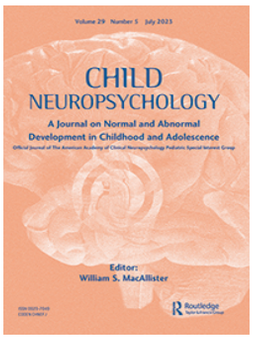

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REVIEW ARTICLE

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Perinatal and social risk of poor language, memory, and learning outcomes in a cohort of extremely and very preterm children

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ABSTRACT

Children born extremely preterm (EPT) or very preterm (VPT) are at risk of neurodevelopmental impairment. How the interaction between biological and social risk factors affects cognitive development has not yet been completely understood. The objectives of this study are to analyze and compare the language, memory, and learning outcomes of five-year -old children born EPT (<28 weeks' gestational age) and VPT (28–31^{+6} weeks' gestational age) and to determine the risk of having poor outcomes attending to perinatal and maternal characteristics. The analysis included 377 children born VPT (n = 284) and EPT (n = 93) in 2011–2012. Maternal, neonatal, and clinical information was obtained at birth, and maternal education was obtained at five years using a parental questionnaire. At five years, the language, memory, and learning outcomes were assessed with the developmental NEuroPSYchological assessment second edition (NEPSY-II®). Logistic regression models were applied to assess the association of biological and social risk factors with performance below the expected level for the child's age in language, memory, and learning subtests. Lower maternal age and education increased the odds of having language performance below the expected level for the child's age, while lower maternal educational level and gestational age increased the likelihood of having memory performance below the expected level. Children living in the most social disadvantage contexts are at a higher risk of suboptimal cognitive development. Implementing intervention programs in disadvantaged contexts and targeting specific cognitive domains may enable EPT and VPT children to reach and fulfill their potential in society.

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Introduction

Survivors of extremely preterm (EPT; <28 weeks of gestational age) and very preterm (VPT; 28–31^{+6d} weeks of gestational age) birth are at risk of multiple impairments and neurodevelopmental disabilities (Hutchinson et al., 2013) across multiple cognitive domains (Linsell et al., 2019), such as language (Putnick et al., 2017), memory (Loe et al., 2019), and learning ability (Linsell et al., 2019).

Language is fundamental to daily social functioning and interpersonal skills (Bornstein et al., 2014). There seems to be an inverse linear association between gestational age (GA) and language comprehension in infants of 18–36 months in terms of understanding or responding appropriately to the language utterances of others (Zambrana et al., 2016). These short-term effects of GA on language were still noted further until the age of five years (Zambrana et al., 2021). Even though most preterm children catch up with their siblings by the age of five, those born <34 weeks' gestation still face a risk of language delay (Zambrana et al., 2021). More than one-third of children born <30 weeks' gestation continue to exhibit poorer language outcomes at the age of seven, and there is no evidence of catch-up after that age (Nguyen et al., 2018).

Learning and memory are complex cognitive functions that have subcomponents structured in multiple ways (Brem et al., 2013). Memory englobes encode, store, and retrieve information (Brem et al., 2013). VPT children are also outperformed by full-term children on overall memory, including prospective memory and spatial location memory (Baron et al., 2010). Poor memory outcomes, such as visual memory, tend to persist until adolescence (Molloy et al., 2014).

Learning information may involve acquiring new memories and that knowledge is sometimes based on previous memories (Herszage & Censor, 2018). Additionally, about 10–15% of learning disorders that are not due to intellectual disabilities are attributable to preterm birth (Johnson et al., 2016). About one in five children born EPT have a learning disability, either in reading, mathematics, or both, compared with 3% in full-term children (Johnson et al., 2016), which tend to persist until adolescence (Allotey et al., 2018; Molloy et al., 2014), regardless of the native language (Guarini et al., 2019). This may be due to the abnormal brain structural and functional connectivity common in preterm children (Rogers et al., 2018). Addressing learning disabilities is important because of their association with the worst academic profiles and the risk for special education (Johnson et al., 2016; Lean et al., 2018).

Cognitive development and neurodevelopmental outcomes among children born EPT and VPT are the result of a combination of factors that include not only the perinatal characteristics but also the social factors related to the child's developmental context (Barnes-Davis et al., 2018; Lean et al., 2018; Nguyen et al., 2018; Zambrana et al., 2016, 2021). Growing up in socioeconomically disadvantaged environments – represented by low-income families, low parental education, etc. – may restrict the access to early diagnosis and adequate intervention, which in turn compromises their optimal development (Burnett et al., 2018). The characterization of the role of modifiable environmental risk factors of neurodevelopmental difficulties in longitudinal studies that also consider the perinatal risk factors is lacking (Rogers et al., 2018). As every child is unique, and their development is heterogeneous, identifying those at risk and offering them tailored

interventions is critical to promote optimal development. The objectives of this study are to analyze and compare the language, memory, and learning outcomes of five-year-old children born EPT and VPT. Additionally, the study seeks to identify perinatal and social risk factors for poor language, memory, or learning outcomes.

