Cognitive Development Trajectories of Very Preterm and Typically Developing Children

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Cognitive impairment is common among children born very preterm (VPT), yet little is known about how this risk changes over time. To examine this issue, a regional cohort of 110 VPT (≤ 32 weeks gestation) and 113 full-term (FT) born children was prospectively assessed at ages 4, 6, 9, and 12 years using the Wechsler Preschool and Primary Scale of Intelligence–Revised and then Wechsler Intelligence Scale for Children, 4th ed. At all ages, VPT children obtained lower scores than their FT born peers (p < .001). Growth curve modeling revealed stable cognitive trajectories across both groups. Neonatal white matter abnormalities and family socioeconomic adversity additively predicted cognitive risk. Despite some intraindividual variability, cognitive functioning of typically developing and high-risk VPT children was stable and influenced by early neurologic development and family rearing context.

Although survival rates for infants born very preterm (VPT) have improved dramatically in recent decades, neurodevelopmental outcomes have not and are of major concern. Approximately 10%–15% will develop severe neurosensory impairments including cerebral palsy, blindness, and deafness, and a further 30%–60% will experience clinically significant cognitive, language, executive, attentional, and emotional difficulties (Woodward et al., 2009). The most prevalent of these adverse outcomes is cognitive delay, which is a source of considerable anxiety for parents, particularly during the school-age years.

Relative to their full-term (FT) born peers, children born VPT perform less well on both standardized tests of cognitive functioning such as the Bayley Scales of Infant Development (Vohr et al., 2000; Woodward, Anderson, Austin, Howard, & Inder, 2006) and tests of general intelligence (Anderson & Doyle, 2008; Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Johnson, 2007; Kerr-Wilson, Mackay, Smith, & Pell, 2012; Marlow, 2004; Woodward, Clark, Bora, & Inder, 2012). For example, Bhutta et al.’s (2002) meta-analysis of 15 case-control studies showed that school-age children born VPT obtained average IQ scores that were 10.9 points below their FT born peers. This IQ difference is very similar to the 11.9-point estimate obtained in a more recent meta-analysis by Kerr-Wilson et al. (2012), which included an additional 12 studies, suggesting that this gap is not reducing in size.

Not surprisingly, rates of both mild and severe delay for VPT children are also high at 49% and 16%, respectively, compared to 17% and 4% in the general population (Woodward et al., 2012). Mild and severe delay were defined as a score > 1 SD below the mean and more than 2 SD’s below the mean.
mean of a normative or FT comparison group. Such
general cognitive impairments have been shown to
have significant impacts on school achievement,
with a large proportion of VPT children lagging
behind their FT peers (Aarnoudse-Moens, Weisglas-
Kuperus, van Goudoever, & Oosterlaan, 2009; Litt
et al., 2012; Pritchard, Bora, Austin, Levin, &
Woodward, 2014; Taylor, 2010). Specifically, VPT
children score between 0.48 and 0.76 SDs below
their classmates in mathematics, reading, and spel-
lings (Aarnoudse-Moens et al., 2009) and are 3.4–4.4
times more likely to experience significant delays in
literacy and numeracy (Pritchard et al., 2014). Fur-
thermore, these cognitive difficulties are not con-
finned to childhood, with VPT born adolescents
requiring increased educational support and being
less likely to graduate from high school (Aylward,
2002; Hack et al., 2002; Litt et al., 2012; O’Brien
et al., 2004).

Despite the extensive body of research concerned
with the cognitive outcomes of children born VPT,
longitudinal analyses describing their cognitive
development over time are extremely rare (Ayl-
ward, 2003, 2010). Most studies to date have been
cross-sectional, describing the nature and extent of
cognitive impairments at a single time point. Thus,
little is currently known about whether these cogni-
tive impairments (a) improve, (b) worsen, or (c)
remain stable across childhood. This information is
important for parents and intervention service pro-
viders as knowledge of likely trajectories can help
inform the timing of developmental screening and
assessments, as well as the implementation of inter-
vention services and developmental support.

