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Worse global intellectual and worse neuropsychological functioning in preterm-born children at preschool age: a meta-analysis

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ABSTRACT

Aim: Preterm births (<32 weeks of gestational age) are associated with cognitive problems that are difficult to diagnose in infancy but potentially detectable at preschool age. This review aimed to evaluate the extent to which total intelligence quotient (IQ) and neuropsychological functions at ages three to five years differ between children born at <32 weeks gestational age or <1,500 g birth weight and children born at term. The secondary aim was to determine if cognitive performance differs between extremely preterm (EPT)/extremely low birth weight (ELBW) children and very preterm (VPT) or very low birth weight (VLBW) children.

Methods:
PubMed and PsycINFO databases were searched for cohort studies comparing IQ and neuropsychological functions in term-born and preterm-born children born after 1994.

Results: At ages three to five years, preterm-born children, compared with term-born ones, had worse IQ mean score (d = -0.77 [95% confidence interval -0.88 to -0.66]), attention, memory, visuomotor integration skill, and executive functions. No differences were found between VPT/VLBW and EPT/ELBW children.

Conclusion: Preterm-born children showed poorer IQ and neuropsychological functions compared with term-born subjects already at preschool age. The extent of differences is similar to that detected at a later age.

Key words: extremely preterm children, intelligence quotients (IQ), neuropsychological deficits, preschool age, very preterm children

Key notes

- At three to five years of age, the assessment of IQ and neuropsychological functions becomes feasible, but studies on preterm-born preschoolers have provided inconsistent results.
- IQ difference of 0.77 standard deviation, corresponding to 11.5 IQ points, as well as neuropsychological differences, were similar to those detected at later ages.
- Children born very preterm had three times a higher risk of developing IQ vulnerability compared with term-born controls.

INTRODUCTION

The preterm birth rate, defined as all births lower than 37 weeks of gestational age (GA), is increasing in many countries, with more than one in 10 babies being born preterm (1). With the recent improvements in pre and perinatal care, an increasing number of preterm infants survive to the neonatal period. Although severe sequelae has been reduced (2), a continuing concern regarding the outcome for children born at less than 32 weeks of GA persists in view of the high rate of cognitive, learning, and behavioural difficulties noticeable at school age (3,4). During school years, about 30% of very preterm (VPT) children, defined as born at less than 33 weeks GA (3), and 40% to 60% of extremely preterm (EPT) children, defined as born at less than 26 weeks GA (4), experience academic difficulties requiring individualised learning support. Many children who had been born preterm suffer from wide-ranging cognitive difficulties upon entering school. In most severe cases, all cognitive domains are affected, leading to an intelligence quotient (IQ) deficit. More frequently, preterm-born children develop high prevalence/low severity cognitive difficulties (4) that may be related to specific neuropsychological impairments even in the presence of an average IQ. These milder impairments should be worth considering because low severity does not mean minimal impact on child development, school performance, and daily quality of life.

The high number of preterm children with learning and behavioural problems at the primary school level raises the specific issue of whether an early diagnosis is possible. It is important to establish whether the cognitive difficulties, underpinning learning problems, may be detected and possibly treated before school entry. However, early diagnosis of cognitive difficulties is a challenge for clinicians. In infancy (0 to 2 years), neurodevelopmental assessment is highly specific but poorly sensitive in predicting later cognitive problems (5), in particular in children with milder impairment. A recent meta-analysis (6) suggested that almost half of the children with cognitive difficulties at school age have normal developmental quotient from one to three years. Preschool age, from three to five years of age, is a crucial period, as IQ and most neuropsychological functions can be tested for the first time; however, these years are commonly under-examined, and neuropsychological assessment before school entry is not usual among this high-risk population. This gap is linked to multiple factors: preschool neuropsychological assessment is time consuming, there is a lack of international standardised assessment tools, and developmental neuropsychology is a relatively new profession in many countries. Thus, the majority of studies have analysed cognitive outcomes in infancy, when many neonatal follow-up programmes are still active, or at school age, when milder cognitive impairments become apparent.

Studies at preschool age are scarce, and findings on cognitive difficulties are not homogeneous. A systematic review of the existing literature on preschool neuropsychological outcome can therefore be helpful to shed light on the nature and extent of neuropsychological impairments between three and five years of age. The main aim of this systematic review is to evaluate the extent to which global intellectual functioning, in terms of total IQ score, and neuropsychological functions, such as attention, executive functions, memory, visual perceptual, and visuomotor integration skills, differ between preschool children born at term and those born at less than 32 weeks GA and/or at less than 1,500 g birth weight (BW). The secondary aim is to compare EPT children (≤ 27 weeks GA) and extremely low birth weight (ELBW; <1,000 g BW) to children born VPT (28 to < 32 weeks GA) and very low birth weight (VLBW; 1,000 to <1,500 g BW).

METHODS

Search strategy

The guidelines set forth in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement were followed (7). PubMed and PsycINFO for only English-language articles published between January 2000 and December 2017 were searched. The last search was carried out in June 2018. The following search terms, combined with Boolean operators, were used: (preterm birth or premature or low BW) and (cognitive or neurocognitive or neuropsychological or neurodevelopmental or executive functions or attention or working memory or visual perception or visuospatial or visual-motor) and (preschool* or preschool age). The reference lists of the included studies were manually searched to identify relevant studies.

