

# Executive function deficits in children born preterm or at low birthweight: a meta-analysis

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## ABBREVIATIONS

DST Digit Span Task  
SMD Standardized mean difference

**AIM** To investigate the magnitude of executive function deficits and their dependency on gestational age, sex, age at assessment, and year of birth for children born preterm and/or at low birthweight.

**METHOD** PubMed, PsychINFO, Web of Science, and ERIC were searched for studies reporting on executive functions in children born preterm/low birthweight and term controls born in 1990 and later, assessed at a mean age of 4 years or higher. Studies were included if five or more studies reported on the same executive function measures.

**RESULTS** Thirty-five studies (3360 children born preterm/low birthweight, 2812 controls) were included. Children born preterm/low birthweight performed 0.5 standardized mean difference (SMD) lower on working memory and cognitive flexibility and 0.4 SMD lower on inhibition. SMDs for these executive functions did not significantly differ from each other. Meta-regression showed that heterogeneity in SMDs for working memory and inhibition could not be explained by study differences in gestational age, sex, age at assessment, or year of birth.

**INTERPRETATION** Children born preterm/low birthweight since 1990 perform half a SMD below term-born peers on executive function, which does not seem to improve with more recent advances in medical care or with increasing age.

Preterm birth frequently occurs all over the world. Of all live-born children in the USA in 2015, for instance, 9.6% were born preterm (gestational age <37wks, according to the World Health Organization definition)<sup>1</sup> and 8.1% were born with a low birthweight (<2500g, according to the World Health Organization definition).<sup>1,2</sup> Preterm birth and low birthweight co-occur frequently, with 69.2% of children born preterm also being born with a low birthweight and 49.8% of children born with a low birthweight also being born preterm.<sup>3</sup> Preterm birth and/or low birthweight survivors are at high risk of adverse cognitive, academic, and behavioural outcomes.<sup>1,4,5</sup> Children born preterm/low birthweight have 0.8 standard deviation (SD) lower IQ scores and perform about a 0.5 SD poorer than term-born peers on mathematics, reading, and spelling tests.<sup>4,5</sup> Also, a two to four times higher risk of being diagnosed with attention-deficit/hyperactivity disorder than for term-born peers has been reported.<sup>4,6,7</sup> A large body of studies has also shown impairments in the so-called executive functions in children born preterm/low birthweight.<sup>8,9</sup> 'Executive functions' is an umbrella term for a set of higher-order cognitive functions, with core functions including working memory, inhibition,

and cognitive flexibility, which allow for top-down, goal-directed behaviour.<sup>10,11</sup> Executive functions rely upon lower-order cognitive processes, such as processing speed, to operate effectively.<sup>12</sup>

Executive functions are increasingly studied because of their crucial role in the onset of academic and behavioural problems.<sup>13,14</sup> Even as early as the toddler and preschool years, executive functions are predictive of both (pre-)academic skills and behaviour problems.<sup>15,16</sup> Importantly, executive function deficits have also been shown to be key to the behavioural and academic problems observed in children born preterm/low birthweight.<sup>12,17–23</sup> Recent research showed that executive function is a substantially better predictor of poor behavioural and academic outcomes in children born preterm/low birthweight than IQ and motor functions.<sup>12,17–24</sup> For example, measures of executive functions are highly predictive of mathematic and reading abilities, and attention regulation in children born very preterm and/or very low birthweight.<sup>12,17,22,23</sup>

The initial literature on executive functions in children born preterm/low birthweight was summarized in two meta-studies published in 2009, reporting a 0.36

standardized mean difference (SMD) for working memory, a 0.25 SMD for inhibition, and a 0.49 to 0.50 SMD for cognitive flexibility between children born preterm/low birthweight and term-born comparison children.<sup>8,9</sup> Newly published literature on executive functions since the meta-studies published in 2009 warrants an update of this work. In addition, a meta-analysis on cognitive function, including executive functions, in children born very preterm was published recently.<sup>25</sup> However, this paper only focused on children born at less than 32 weeks of gestation and piled the diverse subdomains within the broad concept of executive functions. Including both newly published studies on executive functions since 2009 and studies into executive functions in children across the entire range of preterm birth (<37wks gestational age) offers the possibility of improving on previous meta-analytic work by examining the profile of executive function difficulties, i.e. whether specific executive function domains are more severely impaired than others, and whether the magnitude of the effect sizes depend on the degree of preterm birth (gestational age), sex,<sup>26</sup> age at assessment,<sup>27–29</sup> and year of birth (as a proxy measure of advances in neonatal care).<sup>30,31</sup> Owing to slightly different inclusion criteria and the large number of studies published on this subject since 2009, only two studies included in this meta-analysis were included in the 2009 meta-analyses.<sup>32,33</sup>

Using meta-regression, this quantitative meta-analysis aimed to aggregate and quantify impairments in executive function domains and assess the impact of gestational age, sex, age at assessment, and year of birth on executive function effect sizes. This unravels the nature and extent of executive function impairments in the population born preterm/low birthweight and contributes to a better understanding of the behavioural and academic problems observed in children born preterm/low birthweight.

