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Lifelong exposure to air pollution and cognitive development in young children: the UK Millennium Cohort Study

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Abbreviations:

ASD	autism spectrum disorder
BAS	British Ability Scales
BSRA	Bracken School Readiness Assessment
BREATHE	Brain Development and Air Pollution Ultrafine Particles
CI	confidence interval
CO	carbon monoxide
Defra	Department for Environment Food & Rural Affairs
EC	elemental carbons
ESCAPE	European Study of Cohorts for Air Pollution Effects
GASPII	Gene and Environment Prospective Study on Infancy in Italy
MAAQ	Modelling of Ambient Air Quality
MCS	Millennium Cohort Study

MOCEH	Mothers and Children's Environmental Health
MRA	magnetic resonance imaging
NFER	National Foundation for Educational Research
NO_2	nitrogen dioxide
NVQ	national vocational qualification
IQ	intelligence quotient
IQR	interquartile range
O_3	ozone
OA	Output Area
PAH(s)	polycyclic aromatic hydrocarbons
PM	particle matters
$PM_{2.5}$	fine particulate matter with diameter of 2.5 μm or less
PM_{10}	particulate matter with diameter of 10 μm or less
RR	relative risk
SD	standard deviation
SO_2	sulphur dioxide
SPM	suspended particle matters
UFP	ultrafine particles
WHO	World Health Organization

Outline of Sections Headers:

Abstract

Background. Evidence about the impact of air pollution on cognitive development of children has been growing but remains inconclusive.

Objectives. To investigate the association of air pollution exposure and the cognitive development of children in the UK Millennium Cohort Study.

Methods. Longitudinal study of a nationally representative sample of 13,058-14,614 singleton births, 2000-2002, analysed at age 3, 5 and 7 years for associations between exposure from birth to selected air pollutants and cognitive scores for: School Readiness, Naming Vocabulary (age 3 and 5), Picture Similarity, Pattern Construction (age 5 and 7), Number Skills and Word Reading. Multivariable regression models took account of design stratum, clustering and sampling and attrition weights with adjustment for major risk factors, including age, gender, ethnicity, region, household income, parents' education, language, siblings and second-hand tobaco smoke.

Results: In fully adjusted models, no associations were observed between pollutant exposures and cognitive scores at age 3. At age 5, particulate matter ($PM_{2.5}$, PM_{10}), nitrogen dioxide (NO_2), sulphur dioxide (SO_2) and carbon monoxide (CO) were associated with lower scores for Naming Vocabulary but no other outcome except for SO_2 and Picture Similarity. At age 7, $PM_{2.5}$, PM_{10} and NO_2 were associated with lower scores for Pattern Construction, SO_2 with lower Number Skills and SO_2 and ozone with poorer Word Reading scores, but $PM_{2.5}$, PM_{10} and NO_2 were associated with *higher* Word Reading scores. Adverse effects of air pollutants represented a deficit of up to around 4 percentile points in Naming Vocabulary at age 5 for an interquartile range increase in pollutant concentration, which is smaller than the impact of various social determinants of cognitive development.

Conclusions: In a study of multiple pollutants and outcomes, we found mixed evidence from this UK-wide cohort study for association between lifetime exposure to air pollutants and cognitive development to age 7 years.

(300 words)

1. **Introduction**

There is accumulating evidence for adverse effects of air pollution on a growing range of health outcomes (Brook et al., 2010, Chen and Hoek, 2020, Huangfu and Atkinson, 2020, Pope et al., 2020, Rajagopalan, Al-Kindi and Brook, 2018), including impacts on cognitive development in children and decline in the elderly (Clifford et al., 2016, Costa et al., 2020, de Prado Bert et al., 2018, Sram et al., 2017, Suades-González et al., 2015, Xu, Ha and Basnet, 2016).

Epidemiological evidence for adverse impacts on cognitive development of children has come from studies in the US (Harris et al., 2015, Perera et al., 2009, Suglia et al., 2008), Europe (Guxens et al., 2014, Lubczynska et al., 2017, Porta et al., 2016, Sunyer et al., 2015) and Asia (Jung, Lin and Hwang, 2013, Kim et al., 2014, Tang et al., 2008, Yorifuji et al., 2016). This evidence has been reported in relation to a range of pollutants or proxies, including particle fractions such as particle matters with diameter of 2.5μm or less ($PM_{2.5}$) and 10μm or less (PM_{10}) (Guxens et al., 2014, Harris et al., 2015, Kim et al., 2014, Lubczynska et al., 2017, Yorifuji et al., 2016), nitrogen dioxide (NO_2) (Guxens et al., 2014, Jung, Lin and Hwang, 2013, Kim et al., 2014, Porta et al., 2016, Sunyer et al., 2015, Yorifuji et al., 2016), polycyclic aromatic hydrocarbons (PAHs) (Edwards et al., 2010, Jedrychowski et al., 2014, Lovasi et al., 2014, Perera et al., 2014, Tang et al., 2008), lead (Perera et al., 2014), proximity to roads and traffic density (Harris et al., 2015, Wilker et al., 2015). Most of them are cohort studies examining postnatal exposure, except a few studies of prenatal exposure (Kim et al., 2014, Perera et al., 2009, Perera et al., 2012, Tang et al., 2008, Yorifuji et al., 2016) and both (Jedrychowski et al., 2014). A wide range of cognitive/developmental outcomes were investigated, including verbal and numerical ability (Harris et al., 2015, Jedrychowski et al., 2014, Perera et al., 2009, Perera et al., 2012, Porta et al., 2016), psychomotor development (Guxens et al., 2014, Kim et al., 2014, Lertxundi et al., 2015), behavioural development milestones (Gong et al., 2017, Mortamais et al., 2017, Newman et al., 2013, Perera et al., 2012), working memory and attention processes (Chiu et al., 2013, Cowell et al., 2015, Sunyer et al., 2015) at various ages to 14 years.

Interpretation of this evidence is complex not only because of the range of exposures and outcomes studied but also because of methodological limitations of some studies, including suboptimal control for confounding factors, measurement of exposure only for limited periods or at large spatial scale, and the fact that outcomes have sometimes not been measured using validated or standardized instruments. Only three cohort studies to date have involved more than 1000 people with reasonable confounding control (Gong et al., 2014, Harris et al., 2015, Sunyer et al., 2015), except two European meta-analysis combining the results from heterogeneous measurements of cognition and psychomotor skills between cities (Guxens et al., 2014, Lubczynska et al., 2017) and two population-based cohort studies that were based on crude exposure measurement and limited confounding control (Jung, Lin and Hwang, 2013, Yorifuji et al., 2016). Taken as whole, the evidence is suggestive but inconclusive.

We now report an analysis of air pollution and cognitive development based on the UK Millennium Cohort Study (MCS). Previously the subset of the UK MCS children (n=8,198 MCS in England and Wales) were analysed to assess the association between the Multiple Environmental Deprivation Index (MEDIx) and cognitive ability at age three years (Midouhas, Kokosi and Flouri, 2018). Their analyses using the MEDIX represented by the national decile groups of annual mean NO_2 and green space at less granularity level (ward) did not find significant impact of NO_2 or green space on cognition ability at age three years. The current study aims to extend the precedent analysis by constructing lifelong exposure to several major air pollutants at finer geospatial scale and to analyse its impact on the development of cognition ability among the all UK MCS children up to seven years of age by maximising the feature of this valuable national cohort.

2. Methods

2.1 Study population

The UK MCS is a nationally-representative longitudinal study of 18,827 children born in the UK between September 2000 and January 2002 and alive and living in the UK at age 9 months (Connelly and Platt, 2014, Joshi and Fitzsimons, 2016). The sample is stratified by country and type of electoral ward, with over-sampling of families in areas of socio-economic disadvantage, high proportion of ethnic minority populations and in Scotland, Wales and Northern Ireland (Plewis et al., 2007).