Study selection

Two authors (EA, FF) independently screened titles and abstracts to select articles that the following criteria: first, studies comparing IQ and neuropsychological functions, such as attention, executive functions, memory, visual perceptual, and visuomotor integration skills, between preterm-born children and those born at term; second, studies considering children born after 1994, as this date characterised a period of relevant improvements in neonatal intensive care; third, studies in which the cognitive assessment was performed at between three to five years of age, both chronological and corrected; fourth, studies in which IQ and neuropsychological functions were assessed by tests commonly used in clinical practice; and finally, studies with total sample sizes of ≥ 20 children. When multiple publications of the same sample of patients were found on a specific outcome, we decided to consider the article with the largest sample size and with the most relevant information. However, as the present research focused on multiple neuropsychological functions, we also included studies from the same cohort reporting different neuropsychological outcomes. Data from the same cohort were not pooled in the meta-analysis. Suitable for inclusion were 13 studies, based on eight different cohorts. The study selection process is displayed in Figure 1. The characteristics of the included studies are reported in Table 1.

Quality assessment

The methodological quality of the studies was appraised by two authors (EA, RD), who assessed three domains: cohort selection, cohort comparability, and outcomes. The criteria used to assess these are shown in Figure 2. Assessment was based on the Newcastle-Ottawa Scale (21). Each domain was scored from one to seven, with seven indicating highest' methodological quality.

Statistical analysis

For each study, the estimate of the measure of association between type of birth (preterm versus term) and IQ and neuropsychological functions were collected. For continuous data, the results were reported as standardised mean difference, whereas for binary data, the risk ratio (RR) was used. The differences expressed in terms of effect size were considered small if they were <0.30, medium if between 0.30 and 0.50, and large if >0.50. These results were then combined using the random effect model. The inverse of variance was used to estimate the weight associated to each study result. These methods were also used in subgroup analyses, in which EPT/ELBW and VPT/VLBW children were compared. The results were graphically presented using forest plots. The presence of publication bias was assessed using the funnel plot.

Outcome measures

Global intellectual functioning

Global intellectual functioning summarises the child's abilities across several cognitive functions and is usually assessed using cognitive assessment providing total IQ score. On the basis of the inclusion criteria, studies using the following tests were included: Wechsler Preschool and Primary Scale of Intelligence Revised (22), Wechsler Preschool and Primary Scale of Intelligence Third Edition (23); Woodcock Johnson Tests of Achievement (24); Differential ability scale-second edition (DAS-2) (25); Kaufman Survey of Early Academic and Language Skills (26). All of them have similar normative scales with mean scores equal to 100 and standard deviation of 15.

Attention

Attention is a complex function that is composed of four main separable sub-components. First, selective visual attention refers to the ability to focus on a target by ignoring distracters. Second, divided attention refers to the ability to respond simultaneously to concurrent stimuli. Third, sustained attention or vigilance refers to the ability to maintain attention over time. Fourth, executive attention refers to the ability to manipulate and recall information. Selective visual attention was the component most investigated and the only one for which meta-analysis was feasible. Studies using the following tests were included: Developmental Neuropsychological Assessment Second Edition (NEPSY-II)/Visual Search (27), Bell test (28), and Visual Search Task of Welsh (29). Children undergoing visual search tasks were asked to search quickly for a target among distractor features. Assessment was based on the number of correct answers.

Memory

Memory refers to the abilities of encoding, storage, and retrieval of information from the past and is composed of various components. For this review, declarative memory, which is divided into long-term or semantic and short-term or episodic memory, was considered. Short-term verbal memory was the only domain for which meta-analysis was possible. Studies using the following tests were included: Digit Span Test (29), DAS-2/digit forward (25), Working Memory Test Battery for Children/digit forward (30), and Comprehensive Test of Phonological Processing/memory for digits (31). Digit repeat tasks required children to repeat forward sequences of increasing number spans. Assessment was based on the number of digits recalled.

Visual perceptual skill

Visual perceptual skill refers to the ability for processing and assigning meaning to visual information. It allows one to recognise a specific shape among a group of confounders, understand directional concepts, recognize an object when its orientation or shape is changed, and perceive and remember a sequence of element. According to the inclusion criteria, no studies focused on this skill were found.

Visuomotor integration skill

Visuomotor integration refers to a broad group of skills sharing the ability to use visual information as guidance for motor behaviour. It is composed of various sub-components, such as the manual dexterity that refers to the ability to grasp and manipulate objects. Graphomotor ability, or the ability to write by hand or copy geometric figures, and visual-constructional ability, or the ability to reproduce two-dimensional constructions, are other examples. Graphomotor ability was the only sub-component for which meta-analysis was feasible. The following paper-pencil tasks were considered: VMI Beery-Buktenica Developmental Test of Visual Motor Integration (32) and NEPSY II/design copy subtest (27). These tasks required children to copy a series of geometric figures of increasing complexity. Assessment was based on the number of geometric figures that were correctly copied.

Executive functions

Executive functions are high-order and inter-related cognitive processes and refer to the ability for suppressing inappropriate behaviour, planning and solving complex tasks, and remembering and manipulating different information sources simultaneously. In accordance with the theoretical models developed by Diamond (33), we considered the following three sub-components: inhibition (i.e. capacity to cope with interfering distractors), working memory (i.e. ability to simultaneously hold in mind multiple verbal or spatial information types and manipulate them), and cognitive flexibility (i.e. ability to change one's perspective and switch fluently across different rules and tasks). Owing to the high heterogeneity among the tests used, meta-analysis was feasible only for parents' questionnaire scores. The questionnaire considered was the Behaviour Rating Inventory of Executive Function-Preschool Version (34). A global executive composite index was obtained by summing up the score obtained in each of the following clinical sub-scales: inhibit, shift, emotional control, working memory, and plan/organise. High global executive composite values suggested difficulties in executive functions. A qualitative analysis of performance-based scores was carried out. The description of tests and tasks used is reported in Table 2 (supplementary online material).

