PAPER • OPEN ACCESS

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To cite this article: Ai Milojevic *et al* 2021 *Environ. Res. Lett.* **16** 055023

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

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Abstract

Evidence about the impact of air pollution on cognitive development of children has been growing but remains inconclusive. To investigate the association of air pollution exposure and the cognitive development of children in the UK Millennium Cohort Study. 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 tobacco smoke. 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 four 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. 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.

Abbreviations

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

NFER	National Foundation for Educational Research
NO2	nitrogen dioxide
NVQ	National Vocational Qualification
IQ	intelligence quotient
IQR	interquartile range
O3	ozone
OA	output area
PAH(s)	polycyclic aromatic hydrocarbons
PM	particle matters
PM2.5	fine particulate matter with diameter of 2.5 μm or less
PM10	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

1. Introduction

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

Epidemiological evidence for adverse impacts on cognitive development of children has come from studies in the US (Suglia *et al* 2008, Perera *et al* 2009, Harris *et al* 2015), Europe (Guxens *et al* 2014, Sunyer *et al* 2015, Porta *et al* 2016, Lubczynska *et al* 2017) and Asia (Tang *et al* 2008, Jung *et al* 2013, Kim *et al* 2014, 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 2.5 μm or less (PM$_{2.5}$) and 10 μm or less (PM$_{10}$) (Guxens *et al* 2014, Kim *et al* 2014, Harris *et al* 2015, Yorifuji *et al* 2016, Lubczynska *et al* 2017), nitrogen dioxide (NO$_2$) (Jung *et al* 2013, Guxens *et al* 2014, Kim *et al* 2014, Sunyer *et al* 2015, Porta *et al* 2016, Yorifuji *et al* 2016), PAHs (Tang *et al* 2008, Edwards *et al* 2010, Jedrychowski *et al* 2014, Lovasi *et al* 2014, Perera *et al* 2014), 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 (Tang *et al* 2008, Perera *et al* 2009, 2012, Kim *et al* 2014, Yorifuji *et al* 2016) and both (Jedrychowski *et al* 2014). A wide range of cognitive/developmental outcomes were investigated, including verbal and numerical ability (Perera *et al* 2009, 2012, Jedrychowski *et al* 2014, Harris *et al* 2015, Porta *et al* 2016), psychomotor development (Guxens *et al* 2014, Kim *et al* 2014, Lertxundi *et al* 2015), behavioural development milestones (Perera *et al* 2012, Newman *et al* 2013, Gong *et al* 2017, Mortamais *et al* 2017), 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 *et al* 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 MCS. Previously the subset of the UK MCS children ($n = 8198$ MCS in England and Wales) were analysed to assess the association between the Multiple Environmental Deprivation Index (MEDIx) and cognitive ability at age 3 years (Midouhas *et al* 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 3 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 7 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 oversampling 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 (available online at stacks.iop.org/ERL/16/055023/mmedia). 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 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 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 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 SO_2 and CO as pollutants of secondary interest. Exposure classification was based on linkage of the child's place of residence to 1×1 km resolution maps of annual average background pollutant concentrations using the Department for Environment Food & Rural Affairs (DEFRA) 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 h running mean) and O_3 (number of days on which daily maximum of 8 hourly concentration is greater than 120 μg 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 (Chowdry *et al* 2010, Côté *et al* 2013, Aggio *et al* 2016, Midouhas *et al* 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 (<2500 g or not). The family level risk factors were household income (quintile group), mother's education (in 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

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 Bracken School Readiness (Bracken 2002)	BAS Naming Vocabulary BAS Pattern Construction BAS Picture Similarity	BAS Word Reading BAS Pattern Construction NFER Number Skills

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 9500 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 (Model 1 and Model 2). 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 1 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 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).

Table 2. Characteristics[a] of the analytic samples of the UK 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	11 410 (88.3%)	12 177 (86.6%)	10 885 (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			
$\geqslant$2.5 kg	12 223 (91.6%)	13 388 (91.4%)	12 000 (91.4%)
<2.5 kg	766 (5.6%)	900 (6.0%)	786 (6.0%)
Unknown	321 (2.8%)	327 (2.6%)	272 (2.6%)
Maternal age at birth in years, mean (s.d.)	28.7 (5.9)	28.7 (5.9)	28.4 (5.9)
Household income[b]			
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[c]			
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[d]	1655 (11.1%)	1891 (11.3%)	1512 (11.6%)
Father's education NVQ[c]			
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	11 518 (90.2%)	12 522 (90.4%)	11 337 (90.1%)
Mostly or half English	1725 (0.3%)	1415 (6.7%)	1192 (6.8%)
Mostly others or others only/Unknown[d]	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[d]	1345 (9.1%)	1918 (11.9%)	2035 (14.6%)
Second-hand tobacco smoke[e]			
Yes	2392 (17.6%)	2107 (14.3%)	1672 (13.5%)
No	10 851 (81.8%)	12 446 (85.3%)	11 330 (86.1%)
Unknown	67 (0.5%)	62 (0.4%)	56 (0.4%)

(Continued)

Table 2. (Continued.)

