Title: The association between perinatal and neonatal variables and neuropsychological development in very and extremely low-birth-weight preterm children at the beginning of primary school.

Author details:

Fernandez-Baizan, Cristina[1,2] ORCID: https://orcid.org/0000-0001-6903-0193

Alcántara-Canabal Leticia[1,3] ORCID: https://orcid.org/0000-0002-3813-8860

Solis, Gonzalo[1,4] ORCID: https://orcid.org/0000-0003-0363-831X

Méndez, Marta[1,2] ORCID: https://orcid.org/0000-0003-1718-7492

1 Neuroscience Institute of Principado de Asturias (INEUROPA). Oviedo, Asturias, Spain.

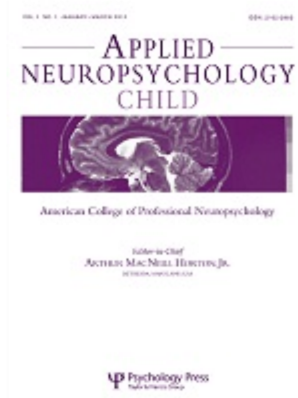
2 Department of Psychology. University of Oviedo. Oviedo, Asturias, Spain.

3 Primary Care Center Paulino Prieto, Sanitary Area IV. Oviedo, Asturias, Spain

4 Pediatric Clinic Area, Neonatology, University Central Hospital of Asturias. Oviedo, Asturias, Spain.

Corresponding author: *Requests for reprints should be addressed to Marta Mendez, Faculty of Psychology, Plaza Feijoo s/n, 33003, Oviedo, Asturias, Spain (e-mail: mendezlmarta@uniovi.es).

Telephone: +34 985104183



The association between perinatal and neonatal variables and neuropsychological development in very and extremely low-birth-weight preterm children at the beginning of primary school.

Journal:	*Applied Neuropsychology: Child*
Manuscript ID	HAPC-2019-0070.R1
Manuscript Type:	Original Article
Keywords:	preterm, neurodevelopment, perinatal risk, neuropsychological profile, memory deficits

Title: The association between perinatal and neonatal variables and neuropsychological development in very and extremely low-birth-weight preterm children at the beginning of primary school.

Abstract

Preterm children with very low birth weight (<1500 g) and extremely low birth weight (<1000 g) have an increased risk of experiencing neuropsychological delays. The purpose of this study is to characterize the neuropsychological profile of very and extremely low birth weight preterm children and discover what maternal conditions, diseases, procedures, and alterations in preterm newborns could be related to their later neuropsychological development. Eighty-nine preterm children (aged from 5 to 7) were assessed on their intelligence quotient (IQ), executive function, memory, and visuospatial memory in a single session, using the RIST and NEPSY-II test. Parents provided sociodemographic data. Preterm children showed lower scores than normative values on impulsivity, visual short-term memory, and spatial relation abilities. Extremely-low-birth weight preterm children also showed less inhibitory control and worse mental rotation skills. Neonatal surgical procedures, late onset sepsis, and periventricular hemorrhages had the greatest impact on neurodevelopment. When one or more of these conditions is present, memory is the most affected neuropsychological function, followed by visuospatial skills, inhibitory control, and IQ. It is important to take into account the presence of maternal conditions, diseases, interventions, and neonatal alterations in preterm newborns in order to determine the risk of neuropsychological delays in later development.

Keywords

Preterm, neurodevelopment, perinatal risk, neuropsychological profile, memory deficits

1. Introduction

Preterm birth, defined as less than 37 completed weeks of gestation, encompasses a wide range of neuropsychological difficulties during childhood (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Delobel-Ayoub et al., 2009), including poorer executive functioning and attentional abilities (Loe, Chatav, & Alduncin, 2015) and some learning difficulties, such as reading, spelling, or mathematical abilities (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Guarini et al., 2019; Hasler & Akshoomoff, 2019). Other cognitive problems have been reported less in preterm children, such as visuospatial abilities (Butcher et al., 2012; van Veen, van Wassenaer-Leemhuis, van Kaam, Oosterlaan, & Aarnoudse-Moens, 2019) and memory (Aanes, Bjuland, Skranes, & Løhaugen, 2015; McCoy, Conrad, Richman, Nopoulos, & Bell, 2013; Omizzolo et al., 2014).

Neuropsychological alterations in this population impact their quality of life (Vieira & Linhares, 2016) and their school achievement (Aarnoudse-Moens et al., 2009; Twilhaar, De Kieviet, Aarnoudse-Moens, Van Elburg, & Oosterlaan, 2017). Therefore, the beginning of the primary school stage is a particularly sensitive period, due to the cognitive difficulties presented by preterm children when faced with a growing academic demand. This lower cognitive achievement can persist even in adulthood (Pyhala et al., 2011), due to a different structural, functional, and metabolic brain status in premature newborns (Duerden, Taylor, & Miller, 2013) that continues along a divergent developmental pathway during childhood and adolescence (Haebich et al., 2019; Ment et al., 2009; Mürner-Lavanchy, Rummel, Steinlin, & Everts, 2018).

Preterm children are usually classified according to their gestational age and birth weight. Neurodevelopmental risk is higher in children with a lower gestational age and lower birth weight (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002). Therefore, very low-birth-weight preterm children (VLBW) (who weigh 1,500 g or less at birth) as well as extremely-low-birth-weight preterm children (ELBW) (who weigh less than 1,000 g at birth) are vulnerable populations, demonstrating increased risk of a lower IQ score and academic and behavioral problems (Fan, Portuguez, & Nunes, 2013; Hutchinson, De Luca, Doyle, Roberts, & Anderson, 2013). They also have a higher risk of attention deficit hyperactivity disorder (ADHD) (Franz et al., 2018). Some of these cognitive and behavioral problems persist until adulthood (Aanes et al., 2015; Van Lieshout et al., 2018).

Apart from this higher vulnerability related to birth weight at the time of a preterm birth and soon after it, diverse diseases, treatments, and conditions can potentially affect the later neurocognitive development of preterm children. Some of these variables are mainly related to the mother's health and delivery or to neonatal diseases and interventions. Therefore, studies have shown that maternal hypertension during pregnancy and antenatal steroids (Spinillo et al., 2009) or the mother's genitourinary infection and chorioamnionitis (Lee et al., 2014) are related to lower cognitive scores at two years of age in preterm children. Gestational age, patent ductus arteriosus, and head circumference are related to IQ scores of seven-year-old premature children (Cooke, 2005). Periventricular hemorrhage is associated with lower IQ in preterm children between four and 12 years old (Roze et al., 2009). Even in adulthood, several variables, such as intraventricular hemorrhage or mechanical ventilation, continue to influence IQ achievement (Breeman, Jaekel, Baumann, Bartmann, & Wolke, 2017). However, the results are still controversial. Thus, preterm children who received early surgery due to post-hemorrhagic ventricular dilatation achieved mean IQ scores at five to eight years of age (Brouwer et al., 2012). Moreover, different cognitive profiles in preterm children at five years old are not explained by medical risk in the neonatal period (Lundequist, Böhm, & Smedler, 2013), and many other variables analyzed in later studies, such as sepsis, premature rupture of membranes, necrotizing enterocolitis, etc., did not reveal significant results (Cooke, 2005; Lee et al., 2014; Spinillo et al., 2009). Thus, we observe that there are still inconclusive results in terms of the subsequent influence of perinatal risk factors. Furthermore, these studies focus their evaluations on IQ, without distinguishing between different neuropsychological capacities.

Other studies have focused on the use of indexes or inventories to measure perinatal risk and relate it to subsequent developmental measures. Thus, it appears that at least part of children's cognitive, motor, and adaptive development (Howe, Sheu, Hsu, Wang, & Wang, 2016), as well as deficits in visuoperceptual abilities (Sanchez-Joya et al., 2017), can be explained by medical complications at birth. However, these studies were carried out before the age of five and do not reveal whether this situation continues in their subsequent development. Likewise, the creation of an index, despite its usefulness for collecting information, makes it difficult to know which of these perinatal and obstetric variables are influencing the child's subsequent development.

The purpose of this study was to define the cognitive and neuropsychological profile of very and extremely low-birth-weight preterm children (less than 1,500 g) and explore the relationship between different perinatal and neonatal variables and the later development of different cognitive functions at the beginning of the school stage. Thus, we can find out which factors present in preterm newborns have more impact on their later cognitive development. This knowledge will make it possible to plan interventions in earlier stages of development in children who present some of these factors, and try to ensure the least possible impact at the onset of primary education, when the cognitive demand level increases markedly and will continue to rise in successive stages of the educational process.

