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The Association between Caesarean Section and Cognitive Ability in Childhood

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Running Title:

CS and Child Cognitive Ability.

Abstract

Purpose: Global rates of Caesarean section (CS) rates have increased rapidly in recent years. This is a growing public health concern as it has been proposed that CS may impact cognitive outcomes in childhood. However the evidence for this association is limited and inconsistent. Therefore, the aim of this study was to investigate the relationship between obstetric mode of delivery and longitudinal cognitive outcomes in childhood.

Methods: We examined this question using data from a longitudinal cohort study of 8,845 participants from the Millennium Cohort Study, a nationally representative UK cohort, who completed a range of verbal and visual-spatial cognitive assessments at ages 3, 5, 7 and 11 years.

Results: We found a statistically significant association between planned CS and visual-spatial cognitive delay in the pattern construction assessment at age 5 (OR 1.31, 95% CI 0.99 to 1.72) and Age 7 (OR 1.42, 95% CI 1.12 to 1.81). Additionally planned CS was also associated with increased odds of "Early Childhood Delay" (OR 1.70, 95% CI 1.15 to 2.50) and borderline increased odds of "Persistent Delay" (OR 1.37, 95% CI 0.99 to 1.89) in visual-spatial cognitive tests. Mode of delivery was not associated with verbal ability or with patterns of delay at any age point in verbal cognitive tests.

Conclusion: We have reported a small association between planned CS and visual-spatial cognitive delay in childhood. However while this result should be interpreted with caution, it highlights the need to further explore this potential relationship and the causal basis of such an association.

Keywords: Caesarean Section, Obstetric Mode of Delivery, Cognitive Ability

Introduction

The World Health Organisation recommend a 15% ceiling of births by Caesarean section (CS) [1]. However globally the rate of CS has increased rapidly [2] and in the UK it has risen from 21.4% in 2000 to 26.4% in 2013 [3]. This is a concern as it is uncertain what long-term sequelae may result [4]. Moreover, given the high incidence of CS, small increases in the risk of adverse outcomes may have a large effect on the population [5]. One outcome that is of increasing interest is cognitive ability in childhood and is of primary interest across health, education and social sectors because it strongly influences future academic performance and mental health well into adulthood [6]. Impaired cognitive ability in childhood has been linked to a range of later adverse health outcomes including smoking habits, depression, cardiovascular disease, cancers and all-cause mortality [6]. This association exists as a gradient across the entire spectrum of cognitive ability and not just at the extremes [6]. Therefore it is important to investigate the determinants of cognitive ability, particularly modifiable factors, in order to better understand the relationship between these determinants and cognitive ability and all-cause morbidity.

A recent paper from Fitzpatrick et al. investigated the association between gestational age and cognitive outcomes in participants of the UK MCS [7]. They found that children born very or moderately preterm had poorer spatial working memory cognitive performance at age 11 but had no difference in verbal cognitive performance compared with those born at term. Previous studies have also used the MCS to find that lower gestational age is associated with increased risk of scoring below -1 standard deviation (SD) in a range of cognitive test at ages 3, 5 and 7 years old [8] and is associated with an overall poorer educational achievement at age 5 compared with those born at term [9].

Mode of delivery is intrinsically associated with gestational age, as the obstetrical circumstances which lead to planned or emergency CS vary in incidence according to the stage of the pregnancy. Our study controls for gestational age and sub group analysis additionally allows us to examine the effect of CS on cognitive outcomes independent of gestational age.

To date only a small number of studies have examined the relationship between CS and cognitive ability in childhood. A large study of ~1.5 million children found a small association between both planned and emergency CS and poor school performance in children aged 16 [10]. Similarly a study of ~4,000 children also found a similar negative association between CS and a range of cognitive outcomes in Australian children aged 4 to 9 years [11]. Moreover a sensitivity analysis revealed that bias by residual confounding was unlikely and that a causal

association was possible [11]. In contrast however, other studies have reported no association between CS and impaired child cognitive ability [12, 13]. This discrepancy in the literature highlights the need for carefully controlled studies examining the association of CS with available cognitive outcomes in childhood.

Therefore the aim of this study was to investigate the relationship between mode of delivery and child cognitive outcomes (verbal and visual-spatial ability) using data from the UK Millennium Cohort Study [14] (MCS).

