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## Neuropsychological abilities underpinning academic attainment in children born extremely preterm

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### ABSTRACT

Children born extremely preterm (EP) have poorer academic attainment than their term-born peers. There is a need to identify the specific cognitive mechanisms that are associated with poor academic attainment in preterm populations to inform the development of intervention strategies. A parallel mediation analysis was conducted with cross-sectional data from 152 EP children (< 27 weeks of gestation) and 120 term-born controls who were assessed at age 11. Mathematics and reading attainment was assessed using the Wechsler Individual Achievement Test 2nd Edition. Controlling for sex and socio-economic status we evaluated the following mediators: verbal working memory, visuospatial working memory, verbal processing speed, attention, and visuospatial processing. These were assessed using subtests from the standardized NEPSY-II test and Wechsler Intelligence Scale for Children-5th Edition. Verbal working memory, visuospatial working memory, visuospatial processing and verbal processing speed, but not attention, were significant independent mediators between EP birth and attainment in reading. No direct relationship between EP birth and reading attainment remained in the mediated model. All five neuropsychological variables mediated the relationship between EP birth and attainment in mathematics, but a direct effect of EP birth on mathematics remained in the mediated model. Together, all five neuropsychological abilities indirectly explained 44% of the variance in reading and 52% of the variance in mathematics. Visuospatial processing was the strongest mediator of both mathematics and reading. Components of executive function, especially visuospatial processing, are important predictors of academic attainment. Interventions to improve visuospatial skills could be trialed in EP populations.

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Children born extremely preterm, before 28 weeks of gestation, have poorer educational outcomes than their term-born peers, including poorer academic attainment and a higher prevalence of special educational needs (Johnson et al., 2011; Twilhaar, de Kieviet et al., 2018). In the United States, 30–35% of children born extremely

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preterm had scores more than 1 SD below the normative mean on standardized tests of reading and spelling and 41% on standardized tests of mathematics at 10 years of age (Joseph et al., 2016). The prevalence of adverse outcomes is even greater among those born at more preterm gestations. At age 11, 44% of children born <26 weeks of gestation in the United Kingdom and Ireland EPICure Study had moderate or severe learning difficulties in mathematics (scores more than 2 SD below the mean of controls) and 30% in reading, compared with just 1–2% of term-born classmates (Johnson et al., 2009).

Whilst it is well documented that children born extremely preterm have lower IQ than term-born children (Twilhaar, Wade et al., 2018), full scale IQ scores may mask discrepancies between the multiple skills which form this composite score (Kaul et al., 2021). For example, at age 6.5 years, children born <27 weeks of gestation had the greatest deficit in the perceptual reasoning index (–1.19 SD) on the WISC-IV IQ test, which involves visuospatial processing (Kaul et al., 2021). Significant deficits in verbal working memory (–0.79 SD) and processing speed (–0.96 SD) were also observed compared with children born at term (Kaul et al., 2021). Other studies have highlighted the importance of considering specific neuropsychological skills in relation to academic attainment in preterm populations. For example, extremely preterm children born <26 weeks of gestation with an intellectual disability or learning difficulties in reading or mathematics but without a neurosensory impairment had significantly poorer neuropsychological skills, including poorer visuospatial processing, attention/executive function and sensorimotor skills, than extremely preterm children who had IQ or academic attainment in the average range (Johnson et al., 2016). These findings highlight the need to assess specific neuropsychological skills, in addition to general cognition, in studies of children born preterm.

Indeed, previous studies of preterm-born children have identified deficits in a range of specific neuropsychological skills which have been associated with academic attainment, including attention, working memory, processing speed, inhibition, visuo-motor integration, language/phonological processing and visuospatial processing (Adrian et al., 2020; Akshoomoff et al., 2017; Mulder et al., 2010; Simms et al., 2015; Twilhaar et al., 2020). For example, processing speed, working memory and preterm birth (<31 weeks of gestation) explained 57% of the variance in teacher-rated academic attainment in middle childhood (Mulder et al., 2010). Deficits in visuospatial processing and working memory have also been shown to be associated with poorer attainment in mathematics in children born <32 weeks of gestation (Simms et al., 2015). In children born <33 weeks of gestation without severe disabilities, inhibition, visuo-motor integration and phonological processing mediated the relationship between preterm birth and arithmetic attainment at age seven (Adrian et al., 2020). Moreover, in very preterm adolescents born <32 weeks of gestation/<1500 g birthweight, visuospatial working memory, sustained attention and processing speed explained 33% of the variance in arithmetic scores and 23% of the variance in reading scores (Twilhaar et al., 2020). A further study of children born <28 weeks of gestation with IQ >70 found that working memory and inhibition predicted both mathematics and reading at age 10, although language and processing speed were additional unique predictors of reading, and visual perception an additional predictor of mathematics (Akshoomoff et al., 2017).

In typically developing children, attainment in mathematics and reading was explained by shared variance in verbal and visuospatial working memory. However verbal working memory uniquely explained more variance in reading, whilst visuospatial working memory explained more unique variance in mathematics (Giofrè et al., 2018). The comparative explanatory power of visuospatial and verbal working memory for attainment in reading and mathematics in the extremely preterm population has not been explored. As such, studies using measures that differentiate between verbal and visuospatial working memory are needed to define the relationship between different components of working memory and academic attainment.

Visuospatial processing is an associated but separable construct from visuospatial working memory. It is typically found to be poorer among preterm than term-born children and has been associated with mathematics attainment in both typically developing (Hawes et al., 2019) and preterm children (Simms et al., 2013, 2015). For example, at age 5–7 years, children born <1500 g without an intellectual disability were shown to have poorer route finding and spatial orientation skills but not mental rotation skills compared with children born at term (Fernandez-Baizan et al., 2020). Deficits in visuospatial skills, specifically the ability to judge line orientation assessed using the NEPSY II Arrows subtest, persisted from primary to secondary education among children born <32 weeks of gestation relative to children born at term. Together with working memory, visuospatial skills accounted for very preterm children's deficits in a range of specific mathematics skills (Clayton et al., 2021). In preschool children, visuospatial processing significantly mediated the relationship between birth <1000 g/<30 weeks of gestation and mathematical skills (Van Veen et al., 2019). Moreover, in a sample of children from one mainstream school, visuospatial processing, specifically the ability to use proportional reasoning to compare between objects, was significantly associated with mathematical attainment at 6–10 years of age (Gilligan, Hodgkiss et al., 2019).