## METHOD

Our (unpublished) protocol was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>34</sup>

### Search strategy

A literature search was performed by one author (CAvH) in PubMed, PsychINFO, Web of Science, and ERIC, on 16th January 2017, using search terms concerning the birth status (e.g. preterm, low birthweight, small for gestational age), executive function measures (working memory, inhibition, cognitive flexibility), and age group (child, adolescent, teenager, young adult, adult, middle aged). An experienced librarian was consulted for construction of the search terms, which are provided in (Appendix S1).

### Study selection

Inclusion criteria for study selection were as follows: (1) the study included participants born preterm (<37wks gestation) and/or with low birthweight (<2500g) and a comparison group of term-born, typical-birthweight participants

## What this paper adds

- Children born preterm/low birthweight perform below term-born children on core executive functions.
- Lower gestational age or male sex are not risk factors for poorer executive functions.
- Executive function difficulties in children born preterm/low birthweight remain stable across childhood.
- Executive function difficulties are similar for children born recently and children born in earlier eras.

(>37wks gestation and >2500g); (2) the mean age at assessment of the participants was at least 4 years (studies with younger participants were not included in this meta-analysis as executive functions cannot be reliably assessed before the age of 4y);<sup>35</sup> (3) the year of birth of the participants was 1990 or later (i.e. after the introduction of antenatal steroids and surfactant supplementation); (4) the study reported administration of working memory, inhibition, and/or cognitive flexibility tasks; and (5) the study was published in an English-language, peer-reviewed journal.

There are many different tasks available to measure executive functions and some executive function tasks may have been used in only one or two studies. Meta-analytic procedures can be applied to a small number of studies; however, the results obtained might then be unstable.<sup>36</sup> Therefore, to maximize the robustness of findings, only executive function tasks reported in at least five papers, as was done in a previous meta-analysis,<sup>8</sup> were included. Papers were thoroughly checked for overlapping cohorts of children born preterm/low birthweight. If multiple papers reported on overlapping cohorts of children born preterm/low birthweight on the same executive function domain, the study with the most complete data for that domain was selected. When multiple papers reported on overlapping cohorts of children born preterm/low birthweight but the papers differed in the executive function domains described, all these papers were included in analyses. If it was not clear whether cohorts were overlapping, the authors of the studies were contacted. Screening of titles and abstracts and assessment of full-text articles was performed by two authors (CAvH, CSHAM).

## Measures

This meta-analysis reports the results for the following executive function tasks; results for each of these tasks were reported in at least five papers.

### Working memory

Working memory is the ability to hold information in mind and actively manipulate this information.<sup>10</sup> Working memory comprises a verbal and a visual-spatial subsystem. For both subsystems, tasks were reported in at least five papers. Both the visual-spatial and verbal working memory tasks reported below have been shown to activate brain areas that are important for working memory.<sup>37–39</sup>

*Visual-spatial working memory.* In the Cambridge Neuropsychological Test Automated Battery Spatial Working Memory task,<sup>40</sup> a number of coloured boxes are shown on a

screen. Children were asked to find a yellow token in these boxes without selecting boxes that have already been found to be empty or revisiting boxes that have already been found to contain a token. Raw scores were used in the analyses.

**Verbal working memory.** In the Digit Span Task (DST),<sup>41–43</sup> children are asked to repeat a number of digits, first in the same order and then in reverse order. The reverse part measures verbal working memory. When the DST reverse score was not available, the DST total score was used instead. For the reversed DST, either raw scores or scaled scores (mean 10 [SD 3]) were used (as indicated in Table SI, online supporting information). For the DST total, scaled scores were used (mean 100 [SD 15]).

In the Letter Number Sequencing task,<sup>42,43</sup> the test administrator reads a sequence of numbers and letters out loud and asks the child to repeat the numbers in ascending order, followed by the letters in alphabetical order. For Letter Number Sequencing, scaled scores were used (mean 10 [SD 3]).

When DST and Letter Number Sequencing scores were not available but the Working Memory Index (i.e. DST, Letter Number Sequencing, and Arithmetic subtests of the fourth and fifth editions of the Wechsler Intelligence Scales for Children)<sup>42,43</sup> was, the Working Memory Index was used instead (scaled scores, mean 100 [SD 15]).