	MCS2 age 3 years ($n = 13\,310$)	MCS3 age 5 years ($n = 14\,614$)	MCS4 age 7 years ($n = 13\,058$)
Chronic health conditions			
Yes	2020 (15.4%)	2756 (18.8%)	2348 (18.4%)
No	11 213 (84.0%)	11 793 (80.8%)	10 657 (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%)

[a] Unweighted N (weighted %) unless stated otherwise.

[b] House hold income: OECD Income weighted quintiles for UK analysis.

[c] NVQ ranging from Level 1 (covering routine tasks) to Level 5 (requiring high level of expertise and senior management).

[d] 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.

[e] Second-hand tobacco smoke: anyone smoke in the same room as the cohort member.

Table 3. Summary of lifelong exposure[a] 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)

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

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 counter-intuitive 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
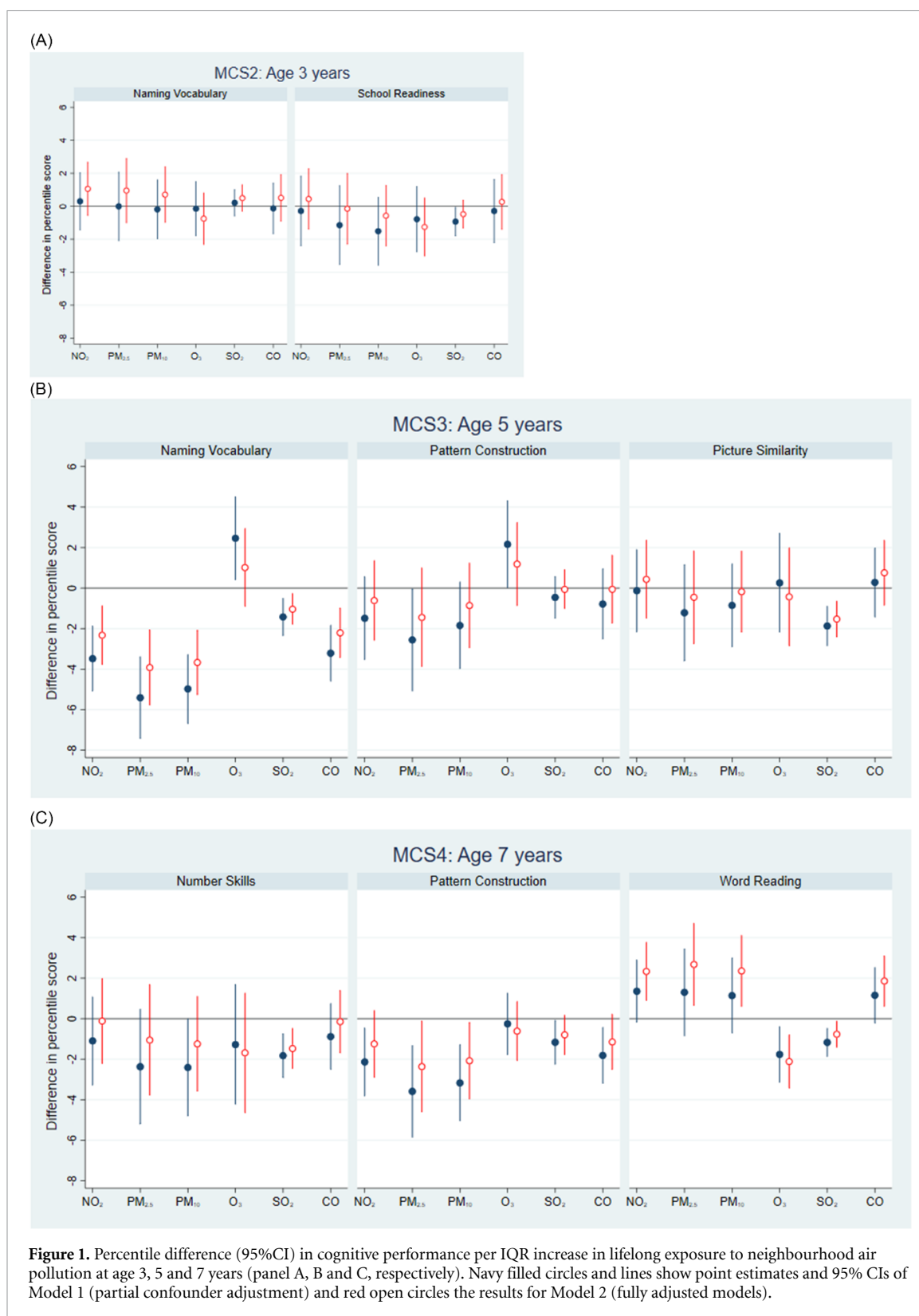
(figure 2). For the pollutants of primary interest, the changes in the percentile score for an IQR increase in pollutant concentration were: $PM_{2.5}$ −3.76 (95% CI −6.27, −1.26), PM_{10} −3.54 (−5.73, −1.36) and NO_2 −2.83 (−4.82, −0.84). The association with O_3 was positive ('protective') and of 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 MCS, provides further evidence of the associations between lifelong exposure to air pollution and the

