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## NeuroToxicology



#### Data article

# Data relating to prenatal lead exposure and child IQ at 4 and 8 years old in the Avon Longitudinal Study of Parents and Children



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#### ABSTRACT

As part of the Avon Longitudinal Study of Parents and Children (ALSPAC), measures of child IQ were collected by trained psychologists. The Wechsler Pre-school and Primary Scale of Intelligence – Revised UK edition (WPPSI) was used at age 4 years in a subsample of children enrolled in ALSPAC (the Children in Focus cohort), chosen at random from the last 6 months of ALSPAC births (about 10% of the participants). At age 8 years all children enrolled in the main cohort were invited to complete a short form of the Wechsler Intelligence Scale for Children (WISC)-III <sup>UK</sup>. Prenatal blood lead (B-Pb) concentrations were measured by inductively-couple plasma mass spectrometry in samples from women at a median gestation age of 11 weeks. Child blood lead was measured by atomic absorption spectrometry in samples from children attending the Children in Focus clinic at age 30 months. Maternal reports at 32 weeks' gestation were used to generate data on a range of potential confounders. The data were used to determine the associations between prenatal exposure to lead and child IQ at 4 and 8 years. The effect of child B-Pb at 3 years as a moderator of these associations was tested. (For results, please see doi: 10.1016/j. neuro.2017.07.003 Taylor et al., (2017)).

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#### Specifications table

Subject area Human Biology Child development More specific subject area Table Type of data Longitudinal cohort study questionnaire data, biological How data was assessment acquired Data format Edited and analysed Experimental Maternal self-completion auestionnaires: maternal and child factors blood assays for lead; clinic assessments of child IQ Mean IQ scores at 4 and 8 years compared with maternal Experimental features prenatal lead levels and child lead levels at 3 years old Data source Former Avon area, centred around Bristol, UK location

#### Value of the data

Data accessibility

 The ALSPAC dataset contains information on a large number of children in a geographically defined population whose development was monitored to age 24–25 years old at present (2017)).

- The data provide a basis for early identification of adverse effects of environmental exposures (metals and other toxicants).
- The data allow detailed analyses of family and social circumstances and their associations with child development.

#### 1. Data

In this paper, we describe data on child IQ at 4 and 8 years, prenatal B-Pb concentrations and child B-Pb concentrations at age 2.5 years (see Tables).

The ALSPAC study website contains details of all the data that are available through a fully searchable data dictionary:http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/. Data can be obtained by bona fide researchers after application to the ALSPAC Executive Committee (http://www.bristol.ac.uk/alspac/researchers/access/).

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Data are within this article

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**Table 1**Publications using prenatal exposures and child IQ in the ALSPAC cohort.

| Authors                         | Exposure   | Outcome          | Results   |
|---------------------------------|--|------------------|---|
| Alati et al. (2008)             | Prenatal smoking and alcohol   | IQ at 8<br>years | Associations of maternal smoking and alcohol consumption were similar to those for paternal smoking and alcohol consumption, suggesting effect not explained by intrauterine exposure |
| Bath et al. (2013)              | Maternal iodine status   | IQ at 8<br>years | Maternal mild-to-moderate iodine deficiency associated with likelihood of child being in the lowest quartile of verbal IO   |
| Bonilla et al.<br>(2012a)       | Prenatal plasma vitamin B <sub>12</sub>                                      | IQ at 8<br>years | No association  |
| Bonilla et al.<br>(2012b)       | Fasting glucose and type 2 diabetes associated genetic variants in pregnancy | IQ at 8<br>years | No association of maternal fasting glucose genetic risk score<br>Positive association of maternal type 2 diabetes genetic risk score  |
| Freitas-Vilela<br>et al. (2017) | Dietary patterns in pregnancy  | IQ at 8<br>years | Positive association of being in the 'fruit and vegetable' cluster on child IQ compared with the 'meat and potato' cluster and the 'white bread and coffee' cluster                   |
| Golding et al. (2017)           | Prenatal blood mercury   | IQ at 8<br>years | No association providing the mother consumes fish   |
| Hibbeln et al. (2007)           | Prenatal fish consumption  | IQ at 8<br>years | Positive association at maternal fish intakes of >340 g/week  |
| Zuccolo et al.<br>(2013)        | Prenatal alcohol   | IQ at 8<br>years | Positive association of moderate drinking compared with light drinking on child IQ, possibly reflecting residual confounding  |