### **Inhibition**

Inhibition is the ability to deliberately inhibit a prepotent response or stop an ongoing response (response inhibition) or suppress disruption by competing responses (interference control).<sup>44</sup> For response inhibition and interference control, tasks were reported in at least five papers. Both the response inhibition and interference control tasks reported below (or tasks very similar to those) have been shown to activate brain areas that are important for inhibition.<sup>45–49</sup> For all tasks, raw scores were used in analyses.

**Response inhibition.** In the Go/No-Go task, children have to press a button in case of a go-trial and have to withhold from responding in case of a no-go trial.<sup>50,51</sup>

In the Test of Everyday Attention for Children Opposite Worlds task,<sup>52</sup> children have to read aloud a series of numbers twice. In the ‘same world’ condition they read the numbers aloud as they appear; in the ‘opposite world’ condition they are asked to say the opposite of each digit (i.e. if they read ‘1’, they need to respond by saying ‘2’ and vice versa).

**Interference control.** In the Test of Everyday Attention for Children Sky Search task,<sup>52</sup> children are asked to find and circle target spaceships as quickly as possible on a sheet filled with similar but not exactly the same distractor spaceships.

### **Cognitive flexibility**

Cognitive flexibility is the ability to shift between multiple tasks or mental sets.<sup>10</sup> For all tasks, raw scores were used in analyses.

In the first part of the Trail Making Test/Trails Preschool Revised,<sup>53–55</sup> children are asked to connect numbers in the correct order (1–2–3). In the second part, children are asked to connect numbers and letters in the correct order (1–A–2–B). The Trails Preschool Revised Test is a version of the Trail Making Test adapted for the use in younger children. In the first part, children are asked to connect dogs in order of increasing size. In the second part, children are asked to alternate connecting dogs and bones in order of increasing size.

### **Data extraction**

Data on working memory, inhibition, and/or cognitive flexibility and the moderators gestational age, sex, age at assessment, and year of birth were extracted from the studies by one author (CAvH) and entered in the database. A second person, not involved in the design and writing of this meta-analysis, independently confirmed the data extracted from the studies. If necessary, authors were contacted for additional data. If studies reported on subgroups of children born preterm/low birthweight, subgroup data were pooled using the formulas  $M_{\text{pooled}} = ((M_1 * n_1) + (M_2 * n_2))/2$  and  $SD_{\text{pooled}} = \sqrt{((n_1 - 1) * SD_1^2 + ((n_2 - 1) * SD_2^2))/(n_1 + n_2 - 2)}$ .<sup>56</sup> Pooled data were used in subsequent analyses.

### **Study quality**

Study quality was assessed with an adapted version (i.e. maximum of 7 points) of the Newcastle–Ottawa Scale for cohort studies and were assessed independently by two authors (CAvH, CSHAM).<sup>57</sup> Inconsistencies between raters were discussed and consensus was reached for all studies.

### **Statistical analyses**

Comprehensive Meta-Analysis V3.0 (Biostat Inc., Englewood, NJ, USA) was used to perform this meta-analysis. Hedges’ *g* was used as measure for the SMDs in executive function between children born preterm/low birthweight and controls. Hedges’ *g* corrects for the bias in Cohen’s *d*, which becomes increasingly more apparent in smaller sample sizes.<sup>58</sup> A SMD of 0.2 translates into a small effect, a SMD of 0.5 is a medium effect, and a SMD of 0.8 is a large effect.<sup>59</sup>

Random effects meta-analyses were used to calculate SMDs and to investigate whether SMDs differed significantly between executive function tasks, executive function subdomains, and executive function domains.

To rule out any dependency of data, data for one executive function task or for one executive function subdomain per study were entered in the analysis. The selection was based on maximizing the number of studies per executive function task or per executive function subdomain. In case no significant differences in SMDs for the diverse executive function tasks or for the diverse executive function subdomains were found, in subsequent analyses the mean SMD aggregated across all executive function tasks

assessing a subdomain or aggregated across executive function subdomains was used respectively.

Variation in SMDs that were used to calculate a mean SMD across studies was tested using Cochran's  $Q$ . The percentage of variation across studies due to heterogeneity rather than chance was expressed as  $I^2$ , with 30% to 60% representing moderate heterogeneity; 50% to 90% representing substantial heterogeneity; and 75% to 100% representing considerable heterogeneity.<sup>60</sup>

Random-effects meta-regressions were performed to explore whether heterogeneity in SMDs between studies was explained by between study differences in gestational age, sex, age at assessment, and year of birth of the children born preterm/low birthweight. Meta-regressions were only performed for those executive function domains of which more than 10 studies were included in the analyses. Associations between study quality and SMDs were assessed with random-effects meta-regressions. Publication bias was assessed by Egger tests.