Given the importance of this issue, a detailed
search of PubMed, PsycINFO, and Google Scholar
was undertaken to identify studies. For inclusion,
studies were required to meet four criteria. These
included (a) peer reviewed, (b) sample of VPT chil-
dren consisted of those born ≤32 weeks gestation
and/or a birth weight ≤1,500 g, (c) cognitive func-
tioning was assessed using a standardized measure
administered at 2 or more age points, and (d) cogni-
tive assessment extended beyond the early child-
hood years. Ten studies were identified. Findings
were mixed, suggesting considerable uncertainty
and debate as to whether VPT children grow into or
out of their cognitive problems. These studies are
summarized in Table S1 and briefly reviewed below.

**Improvement in Cognitive Functioning Over Time**

Three studies, based on the same cohort, suggest
that cognitive outcomes of children born VPT
improve with age. The first by Ment et al. (2003)
assessed 296 very low birth weight (VLBW) infants
(600–1,250 g) at corrected ages 3, 4.5, 6, and 8 years
with the normed Peabody Picture Vocabulary Test–
Revised (PPVT–R; Dunn & Dunn, 1981). VPT chil-
dren’s performance on the PPVT–R improved over
time, with median scores increasing from 88 at age
3 years to 99 at age 8 years. VLBW children were
tested on the Stanford Binet Intelligence test at age
3, the Wechsler Preschool and Primary Scale of
Intelligence–Revised (WPPSI–R) at ages 4.5 and
6 years, and the Wechsler Intelligence Scale for
Children, 3rd ed. (WISC–III) at age 8 years. Based
on these measures of general cognitive functioning,
VLBW children’s average full scale IQ (FSIQ) scores
increased from 90 to 95 and their verbal and perfor-
mance IQ scores increased from 91 to 98 and 89 to
92. Over the study, however, it is important to note
that most VLBW children were in the low average
range and those subject to early onset intraventricu-
lar hemorrhage (IVH), followed by significant cen-
tral nervous system injury neonatally, showed
evidence of declines in cognitive functioning over
time. These findings suggest that the outlook for
children born VPT who are free of neurological
abnormalities is promising, whereas for those with
earlier brain injury the outcome may be less opti-
mistic. A subsequent follow-up of this cohort at age
12 years suggested additional catch-up gains on the
PPVT–R, with hierarchical growth curve analysis
indicating a 1.2-point increase per year between 3
and 12 years (Luu et al., 2009). A commentary on
Ment et al.’s (2003) article highlighted that although
the PPVT–R is a useful measure of receptive vocab-
ulary development, improvements in performance
over time may not generalize to more global
aspects of cognitive development and functioning
(Aylward, 2003). Furthermore, the lack of a concur-
rent FT control group makes changes in IQ difficult
to interpret as scores on standardized intelligence
tests tend to increase several points every few years
(Flynn, 1999). Thus, how these VLBW children were
functioning in comparison to other FT born children
in their community is not easy to discern (Aylward,
2003, 2010). Despite these difficulties, the large sam-
ple size and multiple follow-up assessments were
major strengths of this study.

Building on this work, a subsequent analysis of
the same cohort examined VLBW children’s cogni-
tive and language trajectories across the school
years using the PPVT–R and subtests of the WISC–
III at 8, 12, and 16 years (Luu, Vohr, Allan, Schnei-
der, & Ment, 2011). Consistent with findings at ear-
lier ages, VLBW adolescents demonstrated
significant impairments in general cognition and higher order language skills compared to their FT born peers at age 16. Catch-up gains in receptive vocabulary were again evident in the VLBW group. However, deficits in cognitive scores appeared stable from 8 to 16 years. Subgroups of VLBW children of low biological and social risk had similar cognitive trajectories to FT born children. Although it could be argued that this implies a potential catch-up gain in IQ, the IQ difference between the two groups was constant between 8 and 16 years suggesting the persistence of cognitive impairments over time.

