

## Young adult motor, sensory and cognitive outcomes and longitudinal development after very and extremely preterm birth

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Abstract:	<p>In this narrative review, we report on adult outcomes after very (before 32 week of gestation) and extremely (before 28 weeks of gestation) preterm birth, with a focus on neuromotor function, neurosensory impairment, general cognitive abilities, executive function, and attentional abilities, all of which are important for academic progress, peer relationships, and participation. Longitudinal development from childhood to adulthood is described.</p> <p>Preterm born individuals have a higher risk for impairment of general cognitive abilities, executive function, attention, and neuromotor abilities well into adulthood, with, however, considerable variability in outcomes. Differences between individuals born preterm and their term born peers persist. Long term outcomes of general cognitive ability can be predicted with some degree of certainty from childhood assessments: those who perform poor on early childhood age assessments very likely will not catch up, whereas those who perform within the normal range on early assessments sometimes accelerate their development relative to term born peers. This appears similar for executive function and attention, although data on trajectories for these functions are somewhat inconsistent. In adulthood, some studies describe poorer educational outcomes, employment, independent living, and/or economic situation compared to term born individuals, however large proportion of those born preterm report similar self-perceived quality of life.</p>

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3 **Young adult motor, sensory and cognitive outcomes and longitudinal development**  
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6 **after very and extremely preterm birth**  
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## Abstract

In this narrative review, we report on adult outcomes after very (before 32 week of gestation) and extremely (before 28 weeks of gestation) preterm birth, with a focus on neuromotor function, neurosensory impairment, general cognitive abilities, executive function, and attentional abilities, all of which are important for academic progress, peer relationships, and participation. Longitudinal development from childhood to adulthood is described.

Preterm born individuals have a higher risk for impairment of general cognitive abilities, executive function, attention, and neuromotor abilities well into adulthood, with, however, considerable variability in outcomes. Differences between individuals born preterm and their term born peers persist. Long term outcomes of general cognitive ability can be predicted with some degree of certainty from childhood assessments: those who perform poor on early childhood age assessments very likely will not catch up, whereas those who perform within the normal range on early assessments sometimes accelerate their development relative to term born peers. This appears similar for executive function and attention, although data on trajectories for these functions are somewhat inconsistent. In adulthood, some studies describe poorer educational outcomes, employment, independent living, and/or economic situation compared to term born individuals, however large proportion of those born preterm report similar self-perceived quality of life.

**Keywords:** preterm birth, neuromotor, cognitive, executive function, adulthood, longitudinal development

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3 Approximately 11% of all live births worldwide are preterm with preterm birth rates  
4 continuing to increase and at the same time mortality in the context of preterm birth  
5 decreasing.<sup>1</sup> It is well known that preterm birth, in particular very (<32 weeks of gestation,  
6 wGA) and extremely preterm birth (<28 wGA), is associated with risk for long-term  
7 neurological and developmental impairment. For a number of preterm cohorts adult outcomes  
8 have now been described cross-sectionally, and for some of the cohorts **development from**  
9 **infancy to adulthood has been characterised.** Longitudinal development, and identifying early  
10 predictors, of general and specific cognitive abilities, including executive functions, and  
11 attention abilities which are crucial for academic progress and socio-emotional functioning, is  
12 of particular interest. Knowledge about developmental trajectories, on a group level and on  
13 an individual level, will allow definition of particular subgroups who benefit from enhanced  
14 surveillance and early intervention. In addition, it will improve early counselling.

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31 The aim of this **narrative** literature review is to summarise results of selected studies that have  
32 examined neuromotor function, neurosensory impairment, general cognitive abilities,  
33 executive function, and attentional abilities at adult age, and to present data on trajectories for  
34 these outcomes from early age to adulthood in individuals born very or extremely **preterm. It**  
35 **is acknowledged that there is emerging information on socio-emotional, psychiatric, and**  
36 **somatic adult outcomes of very and extremely preterm birth, however this is beyond the**  
37 **scope of this review.**