## RESULTS

In total, 2079 articles were retrieved from PubMed, 538 articles from PsychINFO, and 2109 articles from Web of Science. After the removal of duplicates, 3030 articles remained. After initial screening of titles and abstracts, 475 full-text articles were assessed. Of all articles that fulfilled the inclusion criteria, executive function tasks used were checked to extract which tasks had been reported on in at least five papers. All articles not reporting on those tasks were excluded. Furthermore, the remaining articles were checked for overlapping cohorts. The selection process is depicted in detail in (Figure S1). A total of 45 studies met all the inclusion criteria. Executive function data were provided by 35 of these studies (3360 children born preterm/low birthweight and 2812 term-born controls) either in the study paper or after a request for additional data sent to the authors.<sup>18,21,24,32,33,61–89</sup> The characteristics and main study results are given in (Tables SI, SII, and SIII, online supporting information; working memory, inhibition, and cognitive flexibility respectively). A total of 25 studies reported data on working memory (2272 children born preterm/low birthweight and 2021 term-born controls), 13 studies reported data on inhibition (1258 children born preterm/low birthweight and 984 term-born controls), and five studies reported data on cognitive flexibility (287 children born preterm/low birthweight and 307 term-born controls). Eight studies reported data on more than one executive function domain. Study quality ranged between 3 and 7, with a mean of 5.7 (SD 1.2). Overall, study quality was considered fair to good (see Tables SI, SII, and SIII).

### SMDs for executive functions

Based on the pooled analysis, children born preterm/low birthweight performed 0.52 SMD (95% confidence interval [CI] 0.65–0.38) lower than controls on working memory (Fig. 1), 0.39 SMD (95% CI 0.55–0.23) lower than

controls on inhibition (Fig. 2), and 0.51 SMD (95% CI 0.72–0.31) lower than controls on cognitive flexibility (Fig. 3). SMDs between domains did not differ significantly ( $Q=1.19$ ,  $p=0.55$ ). Substantial heterogeneity among studies was found for working memory ( $I^2=70.22$ ,  $p<0.001$ ) and inhibition ( $I^2=68.2$ ,  $p<0.001$ ). SMDs for the different tasks for verbal working memory and response inhibition did not differ significantly ( $Q=0.73$  [ $p=0.87$ ] and  $Q=0.34$  [ $p=0.56$ ] respectively). Also, SMDs did not differ significantly between the subdomains verbal and spatial working memory, or between the subdomains response inhibition and interference control ( $Q=0.38$  [ $p=0.54$ ] and  $Q=1.1$  [ $p=0.30$ ] respectively).

### Meta-regression analyses

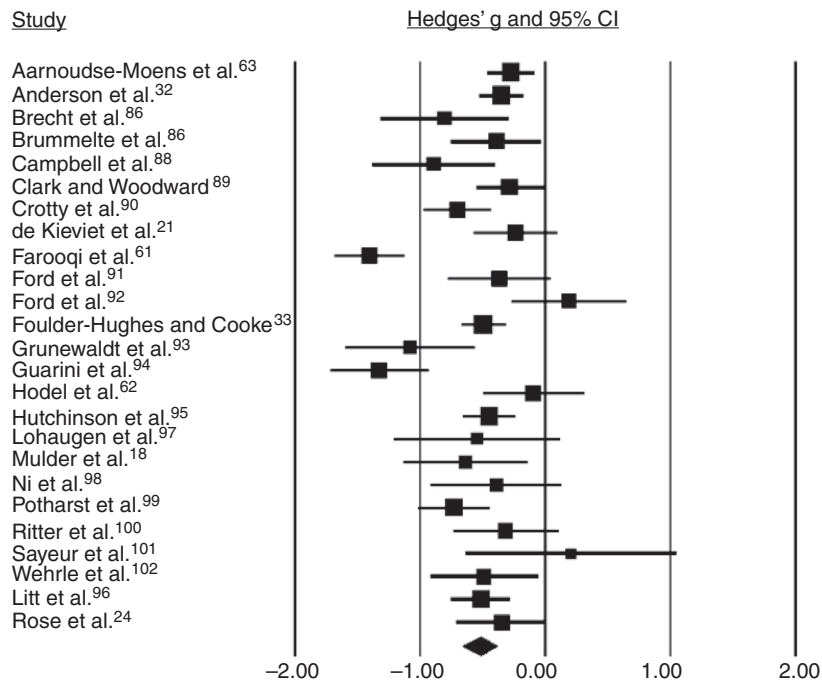
Meta-regression analyses were carried out for working memory and inhibition, as only five studies reported data on cognitive flexibility. In Table I, the range of each moderator (gestational age, sex, age at assessment, year of birth, and study quality) is depicted for working memory and inhibition separately. Meta-regression analyses performed for working memory showed a significant relationship with gestational age ( $\beta=0.07$ ; 95% CI 0.01–0.13;  $R^2=0.15$ ,  $p=0.02$ ). Visual inspection of the scatterplots, however, indicated that this result relied on two studies featuring children at the extreme ends of the gestational age distribution (i.e. 24.4wks and 35.6 wks respectively) (Fig. 4a).<sup>61,62</sup> Rerunning analyses without these two studies yielded a non-significant relationship between gestational age and working memory ( $\beta=0.03$ ; 95% CI –0.05 to 0.11;  $R^2=0.00$ ,  $p=0.48$  (Fig. 4b). No significant relationships with working memory SMDs were found for sex, age at assessment, and year of birth. None of the moderators were significantly associated with SMDs for inhibition. Study quality was not significantly associated with SMDs for working memory or inhibition.