Materials and methods

Participants

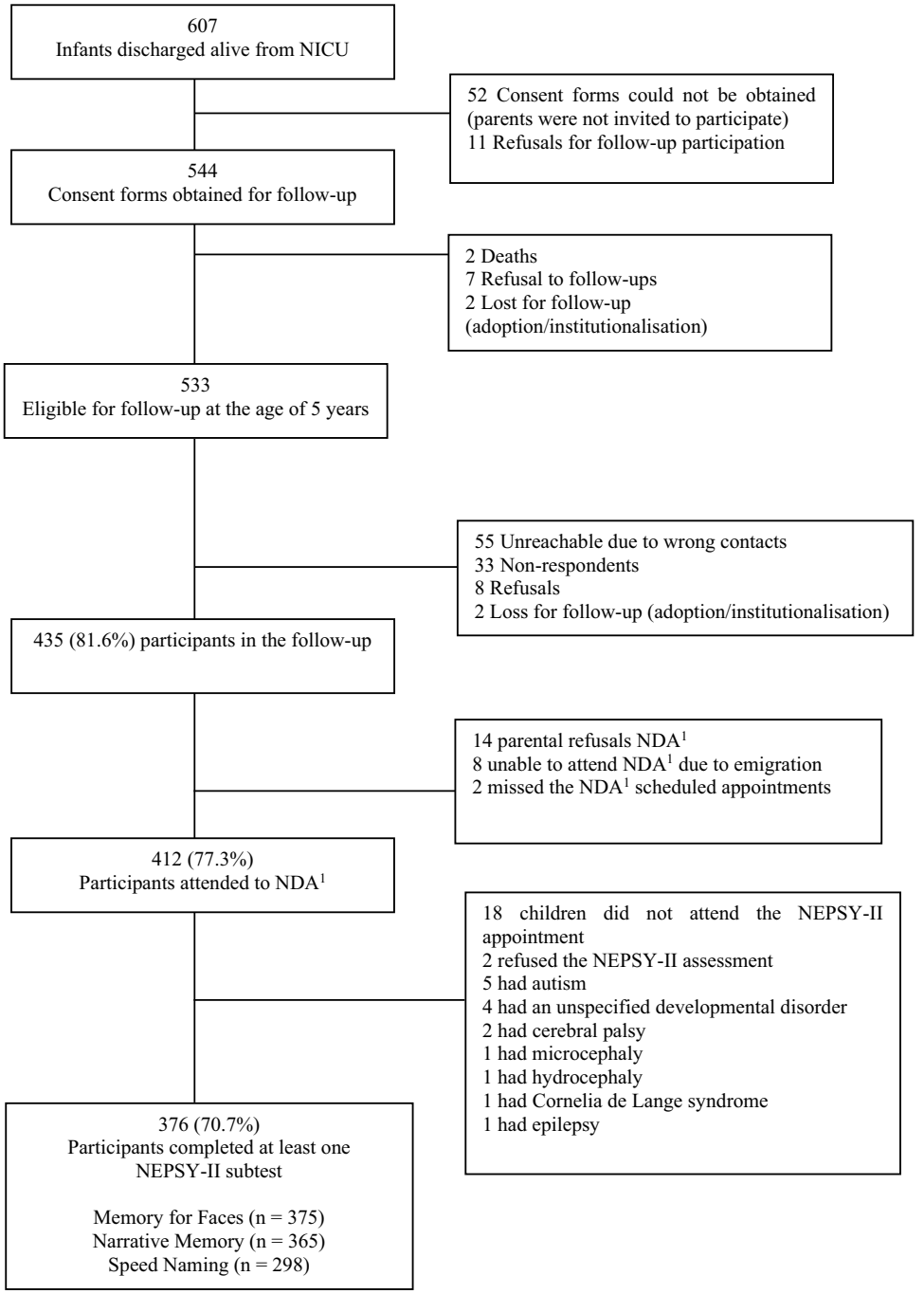
We obtained the data as part of the Screening to Improve Health in Very Preterm Infants in Europe (SHIPS) study, which followed up the Effective Perinatal Intensive Care in Europe (EPICE) cohort of children born VPT (<32 weeks of gestational age) at five years of age. This cohort includes 6792 infants born before the 32nd week of gestation in 2011 and 2012 in 19 regions across 11 European countries (ES, 2011). In this study, children from the Portuguese cohort – from the North region and Lisbon and Tagus Valley – were included. A total of 607 infants were discharged alive from the hospital, and written informed consent for follow-up evaluations was obtained for 544 children. Of those, two died, seven caregivers refused to participate in the follow-up assessments, and two were loss of follow-up. A total of 533 children were eligible for the five-year-old follow-up (Figure 1). Of these, 412 underwent attended to the neurodevelopment assessment, and 377 participants completed at least one developmental NEuroPSYchological assessment second edition (NEPSY-II®) subtest (93 EPT and 284 VPT). In this analysis, children who underwent at least one language, memory, or learning sub-test were included (294 completed the comprehension of instruction subtest, and 298 completed the speed naming subtest; 375 completed the memory for faces/memory for faces delayed subtest, and 365 completed the narrative memory subtest).