Stable Cognitive Problems Over Time

The persistence or stability of cognitive impairments in children born VPT is of major concern. A study by Saigal, Hoult, Streiner, Stoskopf, and Rosenbaum’s (2000) assessed the cognitive abilities of 150 extremely low birth weight (ELBW; 501–1,000 g, M = 27 weeks gestation) children alongside 124 FT comparison children using an abridged version of the WISC–Revised (WISC–R) and found that average IQ scores of the ELBW children were 15 and 12 points lower than FT children at age 8 and during adolescence (12–16 years). Within-group analyses showed that the average estimated FSIQ of these children remained stable and low at 90. Major strengths of this study were the inclusion of a FT born comparison group and the use of consistent measures of IQ over time. However, as FT children also demonstrated a slight but significant decline in WISC–R performance from childhood to adolescence, this finding is difficult to interpret. In accordance with Saigal et al. (2000), Allin et al. (2008) study of 94 VPT (< 33 weeks gestation) and 44 FT adolescents also indicated that general cognitive impairments persist into adulthood rather than change with maturation. Specifically, VPT individuals scored significantly lower on an eight-item WISC–R at 15 years and on the Wechsler Abbreviated Scale of Intelligence at 19 years, with IQ scores 11 and 9 points below the FT group, respectively. Although the average difference between the groups was slightly reduced, no detectable interaction between birth group and age of assessment was observed, suggesting stability in cognitive performance across the two time points.

Although these results imply that cognitive delays or impairments are unlikely to improve over time, it is important to consider that the cohorts described in Saigal et al. (2000) and Allin et al. (2008) were born in the early 1980s, prior to significant improvements in neonatal care, thus limiting generalizability to more recent cohorts. Also, as only two time points were analyzed, few conclusions can be drawn regarding patterns of cognitive development. Nonetheless, findings do highlight the challenges that VPT children face as they move through childhood and as they encounter the increasing cognitive demands of adolescence.

Decline in Cognitive Functioning Over Time

Consistent with evidence that individuals born VPT continue to struggle throughout adolescence, are troubling reports of cognitive decline. Botting, Powls, Cooke, and Marlow’s (1998) study of 138 VLBW (≤ 30 weeks gestation and/or < 1,500 g birth weight) children and 163 FT control children examined performance on the WISC–III short form at age 12 in relation to their earlier scores from the WPPSI at age 6. At age 12, VLBW children obtained lower IQ scores (M = 89.7, SD = 17.2) than FT children (M = 97.8, SD = 17.4, p < .0001), with scores declining significantly from 108 at age 6 to 90 at age 12 years. Comparable declines were, however, also evident in the FT group, suggesting that IQ differences were unlikely to reflect cognitive deterioration. Rather, Botting et al. (1998) attributed the IQ differences to the recent standardization of the WISC. This study demonstrates the importance of a FT born comparison group when investigating cognitive functioning in VPT children over time.

Other studies have also documented a decline or deterioration in cognitive functioning with age in children born VPT (Isaacs et al., 2004; Koller, Lawson, Rose, Wallace, & McCarton, 1997; O’Brien et al., 2004; Stålnecke, Lundequist, Böhm, Forssberg, & Smedler, 2015). Koller et al.’s (1997) prospective longitudinal study of a cohort of 203 VLBW (≤ 1,500 g) children was one of the first to assess cognitive trajectories in VLBW children. Children were tested on the Bayley Scales of Infant Development at ages 1 and 2 years, the Stanford–Binet Intelligence scale at age 4, and the WISC–R at age 6. Cluster analysis revealed five different cognitive trajectories, with most children (67%) showing some degree of decline in function. Other trajectories showed evidence of both stability and improvement, while levels of functioning appeared to stabilize for most children after 3–4 years, demonstrating the poor predictive validity of cognitive assessments in early childhood.