To date, seven MCS 'sweeps' have been completed in 2001-3, 2003-2005, 2006, 2008, 2012-2013, 2015-16 and 2018-2019, corresponding to follow-up of cohort members at 9 months and 3, 5, 7, 11, 14 and 18 years of age. Interviewers visited the cohort members' homes and conducted face-to-face interviews with both resident parents. Parents also answered some questions via self-completion. Collected data include physical, socio-emotional, cognitive and behavioural development, along with individual daily life including physical activities and the families' socio-economic circumstances, parenting, relationships and lifestyle. Detailed information of available datasets and how the data were collected at each sweep is described elsewhere (Centre for Longitudinal Studies). Data collections used in the current study were listed in Supplementary material S1. Briefly, the First to the Fourth Surveys were linked by the cohort member number. Information about the household were added from the Longitudinal Family File. Besides, geographical identifiers (specifically Output Area, OA) were joined at the time of the First to Fourth survey interview.

In this paper, we report the analysis of follow-up for cognitive outcomes up to age 7 years, using data from sweeps 1-4 for singleton births only with complete data on principal covariates (i.e. sex, birth weight, ethnicity, maternal age at birth, cohort member's age, household income and region) and cognitive outcomes and successful linkage to air pollution data for all four sweeps (data from the UK Data Archive, University of Essex obtained through the UK Data Service Secure Lab).

2.2 Cognitive measurements

Measurements of cognitive development are described in detail elsewhere (Harris et al., 2015) and summarised in Table 1 and Supplementary material S2.

The administered tests varied by age. The interviewer conducted age-appropriate cognitive assessments with the cohort member at sweeps 2-4. Most were based on British Ability Scales (BAS), a battery of individually-administered tests of cognitive ability and educational achievements suitable for use with children from 2 years 6 months to 7 years 11 months. The BAS Naming Vocabulary is a verbal scale for young children that measures expressive language skills, vocabulary knowledge of nouns, ability to attach verbal labels to pictures, general knowledge, retrieval of names from long-term memory and language stimulation. BAS Picture Similarity assesses children's problem-solving ability and Pattern Construction spatial awareness, dexterity and coordination as well as traits such as perseverance and determination. At age 7, children were assessed by either the BAS Word Reading in English or The Our Adventures in Welsh depending on parents' choice and also by the UK National Foundation for Educational Research (NFER) Number Skills test.

For all BAS batteries, scores were converted to standardized T-scores by reference to age-specific population norms (mean 50, SD 10). We used age-adjusted school readiness composite standard score (mean 100, SD 15) for Bracken School Readiness and the nationally age adjusted standardised score (mean 100, SD 15) for NFER Number Skills. Higher scores on all cognitive tests indicate higher ability.

2.3 Air pollution exposure

Air pollutant exposure was assessed for particles ($PM_{2.5}$ and PM_{10}), as well as nitrogen dioxide (NO_2) and ozone (O_3) as the pollutants of primary interest and for sulphur dioxide (SO_2) and carbon monoxide (CO) as pollutants of secondary interest. Exposure classification was based on linkage of the child's place of residence to 1 x 1 km resolution maps of annual average background pollutant concentrations using the Department for Environment Food & Rural Affairs (Defra) Modelling of Ambient Air Quality (MAAQ) (Ricardo Energy & Environment, 2018).

For each cohort member, we constructed a history of residential addresses referring to the reported address at interview and dates of moving residence if they changed from the previous sweep. We assumed the cohort member lived in the same address after birth to age 9 months as no residential information was available before the first survey (sweep MCS1).

Lifelong exposure was quantified by occupancy-time-weighted average of the annual mean concentration for all pollutants except CO (maximum of daily 8 hour running mean) and O_3 (number of days on which daily maximum of 8-hourly concentration is greater than 120μg m^{-3}). For linkage we used the centroid of the OA of residence (approximately 300 residents per unit in England and Wales and 114 in Scotland) available through the UK Data Service Secure Lab.

2.4 Other major risk factors

Other major risk factors considered in this paper reflect the collective knowledge from previous studies (Aggio et al., 2016, Chowdry et al., 2010, Côté et al., 2013, Midouhas, Kokosi and Flouri, 2018). The individual level risk factors include age (in days), gender and ethnicity (White, Mixed, Indian, Pakistani and Bangladesh, Black or Black British and Others) and low birth weight (<2500g or not). The family level risk factors were household income (quintile group), mother's education (in National Vocational Qualifications, NVQ), father's education (NVQ), maternal age at birth, language spoken in household (English only, Not-English only), number of siblings (1, 2, 3+), second-hand tobacco smoke (whether anyone smokes in the same room as the cohort member), chronic illness of the cohort member and breast feeding (ever tried or not). Areal identification of the region was also included.

2.5 Statistical analysis

First, we conducted a descriptive analysis including examination of missing data and correlations among the key variables. In order to explore possible bias relating to non-response of items in each survey sweep, we retained observations containing missing data, coding the relevant data item as `unknown', instead of exclusively fitting the model to observations with complete data or using multiple imputation techniques.

Standardized cognition test scores were analysed in relation to lifelong air pollution exposure using multivariable linear regression model.

The MCS is not a random sample, and its sampling design involved clustering by ward (there are just under 9,500 wards in the UK). These clusters were further stratified by deprivation level (and ethnicity in England). There has also been non-random attrition at each successive MCS sweep. Standard errors are adjusted to take account of the survey design and attrition using Stata svyset command (Stata Corp, 2017). Analyses were conducted for the whole UK.

The cognitive outcomes analysed at each age are shown in Table 1. Each analysis was of a specific measure of cognitive outcome at one specific age only using each of two pre-specified models of confounder control (Model1 and Model2). Model 1 included a relatively restricted set of confounder variables: age, gender, low birth weight, ethnicity, maternal age at birth, household income and region; Model 2 included these variables plus additional adjustment for mother's and father's education, language, siblings, second-hand tobacco smoke, chronic illness and breast feeding. For the two outcomes where we had more than one year of outcome measurement (BAS Naming Vocabulary at ages 3 & 5 and BAS Pattern Construction at 5 & 7), we analysed the *change* between the two ages in relation to the mean pollution concentration over the life-course from birth with control for confounders measured at the later date. This model specification has the advantage of removing potentially correlated fixed effects via differencing which may impact on consistency in the levels specification. We did not regress change in cognition scores on *change* in pollution exposure between the two assessments because the Defra MAAQ modelling method had been updated over the study period which may introduce bias in estimates of year-to-year changes. All results are expressed as the change in score for an interquartile range (IQR) increase in mean pollutant concentration.

Example of Stata codes of the Survey Data analysis and how coefficient standard errors are estimated are shown in Supplementary material S3. Non-linearity of the relationship with air pollution was examined by introducing categorical variables, but did not significantly change the results (not shown). Analyses were conducted using Stata version 15.

3. Results

3.1. Study population and lifelong air pollution exposure

The study sample meeting our data completeness and record linkage criteria comprised 13,310 children at age 3, 14,614 at age 5 and 13,058 at age 7 (Table 2). The majority were white (88.3% at first follow-up), 90% spoke English only in their household and 6% had low birth weight. Around 12 % of children were still the only child in the household by age 7. The number of children exposed to ETS at home decreased over time (17.6% at age 3, 13.5% at age 7).For all pollutants, the estimated lifelong mean concentration was highest at the first follow up (age 3) and declined with age/follow-up (Table 3). Correlations between exposure to different air pollutants are reported in the Supplementary material (Table S4).

3.2. Impacts on cognitive ability

Estimated changes in cognitive test scores for an IQR increase in pollution are shown by age at follow-up in Figure 1 and Supplementary material Table S5.

At first follow-up (age 3), there was no clear evidence of pollution-related differences in scores of cognitive function for either Naming Vocabulary or School Readiness in the fully-adjusted model (Model 2), although there was borderline evidence for School Readiness in relation to SO_2 based on the less tightly-controlled Model 1 results: change in percentile score for an IQR increase in pollutant of -0.93 (95%CI -1.79, -0.08) – Figure 1(A).