### 51 **Neuromotor function and development of neuromotor function into adulthood**

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54 There are surprisingly little data on adult rates of severe neuromotor impairment (Cerebral  
55 Palsy, CP) in reports from cohort studies of very or extremely preterm born individuals.  
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3 However, it is clear that preterm birth poses a risk for CP and that this is inversely related to  
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5 the degree of immaturity at birth.  
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9 Birth registry data from Norway on all births from 1967 -1983, looking at adult CP rates (age  
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11 20 -36 years at time of study), report a CP prevalence in relation to gestational age of 9.1%  
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13 for the 22-27 wGA group, 6% for the 28-30 wGA group, 1.9% for the 31-33 wGA group,  
14  
15 and 0.3 % for the 34-26 wGA group, compared with 0.1% for those born at term age.<sup>2</sup> This  
16  
17 is not significantly different from the Norwegian registry data for subsequent birth years  
18  
19 (1967-2001) for which Trønnes et al, 2014,<sup>3</sup> report CP rates (at age 13 years and older) in  
20  
21 relation to gestational age of 8.5% in the 23-27 wGA group, 5.6% at 28 - 30 wGA group,  
22  
23 2.0% at 31-33 wGA, 0.4% at 34 - 36 wGA, and 0.1% for term age. In contrast, recent data  
24  
25 from the Surveillance of Cerebral Palsy in Europe (SCPE) show that the prevalence of severe  
26  
27 neuromotor impairment, i.e. Cerebral Palsy, has been decreasing over the time period 1980 to  
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29 2003.<sup>4</sup> A decrease was seen for the normal birth weight group (>2500g), and also a  
30  
31 significant decrease for preterm born children with moderately low (1500 to 2499g) or very  
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33 low (1500 to 2499g) birth weight (BW), with an indication of a decreasing trend even in  
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35 those with extremely low (<1000g) BW.<sup>4</sup> Similar findings were reported by the Australian  
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37 CP Register for the birth years 1993-2006.<sup>5</sup> Whilst the Norwegian Birth Registry data and the  
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39 CP Register for the birth years 1993-2006.<sup>5</sup> Whilst the Norwegian Birth Registry data and the  
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41 CP registry data appear to be somewhat contradictory, this is most likely explained by  
42  
43 methodological issues.  
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48 Information on CP rates at adult age from prospective longitudinal studies in preterm cohorts  
49  
50 are available, for example, from the Helsinki Study of Very Low Birth Weight Adults  
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52 (<1500g; born 1978 – 1985, assessed age 18-27 years), which reported a prevalence of 6%.<sup>6</sup>  
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54 For the Ontario Extremely Low Birth Weight cohort (BW 501 - 1000 g; born 1977-1982,  
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56 assessed at age 22-25 years), Saigal et al, 2006,<sup>7</sup> reported a CP rate of 13.7%, 20% of those  
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58 having non-ambulatory CP. The participants of these cohorts were, of course, born before  
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3 antenatal steroids and surfactant were routinely used in clinical practice. For most single  
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5 centre or population based cohorts that were born after the introduction of antenatal steroids  
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7 and surfactant, CP rates have been described at school age, and one can, to a certain degree,  
8  
9 infer from these data on adult CP rates. Severe neuromotor impairment (CP) can be reliably  
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11 be diagnosed and/or confirmed in early childhood and it is not expected that a confirmed  
12  
13 diagnosis of CP or overall functional level of impairment will change during individual  
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15 development into adulthood. Therefore, CP rates in adult cohorts would not be expected to be  
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17 different from those in the same cohort established at childhood age.  
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24 At school age, CP rates reported for the EPIPAGE study (population based study in France of  
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26 children born 22-32 wGA in 1997) were 9% overall, with higher rates in the most immature  
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28 group (18% in those born 24-25 wGA, and 2% in those born at 32 wGA); 19% of those had  
29  
30 severe (defined as non-ambulatory) CP.<sup>8,9</sup> For children born extremely preterm, the EPICure  
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32 study (a population based study of a cohort born at 25 or fewer completed wGA, born in 1995  
33  
34 in the United Kingdom and Ireland), at school age, 12% had CP, and 54 % of those with CP  
35  
36 had severe CP (defined as Gross Motor Function Classification Scale level above 3).<sup>10,11</sup> The  
37  
38 CP rate of 12% is not significantly different from that reported for the second recruitment  
39  
40 phase of the EPICure study (children born in the year 2006, <27 wGA), which established a  
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42 CP rate of 14%. However, the rate of severe CP (GMFCS >3) was 35% and thus lower than  
43  
44 in the 1995 cohort.<sup>11</sup> Slightly lower CP rates are reported for the Swedish EXPRESS cohort,  
45  
46 a nationwide cohort of Swedish children born before 27 wGA 2004 – 2007, with a CP rate at  
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48 age 6.5 years of 9.5 %.<sup>12</sup>  
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54 Synnes et al, 2017,<sup>13</sup> reported on a Canadian prospective national cohort study of children  
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56 born <29 wGA between 2009 and 2011, and reported CP rates of 6.4% (approximately 20%  
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58 of those had non-ambulatory CP) at age 21 months. Considering that mild CP might still be  
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3 undiagnosed at this early age and the rate of CP in this cohort at school age therefore might  
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5 be a little higher, overall the data are in accordance with the EPIPAGE, EPiCure, and  
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7 EXPRESS cohort data.  
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10  
11 Cheong et al, 2017,<sup>14</sup> reported CP rates for the Victorian Infant Collaborative Study cohort of  
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13 11-14% in children born extremely preterm (22–27 wGA) in three eras of recruitment, 1991–  
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15 1992; 1997; and 2005, with no significant change over time in CP rates and also in the  
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17 proportion of those with moderate-severe CP (6-7%). These data, and the data from the two  
18  
19 EPiCure cohorts, are consistent with the SCPE and Australian CP Register data, which do not  
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21 (yet) show a decreasing prevalence of CP in the extremely low birth weight group. It will be  
22  
23 interesting to see how CP rates for the prospective population based cohorts of extremely  
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25 preterm born children and adults develop over time for future recruitment eras.  
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29 Relatively little information on adult age outcomes is currently available on minor  
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31 neurological signs and neuromotor function in the absence of CP. This has been described  
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33 mainly for school age cohorts. Broström et al, 2018,<sup>15</sup> in accordance with other studies that  
34  
35 looked at slightly more mature cohorts, for example, the EPIPAGE cohort assessed at age 5  
36  
37 years,<sup>16</sup> did show a higher prevalence of minor neurological dysfunction (assessed with a  
38  
39 simplified version of the Touwen examination) at school age for a regional cohort of  
40  
41 extremely preterm (<27 wGA) born children compared to the term born controls. In addition,  
42  
43 a meta-analysis by DeKieviet et al, 2009,<sup>17</sup> did show persisting poorer neuromotor function  
44  
45 throughout childhood and into adolescence in very low birthweight and very preterm children  
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47 compared to term born children.  
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53 Husby, et al, 2013,<sup>18</sup> compared a very low BW cohort at age 23 years to term born controls,  
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55 using the Grooved Pegboard test, Trail Making Test-5, Movement Assessment Battery for  
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57 Children-2 (Movement ABC-2), and High-level Mobility Assessment Tool (HiMAT). They  
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3 found differences in all measures between the very low BW and the term born normal BW  
4 controls, with motor speed being a particular problem for the very low BW participants. This  
5 cohort had previously been assessed at age 14 years, and the difference in gross and fine  
6 motor co-ordination did not change significantly between these two time points. They also  
7 found an association between impaired motor skills and mental health as well as health  
8 related quality of life.<sup>19</sup> Poole et al, 2015,<sup>20</sup> described adult motor co-ordination outcomes at  
9 ages 22-26 and 29-36 years for the Ontario cohort, a population-based birth cohort of  
10 extremely low BW survivors born between 1977 and 1982 in Ontario, Canada. They used the  
11 Adult Developmental Coordination Disorders/Dyspraxia Checklist, a self-report  
12 questionnaire that measures retrospectively childhood functional difficulties across different  
13 domains arising as a consequence of poor motor skills. They also used the Young Adult Self-  
14 Report Scale that measures, amongst other things, motor behaviours and competencies;  
15 neurosensory impairments (CP, visual, hearing impairment) were controlled for in the  
16 analysis. Significant differences were seen between the extremely low BW and the normal  
17 birth weight group at both ages. In addition, findings remained stable from assessments in  
18 childhood at age 8 years into adulthood, although it has to be kept in mind that different  
19 instruments were used at age 8 years (Bruininks-Oseretsky Test of Motor Proficiency;  
20 Vineland Adaptive Behavior Scales).