2. Materials and methods

2.1. *Participants*

Data for this study were collected between February 2016 and May 2017. Cases were recruited from a cohort of neonates under 1,500 g and 37 weeks of gestation, born between January 2009 and December 2011, and hospitalized in the neonatal intensive care unit (NICU) of Central University Hospital of Asturias (HUCA), Spain.

Children who met the following criteria were included in this study: a chronological age of between 5 and 7 years old at the time the study was carried out, a gestational age of less than or equal to 37 weeks, and a birth weight of less than or equal to 1,500 g. Exclusion criteria were death, lack of follow-up, birth weight greater than 1,500 g, and diagnosis of malformations and/or congenital syndromes that lead to evident neurological alterations.

The study was conducted in accordance with the Helsinki declaration for investigations in human subjects, and it was approved by the regional ethics committee. Parents gave their written informed consent before the study began.

The target sample size was determined based on the number of eligible P147 children. Sample size should be 107 (Confidence interval 95%, Margin of error 5%), but the final sample with reliable measures of all the variables was composed of 89 preterm children. Figure 1 shows the flow of participant selection. Comparing the responders and the non-responders, no statistically significant differences were found in the neonatal variables analyzed (weight, gestational age, sex, type of delivery, multiple gestation, APGAR test at birth, and diagnosis of pathology at discharge). For the analyses, this sample was split, first according to their gestational age in weeks: 36 to 34 (N=17), 33 to 32 (N=10), 28 to 31 (N=41) and <28 (N=21; Range 28-24 weeks), and second according to their birth weight in grams: from 1,500 to 1,001 g (VLBW) (N=62) and below 1,000 g (ELBW) (N=27).

The children's assessments were completed in a single session lasting 120 minutes with breaks to avoid fatigue. Children were evaluated with neuropsychological function tests. Parents were asked about several sociodemographic data. Perinatal and neonatal variables were obtained retrospectively through electronic medical records

2.2. Cognitive measures

Preterm children complete a neuropsychological test battery, including the assessment of IQ and cognitive functioning on executive functions (inhibitory control), memory (visuospatial and verbal), and visuospatial abilities (mental rotation and directionality and spatial relation).

2.2.1. RIST (Reynolds & Kamphaus, 2003)

The *RIST* (*Reynolds Intellectual Screening Test*) provides an IQ estimation score for children and adults between 3 and 94 years old by employing two tasks: G*uess what* for the verbal score and *Odd-item* for the non-verbal score. On "Guess what", the examiner reads some definitions, and the child has to answer with the appropriate word. On "Odd-item", the child is shown several pictures, and s/he has to point to the different or incongruent one.

2.2.2. NEPSY-II (Korkman, Kirk, & Kemp, 2007)

The NEPSY II battery allows us to obtain a neuropsychological profile in children from 3 to 16 years old. The following subtests were used in the present study: *Inhibition*, *Memory for Designs, Geometric Puzzles,* and *Route finding*.

The *"Inhibition"* subtest was used to measure inhibitory control. On this task, the child is shown several black and white geometric shapes (circle and square) or black and white arrows, and s/he has to say the correct (Denomination) and opposite (Inhibition) shape or direction of the arrow. The present study includes the errors made on both parts of the task, *Denomination errors*, mainly related to impulsivity, and *Inhibition errors*, associated with a lack of inhibitory control.

The *"Memory for Designs"* subtest was employed to assess short- and long-term visual and spatial memory. In the short-term assessment, the child is shown a grid containing from 4 to 10 meaningless picture cards per page. Then, the examiner removes the page, and the child must select the designs s/he has seen from a set of target cards and distractors and place them on a grid in the same location s/he was previously shown. This procedure is repeated 15-25 minutes later for the long-term evaluation. This test measures, in addition to short- and long-term visuospatial memory, whether the content, that is, the correct picture and/or spatial position on the grid, was remembered correctly. Therefore, the following variables were included: *Content short-term* and *Content long-term*, both related to visual memory in the short and long term, and *Spatial short-term* and *Spatial long-term*, associated with short- and long-term spatial memory.

The *"Memory for Names"* subtest was used for short- and long-term verbal memory evaluation. To assess short-term memory, the child is shown 6 to 8 cards containing pictures of children while the examiner reads the name of each child on the cards. Then, the cards are shown again, and the examinee is asked to remember the name of the child on each card. To assess long-term memory, the same test is applied after about 25-35 minutes. On this test, the total number of items remembered immediately (*Short-term*) and 20 minutes after their latest presentation (*Long-term*) was registered.

The *"Geometric Puzzles"* subtest was employed to measure mental rotation abilities. The child is shown pages containing a box with several geometric figures, with other geometric figures on the sides of the box. The child must match two of the figures outside the box with two of the figures inside it. On this test, the total number of correct items was considered.

The *"Route finding"* subtest was employed for directionality, spatial relation, and map interpretation assessment. The child is shown a schematic map indicating how to reach a house. The child is then asked to find the house on a larger map with more roads and houses available. On this test, the total number of correct answers was considered.

2.3. Perinatal and neonatal factors

The perinatal and neonatal variables included were described in Table 1 (Stedman, 2011). Early surgery procedures include ventriculoperitoneal shunt for hydrocephalus and colostomy and ileostomy related to necrotizing enterocolitis. Intraventricular hemorrhage includes grades I (N=17), II (N=5), and III (N=2). Sepsis was diagnosed by a positive blood culture or by elevated infection markers (C-reactive protein -CRP-, interleukin 6 -IL-6- and procalcitonine -PCT-) and clinical infection with a negative blood culture.

[Table 1 near here]

Developmental disorders (such as attention-deficit/hyperactivity disorder, learning disorders, infantile cerebral palsy, behavioral disorders, autism spectrum disorders, and language disorders), APGAR at 1 and 5 minutes, and intrauterine growth status, determined with the Fenton growth chart (Fenton & Kim, 2013), were taken into account in describing the sample.

2.4. Statistical analysis

All analyses were performed using SPSS 18.0 for Windows. Descriptive analyses were conducted for age, gender, gestational age, birth weight, intrauterine growth status, APGAR test, and neurodevelopmental disorders in the sample. Means and standard deviations were calculated for the neuropsychological tests, and these data were compared to the normative population using their respective standard scales. Kruskal-Wallis tests were used to compare the gestational age groups. The Mann-Whitney test with Bonferroni correction was used as a post-hoc test. Correlation analysis and lineal multiple regression analyses were conducted in order to relate the RIST performance with the rest of the measures in the whole sample. Mann-Whitney U tests were employed to compare children on whether the perinatal variable was present or absent in each neuropsychological measure, and to compare the birth-weight groups. A p-value of 0.05 was considered significant.

3. Results

3.1. Group characteristics

Table 2 showed characteristics of the participants.

[Table 2 near here]

3.2. Neuropsychological outcomes and comparisons according to gestational age and birth weight.

Table 3 showed the direct neuropsychological scores obtained from the preterm children, as well as the normative values for their age. Table 4 showed the neuropsychological performance of the birth-weight groups.

[Table 3 near here]

[Table 4 near here]

Thus, preterm children had average values on the RIST, Inhibition Errors, short- and long-term scores on Memory for Names, and spatial short-term and content long-term scores on Memory for Designs and Geometric puzzles. However, they obtained slightly below average values on content short-term from Memory for Designs, Denomination Errors, and Route finding. Regarding weight, children with a birth weight from 1,500 to 1,001 g scored mean values on the RIST, Inhibition Errors, short and long-term Memory for Names, spatial short and long-term Memory for Designs, content long-term Memory for Designs and Geometric puzzles, and they showed values slightly below what was expected on Denomination Errors, Route finding, and content short-term Memory for Designs. Preterm children with a birth weight of less than 1,000 g obtained average scores on the RIST, short- and long-term Memory for Names, spatial short- and long-term Memory for Designs, and content long-term Memory for Designs. Scores below normative values were obtained on Denomination Errors, Inhibition Errors, Route finding, content short-term Memory for Designs, and Geometric Puzzles.

In addition, Kruskal-Wallis comparison revealed significant differences between the gestational age groups (36-34 vs. 33-32 vs. 31-28 vs. <28) on spatial short-term Memory for Designs (H_2=10.666, p=0.014) and spatial long-term Memory for Designs (H_2= 9.443, p=0.024). Post hoc analysis corrected by Bonferroni (considering a result to be significant when p<0.008) showed that these differences were observed between 33-

32 and 31-28 only on spatial short-term Memory for Designs (U=92, p=0.007, r=0.376). Analysing the birth weight groups (1,500-1,001 g vs <1,000 g) with Mann-Whitney's test, significant differences were found in Denomination Errors (U=532.5, p=0.006, r=0.289).