At second follow-up (age 5), there was no clear evidence of pollution-related differences in cognitive function scores for Pattern Construction or Picture Similarity, except for Picture Similarity in relation to SO_2. But for Naming Vocabulary, all pollutants except O_3 showed evidence of poorer scores in fully-adjusted (Model 2) results. The differences in percentile scores for an interquartile increase in pollutant were: $PM_{2.5}$: -3.92 (95%CI -5.79, -2.06), PM_{10}: -3.67 (-5.25, -2.09), NO_2: -2.33 (-3.78, -0.87), SO_2: -1.04 (-1.80, -0.28) and CO: -2.20 (-3.44, -0.98) – Figure 1(B).

At third follow-up (age 7), there was no evidence of pollution-related association with Number Skills scores, except in relation to SO_2 (IQR-related percentile difference -1.47, 95%CI -2.47, -0.48, fully-adjusted model). However, for Pattern Construction, there was evidence of poorer scores in relation to both $PM_{2.5}$ (percentile difference for an IQR pollutant increase -2.37, 95%CI -4.62, -0.12) and PM_{10} (-2.08, 95%CI -3.97, -0.19).

The results for Word Reading showed counterintuitive mixed results with positive ('protective') associations for IQR increases in $PM_{2.5}$ (2.68, 95% CI 0.64, 4.72), PM_{10} (2.36, 95% CI 0.61, 4.10), NO_2 (2.33, 95%CI 0.90, 3.76) and CO (1.86, 95%CI 0.61, 3.10); and negative ('adverse') associations for O_3 (-2.12, 95%CI -3.43, -0.81) and SO_2 (-0.77, 95%CI -1.43, -0.11).

Various non-pollutant covariates showed generally stronger associations (larger score differences) with cognitive function than individual pollutants, especially ethnicity, household income, mother's and father's education, being a non-English-speaking household and number of siblings (see Supplementary material Table S7).

3.3. Change in cognitive test scores

Change in the Naming Vocabulary test score between age 3 and 5 years was negatively associated with mean lifelong exposure to all air pollutants except O_3 (Figure 2). For the pollutants of primary interest, the changes in the percentile score for an IQR increase in pollutant concentration were: $PM_{2.5}$ -3.76 (95% CI -6.27, -1.26), PM_{10} -3.54 (-5.73, -1.36) and NO_2 -2.83 (-4.82, -0.84). The association with O_3 was positive ('protective') and of borderline statistical significance – Figure 2. Interestingly, whereas in the levels specification, Model 2 estimates were generally lower than Model 1 estimates as expected, in the difference equations estimates were identical in both models suggesting removing unobserved fixed effects was important. More importantly, the results suggest that the Model 2 specification was sufficient to control for correlated fixed effects, with virtually identical results at age 5 for naming vocabulary in the difference and levels specification (remembering no effect was found at age 3).

However, there was no clear pollution association of the change in Pattern Construction scores between age 5 and 7 years (Figure 2 and Supplementary material Table S6) in contrast to the level's equations.

4. Discussion

4.1. Summary

This study, based on the UK nationally-representative Millennium Cohort Study, provides further evidence of the associations between lifelong exposure to air pollution and the cognitive development of children. To our knowledge, it is the first large nationwide analysis of children from birth to age 7 with standardized measures of cognitive ability.

Given the context of assessing multiple pollutants and multiple endpoints at three time points (ages), the results provide somewhat mixed evidence. There was little evidence of any association of air pollution with poorer cognitive ability at age 3. But at age 5 there was evidence of negative (adverse) associations between pollutant concentrations for all pollutants except O_3 and cognitive scores for Naming Vocabulary though no clear evidence for either of the other outcomes analysed (except for SO_2 in relation to Picture Similarity test scores). At age 7, $PM_{2.5}$, PM_{10} and NO_2 were associated with poorer Pattern Construction scores, SO_2 with poorer Number Skills and Word Reading scores, and O_3 with poorer Word Reading. However, fully-adjusted models also showed $PM_{2.5}$, PM_{10}, NO_2 and CO to have apparently positive ('protective') associations with Word Reading scores measured at age 7. There was also evidence that improvement in Naming Vocabulary between ages 3 and 5 was poorer in higher pollution areas but no association for change in Pattern Construction between age 5 and 7 years. Although there was diversity in findings by age and different instrument (test) to measure cognition ability, overall results suggested broadly consistent direction of the impacts among generally-correlated pollutants, such as NO_2, PM and CO. At age 7, pollution exposure is going to be much more influenced by location of school (not home address) and this may be behind some of the puzzling results observed at that age. Future work should attempt to control for exposure at both home and school. Observed magnitude of the impact from change analysis which accounts for unobserved fixed effects is broadly equivalent to the difference of the two impacts in the level specifications (the second test minus the first test with two years gap) for Model 2 suggesting this specification is robust.

If the observed associations reflect causal effects, they suggest that air pollutants are producing selective deficits of cognitive function of up to around 4 percentile points (wider if confidence intervals are considered) for an interquartile range increase in pollutant concentrations. These ‘deficits' would be broadly comparable to those associated with some non-pollutant social factors, but they are generally smaller than the effect of the more important social determinants such as household income, parental education, ethnicity and whether the household is English-speaking, for example. Although the observed air pollution effects are marginal compared with those of other risk factors, given the ubiquity of the exposure, they could be a substantial health burden in the population from early to later stages of life ((Peters et al., 2019, Power et al., 2016)). These pollutant associations are observed in populations whose exposure generally falls within national air quality standards but above WHO guideline levels.

4.2. Comparison of the results to other studies

It is difficult to compare evidence across studies directly because of differences in outcome measures and design, but our results are broadly consistent with other published research. An earlier, more limited analysis of the MCS (Midouhas, Kokosi and Flouri (2018) also found little evidence to support cognitive differences due to differences in outdoor NO_2 at age 9 months and 3 years, and a European meta-analysis did not observe any impacts of air pollution on cognitive function at age 2.5 years (Guxens et al., 2014). This may reflect absence of effect but may also in part be attributed to the methodological challenge of measuring cognitive ability at very young ages.

With regard to specific pollutants, our (mixed) results show selective evidence for adverse associations with all pollutants at ages 5 and 7, specifically including $PM_{2.5}$, PM_{10}, NO_2, and, for several outcomes/ages, SO_2. This is broadly consistent with the finding of the systematic review of Suades-González *et al*, which supports the hypothesis that pre- and post-natal exposure to ambient pollution, particularly $PM_{2.5}$, nitrogen oxides and PAHs, have a negative impact on neuropsychological development (Suades-González et al., 2015). Cohort studies published after this review also support likely associations between exposure to particles and nitrogen oxides on the one hand and cognitive ability of children on the other (Guxens et al., 2016, Lubczynska et al., 2017, Yorifuji et al., 2016) .

4.3. Mechanisms

Possible mechanisms by which air pollution might affect brain function have been described by Block and Calderón-Garcidueñas (2009) and may entail the interaction of multiple pathways and mechanisms, including oxidative stress, neuroinflammation, cerebrovascular damage, cell death, which are also common features of neurodegenerative disorders, and genetic and epigenetic mechanisms (Genc et al., 2012, Underwood, 2017). Most mechanistic research has been based on animal and *post-mortem* studies of adults. Precise measurement of the changes occurring in the human brain under real conditions is required to provide biological evidence for the air pollution and cognition link reported in epidemiological studies. Recently, magnetic resonance imaging (MRI) has started to be applied to measure brain structure and functioning in assessing the impacts of urban air pollution on the brain, including comparative studies in Mexico-city (Calderón-Garcidueñas et al., 2011, Calderon-Garciduenas et al., 2008), a birth cohort study in New York (Peterson et al., 2015) and BREATHE studies in Barcelona

(Mortamais et al., 2017, Pujol et al., 2016a, Pujol et al., 2016b) as summarised in de Prado Bert et al. (2018).