Figure 1. Percentile difference (95%CI) in cognitive performance per 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% CIs of Model 1 (partial confounder adjustment) and red open circles the results for Model 2 (fully adjusted models).
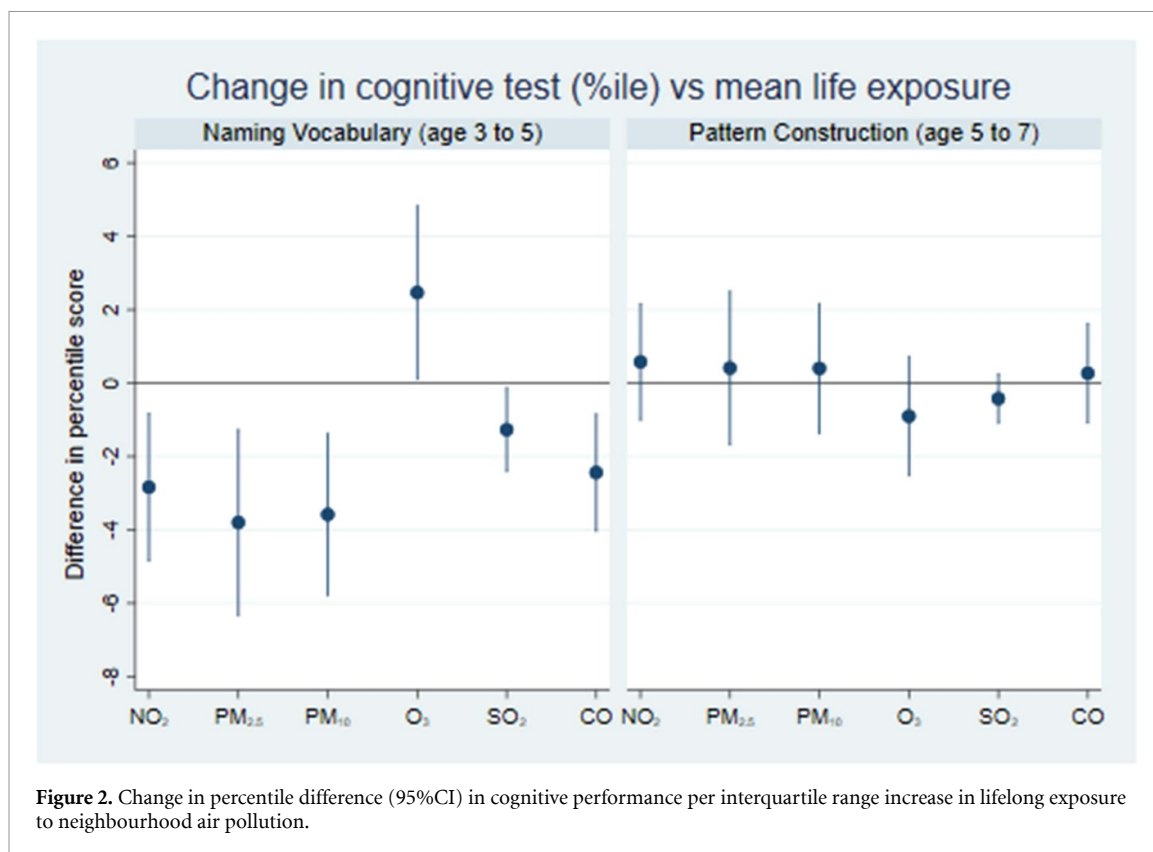
cognitive development of children. To our knowledge, it is the first large nationwide analysis of children from birth to age 7 with standardized measures of cognitive ability.

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

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

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 four 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 (Power *et al* 2016, Peters *et al* 2019). 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 *et al* 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, Yorifuji *et al* 2016, Lubczynska *et al* 2017).

4.3. Mechanisms

Possible mechanisms by which air pollution might affect brain function have been described by Block and Calderón-Garciadueñas (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, 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-Garciadueñas *et al* 2008, 2011), a birth cohort study in New York (Peterson *et al* 2015) and BREATHE studies in Barcelona (Pujol *et al* 2016a, 2016b, Mortamais *et al* 2017) 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 1×1 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 lifelong 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, 2017, 2018), noise (Sunyer *et al* 2015) and indoor air quality and/or dampness (Sunyer *et al* 2015, Midouhas *et al* 2018). 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 *et al* 2018).

4.5. 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.

Data availability statement

No additional data are available.

The data that support the findings of this study are available upon reasonable request from the authors.

Acknowledgments

Ethical approval

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

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