There is evidence that children born preterm have greater deficits in visuospatial relative to verbal skills. At age 11, a smaller proportion of children born <32 weeks of gestation/ $\leq$ 1500 g had average scores on tasks assessing visual memory and the ability to reproduce geometric figures compared with assessments of verbal fluency (Lind et al., 2020). Only one study has assessed the role of visuomotor integration (the ability to reproduce geometric figures) in mathematical skills relative to phonological awareness, verbal working memory, verbal skills and motor skills. Using a mediation model in preschool children born <32 weeks of gestation without severe disability, this study identified verbal skills, phonological awareness and visuomotor integration as significant mediators between very preterm birth and mathematical skills (Hasler & Akshoomoff, 2019). However, as it did not report standardized regression coefficients, it was not possible to identify how much variance in mathematical skills was explained by visuomotor integration compared with the other skills. The relative role of visuospatial skills compared with other neuropsychological skills in academic attainment requires further investigation to guide the development of intervention strategies.

Processing speed is a further important component of information processing that may be considered part of a broader framework of executive control (Anderson, 2002). This theoretical model posits that information processing (which would include processing speed and visuospatial processing), attentional control, cognitive flexibility (working memory) and goal setting or planning are interrelated skills, without a hierarchical

structure. Processing speed has previously been identified as an independent predictor of mathematical attainment at the same hierarchical level as working memory in very preterm children (Mulder et al., 2010). However, in a small sample of children born <37 weeks of gestation, processing speed was shown to mediate the relationship between preterm birth and working memory, and to be a sequential mediator of academic attainment via working memory, rather than an independent predictor of mathematics and reading (Rose et al., 2011). However, in a further study, processing speed no longer predicted mathematics attainment among very preterm children when IQ and visuospatial working memory were included in the model (Aarnoudse-Moens et al., 2013). To examine the relative contribution of processing speed to academic attainment, it will be included as a mediator at the same hierarchical level as the other neuropsychological skills in our mediation model. As there is little evidence for planning difficulties in children born very preterm and as it is a skill less frequently included in the assessment of executive function (Mulder et al., 2009), it was not assessed in the present study.

In summary, there is a need to identify the specific neuropsychological skills that underpin poor academic attainment in preterm populations in order to inform the development of intervention strategies. The aims of the present study were to identify a) whether neuropsychological skills mediate the relationship between extremely preterm birth and academic attainment, b) whether these skills differ for reading and mathematics, and c) to quantify the relative contribution of each.

## Methods

### *Participants*

Surviving children from two geographical regions of the (EPICure2@11) cohort of children born extremely preterm (EP; <27 weeks of gestation) in England in 2006 were invited to participate in a follow-up evaluation at 11 years of age. A term-born control group ( $\geq 37$  weeks of gestation) was recruited by asking teachers to identify three classmates of the same sex and age (ideally  $\pm 3$  months) as an EP child. With a few exceptions, between one and three controls for each EP child attending mainstream school were recruited. Controls were not recruited for EP children attending special schools. Where EP children were assessed at home (18.5%) rather than school (80.5%), parents selected a term-born peer as a control where possible. Two children were assessed at the study center. Three psychologists and two clinical researchers blind to preterm birth status administered the study assessments. Ethical approval was obtained via both the (University College London) Ethics Committee (reference: 10175/001) and (University of Leicester) Research Ethics Committee (ref: 10225). Parents gave informed consent for their child's participation and children's assent was obtained.

## Materials

### *Academic attainment*

The Wechsler Individual Achievement Test 2nd Edition (WIAT-II- UK; Wechsler, 2005) was used to assess attainment in reading and mathematics. This yields a composite score for mathematics from subtests assessing numerical operations

and mathematical reasoning, and a composite score for reading from subtests assessing word reading, pseudoword decoding and reading comprehension. Composite scores have a normative mean of 100 (SD 15; Range 40–160). These were substituted with a score one point below the basal score (39) for 10 EP children for mathematics and 15 EP children for reading who were unable to complete the test due to cognitive impairment. Scores were not substituted for children failing to complete the test for other reasons (e.g., lack of time, poor cooperation, fatigue). The decision to substitute a child's score for children with a cognitive impairment was made by reviewing the notes made by the assessors as to reasons for non-completion and to the results of the clinical assessments. These decisions were reached by consensus between JT and SJ.

Low attainment in reading (reading composite score  $\leq 80$ ; score more than 2 SDs below the control group mean) and mathematics (mathematics composite score  $\leq 76$ ; score more than 2 SDs below the control group mean) were classified using the controls as the reference to account for the upward drift in test scores over time (Flynn, 1999). Inter-rater agreement was 90% for items that comprised the reading composite score (participants  $n = 8$ ) and 99% for items that comprised the mathematics composite score ( $n = 7$ ).

### ***IQ and neurodevelopmental disability***

IQ was assessed using the Kaufman Assessment Battery for Children 2nd Edition (K-ABC-II; Kaufman & Kaufman, 2004) from which a standardized Mental Processing Index (MPI) score was obtained (Mean 100; SD 15; range 43–160). An MPI score of 42 (1 point below the basal test score) was assigned to 5 EP children who were unable to complete the test due to cognitive impairment. Scores were not substituted for children failing to complete the test for other reasons as above.

A clinical assessment of vision, hearing and motor function was conducted. Severe neurodevelopmental disability was classified as follows: one or more of MPI score more than 3 SD below the mean of term-born controls (score  $< 67$ ); Gross Motor Function Classification System (Palisano et al., 1997)/Manual Ability Classification System (Eliasson et al., 2006) level  $\geq 3$ ; no useful hearing with aids; sees gross light/movement only or no useful vision.

### ***Neuropsychological abilities***

#### ***Verbal and visuospatial working memory***

Verbal working memory was assessed using the digit span backwards subtest of the Wechsler Intelligence Scale for Children-5th Edition (WISC-V; Wechsler, 2014) and visuospatial working memory using the WISC-V picture span subtest from which scaled scores (Mean 10; SD 3) were derived. Additional WISC-V subtests were conducted and contributed to a standardized Working Memory Index Score (Mean 100; SD 15; Range 45–155). This score was derived from digit span forwards (repeating digits in the same order as presented by the examiner), digit span backwards (repeating

digits in the reverse order as presented by the examiner), digit span sequencing (repeating back all digits in ascending order from a random order presented by the examiner) and picture span subtests.