Methods

Baseline assessment

At baseline, maternal, pregnancy, and clinical characteristics were extracted from medical records by health-care professionals using a standardized questionnaire.

The information collected included maternal age, country of birth, education and occupational status, type of pregnancy, prenatal infection, gestational hypertension, preeclampsia, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, prepartum hemorrhage, intrauterine growth restriction (IURG), premature rupture of membranes (PROM), use of steroids before birth, sex, birth weight, gestational age at birth (defined as the best obstetric assessment based on information on the last menstrual period and antenatal ultrasounds), the Apgar score at 5 minutes, congenital anomaly, early postnatal infection (within the first 72 h after birth), late postnatal infection (after the first 72 h after birth), intraventricular hemorrhage (IVH – defined according to Papillae), cystic periventricular leukomalacia (cPVL), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD, defined by respiratory assistance or oxygen at 36 weeks postmenstrual age), steroid use for BPD, surgical treatment for patent ductus arteriosus (PDA), use of



[1]Neurodevelopmental assessment

Figure 1. Flowchart of participants.

surfactant, intubation-surfactant-extubation (INSURE) technique, use of continuous positive airway pressure (CPAP), or mechanical ventilation. The need for ventilatory support was considered when at least one of the following: surfactant, INSURE, CPAP, or mechanical ventilation. Severe neonatal morbidity (SNM) was defined as a composite of IVH grade III or IV, cPVL, ROP stages III–V or severe NEC needing surgery.

Five-year-old assessment

At the five-year-old follow-up, questionnaires designed to collect data on the child's health, healthcare use, development, and growth, as well as sociodemographic information were completed by parents at their child's follow-up appointment or sent by e-mail. Neurodevelopmental assessments were performed in Portuguese by trained psychologists.

Parental questionnaire

The parental self-report questionnaire included socio-demographic information, including maternal education (non-tertiary – early childhood education, primary, lower secondary, upper secondary and post-secondary non-tertiary (pre-university courses) vs tertiary – short-cycle tertiary (vocational programs), bachelor's degree or equivalent, master's degree or equivalent, and doctoral degree or equivalent) and maternal professional status (employed vs other).

Language, memory, and learning assessment

Age-appropriate NEPSY-II® subtests (Barnes-Davis et al., 2018) were selected to assess language – comprehension of instructions (CI) and speed naming (SN) subtests – and to assess memory and learning – memory for faces (MF), memory for faces delayed (MFD) and narrative memory (NM) subtests. The CI subtest measures the ability to receive, process and execute oral instructions of increasing syntactic complexity and provides a score. The SN subtest measures rapid semantic access to and production of names of colors, shapes, sizes, letters, or numbers. It provides four scores: SN total correct, SN total self-corrected errors, SN total completion time, and SN combined scaled score. The MF and MFD subtests assess the encoding of facial features and face discrimination and recognition and provide the following scores: (1) MF scaled score, (2) MFD scaled score, and (3) MF vs. MFD contrast scaled score. The NM subtest evaluates memory for organized verbal material under free recall, cued recall, and recognition conditions. It provides four scores: (1) NM free recall scaled score, (2) NM free and cued recall scaled score, (3) NM recognition percentile rank, and (4) NM free and cued recall vs. recognition contrast scaled score (supplementary table S1).

The raw scores were converted into age-adjusted percentile ranks (presented in ranges <2, 2–5, 6–10, 11–25, 26–50, 51–75, and >75) or scaled scores (ranging from 1 to 19), according to the standardized edition of USA norms (Korkman et al., 2007). Following the NEPSY-II® manual instructions, scaled scores ≥8 or percentile ranks ≥26 were considered as indicating performance at or above the expected level for the child's age (henceforward expected or above expected), and lower scaled scores (≤7) or percentile ranks (≤25) were considered as indicating performance below the expected level for the child's age (henceforward below expected) (Barnes-Davis et al., 2018).