In a more recent cluster analysis study, Stålnecke et al. (2015) found that cognitive trajectories become
reasonably well established in late preschool. In this study, the cognitive performance of 118 preterm (< 37 weeks gestation, < 1,500 g birth weight) children at 5.5 years was highly predictive of performance at age 18 years. Those who performed at initially low levels were unlikely to catch up over time, whereas those who performed at or above the normal range were unlikely to deteriorate below this level. Again, however, some children showed improvements in relative performance over time, whereas others became more impaired, signifying the heterogeneous nature of cognitive outcomes and emphasizing the importance of long-term follow-up and monitoring of individuals born VPT. Individual variability in cognitive development is important to acknowledge as different patterns or trajectories may be difficult to detect in group analyses (Stålnacke et al., 2015). Koller et al. (1997) and Stålnacke et al. (2015) considered this important issue yet were limited by several factors. First, children of gestational ages up to 37 weeks were included in both studies, limiting generalizability to VPT (< 33 weeks gestation) populations. Second, although Koller et al. (1997) conducted multiple assessments, they were concentrated in early childhood precluding conclusions about children’s longer term cognitive trajectories. In contrast, Stålnacke et al. (2015) conducted two assessments spanning from late preschool age to late adolescence, yet the nature of patterns of cognitive functioning across middle to later childhood was not clear. Nevertheless, the variability in cognitive outcomes, including the potential for some children to show cognitive deterioration over time, is important to consider.

O’Brien et al. (2004) later administered the WISC–R to 151 VPT children (< 33 weeks gestation) at age 8 years and again at ages 14–15 years and found evidence for both significant cognitive decline and increases in special education need with age. Children’s IQ scores decreased from 104 to 95, and the proportion of children requiring remedial educational assistance increased from 15% to 24% between the ages of 8 and 15 years. This study was strengthened by the use of the same cognitive measure at each assessment. However, with only two assessment points, little could be inferred about the patterns of cognitive development. There was also no FT comparison group. It is also possible that the cognitive deterioration evident in O’Brien et al.’s (2004) study was attributable to neurologically impaired children. There has been suggestion that declines in cognitive functioning over time may be restricted to studies that include VPT children subject to neurological injury in their analyses (Isaacs et al., 2004). However, there is also some evidence to suggest otherwise. Isaacs et al. (2004) restricted their sample to 82 VPT children (< 30 weeks gestation) who were classed as neurologically normal at 7.5–8 years of age and administered the WISC–R in childhood (Mage = 7 years) and the WISC–III in adolescence (Mage = 15 years). They found that even these children exhibited declines in cognitive performance over time, with average verbal and performance IQ scores declining by 9 and 12 points across the two assessments. Unfortunately, again, there was no FT control group. Despite this, these findings suggest that VPT children may show declines in cognitive functioning and that this decline was not only confined to high-risk infants with neurological injury but was also evident in lower risk VPT born children.

Mechanisms of Cognitive Impairment

Vital to reducing the long-term risks associated with VPT birth is an improved understanding of the mechanisms placing these children at risk of cognitive delay. VPT infants are biologically immature and commonly experience medical problems such as respiratory distress, IVH, infection, and cerebral white matter abnormalities (WMA) or injury (Fanaroff et al., 2007; Stoll et al., 2010). In spite of efforts to identify early perinatal markers of neurodevelopmental outcomes, few factors are as strongly associated with long-term cognitive function as cerebral WMA on term magnetic resonance imaging (MRI). These abnormalities are an especially robust predictor of cognitive delay independent of other perinatal risk factors such as gestational age or birth weight (Iwata et al., 2012; Woodward et al., 2012). Diffuse WMA affect the majority of VPT born infants (50%–70%) and include loss of white matter volume, ventriculomegaly, white matter signal abnormalities, corpus callosum thinning, and delayed myelination (Inder, Anderson, Spencer, Wells, & Volpe; 2003; Inder, Wells, Mogridge, Spencer, & Volpe, 2003; Woodward et al., 2006). The presence and severity of these neonatal cerebral abnormalities increase risk of later cognitive impairment for VPT born infants (Iwata et al., 2012; Woodward et al., 2012). For example, Woodward et al. (2012) found that VPT children with mild and moderate to severe WMA on term MRI were at increased risk for a range of cognitive impairments at 4 and 6 years. The cognitive functioning of unaffected VPT children, however, was relatively intact and comparable to FT
controls, highlighting the potential significance of early cerebral white matter connectivity for later cognitive function and providing sufficient rationale for focusing on this perinatal predictor in the investigation of longer term cognitive outcomes.

