Association of Gestational Age With Verbal Ability and Spatial Working Memory at Age 11

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abstract

BACKGROUND: Although children born very preterm (gestation <32 weeks) have an increased risk of cognitive impairment compared with full-term children (39–41 weeks), the risk for children born moderately (32–33 weeks) to late preterm (34–36 weeks) and early term (37–38 weeks) is unclear. This study describes the relationship between gestational age and cognitive outcomes at 11 years and the trajectory of deficits in verbal ability from age 3 to 11 years.

METHODS: Cognitive ability was assessed by using the Spatial Working Memory test from the Cambridge Neuropsychological Test Automated Working Battery (n = 11 395) and British Ability Scale Verbal Similarities test (n = 11 889) in the UK Millennium Cohort Study. Each gestational group was compared with the full-term group by using differences in z scores and odds ratios for delay (scoring ≥1 SD below the mean).

RESULTS: Very and moderately preterm children demonstrated significantly lower working memory scores compared with full-term children (adjusted difference –0.2 to –0.6) and were more likely to be delayed. There was no significant relationship between late-preterm or early-term birth and working memory (adjusted differences < –0.1), or between gestational age and verbal ability at 11 years. There appears to be a general attenuation in odds ratios as the child ages.

CONCLUSIONS: Very preterm children exhibited working memory deficits at 11 years. However, the absence of delayed verbal skills at 11 years despite earlier delays could indicate "catch-up" effects.

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WHAT'S KNOWN ON THIS SUBJECT: Very preterm birth (<32 weeks) is associated with an increased risk of cognitive impairment. The risk for moderate to late preterm (32–36 weeks) and early-term (37–38 weeks) children, and the evolution of deficits over time, remains unclear.

WHAT THIS STUDY ADDS: At age 11, very and moderately preterm children exhibit a higher risk of impaired working memory; late-preterm and early-term children are not at increased risk. There was no increased risk of verbal delay for any degree of prematurity.

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Preterm birth, and notably, very preterm birth (gestational age <32 weeks) is associated with impaired cognitive outcomes.[1] However, it remains uncertain whether the impairment is global or affects specific cognitive domains, which may reflect different study designs, including choice of controls, single-center versus population-based study populations, and differences in neonatal care in older cohorts. Even among contemporaneous cohorts, findings are inconsistent as to whether the impairment is selective to nonverbal domains, notably executive function, or also affects verbal skills.[2–6] Neuroanatomical changes in the frontal and temporal lobes have been noted, in regions affecting language, memory, and executive function.[7,8]

It is also unclear whether children born moderate to late preterm, and at early-term gestations, are at increased risk of impaired cognitive outcomes. Evidence from the UK Millennium Cohort Study (MCS) demonstrated a risk of poorer outcomes across the spectrum of gestational age groups, with variable delays in verbal and nonverbal domains at 3, 5, and 7 years of age.[9] Conversely, a Danish cohort[10] reported no evidence of an association between moderate to late preterm birth and reading, spelling, or arithmetic ability at 10 years. Few studies have performed repeated assessments over time to follow the trajectory of cognitive ability as the child develops.[4,11–13] Findings are mixed among existing studies, with some reporting persistence and others noting an increase in impairment.[4,11–13]

The current study aimed to examine the impact of gestational age at birth on verbal ability and spatial working memory at age 11, and examine the trajectory of impairment in verbal ability from ages 3 to 11 years. Verbal ability is the only domain to be assessed in all MCS surveys, and is a measure of crystallized intelligence.[14] Spatial working memory was selected as a marker of executive function and fluid intelligence, and hypothesized to be specifically impaired in preterm children.[14]

METHODS

The MCS

The MCS is a longitudinal cohort study of 18 818 children born in the United Kingdom.[9] Children born between September 2000 and August 2001 in England and Wales, and between November 2000 and January 2002 in Northern Ireland and Scotland, were recruited at 9 months of age.[9,15] A 2-stage clustered stratified sampling design was used, with initial sampling by electoral ward and oversampling of wards from Scotland, Wales or Northern Ireland, those with high levels of child poverty, or high proportions of ethnic minorities (England only).[16] Children were selected from electoral wards through identification on the Child Benefit records,[16] a form of financial support available except to those who have recently immigrated to the United Kingdom.[9] Children who died before 9 months represented fewer than 1% of the eligible population.[17] Surveys were conducted initially at age 9 months, with follow-up surveys at 3, 5, 7, and 11 years.[16]

Gestational Age

Term births were defined as births after 37^{+0} weeks' gestation, and subdivided into early-term (37^{+0} to 38^{+6} weeks) and full-term births (39^{+0} to 41^{+6} weeks).[18] Preterm births were classified as very preterm (<32 weeks), moderately preterm (32^{+0} to 33^{+6} weeks), and late preterm (34^{+0} to 36^{+6} weeks).[18] Births from 42^{+0} weeks were postterm.[18]