RESULTS

Results of the meta-analysis concerning the main aim of this paper are summarised in Table 3.

Methodological quality assessment

The assessment showed relevant study limitations in terms of representativeness of term-born children and outcome evaluation. Only two studies reported enrolling term and preterm-born children from the same cohort with a recruitment rate more than 80%. Moreover, outcome assessment was blinded in only two studies. Quality assessment is reported in Table 4.

Global intellectual functioning

Seven studies considered total IQ score (8,9,11,13,14,17,19). The meta-analysis showed that preterm-born children had a lower average IQ score compared with term-born ones, with a large effect size (*d* = -0.77 [95% confidence interval {CI} -0.88 to -0.66]). No statistically significant difference was observed in the EPT/ELBW and VPT/VLBW subgroups (I-squared = 0%, p = 0.986) (Fig. 3 supplementary online material). Six studies (8,10,11,14,17,19) also measured IQ vulnerability, defined as an IQ score <1 SD from the standardized mean or <10^{th} centile. Meta-analysis of risk ratio showed that the risk of IQ vulnerability was three times higher in preterm children, risk ratio: 3.61 (95% CI 2.58–5.06). No statistically significant difference was found between EPT/ELBW and VPT/VLBW (I-squared = 4.0%, p = 0.391) (Fig. 4 supplementary online material).

Attention

Selective visual attention was investigated by three studies (8,18,20), and all of them considered only VPT/VLBW children. The meta-analysis revealed that VPT/VLBW children had significantly lower selective visual attention scores compared with term-born children, as indicated by the medium effect sizes (*d* = -0.36 [95% CI -0.53 to -0.19]) (Fig. 5 supplementary online material).

Memory

Four studies examined short-term verbal memory in EPT/ELBW (15,19) and VPT/VLBW (11,20) children. Overall, preterm-born children had significantly lower memory scores compared with term-born ones, as indicated by the medium to large effect sizes (*d* = -0.49 [95% CI -0.75 to -0.22]). The results showed heterogeneity (I-squared = 63.8%, p = 0.041) (Fig. 6 supplementary online material).

Visuomotor integration skill

Five studies were included (8,11,14,19,20). Graphomotor ability was significantly poorer in EPT/ELBW (14,19) and VPT/VLBW (8,11,20) children compared with term-born ones, as indicated by the large effect size (*d* = -0.57 [95% CI -0.72 to -0.43]). No statistically significant heterogeneity was found among the studies (I-squared = 14.9%, p = 0.320) (Fig. 7 supplementary online material).

Executive functions

A qualitative synthesis of inhibition, working memory, and cognitive flexibility was carried out (Table 5). Differences between preterm- and term-born children reached significance, with effect size varying from medium to large across almost all of the tasks. Regarding inhibition, the results suggested that EPT/ELBW and VPT/VLBW preterm children displayed more difficulties compared with term ones in tasks requiring ability to inhibit a) incorrect prevalent responses in favour to correct but non-prevalent ones (i.e. Stroop tasks) (8,13,15) and b) actions in favour to not acting at all (i.e. go/no-go tasks) (9,15,18,19). Verbal and spatial working memory were investigated in three (8,9,11) and two (15,19) studies, respectively. For verbal working memory, the results suggest that VPT/VLBW children displayed more difficulties compared with term ones in storing and manipulating verbal information. Meanwhile, no data on EPT/ELBW were available. For spatial working memory, EPT/ELBW children made more errors and gave less correct responses compared with term-born ones. Similarly, no data on VPT/VLBW were available. Five studies (14,16,18-20) addressing cognitive flexibility reported that all preterm-born children showed more difficulties in shifting across different rules or tasks compared with term-born ones. Meta-analyses based on parents' questionnaires were reported in three studies. Two of them enrolled VPT (11,17) and one, ELBW children (14). Problems in executive functions, in term of global executive composite score, were significantly higher in preterm-born children compared with term ones, with medium to large effect size (d = 0.49 [95% CI 0.32–0.66]). The studies showed no heterogeneity (I-squared = 0%, p = 0.619) (Fig. 8 supplementary online material). The assessment of the funnel plot of studies included in the meta-analysis did not show evidence of publication bias.

DISCUSSION

The main aim of this research was to evaluate the extent to which total IQ and neuropsychological functions differ between preschool children born at term and those born at less than 32 weeks of gestation or with a BW at less than 1,500 g. The meta-analysis revealed that poor IQ and neuropsychological difficulties were already detectable at three to five years of age, with an extent similar to that noticeable at a later age. The differences observed in terms of total IQ score showed that preterm children scored 0.77 SD lower than term-born controls, corresponding to an 11.5-point decrement for total IQ score. The magnitude of this difference was similar to those found in one recent meta-analysis, based on 71 studies, that demonstrated a difference of 0.89 SD between EPT/VPT children and full-term controls aged 5 to 20 years (46). Our results are also comparable to findings of the meta-analysis by Kerr-Wilson and colleagues (47) that found an 11.9-point difference in IQ score in favour of control children. Differences to that extent may have a negative impact on school performance and represent a warning signal for the presence of neuropsychological difficulties. Our findings indicated that neuropsychological functions were worse in preterm-born children, and this cognitive disadvantage may render severe impact on the school learning process.