Methods

Study Design and Participants

The MCS is a nationally representative longitudinal study of 18,818 children born in the UK between 2000 and 2002 [15] that were selected using a stratified cluster sampling framework. 18,552 families were included (for a response rate of 72%) and details on sampling are available elsewhere [16]. Participants were surveyed in their homes across five sweeps at ages 9 months (MCS1), 3 (MCS2), 5 (MCS3), 7 (MCS4) and 11 (MCS5) years (https://cls.ucl.ac.uk/cls-studies/millennium-cohort-study/). Children from the MCS were included in our study if they participated in all five sweeps of the MCS and completed all the cognitive assessments. Subjects were excluded if the natural mother was not the "Main Respondent", if there was a multiple birth (i.e. twins or triplets) or if the obstetric mode of delivery information was not coded as "a normal delivery", "assisted with forceps", "assisted vacuum extraction", "assisted breach", "a planned caesarean" or "an emergency caesarean" (Supplementary Figure 1).

Study Measures

The exposure - mode of delivery.

Obstetric mode of delivery was divided into four categories: 1. normal vaginal delivery; 2. assisted vaginal delivery (included births described in the MCS as "assisted with forceps", "assisted vacuum extraction" and "assisted breech"); 3. planned CS (planned to take place before labour begins); and 4. emergency CS (took place if there is a complication during pregnancy or labour and immediate delivery of the foetus was required).

The outcomes - cognitive ability.

Cognitive Assessments were included in the 2nd (3 years), 3rd (5 years), 4th (7 years) and 5th (11 years) sweeps of the MCS which were carried out in face-to-face interviews in a standardised format. Here we grouped them into;

1. **Verbal Cognition tests** (*British Abilities Scale (BAS) Naming Vocabulary, BAS Word Reading and BAS Verbal Similarities*);

and

2. **Visual-Spatial Cognition tests** (*Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory (SWM) Task and BAS Pattern Construction*)

We used similar criteria for defining cognitive delay as previously reported [7]. For further details of cognitive tests and cut off scores see Supplementary Methods.

Confounding variables.

Potential confounding variables were identified using a directed acyclic graph (supplementary figure 2) and the following *a priori* variables were included in the logistic and linear regression analyses: gender, ethnicity, number of siblings, maternal age, maternal pre-pregnancy body mass index (BMI), maternal highest educational attainment, paternal highest educational attainment, maternal smoking during pregnancy, maternal alcohol use during pregnancy, pre-eclampsia, and index of multiple deprivation (IMD) quintile.

Statistical Analysis

Analysis was performed using Stata SE Version 13 (Stata Corporation, College Station, TX, USA). Descriptive characteristics were all summarised as categorical variables in counts and percentages (n (%)). Multivariate linear regression was performed to investigate the association between performance in each cognitive assessment as a continuous variable and mode of delivery. Multivariate logistic regression was performed to compare the odds of being "delayed" for each cognitive assessment at each time point in relation to mode of delivery groups. In terms of patterns of delay, we also performed multivariate logistic regression to examine the odds of being "never delayed", "delayed only once", having "persistent delay" and "early childhood delay". Children were categorised as "never delayed" if they always scored higher than the delay cut-off score, "delayed only once" if they only scored below the delay cut-off score in one of any of the four assessment measures, "persistent delay" if they scored below the cut-off score at age 11 and in one or more earlier assessments and "early childhood delay" if they scored below the cut off score in two or more of the age 3, 5 or 7 assessments. The general methods and definitions were adopted from a previous study.[14] Sub-group analysis was also performed on the following subsets; males only, females only, very preterm birth excluded, term birth only, low birthweight excluded, first born only, mothers aged 20 – 35 years only, maternal BMI prior to pregnancy 18.5 – 30 kg/m^2 only, white ethnicity only, non-smokers only, never breastfed and ever breastfed.

Ethical Approval

Ethical approval for the original data collection in the MCS was obtained by the Centre for Longitudinal Studies in London from relevant multi-centre research ethics committees for

each phase of the study [16]. As this was an analysis of existing data we did not require ethical approval to perform this study.

Results

Study Population

In the first phase of the MCS 18,552 children were recruited and 12,565 remained in the study at age 11 years of which 70% (8,845 participants) had completed all the cognitive assessments of interest and were included in our analyses. There were 4,346 males (49.1%), 7,736 (87.4%) were of white ethnicity, the majority of participants were born to mothers aged between 20 – 35 years (80.8%) and 2,733 (30.9%) of mothers had a 3rd level education. In terms of the exposure, 6,020 (68%) were born by normal vaginal delivery, 889 (10%) by assisted vaginal delivery, 846 (10%) by planned CS, and 1,090 (12%) by emergency CS (For full demographics see Table 1-3). For comparisons between those in the MCS included and excluded from our study see Supplementary Table 1.