**Table 2**Publications on lead exposure and measures of child development in the ALSPAC cohort.

| Authors                                      | Exposure                                   | Outcome                                     | Results  |
|--|--|---|--|
| Chandramouli et al. (2009)                   | Child blood lead                           | Academic performance and behaviour          | Negative associations with school performance tests and antisocial behaviour   |
| Maisonet et al. (2014)                       | Prenatal blood lead                        | Puberty timing in girls                     | No associations with age at menarche or rate of attainment of pubertal markers   |
| Taylor et al. (2014a)                        | Prenatal blood lead                        | Secondary sex ratio                         | No association with secondary sex ratio  |
| Taylor et al. (2015a)                        | Prenatal blood lead                        | Birth outcomes                              | Negative associations with anthropometry at birth, mean birthweight and preterm delivery, but not low birthweight          |
| Taylor et al. (2015b)                        | Prenatal and child<br>blood lead           | Balance ability at 7 and 10 years           | No associations with balance ability   |
| Taylor et al. (2016)<br>Taylor et al. (2017) | Prenatal blood lead<br>Prenatal blood lead | Birth outcomes<br>Child IQ at 4 and 8 years | No evidence for supralinear dose–response relationship or lower limit of level of concern<br>No associations with child IQ |

#### 2. Experimental design, materials and methods

#### 2.1. Blood lead measurements

#### 2.1.1. Prenatal samples

Whole blood samples were collected in acid-washed heparin vacutainers (Becton and Dickinson) by midwives as early as possible in pregnancy. Midwives' participation in collecting the bloods was voluntary, dependent on time available and consequently was only obtained in two of the three Health Authority areas of the recruitment region. Altogether 4484 samples were collected at a median gestational age of 11 weeks (range 1–42 weeks, mode 10 weeks, interquartile range 9–13 weeks). The social background of the women who gave the samples did not differ from the rest of the ALSPAC population apart from being slightly older and more educated (Taylor et al., 2013). Samples were stored at 4°C at the collection site and then sent to the central Bristol laboratory within 0–4 days. These samples were kept at room temperature for up to 3 h during transfer, and were stored at 4°C as whole blood in the original tubes for 18–19 years before being sent for analysis.

The method of assay of lead has been described in detail elsewhere (Taylor et al., 2013). In brief, the laboratory of Robert

Jones at the Centers for Disease Control and Prevention (CDC) developed methods to prepare the samples for analysis of whole blood lead (CDC method 3009.1). Clotted whole blood was digested to remove all clots before being analysed using inductively coupled plasma dynamic reaction cell mass spectrometry (ICP-DRC-MS). Two levels of bench quality control (QC) materials, as well as a blind QC material, were used for daily quality control.

There were 4484 samples available for lead assays of which 4285 were successfully analysed (tube/vial broken n=7, suspect sample n=3, quantity not sufficient for repeat testing n=67, lab error n=122). One of the samples had a lead concentration below the limit of detection of the assay  $(0.24\,\mu g/dL)$ . For this sample, in consideration of the distribution of the lead concentrations, a value of 0.7 times the limit of detection value (limit of detection/ $\sqrt{2}$ ) was considered to be a better estimate of the value than taking a midpoint (Hornung and Reed, 1990; Centers for Disease Control and Prevention, 2005). The mean level was  $3.67\pm1.47$  (range 0.29-19.14, median 3.41)  $\mu g/dL$ .

#### 2.1.2. Child samples

A randomly selected sample of parents whose babies were born within the last 6 months of enrollment into ALSPAC were invited to bring their children to a research clinic (Children in Focus, CiF) at

**Table 3**Other publications on prenatal and child lead measures in ALSPAC.

| Authors                  | Exposure            | Results   |
|--------------------------|---------------------|---|
| Golding et al. (1998)    | Child blood lead    | Documentation of child blood lead level   |
| Taylor et al. (2013)     | Prenatal blood lead | Environmental factors predicting prenatal blood lead level                            |
| Taylor et al. (2014b)    | Prenatal blood lead | Documentation and review of prenatal blood levels and international levels of concern |
| Warrington et al. (2015) | Maternal blood lead | Association with polymorphism in ALAD   |