Attention and memory are crucial functions for the acquisition of new knowledge. Our data showed that in terms of selective visual attention, preterm children scored 0.38 SD lower compared with term-born peers. The same difference (0.38 SD) was found by Mulder and colleagues (48) in a meta-analysis mainly concerning school-age preterm children.

Memory is deeply linked to academic progress, and there is evidence of widespread memory deficit in preterm children at school age (49). Our data included only short-term verbal memory and showed a difference of 0.49 SD between preterm children and term-born controls. A higher difference was detected in VPT seven-year-olds (1.34 SD) (49), suggesting that memory difficulties may become more apparent with age.

Visuomotor integration abilities play an important role in several school and social activities. Deficits in visuomotor integration and visuospatial skill (design copy, judgement orientation arrows) could increase the risk for mathematical failure (50). In our findings, visuomotor integration (design copy task) was the neuropsychological function with the most pronounced difference (0.57 SD) between preterm- and term-born children. A similar difference (0.69 SD) was revealed by a previous meta-analysis performed with school-age preterm children (51). Poor fine motor skill, frequently observed among these children, may contribute to visuomotor integration difficulties. However, one study performed with computerised tasks (9) that minimised the motor request found consistent poor results. Therefore, visuomotor integration difficulties cannot be explained only with poor motor skills; they likely originate from the difficulty to integrate motor, visual, and proprioceptive sensory information to plan efficient movement.

Executive functions are the cognitive skills that are needed to achieve academic and social goals. Deficits in working memory have been linked to inattention and worse performances in mathematics, which are common in these children during school age (52,53). Children born at earlier than 32 weeks of gestation scored 0.49 SD lower than term-born controls on global measure of executive functioning. Brydges et al. (54), which performed a meta-analysis on children aged 4 to 17 years born at earlier than 32 weeks of gestation, reported a similar difference of 0.51 SD on global executive functioning. A qualitative analysis showed that all preterm children tended to have more difficulties than term-born ones in inhibiting incorrect responses or actions (inhibition), storing and manipulating verbal or spatial information (working memory), and shifting across different tasks (cognitive flexibility). Difficulties in cognitive flexibility should be considered with caution; some evidence suggests that at preschool age, cognitive flexibility cannot be differentiated from working memory (55).

From a developmental perspective, the question is whether neuropsychological difficulties at preschool age reflect transient developmental lags or represent true cognitive impairments that require timely intervention. As 10 of the 13 included studies used the corrected age and not the chronological one, the hypothesis that differences at preschool age may be explained by a transient developmental delay can be ruled out. These early difficulties likely reflect actual impairments. Studies on the stability of cognitive performance over time have shown that for children born at less than 32 weeks of gestation, cognitive functioning is stable from preschool age to adolescence, with no evidence of developmental catch-up (56). As regards the secondary aim of the present research, no significant cognitive differences were found between the two groups of preterm-born children. This is an unexpected finding, as literature (e.g. 47) has consistently shown that the lower the GA, the lower the IQ. This result of the meta-analysis can be explained by the fact that some studies included children born at ≤ 27 weeks of gestation or <1,000 g BW. Furthermore, only two studies involved EPT/ELBW children, reducing the reliability of the statistical analysis results.

Limitations

A few problems were encountered during this systematic review. First, different tools were used in the primary studies, and this heterogeneity impeded the smooth combination of evidence collected. Second, there was a lack of valid assessment tools to evaluate the methodology of cohort studies, and the Newcastle-Ottawa Scale proved to be not completely satisfactory as well. Third, not all neuropsychological functions or not all their sub-components had been assessed. Therefore, it was not possible to explain in detail the strengths and weaknesses of the neuropsychological profile of preterm preschoolers. Fourth, some authors enrolled children born at <32 weeks of GA or <1,500 g BW and defined them as VPT or VLBW. However, the assessment of their characteristics showed that also those born at ≤ 27 weeks GA and <1,000 g BW had been included in that group (Fig.9 supplementary online material). Meanwhile, according to the World Health Organization classification, these children should be classified as EPT or ELBW. Finally, another limitation of our study was in its reliance on the limited number of studies considered for the meta-analysis, which was due to the chosen period of only 24 years for the inclusion of papers. A longer period could have implied different and/or richer results. Nonetheless, improvements in perinatal care during the last two to three decades have contributed to ameliorating the short- and long-term outcomes of these new-born infants, including the broader use of prenatal corticosteroids, less aggressive respiratory support, and the diffusion of developmental care adopted in most neonatal intensive care units.

Clinical implication

Most follow-up programmes stop at two years of age, whereas neuropsychological problems emerge at three to five years of age. Therefore, neuropsychological problems pass under-recognised most of the time. Neuropsychological difficulties, especially for children with an average IQ, often manifest with symptoms that are subtle and nonspecific, and as such, tend to be difficult to recognize without a specific screening plan. It would be advisable to extend the follow-up to preschool age, and the assessment should involve IQ and neuropsychological functions. Compliance of the child at this young age is often discontinuous; thus, the neuropsychological assessment at three to five years of age is often longer and more complex with respect to the assessment at school age.

Both IQ and neuropsychological functions can be assessed at three to five years of age for the first time in life, so the preschool age is a critical and unique period: on the one hand, it accommodates the diagnosis of these problems, and on the other hand, a specific intervention tailored to the child may influence positively the subsequent school career of these fragile infants. The effectiveness of neuropsychological training in preterm-born children remains a matter of debate. Computerised working memory training interventions seem to have positive and persisting long-term effects on working memory (57) even if there is little evidence of benefits in improving academic functioning (58). Memory training induces neuroplastic changes and enhances memory performance (59). Visuomotor difficulties may benefit from occupational therapy training (60). New research will clarify the most effective interventions.