Verbal Cognitive Ability

There was no statistically significant association between mode of delivery and verbal cognitive performance or delay for any of the verbal assessments in multivariate linear (Supplementary Table 3) or logistic regression (Table 4, Supplementary Figure 3). We also investigated patterns of verbal delay over time. The lower section of table 4 shows the percentage of children in each of those categories and the odds of delay. Fewer children born by assisted vaginal delivery were delayed in any of the verbal assessments and were less likely to be delayed only once (OR=0.78; [95% CI: 0.61-1.00], p=0.053). Adjusted logistic regression analysis showed no significant association between planned CS and any patterns of delay.

Visual-Spatial Cognitive Ability

Linear regression showed a positive association between planned CS and cognitive performance in the Age 7 BAS Pattern Construction Assessment (MD=-1.12; [95% CI: -1.86 to -0.37]. A positive association was also observed between delivery by planned CS and cognitive delay in the Age 5, which was of borderline statistical significance, (OR=1.31; [95% CI: 0.99 to 1.72], p = 0.058) and Age 7 (OR=1.42; [95% CI: 1.12 to 1.81], p=0.005) BAS Pattern Construction Assessments. No significant association between the CANTAB SWM assessment and mode of delivery was observed (Table 5, Supplementary Figure 4). In terms of patterns of delay the planned CS group also showed increased odds of “Early Childhood Delay” (OR=1.70; [95% CI 1.15 to 2.50], p = 0.008) and borderline increased odds of “Persistent Delay” (OR=1.37; [95% CI 0.99 to 1.89], p = 0.060).

Sub-Group Analysis

Results of the subgroup analyses are shown in Supplementary Tables 3 to 14. The positive association between planned CS and cognitive delay in the Age 7 BAS Patterns Construction Assessment remained significant in all subgroups “except first born only” and “ever breastfed”. For the Age 5 BAS Assessment the borderline association between cognitive delay and planned CS became significant when those with “low birthweight were excluded”, for “term birth only” and for those who were born to “mothers who never smoked”.

Discussion

We conducted a study of 8,845 children included in the Millennium Cohort Study who all completed a series of cognitive assessments at ages 3, 5, 7 and 11 years. We found that planned CS was associated with an increased likelihood of visual-spatial cognitive delay but not verbal cognitive delay. The association was present at age 5 and age 7, but not age 11. In analysis of patterns of cognitive delay we showed that at age 11 children born by planned CS were more likely to show "Early Childhood Delay" in the visual spatial cognitive domain. Children born by planned CS were more likely to demonstrate cognitive delay in the BAS Pattern Construction assessment at age 5 and age 7 but not later. This may indicate a possible "catch-up" effect as the children get older [7].

Verbal skills were not affected by mode of delivery in this study. However in studies by Curran et al. [10] and Polidano et al. [11] there appeared to be a global cognitive impairment associated with CS. One of the largest difference between our study population and those, is that participants could self-select which elements of the MCS they participated in. As a result 30% of those who participated in the MCS5 were ineligible as they had not completed one or more of the cognitive assessments in the MCS. Those who refused to participate in just those sections of the study may be more likely to perform poorly compared. This may explain why the mean assessment scores for the study cohort were consistently better than the reference population against which their scores were standardised, and why at each progressive phase of the study the scores diverged further from that reference level. This bias may have masked a potential association between verbal ability and mode of delivery.

In terms of how CS may impact neurodevelopmental outcomes, a recent report highlights the importance of mode of delivery on naturally-occurring neuronal cell death in the neonatal brain [17]. Specifically mice born vaginally had an abrupt and widespread pause in cell death occurring in 9 of 13 brain regions when examined 3h post-partum, and at postnatal day one (P1) but not P3. This indicates that vaginally delivery may be neuroprotective, but importantly, this was a transient phenomenon, which normalised later in the postnatal period. While causal mechanisms cannot be inferred, the finding is at least consistent with the possibility of a delay in the development of certain cognitive abilities as a result of birth by CS.