Cognitive Assessments

The cognitive assessments at age 11 years included the British Ability Scales Edition II Verbal Similarities test[19] and the Cambridge Neuropsychological Test Automated Battery Spatial Working Memory test.[20]

The Verbal Similarities test assessed the child's verbal reasoning and knowledge by asking the child how 3 words were related.[16,21,22] Different verbal subtests from the British Ability Scales were available from earlier surveys, including Naming Vocabulary (ages 3 and 5) and the Word Reading test (age 7).[23,24] Although these measures tested different aspects of verbal ability, they are nonetheless thought to provide a measure of the same underlying higher-order verbal skills.[21,24]

The Cambridge Neuropsychological Test Automated Battery Spatial Working Memory test involved the child sequentially searching for a coin in 4 to 8 boxes on a touch screen, where the coin never appeared in the same box twice.[21] An error was recorded if the child searched a box that had previously contained a coin, or had been shown to be empty on the same search for a single coin.[25] Outcomes included the error score, reflecting the number of times a box was incorrectly searched, and the strategy score, which reflected how systematically the child searched, with higher scores indicating a less-ordered search strategy.

Scores were converted to age-sex standardized *z* scores with adjustment for age in 3-month intervals by using the SD of the selected cohort.[9] *Z* scores were dichotomized at 1 SD below the mean to indicate where a child was delayed on a test.[9,26,27] *Z* scores were reverse coded so that poorer performance was reflected in lower standardized scores.

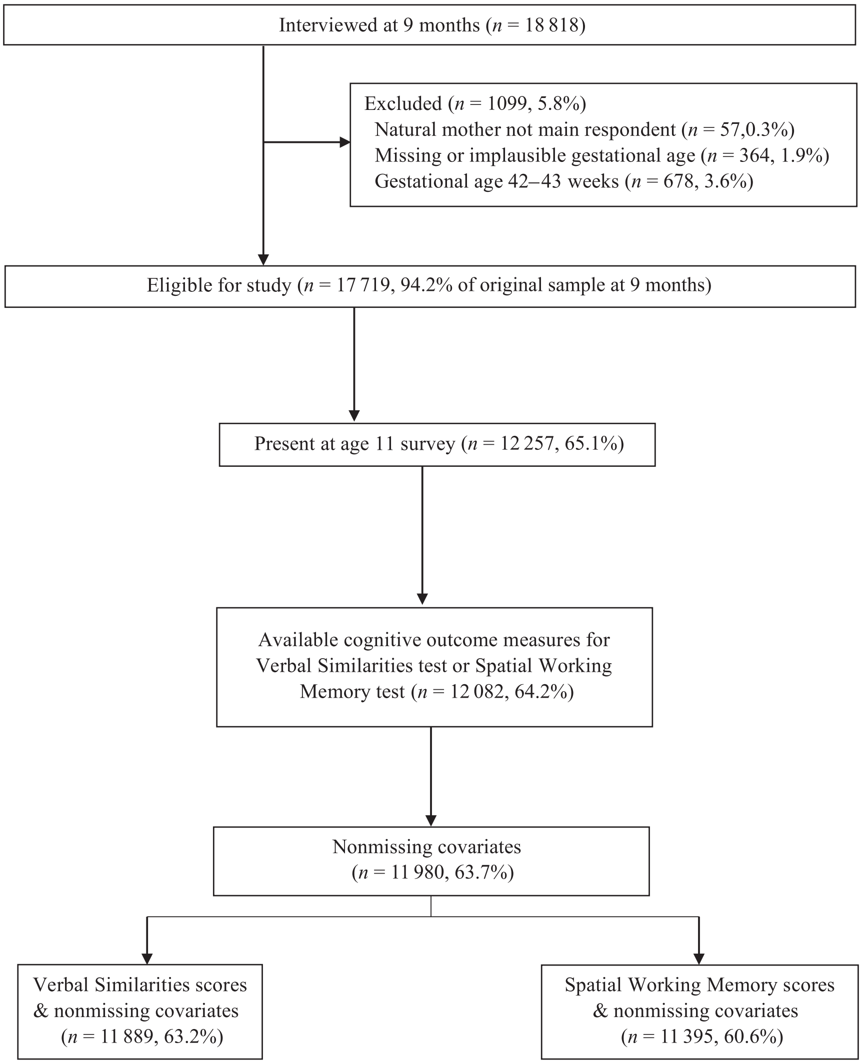

FIGURE 1
Flowchart of study exclusions and participation. The denominator for each percentage is variable; it represents the percentage of the cohort present as a proportion of the sample at the preceding step.