### **Attention**

The NEPSY-II (Korkman et al., 2007) Response Set subtest (Second part of the Auditory Attention and Response Set subtest) was used to assess children's ability to inhibit and shift attention and monitor responses (i.e., sustained and selective attention) from which a scaled score (Mean 10; SD 3) was derived from the number of correct responses and erroneous responses (commission errors).

### **Visuospatial processing**

The Arrows subtest of the NEPSY-II was used to assess children's ability to judge the direction and orientation of lines. A scaled score (Mean 10; SD 3) was derived from the raw score (correct number of responses).

### **Verbal processing speed**

The NEPSY-II Speeded Naming subtest was used to assess children's ability to rapidly access and produce familiar words or identify numbers and letters in alternative patterns. A combined scaled score (Mean 10; SD 3) encompassing response time and response accuracy was used.

### **Socio-economic status (SES)**

An Index of Multiple Deprivation (IMD) decile rank (Smith et al., 2015) was obtained as an indicator of SES using the child's address at the time of the study assessment. IMD is a composite measure of deprivation based on a geographical postcode area. IMD deciles range from 1 (most deprived) to 10 (least deprived). Five EP children and 5 controls with missing IMD data were excluded from the mediation analyses.

### **Statistical analysis**

Group differences were assessed using independent samples t-tests for continuous outcomes and chi-square tests for categorical outcomes. Z-scores were obtained using the control group as the reference to compare effect sizes across tests. Differences between EP children and controls in academic attainment and neuropsychological skills, adjusted by sex and IMD, were analyzed using ANCOVA. Odds ratios were obtained using binary logistic regressions. Bonferroni adjustment was used to correct for multiple comparisons. Analyses were conducted using SPSS version 25 and STATA 15.1. Children with incomplete data or substituted WIAT-II composite scores were excluded from the mediation analysis, but otherwise where a child's data was collected, it is reported. Parallel mediation analyses were conducted using the PROCESS macro version 3.4 (Hayes, 2017) as we had no prior assumptions about any sequential relationships between the mediators. Sex and IMD



were included as covariates. Point estimates, standard error, lower and upper limits of 95% confidence intervals (CIs) were partially standardized by dividing all values by the standard deviation of the outcome variable (Hayes, 2017). Bootstrapping used 5000 samples for percentile confidence intervals and standard error for indirect effects and contrasts between indirect effects. Each specific indirect effect for the five mediators (e.g., the specific indirect effect of digit span backwards) was considered to significantly mediate the relationship between EP birth and the outcome variable if the 95% confidence intervals for the partially standardized point estimate did not cross zero. Indirect effects were considered to fully mediate the relationship between EP birth and academic outcomes if EP birth was no longer a significant predictor once the mediators were controlled for (direct effect  $c'$ ). The effect size of the variance in mathematics and reading scores mediated by the neuropsychological skills was interpreted using Cohen's  $d$ , whereby Cohen's  $d$  is equal to standard deviation difference between groups (small 0.2, medium 0.5, large 0.8) (Cohen, 1988). To test that the findings were not biased by the inclusion of children with severe neurodevelopmental disability, the mediation models were rerun excluding children with severe disability. Although the EP group had significantly lower IQ than controls, in line with analysis decisions reported in Retzler et al. (2019) we made an a priori decision not to enter IQ as a covariate in our analyses. It has been argued that IQ meets neither the theoretical, statistical, nor logical criteria to be an appropriate covariate in neurodevelopmental research studies, resulting in findings that are not reflective of the performance differences observed in the clinical groups and thus that do not always generate meaningful interpretations (see Dennis et al., 2009 for a full discussion). Moreover, considering the design and theoretical basis underpinning the current study, controlling for IQ may mask the association between prematurity status (born EP versus term) and academic attainment. Partial correlations controlling for IQ showed no significant relationship between mathematical composite standard score and prematurity status ( $r = -.11$ ,  $p = .066$ ,  $n = 272$ ) compared with the bivariate correlation ( $r = -.40$ ,  $p < .001$ ) (see Table S1). The direction of the partial correlation between the reading composite standard score and prematurity status was inverted ( $r = .17$ ,  $p = .005$ ) compared with the bivariate correlation ( $r = -.23$ ,  $p < .001$ ). There was a moderate amount of shared variance between visuospatial WM, verbal WM and visuospatial processing and MPI scores ( $r = .51$  to  $.59$ ,  $p < .001$ ) and a smaller amount of variance between attention and processing speed and MPI ( $r = .33$  to  $.35$ ,  $p < .001$ ). All neuropsychological variables were significantly correlated with each other (bivariate correlations ranged from  $r = .25$  to  $r = .50$ ). As comparing relative variance in academic outcomes explained by individual neuropsychological skills, which might be targeted singly or combination, was the aim of this study, we chose not to include IQ as a covariate or predictor.

## Results

### *Study sample*

Of 1041 survivors to discharge, invitations to take part in an 11-year assessment were sent to the parents of 482 children admitted for care in 17 of the 45 neonatal units and their networked hospitals operating in 2006. Of those invited, families of 220 children consented to participate of which 200 were assessed (41.5% of invited



children; 19.2% of survivors to discharge). Of the 200 EP children assessed, 173 (86.5%) attended a mainstream school, 24 (12%) attended a special school or special unit attached to a mainstream school and 3 (1.5%) were educated at home. In addition, 143 term-born controls ( $\geq 37$  weeks of gestation) were recruited and assessed. Of the EP children without severe disability with complete data, only one child attended a special school.

There were no significant differences in the proportion of males, mean gestational age, mean z-score for birthweight, IMD in infancy and at 3 years of age between children assessed and not assessed at 11 years (Table S2).

Complete data on all five neuropsychological variables, WIAT-II composite scores and IMD were obtained for 152 EP children and 120 controls and included in the mediation analysis, except for one child with a substituted reading composite score (Table 1). EP children with complete data were on average 0.53 years older (95% CI 0.36, 0.69) with MPI 17 points higher (95% CI 10, 25) compared to EP children without complete data ( $n = 48$ ); IMD and gestational age distributions were similar. Controls and EP children with complete data were well matched on sex, age and IMD measures.

### Academic attainment

Children born EP had significantly lower mean composite mathematics and reading scores than controls (Table 2) equating to a deficit of  $-1.1$  SD (95% CI  $-1.4$ ,  $-0.7$ ) in reading and  $-1.4$  SD (95% CI  $-1.8$ ,  $-1.1$ ) in mathematics, after adjusting for sex and IMD. The range of scores for children born EP in reading (39 to 122) and mathematics (39 to 152) was greater than for children born at term in reading (76 to 128) and mathematics (64 to 144). When children with severe neurodevelopmental disability were excluded, the difference in means, adjusted for sex and IMD, remained significant: reading  $-0.4$  SD (95% CI  $-0.7$ ,  $-0.2$ ) mathematics  $-1.0$  SD (95% CI  $-1.2$ ,  $-0.7$ ).