The family environment in which cognitive development takes place must also be considered. High-risk environments characterized by socioeconomic disadvantage and low maternal education are well known to be associated with lower levels of cognitive functioning and school achievement (Bradley & Corwyn, 2002; Duncan, Brooks-Gunn, & Klebanov, 1994; Hackman & Farah, 2009; Noble, Norman, & Farah, 2005; Wong & Edwards, 2013). The co-occurrence of VPT birth and socioeconomic disadvantage thus creates a situation in which newborn infants may be exposed to a potentially hazardous combination of biological and social risk (Blumenshine, Egerter, Barclay, Cubbin, & Brave-man, 2010; Kramer, Seguin, Lydon, & Goulet, 2000; Kramer et al., 2001; Wong & Edwards, 2013). Although the associations between VPT birth and cognitive outcome remain after covariate adjustment for family social risk (Woodward et al., 2012), aside from covarying for social risk few studies have examined their joint impact. Consequently, how biological and social risk factors collectively impact cognitive development in VPT born children has not been established.

The Current Study

Against this general background, the aim of this study was to use growth curve modeling to examine the cognitive development of a cohort of VPT and FT born children between the ages of 4 and 12 years. Data were drawn from a prospective longitudinal cohort study of VPT and FT children born in New Zealand. This study addresses many of the methodological problems that have limited existing research by including a FT born comparison group, conducting four assessments across childhood, and retaining consistency in measures used and constructs assessed. The specific aims of this study were as follows:

1. To compare the cognitive performance of children born VPT and FT at ages 4, 6, 9, and 12 years.
2. To use growth curve modeling to describe patterns of cognitive development from 4 to 12 years in both groups.
3. To identify predictors of children’s cognitive development over time. Predictors examined included family social risk, sex, and the severity of cerebral WMA on MRI at term equivalent age.

Method

Participants

Study participants consisted of two groups of children. The first group was a regional cohort of 110 children born VPT (≤32 weeks gestation) who were consecutively admitted to the level III Neonatal Intensive Care Unit at Christchurch Women’s Hospital (New Zealand) over a 2-year period (November 1998–December 2000). Excluding deaths (n = 3), 99% (n = 106) were followed up at 4 years, 97% (n = 104) at 6 years, 96% (n = 103) at 9 years, and 97% (n = 104) at 12 years.

The second group, recruited at age 2 years, comprised a sample of 113 FT born (37–41 weeks gestation) children. These children were identified from hospital birth records for the same period by alternately selecting, in a forward and backward fashion, the second child listed in the delivery schedule. As a group, they were matched to the VPT cohort for gender, delivery hospital, and date of birth. Of those identified, 62% were recruited at age 2 years. Reasons for nonparticipation included untraced (n = 32), moved overseas (n = 9), refusal (n = 9), and agreed but unable to attend clinic appointments within the 2-week assessment window due to illness or family circumstances (n = 19). No significant differences were found between recruited and nonrecruited term born infants on measures of gestational age, birth weight, socioeconomic status (SES), or race (p > .05). In addition, comparison of the socioeconomic profile of families recruited as part of the FT comparison group with regional census data showed that they were highly representative of the Canterbury region from which they were recruited (Statistics New Zealand, 2001). Retention at the 4- and 6-year follow-up was high at 96% (n = 108) and remained extremely high at the 9- and 12-year follow-up, 97% (n = 110) and 96% (n = 109), respectively. Table 1 describes the clinical characteristics of the two study groups.