It is possible that cognitive outcomes may also be influenced by more indirect mechanisms such as alterations in the neonatal gut microbiome [18]. A recent study has shown that there are differences in the microbiome of vaginally-delivered neonates, and those delivered by CS [19]. Furthermore, the same study showed that CS delivery disrupts the mother to neonate

transmission of specific microbial strains [19]. This is important given that the diversity of the infant gut microbiome is associated with functional connectivity between different areas in the neonatal brain [20], and that the gut microbiome composition is associated with temperament during early childhood [21]. While causality cannot yet be determined, these data from other groups support the suggestion that mode of delivery may alter the gut microbiome which may impact brain structure and function in childhood. However as our study did not directly examine the gut microbiome an exploration of gut biodiversity of children and cognitive performance will be required.

Strengths and limitations

This study has several strengths. Firstly, we used a large UK cohort of 8,845 children that have participated in longitudinal cognitive assessments at ages 3, 5, 7 and 11 years, which provided adequate statistical power. We have examined the same cohort at each of four time points and were able to describe the longitudinal patterns of cognitive performance across the study period. Secondly, we were able to account for a wide variety of potential confounders identified using a DAG. Thirdly, the reliability of the responses given in the MCS is high due to the quality of data collection. Mode of delivery recall has been shown to have a high degree of reliability in this cohort [22]. All the cognitive assessments were carried out in a standardised manner with highly trained interviewers. This limits artificial variance among subject responses and inter-observer bias.

However, there are some limitations. Firstly, confounding by indication cannot be ruled out due to lack of data (e.g. placenta previa, previous CS, maternal request, etc.). Secondly, there may be loss to follow-up bias as the people who choose to participate in a long term study will inherently be different to those who leave it – thereby reducing generalisability. While the researchers who designed the MCS made efforts to recruit subjects from a wide range of diverse demographics and socioeconomic groups, those who choose to leave the study may share qualities that are also associated with our research outcomes, and a limitation of studies of this nature is that many participants have similar characteristics such as high socioeconomic status and education that enable participation in research. Additionally our study population is less likely to include children with cognitive delay and this may have skewed our results. Approximately equal proportions of children were lost to follow-up from each mode of delivery group however it is unclear what bias this may have had on our research outcomes.

Conclusion

In summary, we found that there may be a small association between planned CS and visual-spatial cognitive delay in childhood. This is consistent with other studies investigating CS and cognitive outcomes in children. This has translational applications for healthcare professionals and expectant parents to give them more information to make better informed choices when planning mode of delivery. However, the findings in this study should be interpreted with caution and further research is needed to replicate these findings and to investigate the biological mechanism driving this association.

Conflict of interest statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Tables

Table 1: Characteristics of the children in our study cohort.

Child characteristics		Mode of Delivery			
Study population (n = 8,845)	**Total**	**Normal Delivery (n=6,020)**	**Assisted Vaginal Delivery (n=889)**	**Planned C-section (n=846)**	**Emergency C-section (n=1,090)**
Gender, n (%):					
Male	4,346 (49.1%)	2,877 (47.8%)	482 (54.2%)	396 (46.8%)	591 (54.2%)
Female	4,499 (50.9%)	3,143 (52.2%)	407 (45.8%)	450 (53.2%)	499 (45.8%)
Ethnicity, n (%):					
White	7,736 (87.4%)	5,210 (86.5%)	825 (92.8%)	754 (89.1%)	947 (86.9)
Other	1,094 (12.4%)	796 (13.2%)	63 (7.1%)	92 (10.9%)	143 (13.1%)
Missing	15 (0.2%)	14 (0.2%)	1 (0.1%)	0	0
Gestational Age, n (%):					
Very Pre-Term	63 (0.7%)	23 (0.4%)	2 (0.2%)	1 (0.1%)	37 (3.4%)
Moderate - Late Preterm	966 (10.9%)	561 (9.3%)	71 (8%)	135 (16%)	199 (18.3%)
Term	7,439 (84.1%)	5,205 (86.5%)	754 (84.8%)	693 (81.9%)	787 (72.2%)
Post-Term	306 (3.5%)	182 (3%)	55 (6.2%)	9 (1.1%)	60 (5.5%)
Missing	71 (0.8%)	49 (0.8%)	7 (0.8%)	8 (0.9%)	7 (0.6%)
Birthweight, n (%):					
Very Low Birthweight	52 (0.6%)	15 (0.2%)	1 (0.1%)	2 (0.2%)	34 (3.1%)
Low Birthweight	456 (5.2%)	259 (4.3%)	29 (3.3%)	45 (5.3%)	123 (11.3%)
Normal Birthweight	7,789 (88%)	5,411 (89.9%)	806 (90.7%)	743 (87.8%)	829 (76.1%)
High Birthweight	543 (6.1%)	331 (5.5%)	53 (6%)	55 (6.5%)	104 (9.5%)
Missing	5 (0.1%)	4 (0.1%)	0	1 (0.1%)	0
Birth Order, n (%):					
First Born	3,711 (42%)	2,080 (34.6%)	698 (78.5%)	220 (26%)	713 (65.4%)
Second Born	3,199 (36.2%)	2,394 (39.8%)	149 (16.8%)	404 (47.8%)	252 (23.1%)
≥Third Born	1,935 (21.9%)	1,546 (25.7%)	42 (4.7%)	222 (26.2%)	125 (11.5%)