Covariates

Maternal covariates were ethnicity (white, other), marital status (married, cohabiting, single), smoking status (nonsmoker, quit in pregnancy, smoked throughout pregnancy), and alcohol consumption (none, light [1–2 U per week], heavy [≥3 U per week]).[28] Maternal qualifications were defined by the National Vocational Qualification classification, as university-level or equivalent, A-levels or equivalent (final examinations before university), General Certificate of Secondary Education or equivalent (GCSE; examinations taken in the last year of compulsory school at age 16), and no formal qualifications. Maternal depression at the first postnatal survey was defined as a score of ≥4 on the Rutter Malaise Inventory.[15] The index of multiple deprivation (IMD), a measure of area-based deprivation based on the child's household at age 9 months, was analyzed in quintiles.[29] Socioeconomic status also was assessed by using social housing status and maternal occupation by using the National Statistics Socioeconomic Classification system (high [eg, managerial/professional], intermediate [eg, self-employed/small employers/lower supervisory/technical occupations), low [eg, routine/semiroutine], never worked). Fertility (spontaneous conceptions, normal time to pregnancy <12 months, prolonged time to pregnancy >12 months, requiring assistance reproductive technologies), and breastfeeding duration (never breastfed, <2.0 months, 2.0–3.9 months, ≥4.0 months) were included[30,31] Child-related covariates included sex, age at testing, multiple birth, if firstborn, and language spoken at home (English, English as a second language, non-English language).

Exclusions, Loss to Follow-up, and Missing Data

Children were excluded if the birth mother was not the main respondent at the initial survey, or if the gestational age, as reported by the mother, was missing or implausible for birth weight (Fig 1).[32,33] Implausible birth weight was defined as a weight lying outside the range given by the median plus or minus twice the interquartile range, by using birth weight for gestational age centile charts.[32] Postterm births were excluded, as poor agreement between maternal recall and medical records has been documented in this cohort.[33] This left 17 719 children eligible, of whom 12 257 were present at the age 11 survey (69.2%), most of whom (98.6%) had data on the cognitive tests. The cognitive tests were not administered if the child had a severe disability or behavioral problems, or did not have sufficient English to understand the instructions given. Nonresponse was accounted for by using survey weights, which were derived by using predictors of missingness, including sociodemographic characteristics.[34,35] Due to low levels of missingness in covariates (n = 102, 0.8%, Fig 1), a complete case analysis approach was used.

Statistical Methods

Analyses were survey-weighted to account for the clustered (families within electoral wards and multiples within families), stratified sample design, oversampling, and for nonresponse at successive surveys.[21,34–36] Multivariable linear regression was used to examine the relationship between gestational age groups and continuous test scores, and logistic regression to assess the odds of delay by gestational age groups. The reference group was full-term children (39–41 weeks). Adjustment was made a priori for child sex, multiple birth, age at testing, maternal age, alcohol use, and smoking.[37] The remaining covariates that were statistically significant in univariable analysis ($P < .05$) were added to this model by using a forward stepwise approach and retained only if significantly associated with the outcome ($P < .05$) after adjustment for other covariates (maternal qualifications, IMD, and breastfeeding duration). All models were adjusted for the same covariates to assist comparability.

As verbal ability was tested at the age 3, 5, 7, and 11 surveys, patterns of delay were identified to examine the trajectory of verbal skill development over time. Children were classified as "delayed once only" (delayed on only 1 test at ages 3, 5, 7, or 11), having "persistent delay" (delayed at age 11 and an earlier verbal test) and "early childhood delay" (delayed at 2 or more ages of 3, 5, and 7 years, but not age 11). Multivariable logistic regression models assessed the effect of gestational age on the risk of each separate pattern of delay compared with never delayed.

Analyses were conducted by using Stata SE version 13 (Stata Corp, College Station, TX). Ethical approval for the age 11 survey was granted by Yorkshire and the Humber-Leeds East Medical Research Ethics Committee.[16]

RESULTS

The final cohort included 11 395 children with Spatial Working Memory test results and 11 889 children with Verbal Similarities test results. Approximately 8.9% of the children were preterm. In univariable analyses, increasing prematurity was associated with nonwhite ethnicity, lower maternal educational qualifications, multiple births, and shorter duration of breastfeeding (Table 1). Although gestational age was also significantly associated with younger maternal age, there was no evidence of a dose-response relationship.

Children born very (<32 weeks) and moderately preterm (32–33 weeks) demonstrated significantly lower scores in the Spatial Working Memory test compared with their full-term peers in unadjusted and adjusted analyses. As presented in Table 2 and Fig 2A (i) to (ii), children born at <32 weeks and 32 to 33 weeks demonstrated, on average, 0.2 to 0.3 points lower strategy scores than children born at full-term. The prevalence of delay on the strategy measure also increased with prematurity from 12.9% in children born full-term to 21.7% in those born moderately preterm and 18.5% in those born very preterm. After adjustment for covariates, children born at 32 to 33 weeks experienced significantly greater odds of being delayed on the strategy measure (odds ratio [OR] 2.09, 95% confidence interval [CI] 1.21 to 3.61). Similarly, as summarized in Table 2 and Fig 2B (i) to (ii), error scores were on average 0.6 points lower in children born <32 weeks and 0.2 points lower in children born 32 to 33 weeks than their full-term peers, with children born <32 weeks demonstrating a significantly increased prevalence of delay compared with full-term children (34.1% vs 17.0%, OR 2.47, 95% CI 1.48 to 4.12). Children born late preterm or early term were not significantly different from the full-term group on the strategy or error scores.