Moreover, the RIST was significantly associated with Inhibition errors (r=-0.276, p=0,009), short- (r=0.355, p=0.001) and long-term (r=0.273, p=0.010) Memory for Names, Geometric puzzles (r=0.293, p=0.006), spatial short-term Memory for Designs (r=0.218, p=0.042), and Route finding (r=0.330, p=0.002). Then, multiple linear regression was performed, revealing that these correlated variables explained 21.6% of the variance in the RIST test ($F_{8,79}$=3.998, p=0.001). However, only spatial short-term Memory for Names (β=0.297, p=0.045) and Route Finding (β=0.299, p=0.014) were significant independent predictors.

Relation between perinatal and neonatal factors and cognitive scores

Perinatal variables, neonatal treatments, neonatal diseases, and neonatal neurological impairments were related to the neuropsychological test outcome. Significant results are shown in Table 5.

[Table 5 near here]

For each neonatal variable, children were divided into two groups, depending on whether the condition was present in their perinatal and neonatal period or not. Therefore, on the one hand, memory difficulties (*Memory for names* and *Memory for designs)* were significantly associated with perinatal variables such as cesarean and maternal hypertension, neonatal treatments such as surgery, inotropic medications, and CPAP, neonatal diseases such as PDA, apnea, and later sepsis, and neurological impairments such as intraventricular hemorrhage and leukomalacia.

On the other hand, worse visuospatial skill scores (*Geometric puzzles* and *Route finding*) were significantly related to the presence of perinatal variables such as corticosteroid and cesarean section, neonatal treatments such as surgery or CPAP, neonatal diseases such as NEC or later sepsis, and neurological impairments such as intraventricular hemorrhage. Worse results on *Inhibition* were significantly associated with neonatal diseases such as NEC, RSD, or late sepsis, as well as intraventricular hemorrhages. Lastly, lower IQ scores (*RIST*) were significantly associated with treatments such as surgery and diseases such as NEC.

Finally, perinatal variables that were considered in the analysis but did not show significant results were multiple delivery, in vitro fecundation, chorioamnionitis, intubation, mechanical ventilation, surfactant, and transfused anemia.

4. Discussion

Although very low-birth-weight preterm children seem to present a neuropsychological profile that is relatively appropriate for their age, those who undergo neonatal interventions or have neonatal diseases and those whose mothers have certain conditions during pregnancy or delivery have a greater risk of showing later cognitive difficulties during development, compared to preterm children without these circumstances.

First, the results showed that all the preterm children obtained a neuropsychological profile with an increased risk of higher impulsivity, lower visual short-term memory, and lower directionality and spatial relation abilities. On other functions, such as general intelligence, verbal and spatial memory, and mental rotation abilities, they achieved normative values. These results partially coincide with previous studies in which these functions seem to be impaired (Butcher et al., 2012; Reveillon, Huppi, &

Barisnikov, 2018; van Veen et al., 2019). These lower neuropsychological achievements could lead VLBW and ELBW preterm children to show more frequent difficulties in slowing down and avoiding unreflective responses or taking turns, learning and later remembering visual material, and interpreting maps or directions. These neuropsychological problems could have social and academic consequences. Thus, impulsivity, which can also be present in comorbid hyperactivity/impulsivity ADHD disorder, frequently diagnosed in preterm children (Franz et al., 2018), can lead to problems in social relations with peers (Andrade & Tannock, 2014). Visual memory and visuospatial skill problems could have a negative impact on school results. This could be especially important in subjects with important numerical, visual, and spatial content (Cornu, Schiltz, Martin, & Hornung, 2018; Crollen & Noel, 2015), where visuospatial abilities are related to arithmetic and mathematical performance even in typically developing children (Foley, Vasilyeva, & Laski, 2017; Li & Geary, 2013, 2017). However, other functions that are frequently altered in premature children, such as IQ, are not impaired in the sample, perhaps because a screening test is used for IQ or global intelligence estimation assessment. Thus, in studies that used brief IQ assessments such as the K-BIT test, even when very preterm children performed significantly worse than term-born, they scored within the normative range (Guarini et al., 2019). Therefore, in future research, more extensive IQ assessment should be carried out. Despite this, we found that the cognitive profile is related to performance on directionality and spatial relations, short- and long-term verbal memory, spatial short-term memory and inhibitory control. However, based on all these functions, their level of general intelligence could be predicted by short-term verbal memory and directionality abilities. Thus, we would expect preterm children who show low verbal memory and low directionality and map interpretation skills to present low IQ scores. This low IQ performance, pointed out by previous studies (Bhutta et al., 2002; Mangin, Horwood, & Woodward, 2017), seems to have its brain correlate in prematurity, with alterations in both the white and deep grey matters (Anderson et al., 2017), as well as in the cortical thickness (Sripada et al., 2018). Moreover, IQ achievements affected academic performance in preterm children, revealing that IQ predicted the level of attention reported by the teachers and the children's mathematics performance (Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, van Goudoever, & Oosterlaan, 2013). However, it should be noted that the predictive power of these variables is not very high, and, therefore, the influence they might have on IQ would be quite limited. Even so, it is important to consider that different cognitive functions may influence IQ performance, which should be taken into account during the neuropsychological assessment of the premature population.

On the one hand, different neuropsychological profiles can be found based on birth weight. Although several similarities were found in both groups, showing that functions such as impulsivity, directionality, and short-term visual memory were below the expected values, ELBW preterm children also presented low values on inhibition and mental rotation skills. In addition, when comparing the raw scores of the two groups, the ELBW group showed greater impulsivity. Thus, children born with extremely low weight tend to present greater difficulties in their visuospatial skills, inhibitory control, and impulsivity, compared to those with a very low birth weight. Therefore, the ELBW population will have greater difficulties in controlling their behavior and stopping automatic responses, as well as in adequately processing visuospatial information. Previous literature pointed out that lower birth weight is associated with lower inhibitory control in extremely low birth weight and extremely preterm children (Ford et al., 2011), as well as lower achievement on visuospatial skills, which could affect later academic performance (Johnson, Wolke, Hennessy, & Marlow, 2011).

On the other hand, short-term spatial memory performance seems to depend on the gestational age of the preterm child. Specifically, 32- or 31-week-old children performed this task better than 31 to 28-week-old children. Previous studies showed that preterm children who were born before 33 weeks of gestation showed lower visuospatial memory scores, which were related to the severity of the white matter and grey matter impairment (Clark & Woodward, 2010). However, it is necessary to consider that there does not seem to be a progression in this capacity; that is, the older gestational age children did not perform better than those in the immediately lower group, and so on. Therefore, we could not consider gestational age to be a determining factor in spatial memory results, although based on the data found, it seems advisable to keep in mind that children with a lower gestational age may present greater difficulties on this function.

Regarding perinatal variables and their relationship with neuropsychological performance, the results showed that the maternal perinatal variables most related to cognitive functioning were the type of delivery, maternal hypertension, and corticosteroids. First, a caesarean delivery was associated with lower short-term verbal memory, directionality, and spatial relation scores. Some studies did not find a relationship between the type of delivery and later developmental outcomes in low gestational age preterm children (Kimura et al., 2017) or very low-birth-weight children (Zhu, Bao, Zhang, Ma, & Wu, 2014), whereas others reported an association with a later diagnosis of autism spectrum disorder (Curran et al., 2015; Gardener, Spiegelman, & Buka, 2011). Therefore, the relationship between the type of delivery and subsequent cognitive development is not very clear. Second, maternal hypertension was related to worse short- and long-term verbal memory. In term-born children, hypertension during pregnancy seems to be associated with social, cognitive, and executive function difficulties (Wade & Jenkins, 2016), as well as a higher risk of ADHD and/or autism spectrum disorder diagnoses (Maher et al., 2018). On the other hand, in mothers with preeclampsia and preterm children, results are varied. Some of them found negative effects, such as a greater association with cerebral palsy (Backes et al., 2011; Spinillo et al., 2009) and higher neurocognitive risk, whereas others showed a protective effect, with better scores on cognitive scales (Backes et al., 2011). Thus, the results of the present study show that maternal hypertension and cognitive difficulties in childhood were not clearly associated. Finally, the use of corticosteroids was associated with lower scores on spatial processing and directionality. Corticosteroids are usually administered to the mother when there is a risk of preterm delivery (Roberts, Brown, Medley, & Dalziel, 2017), and so this treatment has been associated with lower rates of perinatal and neonatal death (Travers et al., 2017). However, it appears that corticosteroid treatment is not related to intellectual impairment (Roberts et al., 2017), and only one study, to our knowledge, reported neurodevelopmental delay (Roberts et al., 2017).

