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Perinatal and Maternal Characteristics Associated with Poor Neurodevelopmental Outcomes in the Portuguese EPICE/SHIPS Cohort

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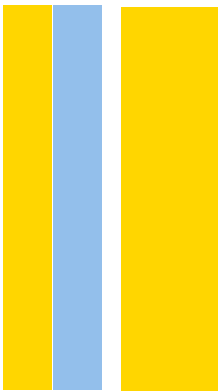

Perinatal and Maternal Characteristics Associated with Poor Neurodevelopmental Outcomes in the Portuguese EPICE/SHIPS Cohort

Dissertation of application for the master's degree in Public Health, presented to the Faculty of Medicine of the University of Porto and to the Institute of Biomedical Sciences Abel Salazar of the University of Porto

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Acknowledgment

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Abbreviations list

ADHD: attention deficit and hyperactivity disorder

ASD: autism spectrum disorder

BPD: bronchopulmonary dysplasia

CI: confidence interval

CP: cerebral palsy

CPAP: continuous positive airway pressure

EPICE: Effective Perinatal Intensive Care in Europe

EPT: extremely preterm

GA: gestational age

INE: Portuguese National Institute of Statistics

IURG: intrauterine growth restriction

IVH: intraventricular haemorrhage

LMT: long-term memory

M-ABC-2: Movement Assessment Battery for Children 2nd edition

MLPT: moderate to late preterm

NDA: neurodevelopmental assessment

NDI: neurodevelopmental impairments

NEC: necrotizing enterocolitis

NEPSY-II®: Developmental Neuropsychological Assessment, 2nd Edition

OR: odds ratios

PDA: patent ductus arteriosus

PROM: premature rupture of membranes

PVL: periventricular leukomalacia

ROP: retinopathy of prematurity

SHIPS: Screening to Improve Health in Very Preterm Infants in Europe

STM: short-term (working) memory

VPT: very preterm

WIPPSI-R: Wechsler Preschool and Primary Scale of Intelligence – Revised

WHO: World Health Organization

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Resumo

Resumo

Introdução: O nascimento prematuro é um grande problema de saúde pública global. Tem consequências de longo prazo, aumentando o fardo e os custos económicos para as famílias e problemas de desenvolvimento para as crianças.

Métodos: Nesta coorte de base populacional, pretendemos analisar e comparar a linguagem, bem como a memória e aprendizagem aos cinco anos de idade em crianças nascidas extremamente prematuras (EPT; <28 semanas de idade gestacional) e muito prematuras (VPT; 28-31^{+6d} semanas de idade gestacional). Além disso, pretendemos determinar o risco de problemas de linguagem, memória e aprendizagem atendendo às características maternas e perinatais. A amostra é composta por 412 (305 VPT e 107 EPT) crianças nascidas antes da 32ª semana de gestação em 2011 e 2012 nas regiões do Norte e Lisboa e Vale do Tejo, participantes no Screening to Improve Health in Very Preterm Infants in Europe (SHIPS), um projeto que se baseia nos Effective Perinatal Intensive Care in Europe (EPICE). Os dados perinatais foram extraídos dos relatórios clínicos e os subtestes do NEPSY-II® para avaliação da linguagem, memória e aprendizagem foram administrados aos cinco anos de idade. Foi efetuada a análise estatística descritiva dos dados. O teste do qui-quadrado (χ^2) de Pearson foi realizado para variáveis dicotómicas. Modelos de regressão logística foram testados.

Resultados: A maioria das crianças é do sexo masculino (57,4%), de gestação única (78,9%), peso ao nascer ≥ 750g (92,6%), cujas mães têm menos de 35 anos (66,4%), principalmente portuguesas (87,5%), sem frequência do ensino superior (61,7%) e empregadas (74,5%). As mães das crianças nascidas EPT tiveram com maior frequência infecção pré-natal e ruptura prematura de membranas comparativamente às mães das crianças nascidas VPT. As crianças nascidas EPT tiveram com maior frequência índice de Apgar (ao 5º minuto) abaixo de 7, hemorragia intraventricular grau ≥ III, leucomalácia periventricular, infecção precoce, infecção tardia, retinopatia de prematuridade grau ≥3, tratamento cirúrgico para persistência do canal arterial e anomalia congénita, displasia broncopulmonar (DBP), uso de corticóide para DBP, tratamento com recurso a surfactante ou a ventilação mecânica, comparativamente com as ciranças nascidas VPT. Aos 5 anos de idade, as crianças nascidas EPT tinham com maior frequência deficiência visual, problemas de destreza manual, educação especial, transtorno de défice de atenção e hiperactividade, atraso na fala e atraso no desenvolvimento em comparação com as crianças nascidas VPT. A maioria das crianças recorreu ao serviço de urgência (70,9%), ao pediatra (58,9%), ao oftalmologista (57,6%) ou ao médico de família (53,6%). As crianças nascidas EPT utilizaram serviços de saúde especializados com mais frequência comparativamente com as crianças nascidas VPT.

Menor idade gestacional, morbidade neonatal, menor idade e educação materna estão associadas ao risco aumentado de ter desempenho limítrofe ou abaixo do esperado na escala de Speeded Naming Completion Time Scaled. Menor idade gestacional, morbidade neonatal e displasia broncopulmonar estão associadas a risco aumentado de ter desempenho limítrofe ou abaixo do esperado na Narrative Memory Recognition Total Score Scaled. Menor idade gestacional e escolaridade materna estão associadas a risco aumentado de desempenho limítrofe ou abaixo do esperado no Memory for Faces Total Score. A menor escolaridade materna aumentou o risco de ter um desempenho limítrofe ou abaixo do esperado em Comprehension of Instruction Total Score scaled, Speeded Naming Combined, Memory for Faces Delayed Total Score scaled, Narrative Memory Free & Cued Recall Total Score scaled e Narrative Memory Contrast.

A modelagem preditiva mostra que menor idade gestacional (OR [IC 95%] 1,870 [1,113-3,141]) e menor escolaridade materna (OR [IC 95%] 2,135 [1,276-3,573]) está associada a pior performance no Memory for Faces Total Score. Morbidade neonatal (OR [IC 95%] 2,926 [1,127-7,594]) e menor escolaridade materna (OR [IC 95%] está associada a pior performance em termos de linguagem.

Conclusão: Fatores neonatais e sociais estão associados a diferentes habilidades primárias relacionadas com memória, aprendizagem e linguagem em crianças nascidas EPT e VPT. A implementação de um programa nacional que desenvolva modelagem preditiva para identificar crianças em risco antes que apresentem sintomas deve ser um foco de saúde pública.

Palavras-chave: Neurodesenvolvimento, Memória, Linguagem, Aprendizagem, NEPSY, Prematuridade

Abstract

Abstract

Background: Preterm birth is a major global public health issue. It has long-term consequences, increasing the burden and economic costs for families and developmental problems for children.

Methods: In this population-based cohort study, we aim to analyse and compare language, as well as memory and learning outcomes at the age of 5-year-old in children born extremely preterm (EPT; <28 weeks gestational age) and very preterm (VPT; 28-31^{+6d} weeks gestational age). Additionally, we intend to determine the risk of having poor language, memory and learning outcomes attending to maternal and perinatal characteristics. The sample is composed of 412 (305 VPT and 107 EPT) children born before the 32nd week of gestation in 2011 and 2012 in the Portuguese North and Lisbon and Tagus Valley regions, participants in the Screening to Improve Health in Very Preterm Infants in Europe (SHIPS), a project that builds on the Effective Perinatal Intensive Care in Europe (EPICE). Perinatal data were extracted from medical records and the NEPSY-II® subtests to assess language, memory and learning domain were administered at the age of 5 years-old. Descriptive statistical analysis was calculated. Pearson's chi-square (χ^2) test was performed to dichotomic variables. Logistic regression models were tested.

Results: Most of the infants are male (57.4%), from singleton pregnancies (78.9%), birth weight ≥ 750g (92.6%), whose mothers are under 35 years-old (66.4%), mainly Portuguese (87.5%), with less than tertiary education (61.7%), and employed (74.5%). Mothers of EPT were more likely to have prenatal infection and premature rupture of membranes. EPT were more likely to have a 5' Apgar below 7, intraventricular haemorrhage grade ≥ III, periventricular leukomalacia, early infection, late infection, retinopathy of prematurity grade ≥3, surgical treatment for patent ductus arteriosus, and congenital anomaly, bronchopulmonary dysplasia (BPD), use of steroids for BPD, receive surfactant and stay in mechanical ventilation. At 5 years old, EPT were more likely to have vision impairment, manual dexterity difficulty, educational support, attention deficit and hyperactivity disorder, speech delay, and developmental delay compared to VPT. Most children went to emergency room (70.9%), paediatrician (58.9%), and ophthalmologist (57.6%), and family doctor (53.6%), EPT children were more likely to use specialized health services compared to VPT.

Lower gestational age, neonatal morbidity, lower maternal age, and education are associated with increased risk of having borderline or below expected performance on Speeded Naming Completion Time scaled. Lower gestational age, neonatal morbidity, and bronchopulmonary dysplasia are associated with increased risk of having borderline or below expected performance on Narrative Memory Recognition Total Score scaled. Lower gestational age and

maternal education are associated with increased risk of having borderline or below expected performance on Memory for Faces Total Score. Lower maternal education increased the risk of having borderline or below expected performance on Comprehension of Instruction Total Score scaled, Speeded Naming Combined, Memory for Faces Delayed Total Score scaled, Narrative Memory Free & Cued Recall Total Score scaled and Narrative Memory Contrast.

Predictive modelling shows that lower gestational age (OR [95% CI] 1.870 [1.113-3.141]) and lower maternal education (OR [95% CI] 2.135 [1.276-3.573]) is associated with poor outcomes on Memory for Faces Total Score. Neonatal morbidity (OR [95% CI] 2.926 [1.127-7.594]) and lower maternal education (OR [95% CI] is associated with poor language outcomes.

Conclusion: Neonatal and social factors are associated with different primary abilities related to memory, learning and language in children born VPT. To implement a national program that develops predictive modelling to identify children at risk before they present symptoms should be a public health focus.

Keywords: Neurodevelopment, Memory, Language, Learning, NEPSY, Prematurity

Introduction

Introduction

Premature birth

The World Health Organization (WHO) is committed to address the premature birth problem (1), since this is part of the framework of the "Global Strategy for Women's, Children and Adolescent's Health and the Every Newborn Action Plan" (1). The WHO "Born Too Soon" report concluded that resource-poor countries can reduce preterm birth specific mortality by 2025 (2), and all countries should be committed to achieve the Sustainable Development Goal 3 - "ensure healthy lives and promote well-being for all ages". To reach this goal the quality of care must be improved and the quantity of data regarding epidemiological, medical complications, and treatments for preterm birth, as well as to increase research to identify, prevent and manage the lifelong consequences of preterm birth (1).

Since 1976, the WHO's definition of prematurity is established as a birth that happens prior to 37 completed weeks of gestation or fewer than 259 days from the first date of a woman's last menstrual period (3). It can be classified as extremely preterm (EPT, less than 28 weeks), very preterm (VPT, between 28 and 31^{+6} weeks), and moderate to late preterm birth (MLPT, from 32 through 36^{+6} weeks) (3). This classification helps clinicians and researchers to improve care to those infants, since the approach to their needs may differ (4).
In 2014, it was estimated that 14.8 million babies – more than 1 in 10 births - were born preterm worldwide (1), and from those 16% were VPT (5). In Europe, it is estimated that in 2014, more than 690 thousand births were preterm, representing 4.7% of preterm births worldwide, and with a preterm rate of approximately 8.7% in the continent (figure 1). As reported by the latest report of the Portuguese National Institute of Statistics (INE) 6,341 labours from 86,256 (7.35% of total labours) were preterm in Portugal in 2018(6) (figure 2 and 3).