Conversely, there was no statistically significant relationship between any of the gestational age groups and Verbal Similarities test scores at age 11 (Table 2 and Fig 2C [i]–[ii]).

Complete assessments of verbal ability from the MCS surveys at ages 3, 5, 7, and 11 years were available for 9009 children (the "age 3–11 cohort"). Table 2 and Fig 3 demonstrate the longitudinal progression of risk of delay on the verbal test at each testing age in this cohort according to gestational age groups. There appears to be a general attenuation in ORs as the child ages. Table 2 also demonstrates that 70% of full-term children had no delay at ages 3 to 11, whereas 6.2% were persistently delayed and 5.5% experienced early childhood delay. The very preterm children were significantly more likely be persistently delayed (OR 3.42, 95% CI 1.59 to 7.39) and experience early childhood delay (OR 4.39, 95% CI 1.96 to 9.87). Late preterm children were more likely to be persistently delayed (OR 1.81, 95% CI 1.12 to 2.94), whereas early-term children were at greater risk of early childhood delay (1.42, 95% CI 1.03 to 1.95).

DISCUSSION

This analysis examined the impact of prematurity on verbal skills and spatial working memory at age 11 years. Although very preterm and moderately preterm children exhibited an increased risk of poorer performance on tests of spatial working memory, there was no increased risk at late-preterm and early-term gestations. Furthermore, there was no statistically significant relationship between gestational age and verbal ability at any degree of prematurity. Among the 9009 children with complete

TABLE 1 Descriptive Characteristics of MCS Cohort Present at Age 11 Survey According to Gestational Age (n = 11 980)

	Total n = 11 980	Gestational Age Group					P
		<32 wk; Very Preterm; n = 145	32–33 wk; Moderate Preterm; n = 133	34–36 wk; Late Preterm; n = 720	37–38 wk; Early Term; n = 2434	39–41 wk; Full Term; n = 8548	
Gestational age at birth, wk, mean (SD)	39.0 (2.1)	29.0 (1.9)	32.7 (0.5)	35.3 (0.7)	37.7 (0.5)	40.0 (0.8)	—
Sociodemographic characteristics, maternal							
Ethnicity, n (%)[a]							
White	10199 (87.1)	113 (78.6)	114 (90.8)	618 (88.5)	2029 (85.1)	7325 (87.7)	.01
Other ethnicity[b]	1759 (12.9)	32 (21.4)	19 (9.2)	101 (11.5)	402 (14.9)	1205 (12.3)	
Maternal education, n (%)							
No formal qualification	1580 (14.9)	30 (21.3)	14 (9.6)	103 (18.6)	354 (16.2)	1079 (14.2)	.09
Lower, GCSE[c] or equivalent, overseas/other	4712 (42.4)	54 (39.0)	62 (47.7)	315 (44.6)	957 (42.9)	3324 (42.0)	
Medium, A-level[d] or equivalent	1761 (14.0)	15 (11.1)	15 (12.5)	83 (11.5)	371 (14.4)	1277 (14.2)	
Higher, university degree or equivalent	3927 (28.7)	46 (28.6)	42 (30.3)	219 (25.3)	752 (26.5)	2868 (29.7)	
IMD quintile, n (%)							
Lowest quintile	3524 (26.0)	50 (25.7)	36 (19.1)	228 (27.4)	720 (25.6)	2490 (26.2)	.57
Highest quintile	1952 (17.0)	20 (14.5)	24 (21.4)	122 (19.0)	380 (15.9)	1406 (17.1)	
Pregnancy-associated characteristics							
Maternal age, mean (SD)	28.2 (6.0)	27.9 (5.8)	29.7 (6.1)	28.4 (6.1)	28.5 (5.9)	28.1 (6.0)	.05
Alcohol use in pregnancy, n (%)							
Never	8393 (69.2)	116 (79.0)	100 (71.0)	524 (70.5)	1764 (71.7)	5889 (68.1)	.11
Light, 1–2 U/wk/occasion	2763 (23.6)	19 (14.0)	22 (21.1)	145 (21.6)	520 (21.8)	2057 (24.6)	
Moderate/heavy (≥3 U/wk/ occasion	824 (7.2)	10 (7.0)	11 (8.0)	51 (8.0)	150 (6.5)	602 (7.3)	
Smoking in pregnancy, n (%)							
Nonsmoker	8039 (63.5)	89 (64.9)	79 (57.6)	438 (57.6)	1663 (64.3)	5770 (63.9)	.23
Quit during pregnancy	1452 (12.9)	19 (10.4)	21 (15.6)	100 (14.0)	263 (12.0)	1049 (13.0)	
Continued smoking	2489 (23.6)	37 (24.8)	33 (26.8)	182 (28.4)	508 (23.8)	1729 (23.1)	
Environmental and psychosocial factors							
Breastfeeding duration, mo, n (%)							
Never breastfed	3709 (35.0)	49 (38.0)	39 (34.2)	265 (42.6)	798 (36.8)	2558 (33.7)	<.001
<2.0	3183 (24.5)	40 (26.3)	48 (30.8)	207 (26.3)	686 (25.7)	2202 (23.9)	
2.0–3.9	1267 (10.2)	27 (18.2)	17 (14.1)	78 (9.6)	251 (10.6)	894 (10.0)	
≥4.0	3821 (30.3)	29 (17.5)	29 (21.0)	170 (21.5)	699 (27.0)	2894 (32.4)	
Child characteristics							
Boy, n (%)	5992 (50.8)	69 (48.5)	72 (62.4)	380 (52.8)	1244 (51.7)	4227 (50.2)	.13
Mean age of child at testing, mean (SD)	11.1 (0.3)	11.1 (0.3)	11.1 (0.3)	11.1 (0.3)	11.1 (0.3)	11.1 (0.3)	.23
Multiple, n (%)	322 (2.9)	38 (25.9)	28 (22.0)	102 (14.2)	118 (5.2)	36 (0.5)	<.001