Regarding neonatal treatments, early surgery, continuous positive airway pressure, and inotropic treatment had a great impact on the different cognitive functions. Thus, surgical procedures have been associated with lower IQ, visuospatial and verbal memory, and visuospatial abilities scores. According to previous studies, early surgery in preterm children seems to be related to a greater risk of suffering future sensorineural disability (Hunt et al., 2018). More specifically, surgeries performed in the sample in the present study were due, on the one hand, to hydrocephalus and, on the other, to necrotizing enterocolitis. Hydrocephalus is also related to delays in motor and linguistic development at two years of age (Gilard et al., 2018). However, there seems to be no relationship between an increased risk of disability in childhood and a specific surgical procedure (Hunt et al., 2018), although the invasiveness of the procedure, intubation, and possible complications during the procedure could be potential causes of the worse neuropsychological results in this population. Second, the administration of continuous positive airway pressure was related to worse visuospatial long-term memory and mental rotation abilities. Contrary to the findings, this intervention does not seem to have a negative impact on the subsequent neurological development (Wintermark, Tolsa, Van Melle, Forcada-Guex, & Moessinger, 2007), probably due to a better perfusion of brain tissue in the low-birth-weight newborn (Sadeghnia, Zamani, & Badiei, 2017). These cerebral vascularization problems can also explain neuropsychological results: premature children who received continuous positive airway pressure had a previous respiratory pathology and, therefore, were subjected to irregularities in their brain blood flow and brain oxygen supply, compared to those children who did not have this pathology. Lower regional cerebral tissue oxygen saturation has been found to be associated with worse cognitive performance at 2 to 3 years old in preterm children (Verhagen et al., 2015). Thus, in an adolescent preterm population, those who received a longer period of oxygen in NICU showed worse performance on language evaluation tests (Taylor, Minich, Bangert, Filipek, & Hack, 2004). Therefore, it does not mean that this treatment is related to memory and visuospatial problems, but rather that worse oxygenation and cerebral blood flow prior to treatment explain these results. Finally, the results of the present study revealed that inotropic treatment was associated with lower scores on visuospatial long-term memory. This treatment is related to reduced brain growth (Kidokoro et al., 2014), which could affect later cognitive outcomes.

Late onset sepsis seems to be the neonatal disease that causes greater cognitive dysfunction, followed by necrotizing enterocolitis, respiratory distress syndrome, patent ductus arteriosus, and apnea. First, late onset sepsis was related, in the long term, to worse results on inhibitory control, visuospatial and verbal memory, and visuospatial abilities. Previous literature has related sepsis to other disorders, such as cerebral palsy, and brain alterations, such as white matter abnormalities (Mallard & Wang, 2012), as well as lower performance on IQ, memory, and attention, but not executive function or visuospatial abilities (van der Ree, Tanis, Van Braeckel, Bos, & Roze, 2011), contrary to the results obtained in this study. On the one hand, necrotizing enterocolitis was related to worse IQ achievement, inhibition capacity, and visuospatial abilities, which have previously been related to changes in brain structure (Lee et al., 2014), less brain growth (Kidokoro et al., 2014), and white matter alterations (Rand, Austin, Inder, Bora, & Woodward, 2016), as well as lower IQ scores. (Rand et al., 2016), although other studies did not find a greater risk of cognitive dysfunction in the presence of this disease (Lee et al., 2014; Mitha et al., 2013). On the other hand, patent ductus arteriosus has been associated with lower scores on visuospatial long-term memory, which in previous studies have been related to small brain width (Kidokoro et al., 2014). Finally, the apnea diagnosis was related to worse visuospatial short-term memory, which has been associated with lower cerebral oxygenation (Horne et al., 2017). Thus, the results point out that neonatal infectious diseases could be related to later cognitive impairment, although previous results do not always support this. Therefore, the role of these neonatal diseases in neuropsychological development is still controversial, and more research would be necessary to establish clear conclusions.

Regarding neurological impairments, intraventricular hemorrhages were associated with worse achievement on all the neuropsychological functions, except IQ, whereas periventricular leukomalacia was related to lower scores on short-term verbal memory. This early brain damage in premature children has been previously associated with later neuropsychological problems in childhood (Roze et al., 2009) and adolescence (Nosarti et al., 2011), even in the lowest grades (I and II) (Patra, Wilson-Costello, Taylor, Mercuri-Minich, & Hack, 2006), which could be due to different patterns of brain activation that persist even in early adulthood in preterm children (Kalpakidou et al., 2014). Moreover, of all the neonatal variables considered in this study, the one that seems to be related to a greater number of altered neuropsychological functions is intraventricular haemorrhage. This finding is not surprising: it is to be expected that this early brain damage would cause greater later cognitive impairment than other factors that affect brain development indirectly.

This study has some limitations. First, the neuropsychological data provided were not compared to a control group, but rather to the normative scores provided by the tests. Although the normative values are expected to fit these children, there is a possibility that the neuropsychological profile of very low-birth-weight preterm children would be different if directly compared to children of the same age, geographical area, socioeconomic level, etc. In addition, a more extensive neuropsychological evaluation that assesses executive functions and IQ in greater depth would be appropriate.

Second, due to the unequal size of the groups in the different prenatal risk variables, they are inadequate for multivariate analysis, making it impossible to control the effects of possible influential variables. For example, cases presenting necrotizing enterocolitis, surgery procedure, and periventricular leukomalacia are scarce, and so the results found need to be considered carefully.

In conclusion, a general neuropsychological profile of very low-birth-weight premature children has been found, characterized by increased impulsivity, low visual memory performance, and low directionality, spatial relation, and map-related skills. This same performance has been found in the extremely low-birth-weight preterm children, as well as less inhibitory control and worse mental rotation skills. We have also been able to verify that, in these populations, the IQ achieved is partially determined by verbal memory performance and directionality and spatial relation skills. In addition, some of the factors that could potentially affect the future neuropsychological performance of very low-birth-weight preterm children at the beginning of primary school have been detected, such as surgery as a neonatal treatment, late onset sepsis as a neonatal disease, and intraventricular hemorrhages as a neonatal neurological impairment. The most altered neuropsychological abilities in the presence of these variables are verbal and spatial memory, followed by visuospatial skills, inhibitory control, and IQ. These data can help to prioritize treatments and preventive actions in order to avoid later problems in the development of these children. However, the role of some of these conditions in subsequent neuropsychological performance is not yet clearly defined, and, therefore, more research is needed to determine the exact factors that can impact the cognitive development of premature children.

5. Acknowledgments

Fundación AINDACE, Ayuda a la Investigación del Daño y Enfermedades Cerebrales.

6. References

Aanes, S., Bjuland, K. J., Skranes, J., & Løhaugen, G. C. C. (2015). Memory function and hippocampal volumes in preterm born very-low-birth-weight (VLBW) young adults. *NeuroImage*, *105*, 76–83. https://doi.org/10.1016/j.neuroimage.2014.10.023

Aarnoudse-Moens, C. S. H., Weisglas-Kuperus, N., van Goudoever, J. B., & Oosterlaan, J. (2009). Meta-Analysis of Neurobehavioral Outcomes in Very Preterm and/or Very Low Birth Weight Children. *Pediatrics*, *124*(2), 717–728. https://doi.org/10.1542/peds.2008-2816

Aarnoudse-Moens, Cornelieke Sandrine Hanan, Weisglas-Kuperus, N., Duivenvoorden, H. J., van Goudoever, J. B., & Oosterlaan, J. (2013). Executive Function and IQ Predict Mathematical and Attention Problems in Very Preterm Children. *PLoS ONE*, *8*(2), 1–7. https://doi.org/10.1371/journal.pone.0055994

Anderson, P. J., Treyvaud, K., Neil, J. J., Cheong, J. L. Y., Hunt, R. W., Thompson, D. K., … Inder, T. E. (2017). Associations of newborn brain MRI with long-term neurodevelopmental impairments in very preterm children. *Journal of Pediatrics*, *187*, 58–65. https://doi.org/10.1016/j.physbeh.2017.03.040

Andrade, B. F., & Tannock, R. (2014). Sustained impact of inattention and hyperactivity-impulsivity on peer problems: Mediating roles of prosocial skills and conduct problems in a community sample of children. *Child Psychiatry and Human Development*, *45*(3), 318–328. https://doi.org/10.1007/s10578-013-0402-x

Backes, C. H., Markham, K., Moorehead, P., Cordero, L., Nankervis, C. A., & Giannonne, P. J. (2011). Maternal Preeclampsia and Neonatal Outcomes. *Journal of Pregnancy*, *2011*, 1–7. https://doi.org/10.1155/2011/214365