**Table 4**Characteristics of ALSPAC participants included and excluded in the study (complete cases).

|                    | Age 4 years    |                |         | Age 8 years    | Age 8 years    |         |  |  |
|--------------------|----------------|----------------|---------|----------------|----------------|---------|--|--|
|                    | Included       | Excluded       | P value | Included       | Excluded       | P value |  |  |
| Mother             |                |                |         |                |                |         |  |  |
| Education          |                |                |         |                |                |         |  |  |
| None/CSE           | 47 (13.5%)     | 2464 (20.4%)   | 0.004   | 223 (12.2%)    | 2288 (21.5%)   | < 0.001 |  |  |
| Vocational         | 28 (8.0%)      | 1198 (9.9%)    |         | 141 (7.7%)     | 1085 (10.2%)   |         |  |  |
| O level            | 123 (35.3%)    | 4194 (34.6%)   |         | 600 (32.9%)    | 3717 (35.0%)   |         |  |  |
| A level            | 95 (27.3%)     | 2703 (22.3%)   |         | 499 (27.4%)    | 2299 (21.6%)   |         |  |  |
| Degree             | 55 (15.8%)     | 1549 (12.8%)   |         | 360 (19.7%)    | 1244 (11.7%)   |         |  |  |
| Whole life in Avon |                |                |         |                |                |         |  |  |
| Yes                | 174 (50.0%)    | 6848 (53.6%)   | 0.192   | 877 (48.1%)    | 6145 (54.3%)   | < 0.001 |  |  |
|                    | 174 (50.0%)    | 5939 (46.4%)   |         | 946 (51.9%)    | 5167 (45.7%)   |         |  |  |
| Parity             |                |                |         |                |                |         |  |  |
| 0                  | 158 (45.4%)    | 5604 (46.4%)   | 0.870   | 839 (46.0%)    | 4923 (44.8%)   | 0.331   |  |  |
| ≥1                 | 190 (54.6%)    | 6860 (53.6%)   |         | 984 (54.0%)    | 6066 (55.2%)   |         |  |  |
| Smoking            |                |                |         |                |                |         |  |  |
| No                 | 301 (86.5%)    | 9432 (79.0%)   | 0.001   | 1567 (86.0%)   | 8166 (78.1%)   | < 0.001 |  |  |
| Yes                | 47 (13.5%)     | 2501 (21.0%)   |         | 256 (14.0%)    | 2292 (21.9%)   |         |  |  |
| Age                |                |                |         |                |                |         |  |  |
| < 25               | 48 (13.8%)     | 3307 (24.2%)   | < 0.001 | 227 (12.5%)    | 3128 (25.6%)   | < 0.001 |  |  |
| ≥25–29             | 130 (37.4%)    | 5302 (38.7%)   |         | 697 (38.2%)    | 4735 (38.7%)   |         |  |  |
| _<br>≥30–34        | 125 (35.9%)    | 3744 (27.3%)   |         | 659 (36.1%)    | 3210 (26.3%)   |         |  |  |
| _<br>≥35           | 45 (12.9%)     | 1347 (9.8%)    |         | 240 (13.2%)    | 1152 (9.4%)    |         |  |  |
| Housing            |                |                |         |                |                |         |  |  |
| Mortgaged/owned    | 283 (81.3%)    | 9318 (73.1%)   | 0.001   | 1538 (84.4%)   | 8063 (71.3%)   | < 0.001 |  |  |
| Rented/other       | 65 (18.7%)     | 3425 (26.9%)   |         | 285 (15.6%)    | 3205 (28.4%)   |         |  |  |
| Child              |                |                |         |                |                |         |  |  |
| Gestation (weeks)  | $39.6 \pm 1.7$ | $39.3 \pm 2.1$ | 0.009   | $39.5 \pm 1.8$ | $39.3 \pm 2.1$ | 0.003   |  |  |
| Birthweight (g)    | $3495 \pm 535$ | $3382 \pm 574$ | < 0.001 | $3432 \pm 568$ | $3378 \pm 573$ | < 0.001 |  |  |
| Sex                |                |                |         |                |                |         |  |  |
| Female             | 151 (43.4%)    | 9057 (50.8%)   | 0.064   | 899 (49.3%)    | 8309 (48.2%)   | 0.364   |  |  |
| Male               | 197 (56.6%)    | 9658 (47.6%)   |         | 924 (50.7%)    | 8931 (51.8%)   |         |  |  |

age 30 months. Parental consent for a venous blood sample was obtained from 81% of the 1135 children in the CiF group. A venous blood sample was collected in lead-free tubes from 71% (n = 653) of clinic attenders; 69 samples had insufficient volume for analysis, leaving 582 samples for analysis.

The blood lead concentration was measured at Southampton General Hospital, UK, by atomic absorption spectrometry using micro-sampling flame atomisation. Details of the quality control procedures have been published (Chandramouli et al., 2009). The mean level was  $4.22 \pm 3.12$  (range 0.83-27.56, median 3.31) µg/dl.

