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ORIGINAL ARTICLE

Antenatal and neonatal risk factors in very preterm children were associated with language difficulties at 9 years of age

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Abstract

Aim: This Finnish study compared language and reading abilities between schoolchildren born at a very low gestational age (VLGA) of <32 weeks and at term and analysed any associations between antenatal and neonatal risk factors and language skills in the VLGA group.

Methods: We prospectively followed 76 children born at a VLGA and 50 children born at term when they reached a mean age of 9.0 (8.1–10.0) years. They attended mainstream schools and had no severe neurosensory disabilities. Receptive language ability, rapid naming and word reading were evaluated using standardised tests.

Results: Children in the VLGA group had lower scores for receptive language abilities (median 55.0 vs. 57.0, $p = 0.01$) and word reading (mean 4.4 vs. 5.1, $p = 0.03$) than the children in the term group. In the VLGA group, foetal growth restriction was associated with lower scores for rapid naming, early intraventricular haemorrhage was associated with poor word reading and respiratory distress syndrome was associated with poor rapid naming ($p < 0.05$).

Conclusion: Schoolchildren born at a VLGA had more difficulties with receptive language abilities and word reading than children born at term. Foetal growth restriction and early neonatal morbidities were associated with language difficulties.

KEYWORDS
expressive language skills, foetal growth restriction, reading, receptive language abilities, very low gestational age

1 | INTRODUCTION

Survival after very preterm birth has improved in the last two decades and attention has turned to long-term neurodevelopmental morbidities. Prematurity continues to be a risk factor for major deficits in intelligence,[1] and for subtler neurodevelopmental impairments, such as problems in executive functioning, language and learning.[2,3]

Language abilities are key factors for successful communication and social interaction, and educational achievement. Up to 20% of very preterm children have been diagnosed with a language disability at school age.[4] Delays in the development of both receptive and expressive language abilities have been seen in preterm children,[2,5] and more specific deficits in various language subdomains, such as phonological awareness, semantics, grammar, discourse and pragmatics.[6]

Abbreviations: VLGA, very low gestational age.

According to the Simple View of Reading,[7] key skills for reading are linguistic comprehension and decoding, which involves the quick and accurate reading of isolated words. It has been hypothesised that linguistic comprehension will become more important than decoding in higher school grades.[8] Rapid naming has also been shown to predict reading skills.[9] Assessing the core skills for reading, namely language comprehension, rapid naming and word reading, makes it possible to identify the early signs of later reading difficulties.

In addition to prematurity itself, a number of other factors have been associated with neurodevelopmental impairment in preterm children. These include other prenatal and postnatal factors, such as poor foetal growth,[10,11] intraventricular haemorrhage,[12] severe lung disease,[13] infections[14] and sociodemographic factors.[15] These may also be contributory risk factors for language impairment or deficits, even if children do not have a general cognitive delay. However, only a few studies have focussed on antenatal and neonatal risk factors for language disabilities, especially in schoolchildren born very preterm.

The main aim of this study was to analyse how receptive and expressive language abilities, and technical reading skills differ between very preterm and term-born children and how risk factors affect language results. Receptive language abilities were assessed by using verbal instructions to measure language comprehension and expressive language skills were evaluated using rapid naming. Technical reading skills were assessed through word reading. We hypothesised that children born at a very low gestational age (VLGA) of less than 32 weeks would have impaired performance in these skills at school age, especially those with poor foetal growth. Our further aims were to investigate whether other perinatal adverse events and gender and maternal education were risk factors for language disabilities.

Key Notes

- This Finnish study prospectively followed the reading and language abilities of 76 children born at a very low gestational age (VLGA) of less than 32 weeks and 50 children born at term.
- The children born at a VLGA had more difficulties with receptive language abilities and word reading when they reached 9 years of age than the controls.
- Foetal growth restriction and early neonatal morbidities were associated with language difficulties.