### Publication bias

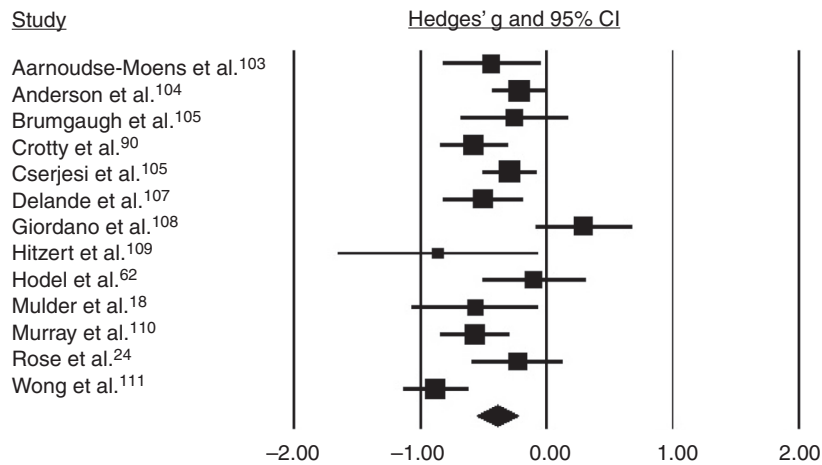
Egger's tests were non-significant for all three executive function domains, as well as for subdomains within working memory and inhibition, indicating that there is no evidence for publication bias.

## DISCUSSION

This meta-analysis aggregated the literature on the three core executive functions (working memory, inhibition, and cognitive flexibility), in children born preterm/low birthweight after the introduction of antenatal steroids and surfactant supplementation. Results show that, compared with term-born peers, children born preterm/low birthweight perform 0.5 SMD lower on working memory and cognitive flexibility measures (medium effect) and 0.4 SMD lower on inhibition measures (small-to-medium effect). Analysis indicated no significant differences between the SMDs for working memory, cognitive flexibility, and inhibition measures, indicating that all three executive functions seem to be affected to a similar degree. There was significant



**Figure 1:** Forest plot of the studies on working memory. CI, confidence interval.

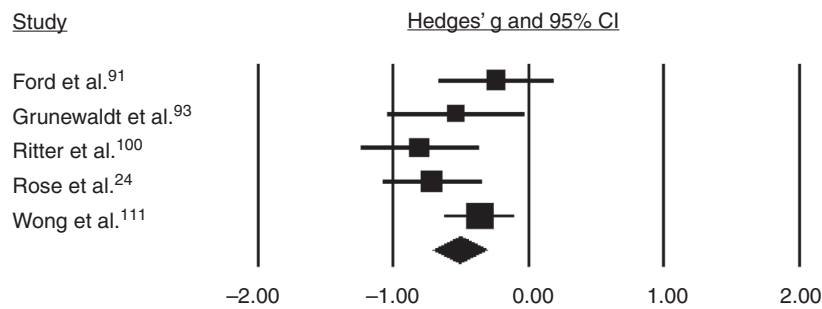


**Figure 2:** Forest plot of the studies on inhibition. CI, confidence interval.

heterogeneity in effect sizes for working memory and inhibition. Heterogeneity in working memory, but not inhibition, could partly be explained by study differences in gestational age; however, this effect was driven by two studies at the extreme ends of the gestational age range. Heterogeneity could not be explained by study differences in sex, age at assessment, or year of birth.