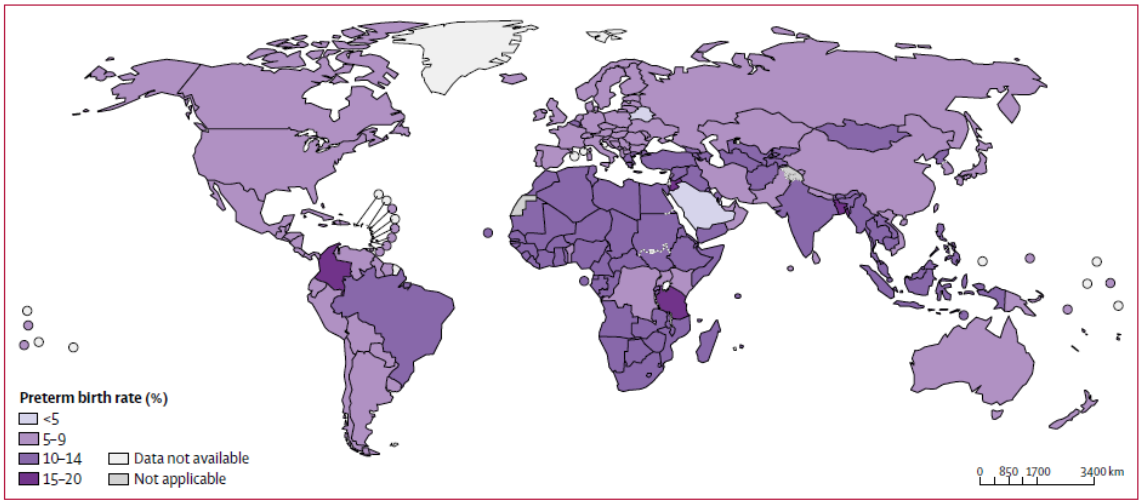

Figure 1 (1): Estimated preterm birth rates in 2014

2018 Unidade: n.º

Idade da mãe (grupo etário)	Total	Simples							
		Total	< 22 semanas	22 a 27 semanas	28 a 31 semanas	32 a 36 semanas	37 a 41 semanas	> 41 semanas	Ignorada
Total	**86 256**	**84 859**	**1**	**260**	**645**	**4 560**	**79 175**	**108**	**110**
10-14	35	35	0	0	0	2	33	0	0
15-19	1 986	1 972	0	6	18	120	1 814	7	7
20-24	8 662	8 587	0	30	73	458	7 999	13	14
25-29	18 961	18 722	1	52	141	969	17 517	22	20
30-34	28 390	27 893	0	79	192	1 387	26 167	38	30
35-39	21 893	21 456	0	65	160	1 201	19 980	24	26
40-44	5 943	5 828	0	24	57	392	5 341	4	10
45-49	353	335	0	2	2	29	302	0	0
50 e +	25	23	0	0	0	1	22	0	0
Ignorada	8	8	0	2	2	1	0	0	3

Fonte: INE, Partos

Figure 2 (7): Gestational age at birth in singleton gestation considering the mother's age

2018 Unidade: n.º

Idade da mãe (grupo etário)	Total	Gemelar							
		Total	< 22 semanas	22 a 27 semanas	28 a 31 semanas	32 a 36 semanas	37 a 41 semanas	> 41 semanas	Ignorada
Total	**86 256**	**1 397**	**0**	**52**	**109**	**714**	**521**	**0**	**1**
10-14	35	0	0	0	0	0	0	0	0
15-19	1 986	14	0	1	1	9	3	0	0
20-24	8 662	75	0	5	3	34	33	0	0
25-29	18 961	239	0	7	21	123	88	0	0
30-34	28 390	497	0	22	42	240	193	0	0
35-39	21 893	437	0	14	32	225	165	0	1
40-44	5 943	115	0	3	9	67	36	0	0
45-49	353	18	0	0	1	14	3	0	0
50 e +	25	2	0	0	0	2	0	0	0
Ignorada	8	0	0	0	0	0	0	0	0

Fonte: INE, Partos

Figure 3 (7): Gestational age at birth in multiples' gestation considering the mother's age

The mortality due to premature birth and its complications is the first cause of death for children under 5 years old (1, 8-10), and in 2016, preterm birth complications were responsible for 16% of all deaths and 35% of deaths among newborns (10).

There are multiple risk factors associated with preterm birth (5, 11-13), that can be divided in:

1. Maternal characteristics: low socio-economic status, family history of preterm birth, ethnicity, smoking, maternal education level, low or high body mass index, and maternal age (low and high).
2. Medical history: cervical surgery, uterus anomaly, chronical illness.
3. Obstetrical history: prior preterm birth, prior stillbirth, prior pregnancy loss > 16 weeks GA, cervical insufficiency, preeclampsia.
4. Current pregnancy: multiple pregnancy, nulliparity, vaginal bleeding, polyhydramnios, mode of conception, short cervix, male sex.

In recent decades, neonatal intensive care improved substantially and the survival rate in this population exceeded 85% (14) and is rising (9). Even so, these medical procedures do not exempt the risk of morbidity(15), such as patent ductus arteriosus (PDA) persistent after 72 hours (16). Although major neonatal impairment morbidities, such as periventricular leukomalacia (PVL), severe necrotizing enterocolitis (NEC) (17, 18), cerebral palsy (CP), and severe retinopathy of prematurity (ROP) (19, 20), are decreasing, short and long term developmental problems, such as cognitive or motor difficulties, are increasing (9, 21, 22) since the 1990s. The survivors of EPT and VPT birth are at risk of multiple impairments and neurodevelopmental disabilities that can compromise multiple domains (23), such as language (24), memory (25), and learning ability (23). There are several studies comparing VPT with

term children regarding language (26, 27) and memory (28), as well as EPT children with term children's in memory abilities (28) and also VPT with MLPT in terms of language (29). These deficits may remain through life (30), leading to suboptimal academic performance (31), increased behaviour problems (23), lower financial income (31) and less likelihood to establish a family, thus leading to social and economic inequities (32-35). Besides, there are direct economic costs, related to hospital treatment, ambulatory appointments, medication, and even parental workforce drop out to take care of their child (36).

Neurodevelopment

In humans, the embryonic period begins at conception and goes until the 8th gestational week (37). In the third gestational week, the human brain starts to develop with the differentiation of the neural cells and extends at least through late adolescence (38). The processes that contribute to brain development range from the molecular events of gene expression to environmental input (37). At the end of the embryonic period, the rudimentary structures of the brain and central nervous system are formed, and the major compartments of both central and peripheral nervous systems are defined. The foetal period of human development extends from the ninth gestational week through the end of gestation (38). In the beginning of the foetal development, the longitudinal fissure that separates both hemispheres is formed. The rostral regions proceed to the caudal regions, the primary sulci emerge after the end of the first trimester, the secondary sulci develop almost at the middle of the third trimester, and at last the tertiary sulci begin to form in the last month of pregnancy, extending into the postnatal period (38).

Foetal development is a continuum (39) and premature birth interrupts that process which has an adverse clinical impact. There are two mechanisms that could explain this increased risk of preterm birth interference on the brain's development of the connectome and signalling (38): [1] maladaptation, in which the foetus or neonate is not able to properly adapt to the environmental changes, and [2] direct injury, than can happen in a case of oxidative stress, sepsis, or poor perfusion (40). Consequently, lower gestational age (GA) is associated with worse neurodevelopmental outcome (26, 41) in general, including in terms of language, memory and learning ability.

Language is fundamental to daily social functioning and interpersonal skills. It is not a unidimensional domain, it includes phonology, morphology, semantics, syntax, and pragmatics(42). The language development starts in the uterus, as the auditory system is formed between 23rd and 30th week (43). It continues to develop in increasing complexity from uterus (early language processing) to early years in life (later language processing), including not only perception comprehension but also production of sounds, actions and behaviours (43). The normal language development (figure 4) can be divided in 4 phases (43): [1]

prelingual, [2] early-lingual, [3] differentiation phase, and [4] completion phase. The prelingual phase occurs during the first year of life in which the infant will learn to understand the caregiver and how to respond in an adequate manner. This phase includes vocalization, eye movements/gaze, gesture and shared attention with a caregiver (43). The successful accomplishment of this skills, relies on infant direct speech and uncompromised hearing (43). In the early-lingual phase – from one to two and a half years - the vocabulary will be developed and in the differentiation phase, the child will experience the expressive language, understanding the changes of the word forms in different contexts and learn to construct sentences (43). The completion phase occurs after the age of five and year after year, the child will evolve, mastering language (43). This will be stimulated by education and will be the basis for reading skills (43).

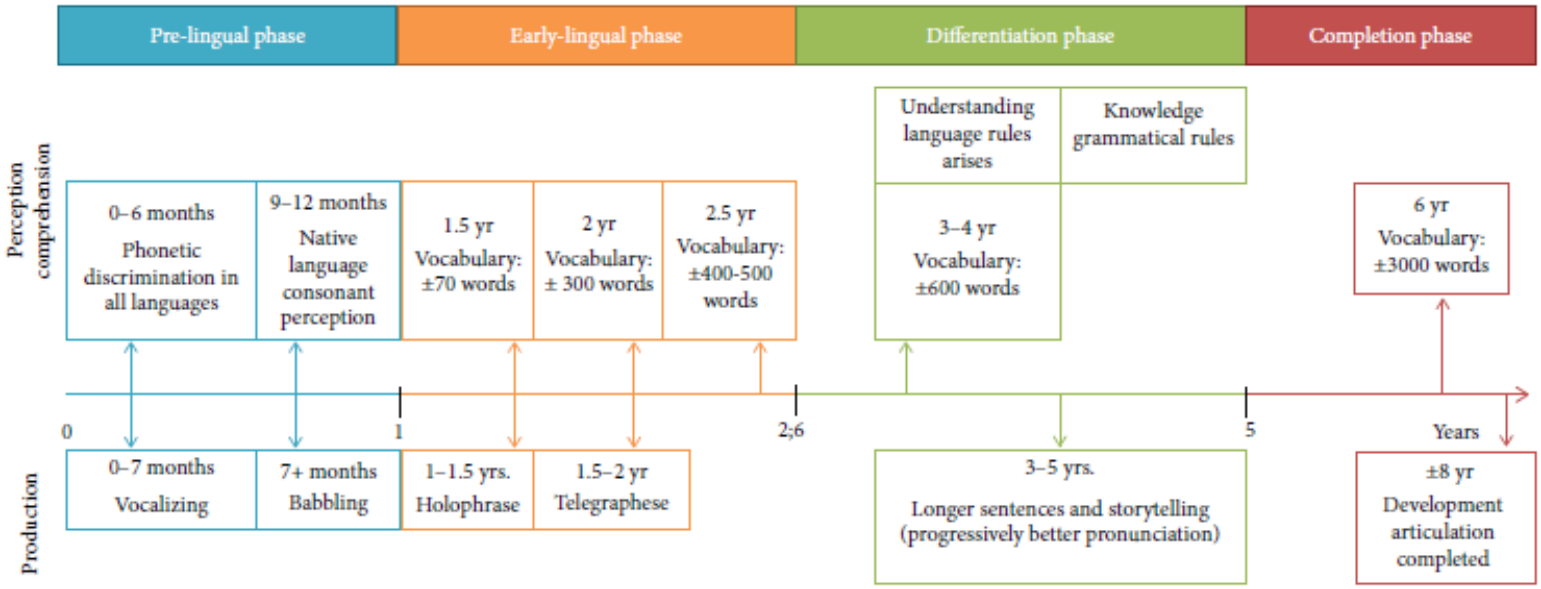

Figure 4 (43): The four language developing phases and the changes that occur in speech perception/comprehension and production in typically developing children during their first years of life. Premature children may have language impairment or delay at different levels and for distinct causes, as it can be affected in more than one developmental stage (43).