Ethics

Data from the two Portuguese regions, the Northern region and Lisbon and Tagus Valley, were used in this study. In these regions, the study was approved by the National Commission for Data Protection (reference 7426/2011) and by the ethics committee of Northern Regional Health Administration (ARS Norte; reference 91/2016) and the Lisbon and Tagus Valley Regional Health Administration (ARS LVT; reference 053/CES/INV/2016). A written informed parental consent was obtained for participation at baseline and follow-ups.

Statistical analysis

Descriptive statistics were calculated for continuous variables (means and standard deviations) and categorical variables (frequency counts and percentages) to determine the characteristics of the sample.

The characteristics of participants and non-participants were compared using a chi-squared test based on mother's age, country of origin, education, occupational status, type of pregnancy, prenatal infection, gestational hypertension, preeclampsia, HELLP, prepartum hemorrhage, IURG, PROM, antenatal steroid, infant's sex, birthweight, the Apgar 5-min score, congenital anomaly, early infection, late infection, IVH, cPVL, ROP, NEC, BPD, steroid use for BPD, surgical treatment for PDA, use of surfactant, use of INSURE, use of CPAP, or use of mechanical ventilation.

A Pearson's chi-square (χ^2) test was performed to analyze differences in the proportion of EPT and VPT with a performance borderline/below expected on language or memory and learning subtests. Mother's age, mother's educational level, gestational age, postnatal infection, BPD, ventilatory support, SNM, and severe NEC were included in unadjusted logistic regression models to estimate the odds of having a borderline or below expected outcome in a language or memory and learning subtest. Each domain subtest was categorized in dichotomized variables, expected or above expected vs. borderline or below expected. The following independent variables were selected based on clinical knowledge and scientific literature on characteristics likely to affect language, memory, or learning outcomes: mother's age (Ancel et al., 2015; Germany et al., 2015; Lean et al., 2018), mother's educational level (Lean et al., 2018; Ruiz et al., 2015), gestational age (Burnett et al., 2018; Pugliese et al., 2013; Zambrana et al., 2016, 2021), postnatal infection (Zeitlin et al., 2020), BPD (Draper et al., 2020), SNM (Zeitlin et al., 2020) and ventilatory support (Zeitlin et al., 2020). Only those variables significant in unadjusted models were tested in the adjusted models, and possible interactions between the independent variables were also tested in those models. We did not correct for multiple comparisons to diminish the errors of interpretation since we used actual observations on nature (Rothman, 1990). The results were reported as odds ratios (ORs) with corresponding 95% confidence intervals (95% CI), and a two-tailed $p < .05$ was considered significant. Missing values were not inputted. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) v. 26.

Table 1. Maternal, pregnancy, neonatal, and clinical characteristics.

	EPT (<28 weeks; *n* = 93)		VPT (≥28 weeks; *n* = 284)			Participants (*n* = 376)		Non-participants (*n* = 157)		
	n	%	*n*	%	*p*	*n*	%	*n*	%	*p*
Mother age (≥35 years)	28	37.3	70	32.3	.422	98	33.6	42	28.4	.340
Mother country of origin (foreign)	15	17.6	26	10.7	.098	41	12.5	41	25.9	<.001
Mother education (tertiary education or higher)	36	40.0	102	37.4	.655	138	38.0	18	36.7	.759
Mother's occupational status (employed)	69	75.8	207	74.8	.848	276	75.1	35	66.0	.180
Type of pregnancy (multiples)	17	20.0	52	21.5	.772	69	21.1	21	13.3	.518
Prenatal infection	13	15.3	17	6.6	.014	30	8.9	9	5.7	.467
Gestational hypertension	12	14.3	42	17.4	.505	54	16.6	18	11.4	.226
Preeclampsia	13	15.5	54	22.3	.181	67	20.6	24	15.2	.384
HELLP syndrome	5	5.9	8	3.3	.296	13	4.0	5	3.2	.999
Prepartum hemorrhage	16	17.4	32	11.3	.153	48	13.0	26	16.5	.275
IURG	11	13.1	51	21.8	.082	63	19.6	27	17.3	.713
PROM	35	38.0	70	24,7	.014	105	28.0	51	32.7	.298
Use of antenatal steroids	80	94.1	220	90.9	.466	300	92.3	146	92.4	.854
Sex (male)	53	57.0	163	57.8	.898	216	57.6	91	56.6	.999
Birth weight (<750 g)	21	22.6	6	2.5	<.001	27	7.4	19	12.0	.090
5′ Apgar score (<7)	15	16.1	14	5.0	.001	29	7.8	19	12,0	.137
Congenital anomaly	5	5.4	11	3.9	.475	16	4.2	12	7,6	.137
Early infection	9	9.7	6	2.1	<.001	15	4.0	6	3,8	.999
Late infection	60	64.5	70	25.4	<.001	131	35.0	72	45,6	.025
IVH (grade III or higher)	9	9.7	6	2.5	.003	15	4.0	8	5.1	.642
cPVL	7	7.5	6	2.1	.021	13	3.5	8	5.1	.464
ROP (grade 3 or higher)	13	24.5	1	0.4	<.001	14	3.9	9	22,0	.200
NEC	5	5.4	6	2.1	.148	11	2.9	5	3.2	.055
BPD	24	25.8	17	6.0	<.001	41	10.8	29	18.4	.025
Steroid use for BPD	10	10.8	1	0.4	<.001	11	2.9	11	7.0	.053
Surgical treatment for PDA	8	8.6	1	0.4	<.001	9	2.4	7	4.4	.265
Use of surfactant	77	82.8	115	40.5	<.001	192	50.9	92	58.2	.154
Use of INSURE	12	12.9	52	18.3	.258	64	17.0	25	15.8	.800
Use of CPAP	91	97.8	253	88.7	.006	343	91.0	140	88.6	.426
Use of mechanical ventilation	81	87.1	106	37.7	<.001	188	50.1	68	43.0	.154