In the literature, executive function deficits have been described to be proportional to decreasing gestational age.<sup>8,9,63,90</sup> The magnitude of the difficulties in working memory as observed in our meta-analysis was dependent

on gestational age; however, we are cautious in interpreting this result as it was driven by two studies featuring children at the extreme ends of the gestational age range, and with these studies removed the gestational age of included studies only ranged between 26 and 30 weeks. Also, for inhibition, there were only a small number of studies investigating the ends of the gestational age range. To be able to draw robust conclusions on whether there is an effect of gestational age on executive function, more studies in children born extremely preterm (<26wks gestational age) and moderate-to-late preterm (32–37wks gestational



**Figure 3:** Forest plot for studies on cognitive flexibility. CI, confidence interval.

age) are clearly needed. In our analysis, executive function difficulties were not related to male sex, even though male sex is a risk factor for multiple medical adverse outcomes.<sup>26</sup> This suggests that male as well as female children born preterm/low birthweight are at substantial risk for poor executive function.

There is debate about whether executive function deficits in children born preterm/low birthweight represent a stable deficit, a deficit that increases during development (growing into deficit), or a delay in maturation in which children 'catch up' over time.<sup>27–29</sup> In our meta-analysis, there was no significant association between age at assessment and the SMDs for both working memory and inhibition, suggesting that difficulties in these areas in children born preterm/low birthweight are stable and do not deteriorate or diminish as these children grow older. It should be noted that in our meta-analysis age at assessment ranged between 4 years 6 months and 14 years 10 months for working memory studies, and between 4 years 6 months and 11 years 2 months for the inhibition studies. There might be catch-up in these executive functions after this age, but at least until primary school age (inhibition) or secondary school age (working memory), we found no evidence for this.

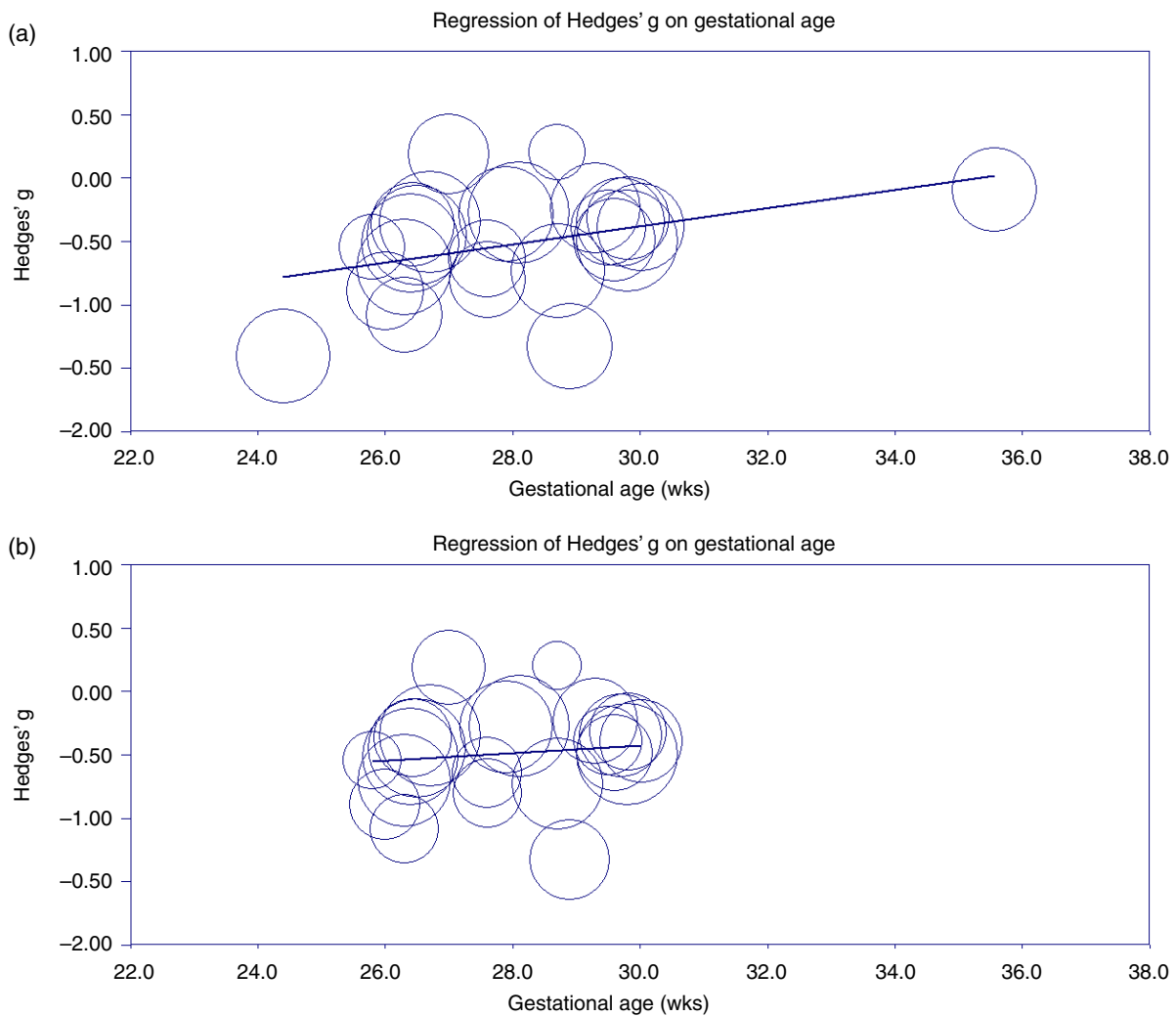
Year of birth of children born preterm/low birthweight was not a factor of relevance for the size of the executive function difficulties. This finding suggests that for working memory and inhibition, outcomes are not improving with advances in medical care. Burnett et al.<sup>91</sup> have recently investigated whether executive function outcomes of children born extremely preterm (<28wks gestational age) have improved by comparing three cohorts born respectively in 1991 to 1992, 1997, and 2005. They found that the outcomes of the three cohorts did not improve and that some outcome measures were even deteriorating. Although