Gestational Age: Very Pre-term = <32 weeks; Moderate – Late Preterm = 32 to 37 weeks; Term = 37 to 42 weeks; Post-Term = >42 weeks.
Birthweight: Very Low Birthweight = <1.5kg; Low Birthweight = 1.5kg to 2.5kg; Normal Birthweight = 2.5kg to 4.2kg; High Birthweight = >4.2kg.

Table 2: Pregnancy related characteristics of our study cohort.

Pregnancy related characteristics		Mode of Delivery			
Study population (n = 8,845)	**Total**	**Normal Delivery (n=6,020)**	**Assisted Vaginal Delivery (n=889)**	**Planned C-section (n=846)**	**Emergency C-section (n=1,090)**
Maternal Age, n (%):					
<20 years old	494 (5.6%)	370 (6.1%)	59 (6.6%)	18 (2.1%)	47 (4.3%)
20 – 35 years old	7,147 (80.8%)	4,897 (81.3%)	715 (80.4%)	651 (77%)	884 (81.1%)
>36 years old	1,204 (13.6%)	753 (12.5%)	115 (12.9%)	177 (20.9%)	159 (14.6%)
Mat. BMI prior to Pregnancy, n (%):					
Underweight	406 (4.6%)	305 (5.1%)	38 (4.3%)	24 (2.8%)	39 (3.6%)
Normal BMI	5,378 (60.8%)	3,758 (62.4%)	590 (66.4%)	435 (51.4%)	595 (54.6%)
Overweight	1,711 (19.3%)	1,103 (18.3%)	162 (18.2%)	197 (23.3%)	249 (22.8%)
Obese Class I	522 (5.9%)	318 (5.3%)	39 (4.4%)	75 (8.9%)	90 (8.3%)
Obese Class II	158 (1.8%)	90 (1.5%)	8 (0.9%)	9 (1.1%)	10 (0.9%)
Obese Class III	62 (0.7%)	35 (0.6%)	8 (0.9%)	9 (1.1%)	10 (0.9%)
Missing	608 (6.9%)	411 (6.8%)	44 (4.9%)	78 (9.2%)	75 (6.9%)
Preeclampsia, n (%):					
Yes	683 (7.7%)	358 (5.9%)	83 (9.3%)	75 (8.9%)	167 (15.3%)
No	8,162 (92.3%)	5,662 (94.1%)	806 (90.7%)	771 (91.1%)	923 (84.7%)
Alcohol during Pregnancy, n (%):					
Never	5,978 (67.6%)	4,039 (67.1%)	594 (66.8%)	578 (68.3%)	767 (70.4%)
<Once per Month	1,309 (14.8%)	904 (15%)	145 (16.3%)	121 (14.3%)	139 (12.8%)
1-2 Times per Month	686 (7.8%)	479 (8%)	73 (8.2%)	63 (7.4%)	71 (6.5%)
Every Week	871 (9.8%)	597 (9.9%)	77 (8.7%)	84 (9.9%)	113 (10.4%)
Missing	1 (0.01%)	1 (0.01%)	0	0	0
Smoking During Pregnancy, n (%):					
Non-Smoker	5,862 (66.3%)	3,935 (65.4%)	596 (67%)	589 (69.6%)	742 (68.1%)
Stopped Smoking during Pregnancy	1,068 (12.1%)	691 (11.5%)	135 (15.2%)	95 (11.2%)	147 (13.5%)
Continued Smoking during Pregnancy	1,903 (21.5%)	1,387 (23%)	155 (17.4%)	161 (19%)	200 (18.3%)
Missing	12 (0.1%)	7 (0.1%)	3 (0.3%)	1 (0.1%)	1 (0.1%)

Maternal Body Mass Index (Mat. BMI) prior to Pregnancy: Underweight = <18.5 kg/m2; Normal BMI = 18.5 kg/m2 to 25 kg/m2; Overweight = 25 kg/m2 to 30 kg/m2; Obese Class I = 30 kg/m2 to 35 kg/m2; Obese Class II = 35 kg/m2 to 40 kg/m2; Obese Class III = >40 kg/m2.