IURG: intrauterine growth restriction; PROM: premature rupture of membranes; IVH: intraventricular hemorrhage; cPVL: cystic leukomalacia periventricular; ROP: retinopathy of prematurity; NEC: necrotizing enterocolitis; BPD: bronchopulmonary dysplasia; PDA: patent ductus arteriosus; INSURE: Intubation-surfactant-extubating technique; CPAP: continuous positive airway pressure.

Results

The characteristics of the participants are shown in Table 1. Most infants were from singleton pregnancies and had a birth weight ≥750 g, and their mothers were under 35 years of age, Portuguese, had less than tertiary education, and were employed. Mothers of children born EPT were more likely to had prenatal infection and PROM compared with mothers of children born VPT. Children born EPT were more likely to had a birth weight <750 g, 5' Apgar score below seven, early infection, late infection, IVH grade ≥ III, cPVL, ROP grade ≥3, BPD, used steroids for BPD, underwent surgical treatment for PDA, received surfactant, CPAP, or mechanical ventilation (Table 1). Factors associated with nonparticipation were maternal country of origin, late infection, and BPD (Table 1).

The highest proportion of children born VPT or EPT classified with a performance below expected was observed in terms of SN total completion time, SN combined scaled score and MF scaled score (VPT/EPT – 31.9%/46.4%, 30.6%/37.7%, and 24.7%/37.6%, respectively). In the subtests, the lowest proportion of children with a performance below expected were observed in terms of the NM free recall scaled score and the CI scaled

Table 2. Language, memory, and learning outcomes in children born extremely preterm and very preterm.

	EPT		VPT		
	n	%	*n*	%	*p*
Language					
CI scaled score					.257
Expected/above expected	56	81.2	194	86.7	
Below expected	13	18.8	30	13.3	
SN total completion time					.027
Expected/above expected	37	53.6	156	68.1	
Below expected	32	46.4	72	31.9	
SN total correct					.250
Expected/above expected	52	75.4	186	81.7	
Below expected	17	24.6	42	18.3	
SN total self-corrected errors					.619
Expected/above expected	55	79.7	175	76.9	
Below expected	14	20.3	53	23.1	
SN combined scaled score					.268
Expected/above expected	43	62.3	158	69.4	
Below expected	26	37.7	70	30.6	
Memory and learning					
MF scaled score					.016
Expected/above expected	58	62.4	213	75.3	
Below expected	35	37.6	69	24.7	
MFD scaled score					.234
Expected/above expected	69	75.0	227	80.8	
Below expected	23	25.0	53	19.2	
MF vs. MFD contrast scaled score					.875
Expected/above expected	75	81.5	226	80.8	
Below expected	17	18.5	54	19.2	
NM free recall scaled score					.341
Expected/above expected	74	84.1	245	88.1	
Below expected	14	15.9	32	11.9	
NM free & cued recall scaled score					.400
Expected/above expected	70	79.5	232	83.5	
Below expected	18	20.5	45	16.5	
NM recognition					.024
Expected/above expected	63	72.4	229	83.3	
Below expected	24	27.6	46	16.7	
NM free & cued recall vs. recognition contrast scaled score					.330
Expected/above expected	76	81.7	229	83.0	
Below expected	11	12.6	46	17.0	

EPT: extremely preterm; VPT: very preterm; CI: comprehension of instructions; SN: speed naming; MF: memory for faces; MFD: memory for faces delayed; NM: narrative memory.

score for children born VPT (11.9% and 13.3%, respectively) and the NM free and cued recall vs recognition contrast scaled score and NM free recall scaled score for children born EPT (12.6% and 15.9% respectively). EPT children's performance was more frequently below expected based on SN total completion time; MF scaled score; and NM recognition compared with VPT children (VPT/EPT – 31.9%/46.4%, $p < .027$ 24.7%/37.6%, $p < .016$; 16.7%/27.6%, $p < .024$, respectively) (Table 2).