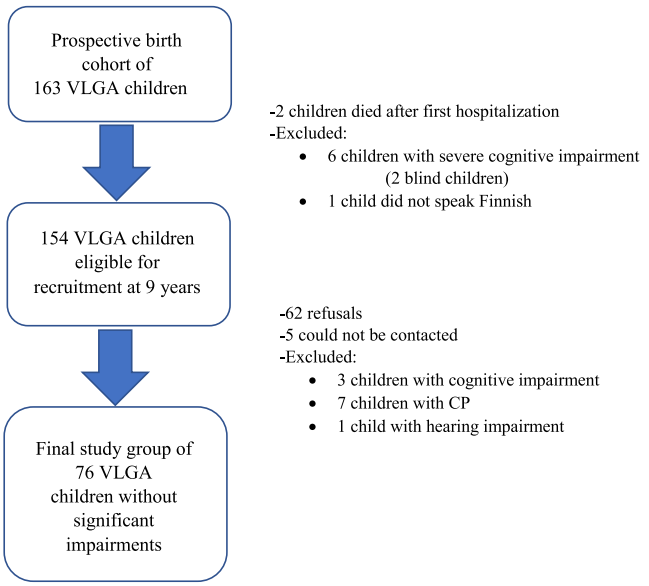

FIGURE 1 The prospective study group of children born at a very low gestational age (VLGA) of <32 weeks

2 | METHODS

2.1 | Participants

The participants were part of a prospective cohort study of 163 children born at a VLGA at Oulu University Hospital between 1 November 1998 and 30 November 2002. The cohort has previously been described in detail.[10] Figure 1 presents how the VLGAs were recruited. The original population represented 76% of the surviving children born at a VLGA at Oulu University Hospital during this time. All children attended mainstream schools and had no severe neurosensory disabilities. The exclusion criteria were: cognitive impairment, cerebral palsy, blindness or severe visual impairment and the need for a hearing aid. All the children spoke Finnish fluently. Altogether, 76 children born at a VLGA underwent language assessments at a mean age of 9.0 (8.6–9.3) years.

We subsequently recruited 50 term-born children during the 4-year period between November 2007 and November 2011 for comparison purposes. These comprised 26 children from the Oulu University Hospital birth register. A letter containing information about the study was sent to the 90 families and all parents were contacted by phone a number of times if needed. Since a large enough control group was not obtained through the birth registry, we also recruited 24 children from elementary schools in Oulu. Local school teachers were contacted and families were informed about the study protocol. There were 25 term-born children who returned the permission and who underwent language testing procedure, one of them later excluded due to insufficient Finnish language skills. All controls were born at ≥37 + 0 weeks of gestation and were matched for age and gender at the VLGA group level. They underwent the same evaluations as the VLGA group at a mean age of 9.0 (8.1–10.0) years. The study protocol was approved by the Ethics Committee of Oulu University Hospital. Written, informed assent was obtained from the children and consent from their parents before they entered the study.

2.2 | Clinical characteristics

Foetal growth restriction was defined as a birth weight that was two standard deviations below the mean of the gestation-adjusted

birth weight and documented evidence of placental insufficiency, identified by Doppler ultrasound. A histological placental perfusion defect coexisted in 13 of the 18 children with foetal growth restriction.[10] Histological chorioamnionitis was defined according to the criteria proposed by Salafia et al.[16] Respiratory distress syndrome was defined as radiological findings and a need for surfactant administration or additional oxygen for at least 48 h. Bronchopulmonary dysplasia was defined as a chronic respiratory disease that required extra oxygen or any form of therapy that caused distension of the airways at 36 weeks of postmenstrual age.

According to the study protocol, serial brain ultrasounds were performed during the neonatal period and intraventricular haemorrhage was defined using the standard criteria by Papile.[17] Early intraventricular haemorrhage was diagnosed within 3 days of life.

Cognitive impairment, defined by an intelligence quotient of less than 70, was based on previous age-appropriate psychological evaluations and the children were diagnosed by a child neurologist. Data about cognitive impairment were obtained from medical records. The diagnoses of cerebral palsy were made by a child neurologist and confirmed at the age of 5 years, based on criteria established by the Surveillance of Cerebral Palsy in Europe network. None of the term children were diagnosed with cerebral palsy.[10]

The mothers' educational levels were divided into two levels. Low referred to attending 9 years of compulsory schooling, with or without vocational education. High referred to 12 years of education, with vocational education, polytechnic or university degree.

2.3 | Assessments

The children's language skills were evaluated with a comprehensive set of standardised assessment methods. The Token Test for Children was used to assess receptive language abilities and the Rapid Automatized Naming and Word Chain tests were chosen to assess expressive language and decoding.

The Token Test measures how well the child understands verbal instructions with increasing length and complexity,[18] by pointing to arrangements of tokens with various shapes and colours. For example, the child may be asked to touch the yellow circle or pick up the red square before touching the yellow circle. The overall score is obtained by adding all five test subdomain scores together and the maximum score is 61 points.