#### 2.2. Child IQ measurements

#### 2.2.1. IQ at age 4 years

Mental development at age 4 years was measured using the Wechsler Pre-school and Primary Scale of Intelligence – Revised UK edition (WPPSI) (Wechsler, 1990) at a research clinic for children in the CiF subsample. All cores scales were administered. The children were also given a digit span test of short term memory, devised and standardised by Professor Susan Gathercole (research psychologist).

Inter-rater reliability was ensured as follows. The testers were overseen by Steve Gibbs, a tester with long experience of psychometric testing with ALSPAC. He observed each tester, met with the group regularly to discuss the precise administration of each test, and supervised and checked their scoring. Each tester scored four videos of tests and interindividual scores were compared.

The WPPSI comprises ten subtests: five verbal and five performance. The verbal subtest scores were combined to make up the *verbal IQ*, and the performance scores combined to make up the *performance IQ*. The ten subtest scores were combined to produce a full-scale IQ score. Following each child's session, which usually lasted 50–60 min, the parent or carer was given a short

questionnaire asking whether the child's behaviour and performances was typical, and if not, how and why.

If a child completed fewer than four subtests on the performance scale then the final performance IQ score was not calculated (and therefore not the full-scale score either). If, however, the child completed four out of the five subtests, the mean of the four subtests was calculated and imputed for the subtest not completed, so that a performance score could be computed. This *prorating* is standard WPPSI practice. Identical rules applied to the verbal score. Thus, some children, although not completing a subtest, had a score for that subtest.

#### 2.2.2. IQ at 8 years

Mental development at age 8 years was measured by the Wechsler Intelligence Scale for Children WISC-III UK (Wechsler et al., 1992) at a research clinic for all children enrolled in the ALSPAC cohort. A short form of the measure was employed, where alternate items were used for all subtests, with the exception of the coding subtest which was administered in full. Hence the length of the sessions was reduced and the children were less likely to become tired. The WISC comprises five verbal subtests (Information, Similarities, Arithmetic, Vocabulary, Comprehension) and five performance subtests (picture completion, coding, picture arrangement, block design, object assembly). The children were also given the forwards and backwards digit span task (a measure of short-term memory). The verbal subtest scores were combined to make up the verbal IQ and the performance scores were combined to make the performance IQ. The ten subtest scores were combined to produce a full-scale (total) IQ score.

Inter-rater reliability was ensured as follows: the testers were trained psychologists, who were overseen by Dr Claire Bell, a senior psychologist with long experience of psychometric testing within the study. She observed each tester, and met with the group