Unweighted counts and weighted percentages.

[a] Twenty-two children did not have maternal ethnicity recorded; number of children with known maternal ethnicity = 11 958.

[b] Other ethnicity includes individuals of mixed, Indian, Bangladeshi, Pakistani, Black African, Black Caribbean, and other background.

[c] GCSE are national examinations in the last year of compulsory schooling at age 16.

[d] A-levels are the final examinations taken before university.

assessments of verbal ability at all 4 surveys, the risk of verbal delay generally decreased at each survey and a similar number of children experienced persistent delay as early childhood delay. These findings raise questions about the selective effect of preterm birth on cognitive domains and possible "catch-up" effects.

Very preterm and moderately preterm children demonstrated significantly lower scores on the error and strategy measures of the Spatial Working Memory test. The absence of a significantly increased risk of delay on the error measure for moderately preterm children despite lower total scores than full-term children suggests that the decrease in scores was not clinically significant. Only moderately preterm children were at significantly increased risk of delay on the strategy measure. Given that very preterm children had lower test scores than moderately preterm children, and the risk for very preterm children just reached nonsignificance, this may reflect chance or small numbers rather

TABLE 2 Relationship Between Gestational Age and Cognitive Outcomes at Age 11 Years (Age 11 Cohort, n = 11 889) and at Ages 3, 5, 7, and 11 Years (Age 3–11 Cohort for Children Present at All 4 Surveys; n = 9009) in the MCS