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The information on adult neuromotor outcomes in the absence of CP is mainly based on  
information from cohorts who were born before the antenatal steroid and surfactant era. More  
studies are needed for the adult age and it remains to be seen whether over time a similar  
trend as for CP rates occurs.

### **Hearing and visual impairment**



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3 There is relatively little information available on hearing and visual outcomes for adult age  
4 specifically. Similar to neuromotor outcomes, this has mainly been reported for school age. A  
5  
6 national register study of all live-born infants in Finland 1991-2008, including 1,018 256  
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8 participants, investigated the incidence of hearing impairment, visual impairment or  
9  
10 blindness, and ROP according to gestational age.<sup>21</sup> Three gestational age groups were  
11  
12 defined, <32 wGA (very preterm), 32- 33 + 6 wGA (moderately preterm), 34–36 + 6 wGA  
13  
14 (late preterm), and  $\geq 37$  wGA. Keeping in mind that diagnoses were made in early childhood  
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16 and up to school age only, this large study nevertheless provides relevant information in the  
17  
18 context of long term outcomes. Preterm birth across the preterm gestational age range did  
19  
20 pose a risk for visual impairment. Very and late preterm birth, but not moderate preterm birth,  
21  
22 posed a risk for hearing impairment. The study did show that the prevalence of hearing and  
23  
24 visual impairment (with or without a history of retinopathy of prematurity) is inversely  
25  
26 related to immaturity at birth, with extremely preterm/low BW posing the highest risk, even  
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28 after adjusting for relevant background factors.