Learning and memory are complex cognitive functions, since they are, as well as language, inserted in social-cultural contexts (44) and have subcomponents structured in multiple ways (45). Memory consists of encoding, storing, consolidating and retrieving information (46). Besides, memory and learning have overlapping system models (47). Memory systems (figure 5) can be divided short-term (working) memory (STM) or long-term memory (LTM) (46). Additionally, LTM is divided in declarative (explicit) that is related to facts and events mediated by the hippocampus, medial, temporal lobe and diencephalon; and nondeclarative (implicit), that is highly related to learning abilities (47).

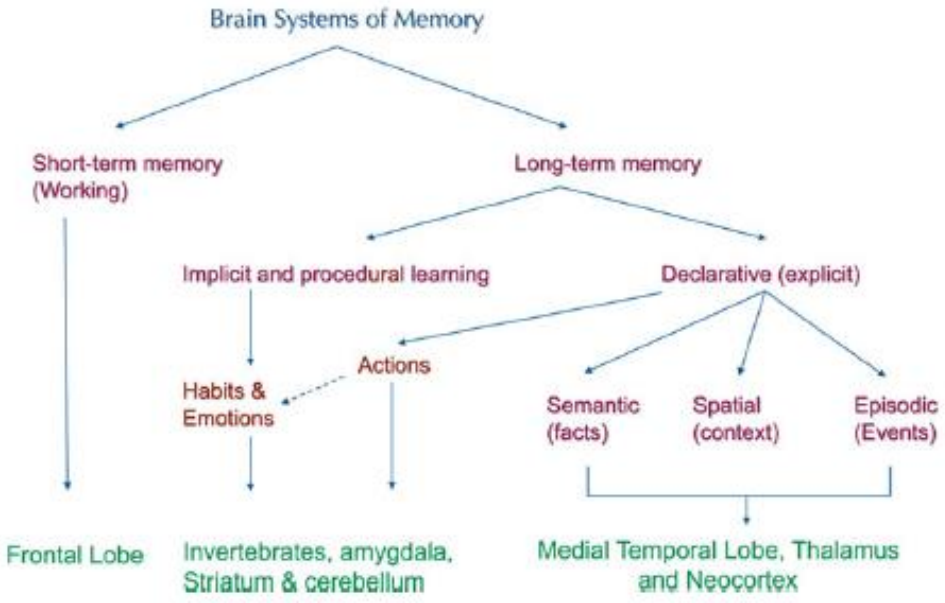

Figure 5 (46): taxonomy of brain systems of memory.

Working memory is a system that holds onto spoken information to visual information, and coordinates information about the recent past (46).

Long-term memory involves an active encoding phase and a passive phase, so that the representations formed before can be retrieved and triggered (46). Declarative memory is divided in semantic, spatial, and episodic memory. They have a “truth value”, since humans can declare it, being a private knowledge, that can be expressed in language or expressed through behaviour. Implicit memory and procedural learning relate to habits and emotions, and with actions that can as well be a declarative memory. Learning information may involve acquiring new memories and sometimes that is related with previous memories (48). So, an interaction between the past and the present is inevitable (48). So that, skill learning is considered a “trial-and-error” experience (46).

State of the art

In the initial studies regarding neurodevelopment outcomes in preterm infants, the aim was to have follow-up care, to screen for developmental problems early in life. The focus was in the early detection of major neurodevelopmental impairments (NDI) such as CP (49, 50), intellectual disability, epilepsy, and severe visual/hearing problems (19) not only in children born preterm but also in children born at term, to allow for early intervention and therefore minimize future sequelae (51). More recently, the incidence of major NDI has decreased (19), but the incidence of mild dysfunctions such as learning disabilities, attention deficit/ hyperactivity, autism symptoms, borderline intelligence, and behavioural problems has increased (19). With this shift in incidence, resources are now focused on quantify, intervene,

and minimize the mild dysfunctions that have a great impact on the lives of those children and their families.

In the Norwegian Mother and Child Birth Cohort Study (MoBa), *Zambrana and colleagues* (52) concluded that there is an inverse trending relating GA and language comprehension in infants from 18 to 36 months, with a higher effect in the group born with < 34 weeks' gestation when compared with their at full-term siblings. More recently, *Zambrana and colleagues* (53), added that those short-term effects of GA on language were still noted later on at the age of five, and even though the majority of preterm children catch up with their siblings by the age of five, the preterm group born < 34 weeks' gestation were still in risk for language delay. Consistent findings regarding language developmental trajectories come from two studies from *Nguyen and colleagues* (54, 55) showing that many children born < 30 weeks' gestation have a stable catch-up until the age of 7 years, nonetheless a considerable portion still have poorer language abilities, with no evidence of a complete catch-up after the age of seven (54, 55). Comparing with their full-term peers, almost half of those children have at least one language domain compromised, with odds ratios (OR) ranged from 2.1 to 8.1 across the domains (55). *Putnick and colleagues* (24) used data from the prospective Bavarian Longitudinal study, that started in 1980's to evaluate if VPT children had lower language outcomes compared to their MLPT and full-term peers from five months to eight years of old. They concluded that VPT children had the poorest language skills, which sustained and stabilized throughout the years included in the study (24).

Structural neuroimaging of lateralization of receptive and expressive language may be important to understand language dysfunctions presumed by brain injuries associated with prematurity. *Barnes-Davis and colleagues* (56) found increased functional connectivity in language network in preterm children, and those altered regions, especially right hemi drivers, are important for subsequent language development.

Mürner-Lavanchy and colleagues (57)*,* found that global cortical thickness from both hemispheres were positively correlated with executive control and verbal learning performance, as in full-term controls only the right hemisphere were positively associated with verbal learning.

Other factors may also explain language outcomes in children born VPT, such as familial (52) or social risk factors (lower parental education, lower income, family structure) and absence of early child support and intervention (54, 58). *Lean and colleagues* (58) found an association between social risk and a worst language outcome among VPT children at five years of old. However, a maternal affective involvement and mother's intellectual ability impact positively the language development, it may indicate that those mothers could be using rich and diverse language to their children (58).

Learning disorders are also a major concern in children born VPT. Recently, *Rogers and colleagues* (59) claimed that 10-15% of learning disorders that were not intellectual disabilities are attributable to preterm birth. *Johnson and colleagues* (60) showed that 20% of EPT can have a learning disability, either reading, mathematic or disability in both areas, compared to 3% of the full-term. Mathematics difficulties were more common than reading problems in EPT. Furthermore, when children born EPT and with learning disabilities had worst academic outcomes compared to their preterm peers without learning disabilities (60). Learning disability increased the need for special education up to three times in the EPT (60).

Two studies from *Allotey and colleagues* (61) and *Guarini and colleagues* (62) showed that difficulties in reading, mathematic and spelling in primary school are higher among children born VPT, and tends to persist until secondary school in reading and spelling (61), regardless the spoken language (62).

In one article from the ELGAN study (a multi-centre observational study designed to identify characteristics and exposures associated with increased risk of structural and functional neurologic disorders in EPT), *Leviton and colleagues* (63) found that neonatal clinical status is a risk factor for math and combined reading and math outcomes, whereas bronchopulmonary dysplasia/chronic lung was associated with increased risk of the combined limitations, and the apparent need for postnatal hydrocortisone was associated with the reading limitations.

Previous studies (57, 59, 60) that explore learning outcomes in VPT children focused on the executive function component, but other cognitive processes such as memory and language should be also be addressed (60). The characterization of the role of modifiable risk factors for neurodevelopmental difficulties in longitudinal studies is lacking in the literature (59). Most studies use few specific standardized neurodevelopment domain tests to evaluate children specific abilities, that do not cover memory and learning in details (61). In addition, learning limitations are not homogeneous, and identifying a broader group of dysfunctions is only achievable with multiple subtests (63).

Longitudinal studies regarding language (55) with longer follow-ups and repeated observations (58) would help getting a broader understanding of these children's developmental trajectories.

Importance to public health

Preterm birth is a major global public health issue, since it has long-term consequences, increasing the burden and economic costs from those children and their families (33). In order to improve health care of children born preterm we must have detailed information regarding neurodevelopmental outcomes and their possible associations with identifiable antenatal, neonatal, perinatal, and socio-demographic factors (64). As every child is unique and their development is heterogeneous, to identify those at risk and offer them specific interventions to

promote their optimal development is a duty. To involve stakeholders and policy makers is crucial for public health, since it will promote early intervention via valid screening instruments and promote a better longitudinal outcome(65, 66).

To analyse an exclusive Portuguese cohort that includes VPT and EPT children from the EPICE/SHIPS Cohort will allow us to explore the data regarding this population and its singularity, as it will provide new knowledge and better understanding of this vulnerable group, in order to act in a better-oriented way, promoting their best interest. This follows the "synthesis, exchange and application of knowledge by relevant stakeholders" to accelerate health innovation (66).

Objective

Objective

The objectives are to analyse and compare language, memory and learning outcomes of 5-year-old children born EPT (<28 weeks gestational age) and VPT (28-31^{+6d} weeks gestational age) and to determine the risk of having poor language, memory or learning outcomes attending to perinatal and maternal characteristics.

Methods

Methods

Study design

Observational cohort study.

Data collection at birth

Data from obstetric and neonatal records were obtained using a pretested standardised questionnaire. Data were collected up until discharge home from hospital or into long-term care (67).

Maternal and pregnancy characteristics included in the analysis were maternal age, multiple pregnancy, and pregnancy complications, defined as hypertensive diseases (preeclampsia, eclampsia, and HELLP syndrome), infection before birth, premature rupture of membranes (PROM), intrauterine growth restriction (IURG), prepartum haemorrhage and use of steroids for foetal maturation before birth. Infant characteristics included in the analysis were GA at birth (defined as the best obstetric assessment based on information for last menstrual period and antenatal ultrasounds), birth weight, sex, and Apgar at 5 minutes. After birth medical interventions included in the analysis were use of surfactant, use of continuous positive airway pressure (CPAP), use of mechanical ventilation, steroids use for bronchopulmonary dysplasia (BPD - defined as need for oxygen supplement at 36 + 0 weeks of gestation) and PDA surgical treatment. Neonatal morbidities included were BPD, intraventricular haemorrhage (IVH - defined according to Papillae grade 3-4), PVL, early infection after birth (within the first 72 hours of life), late infection after birth (after the first 72 hours of life), ROP (grade ≥3), NEC (Bell Stage 2-3 or need to peritoneal drainage), and congenital anomaly.

Five-year-old follow up

The follow-up included two parts: [1] a parental questionnaire and [2] the Neurodevelopment Assessment (NDA), conducted by a trained clinical psychologist and divided in two sessions: the [2a] Wechsler Preschool and Primary Scale of Intelligence – Revised (68) (WIPPSI-R) and the Raven Progressive Matrices Test (69) were administered in the first session and the [2b] Movement Assessment Battery for Children second edition (M-ABC-2) (70) and NEPSY-II® (71) – in the second session.