Age	Assessment	Early Preterm; <32 wk	Moderately Preterm; 32–33 wk	Late Preterm; 34–36 wk	Early Term; 37–38 wk	Full Term; 39–41 wk, Reference
Age 11 cohort, n = 11 395 for Spatial Working Memory and n = 11 889 for Verbal Similarities						
11	Spatial Working Memory – Strategy: difference in scores (95% CI)[a]	−0.33 (−0.50 to −0.16)	−0.23 (−0.45 to −0.00)	−0.05 (−0.15 to 0.04)	−0.07 (−0.12 to −0.01)	0
11	Spatial Working Memory – Strategy: difference in scores (95% CI)[b]	−0.30 (−0.46 to −0.13)	−0.24 (−0.45 to −0.03)	−0.02 (−0.11 to 0.07)	−0.05 (−0.11 to 0.00)	0
	Spatial Working Memory – Strategy: % with delay[c]	18.5	21.7	14.6	14.3	12.9
11	Spatial Working Memory – Strategy: OR of delay (95% CI)[a]	1.54 (0.96 to 2.48)	1.88 (1.07 to 3.28)	1.16 (0.82 to 1.63)	1.13 (0.94 to 1.35)	1
11	Spatial Working Memory – Strategy: OR of delay (95% CI)[b]	1.61 (0.97 to 2.67)	2.09 (1.21 to 3.61)	1.16 (0.83 to 1.62)	1.13 (0.94 to 1.36)	1
11	Spatial Working Memory – Error: difference in scores (95% CI)[a]	−0.62 (−0.96 to −0.29)	−0.18 (−0.35 to 0.00)	−0.11 (−0.20 to −0.02)	−0.06 (−0.11 to −0.00)	0
11	Spatial Working Memory – Error: difference in scores (95% CI)[b]	−0.58 (−0.93 to −0.23)	−0.20 (−0.38 to −0.03)	−0.07 (−0.16 to 0.01)	−0.04 (−0.09 to 0.01)	0
	Spatial Working Memory – Error: % with delay[c]	34.1	16.4	20.2	17.8	17.0
11	Spatial Working Memory – Error: OR of delay (95% CI)[a]	2.53 (1.57 to 4.08)	0.96 (0.56 to 1.65)	1.23 (0.94 to 1.62)	1.05 (0.91 to 1.21)	1
11	Spatial Working Memory – Error: OR of delay (95% CI)[b]	2.47 (1.48 to 4.12)	1.01 (0.58 to 1.79)	1.17 (0.88 to 1.54)	1.02 (0.89 to 1.17)	1
11	Verbal Similarities: difference in scores (95% CI)[a]	−0.23 (−0.47 to 0.02)	0.04 (−0.19 to 0.27)	−0.07 (−0.19 to 0.05)	−0.04 (−0.09 to 0.01)	0
11	Verbal Similarities: difference in scores (95% CI)[b]	−0.18 (−0.42 to 0.07)	0.01 (−0.21 to 0.24)	−0.03 (−0.13 to 0.08)	−0.02 (−0.07 to 0.02)	0
	Verbal Similarities: % with delay[c]	15.8	12.9	15.9	12.8	12.4
11	Verbal Similarities: OR of delay (95% CI)[a]	1.32 (0.71 to 2.45)	1.04 (0.58 to 1.88)	1.34 (1.01 to 1.77)	1.03 (0.87 to 1.22)	1
11	Verbal Similarities: OR of delay (95% CI)[b]	1.16 (0.62 to 2.15)	1.19 (0.65 to 2.16)	1.25 (0.94 to 1.67)	1.00 (0.83 to 1.19)	1
Age 3–11 cohort assessed at ages 3, 5, 7, and 11, n = 9009						
11	Verbal Similarities: OR of delay (95% CI)[b]	1.78 (0.92 to 3.45)	1.09 (0.52 to 2.29)	1.44 (0.99 to 2.08)	0.83 (0.67 to 1.04)	1
7	Word Reading: OR of delay (95% CI)[b]	1.84 (1.04 to 3.27)	1.08 (0.58 to 2.00)	1.55 (1.18 to 2.05)	1.16 (0.94 to 1.42)	1
5	Naming Vocabulary: OR of delay (95% CI)[b]	1.96 (1.04 to 3.69)	0.77 (0.38 to 1.54)	1.17 (0.82 to 1.67)	1.04 (0.84 to 1.29)	1
3	Naming Vocabulary: OR of delay (95% CI)[b]	2.62 (1.38 to 4.98)	1.66 (0.82 to 3.35)	1.15 (0.82 to 1.62)	1.25 (1.03 to 1.52)	1
3–11	Never delayed: % with no delay[c]	50.6	72.1	59.4	68.2	70.4
3–11	Delayed once only: % with delay[c]	17.8	14.9	24.2	19.3	17.9
3–11	Delayed once only: OR of delay (95% CI)[b]	1.23 (0.66 to 2.29)	0.84 (0.40 to 1.76)	1.49 (1.15 to 1.94)	1.08 (0.91 to 1.29)	1
3–11	Persistent delay: % with delay[c]	14.8	7.4	10.8	5.2	6.2
3–11	Persistent delay: OR of delay (95% CI)[b]	3.42 (1.59 to 7.39)	1.70 (0.70 to 4.16)	1.81 (1.12 to 2.94)	0.87 (0.64 to 1.18)	1

TABLE 2 Continued

Age	Assessment	Early Preterm; <32 wk	Moderately Preterm; 32–33 wk	Late Preterm; 34–36 wk	Early Term; 37–38 wk	Full Term; 39–41 wk, Reference
3–11	Early childhood delay: % with delay[c]	16.8	5.7	5.7	7.3	5.5
3–11	Early childhood delay: OR of delay (95% CI)[b]	4.39 (1.96 to 9.87)	1.34 (0.58 to 3.11)	1.20 (0.64 to 2.23)	1.42 (1.03 to 1.95)	1

Delay is defined as a score ≥1 SD below the mean score recorded for each test by the children in the MCS cohort at each testing age. "Delayed once only" indicates the child was delayed on only 1 verbal test at ages 3, 5, 7, and 11 years. "Persistent delay" indicates the child was delayed at age 11 and 1 earlier testing age. "Early childhood delay" indicates the child was delayed on at least 2 tests at ages 3, 5, and 7 years, but not at age 11. ORs represent risk of each pattern of delay (once only/persistent delay/early childhood delay) versus never delayed.
a Unadjusted results.
b Adjusted for maternal age, smoking and alcohol use in pregnancy, child age at testing, sex, multiplicity, maternal education, IMD, and breastfeeding.
c Weighted percentages.

than absence of risk. Differences in observed patterns in the strategy and error outcomes may reflect differences in cortical lesions associated with preterm birth, separately affecting spatial memory and strategic factors that contribute to spatial working memory.[38,39] The finding of impaired spatial working memory in very and moderately preterm children is supported by Aarnoudse-Moens et al,[40] who identified small deficits in working memory in a meta-analysis of 4125 very preterm children. The lack of effect in late-preterm and early-term children in the MCS cohort is unlikely to reflect small sample size. It may be due to very small effects that could not be discriminated by the Spatial Working Memory test; alternatively, late-preterm and early-term children may not be at increased risk.