Table 3 shows the unadjusted logistic regression models. Lower maternal age increases the likelihood of children having a performance below expected based on SN total completion time. The mother having lower educational qualification increased the odds of the child having a performance below expected in more than half of the subtests: CI scaled score, SN total completion time, SN combined scaled score, MF scaled score, MFD scaled score, NM free & cued recall scaled score, and NM free and cued recall vs.

Table 3. Associations between maternal, neonatal, and clinical characteristics and performance below expected level on language, memory, and learning subtests.

	Mother's age (ref. <35 years) OR (95% CI)	Mother's education (ref. tertiary education or higher) OR (95% CI)	GA (ref. ≥28 weeks) OR (95% CI)	Postnatal infection (ref. no) OR (95% CI)	BPD (ref. no) OR (95% CI)	Severe neonatal morbidity (ref. no) OR (95% CI)	Ventilatory support (ref. no need) OR (95% CI)
Language							
CInf scaled score	1.700 (0.832–3.474)	**4.426 (1.792–10.929)**	1.509 (0.738–3.086)	0.918 (0.466–1.810)	1.189 (0.429–3.298)	0.953 (0.313–2.897)	3.500 (0.456–26.854)
SN total completion time	**0.568 (0.325–0.992)**	**1.726 (1.039–2.868)**	**1.848 (1.068–3.199)**	1.609 (0.984–2.632)	1.725 (0.824–3.614)	**2.415 (1.101–5.299)**	0.970 (0.374–2.513)
SN total correct	0.946 (0.497–1.800)	1.857 (0.968–3.563)	1.289 (0.694–2.395)	1.549 (0.876–2.739)	1.889 (0.871–4.099)	1.335 (0.556–3.204)	1.216 (0.349–4.235)
SN total self-corrected errors	1.526 (0.863–2.700)	1.434 (0.805–2.554)	0.772 (0.406–1.468)	1.094 (0.630–1.898)	1.833 (0.868–3.874)	1.118 (0.469–2.669)	4.923 (0.652–37.196)
SN combined	0.787 (0.450–1.376)	**1.850 (1.095–3.125)**	1.373 (0.783–2.410)	1.139 (0.687–1.888)	1.300 (0.607–2.782)	2.051 (0.933–4.511)	0.835 (0.322–2.168)
Memory and learning							
MF scaled score	0.865 (0.518–1.444)	**2.083 (1.251–3.468)**	**1.836 (1.115–3.024)**	0.928 (0.579–1.487)	1.226 (0.609–2.470)	1.268 (0.612–2.628)	1.426 (0.515–3.945)
MFD scaled score	0.791 (0.438–1.427)	**1.770 (1.003–3.123)**	1.401 (0.802–2.447)	0.691 (0.402–1.190)	1.767 (0.853–3.661)	1.323 (0.594–2.947)	0.569 (0.225–1.438)
MF vs. MFD contrast scaled score	1.375 (0.776–2.435)	1.243 (0.713–2.168)	0.953 (0.521–1.744)	0.941 (0.547–1.618)	1.726 (0.817–3.647)	0.841 (0.336–2.105)	0.509 (0.201–1.289)
NM free recall scaled score	0.866 (0.433–1.733)	1.660 (0.804–3.282)	1.405 (0.714–2.764)	0.862 (0.452–1.642)	1.032 (0.382–2.790)	0.625 (0.183–2.130)	1.607 (0.364–7.088)
NM free & cued recall scaled score	0.620 (0.317–1215)	**2.181 (1.165 –4.080)**	1.297 (0.707–2.380)	1.112 (0.638–1.936)	1.540 (0.691–3.435)	0.786 (0.292–2.116)	1.463 (0.421–5.079)
NM recognition	0.562 (0.294–1.073)	1.523 (0.848–2.735)	**1.800 (1.026–3.156)**	1.316 (0.772–2.241)	**2.593 (1.279–5.254)**	**2.349 (1.115–4.949)**	1.083 (0.357–3.292)

(*Continued*)

Table 3. (Continued).