4.4. Strengths and limitations

The advantages of our analyses include the wide contrasts in exposures across the UK, large sample size, the availability of standardized measures of cognitive function and generally good confounder control. In these respects, we believe the study provides fairly robust evidence.

However, the positive correlations between pollutant levels and Word Reading scores at age 7 are counter-intuitive and difficult to interpret as a causal effect of pollution. Some bias is possible from the limitation in capturing pollution exposure only at each child's residential neighbourhood, not at school or commuting, although only specific forms of misclassification are likely to introduce an appreciable positive association rather than biasing the results towards the null. More likely possibilities are chance or residual confounding from effects such as of school quality, outside-school learning activities and availability of supporting learning resources in (polluted) urban areas that begin to take effect at older ages. It is worth noting that the positive association was observed in only in one of the examined cognitive measures and only at the oldest age examined (7 years). Naming Vocabulary results showed negative correlation at age 5.

The (mixed) results for O_3 are largely understandable given its negative or weak correlation with most other air pollutants, especially NO_2. O_3 is a highly reactive oxidative gas formed by chemical reactions in the atmosphere involving oxides of nitrogen, volatile organic compounds and driven by solar radiation. In urban areas with high traffic density, nitrogen oxides (NO and NO_2) are commonly high and often negatively correlated with O_3 during daylight hours. Due to complexity of such titration process, it is not unusual to find the impacts of O_3 opposite from those of nitrogen oxides in air pollution epidemiology. The tendency for several O_3 results to show patterns opposite to NO_2 and PM in particular may therefore reflect the fact that it is acting as a negative proxy for such pollutants which *might* be causally-related to the outcome.

Among our study's limitations are its reliance on modelled air pollution levels at 1 x 1 km resolution, which will have led to imperfect exposure classification especially for the more spatially-varying pollutants such as NO_2. However, this is the optimally best available data to construct the proxy of life-long exposure to studied air pollution among more than 13 thousands children who reside across the UK. Although we cannot exclude the possibility of misclassification of air pollution exposure, any misclassification would be nondifferential, moving the effect estimates toward the null. In that sense, our estimates of air pollution impacts could be underestimated. Moreover, changes in pollutant modelling methods over time meant that we were unable to analyse changes in cognitive ability specifically in relation to changes in pollutant concentrations (confining analyses instead to spatial differences in cumulative lifetime exposure from birth). We also were unable to construct estimates of prenatal exposure, which is a gap as prenatal exposure may be relatively important for cognitive development (Harris et al., 2015, Porta et al., 2016). Furthermore, we did not have data on other potentially important environmental factors including green space (Dadvand et al., 2015, Dadvand et al., 2018, Dadvand et al., 2017), noise (Sunyer et al., 2015) and indoor air quality and/or dampness

(Midouhas, Kokosi and Flouri, 2018, Sunyer et al., 2015). Aircraft noise has been shown to be associated with impaired cognitive development of school-aged children (Stansfeld et al., 2005) and it is likely other forms of environmental noise would also be detrimental. Finally, the current paper describes limited sensitivity analysis, apart from exploration of two sets of covariates in a minimum adjusted model and a further adjusted model by crucial individual and family determinants with relaxed concerns of collinearity based on the empirical evidence (Chowdry et al., 2010), and examination of the potential (but less likely to impact extensively, given marginal environmental impacts in general) effect modification (not reported). Further model identification to disentangle complicated individual, social and environmental factors is expected (Zivin and Neidell, 2013, Zhang, Chen and Zhang, 2018).

4.4. Conclusions

In conclusion, our results provide further but mixed evidence for the detrimental impact on air pollutants on cognitive development in early childhood, which is broadly consistent with other published research and mechanistic evidence. It adds to the weight to calls for policy action to reduce air pollution exposure, especially for vulnerable groups such as children, but further work is needed to characterize risks with greater certainty, including in relation to specific pollutants and the critical periods of exposure.

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Ethical approval

This study was approved by the LSHTM Ethics Committee. Data access was covered by Secure Access User Agreement with UK Data Service.

Data availability statement

No additional data are available.

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References

Aggio, D., Smith, L., Fisher, A. and Hamer, M. (2016). "Context-Specific Associations of Physical Activity and Sedentary Behavior With Cognition in Children". *Am J Epidemiol.,* Vol. 183, no. 12, pp. 1075-82. doi: 10.93/aje/kww031. Epub 2016 May 24.

Block, M.L. and Calderón-Garcidueñas, L. (2009). "Air Pollution: Mechanisms of Neuroinflammation & CNS Disease". *Trends Neurosci.,* Vol. 32, no. 9, pp. 506-16. Epub 2009 Aug 26 doi:10.1016/j.tins.2009.05.009.

Bracken, B.A. (2002). *Bracken School Readiness Assessment: Administration Manual.* San Antonio, Texas: Psychological Corporation.

Brook, R.D., Rajagopalan, S., Pope, C.A., 3rd, Brook, J.R., Bhatnagar, A., Diez-Roux, A.V. et al. (2010). "Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association". *Circulation.,* Vol. 121, no. 21, pp. 2331-78. doi: 10.1161/CIR.0b013e3181dbece1. Epub 2010 May 10.

Calderón-Garcidueñas, L., Engle, R., Mora-Tiscareño, A., Styner, M., Gómez-Garza, G., Zhu, H. et al. (2011). "Exposure to severe urban air pollution influences cognitive outcomes, brain volume and systemic inflammation in clinically healthy children". *Brain and Cognition,* Vol. 77, no. 3, pp. 345-55.

Calderon-Garciduenas, L., Mora-Tiscareno, A., Ontiveros, E., Gomez-Garza, G., Barragan-Mejia, G., Broadway, J. et al. (2008). "Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs". *Brain Cogn.,* Vol. 68, no. 2, pp. 117-27. doi: 10.1016/j.bandc.2008.04.008. Epub 08 Jun 11.

Centre for Longitudinal Studies, I.o.E., UCL,. (2021). *Millennium Cohort Study*. Available from: https://cls.ucl.ac.uk/cls-studies/millennium-cohort-study/ [Accessed 16/02/2021].

Chen, J. and Hoek, G. (2020). "Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis". *Environ Int*, p. 105974.

Chiu, Y.H., Bellinger, D.C., Coull, B.A., Anderson, S., Barber, R., Wright, R.O. et al. (2013). "Associations between traffic-related black carbon exposure and attention in a prospective birth cohort of urban children". *Environ Health Perspect.,* Vol. 121, no. 7, pp. 859-64. doi: 10.1289/ehp.1205940. Epub 2013 May 10.

Chowdry, H., Crawford, C., Dearden, L., Joyce, R., Sibieta, L., Sylva, K. et al. (2010). *Poorer children's educational attainment: how important are attitudes and behaviour?* Joseph Rowntree Foundation.

Clifford, A., Lang, L., Chen, R., Anstey, K.J. and Seaton, A. (2016). "Exposure to air pollution and cognitive functioning across the life course - A systematic literature review". *Environ Res.,* Vol. 147:383-98., no. doi, p. 10.1016/j.envres.2016.01.018. Epub 16 Mar 4.

Connelly, R. and Platt, L. (2014). "Cohort Profile: UK Millennium Cohort Study (MCS)". *International Journal of Epidemiology,* Vol. 43, no. 6, pp. 1719-25.

Costa, L.G., Cole, T.B., Dao, K., Chang, Y.-C., Coburn, J. and Garrick, J.M. (2020). "Effects of air pollution on the nervous system and its possible role in neurodevelopmental and neurodegenerative disorders". *Pharmacology & Therapeutics,* Vol. 210, p. 107523.