CONCLUSIONS

Differences between preterm- and term-born children in global intellectual functioning and singular or plural neuropsychological functions are manifested in preschool age. Preterm-born children should be closely monitored at ages three to five years, as those with neuropsychological problems may benefit from early intervention. Future research should examine in depth the neuropsychological problems outlined by this pioneering meta-analysis. Longitudinal studies, in which a comprehensive set of neuropsychological functions can be analysed in relation to the behavioural attitudes of these children, should be planned. International consensus on the tools and the investigations to be used at this age would also allow for comparison across studies.

Abbreviations:

ELBW: Extremely low birth weight; EPT: Extremely preterm; IQ: Intelligence quotient; SD: Standard deviation; VLBW: Very low birth weight; VPT: Very preterm

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Figure 1: PRISMA flow diagram for studies selection process

Figure 2: Criteria for assessing methodological quality

Figure 3: Global Intellectual functioning (supplementary online material)

Figure 4: Intelligence quotient vulnerability (supplementary online material)

Figure 5: Selective visual attention (supplementary online material)

Figure 6: Short term verbal memory (supplementary online material)

Figure 7: Visuomotor integration-paper pencil task (supplementary online material)

Figure 8: Executive Functions-parents' questionnaire (supplementary online material)

Figure 9: Studies including EPT/ELBW children in VPT/VLBW samples (supplementary online material)

Table 1 - Main characteristic of the studies: reference, type and number of children in the two cohorts, country and time of birth, age at time of assessment, exclusion criteria, study design, assessment tools.

Table 2 - Description of executive functions tasks used across studies (supplementary online material)

Legend: DRB, Detour Reaching Box; FIST Flexibility Item Selection Task; NBT, Nebraska Barnyard Task; P-CPT, Preschool Continuous Performance Test; TPT-R Trail Preschool Test-Revised (adapted from Espy & Cwik,2004) ; WISC III, Wechsler Intelligence Scale for Children, 3rd ed.; WMTB-C Working Memory Test Battery for Children

Table 3 - Summary of meta-analysis results about cognitive differences between preterm-born (< 32 weeks and/or < 1,500 g) and term-born children

Cognitive domain (total intelligence quotient, attention, memory, visual perceptual skill, visuomotor integration skill, executive functions), reference, total number of preterm-born children, effect size (95% confidence interval)

Table 4 - Quality assessment of studies

Table 5 - Performance-based measures of executive functions: reference, time of birth, assessment tools, task assessment, simple size and mean (Standard Deviation) in preterm-born and term-born group, effect size (95% Confidence Interval)

Table 1 - Main characteristic of the studies: reference, cohort, type and number of children in the two cohorts, country and time of birth, age at time of assessment, exclusion criteria, study design, assessment tools

Study/Year	Cohort	Population: Preterm n Author's definition	Population: Term n	Country; birth period	Age (y)	Exclusion criteria	Single/multicentre study (Study design)	Assessment tools: Test	Assessment tools: Cognitive domain assessed
Lind et al., 2011 (8)	1	*n*=97 VLBW ≤ 1500 g	*n* =161 FULL	Finland; 2001-2003	5	Congenital anomalies, genetic/chromosomal syndromes, mother's use of drugs or alcohol	Single (Prospective study)	WPPSI-R NEPSY-II	global intellectual functioning selective visual attention inhibition working memory visuomotor integration
Potharst et al., 2012 (9)	2	*n* =102 VPT < 30 wks <1000 g	n=95 FULL	Netherlands; 2002-2004	5 CA	Participation other studies, genetic syndrome, too disabled to be assessed	Single (Prospective study)	WPPSI-R SST WISC–III	global intellectual functioning inhibition verbal working memory
Van Hus et al., 2013 (10)	2	*n = 81* VPT < 30 wks <1000 g	*n = 84* FULL	Netherlands; 2002-2004	5 CA	Genetic syndrome, too disabled to be assessed	Single (Prospective study)	WPPSI-III	global intellectual functioning
Roberts et al, 2011 (11)	3	*n* = 195 VPT < 30 wks <1250 g	*n* = 70 FULL	Australia; 2001-2004	5 CA	Congenital abnormalities, deafness, blindness, severe cerebral palsy	Single (Prospective study)	K-SEALS BRIEF-P WMTB-C VMI	global intellectual functioning executive functions working memory visuomotor integration
Verkerk et al, 2014 (12)	4	*n* =147 VPT/VLBW < 32 wks < 1500 g	*n* = 41 FULL	Netherlands; 2004-2006	3 ½ CA	Cerebral palsy	Multicentre (Prospective study)	BRIEF-P VMI	global executive functions visuomotor integration visual perception motor coordination
Geldof et al., 2013 (13)	4	*n= 108* VPT/VLBW < 32 wks < 1500 g	*n =72* FULL	Netherlands; 2003-2006	5.5 ½ CA	Congenital abnormalities, severe maternal of physical illness, no Dutch language	Multicentre (Prospective study)	WPPSI III Attention NT	global intellectual functioning inhibition
Baron et al., 2011 (14)	5	*n*= 60 ELBW ≤ 33 wks < 1000 g	*n*= 90 FULL	United States; 2004-2006	3 CA	Incomplete data	Single (Retrospective study)	DAS-II VMI BRIEF-P Verbal fluency	global intellectual functioning visuomotor integration executive functions cognitive flexibility