Conversely, there was no association between gestational age at birth and verbal ability at age 11 years. Previously apparent verbal delays in late-preterm and early-term children were no longer evident; however, the result is most striking for its absence of effect in the very preterm group.[9] Possible explanations for this finding include a lack of comparability between verbal tests, attrition bias, low power, or a catch-up effect. It is possible that there was a small effect of prematurity in the very preterm group (n = 145) that our study was not adequately powered to detect at age 11. In particular, the very preterm group included only a small number of children born at <28 weeks, who are at greater risk of delay, compared with children born 29 to 31 weeks.

The interpretation of a catch-up effect is strengthened by evidence of amelioration in the ORs of delay across the 4 surveys. A possible explanation is attrition bias, where children with greater impairment were more likely to drop out. The study had ~30% study attrition, and although survey weights for nonresponse were used, it is not possible to rule out residual bias. The impact of attrition was tested by comparing the association between age 7 test scores and gestational age groups in the current study cohort, and previously published analyses of the same associations in the cohort of children at age 7 years (data available on request).[9] The comparison revealed similar effect sizes; where differences occurred, they suggested an attrition bias away from the null in the age 11 study population. This finding is reassuring in that attrition is unlikely to be the sole explanation for the lack of effect of gestational age on verbal skills at age 11.

In longitudinal analyses, ~6% of full-term children experienced persistent delay and a similar proportion experienced early childhood delay or a possible catch-up effect. These proportions were considerably higher in the very preterm group (15% and 17%, respectively), suggesting that very preterm birth is associated with both persistent delay and catch-up. Although these definitions aggregate multiple patterns of delay into a single measure and should be interpreted with caution, the findings nonetheless suggest heterogeneous trajectories that merit further investigation.

The key strength of this study is that it was a large, nationally representative and prospectively recruited cohort with objective assessment of cognitive outcomes. As outlined previously, the study was limited by ~30% attrition. Different verbal tests were used at different ages, introducing potential heterogeneity into the interpretation of a catch-up effect. All of the verbal assessments except Word Reading (age 7) were derived from the "core scales" and should therefore theoretically[24] capture the same underlying measure of higher verbal ability, although direct comparability cannot be ensured. Finally, it is not possible in the study to separate out the impact of preterm birth from maternal and neonatal complications that may have triggered or prompted early delivery, such as the development of intrauterine growth restriction.[41]

The overall results suggest that any early deficits in verbal skills may improve by early adolescence. This contrasts with the findings of a previous meta-analysis by van Noort-van der Spek et al,[42] who reported that the magnitude of impairment in assessments of "complex language" persisted or increased over time