While children were completing the NDA, parents were completing a questionnaire that included (1) socio-demographic information, namely parental educational level (non-tertiary - early childhood education, primary, lower secondary, upper secondary and post-secondary non-tertiary (pre-university courses) *vs* tertiary - short cycle tertiary (vocational programmes), bachelor degree or equivalent, master degree or equivalent and doctoral degree or equivalent) and maternal professional status (employed – including self-employment *vs* other), (2)

children's need for special educational support, (3) sensory impairment – vision ("no difficulties with vision" *vs* "needs to wear glasses but sees well when wearing them", or "has difficulties seeing, even wearing glasses", or "is blind, or able to see light only") and hearing ("no difficulties hearing" *vs* "some difficulties hearing but does not require hearing aids or cochlear implants", or "needs hearing aids or cochlear implants, but hears well with them", or "has difficulty hearing, even with hearing aids or cochlear implants", or "my child is deaf") -, (4) motor impairment – difficulties handling objects ("no difficulties using hands and fingers" *vs* "some difficulties, but is able to handle small objects without help", or "needs help from an adult to handle small objects", or "is unable to handle small objects at all"), or walking ("no difficulties walking" *vs* "can walk alone but is unsteady", or "can only walk with help from an adult or walking aid", or "unable to walk even with help from an adult or walking aid"), (5) clinical problems such as CP, asthma, speech delay, developmental delay, epilepsy, attention deficit and hyperactivity disorder (ADHD), or Autism Spectrum Disorder (ASD), (6) use of health care services in the past year, such as paediatrician, family doctor, emergency room, neurologist, ear-nose-throat specialist, ophthalmologist, language therapist, psychologist, psychiatrist, physiotherapist, pulmonologist, dietician, school nurse, occupational therapist, early intervention, and nurse.

The neurodevelopmental assessment

The Developmental Neuropsychological Assessment (NEPSY®) provides a comprehensive neuropsychological assessment of children aged 3–12 years (72). This instrument has been translated to multiple languages and uses the Luria theoretical approach to the assessment of neurological functioning (71, 73). NEPSY-II® is the newest version and is designed for children from 3 to 16.11 years old, it has 32 subtests that are divided into six content domains: Attention and Executive Functioning, Language, Memory and Learning, Social Perception, Sensorimotor, and Visuospatial Processing (74). The NEPSY-II® scores are: primary, process, contrast scores and behavioural observations. The primary scores are expressed as scales scores or percentile ranks, representing the global aspects of the subtests (74).
In this study we analysed data from language and memory and learning domains that includes four sub-tests, two for each domain:

1. Language – comprehension of instruction and speed naming.
2. Memory and Learning – memory for faces/ memory for faces delayed, and narrative memory.

From the language domain sub-tests, five scores are available: comprehension of instruction total score scaled, speeded naming total correct scaled, speeded naming total self-corrected errors scaled, speeded naming total completion time scaled speeded naming combined. From

the memory and learning dimension sub-tests six scores are available: memory for faces total score scaled, memory for faces delayed total score scaled, narrative memory free recall total score and narrative memory free & cued recall total score scaled, memory for faces contrast and narrative memory contrast. A conclusion on the child's neurodevelopment is driven from each of these scores: at the expected level or above expected level (scaled score ≥ 8; percentile rank ≥ 26), or borderline or below the expected level (scaled score ≤ 7; percentile rank ≤ 25) considering the child's age (Table 1).

Table 1 – Scores derived from Memory and Learning, and Language test

Domain test	Score	Description	Primary Ability Assessed	Score for Analysis
Memory and Learning				
Memory for Faces	Total	A face recall task involving recalling a series of photographs of children's faces.	Face discrimination and recognition after one learning	Scaled score
	Delayed		Face discrimination and recognition after delay	Scaled score
	Contrast		Memory decay if the child has forgotten more information than expected	Contrast scale score
Narrative Memory	Free Recall Total	A story recall task that involves the examiner reading a story to the child, followed by immediate free recall, immediate cued recall, and immediate recognition	Free recall: Adequate expressive language functioning and receptive understanding	Scaled score
	Free & Cued Recall Total		Cued: prompt recall and demonstrate encoding versus memory search capacity	Scaled score
	Recognition Total		Recognition: the degree to which encoding deficit versus an information retrieval deficit is present	Scaled score
	Contrast		Describes the child's performance on Recall given the child's basic encoding of the information	Contrast scale score
Language				
Comprehension of Instruction		Auditory comprehension task that requires the child to point to the correct picture in response to examiner commands of increasing syntactic complexity.	Receptive language, linguistic or semantic knowledge, or following multistep commands	Scaled score
Speeded Naming Total	Completion Time	Asses the ability to rapidly assess and produce familiar words or identify numbers and letters in alternating patterns	Speed of processing, retrieval, or production of verbal labels	Scaled score
	Corrected		Self-monitoring, impulsive responding	Percentile score
	Self-Corrected Errors		Self-monitoring, impulsive responding	Percentile score
	Combined		Automaticity of naming, slow processing speed, or naming ability	Scaled score

Table adapted from NEPSY-II clinical and interpretative manual p.148-164(75).

Study population

Screening to Improve Health in Very Preterm Infants in Europe (SHIPS) is a European research project about follow-up programmes for children born VPT. The project builds on the *Effective Perinatal Intensive Care in Europe* (EPICE) cohort which includes 6792 infants born before the 32nd week of gestation in 2011 and 2012 in 19 regions in 11 European countries(76). In this study, children born in Portugal – North region and Lisbon and Tagus Valley – were included. In the Portuguese regions, of 724 very preterm live births, 607 infants were discharged alive from the hospital and written informed consent for follow-up evaluations was obtained for 544 children (89.6%). Of these, 542 children survived until the age of five, there were seven refusals to follow-up, two lost contacts and therefore 533 were eligible to the five-year-old follow-up. From those 48 could not be contacted, 52 were non respondents, and four refused to participate. Of the 429 families that agreed to participate, 17 families only answered parental questionnaire, and 412 (305 VPT and 107 EPT) children participated in the NDA (flowchart figure 7). Written parental consent was obtained at baseline and again in the five-year follow-up.

Figure 6 (67). Regions included in the EPICE/SHIPS cohort: Flanders in Belgium; the Eastern Region of Denmark; Estonia (entire country); Burgundy, Ile-de-France and the Northern regions in France; Hesse and Saarland in Germany; Emilia- Romagna, Lazio and Marche regions in Italy; the Central and Eastern regions of The Netherlands; Wielkopolska in Poland; the Lisbon and Northern regions of Portugal; and the East Midlands, Northern and Yorkshire and Humber regions in the UK; and the Stockholm region in Sweden.

Selected sample

Data from a subsample of 377 children that participated in the NDA were included. Of these, 294 completed the Comprehension of Instruction and 298 completed the Speed Naming subtests; 373 completed the Memory for Faces/ Memory for Faces Delayed and 363 completed the Narrative Memory sub-tests of the NEPSY-II® (71).

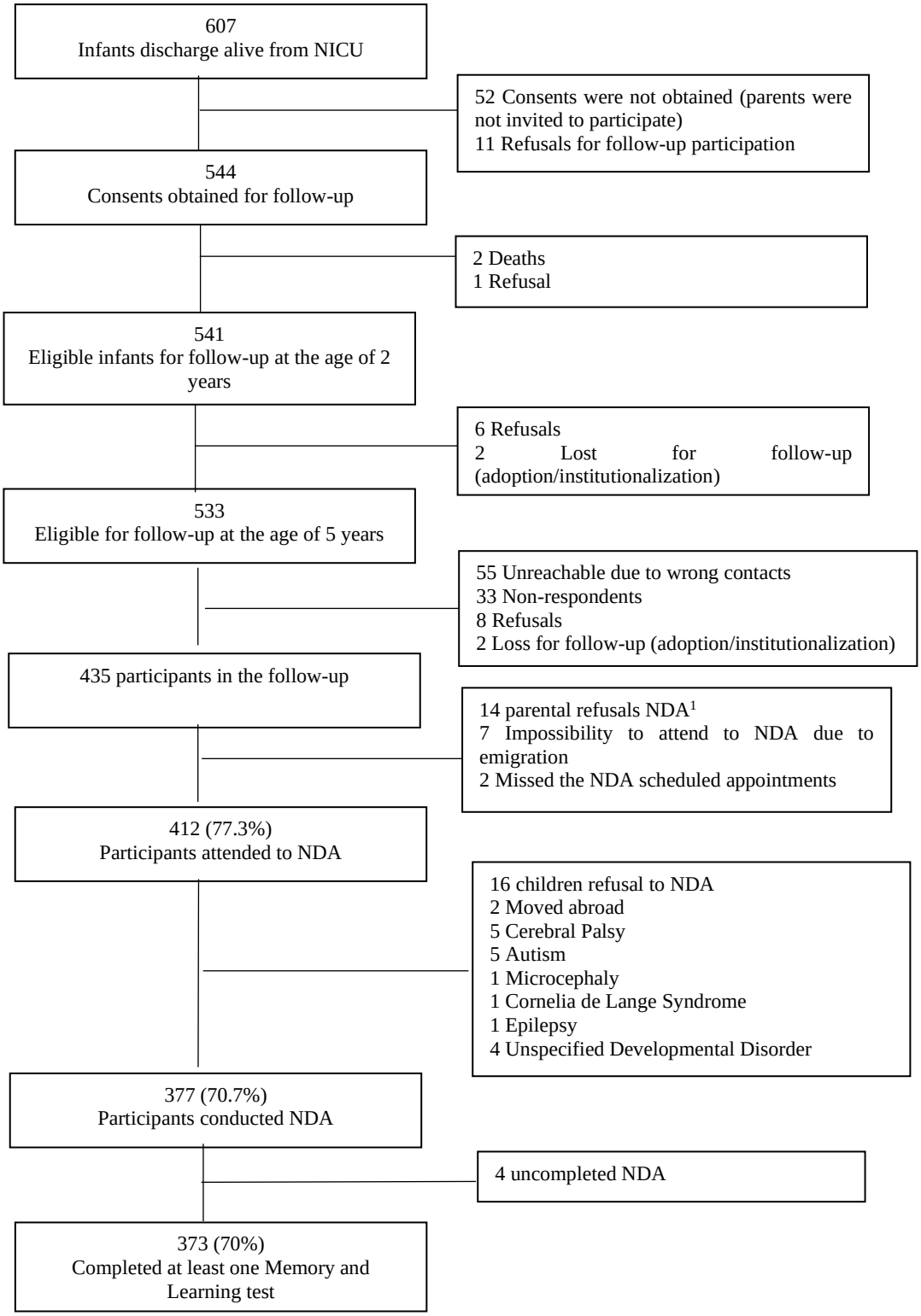

Figure 7. Flowchart of participants

[1]Neurodevelopmental Assessment

Sample size

The "Select Statistical Services" ® (https://select-statistics.co.uk/calculators/sample-size-calculator-population-proportion/) was used to calculate the adequate sample size for this study. After literature review, we estimated a frequency of at least 36% (77, 78) of unfavourable evaluation in any domain for the VPT and of 50% (78) in any domain for the EPT children. For a precision of 5% with a 95% Confidence Interval (CI) and 80% of power, the necessary sample would include 158 VPT children and 76 EPT children. Children that even though completed some NDA subtests, did not perform at least one subtest from the NEPSY-II® language and memory and learning domains were excluded. Therefore, 284 VPT children and 93 EPT were included in the analysis. The sample size is consistent with minimum criterion of ten participants per event in a predictive modelling (79-81).

Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences v. 26 (SPSS).