Table 3: Sociodemographic characteristics of our study cohort.

Sociodemographic characteristics		Mode of Delivery			
Study population (n = 8,845)	**Total**	**Normal Delivery (n=6,020)**	**Assisted Vaginal Delivery (n=889)**	**Planned C-section (n=846)**	**Emergency C-section (n=1,090)**
Maternal Education, n (%): No Formal Qualification	1,125 (12.7%)	856 (14.2%)	57 (6.4%)	112 (13.2%)	100 (9.2%)
Lower; GCSE	3,853 (43.6%)	2,664 (44.3%)	361 (40.6%)	376 (44.4%)	452 (41.5%)
Medium; A-level	938 (10.6%)	649 (10.8%)	112 (12.6%)	63 (7.4%)	114 (10.5%)
Higher; 3rd Level Degree	2,733 (30.9%)	1,710 (28.4%)	346 (38.9%)	278 (32.9%)	399 (36.6%)
Missing	196 (2.2%)	141 (2.3%)	13 (1.5%)	17 (2%)	25 (2.3%)
Paternal Education, n (%): No Formal Qualification	1,075 (12.2%)	753 (12.5%)	95 (10.7%)	107 (12.6%)	120 (11%)
Lower; GCSE	2,935 (33.2%)	1,992 (33.1%)	288 (32.4%)	286 (33.8%)	369 (33.9%)
Medium; A-level	603 (6.8%)	395 (6.6%)	67 (7.5%)	61 (7.2%)	80 (7.3%)
Higher; 3rd Level Degree	2,296 (26%)	1,474 (24.5%)	281 (31.6%)	237 (28%)	304 (27.9%)
Missing	1,936 (21.9%)	1,406 (23.4%)	158 (17.8%)	155 (18.3%)	217 (19.9%)
IMD Quintile, n (%): Lowest Quintile	2,184 (24.7%)	1,610 (26.7%)	146 (16.45)	194 (22.9%)	234 (21.5%)
2nd Quintile	1,969 (22.3%)	1,321 (21.9%)	207 (23.3%)	199 (23.5%)	242 (22.2%)
3rd Quintile	1,655 (18.7%)	1,102 (18.3%)	184 (20.7%)	157 (18.6%)	212 (19.4%)
4th Quintile	1,435 (16.2%)	942 (15.6%)	166 (18.7%)	141 (16.7%)	186 (17.1%)
Highest Quintile	1,602 (18.1%)	1,045 (17.4%)	186 (20.9%)	155 (18.3%)	216 (19.8%)
Breastfeeding (for Sub-Group Analysis)					
Breastfeeding, n (%): Never Breastfed	2,940 (33.2%)	2,051 (34.1%)	255 (28.7%)	314 (37.1%)	320 (29.4%)
< 2 months Breastfed	1,541 (17.4%)	966 (16.1%)	179 (20.1%)	157 (18.6%)	239 (21.9%)
2 – 4 months Breastfed	1,820 (20.6%)	1,233 (20.5%)	200 (22.5%)	145 (17.1%)	242 (22.2%)
>4 months Breastfed	1,385 (15.7%)	960 (16.0%)	155 (17.45)	123 (14.5%)	147 (13.5%)
Missing	1,159 (13.1%)	810 (13.5%)	100 (11.3%)	107 (12.7%)	142 (13.0%)
IMD = Index of Multiple Deprivation					

Table 4: Odds of Delay by mode of delivery for verbal cognitive ability and patterns of verbal delay.