The Rapid Automatized Naming test was used to evaluate the ability to retrieve familiar words, such as colours and letters. Fluency of naming was also assessed. This referred to speaking rapidly and accurately without stopping and pronouncing words well and clearly. The Rapid Automatized Naming test and the Rapid Alternating Stimulus test are both considered gold standards for evaluating fluency and accuracy of naming.[9] The first consists of colours, numbers, letters and objects, while the second consists of two-item sets of letters and numbers and three-item sets of letters, numbers and colours. The child is asked to name each stimulus item as quickly as possible without making any mistakes. Scoring is based on the time required to name all the items on each test. The number of mistakes is also recorded. Raw scores are converted into standard deviation scores using age equivalents. In this study, the overall score was obtained by adding all the standard deviation scores together.

The Word Chain test[19] measures technical word reading skills. It consists of four subtests that measure word recognition and identify real words and fake words, orthography and word segmentation. Orthography refers to error detection and word segmentation means word syllabification. Each subtest has a time limit. Raw subtest scores are converted into scaled scores from 1 to 8. Scores of 4–5 are considered average and eight is the maximum. We combined the scaled scores from all but the word segmentation subtest and used the mean value to describe the overall performance in word reading.

2.4 | Statistical analyses

Statistical analyses were performed using SPSS, version 26.0 (IBM Corp, New York, USA). Categorical data between the VLGA and term groups were assessed by cross-tabulation with the chi-squared test or Fisher's exact test. Because the distributions of the Token Test and rapid naming scores were skewed, the Mann–Whitney *U* test was used to analyse differences between the VLGA and term groups. As the Word Chain test scores were normally distributed, the Student's *t*-test was employed to analyse the differences between the two groups. The effect of prenatal and postnatal factors on language abilities was analysed using the Student's *t*-test or the Mann–Whitney *U* test, depending on how skewed the language test scores were, as mentioned above. The following prenatal and neonatal parameters were included in the analyses: gestational age at birth, foetal growth restriction, gender, chorioamnionitis, administration of antenatal corticosteroids, respiratory distress syndrome, intraventricular haemorrhage, sepsis at more than 72 h of age, bronchopulmonary dysplasia and maternal education level. We used multiple linear regression to carry out a secondary analysis, to evaluate covariates as independent predictors for each of the language test scores. Variables that reached a significance level of $p < 0.1$ in the univariate analysis were selected as covariates for the secondary analyses. As gender had an impact on language abilities in certain subgroup comparisons, it was used as a covariate in the secondary analyses when we compared the VLGA and term groups. All tests were two-tailed. The level of significance was set at $p < 0.05$.

3 | RESULTS

The clinical characteristics of the VLGA group are shown in Table 1 and this shows that the term-born children did not differ significantly from the VLGA group in terms of gender distribution or maternal

TABLE 1 Clinical background of VLGA and term groups

	VLGA, $n = 76$	TERM, $n = 50$
Gestational age in weeks[a]	29.0 (24.1–31.9)	
GA < 28 weeks, *n* (%)	21 (28)	
GA < 26 weeks, *n* (%)	3 (4)	
Birth weight (grams)[a]	1205 (370–2295)	
Male, *n* (%)	40 (53)	23 (46)
FGR, *n* (%)	18 (24)	
Chorioamnionitis, *n* (%)	26 (34)	
Apgar score at 5 min <7, *n* (%)[b]	27 (36)	
Antenatal corticosteroids, *n* (%)	65 (86)	
Respiratory distress syndrome, *n* (%)	48 (63)	
Bronchopulmonary dysplasia, grade 2–3, *n* (%)	17 (22)	
Early IVH (≤72 h), *n* (%)[c]	10 (13)	
Late IVH (>72 h), *n* (%)[d]	16 (21)	
PVL gr 2–4, *n* (%)	2 (3)	
Sepsis>72 h, *n* (%)	22 (29)	
Low maternal education, *n* (%)	31 (41)	17 (34)

Abbreviations: FGR, foetal growth restriction; GA, gestational age; IVH, intraventricular haemorrhage; PVL, periventricular leukomalacia; VLGA, very low gestational age.

[a]Data are given as mean values (min–max).

[b]Data are missing for four cases.

[c]Severity of IVH cases: grade 1, $n = 9$; grade 2, $n = 1$; grade 3–4, $n = 0$.

