogen dioxide (µg/m³) - Home address - P10
Home_NOX_P10	Nitrogen oxide (µg/m³) - Home address - P10
Home_PM25_P10	Particulate matter 2.5 (µg/m³) - Home address - P10
Home_PM10_P10	Particulate matter 10 (µg/m³) - Home - P10
P10CACORNCategory	Acorn Category at Age 10 based on 2001 CENSUS
NMOVEL510	Number of residence changes 5 to 10, LHC

Age 12

FSIQ12E_STD	Standardised values of fsiq12e, m(100) sd(15) – Elder
MRE_SS12	Matrix Reasoning Scaled Score, 12E
INFE_SS12	Information Scaled Score, 12E

DSE_SS12	Digit Span Scaled Score, 12E
FHANYPM12	Proportion of family members with valid data with any psychiatric disorder
LC5M12	N changes of address – since age 10

Age 18

DXMDEE18	Major depressive episode, dsm4 – P18 – Elder
DXGADE18	Gen Anxiety Disorder, dsm4_based - P18 – Elder
DXADHD5X_18E	DSM-5 ADHD Dx (based on >=5 Symp) [incl 4 NEET & meds] - P18 – ET
CDMODE18	Moderate Conduct Disorder (>=5 count) - P18 - Elder
SMKDLYE18	Ever a daily smoker, elder
NEIGBRHDE1218	Neighbourhood address across phases 12 and 18 – Elder

References cited:

1. World Health Organization. WHO Global Air Quality Guidelines: Particulate Matter ($PM_{2.5}$ and PM_{10}), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide. World Health Organization; 2021. https://apps.who.int/iris/handle/10665/345329

2. COMEAP. Associations of Long-Term Average Concentrations of Nitrogen Dioxide with Mortality. Committee on the Medical Effects of Air Pollutants; 2018. https://www.gov.uk/government/publications/nitrogen-dioxide-effects-on-mortality

3. World Bank Group. The Global Health Cost of $PM_{2.5}$ Air Pollution: A Case for Action beyond 2021. World Bank; 2021. http://hdl.handle.net/10986/36501

4. Zundel CG, Ryan P, Brokamp C, et al. Air pollution, depressive and anxiety disorders, and brain effects: A systematic review. NeuroToxicology. 2022;93:272-300. doi:10.1016/j.neuro.2022.10.011

5. Braithwaite I, Zhang S, Kirkbride JB, Osborn DPJ, Hayes JF. Air pollution (particulate matter) exposure and associations with depression, anxiety, bipolar, psychosis and suicide risk: A systematic review and meta-analysis. Environ Health Perspect. 2019;127(12):126002. doi:10.1289/EHP4595

6. Borroni E, Pesatori AC, Bollati V, Buoli M, Carugno M. Air pollution exposure and depression: A comprehensive updated systematic review and meta-analysis. Environ Pollut. 2022;292:118245. doi:10.1016/j.envpol.2021.118245

7. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9(2):137-150. doi:10.1016/S2215-0366(21)00395-3

8. Solmi M, Radua J, Olivola M, et al. Age at onset of mental disorders worldwide: Large-scale meta-analysis of 192 epidemiological studies. Mol Psychiatry. 2022;27(1):281-295. doi:10.1038/s41380-021-01161-7

9. Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: Developmental follow-back of a prospective-longitudinal cohort. Arch Gen Psychiatry. 2003;60(7):709. doi:10.1001/archpsyc.60.7.709

10. Reuben A, Manczak EM, Cabrera LY, et al. The interplay of environmental exposures and mental health: Setting an agenda. Environ Health Perspect. 2022;130(2):25001. doi:10.1289/EHP9889

11. Bhui K, Newbury JB, Latham RM, et al. Air quality and mental health: Evidence, challenges and future directions. BJPsych Open. 2023;9(4):e120. doi:10.1192/bjo.2023.507

12. Newbury JB, Arseneault L, Beevers S, et al. Association of air pollution exposure with psychotic experiences during adolescence. JAMA Psychiatry. 2019;76(6):614. doi:10.1001/jamapsychiatry.2019.0056

13. Reuben A, Arseneault L, Beddows A, et al. Association of air pollution exposure in childhood and adolescence with psychopathology at the transition to adulthood. JAMA Netw Open. 2021;4(4). doi:10.1001/jamanetworkopen.2021.7508

14. Roberts S, Arseneault L, Barratt B, et al. Exploration of NO_2 and $PM_{2.5}$ air pollution and mental health problems using high-resolution data in London-based children from a UK longitudinal cohort study. Psychiatry Res. 2019;272:8-17. doi:10.1016/j.psychres.2018.12.050

15. Latham RM, Kieling C, Arseneault L, et al. Childhood exposure to ambient air pollution and predicting individual risk of depression onset in UK adolescents. J Psychiatr Res. 2021;138:60-67. doi:10.1016/j.jpsychires.2021.03.042

16. Meehan AJ, Latham RM, Arseneault L, Stahl D, Fisher HL, Danese A. Developing an individualized risk calculator for psychopathology among young people victimized during childhood: A population-representative cohort study. J Affect Disord. 2020;262:90-98. doi:10.1016/j.jad.2019.10.034

17. COMEAP. Cognitive decline, dementia and air pollution: A report by the Committee on the Medical Effects of Air Pollutants. Committee on the Medical Effects of Air Pollutants; 2022. https://www.gov.uk/government/publications/air-pollution-cognitive-decline-and-dementia