Bhutta, A. T., Cleves, M. A., Casey, P. H., Cradock, M. M., & Anand, K. J. S. (2002). Cognitive and behavioral outcomes of school-aged children who were born preterm. *Journal of the American Medical Association*, *288*(6), 728–737. https://doi.org/10.1001/jama.288.6.728

Breeman, L. D., Jaekel, J., Baumann, N., Bartmann, P., & Wolke, D. (2017). Neonatal predictors of cognitive ability in adults born very preterm: a prospective cohort study. *Developmental Medicine and Child Neurology*, *59*(5), 477–483. https://doi.org/10.1111/dmcn.13380

Brouwer, A. J., Van Stam, C., Uniken Venema, M., Koopman, C., Groenendaal, F., & De Vries, L. S. (2012). Cognitive and neurological outcome at the age of 5-8 years of preterm infants with post-hemorrhagic ventricular dilatation requiring neurosurgical intervention. *Neonatology*, *101*(3), 210–216. https://doi.org/10.1159/000331797

Butcher, P. R., Bouma, A., Stremmelaar, E. F., Bos, A. F., Smithson, M., & Van Braeckel, K. N. J. A. (2012). Visuospatial perception in children born preterm with no major neurological disorders. *Neuropsychology*, *26*(6), 723–734. https://doi.org/10.1037/a0029298

Clark, C. A. C., & Woodward, L. J. (2010). Neonatal Cerebral Abnormalities and Later Verbal and Visuospatial Working Memory Abilities of Children Born Very Preterm. *Developmental Neuropsychology*, *35*(6), 622–642. https://doi.org/10.1080/87565641.2010.508669

Cooke, R. W. I. (2005). Perinatal and postnatal factors in very preterm infants and sequent cognitive and motor abilities. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, *90*(1), 60–63. https://doi.org/10.1136/adc.2004.059188

Cornu, V., Schiltz, C., Martin, R., & Hornung, C. (2018). Visuo-spatial abilities are key for young children's verbal number skills. *Journal of Experimental Child Psychology*, *166*, 604–620. https://doi.org/10.1016/j.jecp.2017.09.006

Crollen, V., & Noel, M.-P. (2015). Spatial and numerical processing in children with high and low visuospatial abilities. *Journal of Experimental Child Psychology*, *132*, 84–98. https://doi.org/10.1016/j.jecp.2014.12.006

Curran, E. A., O'Neill, S. M., Cryan, J. F., Kenny, L. C., Dinan, T. G., Khashan, A. S., & Kearney, P. M. (2015). Research Review: Birth by caesarean section and development of autism spectrum disorder and attention-deficit/hyperactivity disorder: A systematic review and meta-analysis. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *56*(5), 500–508. https://doi.org/10.1111/jcpp.12351

Delobel-Ayoub, M., Arnaud, C., White-Koning, M., Casper, C., Pierrat, V., Garel, M., … Larroque, B. (2009). Behavioral Problems and Cognitive Performance at 5 Years of Age After Very Preterm Birth: The EPIPAGE Study. *Pediatrics*, *123*(6), 1485–1492. https://doi.org/10.1542/peds.2008-1216

Duerden, E. G., Taylor, M. J., & Miller, S. P. (2013). Brain development in infants born preterm: Looking beyond injury. *Seminars in Pediatric Neurology*, *20*(2), 65–74. https://doi.org/10.1016/j.spen.2013.06.007

Fan, R., Portuguez, M., & Nunes, M. (2013). Cognition, behavior and social competence of preterm low birth weight children at school age. *Clinics*, *68*(7), 915–921. https://doi.org/10.6061/clinics/2013(07)05

Fenton, T. R., & Kim, J. H. (2013). A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatrics*, *13*(1).

https://doi.org/10.1186/1471-2431-13-59

Foley, A. E., Vasilyeva, M., & Laski, E. V. (2017). Children's use of decomposition strategies mediates the visuospatial memory and arithmetic accuracy relation. *The British Journal of Developmental Psychology*, *35*(2), 303–309. https://doi.org/10.1111/bjdp.12166

Ford, R. M., Neulinger, K., O'Callaghan, M., Mohay, H., Gray, P., & Shum, D. (2011). Executive function in 7-9-year-old children born extremely preterm or with extremely low birth weight: Effects of biomedical history, age at assessment, and socioeconomic status. *Archives of Clinical Neuropsychology*, *26*(7), 632–644. https://doi.org/10.1093/arclin/acr061

Franz, A. P., Bolat, G. U., Bolat, H., Matijasevich, A., Santos, I. S., Silveira, R. C., … Moreira-Maia, C. R. (2018). Attention-Deficit/Hyperactivity Disorder and Very Preterm/Very Low Birth Weight: A Meta-analysis. *Pediatrics*, *141*(1), e20171645. https://doi.org/10.1542/peds.2017-1645

Gardener, H., Spiegelman, D., & Buka, S. L. (2011). Perinatal and Neonatal Risk Factors for Autism: A Comprehensive Meta-analysis. *Pediatrics*, *128*(2), 344–355. https://doi.org/10.1542/peds.2010-1036

Gilard, V., Chadie, A., Ferracci, F. X., Brasseur-Daudruy, M., Proust, F., Marret, S., & Curey, S. (2018). Post hemorrhagic hydrocephalus and neurodevelopmental outcomes in a context of neonatal intraventricular hemorrhage: An institutional experience in 122 preterm children. *BMC Pediatrics*, *18*(1), 1–8. https://doi.org/10.1186/s12887-018-1249-x

Guarini, A., Bonifacci, P., Tobia, V., Alessandroni, R., Faldella, G., & Sansavini, A. (2019). The profile of very preterm children on academic achievement. A crosspopulation comparison with children with specific learning disorders. *Research in Developmental Disabilities*, *87*(August 2018), 54–63. https://doi.org/10.1016/j.ridd.2019.02.001

Haebich, K. M., Willmott, C., Scratch, S. E., Pascoe, L., Lee, K. J., Spencer-smith, M. M., … Anderson, P. J. (2019). Neonatal brain abnormalities and brain volumes associated with goal setting outcomes in very preterm 13-year-olds. *Brain Imaging and Behavior*, 1–12.

Hasler, H. M., & Akshoomoff, N. (2019). Mathematics ability and related skills in preschoolers born very preterm. *Child Neuropsychology*, *25*(2), 162–178. https://doi.org/10.1080/09297049.2017.1412413

Horne, R. S. C., Fung, A. C. H., NcNeil, S., Fyfe, K. L., Odoi, A., & Wong, F. Y. (2017). The Longitudinal Effects of Persistent Apnea on Cerebral Oxygenation in Infants Born Preterm. *Journal of Pediatrics*, *182*, 79–84. https://doi.org/10.1016/j.jpeds.2016.11.081

Howe, T. H., Sheu, C. F., Hsu, Y. W., Wang, T. N., & Wang, L. W. (2016). Predicting neurodevelopmental outcomes at preschool age for children with very low birth weight. *Research in Developmental Disabilities*, *48*, 231–241. https://doi.org/10.1016/j.ridd.2015.11.003

Hunt, R. W., Hickey, L. M., Burnett, A. C., Anderson, P. J., Cheong, J. L. Y., & Doyle, L. W. (2018). Early surgery and neurodevelopmental outcomes of children born extremely preterm. *Archives of Disease in Childhood - Fetal and Neonatal Edition*, *103*(3), F227 LP-F232. Retrieved from http://fn.bmj.com/content/103/3/F227.abstract

Hutchinson, E. A., De Luca, C. R., Doyle, L. W., Roberts, G., & Anderson, P. J. (2013).

School-age outcomes of extremely preterm or extremely low birth weight children. *Pediatrics*, *131*(4). https://doi.org/10.1542/peds.2012-2311

Johnson, S., Wolke, D., Hennessy, E., & Marlow, N. (2011). Educational outcomes in extremely preterm children: neuropsychological correlates and predictors of attainment. *Developmental Neuropsychology*, *36*(1), 74–95. https://doi.org/10.1080/87565641.2011.540541

Kalpakidou, A. K., Allin, M. P. G., Walshe, M., Giampietro, V., McGuire, P. K., Rifkin, L., … Nosarti, C. (2014). Functional neuroanatomy of executive function after neonatal brain injury in adults who were born very preterm. *PLoS ONE*, *9*(12), 1–17. https://doi.org/10.1371/journal.pone.0113975

Kidokoro, H., Anderson, P. J., Doyle, L. W., Woodward, L. J., Neil, J. J., & Inder, T. E. (2014). Brain Injury and Altered Brain Growth in Preterm Infants: Predictors and Prognosis. *Pediatrics*, *134*(2), e444–e453. https://doi.org/10.1542/peds.2013-2336

Kimura, K., Reichert, J. F., Olson, A., Pouya, O. R., Wang, X., Moussavi, Z., & Kelly, D. M. (2017). Orientation in Virtual Reality Does Not Fully Measure Up to the Real-World. *Scientific Reports*, *7*(1), 18109. https://doi.org/10.1038/s41598-017-18289-8

Korkman, M., Kirk, U., & Kemp, S. (2007). *NEPSY-II* (Second Edi; H. Assessment, ed.). San Antonio, TX.