Descriptive statistical analysis was conducted to determine the characteristics of the sample. Pearson's chi-square (χ^2) tests were performed to analyse differences between EPT and VPT in terms of the dichotomic variables gender (male vs female), type of pregnancy (singleton vs multiple), birth weight (<750g vs ≥ 750g), mother's age (< 35year-old vs ≥ 35 year-old), mother's country of origin (Portugal vs foreign), mother's education level (< Tertiary Education vs ≥ Tertiary Education), mother's occupational status (employed vs other), infection before birth, IUGR, gestational hypertension, pre-eclampsia, eclampsia, HELLP syndrome, steroids for foetal maturation before birth, prepartum haemorrhage, PROM, 5' Apgar, surfactant, INSURE, CPAP, mechanical ventilation, BPD, steroids for BPD, IVH, PVL, NEC, ROP, early infection, late infection, congenital anomaly and surgical treatment for PDA, vision impairment, hearing impairment, CP, manual dexterity difficulty, difficulty walking, asthma, epilepsy, ADHD, ASD, speech delay, developmental delay, educational support, and use of specific health services in the last 12 months – paediatrician, family doctor, emergency room, neurologist, ear, nose and throat specialist, ophthalmologist, language therapist, psychologist, psychiatrist, physiotherapist, pulmonologist, dietitian, school nurse, occupational therapist, early intervention, nurse. Pearson's chi-square (χ^2) test were performed to analyse differences in the proportion of EPT and VPT with a performance below expected for their age on the scores of language and memory and learning subtests: Comprehension of Instruction Total Score scaled, Speeded Naming Total Completion Time scaled, Speeded Naming Total Correct scaled, Speeded Naming Total Self-Corrected Errors scaled and Speeded Naming Combined, Memory for Faces Total Score scaled, Memory for Faces Contrast, Memory for Faces Delayed

Total Score scaled, Narrative Memory Free Recall Total Score scaled, Narrative Memory Free Recall Total Score scaled, Narrative Memory Free & Cued Recall Total Score scaled, Narrative Memory Recognition Total Score scaled and Narrative Memory Contrast

Unadjusted logistic regression models were conducted to assess the association of each independent variable with a performance borderline or below the expected level in language, and memory and learning NEPSY-II® subtests. Variables for the models were selected based on clinical knowledge and the scientific literature on characteristics likely to affect neurodevelopment outcomes (11, 14, 18, 52, 53, 58, 82-84). We used the following variables: [1] GA (reference ≥ 28 weeks of GA) , [2] Neonatal morbidity (reference absence of all of the following: IVH grade III or IV, PVL, ROP grade ≥ 3, and NEC stage ≥ 2); [3] BPD (reference absence of BPD); [4] Ventilatory support (reference no need of surfactant, nor INSURE nor CPAP nor Mechanical Ventilation); [5] Infection after birth (reference absence of any infection after birth); [6] Mother's age (reference mother's age < 35 years of old); and [7] Mother's Educational level (reference ≥ tertiary education). Possible interactions between independent variables were also tested. Binomial logistic regression models that included the significant independent variables after mutual adjustment and significant interaction terms if present were performed for all the NEPSY-II subtests. Results are reported as odds ratios (ORs) with 95%CIs, and a 2-tailed $P < .05$ was considered significant. Missing values were not imputed.

Ethics/data protection

Ethics approval was obtained in each study region from regional and/or hospital ethics committees, as required by national legislation. In Portugal, the study was approved by the National Commission for Data Protection (authorization 7426/2011) and by the ethical commission of every hospital involved. A written informed consent was obtained from all participants.

Results

Results

The SHIPS Portuguese Cohort.

The characteristics of participants are shown in table 2. Most of the infants are male, from singleton pregnancies, birth weight ≥ 750g, whose mothers are under 35 years-old, mainly Portuguese, with less than tertiary education, and employed.

Table 2 – Participants' characteristics according to the gestational age

	EPT (< 28 weeks)		VPT (≥ 28 weeks)				Total	
Characteristics	N	%	N	%	χ^2	*p*	N	%
Gender					0.016	0.898		
Male	53	57	164	57.7			217	57.4
Female	40	43	120	42.3			160	42.4
Type of pregnancy					0.084	0.772		
Singleton	68	80	190	78.5			258	78.9
Multiples	17	20	52	21.5			69	21.1
Birth weight					41.232	<0.001		
≥ 750g	72	77.4	277	97.5			349	92.6
<750g	21	22.6	7	2.5			28	7.4
Mother's age					0.644	0.422		
< 35-year-old	47	62.7	147	67.7			194	66.4
≥ 35-year-old	28	37.3	70	32.3			98	33.6
Mother's country of origin					2.734	0.098		
Portugal	70	82.4	216	89.3			286	87.5
Foreigner	15	17.6	26	10.7			41	12.5
Mother's educational level					0.2	0.655		
< Tertiary Education	54	60	171	62.6			195	61.7
≥ Tertiary Education	36	40	102	37.4			121	38.3
Mother's occupational status					0.037	0.848		
Employed	69	75.8	208	74.8			239	74.5
Other	22	24.2	70	25.2			82	25.5
Gestational and Perinatal Risk Factor								
Infection before birth					5.986	0.014		
No	71	83.5	225	93.4			296	91.1
Yes	13	15.3	16	6.6			29	8.9
IURG					3.023	0.082		
No	73	86.9	186	78.2			259	80.4
Yes	11	13.1	52	21.8			63	19.6
Gestational Hypertension					0.444	0.505		
No	72	85.7	199	82.2			271	83.4
Yes	12	14.3	42	17.4			54	16.6

Table 2 – Participants' characteristics according to the gestational age

	EPT		VPT				Total	
Characteristics	N	%	N	%	χ^2	*p*	N	%
Pre-eclampsia					1.786	0.181		
No	71	83.5	188	77.7			259	79.4
Yes	13	15.5	54	22.3			67	20.6
Eclampsia					1.063	0.302		
No	85	100	239	98.8			324	99.1
Yes	0	0	3	1.2			3	0.9
HELLP Syndrome					1.094	0.296		
No	80	94.1	234	96.7			314	96
Yes	5	5.9	8	3.3			13	4
Steroids for foetal maturation before birth					0.531	0.466		
No	5	5.9	20	8.3			25	7.6
Yes	80	94.1	220	90.9			300	92.3
Prepartum haemorrhage					1.085	0.367		
Yes	31	36.9	32	13.2			47	14.4
No	53	63.1	210	86.8			279	85.6
PROM					4.197	0.041		
No	62	69.1	223	79.4			241	7.6
Yes	28	31.1	58	20.6			80	24.9
Risk Factor after Birth								
5' Apgar					12.138	0.001		
<7	15	16.1	14	5			29	7.8
≥7	78	83.9	267	95			345	92.2
Needed any respiratory support								
Surfactant					50.166	<0.001		
No	16	17.2	169	59.5			185	49.1
Yes	77	82.8	115	40.5			192	50.9
INSURE					1.278	0.258		
No	79	84.9	232	81.7			311	83
Yes	12	12.9	52	18.3			64	17
CPAP					7.097	0.006		
No	2	2.2	32	11.3			34	9
Yes	91	97.8	252	88.7			343	91
Mechanical Ventilation					68.445	<0.001		
No	12	12.9	177	62.3			189	50.1
Yes	81	87.1	107	37.7			188	49.9
BPD					28.396	<0.001		
No	69	74.2	267	94			336	89.2
Yes	24	25.8	17	6			41	10.8
Steroids for BPD					26.754	<0.001		
No	83	89.2	283	99.6			366	97.1
Yes	10	10.8	1	0.4			11	2.9

Table 2 – Participants' characteristics according to the gestational age

	EPT		VPT				Total	
Characteristics	N	%	N	%	χ^2	*p*	N	%
Severe neonatal morbidity at discharge								
IVH					8.968	0.003		
No	84	90.3	277	97.5			361	95.8
Yes	9	9.7	7	2.5			16	4.2
PVL					6.168	0.021		
No	86	92.5	278	97.9			364	96.6
Yes	7	7.5	6	2.1			13	3.4
ROP					34.415	<0.001		
No	40	75.5	268	99.6			348	96.1
Yes	13	24.5	1	0.4			14	3.9
NEC					2.634	0.148		
No	88	94.6	278	97.9			366	97.1
Yes	5	5.4	6	2.1			11	2.9
Infection after birth								
Early infection					10.494	0.001		
No	84	90.3	278	97.9			362	96
Yes	9	9.7	6	2.1			15	4
Late Infection					47.226	<0.001		
No	33	35.5	212	74.6			245	65
Yes	60	64.5	72	25.4			132	35
Congenital anomaly					0.834	0.475		
No	88	94.6	273	96.1			361	97.6
Yes	5	5.4	11	3.9			16	4.2
Surgical Treatment for PDA					20.463	<0.001		
No	85	91.4	283	99.6			368	97.6
Yes	8	8.6	1	0.4			9	2.4

Mothers of EPT were more likely to have prenatal infection and PROM, but not IURG, prepartum haemorrhage, gestational hypertension, pre-eclampsia, eclampsia, or HELLP syndrome (table 2).

After birth (table 2), EPT were more likely to have a 5' Apgar below 7, receive surfactant and stay in mechanical ventilation, BPD, use of steroids for BPD. IVH grade ≥ III, PVL, early infection, late infection, ROP grade ≥3, Surgical treatment for PDA, and congenital anomaly.

Difference between participants and non-participants

Participants and non-participants differed in some characteristics (table 3). Among the EPT non-participants had younger mothers; were more likely to have BPD; steroids for BPD; and late infection. Among the VPT non-participants were more likely to have foreign mothers.

Table 3 - Characteristics associated with loss to follow-up at 5 years: SHIPS Portuguese cohort

	EPT						VPT						Total					
	Follow up at 5 years old						Follow up at 5 years old						Follow up at 5 years old					
	Participants		Non-participants				Participants		Non-participants				Participants		Non-participants			
Characteristics	N	%	N	%	χ^2	*p*	N	%	N	%	χ^2	*p*	N	%	N	%	χ^2	*p*
Gender					0.229	0.632					0.054	0.817					0.212	0.645
Male	53	57	34	53.1			164	57.7	94	56.6			217	57.6	128	55.7		
Female	40	43	30	46.9			120	42.3	72	43.3			160	42.4	102	44.3		
Type of pregnancy											0.015	0.901					0.129	0.720
Singleton	68	73.1	50	78.1	0.509	0.476	190	66.9	112	67.5			258	78.9	162	70.4		
Multiples	16	18.8	14	21.9			52	21.7	54	32.5			69	21.1	40	29.6		
Birth weight					1.477	0.224					0.208	0.648					1.229	0.268
≥ 750g	72	77.4	44	68.8			277	97.5	163	98.2			349	92.6	207	90		
<750g	21	22.6	20	31.3			7	2.5	3	1.8			28	7.4	23	10		
Mother's age					4.087	0.043					0.092	0.762					1.530	0.216
< 35-year-old	47	62.7	46	79.3			147	67.7	104	66.7			194	66.4	135	71.8		
≥ 35-year-old	28	37.3	12	20.7			70	32.3	52	33.3			98	33.6	53	28.2		
Mother’s country of origin					3.410	0.065					23.099	<0.001					21.474	<0.001
Portugal	70	82.4	45	70.3			216	89.3	120	72.3			286	87.5	144	71.3		
Foreigner	15	17.6	19	29.7			26	10.7	46	27.7			41	12.5	58	28.7		
Mother's educational level					3.540	0.066					1.429	0.232					0.412	0.521
< Tertiary Education	54	60	15	16.7			171	62.6	16	51.6			195	61.7	30	66.7		
≥ Tertiary Education	36	40	3	83.3			102	37.4	15	48.4			121	38.3	15	33.3		
Mother's occupational status					0.105	0.746					1.9	0.168					1.515	0.218
Employed	69	75.8	13	72.2			208	74.8	21	63.6			239	74.5	31	66		
Other	22	24.2	5	27.8			70	25.2	12	36.4			82	25.5	16	34		