		Crude				Adjusted			
Age	**Test (n = 8,845)**	**Normal Delivery (Ref.) (n = 6,020)**	**Assisted Vaginal Delivery (n = 889)**	**Planned C-section (n = 846)**	**Emergency C-section (n = 1,090)**	**Normal Delivery (Ref.)**	**Assisted Vaginal Delivery**	**Planned C-section**	**Emergency C-section**
Verbal Cognitive Ability									
11	BAS Verbal Similarities Delay: n (%)	216 (3.6%)	25 (2.8%)	29 (3.4%)	29 (2.7%)				
7	BAS Word Reading Delay: n (%)	317 (5.3%)	24 (2.7%)	48 (5.7%)	48 (4.4%)				
5	BAS Naming Vocabulary Delay: n (%)	404 (6.7%)	35 (3.9%)	43 (5.1%)	64 (5.9%)				
3	BAS Naming Vocabulary Delay: n (%)	918 (15.2%)	79 (8.9%)	114 (13.5%)	148 (13.6%)				
11	BAS Verbal Similarities Delay: OR (95% CI)	1	0.78 (0.51 to 1.18)	0.95 (0.64 to 1.42)	0.73 (0.50 to 1.09)	1	1.28 (0.82 to 2.00)	1.04 (0.69 to 1.56)	1.02 (0.68 to 1.54)
7	BAS Word Reading Delay: OR (95% CI)	1	0.50 (0.33 to 0.76)	1.08 (0.79 to 1.48)	0.83 (0.61 to 1.13)	1	0.73 (0.47 to 1.14)	1.15 (0.83 to 1.60)	0.99 (0.71 to 1.38)
5	BAS Naming Vocabulary Delay: OR (95% CI)	1	0.57 (0.40 to 0.81)	0.74 (0.54 to 1.03)	0.87 (0.66 to 1.14)	1	1.08 (0.74 to 1.59)	0.84 (0.59 to 1.20)	1.17 (0.87 to 1.59)
3	BAS Naming Vocabulary Delay: OR (95% CI)	1	0.54 (0.43 to 0.69)	0.87 (0.70 to 1.07)	0.87 (0.72 to 1.05)	1	0.92 (0.70 to 1.21)	0.96 (0.76 to 1.22)	1.11 (0.90 to 1.38)
Patterns of Verbal Delay									
3-11	Never Delayed: n (%)	4,688 (77.9%)	770 (86.6%)	666 (78.7%)	875 (80.3%)				
3-11	Delayed Once Only: n (%)	921 (15.3%)	82 (9.2%)	136 (16.1%)	154 (14.1%)				
3-11	Persistent Delay: n (%)	131 (2.2%)	13 (1.5%)	19 (2.2%)	19 (1.7%)				
3-11	Early Childhood Delay: n (%)	342 (5.7%)	29 (3.3%)	32 (3.8%)	51 (4.7%)				
3-11	Odds of Never Delayed: OR (95% CI)	1	1.84 (1.50 to 2.25)	1.05 (0.88 to 1.25)	1.16 (0.98 to 1.36)	1	1.14 (0.91 to 1.42)	0.96 (0.79 to 1.17)	0.91 (0.75 to 1.09)
3-11	Delayed Once Only: OR (95% CI)	1	0.56 (0.44 to 0.71)	1.06 (0.87 to 1.29)	0.91 (0.76 to 1.10)	1	0.78 (0.61 to 1.00)	1.13 (0.92 to 1.38)	1.06 (0.87 to 1.29)
3-11	Persistent Delay: OR (95% CI)	1	0.67 (0.38 to 1.18)	1.03 (0.63 to 1.68)	0.80 (0.49 to 1.30)	1	1.36 (0.74 to 2.51)	1.23 (0.74 to 2.04)	1.24 (0.75 to 2.07)
3-11	Early Childhood Delay: OR (95% CI)	1	0.56 (0.38 to 0.82)	0.65 (0.45 to 0.94)	0.81 (0.60 to 1.10)	1	1.19 (0.78 to 1.84)	0.73 (0.49 to 1.09)	1.14 (0.81 to 1.60)

Abbreviations: BAS = British Abilities Scales, OR = Odds Ratio, CI = Confidence Interval, Ref. = Reference Group
Delay = Score less than one standard deviation (-1 SD) below the mean score of the test (i.e. score less than 40 for all tests except BAS Word Reading where 85 is the cut-off)
Never Delayed = Subjects who always scored above the -1 SD cut-off;
Delayed Only Once = Subjects who only scored below the -1 SD cut-off score in one of the four assessment measures
Persistent Delay = Subjects who scored below the -1 SD cut-off at age 11 and in one or more earlier assessments;
Early Childhood Delay = Subjects who scored below the cut off score in two or more of the age 3, 5 or 7 assessments

Table 5: Odds of delay by mode of delivery for visual-spatial cognitive ability and patterns of visual-spatial delay.