**Table 5** Maternal characteristics by  $\le 5$  or  $> 5 \mu g/dl (n (%))$  (complete cases at age 8 years).

|                        | Maternal B-Pb ( | ug/dl)         | P value |
|------------------------|-----------------|----------------|---------|
|                        | ≤5              | >5             |         |
| Mother                 | -               |                |         |
| Education              |                 |                |         |
| None/CSE               | 191 (12.3%)     | 32 (11.9%)     | < 0.001 |
| Vocational             | 127 (8.2%)      | 14 (5.2%)      |         |
| O level                | 518 (33.3%)     | 82 (30.5%)     |         |
| A level                | 439 (28.2%)     | 60 (22.3%)     |         |
| Degree                 | 279 (18.0%)     | 81 (30.1%)     |         |
| Whole life in Avon     |                 |                |         |
| No                     | 793 (51.0%)     | 153 (56.9%)    | 0.076   |
| Yes                    | 761 (49.0%)     | 116 (43.1%)    |         |
| Parity                 | ( ,             | , ,            |         |
| 0                      | 705 (45.4%)     | 134 (49.8%)    | 0.177   |
| >1                     | 849 (54.6%)     | 135 (50.2%)    |         |
| Smoking                | ()              | ()             |         |
| Yes                    | 191 (12.3%)     | 65 (24.2%)     | < 0.001 |
| No                     | 1363 (87.7%)    | 204 (75.8%)    | (0.00   |
| Age                    | 1505 (071770)   | 201 (75.0%)    |         |
| <25                    | 206 (13.2%)     | 21 (7.7%)      | 0.008   |
| ≥25-29                 | 597 (38.4%)     | 100 (37.2%)    | 0.000   |
| ≥30-34                 | 562 (36.2%)     | 97 (36.1%)     |         |
| >35                    | 189 (12.2%)     | 51 (19.0%)     |         |
| Alcohol                | 103 (12.2%)     | 31 (13.0%)     |         |
| Yes                    | 407 (32.8%)     | 110 (55.8%)    | 0.002   |
| No                     | 832 (67.2%)     | 87 (44.2%)     | 0.002   |
| Housing                | 032 (07.2%)     | 07 (11.270)    |         |
| Mortgaged/owned        | 1299 (83.6%)    | 239 (88.8%)    | 0.028   |
| Rented/other           | 255 (16.4%)     | 30 (11.2%)     | 0.020   |
| Family adversity index | 233 (10.1%)     | 30 (11.270)    |         |
| 0–5                    | 1532 (98.6%)    | 260 (96.7%)    | 0.024   |
| 6–11                   | 22 (1.4%)       | 8 (3.3%)       | 0.024   |
| Crowding index         | 22 (1.470)      | 0 (3.5%)       |         |
| <0.5                   | 738 (47.5%)     | 157 (58.4%)    | 0.011   |
| >0.5-0.75              | 507 (32.6%)     | 70 (26.0%)     | 0.011   |
| >0.75-0.75<br>>0.75-1  | 255 (16.4%)     | 36 (13.4%)     |         |
| >1                     | 54 (3.5%)       | 6 (2.2%)       |         |
|                        | 31 (3.2.0)      | 3 (2.2.0)      |         |
| Child                  |                 |                |         |
| Gestation (weeks)      | $39.5 \pm 1.75$ | $39.2 \pm 2.1$ | 0.028   |
| Birthweight (g)        | $3442 \pm 559$  | $3373 \pm 613$ | 0.068   |
| Sex                    |                 |                |         |
| Female                 | 756 (48.6%)     | 143 (53.2%)    | 0.172   |
| Male                   | 798 (51.4%)     | 126 (46.8%)    |         |

Chi-square/ANOVA.

regularly to discuss the precise administration of each subtest and checked their scoring.

The task was made as reassuring and unstressful for the child as possible, with the tester explaining that the child would be playing lots of games: looking at pictures, doing puzzles, making patterns

**Table 7**Association of prenatal B-Pb > 5  $\mu$ g/dl with child IQ at age 4 and 8 years (logistic regression) in ALSPAC: multiple imputation.

| Age (years) | IQ test  |                | n    | Regression analyse | s: Model 3 |
|-------------|----------|----------------|------|--------------------|------------|
|             |          |                |      | OR (95% CI)        | P          |
| Multiple im | putation |                |      |                    |            |
| 4           | WPPSI    | Verbal IQ      | 404  | 1.43 (0.63, 3.23)  | 0.397      |
|             |          | Performance IQ | 404  | 0.99 (0.42, 2.33)  | 0.981      |
|             |          | Total IQ       | 404  | 0.91 (0.37, 2.24)  | 0.838      |
| 8           | WISC     | Verbal IQ      | 2217 | 0.72 (0.52, 1.00)  | 0.053      |
|             |          | Performance IQ | 2217 | 1.00 (0.74, 1.35)  | 0.995      |
|             |          | Total IQ       | 2217 | 0.74 (0.53. 1.02)  | 0.065      |

Reference: highest three quartiles of IQ score elided (vs lowest IQ quartile) See Methods for details of variables.

Model 3: adjusted for sex, actual age at testing, maternal education, smoking in pregnancy, alcohol in pregnancy, maternal age, parity, time resident in Avon, housing tenure, household crowding, family adversity index, weighted life events

and answering some questions. It was explained that some of the things might get quite difficult but not to worry as they were the same things we would ask older children to play. All children were encouraged to have a go at things, even if they thought they were just guessing.

Raw scores were calculated according to the items used in the alternate item form of the WISC. This was achieved by summing the individual items within each subtest and multiplying by 2 for picture completion, information, arithmetic, vocabulary, comprehension and picture arrangement; multiplying by 5/3 for similarities, multiplying by 3/2 for object assembly and block design, thus, making the raw scores comparable to those that would have been obtained had the full test been administered (the raw score for the coding subtest was calculated in the standard way as the full subtest was administered). It is because of this multiplication that some of the scores do not follow a smooth distribution.

For a small number of cases, scores could be imputed where a tester or computer error had been made and such a score would otherwise have been missing. Dr Bell made such decisions on a case by case basis.

#### 2.3. Questionnaire assessments

The ALSPAC study included the distribution of questionnaire by mail to the pregnant woman for self-completion and return in a pre-paid envelope at 32 weeks' gestation.