Baron et al., 2012 (15)	5	*n* = 52 ELBW ≤ 33 wks < 1000 g	*n* = 121 FULL	United States; 2004-2006	3 CA	Genetic disorders, sensory loss, non-English speaking	Single (Retrospective study)	P-CPT inhibition Boy-Girl S inhibition Go/No Go inhibition Jack's Box spatial working memory DAS-II short term verbal memory
Edgin et al., 2008 (16)	6	*n = 88* VPT/VLBW ≤ 32 wks < 1500 g	*n* 98 FULL	New Zealand; 1998-2000	4 CA	Congenital abnormalities, non-English speaking	Single (Prospective study)	DRB cognitive flexibility
Pritchard et al., 2014 (17)	6	*n = 105* VPT ≤ 32 wks	*n = 107* FULL	New Zealand; 1998-2000	4 CA	Congenital anomalies, foetal alcohol syndrome, non-English speaking	Single (Prospective study)	WPPSI-R global intellectual functioning BRIEF-P executive functions
Woodward et al., 2011 (18)	6	*n = 104* VPT ≤ 32 wks	*n = 105* FULL	New Zealand; 1998-2000	4 CA	Congenital abnormalities, non-English speaking	Single (Prospective study)	WPPSI-R global intellectual functioning Visual Search selective visual attention FIST cognitive flexibility ShScT inhibition/cognitive flexibility
Orchinik et al., 2011 (19)	7	*n = 148* EPT/ELBW < 28 wks < 1000 g	*n* = 111 FULL	United States; 2001-2003	5	Congenital infection and malformation, non-English speaking	Single (Retrospective study)	WJ-III global intellectual functioning VMI visuomotor integration CTOPP short term verbal memory Shape School inhibition, cognitive flexibility NBT spatial working memory TIA inhibition TPT-R cognitive flexibility
Dall'Oglio et al., 2010 (20)	8	*n = 35* VPT ≤ 32 wks	*n= 50* FULL	Italy; 1998-1999	4	Congenital malformation, IVH 3°-4°, ROP 3°-4°, seizures, periventricular leukomalacia, disability at 2y	Single (Retrospective study)	Category Test cognitive flexibility VMI visuomotor integration DIGIT TEST short term verbal memory BELLS TEST selective visual attention

Legend: CA, corrected age; FULL TERM (≥ 37 wks and/or ≥ 2500 gr); Attention NT, Attention Network Test; ANT, Amsterdam Neuropsychological Tasks; Boy-Girl S, Boy-Girl Stroop; BRIEF-P, Behaviour Rating Inventory of Executive Function Preschool version; CTOPP, Comprehensive Test of Phonological Processing; DAS II, Differential Ability Scale 2nd Ed; DRB, Detour Reaching Box; FIST, Flexible Item Selection Task; NA, not available; NBT, Nebraska Barnyard task; P-CPT, Preschool Continuous Performance Test; SST, Stop Signal Task; TIA, Test of Inhibition and Attention; TPT-R, Trails Preschool Test-Revised; VMI, Beery-Buktenica Developmental Test of Visual Motor Integration; WISC III, Wechsler Intelligence Scale for Children, 3rd ed.; WJ-III, Woodcock Johnson Tests of Achievement 3rd ed.; WMTB-C, Working Memory Battery Test for Children; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence – revised; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence 3rd Ed; K-SEALS, Kaufman Survey of Early Academic and Language Skills

Table 3 – Summary of meta-analysis results about cognitive differences between preterm-born (< 32 weeks and/or < 1,500 g) and term-born children

Cognitive domains (total intelligence quotient, attention, memory, visual perceptual skills, visuomotor integration skills, executive functions), reference, total number of preterm-born children, effect size (95% Confidence Interval)

COGNITIVE DOMAINS	REFERENCE	*PRETERM n*	COHEN'S *d* EFFECT SIZE (95% CI)
GLOBAL INTELLECTUAL FUNCTIONING			
Total intelligence quotient	8,9,11,13,14,17,19	758	-0.77 (-0.88 to -0.66)*
ATTENTION			
Selective attention	14,24,26	236	-0.36 (-0.53 to -0.19)*
Divided attention	Data not found		
Sustained attention	Data not found		
Executive attention	Data not found		
MEMORY			
Short-term verbal memory	11,15,19,20	431	-0.49 (-0.75 to -0.22)*
Short-term visual memory	Data not found		
Long-term verbal memory	Data not found		
Long-term visual memory	Data not found		
VISUAL PERCEPTUAL SKILL	Data not found		
VISUOMOTOR INTEGRATION SKILL			
Graphomotor skill	8,11,14,19,20	534	-0.57 (-0.72 to -0.43)*
Visual-constructional ability	Data not found		
Manual dexterity	Data not found		
EXECUTIVE FUNCTIONS			
Global executive composite score	11,14,17	360	0.49 (0.32 – 0.66)*

* In favour to term-born children

Table 4 - Quality assessment of studies

Study	Selection			Comparability		Outcome	
	1	2	3	4	5	6	7
Lind et al., 2011 (8)	☆	☆	☆		☆		☆
Potharst et al., 2012 (9)	☆	☆		☆	☆		☆
Van Hus et al., 2013 (10)	☆	☆		☆	☆		☆
Roberts et al., 2011 (11)	☆	☆	☆	☆	☆		☆
Verkerk et al., 2014 (12)	☆	☆		☆	☆		☆
Geldof et al., 2013 (13)	☆			☆	☆		☆
Baron et al., 2011 (14)	☆	☆		☆		☆	☆
Baron et al., 2012 (15)	☆			☆	☆		
Edgin et al., 2008 (16)	☆	☆		☆			☆
Pritchard et al., 2014 (17)	☆	☆		☆			☆
Woodward et al., 2011 (18)	☆	☆		☆			☆
Orchinick et al., 2011 (19)	☆		☆	☆	☆	☆	☆
Dall'Oglio et al., 2010 (20)	☆						☆