[d]Severity of IVH cases: grade 1, $n = 14$; grade 2, $n = 1$; grade 3, $n = 1$; grade 4, $n = 0$.

education. Children born at a VLGA performed significantly poorer in receptive language abilities compared with term-born children after adjustment for gender and maternal education. Compared with term-born children, children born at a VLGA had more difficulties in word reading, after adjustment for gender. There were no significant differences in rapid naming between the groups (Table 2). However, children born at a VLGA were more accurate in naming compared with term-born children, and the mean number of mistakes was 8.8 and 12.5, respectively ($p = 0.01$).

In the VLGA group, the children with foetal growth restriction had lower scores for rapid naming than the children without this condition (median −2.0 vs. 0.0, $p = 0.01$) and this was also the case for respiratory distress syndrome (median −1.0 vs. −0.5, $p = 0.03$; Table 3). We carried out a multivariate analysis that included all children born at a VLGA with chorioamnionitis, foetal growth restriction and respiratory distress syndrome as covariates. This showed that foetal growth restriction was the main predictor for poor naming skill, while respiratory distress syndrome also partly explained the variance in the rapid naming scores (Table 4).

Children in the VLGA group who had early intraventricular haemorrhage had poorer word reading abilities than children without this condition (mean 3.40 vs. 4.58, $p = 0.04$; Table 3). Early intraventricular haemorrhage and foetal growth restriction explained 9.3% in the variance of the word reading scores (Table 4). In the VLGA group, lower maternal education was associated with lower childhood scores for receptive language abilities than higher educational level (median 53.5 vs. 56.0, $p = 0.04$; Table 3). The maternal educational level had no effect on the receptive language skills of the term-born children (data not shown).

Girls in the VLGA group displayed a poorer performance in word reading (mean 4.49 vs. 5.50, $p = 0.02$) and receptive language abilities (median 55.5 vs. 58.0, $p = 0.002$) than the term-born girls. There were no differences in the test scores between the boys in the VLGA and term groups (Appendix S2) or between the boys and girls in the VLGA group (Appendix S1). Term-born boys displayed significantly poorer receptive language abilities than term-born girls (median 56.0 vs. 58.0, $p = 0.001$). No differences between genders were found in word reading or rapid naming skills in the term group (Appendix S1). Other antenatal and neonatal factors, namely gestational age, chorioamnionitis, antenatal corticosteroids, sepsis for more than 72 h and bronchopulmonary dysplasia, had no significant effect on language skills among children born at a VLGA (Table 3).

4 | DISCUSSION

This study found that children born at a VLGA of less than 32 weeks of gestation, without severe neurosensory disabilities, had more problems with receptive language abilities and word reading at 9 years of age than term-born children. In addition, poor foetal growth was associated with deficits in rapid naming in the VLGA group. We also found evidence that early neonatal morbidities might affect certain language skills in a way that continues into school age.

The finding that children born at a VLGA had more difficulties in receptive language abilities than their term-born peers was consistent with a meta-analysis.[5] In addition to receptive language abilities, successful performance in the Token Test requires cognitive processing, good attention and working memory, which have been shown to be poorer in preterm children.[10] We previously demonstrated that this VLGA group had significantly more problems in attention-executive functions, which might be a risk factor for poorer receptive language abilities. The same was true for visuospatial and sensorimotor skills, which may be as a risk factor for poorer technical word reading skills.[10] The problems with technical reading that were found in the present VLGA cohort were in line with previous studies.[2] Learning to read requires good phonological awareness, an important prereading skill that enables later word recognition and decoding.[9] Fluent word decoding supports reading comprehension, which is the final goal of reading.[20]

A previous study, which followed up on language development from 2 to 13 years, reported that most children born very preterm demonstrated early catch-up, and more than a half had language abilities within the normal range at 7 years of age. However, across childhood, very preterm children were still eight times more likely to have poorer language development than term controls.[21]

TABLE 2 Language test scores in children born at a VLGA and term

	VLGA			Term			
	n	Average	Min–max	*n*	Average	Min–max	*p*
Receptive language abilities (Token Test)[a]	74	55.0 (6.0)[b]	34.0 to 60.5	50	57.0 (3.6)[b]	41.0 to 61.0	0.01[c]
Word reading (Word chain)[d]	75	4.4 (1.7)[e]	1 to 8	49	5.1 (1.6)[e]	1 to 8	0.03[f]
Rapid naming (RAN-RAS)[g]	76	−1.0 (3)[b]	−12 to 5	50	0.0 (2)[b]	−10 to 5	0.33[c]

Abbreviations: RAN, Rapid Automatized Naming test; RAS, Rapid Alternating Stimulus test; Token Test, Token Test for Children; VLGA, very low gestational age.