Procedure

All children underwent a comprehensive neurodevelopmental assessment within 2–4 weeks either side of their 4th, 6th, 9th, and 12th birthdays (corrected for gestational age at birth). Procedures and measures were approved by the Canterbury
Regional Ethics Committee, and written informed consent was obtained from all parents or guardians. Assessments at each follow-up were completed by a clinical psychologist and supervised postgraduate level research assistants, blind to birth group and perinatal history.

**General Cognitive Functioning**

At ages 4 and 6 years (corrected), general cognitive functioning was assessed with a short form of the WPPSI-R. This consisted of two verbal subtests (comprehension and arithmetic) and two performance subtests (picture completion and block design). This short form is reliable and valid, with a split half reliability coefficient of .93 and a validity coefficient of .92, indicating a strong linear relationship between short form IQ scores and those obtained from the full WPPSI-R (LoBello, 1991).

Composite scores calculated from subtest scores provided an estimate of FSIQ and thus the general intellectual ability of each child. One VPT child at age 4 and two at age 6 were assigned a minimum possible estimated FSIQ score of 40 due to severe disability or inability to complete the assessment. Additionally, one FT child was excluded at age 4 due to an incomplete assessment, and one VPT child’s IQ score was excluded at age 6 due to an administration error.

At ages 9 and 12 years (corrected) a short form of the WISC-IV was administered to all children (Wechsler, 2003). Although correcting for gestational age to age 12 is conservative in nature, this method helps ensure that rates of cognitive impairment among VPT children are underestimated as opposed to overestimated. This short form consisted of the following five subtests: block design, similarities, coding, vocabulary, and arithmetic, thus encompassing each of the four indices of the WISC-IV full form: verbal comprehension, perceptual reasoning, working memory, and processing speed. Composite scores were calculated to provide an estimate of FSIQ. Short forms of the WISC-IV with combinations of four and five subtests have been shown to achieve validity coefficients of .93 and are commonly used for research purposes (Sattler & Dumont, 2004). At the 9-year follow-up, three VPT children were assigned a lowest possible score of 40 due to their inability to complete the assessment, and one VPT child had their FSIQ estimated from two subtests (vocabulary and matrix reasoning). In addition, six VPT children were tested on the full WISC-IV as part of a parallel study and could not be retested by the current study. These children’s FSIQ scores were used to provide a measure of cognitive functioning at age 9. In addition, one FT child was untestable. At the 12-year follow-up, two VPT children were assigned an IQ score of 40 due to severe disability.

**MRI Scanning (Term Equivalent Age)**

All VPT infants underwent MRI at term equivalent age (full details reported in Woodward et al., 2006). All scans were independently assessed by a pediatric neurologist and neuroradiologist unaware of infant perinatal history. WMA were scored according to five scales which assessed the nature and degree of white matter signal abnormality, the loss in volume of periventricular white matter, the
magnitude of any cystic abnormalities, ventricular dilation, or thinning of the corpus callosum. Composite scores were then used to categorize infants into four groups according to the severity of observed WMA. These categories were none (a score of 5–6), mild (a score of 7–9), moderate (a score of 10–12), and severe (a score of 13–15). Given the small number of children with severe WMA, children with moderate and severe WMA were combined into one group. As only a small subsample of FT children (n = 10) had a term MRI and no evidence of cerebral WMA was found, for the purposes of statistical analysis, all FT children were assigned a score of 0 for WMA commonly associated with VPT birth.

**Family Social Risk**

Five measures of family social risk were assessed for all children during the first 2 years of life, including maternal minority ethnicity (non-New Zealand European), maternal age at child birth (< 21 years), maternal education (did not graduate from high school), single parent family, and family SES (professional or semiskilled, unskilled or unemployed). Each variable was coded as either 1 = present or 0 = absent, and then summed to form a composite family social risk index (scaled 0–5). As few children were exposed to more than two of these risk factors, the index was scaled to represent the presence of 0, 1, or ≥ 2 family social risk factors.

**Statistical Analysis**

**Independent Samples t Test**

To assess differences in IQ between the FT and VPT children at each age of assessment, independent samples t tests were conducted in SPSS 22.0 (IBM Corp, 2013). Results were considered to be significant at (p < .05).