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31 With regards to visual impairment, prevalences for blindness range from 7% -9% (extremely  
32  
33 preterm birth) to around 0.5 -2% (very preterm birth).<sup>22,23,7,24</sup> For extremely preterm  
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35 populations, the Swedish EXPRESS study reports ophthalmological problems at age 6.5  
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37 years in 37.9% of the preterm children, compared to 6.2 % of the term born controls, with  
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39 blindness in 2.1%, and visual impairment according to World Health Organization criteria in  
40  
41 4.8% of the preterm children. Strabismus was present in 17.4%, and refractive errors in  
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43 29.7%. Interestingly, no significant associations between GA at birth and visual impairment  
44  
45 were seen when treatment-requiring ROP was adjusted for; in contrast, an association  
46  
47 remained between refractive errors and GA at birth.<sup>25</sup> Adult (age 19 years) outcome data for  
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49 the EPIcure cohort<sup>26</sup> show that extremely preterm birth influences fovea maturation and  
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3 visual function into early adult life, and that early treatment for ROP is associated with poorer  
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5 visual acuity at adult age.  
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8 Severe hearing impairment (deafness) has been reported for up to 1.8 % for very preterm  
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10 born children <sup>e.g. 24, 27</sup> and for up to 4 % of those born extremely preterm. <sup>e.g. 22, 28</sup> At age 6.5  
11  
12 years severe hearing impairment was present for 2.1% of the extremely preterm participants  
13  
14 in the Swedish EXPRESS study<sup>12</sup>, and 2% for the EPICure extremely preterm children at age  
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16 11 years.<sup>29</sup> These findings are, overall, in accordance with other similar cohorts. <sup>e.g. 28</sup>  
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### 23 **General cognitive abilities and executive function**

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26 Although variability in outcome is large, the majority of children born very or extremely  
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28 preterm present at least subtle dysfunctions that impact cognitive abilities, educational  
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30 outcome and behaviour.<sup>30,31</sup> IQ is a global measure of cognitive function and is predictive of  
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32 educational attainment and life adjustment. Level of IQ affects, as well as is the result of,  
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34 development of a range of cognitive skills. Investigation into the effect of preterm birth on  
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36 attention, language, and executive skills related to general cognitive ability has increased our  
37  
38 knowledge into more specific weaknesses and areas of concern warranting monitoring and  
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40 interventions. The more specific skills and abilities are measured using cognitive tasks of  
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42 attention and executive function, ratings of scholastic abilities (i.e. mathematics, reading,  
43  
44 spelling) and behaviour ratings of everyday function. Executive function has been identified  
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46 as a particular area in which very and extremely preterm born individuals may develop  
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48 problems. It refers to cognitive processes **that are involved in goal-directed, self-regulation of**  
49  
50 **emotion, thought and behaviour**. Definitions and measurements of executive functions vary  
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52 and comparisons are not always easily made. Typically executive function tasks include  
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54 aspects of inhibition, working memory, cognitive flexibility, fluency and planning. Attention  
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3 and mental speed are sometimes included under the executive function umbrella. In real life,  
4 executive function deficits manifest themselves, for example, in problems with socio-  
5 emotional regulation, poor organizational and self-monitoring skills.  
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10 With regards to general cognitive ability, as measured by IQ, the majority of school-aged  
11 children born very or extremely preterm perform within the normal range, albeit on group  
12 level close to one standard deviation lower than term born peers, and this remains mainly  
13 unchanged when those individuals with CP are excluded from analyses.<sup>32,33,34</sup> There is strong  
14 evidence from several large cohorts in different countries that this difference continues to  
15 persist throughout adolescence and into adulthood, with the largest difference in IQ compared  
16 to term born individuals observed in those born extremely preterm.<sup>24,35,36,37,38,39,40,41,42,43</sup> Data  
17 from childhood and teenage age indicate that, in contrast to major neuromotor impairment,  
18 i.e. Cerebral Palsy, there has not been a significant change in cognitive/and or behavioural  
19 outcomes over time, with a negative correlation of measures of general cognitive ability and  
20 gestational age at birth across the preterm birth range.<sup>33</sup> This has not significantly changed for  
21 those born in the era of prenatal steroids and surfactant.<sup>34</sup>  
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39 Executive function difficulties at school age,<sup>44</sup> and, more recently, also at adolescent or adult  
40 age have been described for some of the large very or extremely preterm cohorts, with  
41 assessments based on questionnaires or test based performance. Overall, executive function  
42 difficulties are seen more frequently in individuals born very or extremely preterm than in  
43 their term born peers, and this occurs even in the context of general cognitive ability being in  
44 the normal range.<sup>45,46,47,48,49,50</sup> Meta-analyses have established differences to term born  
45 children on measures of executive function of 0.3 - 0.6 standard deviations in very preterm  
46 children<sup>44,51</sup> and cohort studies have found up to 1 standard deviation difference in extremely  
47 preterm children<sup>52</sup>. Similar to general cognitive ability, there is a correlation with immaturity  
48 at birth<sup>44</sup>, and associations with socio-economic status of the family<sup>47</sup>, and a number of  
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3 various perinatal and neonatal risk factors, including preterm brain injury, have been  
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5 described (see Taylor & Clark, 2016, for review<sup>53</sup>).  
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## 11 **Attention**