the study of Burnett et al. relied on a questionnaire to assess executive function, their outcomes on year of birth for working memory and inhibition are in accordance with the results of our meta-regression analyses.<sup>92</sup> To ensure that gestational age-related survival bias did not explain the lack of executive function improvement in more recent years, we examined the relationship between mean gestational age and year of birth for the studies included in our meta-analysis (data available upon request). No significant relationship was found, suggesting that studies reporting on more recent cohorts of children did not contain a larger number of children at the lower end of the gestational age range.

Preterm/low birthweight birth is associated with substantial reductions in cognitive outcomes, as measured by IQ,<sup>4</sup> deficits in academic performance,<sup>4,5</sup> and children born preterm/low birthweight have a two to four times higher risk of receiving a diagnosis of attention-deficit/hyperactivity disorder than term-born peers.<sup>6,7</sup> Importantly, deficits in executive function may underlie these adverse outcomes in children born preterm/low birthweight. The neuro-anatomical sequels of preterm/low birthweight support the idea that executive function might be crucially involved in the adverse outcome of children born preterm/low birthweight. Executive function is highly dependent on white matter network integrity, which is often compromised after preterm birth.<sup>93–96</sup> Furthermore, research has shown that hypoxic-ischaemic events lead to damage in the striatum and its connections with the prefrontal cortex.<sup>97</sup> These brain structures are known to be very important for executive functions,<sup>98–101</sup> and children born preterm/low birthweight are vulnerable to damage in these brain areas as repeated hypoxic-ischaemic events are common in these children.<sup>97</sup>

**Table 1:** Moderator ranges for the working memory and inhibition subdomains

| Executive function domain | Gestational age range (wks) | Percentage of males (%) | Age range at assessment (y:mo) | Year of birth (range) | Study quality (range) |
|---------------------------|-----------------------------|-------------------------|--------------------------------|-----------------------|-----------------------|
| Working memory            | 24.4–35.6                   | 31–65                   | 4:6–14:10                      | 1991–2007             | 4–7                   |
| Inhibition                | 26.0–35.8                   | 45–65                   | 4:6–11:2                       | 1996–2011             | 3–7                   |



**Figure 4:** (a) Meta-regression of gestational age on working memory. (b) Meta-regression of gestational age on working memory after excluding two outliers with gestational ages of 24.4 and 35.6 weeks respectively. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)].

Early interventions are warranted to improve outcomes for children born preterm/low birthweight. There is evidence that effects of a computerized executive function training programme do not generalize to other functions than the trained executive function.<sup>102–104</sup> However, this literature is based on solely training working memory, while other executive functions, such as inhibitory control and cognitive flexibility, are also impaired in this population and may benefit from computerized interventions. Given the fact that executive function remains a vulnerable area of cognitive function in the population born preterm, future studies should be conducted on which type of interventions may be effective to diminish the encountered difficulties in executive function.<sup>103,105–110</sup>

### LIMITATIONS

First, because of the limited number of studies on executive function in children born moderate-to-late preterm/low

birthweight (i.e. >32wks gestational age), analyses for working memory included only one study within this gestational age range. Second, not enough studies presented data on cognitive flexibility to perform meta-regressions. Third, we were not able to obtain executive function data for 10 of the 45 studies that met all inclusion criteria and could not include these studies in our analyses. Of those 10 studies, three reported on inhibition and three reported on working memory in children and adolescents with a mean gestational age above 30 weeks. Lastly, unwelcome and potentially biasing heterogeneity could be introduced when the different instruments that are summarized with meta-analytic techniques are, in fact, not all measuring the same construct.<sup>111</sup> Therefore, we excluded executive function tasks that were used in less than five papers and we analysed the executive function tasks separately at first. However, as there were no significant differences in effect sizes between the separate executive function tasks within one executive function domain, and as there

is empirical evidence that similar brain regions are activated by these tasks, we combined the effect sizes of the tasks into aggregated effect sizes for each specific executive function domain.