**Growth Curve Modeling**

A linear mixed effects model analysis, also known as multilevel growth curve modeling, was used to examine children’s general cognitive functioning over time. This analysis was conducted in Stata 12 (StataCorp, 2011), with model parameters estimated by restricted maximum likelihood. A series of growth curve models were fitted to the data in which trajectories of IQ scores over time were modeled as a linear function of age, group status, and other factors, with allowance for individual-specific variability in the intercept and slope of the trajectories over time. The initial model fitted to the data was of the form:

\[ y_{it} = \beta_0 + \beta_1 \text{AGE}_{it} + \beta_2 \text{GROUP}_{i} + \epsilon_{0i} + \epsilon_{1i} \text{AGE}_{it} + u_{it} \]

where \( y_{it} \) was the IQ score for the \( i \)th individual at age \( t \), \( \text{AGE}_{it} \) was the individual’s age in years (corrected for gestation) at time \( t \) scaled relative to a baseline age of 4 years, \( \text{GROUP}_{i} \) was a dummy (0 or 1) variable representing the individual’s group status (FT = 1; VPT = 0), \( \epsilon_{0i} \) and \( \epsilon_{1i} \) were individual-specific random effects representing individual-specific variations in the intercept and slope of the growth curve, respectively, and \( u_{it} \) was a random disturbance term. In this model, the parameter \( \beta_0 \) represents the intercept of the average growth trajectory for the total sample, \( \beta_1 \) represents the average change in IQ scores in the total sample for each additional year of age, and \( \beta_2 \) can be interpreted as the impact of FT birth status on average cognitive ability at a given age. Thus, in effect this model partitions variability in individual IQ scores over time into three components: a fixed effects component \( (\beta_0 + \beta_1 \text{AGE}_{it} + \beta_2 \text{GROUP}_{i}) \) representing the average IQ trajectory over time in each group, a random effects component \( (\epsilon_{0i} + \epsilon_{1i} \text{AGE}_{it}) \) representing individual-specific deviations around the average intercept and slope of the growth curve over time, and a component due to random error \( (u_{it}) \). The random effects \( (\epsilon_{0i}, \epsilon_{1i}, u_{it}) \) were each assumed to be normally distributed with mean zero and unknown variance, with these variance parameters to be estimated as part of fitting the model. The individual-specific random effects \( (\epsilon_{0i}, \epsilon_{1i}) \) were permitted to be correlated with each other but were assumed to be independent of the other terms in the model.

This model was subsequently extended to include main effects of sex, family social risk, mild WMA, and moderate to severe WMA, to assess their impact on average cognitive performance at a given age. Interactions between all model variables were also assessed. Specifically, differences in slope were investigated through testing interactions of age with birth group, sex, family social risk, and WMA, whereas the differential influence of these additional predictors for FT and VPT children were assessed through interactions with birth group. Interactions between sex and family social risk, sex, and WMA, as well as family social risk and WMA were also tested. The significance level was set at \( p < .05 \), and only significant interactions were
Results

Characteristics of the Sample

Table 1 shows the neonatal and family characteristics of the two birth groups. The VPT group was born of lower gestational age \( (p < .001) \) and birth weight \( (p < .001) \), with the majority (75%) presenting with WMA at term equivalent age, graded as either mild (57.8%), moderate (14.7%), or severe (2.8%). VPT children were also characterized by elevated family social risk \( (p < .001) \). Comparable proportions of the VPT (29.9%) and FT (26.1%) group were exposed to a single family social risk factor during the first 2 years of life, however 32.7% of VPT children were exposed to two or more risk factors, compared to only 12.6% of the FT children. The proportions of children exposed to each family social risk factor are shown in Table 1.