**Table 6**Effect sizes of selected variables in model 3 in Table 2 in Taylor et al., 2017 (R<sup>2</sup>) (complete cases).

| Variable                    | R <sup>2</sup> (4 years) |                |          | $\Delta R^2$ (8 years) |                |          |  |  |
|-----------------------------|--------------------------|----------------|----------|------------------------|----------------|----------|--|--|
|                             | Verbal IQ                | Performance IQ | Total IQ | Verbal IQ              | Performance IQ | Total IQ |  |  |
| Maternal Pb                 | 0.001                    | 0.001          | 0.001    | 0.001                  | 0.000          | 0.001    |  |  |
| Sex                         | 0.011                    | 0.009          | 0.013    | 0.001                  | 0.004          | 0.000    |  |  |
| Age at testing              | 0.008                    | 0.000          | 0.003    | 0.008                  | 0.010          | 0.009    |  |  |
| Maternal education          | 0.018                    | 0.022          | 0.026    | 0.036                  | 0.035          | 0.047    |  |  |
| Smoking                     | 0.003                    | 0.002          | 0.003    | 0.000                  | 0.000          | 0.000    |  |  |
| Alcohol                     | 0.003                    | 0.005          | 0.005    | 0.000                  | 0.000          | 0.000    |  |  |
| Age                         | 0.020                    | 0.002          | 0.012    | 0.011                  | 0.000          | 0.003    |  |  |
| Parity                      | 0.028                    | 0.003          | 0.016    | 0.006                  | 0.000          | 0.000    |  |  |
| Time in Avon                | 0.002                    | 0.002          | 0.003    | 0.009                  | 0.001          | 0.006    |  |  |
| Housing tenure              | 0.003                    | 0.010          | 0.007    | 0.003                  | 0.002          | 0.003    |  |  |
| Household crowding          | 0.001                    | 0.006          | 0.003    | 0.001                  | 0.000          | 0.001    |  |  |
| Family adversity index      | 0.000                    | 0.006          | 0.003    | 0.002                  | 0.003          | 0.004    |  |  |
| Weighted life events scores | 0.001                    | 0.006          | 0.003    | 0.000                  | 0.000          | 0.000    |  |  |

 $R^2 > 0.010$  shown in bold.

**Table 8**Association of prenatal B-Pb on child IQ at age 8 years by sex in ALSPAC: multiple imputation.

| Age<br>(years) | IQ test   |             | IQ scores        |                  |       | Regression analyses: Model 3 <sup>a</sup> |                                       |       |                    |                                       |      |  |
|----------------|-----------|-------------|------------------|------------------|-------|---|---------------------------------------|-------|--------------------|---------------------------------------|------|--|
| (years)        |           |             | Boys             | Girls p          | p     | Boys                                      |                                       |       | Girls              |                                       |      |  |
|                |           |             |                  |                  |       | R <sup>2</sup>                            | Unstandardised B coefficient (95% CI) | p     | R <sup>2</sup>     | Unstandardised B coefficient (95% CI) | p    |  |
| Multiple       | imputatio | on          |                  |                  |       |   |                                       |       |                    |                                       |      |  |
| 4              | WPPSI     | n           | 230              | 174              |       |   |                                       |       |                    |                                       |      |  |
|                |           | Verbal IQ   | $99.2 \pm 13.4$  | $102.2\pm13.2$   | 0.022 | $0.192^{b}$                               | -0.01 (-1.26, 1.24)                   | 0.989 | 0.205              | -0.65(-1.95, 0.65)                    | 0.32 |  |
|                |           | Performance | 106.8 + 15.2     |                  |       |   | 0.24 (-0.20, 1.77)                    | 0.744 | 0.157              | -0.12 (-1.47, 1.23)                   | 0.80 |  |
|                |           | IQ          |                  |                  |       |   | ,,                                    |       |                    | (,,                                   |      |  |
|                |           | Total IQ    | $103.1 \pm 14.3$ | $107.1 \pm 13.5$ | 0.005 | $0.220^{b}$                               | 0.20 (-1.12, 1.51)                    | 0.767 | 0.212              | -0.48 (-1.80, 0.84)                   | 0.47 |  |
|                |           |             |                  |                  |       |   | , , , ,                               |       |                    | ,                                     |      |  |
| 8              | WISC      | n           | 1113             | 1104             |       |   |                                       |       |                    |                                       |      |  |
| _              |           | Verbal IQ   | $108.1 \pm 17.6$ | $107.3 \pm 16.0$ | 0.284 | 0.181 <sup>b</sup>                        | -0.01 (-0.68, 0.67)                   | 0.985 | 0.233 <sup>b</sup> | 0.75 (0.18, 1.31)                     | 0.00 |  |
|                |           | Performance | $98.7 \pm 17.4$  | $100.6 \pm 16.4$ |       | _   |                                       |       |                    | 0.56 (-0.06, 1.19)                    | 0.07 |  |
|                |           | IQ          | 20.7 ± 17.1      | 100.0 ± 10.1     | 0.500 | 0.000                                     | 3.23 ( 3.23, 0.17)                    | 0.027 | 0.103              | 0.00 ( 0.00, 1.10)                    | 3.0  |  |
|                |           | Total IQ    | $104.2 \pm 17.0$ | $104.8 \pm 15.7$ | 0.412 | 0.175                                     | -0.12 (-0.77, 0.54)                   | 0.727 | 0 221 <sup>b</sup> | 0.74 (0.19, 1.30)                     | 0.0  |  |
|                |           | Total IQ    | 10-1.2 ± 17.0    | 104.0 ± 15.7     | 0.412 | b.173                                     | -0.12 (-0.77, 0.54)                   | 0.727 | 0.221              | 0.74 (0.13, 1.30)                     | 0.0  |  |