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14 Attention abilities are often being assessed as part of executive function. However, studies  
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16 specifically looking at attention deficits are available, and there is strong evidence that very  
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18 preterm and, in particular, extremely preterm children are at increased risk for difficulties  
19  
20 with attention, and attention deficit hyperactivity disorder (ADHD) is diagnosed in a  
21  
22 considerable proportion of very and extremely preterm children<sup>44</sup>, with an Odds Ratio of  
23  
24 about 3 for a risk of ADHD diagnosis when compared to term born children, and highest risk  
25  
26 for those born extremely preterm.<sup>54</sup> Some studies report predominantly problems with  
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28 inattention rather than hyperactivity; however, recent meta-analyses found an increased risk  
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30 for difficulties in inattention or hyperactivity, or both combined.<sup>54,55</sup> Several studies report  
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32 adult outcomes and overall the risk for attention problems continues to persist into  
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34 adolescence and adulthood.<sup>e.g. 56,57,58</sup>  
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## 43 **Longitudinal characterisation**

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46 For some cohorts developmental trajectories into adulthood have now been characterised.  
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48 Overall, the available data suggest that general cognitive ability, measured by IQ, is stable  
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50 over time and that differences between preterm born and term born individuals persist over  
51  
52 time. They also indicate that adult outcomes can be predicted with some degree of certainty  
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54 from assessments in early childhood. This is less clear for executive function development  
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56 and different studies report slightly different findings with regards to trajectories and stability  
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58 over time.  
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3 The Dutch Project On Preterm and Small for gestational age infants (POPS) has followed a  
4 large cohort of individuals born in 1983 at <32 wGA or with BW <1500g up to the age of 19  
5 years, with assessments at ages 5, 9, 11, 14, and 19 years. They found that major disability  
6 rates (based on cognitive and neurosensory functioning defined according to WHO criteria)  
7 remained stable throughout childhood and into young adulthood, but that minor disability  
8 rates increased with age.<sup>27</sup> At age 19 years, cognitive function as assessed with the  
9 Multicultural Capacity Test—Intermediate Level, a computer based intelligence test, were in  
10 the normal range, but still 24% of the preterm individuals reported difficulties in education.  
11 Predictors of intelligence were parental education, birthweight, and gestational age.<sup>60</sup>

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17 Allin et al, 2008,<sup>36</sup> report findings from a cohort of very preterm (<33 wGA) born young  
18 adults, assessed for IQ, and, as part of the executive function system, phonological and  
19 semantic verbal fluency, at ages 15 years and 19.5 years. They found similar differences  
20 between the preterm and the term born control group at both ages, which is similar to other  
21 reports, but also a decrease over time of Full Scale and Verbal IQ in the preterm group. This  
22 was only seen in males; no deterioration was found in females. Semantic verbal fluency  
23 increased over time in the term born participants but not in the preterm participants, whereas  
24 phonological verbal fluency increased in both groups over time. Interestingly, neither  
25 gestational age, nor birthweight, or neonatal ultrasound findings were related to the observed  
26 changes in performance over time. The same cohort was examined previously at ages 8 and  
27 15 years and a decrease in IQ in the preterms was also seen between these two time points,  
28 suggesting that in this cohort, on a group level, **that a decline** of general cognitive abilities  
29 **over time** occurred.