Côté, S.M., Doyle, O., Petitclerc, A. and Timmins, L. (2013). "Child Care in Infancy and Cognitive Performance Until Middle Childhood in the Millennium Cohort Study". *Child Development,* Vol. 84, no. 4, pp. 1191-208.

Cowell, W.J., Bellinger, D.C., Coull, B.A., Gennings, C., Wright, R.O. and Wright, R.J. (2015). "Associations between Prenatal Exposure to Black Carbon and Memory Domains in Urban Children: Modification by Sex and Prenatal Stress". *PLoS One,* Vol. 10, no. 11, p. e0142492.

Dadvand, P., Nieuwenhuijsen, M.J., Esnaola, M., Forns, J., Basagana, X., Alvarez-Pedrerol, M. et al. (2015). "Green spaces and cognitive development in primary schoolchildren". *Proc Natl Acad Sci U S A.,* Vol. 112, no. 26, pp. 7937-42. doi: 10.1073/pnas.1503402112. Epub 2015 Jun 15.

Dadvand, P., Pujol, J., Macia, D., Martinez-Vilavella, G., Blanco-Hinojo, L., Mortamais, M. et al. (2018). "The Association between Lifelong Greenspace Exposure and 3-Dimensional Brain Magnetic Resonance Imaging in Barcelona Schoolchildren". *Environ Health Perspect.,* Vol. 126, no. 2, p. 027012. doi: 10.1289/EHP1876.

Dadvand, P., Tischer, C., Estarlich, M., Llop, S., Dalmau-Bueno, A., Lopez-Vicente, M. et al. (2017). "Lifelong Residential Exposure to Green Space and Attention: A Population-based Prospective Study". *Environ Health Perspect.,* Vol. 125, no. 9, p. 097016. doi: 10.1289/EHP694.

de Prado Bert, P., Mercader, E.M.H., Pujol, J., Sunyer, J. and Mortamais, M. (2018). "The Effects of Air Pollution on the Brain: a Review of Studies Interfacing Environmental Epidemiology and Neuroimaging". *Curr Environ Health Rep.,* Vol. 5, no. 3, pp. 351-64. doi: 10.1007/s40572-018-0209-9.

Edwards, S.C., Jedrychowski, W., Butscher, M., Camann, D., Kieltyka, A., Mroz, E. et al. (2010). "Prenatal exposure to airborne polycyclic aromatic hydrocarbons and children's intelligence at 5 years of age in a prospective cohort study in Poland". *Environ Health Perspect.,* Vol. 118, no. 9, pp. 1326-31. doi: 10.289/ehp.0901070. Epub 2010 Apr 14.

Genc, S., Zadeoglulari, Z., Fuss, S.H. and Genc, K. (2012). "The adverse effects of air pollution on the nervous system". *J Toxicol,* Vol. 2012, p. 782462.

Gong, T., Almqvist, C., Bölte, S., Lichtenstein, P., Anckarsäter, H., Lind, T. et al. (2014). "Exposure to air pollution from traffic and neurodevelopmental disorders in Swedish twins". *Twin Res Hum Genet,* Vol. 17, no. 6, pp. 553-62.

Gong, T., Dalman, C., Wicks, S., Dal, H., Magnusson, C., Lundholm, C. et al. (2017). "Perinatal Exposure to Traffic-Related Air Pollution and Autism Spectrum Disorders". *Environ Health Perspect.,* Vol. 125, no. 1, pp. 119-26. doi: 10.1289/EHP118. Epub 2016 Aug 5.

Guxens, M., Garcia-Esteban, R., Giorgis-Allemand, L., Forns, J., Badaloni, C., Ballester, F. et al. (2014). "Air pollution during pregnancy and childhood cognitive and psychomotor development: six European birth cohorts". *Epidemiology.,* Vol. 25, no. 5, pp. 636-47. doi: 10.1097/EDE.0000000000000133.

Guxens, M., Ghassabian, A., Gong, T., Garcia-Esteban, R., Porta, D., Giorgis-Allemand, L. et al. (2016). "Air Pollution Exposure during Pregnancy and Childhood Autistic Traits in Four European Population-Based Cohort Studies: The ESCAPE Project". *Environ Health Perspect.,* Vol. 124, no. 1, pp. 133-40. doi: 10.1289/ehp.1408483. Epub 2015 Jun 12.

Harris, M.H., Gold, D.R., Rifas-Shiman, S.L., Melly, S.J., Zanobetti, A., Coull, B.A. et al. (2015). "Prenatal and Childhood Traffic-Related Pollution Exposure and Childhood Cognition in the Project Viva Cohort (Massachusetts, USA)". *Environ Health Perspect.,* Vol. 123, no. 10, pp. 1072-8. doi: 10.289/ehp.1408803. Epub 2015 Apr 3.

Huangfu, P. and Atkinson, R. (2020). "Long-term exposure to NO(2) and O(3) and all-cause and respiratory mortality: A systematic review and meta-analysis". *Environ Int,* Vol. 144, p. 105998.

Jedrychowski, W.A., Perera, F.P., Camann, D., Spengler, J., Butscher, M., Mroz, E. et al. (2014). "Prenatal exposure to polycyclic aromatic hydrocarbons and cognitive dysfunction in children". *Environmental Science and Pollution Research,* Vol. 22, no. 5, pp. 3631-39.

Joshi, H. and Fitzsimons, E. (2016). "The Millennium Cohort Study: the making of a multi-purpose resource for social science and policy". *2016,* Vol. 7, no. 4, p. 22.

Jung, C.R., Lin, Y.T. and Hwang, B.F. (2013). "Air pollution and newly diagnostic autism spectrum disorders: a population-based cohort study in Taiwan". *PLoS One,* Vol. 8, no. 9, p. e75510.

Kim, E., Park, H., Hong, Y.C., Ha, M., Kim, Y., Kim, B.N. et al. (2014). "Prenatal exposure to PM_{10} and NO_2 and children's neurodevelopment from birth to 24 months of age: mothers and Children's Environmental Health (MOCEH) study". *Sci Total Environ,* Vol. 481, pp. 439-45.

Lertxundi, A., Baccini, M., Lertxundi, N., Fano, E., Aranbarri, A., Martínez, M.D. et al. (2015). "Exposure to fine particle matter, nitrogen dioxide and benzene during pregnancy and cognitive and psychomotor developments in children at 15 months of age". *Environment International,* Vol. 80, pp. 33-40.

Lovasi, G.S., Eldred-Skemp, N., Quinn, J.W., Chang, H.W., Rauh, V.A., Rundle, A. et al. (2014). "Neighborhood Social Context and Individual Polycyclic Aromatic Hydrocarbon Exposures Associated with Child Cognitive Test Scores". *J Child Fam Stud,* Vol. 23, no. 5, pp. 785-99.

Lubczynska, M.J., Sunyer, J., Tiemeier, H., Porta, D., Kasper-Sonnenberg, M., Jaddoe, V.W.V. et al. (2017). "Exposure to elemental composition of outdoor PM2.5 at birth and cognitive and psychomotor function in childhood in four European birth cohorts". *Environ Int.,* Vol. 109:170-180., no. doi, p. 10.1016/j.envint.2017.09.015. Epub 17 Oct 5.

Midouhas, E., Kokosi, T. and Flouri, E. (2018). "Outdoor and indoor air quality and cognitive ability in young children". *Environ Res.,* Vol. 161:321-328., no. doi, p. 10.1016/j.envres.2017.11.026. Epub 17 Nov 25.

Mortamais, M., Pujol, J., van Drooge, B.L., Macià, D., Martínez-Vilavella, G., Reynes, C. et al. (2017). "Effect of exposure to polycyclic aromatic hydrocarbons on basal ganglia and attention-deficit hyperactivity disorder symptoms in primary school children". *Environ Int,* Vol. 105, pp. 12-19.

Newman, N.C., Ryan, P., Lemasters, G., Levin, L., Bernstein, D., Hershey, G.K. et al. (2013). "Traffic-related air pollution exposure in the first year of life and behavioral scores at 7 years of age". *Environ Health Perspect,* Vol. 121, no. 6, pp. 731-6.