	Mother's age (ref. <35 years) OR (95% CI)	Mother's education (ref. tertiary education or higher) OR (95% CI)	GA (ref. ≥28 weeks) OR (95% CI)	Postnatal infection (ref. no) OR (95% CI)	BPD (ref. no) OR (95% CI)	Severe neonatal morbidity (ref. no) OR (95% CI)	Ventilatory support (ref. no need) OR (95% CI)
NM free and cued recall vs. recognition contrast scaled score	0.999 (0.532–1.876)	**2.083 (1.091–3.977)**	0.705 (0.348–1.428)	0.811 (0.447–1.471)	0.590 (0.201–1.732)	0.669 (0.226–1.977)	2.100 (0.479–9.211)
Model 1 SN total completion time[1]	**0.547 (0.300–0.999)**	**2.288 (1.298–4.033)**	**1.465 (0.761–2.821)**	-	-	**2.509 (0.933–6.745)**	-
Model 2 MF scaled score[2]	-	**2.135 (1.276–3.573)**	**1.870 (1.113–3.141)**	-	-	-	-
Model 3 NM recognition[3]	-	-	**1.402 (0.748–2.629)**	-	**2.136 (0.995–4.584)**	**1.728 (0.771–3.876)**	-

OR: odds ratio: CI: confidence interval; CInf: comprehension of instructions; SN: speed naming; MF: memory for faces; MFD: memory for faces delayed; Note: NM: narrative memory; GA: gestational age; BPD: bronchopulmonary dysplasia; severe neonatal morbidity was defined as a composite of intraventricular hemorrhage grade III or IV, cystic periventricular leukomalacia, retinopathy of prematurity stages III–V or severe necrotizing enterocolitis needing surgery; ventilatory support was considered when at least one of the following was used: surfactant or INSURE or continuous positive airway pressure or mechanical ventilation. Bold: values are statistically significant.

[1]Adjusted model for maternal age, education, and gestational age.

[2]Adjusted model for maternal education and gestational age.

[3]Adjusted model for gestational age, BPD, and severe neonatal morbidity.

recognition contrast scaled score. EPT increased the likelihood of children having a performance below expected based on SN total completion time, MF scaled score, and NM recognition score. BPD increased the odds of children having a performance below expected based on NM recognition score. SNM increases the likelihood of children having a performance below expected based on SN total completion time and NM recognition score. Ventilatory support and postnatal infection were not associated with any of the language, memory, and learning subtests.

Table 3 also shows the adjusted models for SN total completion time, MF scaled score, and NM recognition. Lower maternal age and education increased the odds of children having a performance below expected in terms of SN total completion time, whereas lower maternal education and gestational age increased the odds of children having a performance below expected in terms of MF scaled score.

Discussion

This study was conducted to analyze and compare language, memory, and learning outcomes in five-year-old children born EPT and to determine the risk of having below expected language, memory, or learning outcomes attending to perinatal and maternal characteristics. Overall, the results of our study show that the most compromised neurodevelopmental areas in both children born VPT and EPT are those related to specific language and memory skills such as the ability to assess and produce familiar words or identify colors, shapes, and sizes as well as below expected automaticity of naming, slow processing speed, or below expected naming ability and difficulties with initial encoding or discriminating novel facts. In these areas, children born EPT are at a higher risk compared with children born VPT. Lower maternal educational level seems to be one of the most important factors accounting for neurodevelopmental difficulties among children born VPT and EPT.

Language

Our study shows that about one in every three children born VPT have difficulties in specific aspects of language related to the ability to assess and produce familiar words or identify colors, shapes, and sizes as well as below expected automaticity of naming, slow processing speed, or below expected naming ability, and this proportion is higher for children born EPT. Additionally, children born EPT or with SNM or with younger or less-educated mothers are more likely to have difficulties in rapidly assessing and producing familiar words or identify colors, shapes, and sizes, which is reflected in the higher proportion of classification below expected based on speed naming total completion time (Korkman et al., 2007). These children seem to have poor processing speed or difficulties with retrieving words or producing verbal labels (Korkman et al., 2007).

Nonetheless, in the adjusted models, the influence of perinatal characteristics and maternal age was no longer significant, and education seems to be critical for these outcomes. Furthermore, children of mothers with lower educational level are more likely to exhibit a performance below expected in the comprehension of instructions and speed naming combined. This indicates that these children seem to have difficulties in the

comprehension of linguistically and syntactically complex verbal instructions, automaticity of naming difficulties, slow processing speed, or naming ability difficulties. Previous studies have also indicated an association between lower gestational age and language difficulties (Putnick et al., 2017; Sanchez et al., 2019).