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3 Eryigit Madzwamuse et al 2015,<sup>47</sup> reported findings on IQ (measured with the Wechsler  
4 Adult Intelligence Scale) and executive function (assessed were selective attention, verbal  
5 inhibition, visual selectivity and attention, divergent thinking, and verbal processing) at age  
6 26 years for the the Bavarian Longitudinal Study cohort of very preterm born individuals  
7 (<32 wGA or BW<1500g), and compared this to age 6 years. At 26 years there was still a  
8 difference between the preterm participants and the term born controls in IQ and all executive  
9 function areas assessed. The results pointed to the preterms having more global problems  
10 rather than specific executive function deficits in contrast to the term born controls in whom  
11 problems in only one or two specific cognitive functions were seen. Socio-economic status of  
12 the family had a significant effect on outcomes at age 26 years. Over time, the difference  
13 between groups for IQ remained, indicating that there was no catch-up in the preterm group.  
14 Furthermore, for the same cohort, Breeman et al, 2015,<sup>41</sup> reported more stable general  
15 cognitive abilities over time in the very low BW/very preterm group (32 wGA or BW<1500g  
16 at birth) when measured at ages 5 months (cGA), 20 months (cGA), 4, 6, 8, and 26 years,  
17 than in the term born controls. The stability over time in the very low BW/very preterm group  
18 remained after adjusting for the family's socio-economic status. However, once those preterm  
19 participants with severe cognitive impairment had been excluded, there was no longer a  
20 difference in stability over time between the groups. This suggests that the predictive value of  
21 early assessments is strongest for those with severe cognitive impairment and that little  
22 change over time is expected in this subgroup. It also suggests that there are limitations to  
23 plasticity in brain development after preterm birth; this is consistent with previous work by  
24 Taylor et al, 2004,<sup>60</sup> in a longitudinal study children with low and extremely low BW. This  
25 study did show that some catch up in cognitive performance and a moderating effect of  
26 environmental factors was observed in those born with very low BW and few neonatal risk  
27 factors, but not in those born extremely preterm and/or with more neonatal risk factors.  
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3 Interestingly, in the study by Breeman et al, 2015,<sup>41</sup> adult Full Scale IQ at age 26 years could  
4 be predicted fairly well from very early assessments (Griffiths Mental Development Scale;  
5 total developmental quotient) at age 20 months in the very low BQ/very preterm group,  
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10 whereas for the term born controls predictive value of the 6 year assessment was best.  
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15 Similar to the Bavarian cohort, for the Stockholm Neonatal Project (SNP) cohort, where  
16 preterm participants (and <1500g BW and <37 wGA; the majority of which were born <27  
17 wGA) and term born controls were assessed at age 5.5 and age 18 years, overall stability of  
18 IQ and executive function over time was seen,<sup>61,62</sup> with developmental trajectories being  
19 fairly well established at pre-school age for the majority of the preterm born participants.  
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21 Lundequist et al, 2015<sup>61</sup> report that the extremely preterm group (22-27 wGA), performed  
22 poorest on all the cognitive tests, in particular on executive function tasks. Compared to  
23 results at age 5.5 years the effect had not diminished but rather strengthened over time. At  
24 age 18 years, young adults born very preterm, i.e. after 28 wGA, with appropriate BW and no  
25 perinatal complications, functioned like term-born, whereas extreme prematurity, intrauterine  
26 growth retardation, and neonatal complications were associated with poorer outcome in IQ  
27 and executive function. A person-oriented approach for determination of individual  
28 developmental trajectories was used by Stålnacke et al, 2015,<sup>62</sup> for the SNP cohort to identify  
29 multivariate distinct cognitive profiles at ages 5.5 years and at age 18 years, and to  
30 investigate individual stability over time. They showed that, overall, performance at age 5.5  
31 years was highly predictive of performance at age 18 years. However, when individual  
32 trajectories were examined, different patterns, depending on level of performance at age 5.5  
33 years, emerged: those who performed low at young age did not improve or even deteriorated  
34 at age 18 years; those who had performed above the norm at young age, generally improved  
35 in relative performance, and for those who were around the norm at young age, half improved  
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3 in relative performance and the other half did not or had increased problems. Individual  
4 cluster membership and movement between clusters could not **conclusively** be predicted by  
5 background variables, which points to the inter-individual variability in outcome even among  
6 individuals with similar medical background with regards to neonatal complications.  
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10 Overall, these findings on individual trajectories are consistent with the Bavarian  
11 Longitudinal Study group level data that indicate that, for those with severe impairment high  
12 stability in development of cognitive function can be expected, and that for those with normal  
13 or above normal cognitive abilities early in childhood, prediction of adult outcomes is more  
14 uncertain. With regards to executive function development, Stålnacke, et al, 2019,<sup>63</sup>  
15 investigated developmental stability of two core executive function components, working  
16 memory and cognitive flexibility, in the extremely or very preterm born (<32wGA) in the  
17 SNP cohort. Using a multiple mediator structural equation model, they found that both  
18 components of executive function were highly stable over time. Development, however,  
19 followed slightly different pathways. Male sex, lower gestational age at birth, intrauterine  
20 growth restriction, and perinatal medical complications adversely affected executive function  
21 outcome, and these effects were apparent already in infancy, as reflected by Griffiths Mental  
22 Development Scale at 10 months (corrected age). Level of parental education had a positive  
23 effect on outcome, which was apparent by age 5.5 years  
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46 Linsell et al, 2018,<sup>43</sup> reported longitudinal development of general cognitive ability for the  
47 participants of the EPICURE cohort, which is a study with focus on extreme preterm birth  
48 (<26+5 wGA at birth), with assessments at age 2.5, 6, 11, and 19 years of age. General  
49 cognitive abilities were assessed with the Bayley Scales of Infant Development at 2.5 year, at  
50 ages 6 and 9 years with the Kaufman Assessment Battery for Children, and at 19 years with  
51 the Wechsler Abbreviated Scale of Intelligence. In this study, no significant improvement or  
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3 deterioration over time was seen in the extremely preterm group, which, similar to the above  
4 mentioned studies in slightly less immature cohorts, indicates that also in extremely preterm  
5 born individuals general cognitive ability can be fairly well predicted from early assessments.  
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7 Trajectories in the extremely preterm and the term born control group overall were similar,  
8 with, however, larger within individual variability and larger variability between individuals  
9 in the preterm group, with this pattern increasing over time. Maternal education (in both the  
10 preterm and the term born group), male sex, and neonatal brain injury influenced cognitive  
11 outcome.<sup>43</sup>