18. Castagna A, Mascheroni E, Fustinoni S, Montirosso R. Air pollution and neurodevelopmental skills in preschool- and school-aged children: A systematic review. Neurosci Biobehav Rev. 2022;136:104623. doi:10.1016/j.neubiorev.2022.104623

19. Lopuszanska U, Samardakiewicz M. The Relationship Between Air Pollution and Cognitive Functions in Children and Adolescents: A Systematic Review. Cogn Behav Neurol. 2020;33(3):157-178. doi:10.1097/WNN.0000000000000235

20. Khandaker GM, Stochl J, Zammit S, Goodyer I, Lewis G, Jones PB. Childhood inflammatory markers and intelligence as predictors of subsequent persistent depressive symptoms: a longitudinal cohort study. Psychol Med. 2018;48(9):1514-1522. doi:10.1017/S0033291717003038

21. Morales-Muñoz I, Upthegrove R, Mallikarjun PK, Broome MR, Marwaha S. Longitudinal associations between cognitive deficits in childhood and psychopathological symptoms in adolescence and young adulthood. JAMA Netw Open. 2021;4(4):e214724. doi:10.1001/jamanetworkopen.2021.4724

22. Glaser B, Gunnell D, Timpson NJ, et al. Age- and puberty-dependent association between IQ score in early childhood and depressive symptoms in adolescence. Psychol Med. 2011;41(2):333-343. doi:10.1017/S0033291710000814

23. Kjelkenes R, Wolfers T, Alnæs D, et al. Mapping normative trajectories of cognitive function and its relation to psychopathology symptoms and genetic risk in youth. Biol Psychiatry Glob Open Sci. 2023;3(2):255-263. doi:10.1016/j.bpsgos.2022.01.007

24. Koenen KC, Moffitt TE, Roberts AL, et al. Childhood IQ and adult mental disorders: A test of the cognitive reserve hypothesis. Am J Psychiatry. 2009;166(1):50-57. doi:10.1176/appi.ajp.2008.08030343

25. Flouri E, Papachristou E, Midouhas E, Ploubidis GB, Lewis G, Joshi H. Developmental cascades of internalising symptoms, externalising problems and cognitive ability from early childhood to middle adolescence. Eur Psychiatry. 2019;57:61-69. doi:10.1016/j.eurpsy.2018.12.005

26. Schaefer JD, Scult MA, Caspi A, et al. Is low cognitive functioning a predictor or consequence of major depressive disorder? A test in two longitudinal birth cohorts. Dev Psychopathol. Published online November 16, 2017:1-15. doi:10.1017/S095457941700164X

27. Beaujean AA, Parker S, Qiu X. The relationship between cognitive ability and depression: a longitudinal data analysis. Soc Psychiatry Psychiatr Epidemiol. 2013;48(12):1983-1992. doi:10.1007/s00127-013-0668-0

28. Scult MA, Paulli AR, Mazure ES, Moffitt TE, Hariri AR, Strauman TJ. The association between cognitive function and subsequent depression: a systematic review and meta-analysis. Psychol Med. 2017;47(1):1-17. doi:10.1017/S0033291716002075

29. de Prado Bert P, Mercader EMH, Pujol J, Sunyer J, Mortamais M. The effects of air pollution on the brain: a review of studies interfacing environmental epidemiology and neuroimaging. Curr Environ Health Rep. 2018;5(3):351-364. doi:10.1007/s40572-018-0209-9

30. Li Z, Yan H, Zhang X, et al. Air pollution interacts with genetic risk to influence cortical networks implicated in depression. Proc Natl Acad Sci. 2021;118(46):e2109310118. doi:10.1073/pnas.2109310118

31. Martins-Silva T, Bauer A, Matijasevich A, et al. Early risk factors for conduct problem trajectories from childhood to adolescence: the 2004 Pelotas (BRAZIL) Birth Cohort. Eur Child Adolesc Psychiatry. 2024;33(3):881-895. doi:10.1007/s00787-023-02178-9

32. Huang-Pollock C, Shapiro Z, Galloway-Long H, Weigard A. Is poor working memory a transdiagnostic risk factor for psychopathology? J Abnorm Child Psychol. 2017;45(8):1477-1490. doi:10.1007/s10802-016-0219-8

33. McQuade JD, Murray-Close D, Shoulberg EK, Hoza B. Working memory and social functioning in children. J Exp Child Psychol. 2013;115(3):422-435. doi:10.1016/j.jecp.2013.03.002

34. Moilanen KL, Shaw DS, Maxwell KL. Developmental cascades: Externalizing, internalizing, and academic competence from middle childhood to early adolescence. Dev Psychopathol. 2010;22(3):635-653. doi:10.1017/S0954579410000337

35. Newbury JB, Arseneault L, Moffitt TE, et al. Socioenvironmental adversity and adolescent psychotic experiences: Exploring potential mechanisms in a UK longitudinal cohort. Schizophr Bull. 2023;49(4):1042-1054. doi:10.1093/schbul/sbad017

36. VanderWeele T, Vansteelandt S. Mediation analysis with multiple mediators. Epidemiol Methods. 2014;2(1). doi:10.1515/em-2012-0010

37. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: Introducing the E-value. Ann Intern Med. 2017;167(4):268. doi:10.7326/M16-2607