Perera, F., Weiland, K., Neidell, M. and Wang, S. (2014). "Prenatal Exposure to Airborne Polycyclic Aromatic Hydrocarbons and IQ: Estimated Benefit of Pollution Reduction". *J Public Health Policy.,* Vol. 35, no. 3, pp. 327-36. Epub 2014 May 08 doi:10.1057/jphp.2014.14.

Perera, F.P., Li, Z., Whyatt, R., Hoepner, L., Wang, S., Camann, D. et al. (2009). "Prenatal Airborne Polycyclic Aromatic Hydrocarbon Exposure and Child IQ at Age 5 Years". *Pediatrics,* Vol. 124, no. 2, pp. e195-e202.

Perera, F.P., Tang, D., Wang, S., Vishnevetsky, J., Zhang, B., Diaz, D. et al. (2012). "Prenatal Polycyclic Aromatic Hydrocarbon (PAH) Exposure and Child Behavior at Age 6–7 Years". *Environ Health Perspect.,* Vol. 120, no. 6, pp. 921-6. Epub 2012 Mar 14 doi:10.1289/ehp.1104315.

Peters, R., Ee, N., Peters, J., Booth, A., Mudway, I. and Anstey, K.J. (2019). "Air Pollution and Dementia: A Systematic Review". *J Alzheimers Dis,* Vol. 70, no. s1, pp. S145-S63. doi: 10.3233/JAD-180631.

Peterson, B.S., Rauh, V.A., Bansal, R., Hao, X., Toth, Z., Nati, G. et al. (2015). "Effects of prenatal exposure to air pollutants (polycyclic aromatic hydrocarbons) on the development of brain white matter, cognition, and behavior in later childhood". *JAMA Psychiatry,* Vol. 72, no. 6, pp. 531-40.

Plewis, I., Calderwood, L., Hawkes, D., Hughes, G. and Joshi, H. (2007). *The Millennium Cohort Study: Technical Report on Sampling 4th Edition.* London: Institute of Education, University of London.

Pope, C.A., 3rd, Coleman, N., Pond, Z.A. and Burnett, R.T. (2020). "Fine particulate air pollution and human mortality: 25+ years of cohort studies". *Environ Res,* Vol. 183, p. 108924.

Porta, D., Narduzzi, S., Badaloni, C., Bucci, S., Cesaroni, G., Colelli, V. et al. (2016). "Air Pollution and Cognitive Development at Age 7 in a Prospective Italian Birth Cohort". *Epidemiology.,* Vol. 27, no. 2, pp. 228-36. doi: 10.1097/EDE.0000000000000405.

Power, M.C., Adar, S.D., Yanosky, J.D. and Weuve, J. (2016). "Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: A systematic review of epidemiologic research". *NeuroToxicology,* Vol. 56, pp. 235-53.

Pujol, J., Fenoll, R., Macià, D., Martínez-Vilavella, G., Alvarez-Pedrerol, M., Rivas, I. et al. (2016a). "Airborne copper exposure in school environments associated with poorer motor performance and altered basal ganglia". *Brain Behav,* Vol. 6, no. 6, p. e00467.

Pujol, J., Martinez-Vilavella, G., Macia, D., Fenoll, R., Alvarez-Pedrerol, M., Rivas, I. et al. (2016b). "Traffic pollution exposure is associated with altered brain connectivity in school children". *Neuroimage.,* Vol. 129:175-84., no. doi, p. 10.1016/j.neuroimage.2016.01.036. Epub 16 Jan 26.

Rajagopalan, S., Al-Kindi, S.G. and Brook, R.D. (2018). "Air Pollution and Cardiovascular Disease: JACC State-of-the-Art Review". *Journal of the American College of Cardiology,* Vol. 72, no. 17, pp. 2054-70.

Ricardo Energy & Environment. (2018). *Technical report on UK supplementary assessment under The Air Quality Directive (2008/50/EC), The Air Quality Framework Directive (96/62/EC) and Fourth Daughter Directive (2004/107/EC) for 2018.* Defra.

Sram, R.J., Veleminsky, M., Jr., Veleminsky, M., Sr. and Stejskalová, J. (2017). "The impact of air pollution to central nervous system in children and adults". *Neuro Endocrinol Lett,* Vol. 38, no. 6, pp. 389-96.

Stansfeld, S.A., Berglund, B., Clark, C., Lopez-Barrio, I., Fischer, P., Ohrstrom, E. et al. (2005). "Aircraft and road traffic noise and children's cognition and health: a cross-national study". *Lancet.,* Vol. 365, no. 9475, pp. 1942-9.

Stata Corp. (2017). *Stata survey data reference manual, release 15.* Texas, US; Available from: https://www.stata.com/manuals15/svy.pdf [Accessed 16/02/2021].

Suades-González, E., Gascon, M., Guxens, M. and Sunyer, J. (2015). "Air Pollution and Neuropsychological Development: A Review of the Latest Evidence". *Endocrinology,* Vol. 156, no. 10, pp. 3473-82.

Suglia, S.F., Gryparis, A., Wright, R.O., Schwartz, J. and Wright, R.J. (2008). "Association of black carbon with cognition among children in a prospective birth cohort study". *Am J Epidemiol.,* Vol. 167, no. 3, pp. 280-6. Epub 2007 Nov 15.

Sunyer, J., Esnaola, M., Alvarez-Pedrerol, M., Forns, J., Rivas, I., Lopez-Vicente, M. et al. (2015). "Association between traffic-related air pollution in schools and cognitive development in primary school children: a prospective cohort study". *PLoS Med.,* Vol. 12, no. 3, p. e1001792. doi: 10.1371/journal.pmed.92. eCollection 2015 Mar.

Tang, D., Li, T.Y., Liu, J.J., Zhou, Z.J., Yuan, T., Chen, Y.H. et al. (2008). "Effects of prenatal exposure to coal-burning pollutants on children's development in China". *Environ Health Perspect,* Vol. 116, no. 5, pp. 674-9.

Underwood, E. (2017). "The polluted brain". *Science,* Vol. 355, no. 6323, p. 342.

Wilker, E.H., Preis, S.R., Beiser, A.S., Wolf, P.A., Au, R., Kloog, I. et al. (2015). "Long-term exposure to fine particulate matter, residential proximity to major roads and measures of brain structure". *Stroke.,* Vol. 46, no. 5, pp. 1161-6. doi: 10.61/STROKEAHA.114.008348.

Xu, X., Ha, S.U. and Basnet, R. (2016). "A Review of Epidemiological Research on Adverse Neurological Effects of Exposure to Ambient Air Pollution". *Front Public Health.,* Vol. 4:. no. doi, p. 10.3389/fpubh.2016.00157.

Yorifuji, T., Kashima, S., Higa Diez, M., Kado, Y., Sanada, S. and Doi, H. (2016). "Prenatal Exposure to Traffic-related Air Pollution and Child Behavioral Development Milestone Delays in Japan". *Epidemiology,* Vol. 27, no. 1, pp. 57-65.

Zhang, X., Chen, X. and Zhang, X. (2018). "The impact of exposure to air pollution on cognitive performance". *Proc Natl Acad Sci U S A,* Vol. 115, no. 37, pp. 9193-97.

Zivin, J.G. and Neidell, M. (2013). "Environment, Health, and Human Capital". *Journal of Economic Literature,* Vol. 51, no. 3, pp. 689-730.

Table 1. Summary of measurements used for assessment of cognitive development by age at follow-up

	Age at follow-up		
	3 years	5 years	7 years
Measurement scales used	BAS Naming Vocabulary	BAS Naming Vocabulary	BAS Word Reading
	Bracken School Readiness (Bracken, 2002)	BAS Pattern Construction	BAS Pattern Construction
		BAS Picture Similarity	NFER Number Skills

Table 2. Characteristics[1] of the analytic samples of the UK Millennium Cohort Study (MCS) children at \age 3, 5 and 7 years.