Table 3 - Characteristics associated with loss to follow-up at 5 years: SHIPS Portuguese cohort

	EPT						VPT						Total					
	Follow up at 5 years old						Follow up at 5 years old						Follow up at 5 years old					
	Participants		Non-Participants				Participants		Non-Participants				Participants		Non-Participants			
Characteristics	N	%	N	%	χ^2	*p*	N	%	N	%	χ^2	*p*	N	%	N	%	χ^2	*p*
Gestational and Perinatal Risk Factor																		
Infection before birth					1.476	0.224					0.663	0.416					1.544	0.214
No	71	83.5	59	92.2			225	93.4	159	95.8			296	91.1	190	94.1		
Yes	13	15.3	5	7.8			16	6.6	7	4.2			29	8.9	12	5.9		
IURG					0.181	0.671					0.678	0.410					0.090	0.764
No	73	86.9	54	85.7			186	78.2	135	81.8			259	80.4	163	81.5		
Yes	11	13.1	9	14.3			52	21.8	30	18.2			63	19.6	37	18.5		
Gestational Hypertension					0.768	0.372					1.699	0.192					2.730	0.098
No	72	85.7	58	90.6			199	82.2	147	88.6			271	83.4	179	89.1		
Yes	12	14.3	6	9.4			42	17.4	19	11.4			54	16.6	23	10.9		
Pre-eclampsia					0.067	0.796					2.768	0.096					2.236	0.135
No	71	83.5	54	84.4			188	77.7	143	86.1			259	79.4	171	85.7		
Yes	13	15.5	10	15.6			54	22.3	23	13.9			67	20.6	31	14.3		
Eclampsia					*	*					0.021	1					0.007	1
No	85	100	64	100			239	98.8	164	98.8			324	99.1	200	99.1		
Yes	0	0	0	0			3	1.2	2	1.2			3	0.9	2	0.9		
HELLP Syndrome					1.5	0.402					0.637	0.425					0.089	0.765
No	80	94.1	63	98.4			234	96.7	159	95.8			314	96	195	96.5		
Yes	5	5.9	1	1.6			8	3.3	7	4.2			13	4	8	3.5		
Steroids for foetal maturation before birth					1.661	0.197					0.022	0.882					0.478	0.489
No	5	5.9	7	10.9			20	8.3	13	7.8			25	7.6	19	8.7		
Yes	80	94.1	57	89.1			220	90.9	153	92.2			300	92.3	183	91.3		

Table 3 - Characteristics associated with loss to follow-up at 5 years: SHIPS Portuguese cohort

	EPT						VPT						Total					
	Follow up at 5 years old						Follow up at 5 years old						Follow up at 5 years old					
	Participants		Non-Participants				Participants		Non-Participants				Participants		Non-Participants			
Characteristics	N	%	N	%	χ^2	*p*	N	%	N	%	χ^2	*p*	N	%	N	%	χ^2	*p*
Prepartum haemorrhage					0.489	0.485					0.261	0.655					0.560	0.454
No	31	36.9	50	78.1			32	13.2	144	86.7			47	14.4	168	83.2		
Yes	53	63.1	14	21.9			210	86.8	22	13.3			279	85.6	34	16.8		
PROM					0.157	0.692					2.575	0.109					0.353	0.552
No	62	69.1	42	68.9			223	79.4	120	72.7			241	75.1	144	72.7		
Yes	28	31.1	19	31.1			58	20.6	45	27.3			80	24.9	54	27.3		
Risk Factor after Birth																		
5' Apgar					1.883	0.170					0.237	0.626					2.220	0.136
<7	15	16.1	16	25			14	5	10	6.1			29	7.8	26	11.3		
≥7	78	83.9	48	75			267	95	155	93.9			345	92.2	203	88.3		
Surfactant					1.191	0.275					0.434	0.510					0.038	0.846
No	16	17.2	7	10.9			169	59.5	104	62.7			185	49.1	111	48.3		
Yes	77	82.8	57	89.1			115	40.5	62	37.3			192	50.9	119	51.7		
INSURE					0.177	0.674					0.512	0.474					0.783	0.376
No	79	84.9	57	89.1			232	81.7	140	84.3			311	82.5	197	85.7		
Yes	12	12.9	7	10.9			52	18.3	26	15.7			64	17	33	14.3		
CPAP					0.070	1					0.391	0.532					0.162	0.688
No	2	2.2	1	1.6			32	11.3	22	13.3			34	9	23	10		
Yes	91	97.8	63	98.4			252	88.7	144	86.7			343	91	207	90		
Mechanical Ventilation					1.018	0.313					0.192	0.661					1.148	0.284
No	12	12.9	5	7.8			177	62.3	100	60.2			189	50.1	105	45.7		
Yes	81	87.1	59	92.2			107	37.7	66	39.8			188	49.9	125	54.3		

Table 3 - Characteristics associated with loss to follow-up at 5 years: SHIPS Portuguese cohort

	EPT						VPT						Total					
	Follow up at 5 years old						Follow up at 5 years old						Follow up at 5 years old					
	Participants		Non-Participants				Participants		Non-Participants				Participants		Non-Participants			
Characteristics	N	%	N	%	χ^2	*p*	N	%	N	%	χ^2	*p*	N	%	N	%	χ^2	*p*
BPD					7.825	0.005					0.148	1					5.346	0.021
No	69	74.2	32	51.6			267	94	165	99.4			336	89.2	189	82.8		
Yes	24	25.8	30	48.4			17	6	1	0.6			41	10.8	40	17.5		
Steroids for BPD					4.556	0.033					0.159	0.690					5.482	0.019
No	83	89.2	49	76.6			283	99.6	156	94.5			366	97.1	214	93		
Yes	10	10.8	15	23.4			1	0.4	9	5.5			11	2.9	16	7		
IVH					0.339	0.560					0.353	0.552					0.923	0.337
No	84	90.3	54	87.1			277	97.5	160	97			361	95.8	214	94.3		
Yes	9	9.7	8	12.9			7	2.5	5	3			16	4.2	13	5.7		
PVL					0.543	0.461					0.047	1					0.688	0.407
No	86	92.5	57	89.1			278	97.9	161	97.6			364	96.6	218	95.2		
Yes	7	7.5	7	10.9			6	2.1	4	2.4			13	3.4	11	4.8		
Early infection					0.586	0.562					0.910	0.340					0.049	0.824
No	84	90.3	60	93.8			278	97.9	160	96.4			362	96	220	95.7		
Yes	9	9.7	4	6.4			6	2.1	6	3.6			15	4	10	4.3		
Late Infection					5.192	0.023					0.472	0.492					3.908	0.048
No	33	35.5	12	18.8			212	74.6	119	71.7			245	65	131	57		
Yes	60	64.5	52	81.3			72	25.4	47	28.3			132	35	99	43		
ROP					0.098	0.754					4.336	0.057					0.579	0.447
No	40	75.5	52	83.9			59	98.3	144	97.3			348	96.1	200	94.8		
Yes	13	24.5	10	16.1			1	1.7	4	2.7			14	3.9	11	5.2		

Table 3 - Characteristics associated with loss to follow-up at 5 years: SHIPS Portuguese cohort

	EPT						VPT						Total					
	Follow up at 5 years old						Follow up at 5 years old						Follow up at 5 years old					
	Participants		Non-Participants				Participants		Non-Participants				Participants		Non-Participants			
Characteristics	N	%	N	%	χ^2	*p*	N	%	N	%	χ^2	*p*	N	%	N	%	χ^2	*p*
NEC					4.491	0.065					1.230	0.267					0.444	0.505
No	88	94.6	59	95.2			278	97.9	162	97.6			366	97.1	221	96.1		
Yes	5	5.4	3	4.8			6	2.1	4	2.4			11	2.9	9	3.9		
Congenital anomaly					0.061	1					1.054	0.304					1.022	0.312
No	88	94.6	58	93.5			273	96.1	156	94			361	97.6	214	93.9		
Yes	5	5.4	4	6.5			11	3.9	10	6			16	4.2	14	6.1		
Surgical Treatment for PDA					1.842	0.175					0.029	0.864					1.811	0.178
No	85	91.4	54	84.4			283	99.6	156	94			368	97.6	210	91.3		
Yes	8	8.6	10	15.6			1	0.4	10	6			9	2.4	20	8.7		

Developmental outcomes and Health Service use

At 5 years old, EPT were more likely to have vision impairment, manual dexterity difficulty, educational support, ADHD, speech delay, and developmental delay compared to VPT (table 4).

Table 4 - Outcome characteristics of participants at five-year follow-up in the Portuguese EPICE/SHIPS cohort

	EPT		VPT				Total	
Characteristics	N	%	N	%	x^2	p	N	%
Vision impairment					4.027	0.045		
Yes	24	25.8	46	16.4			60	16.1
No	69	74.2	234	83.6			313	83.9
Hearing impairment					2.431	0.119		
Yes	11	11.9	19	6.8			30	8
No	82	88.2	262	93.2			344	92
Cerebral Palsy					2.636	0.148		
Yes	5	5.4	6	2.1			11	3
No	87	94.6	275	97.9			362	97
Manual dexterity difficulty					9.918	0.002		
Yes	23	24.7	32	11.4			45	14.7
No	70	75.3	249	88.6			319	85.3
Difficulty walking					1.332	0.324		
Yes	5	5.4	8	2.8			13	3.5
No	88	94.6	273	97.2			361	96.5
Asthma					0.313	0.576		
Yes	7	7.95	27	10			34	9.2
No	81	92.05	244	90			325	88.1
Epilepsy					0.774	0.408		
Yes	3	3.3	5	1.8			16	4.3
No	85	93.4	269	97.8			331	89.9
ADHD					6.082	0.014		
Yes	8	9.5	8	3.1			16	10.1
No	76	90.5	255	96.9			331	89.9
ASD					0.715	0.597		
Yes	2	2.2	3	1.1			5	1.4
No	85	93.4	273	98.6			358	97.3
Speech delay					5.437	0.020		
Yes	27	29.3	49	17.7			76	20.6
No	64	69.6	221	79.8			285	77.2
Developmental delay					18.180	<0.001		
Yes	19	20.9	16	5.8			35	9.5
No	71	78	258	93.5			329	89.6

Table 4 - Outcome characteristics of participants at five-year follow-up in the Portuguese EPICE/SHIPS cohort

	EPT		VPT				Total	
Characteristics	N	%	N	%	x^2	p	N	%
Educational support					10.697	0.001		
Yes	25	26.9	35	12.5			60	16.1
No	68	73.1	245	87.5			313	83.9

Table 5 - Use of a specific health service in the last 12 months

	EPT		VPT				Total	
Service	N (93)	%	N (284)	%	x^2	p	N (377)	%
Paediatrician	52	63.4	133	57.3	0.927	0.336	185	58.9
Family Doctor	39	50.6	125	54.6	0.359	0.549	164	53.6
Emergency Room	62	74.7	177	69.7	0.736	0.383	239	70.9
Neurologist	9	13.2	12	6.3	3.207	0.073	21	8.1
ENT specialist	42	53.8	96	44	2.221	0.136	138	46.6
Ophthalmologist	51	65.4	124	54.9	2.626	0.105	175	57.6
Language therapist	31	41.3	60	29.7	3.354	0.067	91	32.9
Psychologist	23	31.5	48	24.7	1.243	0.265	71	26.6
Psychiatrist	4	6.1	6	3.3	0.992	0.298	10	4.0
Physiotherapist	11	15.7	16	8.7	2.581	0.108	27	10.7
Pulmonologist	20	27.8	28	14.4	6.323	0.012	48	18.0
Dietician	4	6.1	7	3.8	0.602	0.486	11	4.4
School Nurse	5	7.9	16	8.4	0.012	0.912	10	4.0
Occupational therapist	14	19.7	14	7.5	7.958	0.005	21	8.3
Early intervention	19	27.9	27	14.7	5.857	0.016	28	10.9

ENT ear, nose, throat

Regarding the use of specific health services in the last 12 months (table 5), most children went to emergency room, paediatrician, and ophthalmologist, and family doctor. EPT children were more likely to use specific service - pneumologist, occupational therapist, and early intervention - compared to VPT.