		Crude				Adjusted			
Age	**Test (n = 8,845)**	**Normal Delivery (Ref) (n = 6,020)**	**Assisted Vaginal Delivery (n = 889)**	**Planned C-section (n = 846)**	**Emergency C-section (n = 1,090)**	**Normal Delivery (Ref)**	**Assisted Vaginal Delivery**	**Planned C-section**	**Emergency C-section**
Visual-Spatial Cognitive Ability									
11	CANTAB SWM Strategy Delay: n (%)	459 (7.6%)	64 (7.2%)	63 (7.5%)	103 (9.5%)				
11	CANTAB SWM Errors Delay: n (%)	919 (15.3%)	131 (14.7%)	136 (16.1%)	160 (14.7%)				
7	BAS Pattern Construction Delay: n (%)	518 (8.6%)	59 (6.6%)	93 (11.0%)	84 (7.7%)				
5	BAS Pattern Construction Delay: n (%)	414 (6.9%)	60 (6.8%)	68 (8.0%)	74 (6.8%)				
11	CANTAB SWM Strategy Delay: OR (95% CI)	1	0.94 (0.72 to 1.23)	0.97 (0.74 to 1.28)	1.26 (1.01 to 1.58)	1	1.03 (0.78 to 1.37)	0.99 (0.75 to 1.30)	1.31 (1.03 to 1.65)
11	CANTAB SWM Errors Delay: OR (95% CI)	1	0.96 (0.79 to 1.17)	1.06 (0.87 to 1.29)	0.95 (0.80 to 1.15)	1	1.14 (0.92 to 1.41)	1.10 (0.90 to 1.34)	1.01 (0.83 to 1.22)
7	BAS Pattern Construction Delay: OR (95% CI)	1	0.76 (0.57 to 1.0)	1.31 (1.04 to 1.66)	0.89 (0.70 to 1.13)	1	0.93 (0.69 to 1.25)	1.42 (1.12 to 1.81)	0.94 (0.73 to 1.21)
5	BAS Pattern Construction Delay: OR (95% CI)	1	0.98 (0.74 to 1.30)	1.18 (0.91 to 1.55)	0.99 (0.76 to 1.27)	1	1.22 (0.90 to 1.64)	1.31 (0.99 to 1.72)	1.07 (0.82 to 1.40)
Patterns of Visual-Spatial Delay									
5-11	Never Delayed: n (%)	4,415 (73.3%)	673 (75.7%)	600 (70.9%)	812 (74.5%)				
5-11	Delayed Once Only: n (%)	1,246 (20.7%)	167 (18.8%)	182 (21.5%)	212 (19.5%)				
5-11	Persistent Delay: n (%)	281 (4.7%)	42 (4.7%)	49 (5.8%)	50 (4.6%)				
5-11	Early Childhood Delay: n (%)	163 (2.7%)	16 (1.8%)	35 (4.1%)	32 (2.9%)				
5-11	Never Delayed: OR (95% CI)	1	1.13 (0.96 to 1.33)	0.89 (0.76 to 1.04)	1.06 (0.92 to 1.23)	1	0.95 (0.80 to 1.13)	0.84 (0.71 to 0.99)	1.00 (0.85 to 1.17)
5-11	Delayed Once Only: OR (95% CI)	1	0.89 (0.74 to 1.06)	1.05 (0.88 to 1.25)	0.93 (0.79 to 1.09)	1	0.99 (0.82 to 1.20)	1.08 (0.91 to 1.30)	0.97 (0.82 to 1.15)
5-11	Persistent Delay: OR (95% CI)	1	1.01 (0.73 to 1.41)	1.26 (0.92 to 1.72)	0.98 (0.72 to 1.34)	1	1.36 (0.95 to 1.94)	1.37 (0.99 to 1.89)	1.09 (0.79 to 1.51)
5-11	Early Childhood Delay: OR (95% CI)	1	0.66 (0.39 to 1.11)	1.55 (1.07 to 2.25)	1.09 (0.74 to 1.60)	1	0.88 (0.51 to 1.51)	1.70 (1.15 to 2.50)	1.19 (0.79 to 1.79

Abbreviations: CANTAB = Cambridge Neuropsychological Automated Battery, BAS = British Abilities Scales, OR = Odds Ratio, CI = Confidence Interval, Ref. = Reference Group
Delay = Score less than one standard deviation (-1 SD) below the mean score of the test (i.e. score less than 40 for BAS Pattern Construction and less than -1 SD of the cohort mean for CANTAB SWM tests).
Never Delayed = always scoring above the -1 SD cut-off;
Delayed Only Once = only scored below the -1 SD cut-off score in one of the four assessment measures.
Persistent Delay = scored below the -1 SD cut-off at age 11 and in one or more earlier assessments;
Early Childhood Delay = scored below the cut off score at both of age 5 and 7 assessments.