Compared with controls, children born EP had a greater risk of low attainment in reading (16.4% vs. 1.4%; adjusted OR 13.3; 95% CI: 3.1, 56.6) and mathematics (29.9% vs. 0.7%; adjusted OR 57.9; 95% CI: 7.9, 424.7) (Table 3).

### Neuropsychological abilities

Compared with controls, EP children had significantly lower scores for verbal and visuospatial working memory, with adjusted deficits of  $-0.5$  SD (95% CI  $-0.7$ ,  $-0.2$ ) and  $-0.7$  SD (95% CI  $-1.0$ ,  $-0.4$ ), respectively (Table 2). EP children also had significantly lower scores for attention ( $-0.6$  SD, 95% CI  $-0.9$ ,  $-0.4$ ), visuospatial processing ( $-1.1$  SD, 95% CI  $-1.4$ ,  $-0.8$ ) and verbal processing speed ( $-0.6$  SD, 95% CI  $-0.9$ ,  $-0.3$ ). When children with severe disability were excluded there remained significant between-group differences in all five neuropsychological skills, although the magnitude of difference between the EP and control groups decreased (Table S3).

All neuropsychological variables were significantly associated with mathematics and reading composite scores for the combined sample of EP children and controls (Table S1).

**Table 1.** Sample characteristics.

	Total extremely preterm sample (n = 200)	Extremely preterm sample with complete data (n = 152) <sup>b</sup>	Term-born controls with complete data (n = 120)	Extremely preterm vs. controls with complete data; p value <sup>c</sup>
Males, n (%)	100 (50.0)	71 (46.7)	54 (45.0)	Non-significant
Age in years, mean (SD)	11.83 (0.55)	11.96 (0.50)	11.84 (0.58)	Non-significant
Index of Multiple Deprivation decile, mean (SD)	5.21 (2.79)	5.08 (2.83)	5.27 (2.88)	Non-significant
Mental Processing Index score (IQ)	85.3 (18.9)	89.5 (14.7)	102.98 (11.9)	<.001
Severe neurodevelopmental disability <sup>a</sup>	36 (18.0)	12 (7.9)	0	
Gestational age (weeks), median (inter-quartile range), n (%)	25.71 (25.14, 26.43)	25.71 (25.14–26.73)	-	-
23 weeks	15 (7.5)	10 (6.6)	-	
24 weeks	28 (14.0)	21 (13.8)	-	
25 weeks	69 (34.5)	56 (36.8)	-	
26 weeks	88 (44.0)	65 (42.8)	-	
Moderate/severe Bronchopulmonary dysplasia <sup>a</sup>	127 (63.5)	88 (57.9)	-	
Treated Retinopathy of Prematurity	36 (18.0)	26 (17.1)	-	
Surgery for necrotizing enterocolitis	17 (8.5)	11 (7.2)	-	
Significant preterm brain injury <sup>e</sup>	37 (18.6)	24 (15.8)	-	

<sup>a</sup>defined as: one or more of MPI score more than 3 SD below the mean of term-born controls (<67); Gross Motor Function Classification System/Manual Ability Classification System score  $\geq 3$ ; no useful hearing with aids; sees gross light/movement only or no useful vision.

<sup>b</sup>One child included with substituted reading composite score due to severe cognitive impairment, but otherwise complete neuropsychological data.

<sup>c</sup>Chi-squared for sex and T-tests for other variables.

<sup>d</sup>Receiving supplemental oxygen at 36 weeks post menstrual age.

<sup>e</sup>One or more of hydrocephalus (ventricular index >4 mm above 97<sup>th</sup> centile), unilateral or bilateral hemorrhagic parenchymal infarction, porencephalic cyst, cystic periventricular leukomalacia.

**Table 2.** Academic attainment and neuropsychological abilities in extremely preterm children and term-born controls.

	Term-born controls		Extremely preterm		Difference in means (95% CI)	Z score Difference in means (95% CI)	Adjusted Z score Difference in means (95% CI) <sup>a</sup>	P value
	N	Mean (SD)	N	Mean (SD)				
<b>Academic attainment</b>								
<b>WIAT-II Reading Composite</b>	140	103.4 (10.6)	195	91.8 (20.6)	-11.7 (-15.1, -8.3)	-1.1 (-1.4, -0.8)	-1.1 (-1.4, -0.7)	<.001
Word Reading	143	104.8 (9.5)	186	97.9 (15.4)	-6.9 (-9.6, -4.2)	-0.7 (-1.0, -0.4)	-0.7 (-1.0, -0.4)	<.001
Reading Comprehension	141	104.4 (11.7)	180	97.1 (17.1)	-7.3 (-10.4, -4.1)	0.6 (-0.9, -0.4)	-0.6 (-0.9, -0.3)	<.001
Pseudoword Decoding	141	103.1 (9.5)	185	96.4 (13.0)	-6.8 (-9.2, -4.3)	-0.7 (-1.0, -0.5)	0.7 (-0.9, -0.4)	<.001
<b>WIAT-II Mathematics Composite</b>	139	109.4 (15.7)	197	86.6 (26.5)	-22.8 (-27.3, -18.3)	-1.5 (-1.7, -1.2)	-1.4 (-1.8, -1.1)	<.001
Mathematics Reasoning	139	102.9 (12.3)	187	86.3 (20.4)	-16.7 (-20.3, -13.1)	-1.4 (-1.7, -1.1)	-1.3 (-1.7, -1.0)	<.001
Numerical Operations	143	113.9 (16.3)	189	93.3 (25.9)	-20.7 (-25.2, -16.1)	-1.3 (-1.6, -1.0)	-1.2 (-1.5, -0.9)	<.001
<b>Working memory</b>								
<b>WISC-V Working Memory Index</b>	125	100.7 (13.4)	161	91.2 (18.0)	-9.5 (-13.2, -5.9)	-0.7 (-1.0, -0.4)	-0.7 (-0.9, -0.4)	<.001
Digit span backwards scaled score (verbal working memory)	138	9.5 (2.4)	168	8.2 (3.1)	-1.4 (-2.0, -0.8)	-0.6 (-0.8, -0.3)	-0.5 (-0.7, -0.2)	<.001
Picture span overall scaled score (visuospatial working memory)	125	11.0 (2.6)	164	9.2 (3.8)	-1.8 (-2.6, -1.1)	-0.7 (-1.0, -0.4)	-0.7 (-1.0, -0.4)	<.001
<b>Visuospatial processing</b>								
<b>NEPSY-II Arrows (visuospatial processing)</b>	143	9.9 (3.0)	191	6.8 (4.0)	-3.2 (-3.9, -2.4)	-1.1 (-1.3, -0.8)	-1.1 (-1.4, -0.8)	<.001
<b>Attention</b>								
<b>NEPSY-II Response Set (attention)</b>	143	10.0 (2.7)	180	8.3 (3.7)	-1.7 (-2.5, -1.0)	-0.6 (-0.9, -0.4)	-0.6 (-0.9, -0.4)	<.001
<b>Verbal processing speed</b>								
<b>NEPSY-II Speeded Naming (processing speed)</b>	143	10.4 (2.6)	189	8.7 (3.7)	-1.7 (-2.4, -1.0)	-0.6 (-0.9, -0.4)	-0.6 (-0.9, -0.3)	<.001