Besides, in our study, the effect of gestational age is overshadowed by the social risk. This is consistent with previous evidence showing that maternal education seems to be the most relevant factor for language outcomes (Brósch-Fohraheim et al., 2019; Burnett et al., 2018; Ene et al., 2019). The influence of mother's education on language development may be related to the child's exposure to adequate parenting practices, such as storytelling, or adequate relationships to primary caregivers (Lind et al., 2011), as well as a broader vocabulary exposition and assimilation (Boo et al., 2018).

Furthermore, lower maternal educational level is associated with a higher likelihood of the child being exposed to adverse and stressful situations (such as hunger, domestic violence, or poverty) that shape brain development and may alter neuronal pathways (Hurt & Betancourt, 2016; Johnson et al., 2016). Interestingly, none of the biological or social factors that we analyzed in this study were associated with the child's performance in terms of self-monitoring and impulsive response. Although we provide information regarding the proportion of children with a performance below expected in these primary abilities and on the absence of association with gestational age for children born <32 weeks, the design of our study does not allow us to understand whether these primary abilities are more likely to be compromised in these children compared with healthy full-term children.

Further studies could expand our knowledge regarding developmental trajectories in children born EPT and VPT, such as in terms of a possible catch up with their full-term peers at some point of their development.

Memory and learning

More than one-third of children born VPT have difficulties with initial encoding or discriminating novel facts, and this proportion is even higher for children born EPT. Our results show that some aspects of memory and learning may be associated with a combination of biological and social risk, whereas others may be solely linked to social risk.

Children born EPT or with BPD or SNM are more likely to have a performance below the expected level based on narrative memory recognition. For these children, providing information in a format that does not require active recall and expressive language skills does not improve their memory functioning (Korkman et al., 2007). Still, in the adjusted models, most of the previously mentioned biological or social risk factors were not associated with the outcomes.

Children born EPT or having mothers with lower educational level are more likely to have a performance below expected on memory for faces, which indicates difficulties with initial encoding or discriminating novel facts (Korkman et al., 2007). The mother's lower educational level is associated with a higher likelihood of the child exhibiting a performance below expected on memory for faces delayed and narrative memory free and cued recall total as well as NM free and cued recall vs. recognition contrast scaled score. Additionally, these children are more likely to have difficulties with the

recognition of newly learned faces from long-term memory and potential developmental or acquired receptive or expressive language deficits, poor access to language, or poor ability to organize and sequence language (Korkman et al., 2007). Memory and learning are both complex human functions and are associated not only with gestational age but also with social characteristics as already reported by others (Cuevas & Sheya, 2019; Zambrana et al., 2016; Zeitlin et al., 2020). A preterm birth may expose the infant's brain to adverse stimuli, such as toxins or stress (Johnson et al., 2016), which may lead to an altered brain formation and wiring, with negative developmental consequences (Zambrana et al., 2021).

Our data show that memory outcomes are related to maternal education, which strengthens the evidence on the role of social factors in cognitive development in children at risk. We also show that other memory and learning primary abilities such as memory decay (forgetting more information than expected), prompt recall (encoding versus memory search capacity), or the ability to recall (given the child's basic encoding of the information) are associated with neither the biological nor the social factors included in our study.

These results raise questions regarding the reasons why some memory and learning primary abilities are subject to the sole influence of social risk or the combined influence of biological and social risks. On the other hand, these data already provide important information for intervention purposes by indicating which primary abilities are influenced by modifiable risk factors. This study has several strengths, such as the fact that the data come from a population-based cohort of children born <32 weeks of gestation and followed up until the age of five years, using reliable data collection methods. Children's language, memory, and learning performance were assessed using the NEPSY-II®, a clinical standardized age-adjusted test, rather than relying on parental reports. Yet, this study has some limitations. The NEPSY-II® is extremely long and time-consuming, and for that reason, our sample had children who were not able to complete the test either due to parental time constraints or tiredness. This may create a bias since the most resilient children from the cohort were more likely to complete the test. Therefore, our report may be an underestimation of cognitive outcomes in VPT and EPT children. We did in fact find differences between participants and non-participants that limit the generalization of our results.

This study shows that a large proportion of children born VPT and EPT have difficulties in specific language, memory, and learning subtests, which may be implicated in cognitive outcomes, and that there are modifiable risk factors associated with cognitive outcomes. This provides important clues to the follow-up care of children regarding not only the prioritized targets of intervention but also on the focus of intervention strategies to increase their capacity to lead fulfilled lives.

Children living in the most socially disadvantaged contexts, represented by aspects such as the mother's lower educational level, may be at a higher risk of suboptimal cognitive development. Therefore, the implementation of intervention programs that target those specific areas of language, memory, and learning may enable EPT and VPT children to reach and fulfill their potential in society.

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