Table 5 - Performance-based measures of executive functions: reference, time of birth, assessment tools, task assessment, simple size and mean (Standard Deviation) in preterm-born and term-born group, effect size (95% Confidence Interval)

EFs / task Study/ Cohort	Preterm group	Test	Task	Task assessment	Preterm N	 Mean	 (SD)	Term N	 Mean	 (SD)	Cohen's *d* effect size (95% CI)
Inhibition/ Stroop tasks											
Geldof et al. (13) / 4	VPT/VLBW	Attention NT	Executive	% errors	108	35.80	(26.00)	72	20.50	(21.30)	0.63 (0.32-0.93)
			Executive	Mean reaction time	108	1342.00	(24.80)	72	1353	(30.60)	-0.40 (-0.70 to-0.10)
Baron et al. (15) / 5	ELBW	Boy-Girl Stroop	--	Total time	52	70.65	(23.18)	121	53.26	(15,76)	0.95 (0.61-1.29)
			--	# Correct	52	13.26	(4.40)	121	17.71	(3.65)	-1.14 (-1.49 to -0.79)
Lind et al. (8) / 1	VLBW	NEPSY II	Inhibition	# Correct	97	8.30	(3.30)	161	9.90	(3.00)	-0.51(-0.76 to -0.25)
Inhibition/ Go no-go tasks											
Baron et al. (15) / 5	ELBW	P-CPT	--	# commission errors	52	12.74	(10.20)	121	5.99	(8.01)	0.77 (0.43-1.10)
		Go No-Go	--	# commission errors	52	11.84	(7.83)	121	7.05	(5.82)	0.73 (0.40-1.07)
Potharst et al. (9) / 2	VPT	Stop Signal Task	--	Reaction time	102	491.60	(134.30)	95	506.70	(122.10)	-0.11 (-0.39-0.16)
Woodward et al. (18) / 6	VPT	Shape School	Inhibition	Efficiency score §	104	0.33	(0.27)	105	0.43	(0.27)	-0.37 (-0.64 to -0.09)
Orchinick et al. (19) / 7	EPT/ELBW	Shape School	Inhibition	Efficiency score §	136	0.85	(0.34)	109	1.05	(0.41)	-0.53 (-0.79 to -0.28)
		TIA	Go no-go	z (hit rate) – z (false alarm)	143	1.46	(1.19)	111	3.32	(1.15)	-1.58 (-1.87 to -1.30)
			CPT	z (hit rate) – z (false alarm)	143	2.27	(1.31)	111	3.41	(1.36)	-0.85 (-1.11 to -0.59)
Verbal working memory											
Lind et al. (8) / 1	VLBW	NEPSY II	word list	# correct	97	8.40	(4.00)	161	10.10	(2.80)	-0.51(-0.77 to -0.25)
Potharst et al. (9) / 2	VPT	WISC III	digit span‡	# correct	102	6.20	(2.10)	95	7.70	(2.20)	-0.69(-0.98 to -0.41)
Roberts et al. (11) / 3	VPT	WMTB-C	non word	# correct	195	98.80	(19.40)	70	109.30	(15.00)	-0.57(-0.85 to -0.29)
Spatial working memory											
Baron et al. (15) / 5	ELBW	Jack's Box	--	# within errors ╤	52	3.84	(4.71)	121	1.95	(2.40)	0.57 (0.24-0.91)
		Jack's Box	--	# between errors ╤	52	22.48	(8.00)	121	18.33	(7.07)	0.56 (0.23-0.89)
Orchinick et al. (19) / 7	EPT/ELBW	NBT	--	# correct	130	4.67	(2.85)	108	6.29	(2.90)	-0.56 (-0.82 to -0.30)
Cognitive flexibility											
Dall'Oglio et al. (20) / 8	VPT	Verbal Fluency	semantic	# correct	35	16.3	3.5	50	19.6	(4.30)	-0.83 (-1.28 to -0.38)
Baron et al., (15) / 5	ELBW	Verbal Fluency	semantic	# correct	58	3.70	3.01	88	4.9	(2.87)	-0.41(-0.74 to -0.07)
Woodward et al. (18) / 6	VPT	FIST	-	# correct	104	2.83	2.14	105	3.44	(2.19)	-0.28 (-0.55 to -0.01)
		Shape School	switching	Efficiency score §	104	0.05	0.15	105	0.04	(0.16)	0.064 (-0.20 - 0.33)
Orchinick et al. (19) / 7	EPT/ELBW	Shape School	switching	Efficiency score §	134	0.35	0.11	110	0.43	(0.20)	0.50 (-0.76 to -0.25)

		TPT-R	-	Efficiency score §	134	0.94	0.57	108	1.26 (0.62)	0.54 (-0.79 to -0.28)
Edgin et al. (16) / 6	VPT	DRB †	-	# errors	88	1.05	1.05	98	0.54 (0.61)	0.60 (0.31- 0.90)

Legend: ╤ within error: children selected a box in which they had previously looked and not found Jack; between error: children selected a box in which they had previously found Jack. §Efficiency score = # corrects - # errors (accuracy)/time; † Data between Term controls and VPT with mild white matter abnormalities are shown. ‡ Combined data on digits repeat forward and backward; Attention NT Attention Network Test; CPT, Continuous Performance Test; DRB Detour Reaching Box; FIST, Flexible Item Selection Task; NBT, Nebraska Barnyard Task; P-CPT Preschool Continuous Performance Test; TIA, Test of Inhibition and Attention; TPT-R, Trails Preschool Test-Revised; WISC III, Wechsler Intelligence Scale for Children, 3rd ed.; WMTB-C Working Memory Battery Test for Children