[a]Sum of raw scores (max 61 points).

[b]Data are given as medians (IQR).

[c]Mann–Whitney *U* test.

[d]Mean value of skill-level scores (from 1 to 8).

[e]Data are given as mean values (SD).

[f]Student's *t*-test.

[g]Sum of standard deviation scores.

TABLE 3 Univariate associations between antenatal and neonatal factors and language scores in the VLGA group at 9 years of age

	Receptive language[a] abilities (Token Test)		Word reading[b] (Word chain test)		Rapid naming[a] (RAN-RAS test)	
Factors	Difference in medians	*p*	Difference in mean values	*p*	Difference in medians	*p*
GA <28 vs. >28 weeks	−1.00	0.19	0.17	0.71	0.00	0.44
FGR vs. AGA	−2.25	0.15	−0.78	0.098	−2.00	0.01
Boys vs. girls	−0.50	0.55	−0.11	0.78	0.00	0.85
HCA vs. no HCA	1.00	0.16	0.58	0.17	0.50	0.099
ACS vs. no ACS	−1.50	0.55	−0.08	0.90	−1.00	0.52
RDS vs. no RDS	−1.00	0.52	−0.48	0.26	−0.50	0.03
Early IVH vs. no early IVH	−1.75	0.54	−1.18	0.04	0.00	0.47
Sepsis >72 h vs. no sepsis	0.50	0.74	−0.4	0.37	−1.00	0.13
BPD vs. no BPD	0.75	0.44	0.09	0.85	0.00	0.36
High vs. low maternal education	2.50	0.04	0.17	0.69	1.00	0.11

Abbreviations: ACS, antenatal corticosteroids; AGA, appropriate for gestational age; BPD, bronchopulmonary dysplasia; FGR, foetal growth restriction; GA, gestational age; HCA, histological chorioamnionitis; IVH, intraventricular haemorrhage; RAN, Rapid Automatized Naming; RAS, Rapid Alternating Stimulus; RDS, respiratory distress syndrome; Token Test, Token Test for Children.

[a]Mann–Whitney *U* test.

[b]Student's *t*-test.

Severe language disorders are identifiable in preschool years, but milder language difficulties may not become evident until the first years of formal schooling.[22,23] The results of the present and previous studies[5,21] highlight the need for language difficulties among these high-risk children to be identified and managed at an early stage. This will support their school success and prevent academic failure later on.

The present study also demonstrated that children with foetal growth restriction in the VLGA group had significantly poorer scores for rapid naming, compared to those without this condition. Naming skills are an important predictor for later literacy skills, such as reading fluently. Approximately 60%–75% of individuals with reading or learning disabilities have naming difficulties.[9] Prematurity and restricted foetal growth affect brain development and infants with foetal growth restriction have been shown to have decreased total brain and cortical grey matter volumes.[11] Prematurity has also been found to be associated with altered development of white matter microstructure and more widespread microstructural changes have been found in children born at a VLGA with foetal growth restriction.[24] It might be that very premature birth and poor foetal growth interfere with the programming of brain development that involve different pathways in white matter and that this affects language development later on.

Our study found that bronchopulmonary dysplasia was not a significant risk factor for language problems, whereas respiratory distress syndrome was associated with poorer outcomes in rapid

TABLE 4 Multivariate (linear regression) analysis of antenatal and neonatal factors and language scores in the VLGA group at 9 years of age

	Receptive language abilities (Token test)		Word reading (Word chain)		Rapid Naming (RAN-RAS)	
Factors	standardised coefficient	*p*	standardised coefficient	*p*	standardised coefficient	*p*
FGR	-	-	−0.254	0.028	−0.320	0.005
HCA	-	-	-	-	0.127	0.265
RDS	-	-	-	-	−0.217	0.049
Early IVH	-	-	−0.291	0.012	-	-
Maternal education	−0.222	0.059	-	-	-	-
Adjusted R^2	3.6%		9.3%		16.7%	

Abbreviations: FGR, foetal growth restriction; HCA, histological chorioamnionitis; IVH, intraventricular haemorrhage; RAN, Rapid Automatized Naming; RAS, Rapid Alternating Stimulus; RDS, respiratory distress syndrome; Token Test, Token Test for Children.

naming among the VLGA group. Respiratory distress syndrome has previously been associated with long-term developmental impairment in late preterm infants, including language difficulties.[25] The systemic effects of respiratory distress syndrome that can cause damage to the immature brain include hypoxia, acidosis and pulmonary hypertension.[25] According to our study, the combination of foetal growth restriction and respiratory distress syndrome explained altogether 17% of the variance in the rapid naming scores in the VLGA group.