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24 Doyle et al, 2015,<sup>42</sup> reported longitudinal findings from the Victorian Infant Collaborative  
25 study cohort (born <28 w GA or BW <1000g), a slightly more mature cohort than that of the  
26 EPICure study. Participants were assessed with the Bayley Scales at age 2 years and then  
27 with the age appropriate version of the Wechsler Scales at ages 5, 8, and 18 years. The  
28 differences between extremely preterm and term born control group remained unchanged  
29 over time for both measures of general cognitive abilities and academic achievement. Social  
30 factors (social class and maternal education) had a stronger effect on outcomes at older age  
31 but were weaker than biological factors (postnatal steroids, neonatal intraventricular  
32 haemorrhage), which had an effect throughout age. No individual trajectories are reported  
33 for this cohort though. Longitudinal development from 8 -18 years of age of executive  
34 function was investigated for this cohort by Costa et al, 2017,<sup>49</sup> using the parental form of  
35 Behavior Rating Inventory of Executive Function (BRIEF), which looks at executive  
36 dysfunction at home, school, and in social situations. Overall, for the majority of the  
37 participants, stable executive function performance was observed. At both time points more  
38 than half of the participants were in the normal range on both scales, 12-19 % had persistent,  
39 remitting, or late onset executive function difficulties. Sex, social class, and IQ had an effect  
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3 on executive function development, and there was an association between academic  
4 performance and executive function development, with the typical group performing better in  
5 all academic areas (mathematics, reading, spelling), and the remitting group performing  
6 better in reading and spelling than the late onset or persisting group. This study highlighted  
7 that for some preterm born individuals, difficulties with executive function are transient, and  
8 for others there is a late onset of difficulties, which has implications for tailoring support at  
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21 Longitudinal development of attention problems and diagnosis of ADHD from childhood to  
22 adulthood has been studied for some of the cohorts. For example, for the Bavarian  
23 Longitudinal Study cohort of very preterm/very low BW individuals, Breeman et al, 2016,<sup>57</sup>  
24 found between age 6 or 8 years and age 26 years a persisting difference in attention span and  
25 diagnosis of ADHD between the very preterm/very low BW group and the term born  
26 controls. Over time, for both groups attention span increased and attention problems  
27 decreased but while the term born individuals tended to outgrow their problems, the  
28 difficulties persisted for the preterm group. Once those with severe neurodisability were  
29 excluded findings remained unchanged at childhood age, but the differences between  
30 preterms and term borns were no longer seen in adulthood. Linsell et al, 2018, examined  
31 trajectories between age 6 years and age 19 years for extremely preterm individuals in the  
32 EPICure study, using the Strengths and Difficulties questionnaire.<sup>64</sup> Scores for inattention and  
33 hyperactivity were persistently higher in the preterm group than the term born group.  
34 Trajectories over time were similar, however, a slight decline in inattention and hyperactivity  
35 symptoms from childhood to adulthood was seen in the preterm group, which is different to  
36 what was observed in the Bavarian Longitudinal Study cohort.  
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### “Real life” implications at adult age