## CONCLUSION

Children born preterm/low birthweight since the 1990s perform poorer than term-born peers on the three core executive function of working memory, inhibition, and cognitive flexibility, and none of these three core executive functions are more severely affected than the other. The magnitude of executive function difficulties was not associated with gestational age, and male sex was not a specific risk factor for poor executive function. Executive function difficulties remained persistent during transition to adolescence and did not improve with more recent year of birth. Given that executive function deficits are associated with worse academic performance at school age, executive

functions should be assessed at early schoolage in children born preterm/low birthweight to initiate early intervention targeted at improving these executive functions.

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## SUPPORTING INFORMATION

The following additional material may be found online:

**Appendix S1:** Search strategy.

**Table S1:** Details on studies included for working memory

**Table SII:** Details on studies included for inhibition

**Table SIII:** Details on studies included for cognitive flexibility

**Figure S1:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the study selection procedure.

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**RESUMEN****DÉFICIT EN FUNCIONES EJECUTIVAS EN NIÑOS NACIDOS PRETÉRMINO O CON BAJO PESO AL NACER: UN METAANÁLISIS**

**OBJETIVO** Investigar la magnitud del déficit de funciones ejecutivas y su dependencia de la edad gestacional, sexo, edad a la evaluación y año de nacimiento de los niños nacidos pretérmino y/o bajo peso al nacer.

**METODO** Se buscaron en PubMed, PsychINFO, Web of Science y ERIC estudios que reportaran las funciones ejecutivas de los niños nacidos pretérmino y/o bajo peso al nacer y en niños nacidos de término como controles nacidos en 1990 y posterior, evaluados a una edad media de 4 años o más. Los estudios se incluyeron si 5 o más estudios informaban sobre las mismas medidas de la función ejecutiva.

**RESULTADOS** Se incluyeron 35 estudios (3360 niños nacidos pretérmino y/o bajo peso al nacer, 2812 controles). Estos niños tuvieron una diferencia media estandarizada (DME) de 0.5 en la memoria de trabajo y la flexibilidad cognitiva y 0.4 en la inhibición de la DME. La DMEs en funciones ejecutivas no tuvieron diferencias significativas entre ellos. La meta-regresión mostró que la heterogeneidad de las DMEs para el trabajo de memoria y la inhibición no podría explicarse por la diferencia en la edad gestacional, sexo, edad a la evaluación o año de nacimiento.

**INTERPRETACION** Los niños nacidos pretérmino y/o bajo peso al nacer desde 1990 realizan la mitad de un SMD por debajo de sus pares nacidos a término en la función ejecutiva, que no parece mejorar con los avances más recientes en la atención médica o con el aumento de la edad.

**RESUMO****DEFICITS DA FUNÇÃO EXECUTIVA EM CRIANÇAS NASCIDAS PRÉ-TERMO OU COM BAIXO PESO AO NASCER: UMA METANÁLISE**

**OBJETIVO** Investigar a magnitude dos déficits da função executiva e sua dependência da idade gestacional, sexo, idade no momento da avaliação e ano de nascimento de crianças pré-termo e / ou baixo peso ao nascer.

**MÉTODO** PubMed, PsychINFO, Web of Science e ERIC foram pesquisados para estudos sobre funções executivas em crianças nascidas prematuras / com baixo peso ao nascer e controles a termo, nascidos em 1990 e anos posteriores, avaliados em uma idade média de 4 anos ou mais. Os estudos foram incluídos se 5 ou mais estudos relatassem as mesmas medidas de função executiva.

**RESULTADOS** Trinta e cinco estudos (3360 crianças nascidas pré-termo / baixo peso ao nascer, 2812 controles) foram incluídos. As crianças nascidas pré-termo / baixo peso ao nascer apresentaram uma diferença média padronizada (DMP) 0,5 menor na memória operacional e na flexibilidade cognitiva e DMP 0,4 menor na inibição. DMPs para essas funções executivas não diferiram significativamente entre si. Meta-regressão mostrou que a heterogeneidade em DMPs para memória de trabalho e inibição não pode ser explicada pelas diferenças de estudo em idade gestacional, sexo, idade na avaliação ou ano de nascimento.

**INTERPRETAÇÃO** Crianças nascidas pré-termo / baixo peso ao nascer desde 1990 realizam metade de um DMP abaixo de pares nascidos a termo em função executiva, o que não parece melhorar com os avanços mais recentes nos cuidados médicos ou com o aumento da idade.