	MCS2 Age 3 years (n=13,310)	MCS3 Age 5 years (n=14,614)	MCS4 Age 7 years (n=13,058)
Gender - male	6650 (49.6%)	7462 (50.9%)	6578 (50.9%)
Age in months, mean (s.d.)	37.7 (2.5)	62.5 (2.9)	86.8 (3.0)
Ethnicity			
White	11410 (88.3%)	12177 (86.6%)	10885 (85.2%)
Mixed	373 (3.0%)	412 (3.1%)	356 (3.2%)
Indian	329 (1.8%)	372 (1.9%)	333 (2.0%)
Pakistani and Bangladesh	675 (3.4%)	917 (4.1%)	840 (4.7%)
Black or Black British	348 (2.2%)	484 (2.7%)	423 (3.2%)
Others	130 (0.9%)	201 (1.2%)	172 (1.3%)
Unknown	45 (0.4%)	52 (0.4%)	49 (0.4%)
Birth weight			
≥ 2.5kg	12223 (91.6%)	13388 (91.4%)	12000 (91.4%)
< 2.5kg	766 (5.6%)	900 (6.0%)	786 (6.0%)
Unknown	321 (2.8%)	327 (2.6%)	272 (2.6%)
Maternal age at birth in yrs, mean (s.d.)	28.7 (5.9)	28.7 (5.9)	28.4 (5.9)
Household income[2]			
Lowest quintile	2701 (18.9%)	3212 (19.7%)	2652 (19.6%)
Second quintile	2828 (19.3%)	3086 (19.6%)	2665 (19.8%)
Third quintile	2661 (20.3%)	2846 (20.0%)	2658 (20.2%)
Fourth quintile	2551 (20.0%)	2812 (20.0%)	2544 (19.9%)
Highest quintile	2474 (20.8%)	2576 (20.1%)	2526 (20.4%)
Unknown	95 (0.7%)	83 (0.5%)	13 (0.1%)
Mother's education NVQ[3]			
NVQ Level 1	1077 (8.3%)	1110 (7.6%)	894 (7.5%)
NVQ Level 2	3787 (29.3%)	3966 (28.3%)	3426 (27.6%)
NVQ Level 3	1995 (14.7%)	2158 (14.5%)	1985 (14.9%)
NVQ Level 4	3894 (30.1%)	4257 (30.2%)	3984 (29.4%)
NVQ Level 5	538 (4.0%)	778 (5.3%)	871 (6.1%)
Other qualification	364 (2.4%)	455 (2.8%)	386 (2.9%)
None of above / Unknown[4]	1655 (11.1%)	1891 (11.3%)	1512 (11.6%)
Father's education NVQ[3]			
NVQ Level 1	684 (5.2%)	776 (5.4%)	715 (5.9%)
NVQ Level 2	2885 (21.9%)	3170 (22.1%)	2833 (21.8%)
NVQ Level 3	1614 (12.2%)	1760 (12.3%)	1653 (12.5%)
NVQ Level 4	3113 (24.9%)	3314 (24.1%)	3081 (23.5%)
NVQ Level 5	659 (5.1%)	930 (6.5%)	1034 (7.4%)
Other qualification	405 (2.8%)	506 (3.1%)	455 (3.1%)
None of above (baseline)	1234 (7.9%)	1485 (8.7%)	1290 (9.1%)
Unknown	2716 (20.1%)	2674 (17.7%)	1997 (16.8%)
Language spoken in household			
English only	11518 (90.2%)	12522 (90.4%)	11337 (90.1%)
Mostly or half English	1725 (0.3%)	1415 (6.7%)	1192 (6.8%)
Mostly others or others only / Unknown[4]	67 (0.5%)	678 (2.9%)	529 (3.0%)
N of siblings			
0	3380 (25.1%)	2389 (16.4%)	1563 (12.1%)
1	6058 (47.3%)	6821 (48.3%)	5898 (46.2%)
2	2527 (18.5%)	3487 (23.5%)	3562 (27.1%)
3+ / Unknown[4]	1345 (9.1%)	1918 (11.9%)	2035 (14.6%)
Second-hand tobacco smoke[5]			
Yes	2392 (17.6%)	2107 (14.3%)	1672 (13.5%)

No	10851 (81.8%)	12446 (85.3%)	11330 (86.1%)
Unknown	67 (0.5%)	62 (0.4%)	56 (0.4%)
Chronic health conditions			
Yes	2020 (15.4%)	2756 (18.8%)	2348 (18.4%)
No	11213 (84.0%)	11793 (80.8%)	10657 (81.2%)
Unknown	77 (0.6%)	66 (0.4%)	53 (0.4%)
Ever tried breast feeding			
Yes	8844 (67.6%)	9772 (68.1%)	8822 (65.8%)
No	3947 (27.8%)	4318 (27.7%)	3786 (30.1%)
Unknown	519 (4.6%)	525 (4.2%)	450 (4.2%)

[1] Unweighted N (weighted %) unless stated otherwise
[2] House hold income: OECD Income weighted quintiles for UK analysis
[3] National Vocational Qualification ranging from Level 1 (covering routine tasks) to Level 5 (requiring high level of expertise and senior management).
[4] Unknown group with small number is combined with one of other categories to control disclosure risk. However, `unknown' category was used separately in the analysis.
[5] Second-hand tobacco smoke: anyone smoke in the same room as the cohort member

Table 3. Summary of lifelong exposure[ǂ] to neighbourhood air pollution of the study samples

	N of children	NO_2 (μg·m^{-3})	$PM_{2.5}$ (μg·m^{-3})	PM_{10} (μg·m^{-3})	O_3 (days)	SO_2 (μg·m^{-3})	CO (mg·m^{-3})
Birth to Age 3 (A)	13,310	21.73 (10.69)	12.99 (2.85)	20.04 (4.16)	10.32 (6.31)	3.69 (2.30)	1.60 (0.65)
Birth to Age 5 (B)	14,614	20.53 (10.73)	12.35 (2.90)	19.17 (4.11)	9.34 (5.31)	3.51 (2.07)	1.50 (0.56)
Birth to Age 7 (C)	13,058	19.56 (10.57)	11.89 (2.87)	18.24 (3.85)	7.27 (4.12)	3.11 (1.84)	1.34 (0.43)
Average of (A) and (B)	13,285	21.21 (10.96)	12.70 (2.92)	19.66 (4.22)	9.80 (5.77)	3.59 (2.11)	1.56 (.62)
Average of (B) and (C)	12,465	20.15 (10.65)	12.12 (2.90)	18.74 (3.97)	8.30 (4.679)	3.34 (1.93)	1.43 (.49)

ǂ Median (IQR) of occupancy-time-weighted average of annual mean of ambient concentration for all pollutants except CO (maximum of daily 8 hour running mean) and O_3 (the number of days on which daily maximum of 8-hourly concentration is greater than 120μg m^{-3}).

Figure Legends

Figure 1. Percentile difference (95%CI) in cognitive performance per interquartile range (IQR) increase in lifelong exposure to neighbourhood air pollution at age 3, 5 and 7 years (panel A, B and C, respectively). Navy filled circles and lines show point estimates and 95% confidence intervals of Model 1 (partial confounder adjustment) and red open circles the results for Model 2 (fully adjusted models).

Figure 2. Change in percentile difference (95%CI) in cognitive performance per interquartile range increase in lifelong exposure to neighbourhood air pollution.