See Methods for details of variables.

**Table 9**Association of prenatal B-Pb on child IQ at age 4 years and 8 years (linear regression) in ALSPAC: multiple imputation.

| Age (years)  | IQ test           |                       |         | $R^2$              | Unstandardised B coefficient (95% CI) | P values      |                                 |  |
|--------------|-------------------|-----------------------|---------|--------------------|---------------------------------------|---------------|---------------------------------|--|
|              |                   |                       |         |                    |                                       | B coefficient | Sex × prenatal B-Pb interaction |  |
| Multiple imp | outation          |                       |         |                    |                                       |               |                                 |  |
| 4            | WPPSI $(n = 404)$ | Verbal IQ             | Model 3 | 0.182 <sup>b</sup> | -0.17 (-1.06, 0.72)                   | 0.707         | 0.775                           |  |
|              |                   | Performance IQ        | Model 3 | 0.154 <sup>b</sup> | 0.22 (-0.76, 1.20)                    | 0.656         | 0.985                           |  |
|              |                   | Total IQ              | Model 3 | 0.204 <sup>b</sup> | 0.02 (-0.90, 0.94)                    | 0.960         | 0.831                           |  |
| 8            | WISC (n = 2217)   | Verbal IQ             | Model 3 | 0.201 <sup>b</sup> | 0.39 (-0.05, 0.82)                    | 0.082         | 0.079                           |  |
|              | , ,               | Performance IQ        | Model 3 | $0.095^{b}$        | 0.19 (-0.28, 0.65)                    | 0.438         | 0.112                           |  |
|              |                   | Total IQ <sup>a</sup> | Model 3 | 0.192 <sup>b</sup> | 0.33 (-0.10, 0.76)                    | 0.127         | 0.061                           |  |

See Methods for details of variables.

Model 3: adjusted for sex, actual age at testing, maternal education, smoking in pregnancy, alcohol in pregnancy, maternal age, parity, time resident in Avon, housing tenure, household crowding, family adversity index, weighted life events score.

#### 2.4. Publications

Publications on associations of prenatal exposures with child IQ in the ALSPAC cohort are shown in Table 1. Publications on associations of prenatal lead with measures of child development are shown in Table 2. Other publications using the prenatal and child lead measures are shown in Table 3.

#### 2.5. Associations with prenatal lead

In our parallel paper (Taylor et al., 2017) we show that prenatal lead exposure was not associated with adverse effects on child IQ at age 4 or 8 years in ALSPAC. There was, however, some evidence to suggest that boys are more susceptible than girls to prenatal exposure to lead. Here we show:

- (i) Characteristics of ALSPAC participants included and excluded in the study (complete cases) (Table 4)
- (ii) Maternal characteristics by B-Pb  $\leq$ 5 or  $>5 \mu g/dl$  (n (%)) (complete cases at age 8 years) (Table 5)
- (iii) Effect sizes of selected variables in model 3 in Table 2 of the parallel paper (Taylor et al., 2017) (R<sup>2</sup>) (complete cases) (Table 6)