There is a considerable variability in educational outcomes, employment, independent living, economic situation, and relationships. Some studies report similar self-perceived health, well-being, and quality of life (with however, lower self-reported resilience) as those reported for term born individuals, for example, Hack et al, 2007,<sup>65</sup> for a very low BW population born before the prenatal steroid and surfactant era, and Roberts et al, 2013,<sup>66</sup> for an extremely preterm population born after the introduction of prenatal steroids and surfactant. In contrast, Hille et al, 2007,<sup>37</sup> reported for the Dutch POPS cohort significantly lower educational attainment and employment rates compared with the Dutch population. Saigal et al, 2006,<sup>67</sup> examined health related quality of life at adulthood in a cohort of extremely low BW and normal BW term born individuals (born 1977–1982), and found that although the preterm individuals reported significantly more limitations in mobility, cognition, and sensory function than term born individuals, there was no significant difference at young adulthood in self-perceived reported quality of life, even for those with disability. Similarly, in another study, Saigal et al, 2006,<sup>68</sup> reported, once individuals with neurosensory impairment were excluded, no significant differences between extremely preterm born and term born individuals in educational outcomes, employment, living independently, being in a relationship or being parents. Kroll et al, 2017,<sup>69</sup> reported for a cohort very preterm adults at age 28-34 years (born 1979-1984), associations between executive function and functioning in work and in social domains, social adjustment, years in education, and employment status. This was independent of IQ, and also remained unchanged once those with CP and neurosensory impairments were excluded from the analyses. A recent population based study in Germany,<sup>70</sup> assessing participation in young adults born extremely preterm (born 1997-1999), found lower frequency in participation in the areas of autonomy, relationships and community recreation in the preterm population when compared to term born peers. Physical,

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3 cognitive, psychological difficulties, or socio-economic status were related to one or both,  
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5 limited participation in autonomy and relationships. Overall, there are currently inconsistent  
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7 findings on adult age real life implications of cognitive and executive function deficits after  
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9 preterm birth, and further research in contemporary populations is needed.  
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### 16 **Limitations of existing studies and implications for interpretation of the findings**

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19 Some methodological issues need to be kept in mind in the interpretation of study findings  
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21 and when comparing outcomes of different cohort. The majority of currently available  
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23 information on adult outcomes of very or extreme preterm birth comes from cohorts who  
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25 were born before prenatal steroids and surfactant were routinely used in clinical practice; in  
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27 addition in the last couple of decades there have been further advances in perinatal and  
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29 neonatal medicine that might affect long term outcome, and this is not yet reflected in the  
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31 data that are currently available to us. Outcome data are generated from registers, single  
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33 centre cohorts, or population based cohorts, which makes direct comparison difficult. In  
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35 different studies, there are different proportions of very and extreme preterm individuals and  
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37 different proportions of those born small for gestational age, which affects outcome data but  
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39 often this is not reported separately; not always are outcome of those with neuromotor and/or  
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41 neurosensory impairment analysed separately, and in some studies analyses are not controlled  
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43 for all important biological and social factors. Finally, attrition bias is always a concern in  
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45 follow-up studies that span decades.  
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### 55 **Conclusions**

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58 Increasing numbers of individuals born very or extremely preterm survive without major  
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60 neuromotor (Cerebral Palsy) or severe neurosensory impairment. However, even in the

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3 absence of major neuromotor impairment, there remains a significant risk for impairment in  
4 areas that are important for academic success, peer relationships, and participation, with a  
5 large variability in these outcomes. Early prediction of outcomes at adult age remains a  
6 challenge; however, available information suggests that there is stability over time with  
7 regards to general cognitive abilities, and probably also for executive functions and attention.  
8 Childhood assessments are predictive of adult general cognitive and executive function  
9 abilities to a certain degree: those that perform poorly in childhood are likely to continue to  
10 have significant difficulties, whereas those that perform within the normal range sometimes  
11 accelerate their developmental pace relative to term born peers. However, it is important to  
12 remember that adult outcomes cannot be predicted at birth or infancy, and that biological  
13 and/or social variable that affect outcome will take their toll early, others will be increasingly  
14 important in later years.  
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