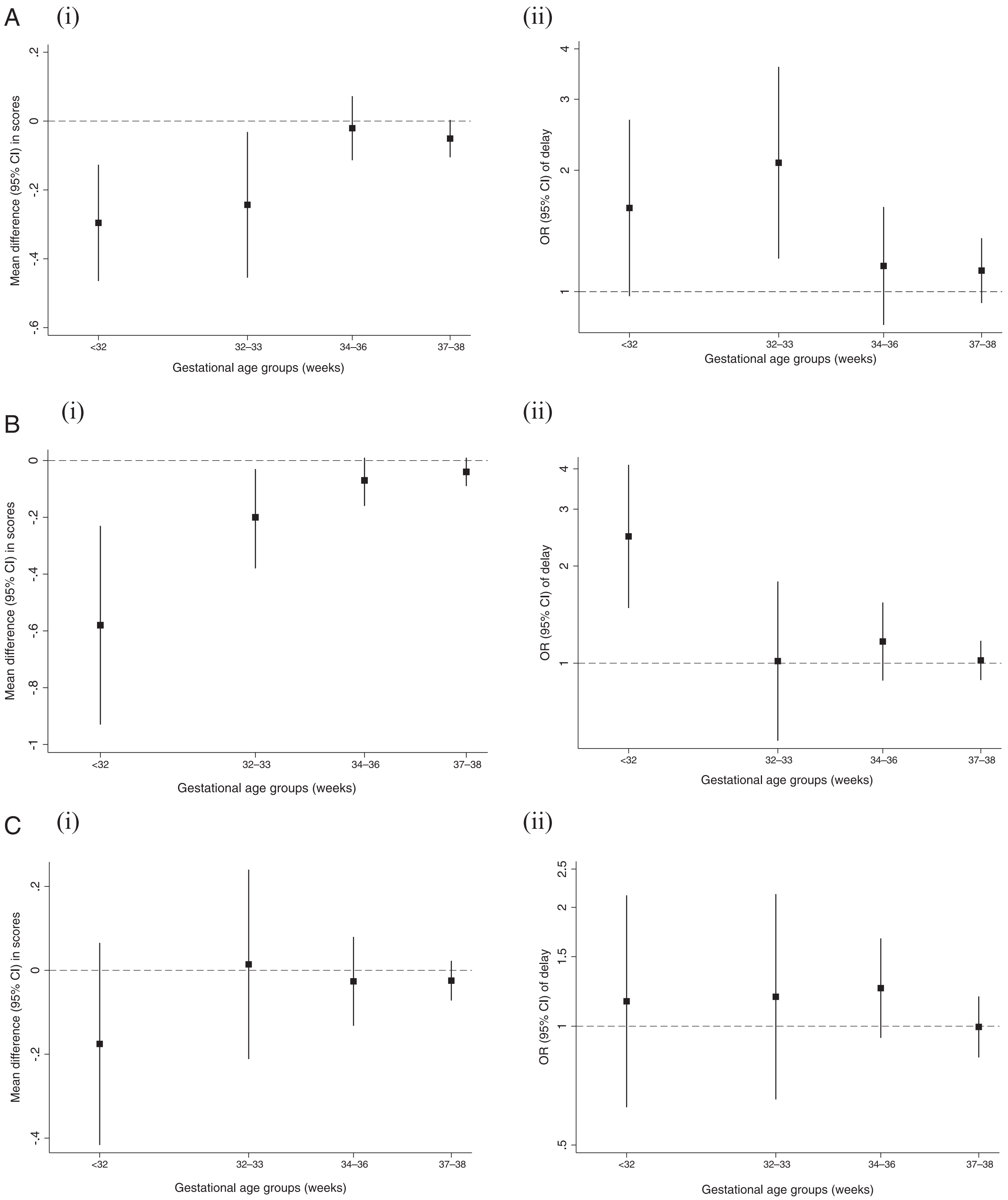

FIGURE 2

(i) Mean differences in scores and (ii) OR of delay on test in (A) Spatial Working Memory strategy test results, (B) Spatial Working Memory error test results, and (C) Verbal Similarities test. Adjusted for child sex, multiple birth, age at testing, maternal age at delivery, alcohol and smoking, maternal qualifications, IMD, and breastfeeding duration; reference group is full-term group (39–41 weeks).

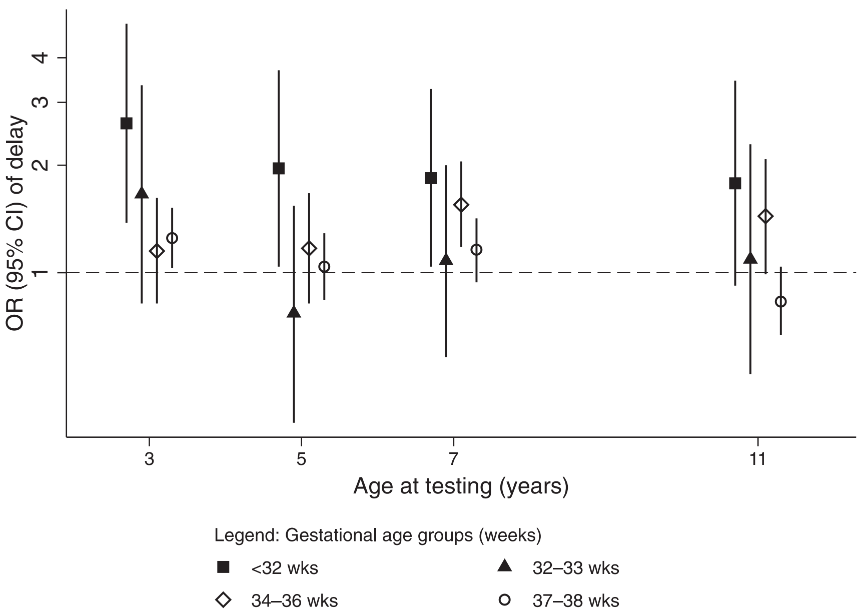

FIGURE 3
OR of delay on verbal test at each testing age according to gestational age. Adjusted for child sex, multiple birth, age at testing, maternal age at delivery, alcohol and smoking, maternal qualifications, IMD, and breastfeeding duration; reference group is full-term group (39–41 weeks).

between preterm and term children. The finding of delays in working memory skills but not verbal ability supports the hypothesis that preterm birth may more specifically affect nonverbal cognitive domains.[11,43–45] Neuroanatomical studies using MRI have detected specific reductions in the volumes of the frontal and temporal lobes in preterm children, which play important roles in the function of memory and language.[7] However, functional MRI findings suggest that preterm children may develop compensating alternative language neural pathways.[7] Executive dysfunction may therefore persist while verbal skills are more amenable to educational or parental interventions.[9,46] Improvements in receptive vocabulary after a preschool intervention in American preterm children had been noted in the Infant Health and Development Program, raising the possibility that the study children benefited from special educational support in British schools.[11,47]

CONCLUSIONS

The study highlights delay in spatial working memory among very and moderately preterm children at age 11 years, but evidence of possible amelioration of delay in verbal skills by early adolescence. This is consistent with a more selective effect of preterm birth on nonverbal domains. Impairments in verbal domains may be more responsive to intervention, justifying further investigation into early educational intervention for preterm children.

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ABBREVIATIONS

CI: confidence interval
GCSE: General Certificate of Secondary Education
IMD: Index of Multiple Deprivation
MCS: Millennium Cohort Study
OR: odds ratio

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