Language, memory and learning outcomes

EPT's performance is more frequently at a borderline or below expected level on Speeded Naming Total Completion Time; Memory for Faces Total Score scaled; and Narrative Memory Recognition compared to VPT. No significant differences were found in any of the remaining subtests (table 6).

Table 6 - NEPSY-II®: Language and Memory and Learning domains' subtest

Classification results	EPT N	EPT %	VPT N	VPT %	χ^2	*p*
Language						
Comprehension of Instruction Total Score scaled					1.283	0.257
Normal or above expected level	56	81.2	195	86.7		
Borderline or below expected level	13	18.8	30	13.3		
Speeded Naming Total Completion Time scaled					4.885	0.027
Normal or above expected level	37	53.6	156	68.1		
Borderline or below expected level	32	46.4	73	31.9		
Speeded Naming Total Correct scaled					1.324	0.250
Normal or above expected level	52	75.4	187	81.7		
Borderline or below expected level	17	24.6	42	18.3		
Speeded Naming Total Self-Corrected Errors scaled					0.248	0.619
Normal or above expected level	55	79.7	176	76.9		
Borderline or below expected level	14	20.3	53	23.1		
Speeded Naming Combined					1.229	0.268
Normal or above expected level	43	62.3	159	69.4		
Borderline or below expected level	26	37.7	70	30.6		
Memory and Learning						
Memory for Faces Total Score scaled					5.787	0.016
Normal or above expected level	58	62.4	213	75.3		
Borderline or below expected level	35	37.6	70	24.7		
Memory for Faces Contrast					0.025	0.875
Normal or above expected level	75	81.5	227	80.8		
Borderline or below expected level	17	18.5	54	19.2		
Memory for Faces Delayed Total Score scaled					1.415	0.234
Normal or above expected level	69	75	227	80.8		
Borderline or below expected level	23	25	54	19.2		
Narrative Memory Free Recall Total Score scaled					0.974	0.341
Normal or above expected level	74	84.1	245	88.1		
Borderline or below expected level	14	15.9	33	11.9		
Narrative Memory Free & Cued Recall Total Score scaled					0.707	0.400
Normal or above expected level	70	79.5	232	83.5		
Borderline or below expected level	18	20.5	46	16.5		
Narrative Memory Recognition Total Score scaled					5.067	0.024
Normal or above expected level	63	72.4	230	83.3		
Borderline or below expected level	24	27.6	46	16.7		
Narrative Memory Contrast					0.948	0.330
Normal or above expected level	76	81,7	229	83		
Borderline or below expected level	11	18,3	47	17		

Table 7 shows the unadjusted logistic regression. EPT have increased odds of having borderline or below expected results in Speeded Naming Total Completion Time scaled, Memory for Faces Total Score scaled, and Narrative Memory Recognition Total Score scaled. Neonatal morbidity increases the odds of having borderline or below expected results in Speeded Naming Total Completion Time scaled and Narrative Memory Recognition Total Score scaled. BPD increased the odds of having borderline or below expected results on Narrative Memory Recognition Total Score scaled. Younger maternal age increased the odd of having a borderline or below expected result in Speeded Naming Total Completion Time scaled. Mother's educational level below tertiary education increased the odds of having a borderline or below expected results in more than half of the subtests: Comprehension of Instruction Total Score scaled, Speeded Naming Total Completion Time scaled; Speeded Naming Combined, Memory for Faces Total Score scaled, Memory for Faces Delayed Total Score scaled, Narrative Memory Free & Cued Recall Total Score scaled and Narrative Memory Contrast.

Table 8 shows the adjusted regression models. The first model was adjusted for neonatal morbidity, mother's age, and mother's educational level, and the second model was adjusted for GA and mother's educational level.

Table 7 - Crude odds ratios for neurodevelopmental outcomes at 5-year-old

Variables	OR (95%CI) *	OR (95%CI) †	OR (95%CI) ω	OR (95%CI) ʁ	OR (95%CI) □	OR (95%CI) ɵ	OR (95%CI) ϕ
Language							
Comprehension of Instruction Total Score scaled	1.509 (0.738 - 3.086)	0.953 (0.313 - 2.897)	1.189 (0.429 - 3.298)	3.5 (0.456- 26.854)	0.918 (0.466 - 1.810)	1.7 (0.832 - 3.474)	4.426 (1.792 - 10.929)
Speeded Naming Total Completion Time scaled	1.848 (1.068 - 3.199)	2.415 (1.101 - 5.299)	1.725 (0.824 - 3.614)	0.970 (0.374 - 2.513)	1.609 (0.984 - 2.632)	0.568 (0.325 - 0.992)	1.726 (1.039 - 2.868)
Speeded Naming Total Correct scaled	1.289 (0.694 - 2.395)	1.335 (0.556 - 3.204)	1.889 (0.871 - 4.099)	1.216 (0.349 - 4.235)	1.549 (0.876 - 2.739)	0.946 (0.497 - 1.8)	1.857 (0.968 - 3.563)
Speeded Naming Total Self-Corrected Errors scaled	0.772 (0.406 - 1.468)	1.118 (0.469 - 2.669)	1.833 (0.868 - 3.874)	4.923 (0.652 - 37.196)	1.094 (0.630 - 1.898)	1.526 (0.863 - 2.7)	1.434 (0.805 - 2.554)
Speeded Naming Combined	1.373 (0.783 - 2.410)	2.051 (0.933 - 4.511)	1.3 (0.607 - 2.782)	0.835 (0.322 - 2.168)	1.139 (0.687 - 1.888)	0.787 (0.450 - 1.376)	1.850 (1.095 - 3.125)
Memory and Learning							
Memory for Faces Total Score scaled	1.836 (1.115 - 3.024)	1.268 (0.612 - 2.628)	1.226 (0.609 - 2.470)	1.426 (0.515 - 3.945)	0.928 (0.579 - 1.487)	0.865 (0.518 - 1.444)	2.083 (1.251 - 3.468)
Memory for Faces Contrast	0.953 (0.521-1.744)	0.841 (0.336-2.105)	1.726 (0.817 - 3.647)	0.509 (0.201 - 1.289)	0.941 (0.547 - 1.618)	1.375 (0.776 - 2.435)	1.243 (0.713 - 2.168)
Memory for Faces Delayed Total Score scaled	1.401 (0.802 - 2.447)	1.323 (0.594 - 2.947)	1.767 (0.853 - 3.661)	0.569 (0.225 - 1.438)	0.691 (0.402 - 1.190)	0.791 (0.438 - 1.427)	1.77 (1.003 - 3.123)
Narrative Memory Free Recall Total Score scaled	1.405 (0.714 - 2.764)	0.625 (0.183 - 2.130)	1.032 (0.382 - 2.790)	1.607 (0.364- 7.088)	0.862 (0.452 - 1.642)	0.866 (0.433 - 1.733)	1.660 (0.804 - 3.282)
Narrative Memory Free & Cued Recall Total Score scaled	1.297 (0.707-2.380)	0.786 (0.292 - 2.116)	1.540 (0.691 - 3.435)	1.463 (0.421 - 5.079)	1.112 (0.638 - 1.936)	0.620 (0.317 - 1215)	2.181 (1.165 - 4.080)
Narrative Memory Recognition Total Score scaled	1.800 (1.026 - 3.156)	2.349 (1.115 - 4.949)	2.593 (1.279 - 5.254)	1.083 (0.357 - 3.292)	1.316 (0.772 - 2.241)	0.562 (0.294 - 1.073)	1.523 (0.848 - 2.735)
Narrative Memory Contrast	0.705 (0.348 - 1.428)	0.669 (0.226 - 1.977)	0.590 (0.201 - 1.732)	2.1 (0.479 - 9.211)	0.811 (0.447 - 1.471)	0.999 (0.532 - 1.876)	2.083 (1.091 - 3.977)

* crude model GA † crude model neonatal morbidity ω crude model for BPD ʁ crude model for ventilatory support

□ crude model for infection after birth ɵcrude model for mother's age ϕcrude model for mother's educational level

Table 8 - Predictive modelling

Factor	OR (95%CI) model 1	p	OR (95%CI) model 2	p
GA	*		1.870 (1.113 - 3.141)	0.018
Neonatal morbidity	2.926 (1.127 - 7.594)	0.027	*	
BPD	*		*	
Mother's age	0.546 (0.3 - 0.995)	0.048	*	
Mother's educational level	2.281 (1.296 - 4.015)	0.004	2.135 (1.276 - 3.573)	0.004

model 1: Speeded Naming Total Completion Time scaled adjusted for neonatal morbidity, mother's age, and mother's educational level.

model 2: Memory for Faces Total Score scaled adjusted model - GA and mother's educational level

Discussion

Discussion

The aim of this study was to determine the risks of having a poor outcome in three specific neurodevelopmental domains in 5-year-old children born EPT or VPT attending to perinatal and maternal characteristics.
Our data indicated that EPT mothers were more likely to have pregnancy complications and the infants were more likely to have neonatal morbidity and respiratory support. In general, EPT had poorer developmental outcomes and used more the health services compared to VPT children.

Our results suggest a protective factor of maternal education for neurodevelopmental outcomes. Lower gestational age was associated with poor memory and learning outcomes, whereas neonatal morbidity was associated with poor language outcomes.

The EPICE/SHIPS Portuguese Cohort

Mothers of EPT were more likely to have prenatal infection and PROM, but not IURG, prepartum haemorrhage, gestational hypertension, pre-eclampsia, eclampsia, or HELLP syndrome. After birth, EPT were more likely to have a 5' Apgar below 7, receive surfactant and stay in mechanical ventilation, BPD, use of steroids for BPD. IVH grade ≥ III, PVL, early infection, late infection, ROP grade ≥3, Surgical treatment for PDA, and congenital anomaly.

Prenatal risks of infection before birth and PROM have significant association with preterm birth in general (5, 13, 83) Our study found that those risks are more associated with EPT than VPT. There is not only one explanation for that increased risk related with preterm birth, but some theories indicate that it may be related with socio-economical inequities, race, migration status or specific phenotypes (5, 13). Multiple pregnancy is a risk factor known in literature (5), but in our cohort multiple pregnancy was not associated with EPT birth, a similar result when compared with the Danish cohort (85). That may be explained since preterm birth has multifactorial risks (5) and it is classified generally as any birth that occurs < 37 weeks of GA and most of preterm children are born between the moderate to the late preterm period, making VPT and EPT still not so frequent events (82, 85), so studies in the preterm subject may be influenced by the higher frequency of moderate and late preterm births, leading to biased associations.

The use of surfactant, mechanical ventilation, BPD, IVH, ROP and treatment of PDA were more frequent in EPT children. Other EPICE/SHIPS cohort also found differences between EPT and VPT (85) regarding surfactant use, mechanical ventilation, BPD and IVH. BPD may relate with GA, since more children EPT and VPT survive after birth, and they are born with immature lungs (86). Nevertheless, there may be an increased difficulty of properly identifying

BPD since surfactant use is a standard procedure, and clinical guidelines associated with early intervention shows that the classical BPD diagnosis is not so easily made (86). Surfactant use and mechanical ventilation use is related with GA (18, 86), being more common the lower the gestational age (18), that relates with after birth complications, especially with respiratory distress syndrome and its consequences (86).