<sup>a</sup>Differences in means adjusted for sex and IMD. Due to missing IMD data the N for each group is slightly smaller than that reported for the means. All comparisons remained significant Bonferroni correction (p < .004).

## Do neuropsychological abilities mediate the relationship between EP birth and attainment in mathematics?

When entered together, all five neuropsychological skills of verbal working memory, visuospatial working memory, visuospatial processing, attention and verbal processing speed significantly mediated the relationship between EP birth and mathematics attainment. This model, including sex and IMD as covariates, explained 52% of the variance in mathematics scores ( $R^2 = 0.52$ ;  $F(8, 263) = 35.77$ ,  $p < .001$ ). Once the five mediators and two covariates were controlled for, the direct effect of EP birth on mathematics attainment was reduced from  $-0.79$  SD to  $-0.37$  SD but remained significant (Table 4). Therefore, collectively, these neuropsychological abilities partially mediated the relationship between EP birth and mathematics attainment; mathematics composite scores for the EP group were  $0.42$  SD lower than controls due to EP children's deficits in the neuropsychological abilities assessed (see Figure 1 for regression coefficients). Visuospatial processing was the strongest predictor: through the indirect effect of visuospatial processing, EP children had a  $-0.15$  SD reduction in mathematics scores relative to controls. Alone however this equates to a small effect size. Visuospatial processing was a significantly stronger mediator compared with attention (mean difference  $0.11$  SD, bootstrapped 95% CI  $0.02, 0.21$ ). There was no significant difference between any of the other mediators (see Table S4).

Excluding children with severe disability, mathematics was still partially mediated by verbal working memory, visuospatial working memory, visuospatial processing, attention and visuospatial processing ( $R^2 = 0.43$ ,  $F(8, 251) = 23.81$ ,  $p < .001$ ). Visuospatial processing remained the strongest mediator, explaining a  $-0.13$  SD reduction in mathematics scores in EP children compared with controls (see Table S5).

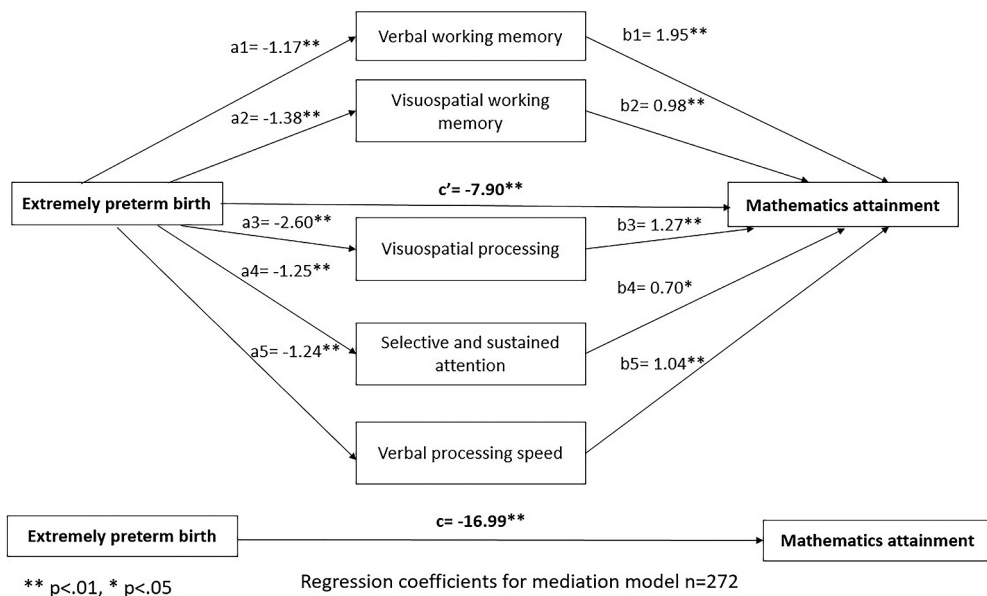


Figure 1. Regression coefficients between EP birth, neuropsychological skills and mathematics scores.

## Do neuropsychological abilities mediate the relationship between EP birth and attainment in reading?

When entered together, verbal working memory, visuospatial working memory, visuospatial processing and verbal processing speed, but not attention, significantly mediated the relationship between EP birth and attainment in reading ( $R^2 = 0.44$ ;  $F(8, 262) = 25.23$ ,  $p < .001$ ). This model, including sex and IMD as covariates, explained 44% of the variance in reading. There was no significant direct effect of EP birth on reading once the effects of five mediators and two covariates were controlled (reduced from  $-0.44$  SD to  $-0.01$  SD; see Table 4). Therefore, the relationship between EP birth and reading attainment was fully mediated by verbal working memory, visuospatial working memory, visuospatial processing and verbal processing speed. Visuospatial processing made a greater contribution to the model than the other three mediators and was the strongest predictor of attainment in reading, explaining a  $-0.20$  SD reduction in reading scores in EP children compared to controls. This equates to a small effect size (see Figure 2 for regression coefficients). Significant differences between indirect effects included visuospatial processing as a stronger mediator than visuospatial working memory (mean difference in reading attainment 0.13 SD, bootstrapped 95% CI  $<.01, 0.25$ ), attention (mean difference 0.22 SD, bootstrapped 95% CI 0.12, 0.33) and processing speed (mean difference 0.13 SD, bootstrapped 95% CI 0.02, 0.26). Visuospatial working memory was a stronger mediator than attention (mean difference 0.09 SD, bootstrapped 95% CI 0.02, 0.19). Verbal working memory was a stronger mediator than attention (mean difference 0.11 SD, bootstrapped 95% CI 0.04, 0.21). See Table S4.