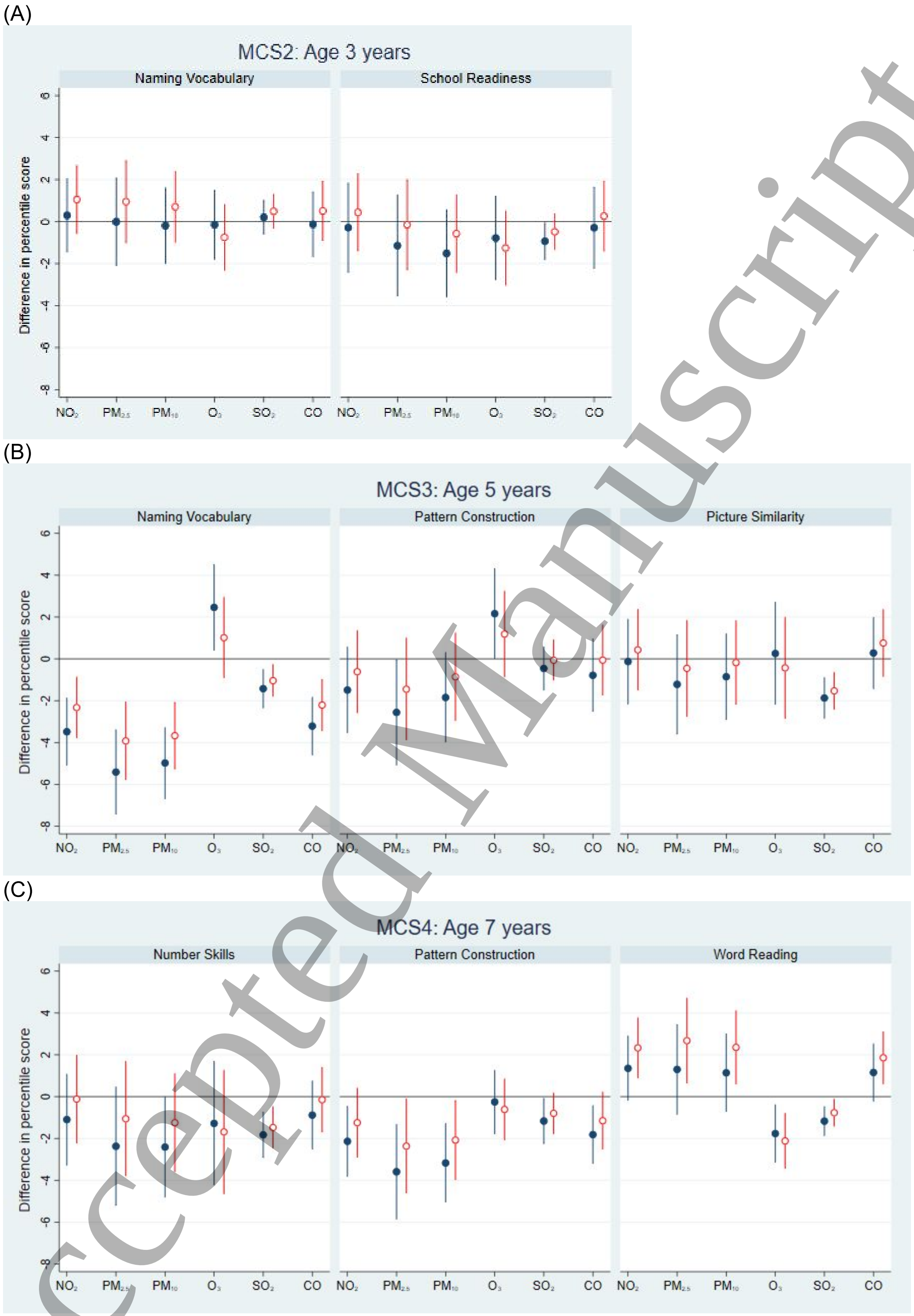
(A)
MCS2: Age 3 years
Naming Vocabulary
School Readiness
Difference in percentile score
-8
-6
-4
-2
0
2
4
6
NO_2
$PM_{2.5}$
PM_{10}
O_3
SO_2
CO
(B)
MCS3: Age 5 years
Naming Vocabulary
Pattern Construction
Picture Similarity
(C)
MCS4: Age 7 years
Number Skills
Pattern Construction
Word Reading

Figure 1. Percentile difference (95%CI) in cognitive performance per interquartile range (IQR) increase in lifelong exposure to neighbourhood air pollution at age 3, 5 and 7 years (panel A, B and C, respectively). Navy filled circles and lines show point estimates and 95% confidence intervals of Model 1 results (partial confounder adjustment), red open circles for Model 2 results (fully-adjusted models).

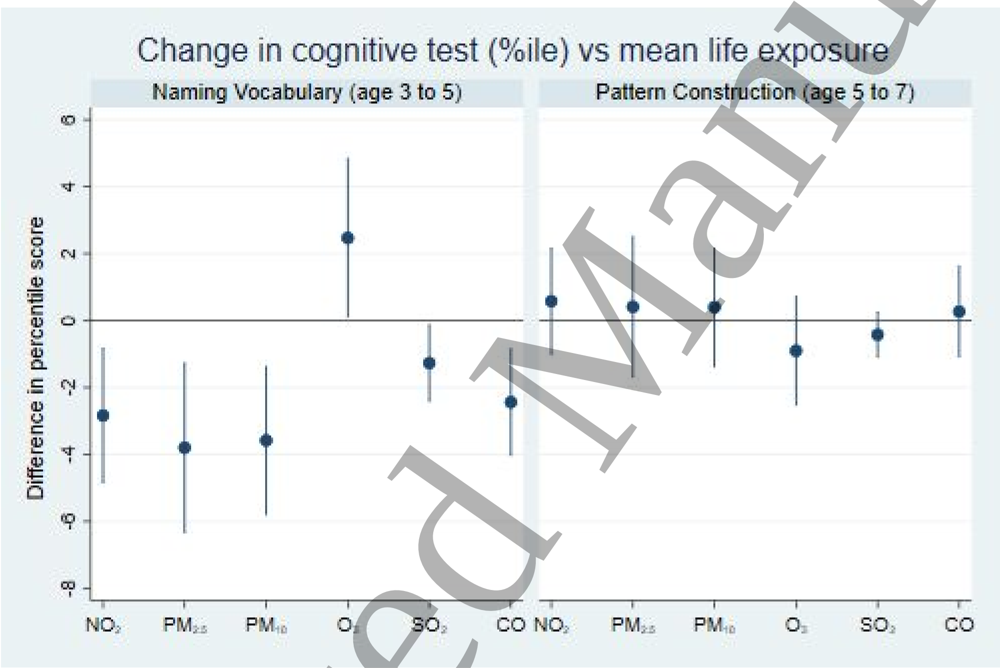

Figure 2. Change in percentile difference (95%CI) in cognitive performance per interquartile range increase in lifelong exposure to neighbourhood air pollution

List of supplementary material

S1. UK Millennium Cohort Study data collection used in this study

S2. Cognition assessment measures in the UK Millennium Cohort Study (MCS) at sweep MCS2-4

S3. Example of Stata codes for Survey Data analysis

Table S4. Correlations between different air pollution exposure

Table S5. Percentile difference (95%CI) in cognitive performance per IQR in lifetime exposure to neighbourhood air pollution among MCS cohort members in the UK at age 3, 5 and 7 years

Table S6. Percentile difference (95%CI) in cognitive development at age 3 to 5 for Naming Vocabulary and at age 5 to 7 for Pattern Construction (per IQR in averaged lifetime exposure to neighbourhood air pollution up to two time points of cognition performance test)

Table S7. Associations between Naming Vocabulary test performance (percentile) at age 5 and risk factors including lifetime exposure to $PM_{2.5}$ among MCS cohort members (n=14,615)

Table S8. Associations between development in Naming Vocabulary (Δ percentile) at age 3 to 5 and risk factors including mean lifetime exposure to $PM_{2.5}$ among MCS cohort members (n=13,285)

Table S9. Associations between development in Pattern Construction (Δ percentile) at age 5 to 7 and risk factors including mean lifetime exposure to $PM_{2.5}$ among MCS cohort members (n=12,465)