Lee, I., Neil, J., Huettner, P. C., Smyser, C. D., Rogers, C. E., Shimony, J. S., … Inder, T. E. (2014). The impact of prenatal and neonatal infection on neurodevelopmental outcomes in very preterm infants. *Journal of Perinatology*, *34*(10), 741–747. https://doi.org/10.1038/jp.2014.79.The

Li, Y., & Geary, D. C. (2013). Developmental Gains in Visuospatial Memory Predict Gains in Mathematics Achievement. *PLoS ONE*, *8*(7). https://doi.org/10.1371/journal.pone.0070160

Li, Y., & Geary, D. C. (2017). Children's visuospatial memory predicts mathematics achievement through early adolescence. *PloS One*, *12*(2), e0172046. https://doi.org/10.1371/journal.pone.0172046

Loe, I. M., Chatav, M., & Alduncin, N. (2015). Complementary assessments of executive function in preterm and full-term preschoolers. *Child Neuropsychology : A Journal on Normal and Abnormal Development in Childhood and Adolescence*, *21*(3), 331–353. https://doi.org/10.1080/09297049.2014.906568

Lundequist, A., Böhm, B., & Smedler, A. C. (2013). Individual neuropsychological profiles at age 51/2 years in children born preterm in relation to medical risk factors. *Child Neuropsychology*, *19*(3), 313–331. https://doi.org/10.1080/09297049.2011.653331

Maher, G. M., O'Keeffe, G. W., Kearney, P. M., Kenny, L. C., Dinan, T. G., Mattsson, M., & Khashan, A. S. (2018). Association of hypertensive disorders of pregnancy with risk of neurodevelopmental disorders in offspring a systematic review and meta-analysis. *JAMA Psychiatry*, *75*(8), 809–819. https://doi.org/10.1001/jamapsychiatry.2018.0854

Mallard, C., & Wang, X. (2012). Infection-induced vulnerability of perinatal brain injury. *Neurology Research International*, *2012*, 1–6. https://doi.org/10.1155/2012/102153

Mangin, K. S., Horwood, L. J., & Woodward, L. J. (2017). Cognitive Development Trajectories of Very Preterm and Typically Developing Children. *Child*

Development, *88*(1), 282–298. https://doi.org/10.1111/cdev.12585

McCoy, T. E., Conrad, A. L., Richman, L. C., Nopoulos, P. C., & Bell, E. F. (2013). Memory processes in learning disability subtypes of children born preterm. *Child Neuropsychology*, *19*(2), 173–189. https://doi.org/10.1080/09297049.2011.648922

Ment, L. R., Kesler, S., Vohr, B., Katz, K. H., Baumgartner, H., Schneider, K. C., … Reiss, A. L. (2009). Longitudinal Brain Volume Changes in Preterm and Term Control Subjects During Late Childhood and Adolescence. *Pediatrics*, *123*(2), 503–511. https://doi.org/10.1542/peds.2008-0025.Longitudinal

Mitha, A., Foix-L'Helias, L., Arnaud, C., Marret, S., Vieux, R., Aujard, Y., … Ancel, P.-Y. (2013). Neonatal Infection and 5-year Neurodevelopmental Outcome of Very Preterm Infants. *Pediatrics*, *132*(2), e372–e380. https://doi.org/10.1542/peds.2012-3979

Mürner-Lavanchy, I., Rummel, C., Steinlin, M., & Everts, R. (2018). Cortical morphometry and cognition in very preterm and term-born children at early school age. *Early Human Development*, *116*(November 2017), 53–63. https://doi.org/10.1016/j.earlhumdev.2017.11.003

Nosarti, C., Walshe, M., Rushe, T. M., Rifkin, L., Wyatt, J., Murray, R. M., & Allin, M. P. (2011). Neonatal Ultrasound Results Following Very Preterm Birth Predict Adolescent Behavioral and Cognitive Outcome. *Developmental Neuropsychology*, *36*(1), 118–135. https://doi.org/10.1080/87565641.2011.540546

Omizzolo, C., Scratch, S. E., Stargatt, R., Kidokoro, H., Thompson, D. K., Lee, K. J., … Anderson, P. J. (2014). Neonatal Brain Abnormalities and Memory and Learning Outcomes at 7 Years in Children Born Very Preterm. *Memory*, *22*(6), 605–615. https://doi.org/10.1080/09658211.2013.809765

Patra, K., Wilson-Costello, D., Taylor, H. G., Mercuri-Minich, N., & Hack, M. (2006). Grades I-II intraventricular hemorrhage in extremely low birth weight infants: Effects on neurodevelopment. *Journal of Pediatrics*, *149*(2), 169–173. https://doi.org/10.1016/j.jpeds.2006.04.002

Pyhala, R., Lahti, J., Heinonen, K., Pesonen, A.-K., Strang-Karlsson, S., Hovi, P., … Raikkonen, K. (2011). Neurocognitive abilities in young adults with very low birth weight. *Neurology*, *77*(23), 2052–2060. https://doi.org/10.1212/WNL.0b013e31823b473e

Rand, K. M., Austin, N. C., Inder, T. E., Bora, S., & Woodward, L. J. (2016). Neonatal Infection and Later Neurodevelopmental Risk in the Very Preterm Infant. *Journal of Pediatrics*, *170*, 97–104. https://doi.org/10.1016/j.jpeds.2015.11.017

Reveillon, M., Huppi, P. S., & Barisnikov, K. (2018). Inhibition difficulties in preterm children: Developmental delay or persistent deficit? *Child Neuropsychology : A Journal on Normal and Abnormal Development in Childhood and Adolescence*, *24*(6), 734–762. https://doi.org/10.1080/09297049.2017.1294665

Reynolds, C. R., & Kamphaus, R. W. (2003). *RIAS (Reynolds Intellectual Assessment Scales) and the RIST (Reynolds Intellectual Screening Test). Professional Manual*. Florida: Psychological Assessment Resources.

Roberts, D., Brown, J., Medley, N., & Dalziel, S. (2017). Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane*. https://doi.org/10.1002/14651858.CD004454.pub3.www.cochranelibrary.com

Roze, E., Van Braeckel, K. N. J. A., van der Veere, C. N., Maathuis, C. G. B., Martijn, A., & Bos, A. F. (2009). Functional outcome at school age of preterm infants with periventricular hemorrhagic infarction. *Pediatrics*, *123*(6), 1493–1500.

Sadeghnia, A., Zamani, M., & Badiei, Z. (2017). A Comparative Study of the Effect of Nasal Intermittent Positive Pressure Ventilation and Nasal Continuous Positive Airway Pressure on the Regional Brain Tissue Oximetry in Premature Newborns Weighing <1500 g. *International Journal of Preventive Medicine*, *8*, 1–5. https://doi.org/10.4103/ijpvm.IJPVM

Sanchez-Joya, M. del M., Sanchez-Labraca, N., Roldan-Tapia, M. D., Moral Rodríguez, T., Ramos Lizana, J., & Roman, P. (2017). Neuropsychological assessment and perinatal risk: A study amongst very premature born 4- and 5-year old children. *Research in Developmental Disabilities*, *69*(March), 116–123. https://doi.org/10.1016/j.ridd.2017.08.008

Spinillo, A., Montanari, L., Gardella, B., Roccio, M., Stronati, M., & Fazzi, E. (2009). Infant sex, obstetric risk factors, and 2-year neurodevelopmental outcome among preterm infants. *Developmental Medicine and Child Neurology*, *51*(7), 518–525. https://doi.org/10.1111/j.1469-8749.2009.03273.x

Sripada, K., Bjuland, K. J., Sølsnes, A. E., Håberg, A. K., Grunewaldt, K. H., Løhaugen, G. C., … Skranes, J. (2018). Trajectories of brain development in school-age children born preterm with very low birth weight. *Scientific Reports*, *8*(1), 1–14. https://doi.org/10.1038/s41598-018-33530-8

Stedman, T. L. (2011). *Stedman's medical dictionary of the health professions and nursing* (Seventh, S). Philadelphia: Lippincot Wiliams&Wilkins.