Fig. 1 PRISMA flow diagram for studies selection process

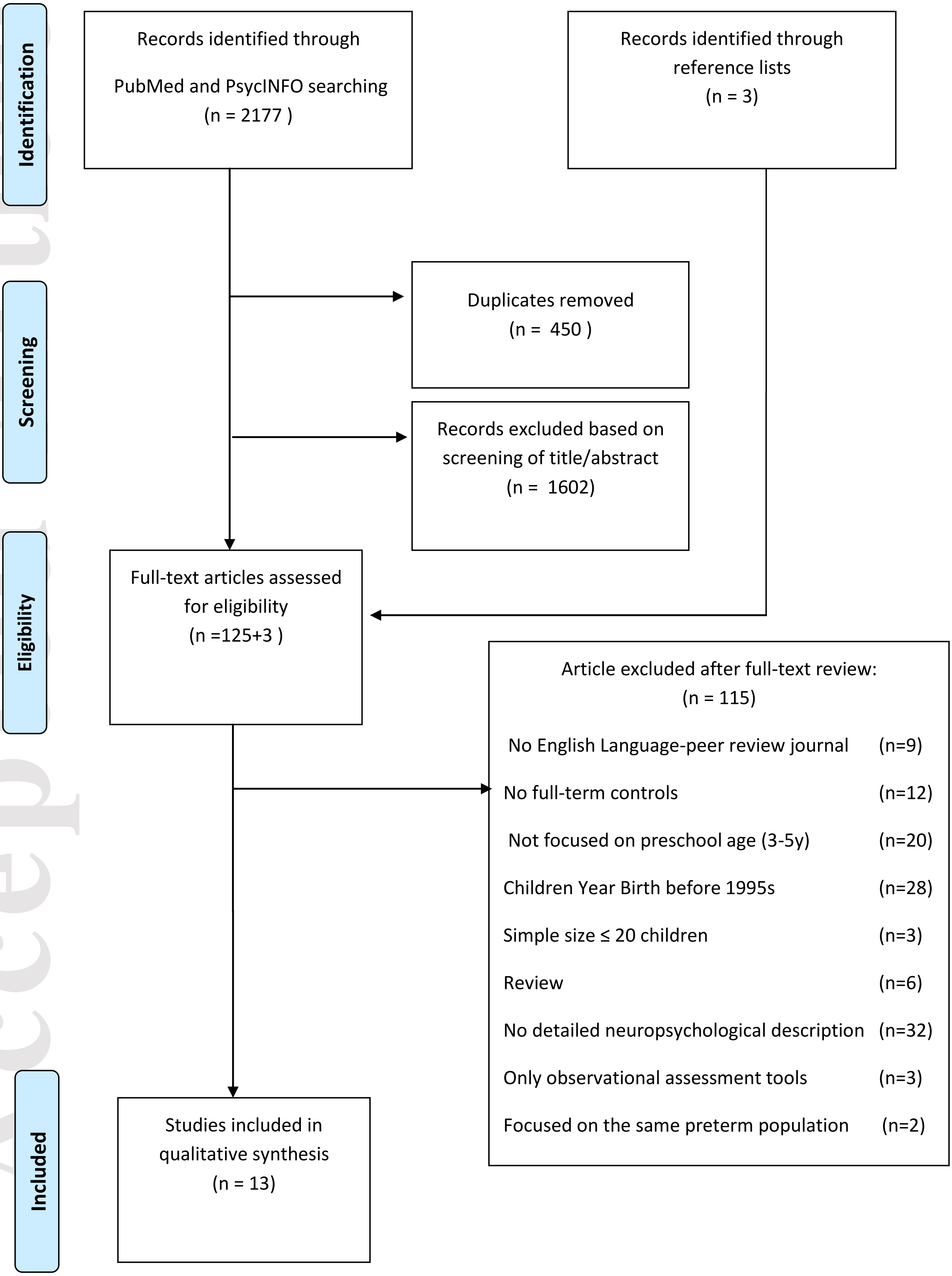

Fig. 2 - Criteria for assessing methodological quality

Cohort selection was assessed on the answers to three questions:

1) Were criteria for assignment of children to preterm group detailed enough? (We awarded one star for relevant details: gestational age and birth weight). **2)** How representative was the preterm cohort? (One star if preterm children were consecutively recruited and if the recruitment rate is at least 80% of eligible children, no star if groups of preterm children were selected or recruitment rate was not described). **3)** How representative was the full-term cohort selected? (One star if drawn from the same community as the preterm cohort and if the recruitment rate is at least 80% of eligible children; no star if drawn from a different source or recruitment rate was not described.

Cohort comparability was assessed by two criteria: **1)** corrected age **2)** social-economic status. Two stars were assigned if preterm sample was assessed considering corrected age and if there was no differences between the two groups in term of social-economic status. One star was assigned if only one of these characteristics was checked.

Outcome was assessed by two criteria: **1)** independent blind assessment of outcome, **2)** drop-out of enrolled patients (retation rate). One star was assigned for information ascertained by independent blind assessment. One star was assigned if no patient or fewer than 20% of patients were lost to follow-up; no star if more than 20% of patients were lost to follow-up, or if the researchers did not provide relevant information.