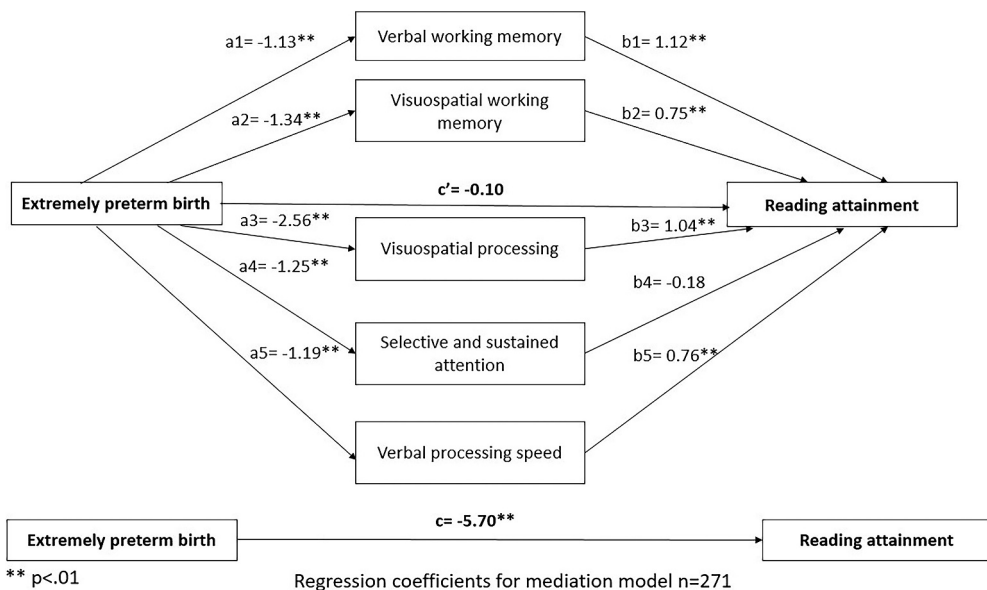


Figure 2. Regression coefficients between EP birth, neuropsychological skills and reading scores.

**Table 3.** Proportion of extremely preterm children and term-born controls with low attainment in reading and mathematics.

	Term-born controls	Extremely preterm	OR (95% CI) Extremely preterm compared to controls	Adjusted OR (95% CI) extremely preterm compared to controls <sup>c</sup>
Reading, n	140	195		
Average/low average attainment n (%) <sup>a</sup>	138 (98.6)	163 (83.6)		
Low attainment n (%) <sup>b</sup>	2 (1.4)	32 (16.4)	13.6 (3.2 to 57.5)	13.3 (3.1, 56.6)
Mathematics, n	139	197		
Average/low average attainment n (%) <sup>a</sup>	138 (99.3)	138 (70.1)		
Low attainment n (%) <sup>b</sup>	1 (0.7)	59 (29.9)	59.0 (8.1 to 431.9)	57.9 (7.9, 424.7)

<sup>a</sup>Defined as less than 2 SD below the control group mean (reading composite score >80, mathematics composite score >76).

<sup>b</sup>Defined as greater than 2 SD below the control group mean (reading composite score ≤80, mathematics composite score ≤76).

<sup>c</sup>OR adjusted for sex and Index of Multiple Deprivation.

After excluding children with severe disability, reading was still fully mediated by verbal working memory, visuospatial working memory and visuospatial processing as significant mediators ( $R^2 = 0.35$ ;  $F(8, 251) = 16.96$ ,  $p < .001$ ). Visuospatial processing remained the strongest mediator, explaining  $-0.17$  SD reduction in reading scores in EP children without severe disability compared with controls (see Table S5).

## Discussion

In this study, children born before 27 weeks of gestation had substantially poorer attainment in reading and mathematics compared to children born at term, with a deficit of 1.1 SD in reading and 1.4 SD in mathematics. For children without severe disability, there was a smaller, but significant deficit in reading (0.4 SD) and mathematics (1.0 SD) compared to controls.

Deficits in verbal and visuospatial working memory, visuospatial processing and verbal processing speed explained a 0.43 SD deficit in reading among the EP children and fully mediated the relationship between EP birth and attainment in this subject. The neuropsychological skills that mediated the relationship between EP birth and mathematics were the same, with the addition of attention as a significant mediator. However, in contrast to reading, there remained a significant direct effect of EP birth on mathematics attainment. Indirect effects of verbal and visuospatial working memory, attention, visuospatial processing and processing speed, accounted for a deficit of 0.42 SD in mathematics scores in children born EP. These findings support existing research that neuropsychological skills explain variance in academic outcomes in children born preterm (Adrian et al., 2020; Akshoomoff et al., 2017; Mulder et al., 2010; Simms et al., 2015; Twilhaar et al., 2020) and that children born preterm have a particular weakness in visuospatial processing (see Fernandez-Baizan et al., 2020; Lind et al., 2020). The full mediation of EP birth on reading attainment through the neuropsychological skills assessed corroborates recent findings from Twilhaar and colleagues in their study of very preterm adolescents (Twilhaar et al., 2020). However, in contrast to their findings, we observed a significant direct effect of EP birth on mathematics scores after controlling for neuropsychological skills.



Table 4. Mediation analysis.