Our work has a different variable considered when compared with other studies related with preterm birth (16, 87), as we tried to analyse differences in the early surgical treatment of PDA in the EPT vs VPT children (8.6% *vs* 0.1%). The lowest GA relates with a delayed closure of the ductus and it increases the need of intervention with coil occlusion during the first year. Our data relates with before hospital discharged approach, which may mean increased gravity in the morbidity.

That additional approach may be interesting since literature claims that up to 70% of EPT and VPT infants have PDA beyond the 72 hours of birth (87) and the non-intervention in proper time for PDA may lead to other complications as pulmonary oedema (87) and mortality (88). Therefore, early intervention before hospital discharge diminish chronical cerebral oxygenation deficit, leading to a better neurodevelopmental outcome at 5 years of age.

Difference between participants and non-participants

In the EPT and in the total participants, lower maternal age was associated with non-participation, like in other European cohorts (82, 85). EPT and total non-participants were more likely to have BPD, use of steroids for BPD, and late infection. Neonatal morbidity was not associated with non-participation in the other European Cohorts (67, 82, 85).

VPT non-participants were more likely to have foreign mothers, which indicates that social, economic, cultural, or language factors are barriers to the participation in research projects (67).

The knowledge on factors associated with non-participation may help improve future recruitment for future specific population follow-ups, as we can develop different strategies to improve the follow up of vulnerable populations.

Developmental outcomes and Health Service use

In the five-year-old follow-up of the cohort, EPT were more likely to have vision impairment, manual dexterity impairment, speech delay, developmental delay, and ADHD diagnose. Those children also had a higher frequency in the need of educational support, attending to occupational therapy, pulmonologist, and early intervention. Those findings are consonant with the other European cohort study at five year old (85), where fine motor difficulties had a

significant association with EPT (85), but EPT children were more likely to go to the paediatrician and psychologist when compared to VPT children (85).

Visual impairment in childhood implies in an increased risk of socioeconomic problems and developmental delay, leading to a major burden to those families and children (89). It is already stablished in literature that ROP, PVL, IVH and VPT are risk factors to visual impairment (90), which compromises the visuospatial cognition ability, and may compromise memory skills (91).

The presence of manual dexterity impairment in our study is not degrees, but only if present/absent, hence this may not reflect the degree of dysfunction in this cohort. Besides, this item is a parent report difficulty, and it should be correlated with other tests as the M-ABC in future studies to verify if there is a positive association (85). Nevertheless, it is important to explore in future studies if the significant association in this area correlates with the positive association with the search of occupational therapy and early intervention for the EPT.

Speech delay is also already cited in previous studies as an impairment that relates with lower GA (52, 53). Although current literature cannot explain all causes and risks associated with this delay (52), there is a relation between preterm birth and an altered brain formation and wiring, which impacts neurodevelopment (53). And different dimensions of adversity (biological, psychosocial, social, infrastructural and monetary) may also impact this neurodevelopmental mark (92).

Regarding developmental delay, it can be divided in specific or global, and it is important to be regularly under surveillance and screened (93). A recent metanalysis mentioned that GA is an important and underestimated factor accounting for developmental delay (94), since EPT infants can have a risk of 32% compared with 8% from VPT (94), and social adversity are the most significant contributors to developmental challenges (93). Normally, red flags in developmental milestones are identified by clinicians, and then the child may be referral for further specific assessments (93) This may explain why in our cohort there was an elevated search for paediatricians in both groups, since they are considered the primary support for families – addressing their needs and concerns - and guideline interventions (93).

As mentioned in a previous meta-analysis (95), ADHD was also more frequent in EPT children in our study, indicating that it relates with a lower GA. Although the specific risk factors associated are not yet fully known, minor neurodevelopmental impairments, mild hearing loss and mild cognitive impairment may be risk factors (96), even after adjusting for familial and socio economical factor (97). This increased risk could be associated with altered brain connections due to preterm birth disruptions associated with other impairments (97), future research should focus in intervene to minimize those neurophysiological impairments through early-intervention protocols.

There is plenty of evidence on the association between low GA and the need for educational support (21), more then with birthweight (77). Besides, birth immaturity increases the use and search of specialized support (77). In other observational cohort study very preterm children receiving educational support at five years old, had enhanced motor outcomes although no cognitive improvement (98). It would be interesting to analyse in further studies if the children in our cohort is having access to educational support and the outcomes associated with health services use.

An interesting, and to our knowledge not previously reported, positive association between GA and the search for pulmonologists, was found in our study, although not in other cohorts (85). This association may relate with the higher BPD incidence in our cohort and that life-long morbidity related with BPD consequences (99) may increase the search for specialists.

Language, memory and learning outcomes

Each subtest in the NEPSY-II® assesses a specific ability (100). Still, an across domains deficit may occur, which implies that for a specific deficit (e.g. language) other related subtests may be altered. The evaluation of each child must be a whole and not only subtest by subtest (100). By linking the data obtained at hospital's discharged and maternal information with neurodevelopmental tests at five years of old, our results suggests a protective factor of higher maternal education for more than half of the subtests domains' results, nevertheless, only a quarter of the results were negatively influenced lower gestational age, that was the most hazardous factor. Besides, our study found that language outcomes are associated with mother's age, mother's educational level and the interaction between GA and neonatal morbidity; and that memory and learning may have specific domains that are associated independently with GA and mother's educational level.

Lower GA is a risk factor for worst neurodevelopmental outcome (101), even if adjusted for socio-economic factors. GA impacts language outcomes in VPT children (24, 102, 103), since a preterm birth may exposed the infant's brain to adverse stimuli, as toxins or stress (104). And that, as previously mentioned, may lead to an altered brain formation and wiring, which impacts neurodevelopment as a whole (53). Only comprehension of instructions was not influenced by the GA in our study. One Finnish study (105) had a similar result when evaluated 5-year-old children born preterm specifically for the speed naming tests, and not the others. A possible explanation may lay in the cultural difference cross countries, and as some language difference may emerge at different ages for different countries (106), which may not alter the results at five years-of-old.

Previous evidence shows that BPD is an important factor in adverse academic performance (21), and could explain up to 78% the variance in VPT. Neonatal morbidity incidence, specially

PVL, also increases an adverse outcome in academic performance (21). Both complications have higher incidence in lower GA (21), that could explain why both factors influenced the results and were significant in our analysis. But it is important to have in mind that preterm birth carries multiple and inter-related risk factors, that combination translates to neurodevelopmental outcomes, as language, and memory and learning (82).

Regarding sociodemographic impact known in literature (52, 53, 104, 107-110), mother's age impacted language development (107), and mother's educational level impacted both memory and learning, and language (52, 53, 108). Mother's education highly influences language, which may be related to the child's exposure to adequate parenting practices, such as storytelling or adequate relation to primary care givers (108), as well as a broader vocabulary exposition and assimilation (109). Furthermore, lower maternal age and education is associated with a higher likelihood that the child can be exposed to adverse and stressful situations (as adverse sociodemographic situations, such as hunger, domestic violence or poverty) that shape brain development, as it may alter neuronal pathways (104, 110).

Our data suggest that neonatal morbidity negatively influences language development as we analyse the model for Speeded Naming Total Completion Time (model 1), and that language is positively influenced by mother's age and educational level. This result suggests that not only a premature brain (105), but also neonatal health problems may impact language development (105); still these results are also influence by parental social characteristics (84, 92, 105). Further studies could enlighten our knowledge regarding developmental trajectories in children born EPT and VPT, namely in terms of a possible catch up with their full-term peers at some point of their development.

In our model 2, the GA negatively influenced Memory for Faces Total Scored after adjustment and higher mother's educational level was a protective factor. Memory and learning are both complexes humans' functions and are impacted not only by morbidities or adverse outcomes at birth factors but by socio-economic characteristics (44, 52, 58). Memory is influenced by GA (61, 111), its' outcomes are also specially impacted by neonatal morbidities (105), a finding that was not reflected in the model. The effect of GA may be due to the adverse outcome at birth, with major risk for oxidative stress and injuries (15), as a neonatal injury could impact the brain structure (105).

Memory for faces/Memory for faces delayed may be a primary sign of primary naming or memory but could also be secondary for social abilities (100). Those primary or secondary impacts may be influenced by GA, since the brain's white and grey matter may be altered, as well as the cortical or subcortical pathway abnormalities (38), but it has no directly relation with brain injuries (112).

Limitations and strengths

There is some limitation regarding this study, namely predictive modelling may only be an idealized simplification of the reality and this approximation may not be robust enough to assume predictions (113). Furthermore, participants and non-participants varied in some few characteristics, which can lead to biased estimates of the prevalence of language, memory, and learning impairment. Additionally, the small sample size for rarer outcomes may increase type-II errors. Although the NEPSY-II is a reliable and internationally recognized neurodevelopmental test it is not adapted for Portuguese population. The USA norms were used, being a minor limitation since these norms were developed in a comparable society. This instrument has subtests to access basic subcomponents of cognitive capacities, and complex ones that occur with the contribution of multiple cognitive domains (75), which could be an advantage.

The SHIPS Portuguese cohort is similar to the other European cohorts (11, 12, 67, 82, 85, 114) in socio-demographic characteristics. Another strength is that the NEPSY-II was used in almost 400 children, and an extensive evaluation was carried out. This is a unique portrait of children born <32 weeks in Portugal since the data is derived from a prospective longitudinal cohort with an almost yearly follow-up, providing insightful and important information about their socio-economic conditions and neurodevelopmental status.

Considerations for future studies and applicability in Public Health

Future studies should focus on follow-up with a full-term population group, and repeat the test batteries to see if those children do a catch up when compared with full term peers, and if those that had intervention in an early age had a better outcome. That is important, because maturation point in distinct skills are different and external influences may emerge at a specific time (84). Furthermore, some cognitive and academic deficits may manifest later in life (84).

To implement a national program that develops predictive modelling to identify children at risk before they present symptoms should be a public health focus, since early screening of vulnerable population may facilitate access to adequate intervention (78).

In order to be successful, it must be provided standardized and adequate tests to prevent, cure and offer continuous and integrated care (85, 115). Besides, a specialized follow up must be available not only after hospital discharge and early years (116), but also during (pre) school years (98).

To improve positive parenting practices is not enough (108). It is fundamental to implement programs that can prevent or reverse adverse neurodevelopmental outcomes (104). Modifiable factors have an important role on those children development and interventions programs should be designed to improve social and environmental factors (116). This may

help those children to have a better neurodevelopmental outcome via tailored interventions and improve their future, mitigating health and social expenses (94).

Conclusion

Conclusion

The long-term consequences of preterm birth lead to a high burden for families and their children, being a public health problem. Our findings suggest that EPT children were more likely to have complications during gestation, neonatal morbidities, and need more support at five years of age with a poorer developmental outcome than VPT children.

Moreover, our results indicate that socio-economic factors have an important contribution to language, learning and memory outcomes in children born EPT and VPT, more than perinatal factors. Specifically, there is a protective factor of maternal education for those neurodevelopmental outcomes. And lower gestational age was associated with poor memory and learning outcomes, whereas neonatal morbidity was associated with poor language outcomes.

Thus, the need to improve modifiable socioeconomical parameters in intervention programs is unquestionable, as well as the need to increase vigilance through evaluation/screening programmes. Otherwise, inequities and economic disadvantages will perpetuate.

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