- (iv) Association of prenatal B-Pb >5  $\mu g/dl$  with child IQ at age 4 and 8 years (logistic regression) in ALSPAC: multiple imputation (Table 7)
- (v) Association of prenatal B-Pb on child IQ at age 8 years by sex in ALSPAC: multiple imputation (Table 8)
- (vi) Association of prenatal B-Pb on child IQ at age 4 years and 8 years (linear regression) in ALSPAC: multiple imputation (Table 9)
- (vii) Effect of maternal haemoglobin in the association of prenatal B-Pb and child IQ (complete cases) (Table 10)
- (viii) Study flow chart (Fig. 1)

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<sup>&</sup>lt;sup>a</sup>Model 3: adjusted for sex, actual age at testing, maternal education, smoking in pregnancy, alcohol in pregnancy, maternal age, parity, time resident in Avon, housing tenure, household crowding, family adversity index, weighted life events score.

<sup>&</sup>lt;sup>b</sup>R<sup>2</sup> for 20th imputation.

 $<sup>^{</sup>a}$  n = 1823.

<sup>&</sup>lt;sup>b</sup> R<sup>2</sup> for 20th imputation.

**Table 10** Effect of maternal Hb in association of prenatal Pb and child IQ (complete cases).

| Age (years) | IQ test         |                       |                          | $R^2$ | Unstandardised B coefficient (95% CI) <sup>a</sup> | P value |
|-------------|-----------------|-----------------------|--------------------------|-------|--|---------|
| 4           | WPPSI (n = 246) | Verbal IQ             | Model 3                  | 0.216 | -0.65 (-1.77, 0.47)                                | 0.254   |
|             |                 |                       | Model 3 plus maternal Hb | 0.216 | -0.63(-1.76, 0.49)                                 | 0.269   |
|             |                 | Performance IQ        | Model 3                  | 0.168 | -0.61 (-1.94, 0.73)                                | 0.372   |
|             |                 |                       | Model 3 plus maternal Hb | 0.168 | -0.62 (-0.96, 0.73)                                | 0.367   |
|             |                 | Total IQ              | Model 3                  | 0.226 | -0.69(-0.19, 0.48)                                 | 0.247   |
|             |                 |                       | Model 3 plus maternal Hb | 0.226 | -0.69 (-1.88, 0.50)                                | 0.252   |
| 8           | WISC (n = 1328) | Verbal IQ             | Model 3                  | 0.189 | 0.23 (-0.35, 0.80)                                 | 0.440   |
|             |                 |                       | Model 3 plus maternal Hb | 0.189 | 0.25 (-0.33, 0.83)                                 | 0.394   |
|             |                 | Performance IQ        | Model 3                  | 0.112 | 0.08 (-0.53, 0.68)                                 | 0.804   |
|             |                 |                       | Model 3 plus maternal Hb | 0.112 | 0.10 (-0.51, 0.71)                                 | 0.743   |
|             |                 | Total IQ <sup>b</sup> | Model 3                  | 0.195 | 0.20 (-0.36, 0.76)                                 | 0.480   |
|             |                 |                       | Model 3 plus maternal Hb | 0.195 | 0.23 (-0.33, 0.79)                                 | 0.421   |

Model 3: adjusted for sex, actual age at testing, maternal education, smoking in pregnancy, alcohol in pregnancy, maternal age, parity, time resident in Avon, housing tenure, household crowding, family adversity index, weighted life events score.

a n=1823.bR2 for 20th imputation.

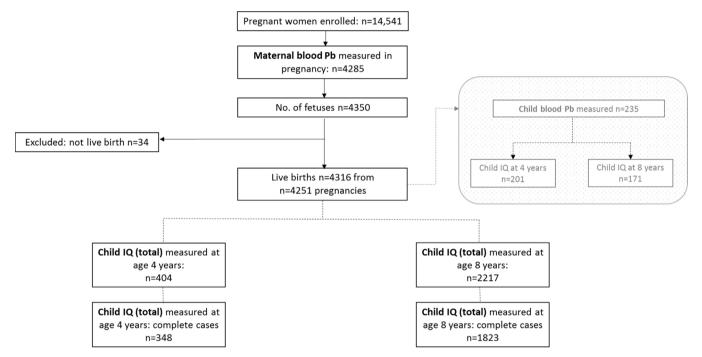


Fig. 1. Study flow chart.

involvement in the study design nor in the collection, analysis and interpretation of the data.

### **Completing financial interests**

The authors have no competing interests.

#### **Ethics approval**

Ethics approval for the study was obtained from the ALSPAC Ethics and Law Committee and Local Research Ethics Committees.

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