Predictor	Partially standardized point estimate	Standard Error <sup>a</sup>	p	95% Confidence Interval of partially standardized point estimate <sup>a</sup>	R <sup>2</sup>
<b>Attainment in mathematics (N = 272), whole sample mean = 99.73, SD 21.64</b>					
Total effect (c) (X to Y)					.20
Direct effect (c') (X to Y controlling for M <sup>1</sup> , M <sup>2</sup> , M <sup>3</sup> , M <sup>4</sup> , M <sup>5</sup> )	-0.79	0.11	<.001	(-1.00, -0.57)	
Prematurity status	-0.37	0.08	.001	(-0.55, -0.18)	.52
Prematurity status					
Indirect effects					
Total indirect effects	-0.42	0.07	Significant	(-0.56, -0.28)	
Verbal working memory (a <sub>1</sub> b <sub>1</sub> )	-0.10	0.04	Significant	(-0.18, -0.04)	
Visuospatial working memory (a <sub>2</sub> b <sub>2</sub> )	-0.06	0.03	Significant	(-0.13, -0.02)	
Visuospatial processing (a <sub>3</sub> b <sub>3</sub> )	-0.15	0.04	Significant	(-0.24, -0.08)	
Selective and sustained attention (a <sub>4</sub> b <sub>4</sub> )	-0.04	0.02	Significant	(-0.09, <-0.01)	
Verbal processing speed (a <sub>5</sub> b <sub>5</sub> )	-0.06	0.03	Significant	(-0.12, -0.02)	
<b>Attainment in reading (N = 271)<sup>b</sup>, whole sample mean = 99.57, SD 13.09</b>					
Total effect (c) (X to Y)					.09
Direct effect (c') (X to Y controlling for M <sup>1</sup> , M <sup>2</sup> , M <sup>3</sup> , M <sup>4</sup> , M <sup>5</sup> )	-0.44	0.12	<.001	(-0.67, -0.20)	
Prematurity status	-0.01	0.10	.94	(-0.21, -0.19)	.44
Prematurity status					
Indirect effects					
Total indirect effects	-0.43	0.09	Significant	(-0.62, -0.27)	
Verbal working memory (a <sub>1</sub> b <sub>1</sub> )	-0.10	0.04	Significant	(-0.18, -0.04)	
Visuospatial working memory (a <sub>2</sub> b <sub>2</sub> )	-0.08	0.03	Significant	(-0.15, -0.02)	
Visuospatial processing (a <sub>3</sub> b <sub>3</sub> )	-0.20	0.05	Significant	(-0.31, -0.11)	
Selective and sustained attention (a <sub>4</sub> b <sub>4</sub> )	0.02	0.02	Non-significant	(-0.02, 0.07)	
Verbal processing speed (a <sub>5</sub> b <sub>5</sub> )	-0.07	0.03	Significant	(-0.15, -0.02)	

<sup>a</sup>Bootstrapped for indirect effects.<sup>b</sup>One child excluded due to substituted reading composite score.



It is possible that birth at earlier gestations (mean gestational age 25.6 weeks in the present study compared with mean gestational age 29.4 weeks in Twilhaar and colleagues' study) may confer additional risk for greater deficit in mathematics that is not fully explained through specific neuropsychological abilities. In a cohort of EP children born <28 weeks of gestation, follow up at 18 years indicated that even those with typical parent-rated executive function had a mean deficit of 0.6 SD in mathematics scores compared to test norms (Costa et al., 2017). This suggests that EP birth confers a direct risk for poorer mathematics attainment that is independent of the neuropsychological skills assessed in this study. One explanation for this may be that there is a direct effect of major neonatal morbidity on long-term outcomes in this population. For example, the duration of hospitalization and ventilation have been shown to have a direct effect on mathematics skills at eight years of age, in addition to an indirect effect on mathematics skills via cognition at 20 months and attention at six years (duration of ventilation only) in very preterm children (Jaekel et al., 2014). Major neonatal morbidities (pulmonary hypertension, intraventricular hemorrhage Grade III/IV, seizures, necrotizing enterocolitis Stage II/II, bronchopulmonary dysplasia and hypoxic-ischemic encephalopathy) are common among children born at 25 weeks of gestation (55%), but affect a smaller proportion of children born at or after 28 weeks (<23%) (Manuck et al., 2016).

Both neonatal and social risk factors have been associated with poor mathematics skills. For example, socioeconomic status, necrotizing enterocolitis requiring surgery or drainage, Bayley Scales of Infant Development II Mental Development and Psychomotor Development Index scores at 30 months, and occipitofrontal circumference SD scores at 30 months explained 43% of the variance in mathematics scores in children born <26 weeks of gestation in the EPICure Study at age 11 (Johnson et al., 2011). Neonatal risk factors cannot be underestimated, as bronchopulmonary dysplasia explained 78% of the variance in academic attainment in children born <32 weeks of gestation in a recent meta-analysis (Twilhaar, de Kieviet et al., 2018). In terms of socioeconomic status, EP children (<28 weeks of gestation) with mathematics scores more than 2 SD below the normative test mean were 3 to 4.5 times more likely to be born to mothers with less than 16 years of education compared with children whose mothers had  $\geq 16$  years of education (Joseph et al., 2018). However, independent of socioeconomic status, sensitive parenting at age 6 has been shown to predict school performance at age 13 in children born very preterm (Wolke et al., 2013). This was considered to be a protective factor as children who experienced highly sensitive parenting had school performance comparative to children born at term (Wolke et al., 2013). To advance the present research, future studies should evaluate the relative contribution of neuropsychological skills in combination with non-cognitive factors, such as social and neonatal factors, to identify salient factors that could be modified through intervention.

The neural underpinnings of mathematics skills following preterm birth have previously been explored. Mathematics skills in childhood have been associated with altered intrinsic functional connectivity of frontal-parietal networks in very preterm adults (Bäumel et al., 2017). In individuals born <37 weeks of gestation, higher mathematics scores in childhood were associated with higher intrinsic functional connectivity (iFC) in the left lateral occipital/middle temporal cortex and the right angular gyrus/middle temporal cortex, whilst higher mathematics scores individuals born at term were

associated with lower iFC in these areas. Conversely, in the superior frontal gyrus of the left fronto-parietal network, decreased iFC was associated with higher mathematics scores in individuals born preterm, whilst the reverse pattern was found for individuals born at term (Bäumel et al., 2017). Whilst the extent of neuronal plasticity in childhood following preterm birth is unknown, further research is needed to evaluate functional connectivity networks and mathematical skills to evaluate whether network connectivity is malleable via intervention to improve neuropsychological skills (Bäumel et al., 2017). With reference to white-matter brain tracts and mathematical skills, similar associations have been found for both very preterm/very low birthweight and term-born children (Collins et al., 2021). Maturation of the fiber density and cross-sectional area that fibers occupy of the posterior body of the corpus callosum has been associated with change in mathematics computation scores from age 7 to 13 in children born <30 weeks of gestation/<1250 g birthweight and in children born at term (Collins et al., 2021). This study also identified that fiber density and fiber bundle cross section of visual, sensorimotor and cortico-thalamic/thalamo-cortical white matter tracts were associated with higher mathematical computation skills both for very preterm and term-born children 7 and 13 years of age (Collins et al., 2021). The authors suggest that better axonal development in these tracts is associated with higher mathematical attainment through improved capacity for integration of numerical information presented in different modalities (verbal or visual) with general executive processes, including working memory (Collins et al., 2021).