Taylor, H. G., Minich, N., Bangert, B., Filipek, P. A., & Hack, M. (2004). Long-term neuropsychological outcomes of very low birth weight: Associations with early risks for periventricular brain insults. *Journal of the International Neuropsychological Society*, *10*(7), 987–1004.

https://doi.org/10.1017/S1355617704107078

Travers, C. P., Clark, R. H., Spitzer, A. R., Das, A., Garite, T. J., & Carlo, W. A. (2017). Exposure to any antenatal corticosteroids and outcomes in preterm infants by gestational age: Prospective cohort study. *BMJ (Online)*, *356*. https://doi.org/10.1136/bmj.j1039

Twilhaar, E. S., De Kieviet, J. F., Aarnoudse-Moens, C. S. H., Van Elburg, R. M., & Oosterlaan, J. (2017). Academic performance of children born preterm: A meta-analysis and meta-regression. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, 322–330. https://doi.org/10.1136/archdischild-2017-312916

van der Ree, M., Tanis, J. C., Van Braeckel, K. N. J. A., Bos, A. F., & Roze, E. (2011). Functional impairments at school age of preterm born children with late-onset sepsis. *Early Human Development*, *87*(12), 821–826. https://doi.org/10.1016/j.earlhumdev.2011.06.008

Van Lieshout, R. J., Ferro, M. A., Schmidt, L. A., Boyle, M. H., Saigal, S., Morrison, K. M., & Mathewson, K. J. (2018). Trajectories of psychopathology in extremely low birth weight survivors from early adolescence to adulthood: a 20-year longitudinal study. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *59*(11), 1192–1200. https://doi.org/10.1111/jcpp.12909

van Veen, S., van Wassenaer-Leemhuis, A. G., van Kaam, A. H., Oosterlaan, J., & Aarnoudse-Moens, C. S. H. (2019). Visual perceptive skills account for very preterm children's mathematical difficulties in preschool. *Early Human Development*, *129*(October 2018), 11–15. https://doi.org/10.1016/j.earlhumdev.2018.12.018

Verhagen, E. A., Van Braeckel, K. N. J. A., van der Veere, C. N., Groen, H., Dijk, P.

H., Hulzebos, C. V., & Bos, A. F. (2015). Cerebral oxygenation is associated with neurodevelopmental outcome of preterm children at age 2 to 3 years. *Developmental Medicine and Child Neurology*, *57*(5), 449–455. https://doi.org/10.1111/dmcn.12622

Vieira, M. E. B., & Linhares, M. B. M. (2016). Quality of life of individuals born preterm: a systematic review of assessment approaches. *Quality of Life Research*, *25*(9), 2123–2139. https://doi.org/10.1007/s11136-016-1259-9

Wade, M., & Jenkins, J. M. (2016). Pregnancy hypertension and the risk for neuropsychological difficulties across early development: A brief report. *Child Neuropsychology : A Journal on Normal and Abnormal Development in Childhood and Adolescence*, *22*(2), 247–254. https://doi.org/10.1080/09297049.2014.958070

Wintermark, P., Tolsa, J. F., Van Melle, G., Forcada-Guex, M., & Moessinger, A. C. (2007). Long-term outcome of preterm infants treated with nasal continuous positive airway pressure. *European Journal of Pediatrics*, *166*(5), 473–483. https://doi.org/10.1007/s00431-006-0272-3

Zhu, J. J., Bao, Y. Y., Zhang, G. L., Ma, L. X., & Wu, M. Y. (2014). No relationship between mode of delivery and neonatal mortality and neurodevelopment in very low birth weight infants aged two years. *World Journal of Pediatrics*, *10*(3), 227–231. https://doi.org/10.1007/s12519-014-0497-6

Figure captions:

Figure 1. Participant selection flowchart

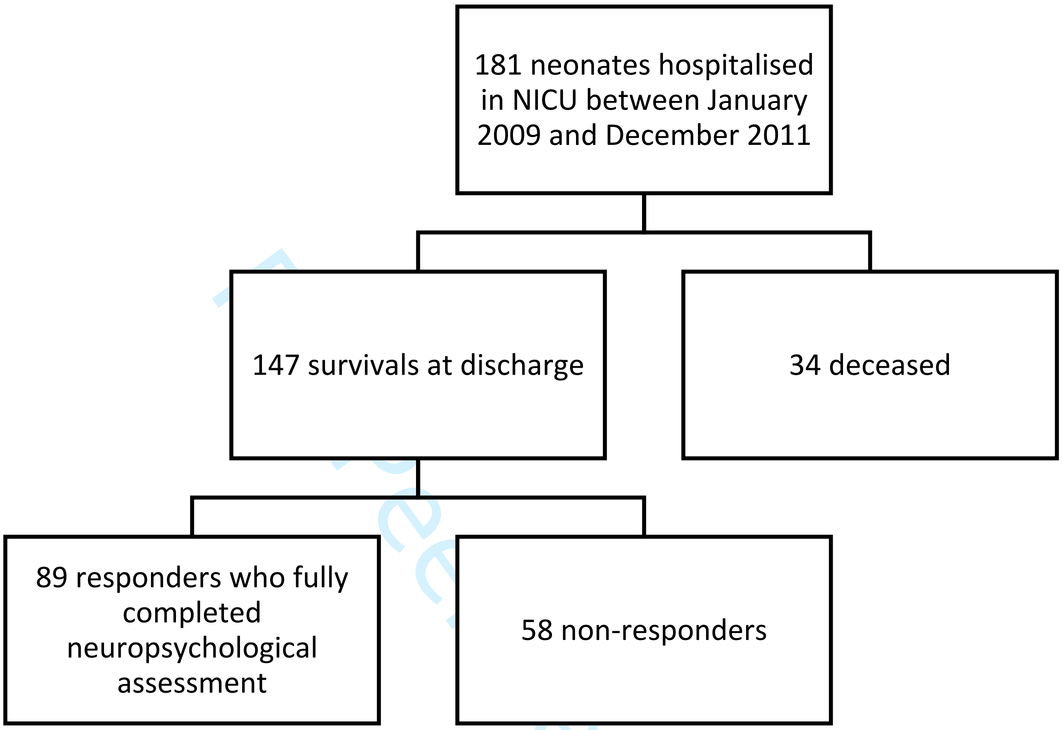


Fig 1. Participant selection flowchart

Table 1. Description of perinatal and neonatal variables of preterm children

Perinatal and maternal variables	Multiple delivery	Procedure of assisting the birth of more than one fetus/newborns and expulsion of their placentas by manual, instrumental, or surgical means
	In vitro fecundation (IVF)	Assisted reproduction treatment of high complexity. It consists of the union of the ovule with a sperm in the laboratory
	Maternal corticosteroids	Maternal drug (with corticosteroids) treatment to mature fetal lungs in case of risk of premature delivery
	Maternal antibiotics	Maternal drug (with antibiotics) treatment to treat possible perinatal infection
	Maternal chorioamnionitis	Acute inflammation of the placental membranes of infectious origin that is accompanied by infection of the amniotic content (fetus, cord and amniotic fluid)
	Maternal arterial hypertension (AHT)	Systolic blood pressure (SBP) greater than 140 mmHg and / or diastolic BP (PAD) greater than 90 mmHg on two or more consecutive occasions and separated by a period of four to six hours
	Type of delivery	Mode and route by which the labor develops (vaginal or caesarean section)
Neonatal treatments in NICU (Neonatal Intensive Care Unit)	Intubation	Act of introducing a tube through the trachea in order to be able to better oxygenate and ventilate a patient
	Continuous positive airway pressure (CPAP)	Non-invasive ventilation mode consisting of applying positive nasopharyngeal pressure at the end of the airflow from the lungs
	Mechanical ventilation	System to oxygenate and ventilate the airways artificially using a mechanical device for this purpose
	Surfactant	Natural substance that prevents the collapse of the lungs. In the premature neonate, there is a surfactant deficit, and so it may be necessary to administer it tracheally
	Inotropic	Pharmacological drugs whose effect is to improve the cardiocirculatory system (dopamine, dobutamine, adrenaline, milrinone, ...)
	Surgery	Branch of medicine concerned with diseases and conditions requiring or amenable to operative or manual procedures
Neonatal diseases	Necrotizing enterocolitis (NEC)	Severe abdominal neonatal disease consisting of intestinal inflammation, which can lead to perforation and peritonitis.
	Respiratory	Neonatal respiratory disease consisting of difficulty in

	distress syndrome (RSD)	oxygenation and ventilation of the lungs of the newborn
	Patent ductus arteriosus (PDA),	Absence of the neonatal physiological closure of the duct that joins the aorta and pulmonary artery in the fetus
	Apnea	Isolated episodes of absence of breathing, which appear frequently in premature babies.
	Transfused anemia	Decrease in the amount of hemoglobin in the blood that needs treatment with administration of hematies external to the patient
	Early and late onset sepsis	Episodes of systemic infection of the patient. Early sepsis occurs in the first days of life and are due to infections of maternal origin. Late sepsis occurs after one week of life and are due to infections of hospital origin
Neonatal neurological impairment	Intraventricular hemorrhage	Hemorrhage that occurs in the patient's brain, inside the brain ventricles
	Periventricular leukomalacia	Injury of the cerebral white matter due to episodes of hypoxia or local ischemia. It is frequently associated with medium- and long-term motor problems