Intraventricular haemorrhage continues to be a problem after a very premature birth. While higher grades (III–IV) of intraventricular haemorrhage have generally been found to be associated with neurodevelopmental problems, the effects of long-term sequelae after low-grade (I–II) intraventricular haemorrhage are less clear.[12,26] Our study supports the possible detrimental role of low-grade intraventricular haemorrhage. This is because children in the VLGA group, who had early, low-grade intraventricular haemorrhage, demonstrated significantly poorer performance in word reading than children without this condition. Intraventricular haemorrhage in very preterm neonates originates in the germinal matrix, which is highly vascularised and vulnerable to bleeding, especially during the first days of life. Inflammatory and hypoxic-ischaemic events may further exacerbate germinal matrix injuries. During brain development, this area undergoes critical changes, including migration of the glial and neuronal cells to the cerebral cortex.

Our findings that neonatal morbidities within the first days of very preterm birth may affect language development, highlight the importance of high-quality standards of neonatal care. Just after birth, very preterm infants are vulnerable to various adverse effects, including hypothermia, hypoglycaemia, infections, pain and noise. Preventing these, and stabilising the respiratory and cardiovascular system, may decrease the risk of brain injuries and thus later neurodevelopmental sequelae.[27]

Previous studies have reported gender-related differences in the development of language.[28] In our study, the impact of gender on language abilities was only seen in certain subgroup comparisons. Girls in the VLGA group had poorer receptive language abilities and word reading skills than term-born girls. However, no differences were found between boys in the VLGA and term groups or between girls and boys in the VLGA group. These results were in line with a previous study that showed that very preterm girls had poorer spontaneous speech and linguistic skills than term-born girls.[28] In contrast, very preterm boys performed almost as well as the control boys in most areas. That study also found that term-born girls had better results than boys in auditory memory, word fluency, grammar and interactions.[28] We found that girls born at term had better receptive language abilities than boys. Thus, gender may be one of the factors that influence language outcome. We also found that gestational age had no significant effect on the language outcomes in our VLGA group, but only three children were born before 26 weeks of gestation, which may explain why the degree of prematurity failed to correlate with the language skills.

A previous study reported that a low level of parental education was associated with cognitive impairment in children born very preterm.[15] Our study showed that a low level of maternal education had a negative impact on the language abilities of the VLGA group, but not on the term controls. Better knowledge of developmental milestones may mean that more highly educated parents were more active in supporting their children's language development and identifying language problems. In turn, the Finnish schooling system offers equal access to education for all children, which may partly explain the lack of difference among the term-born children.

The main strength of this study was the prospectively followed, population-based VLGA cohort. The study protocol was well-defined and included comprehensive, prospectively collected data on prenatal and postnatal risk factors. Furthermore, the children's language comprehension, naming and word reading skills were assessed with validated tests for Finnish-speaking children and the study included a comparison group of term-born children. A potential limitation of this study was the rather high drop-out rate, which could have biased the results. However, there were no differences in the perinatal characteristics between the children who dropped out and the participants, as previously described.[10]

5 | CONCLUSION

Our study demonstrated that children born at a VLGA of less than 32 weeks of gestation, without severe neurosensory disabilities, exhibited poorer receptive language abilities and word reading at 9 years of age than term-born children. Poor foetal growth in the VLGA group was a risk factor for deficits in rapid naming. We also found evidence that language development might be affected by early neonatal diseases during the first days of life, such as respiratory distress syndrome and intraventricular haemorrhage. Our findings indicate the importance of high-quality perinatal and neonatal treatment practices, and the development of preventive strategies for brain injuries. The study findings also emphasise the importance of carrying out early linguistic evaluations on children born at a VLGA and identifying language problems. Providing timely and adequate interventions for difficulties on language comprehension, naming and technical reading skills, may increase the opportunities to achieve better reading comprehension. This can lead to improved social and academic performance at a later stage.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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