Historically, many cohort studies have used IQ as a primary outcome measure for cognitive function which has been shown to be stable among EP populations from infancy to adulthood (Breeman et al., 2015; Linsell et al., 2018). However contemporary cohorts have demonstrated the importance of assessing specific neuropsychological skills due to their unique contribution to mathematics skills above that of IQ in children born very preterm (Aarnoudse-Moens et al., 2013). Even children with low-average cognitive functioning may still have impairments in working memory, sustained and selective attention, inhibition and mental flexibility, therefore their early assessment and further evaluation as possible predictors of later academic functioning is important (Heeren et al., 2017).

Our study identified that a combination of neuropsychological skills including verbal working memory, visuospatial working memory and visuospatial processing may be especially important to target in interventions to improve mathematics and reading outcomes for EP children with average to moderately low IQ. To date, no working memory training interventions have reported significant or sustained effects on academic outcomes in children aged 6–7 years born <35 weeks of gestation (Jaekel et al., 2021) or in children born <28 weeks of gestation/1000 g (Anderson et al., 2018). In contrast, spatial processing is a longitudinal predictor of mathematical attainment in typically developing children (Gilligan et al., 2017; Verdine et al., 2014) and interventions that target spatial thinking have been trialed among typically developing children and demonstrate medium effect sizes (Uttal et al., 2013). However, different measures of visuospatial processing vary in the strength of their association with mathematical skills (Gilligan, Hodgkiss et al., 2019). As such, it is possible that greater variance in mathematics attainment could have been explained through the inclusion of component measures of visuospatial processing, in addition to line judgment orientation assessed the NEPSY-II arrows subtest in the present study. A single training session in mental

rotation improves accuracy in solving arithmetic equations with a missing term in children aged 8 (Gilligan, Thomas et al., 2019). The use of spatial training interventions in the classroom could therefore be trialed with children born EP.

As working memory and visuospatial processing were the primary mediators of mathematics and reading attainment in children without severe disabilities, in addition to exploring interventions to support visuospatial processing, strategies to reduce learner's working memory load in the classroom may be effective. This is supported by previous research that found that the deficit in scores between children born very preterm and at term followed a cognitive workload gradient, whereby the greatest deficit in scores was observed on tasks that required reasoning, followed by tasks that required simultaneous processing, then tasks that required sequential processing (Jaekel et al., 2013). Teaching strategies that focus on reducing the working memory load in accordance with cognitive load theory (see for Sweller et al., 1998 for explanation) could support children born EP who on average have a reduced working memory capacity. For example, the application of this theory includes breaking down problems into simpler steps to reduce working memory load, integrating both text and diagrams to explain concepts, rather than presenting these physically separated on a page to avoid the cognitive effort of mentally integrating two pieces of information (Sweller et al., 1998). Presenting information sequentially rather than simultaneously could also assist children who process information more slowly (Mulder et al., 2010). Indeed, increasing education professionals' awareness of preterm birth was included in recommendations for supporting children in the recent European Standards of Care for Newborn Health (Jaekel et al., 2018). Moreover, in 2019, the top research priority identified to improve the lives of individuals with learning difficulties related to improving the knowledge, skills and training of education professionals to enable them to identify early signs of learning difficulties and provide optimal support for children and young people (Lim et al., 2019). Improving knowledge of the long-term consequences of preterm birth and providing teachers with strategies they can use to support the learning of children born preterm was the focus of a recently developed e-learning resource for education professionals ([www.pretermbirth.info](http://www.pretermbirth.info)). However, the efficacy of this approach for improved educational outcomes for children born preterm is yet to be determined.

### **Strengths**

The strengths of this study comprise the inclusion of contemporaneous term-born controls recruited through the same mainstream schools attended by children born EP. Whilst these data were not pairwise-matched it did ensure that controls had a similar socio-economic profile to the EP children and enabled deficits in academic attainment in children without severe disabilities to be measured relative to children with a similar educational experience. To our knowledge this is the first study to include dissociable measures of visuospatial working memory, verbal working memory and visuospatial processing in a sample of children born EP to evaluate their impact on academic attainment, from which it was evident that visuospatial processing contributed predominantly to academic performance.

## Limitations

Some EP children with severe neurodevelopmental disabilities were unable to complete the entire battery of neuropsychological tests. As only 33% of children with severe disabilities had complete data only a small proportion of children with severe disabilities were included in the mediation model outlined in Table 4. However, this is the largest national cohort of EP children with whom mediation analysis has been conducted to identify the relative strength of predictors of academic outcomes. As controls were recruited only from mainstream schools these may not be representative of the general population. Therefore, it is possible that deficits observed in EP children may have been accentuated. Given the limited time available to assess each child within school, we were unable to include multiple measures of executive function components for use in a latent model. Whilst we acknowledge the limitations of using cross-sectional data for mediation models, mediation models have been used with cross-sectional data to show that executive functions mediate the relationship between very preterm birth and behavioral problems at age 12 (Schnider et al., 2020) and between very preterm birth and academic outcomes at age 13 (Twilhaar et al., 2020). Moreover, as teacher-rated EF has been shown to be a longitudinal predictor of mathematics grade point average in adolescents with and without disabilities (Samuels et al., 2016), it is appropriate to consider executive function as a mediator of academic attainment, rather than academic attainment as a mediator of executive function in adolescence. Whilst socio-economic status using the Index of Multiple Deprivation was controlled for in the analyses, parent education was not available for the full sample. Therefore, parent education could not be adjusted for.

## Conclusions

Poor attainment in mathematics and reading in children born EP are mediated by neuropsychological skills, the strongest predictor of both being visuospatial processing. Whilst the relationship between reading and EP birth was fully mediated by the neuropsychological abilities assessed; mathematics attainment was only partially mediated. Visuospatial processing remained the strongest mediator between EP birth and reading and mathematics including children with and without severe disability. Future interventions to support EP children's learning could evaluate a visuospatial training intervention in combination with reducing working memory load in the classroom.

## Disclosure statement

Neil Marlow declares financial relationships with Shire/Takeda and Novartis outside the submitted work. No other relevant conflicts of interest are present.

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## Data availability statement

Data are available subject to the EPICure Data Sharing Policy ([www.epicure.ac.uk](http://www.epicure.ac.uk)) and will be available as part of the RECAP preterm Cohort Platform (<https://recap-preterm.eu>).

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