Table 2. Preterm children description

		Mean (SD)
Birth weight (grams)		1156.71 (240.92)
Gestational age (weeks)		30.12 (2.83)
APGAR test (1 minute)		7 (2.19)
APGAR test (5 minutes)		8.6 (1.49)
Intrauterine growth status		N (%)
	Small for gestational age (< Percentile 10)	26 (29.20%)
	Appropriate for gestational age	59 (66.30%)
	Large for gestational age (> Percentile 90)	4 (4.50%)
Sex		N (%)
	Boys	49 (55.05%)
	Girls	40 (44.94%)
Age		N (%)
	5 years	30 (33.70%)
	6 years	29 (32.58%)

	7 years		30 (33.70%)
Neurodevelopmental disorders			N (%)
	Any developmental disorder		19 (21.30%)
		ADHD	3 (3.40%)
		Learning disorder	3 (3.40%)
		Cerebral palsy	5 (5.60%)
		Behavioral problems	3 (3.40%)
		Autistic spectrum disorder	3 (3.40%)
		Language disorder	12 (13.50%)

ADHD: attention-deficit/hyperactivity disorder.

Table 3. Neuropsychological characterization of very low-birth weight preterm

	Mean raw scores (SD)	Percentile Median
RIST	90.51 (17.02)	28
Inhibition – Denomination Errors	5.10 (5.31)	11-25 (Range)*
Inhibition – Inhibition Errors	14.65 (14.43)	26-50 (Range)*
Route finding	3.09 (1.05)	11-25 (Range)*
		Scalar Score Median
MFN – Short term	10.16 (4.45)	9
MFN – Long term	3.73 (1.98)	10
MFD – Spatial Short term	15.49 (5.94)	8
MFD – Spatial Long term	4.80 (1.96)	8
MFD – Content Short term	33.36 (8.88)	7
MFD – Content Long term	9.94 (3.24)	8
Geometric puzzles	18.27 (5.78)	9

MFN: Memory for Names; MFD: Memory for Designs

* For subtest Inhibition and Route finding from NEPSY-II, the normative scores provided are divided into ranges.

Table 4. Neuropsychological outcomes of preterm children according to birth weight

	1500-1001 grams of birth weight (N=62)		≤1000 grams of birth weight (N=27)	
	Mean raw scores (SD)	Percentile Median	Mean raw scores (SD)	Percentile Median
RIST	90.34 (16.62)	28	88.63 (18.08)	28
Inhibition – Denomination Errors	4.13 (4.24)	11-25 (Range)*	7.33 (6.77)	11-25 (Range)*
Inhibition – Inhibition Errors	13.19 (12.50)	26-50 (Range)*	18 (17.92)	11-25 (Range)*
Route finding	2.98 (2.62)	11-25 (Range)*	2.85 (2.44)	11-25 (Range)*
		Scalar Score Median		Scalar Score Median
MFN – Short term	9.90 (4.54)	9	10.74 (4.27)	10
MFN – Long term	3.73 (2.07)	10	3.74 (1.78)	10
MFD – Spatial Short term	15.56 (6.01)	8	15.33 (5.91)	8
MFD – Spatial Long term	4.87 (2.03)	8	4.63 (1.82)	8

MFD – Content Short term	33.73 (9.19)	7	32.52 (8.22)	7
MFD – Content Long term	10.16 (3.37)	8	9.44 (2.90)	8
Geometric puzzles	18.82 (5.91)	9	17.04 (5.38)	7

Table 5. Significant neuropsychological results in perinatal variables, neonatal treatments, diseases, and neurological impairments in very and extremely low-birth-weight preterm children at age 5-7.

	Test	Condition present Mean raw scores (SD)	Condition absent Mean raw scores (SD)	P value
Perinatal and maternal variables				
Vaginal delivery (28/89)¶	MFN – Short term	11.82 (4.64)	9.39 (4.18)	0.016
	Route finding	3.89 (3.03)	2.51 (2.19)	0.036
Maternal AHT (14/89)¶	MFN – Short term	7.93 (3.83)	10.43 (4.37)	0.049
	MFN – Long term	2.57 (1.60)	3.94 (1.97)	0.016
Corticosteroids (62/89)¶	Route finding	2.56 (2.28)	3.52 (2.90)	0.046
Neonatal treatments in NICU				
Surgery intervention (6/89)¶	RIST	76.67 (15.42)	91.52 (16.77)	0.045
	MFN – Long term	1.83 (2.48)	3.87 (1.88)	0.015
	MFD – Spatial Short term	10.17 (2.92)	15.88 (5.93)	0.010
	MFD – Spatial Long term	3.33 (1.03)	4.90 (1.97)	0.003

	MFD – Content Long term	7.83 (0.98)	10.10 (3.29)	0.001
	Geometric puzzles	13.83 (3.76)	18.60 (5.78)	0.017
	Route finding	0.83 (0.98)	3.10 (2.56)	0.001
Inotropic treatment (10/89)¶	MFD – Content Long term	8.20 (1.68)	10.16 (3.33)	0.007
CPAP (26/89)¶	MFD – Content Long term	9.61 (2.97)	11.35 (3.99)	0.046
	Geometric puzzles	17.64 (5.67)	21.13 (5.58)	0.028
Neonatal diseases				
NEC (4/89)¶	RIST	71.0 (4.690)	91.44 (16.85)	0.018
	Inhibition – Inhibition Errors	29.25 (12.73)	13.96 (14.20)	0.038
	Route finding	1.0 (0.816)	3.04 (2.57)	0.005
RSD (44/89)¶	Inhibition – Denomination Errors	6.23 (6.26)	4.0 (3.94)	0.047
PDA (21/89)¶	MFD – Spatial Long term	4.05 (1.93)	5.03 (1.93)	0.045
Apnea (16/89)¶	MFD – Content Short term	27.19 (5.35)	34.71 (8.95)	0.001
Sepsis (24/89)¶	Inhibition – Inhibition Errors	24.61 (19.11)	11.18 (10.54)	0.003
	MFN – Long term	2.87 (1.79)	4.03 (1.96)	0.015
	MFD – Spatial Short term	12.70 (3.89)	16.47 (6.24)	0.001
	MFD – Content Short term	30.26 (6.21)	34.44 (9.44)	0.020
	MFD – Content Long term	8.22 (2.17)	10.55 (3.34)	0.001
	Geometric puzzles	15.09 (3.84)	19.33 (5.95)	0.001
	Route finding	1.74 (1.78)	5.18 (2.00)	0.002

Neonatal neurological impairments				
IVH (24/89)[¶]	Inhibition – Denomination Errors	7.96 (7.80)	4.05 (3.57)	0.026
	Inhibition – Inhibition Errors	22.17 (17-54)	11.88 (12.11)	0.013
	MFN – Short term	8.08 (3.97)	10.92 (4.40)	0.007
	MFN – Long term	3.04 (1.73)	3.98 (2.01)	0.046
	MFD – Spatial Short term	11.58 (4.70)	16.94 (5.73)	0.001
	MFD – Content Short term	28.88 (6.34)	35.02 (9.14)	0.030
	MFD – Spatial Long term	7.83 (1.73)	10.72 (3.32)	0.001
	MFD – Content Long term	3.58 (1.38)	5.25 (1.96)	0.001
	Geometric puzzles	14.17 (4.75)	19.81 (5.39)	0.001
	Route finding	1.75 (1.32)	3.38 (2.76)	0.001
PVL (3/89)[¶]	MFN – Short term	7.00 (5.29)	10.48 (4.38)	0.044

NICU: Neonatal Intensive Care Unit; MFN: Memory for Names; MFD: Memory for Designs; AHT: Arterial Hypertension; CPAP: Continuous Positive Airway Pressure; NEC: Necrotizing Enterocolitis; RSD: Respiratory distress syndrome; PDA: Patent Arteriosus Ductus; IVH: Intraventricular Hemorrhage; PVL: Periventricular *Leukomalacia.* [¶] Number of children who present the condition / Total sample