Cognitive Development in VPT and FT Children

Table 2 shows the performance of VPT and FT born children on the standardized tests of general intellectual functioning administered at ages 4, 6, 9, and 12 years. At each age assessment, VPT children obtained significantly lower IQ scores than FT children \( (p < .001) \), with a minimum average decrement of 9 IQ points. Cohen’s \( d \) measure of effect size demonstrated moderately sized effects across all assessments, with the largest decrement at age 6 years \( (d = .87) \). Group differences in IQ remained significant at 4, 6, 9, and 12 years following adjustment for family social risk \( (p < .001) \).

Trajectories of Cognitive Development

Figure 1 displays the IQ score trajectories for VPT and FT born children. As shown, although the performance of some VPT children was comparable to that of their FT born peers, the cognitive trajectories of VPT children were generally characterized by lower average performance and greater intra- and interindividual variability. Additionally, despite this variability, the average overall pattern for both groups appeared relatively stable, with no overwhelming trends of improvement or decline in IQ between the ages of 4 and 12 years.

To further examine patterns of cognitive functioning over time, a linear mixed effects growth curve model analysis was conducted. This analysis was undertaken in three steps and the estimated regression coefficients and standard errors (Est \([SE]\)) for the fixed and random effects of each of the three fitted models are presented in Table 3. A baseline model (Model 1) was fitted with age and birth group as the only predictors. The fixed effects component of Model 1 shows the estimated regression coefficient for the intercept of the fitted model as well as the estimated effect of birth group and age on cognitive performance. The random effects component of the fitted model shows the estimated standard deviation of individual-specific variability in the intercept \((e_0)\), the estimated standard
deviation of individual-specific variability in slope ($\epsilon_{1i}$), and the residual random error ($u_{ii}$). Restricted log-likelihood values were used as a measure of improved model fit to the data and are also presented in Table 3.

Model 1 shows a statistically significant effect of group ($p < .001$) which suggests that at any given age, VPT children scored an average of 10.83 IQ points lower than FT children. The main effect of age was not significant ($p = .24$) indicating the

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**Table 3**

<table>
<thead>
<tr>
<th>Parameters and growth predictors</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
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<td><strong>Fixed effects</strong></td>
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<tr>
<td>Intercept</td>
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<td>101.10 (2.74)**</td>
<td>100.71 (2.75)**</td>
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<td>Group (full term)</td>
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<tr>
<td>Rate of change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.11 (0.10)</td>
<td>0.12 (0.10)</td>
<td>0.32 (0.13)*</td>
</tr>
<tr>
<td>Age x Female Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$SD (\epsilon_{0i})$</td>
<td>12.60 (0.70)</td>
<td>11.47 (0.66)</td>
<td>11.47 (0.66)</td>
</tr>
<tr>
<td>$SD (\epsilon_{1i})$</td>
<td>0.94 (0.11)</td>
<td>0.94 (0.11)</td>
<td>0.91 (0.11)</td>
</tr>
<tr>
<td>Corr ($\epsilon_{0i}, \epsilon_{1i}$)</td>
<td>-0.03 (0.11)</td>
<td>-0.00 (0.12)</td>
<td>-0.00 (0.12)</td>
</tr>
<tr>
<td>$SD (u_{ii})$</td>
<td>6.18 (0.21)</td>
<td>6.19 (0.21)</td>
<td>6.19 (0.21)</td>
</tr>
<tr>
<td>Restricted log-likelihood</td>
<td>-3,113.36</td>
<td>-3,077.86</td>
<td>-3,075.58</td>
</tr>
</tbody>
</table>

**Note.** WMA = white matter abnormalities. *$p < .05$.* **$p < .001$**.
average trajectory of the pooled sample of VPT and FT children was stable over time. Model 1 also indicated evidence of individual-specific variation in the data, showing an estimated random-intercept standard deviation of 12.60 IQ points and an estimated random-slope standard deviation of 0.94 IQ points per year. A log-likelihood ratio chi-square test was used to assess the improvement in model fit using a mixed effects model including these individual-specific components of variation compared to a simple linear fixed effects growth curve model. This result was highly significant, \( \chi^2(3) = 698.61, p < .001 \), demonstrating the presence of substantial random variability and supporting the use of the mixed effects model.

To investigate the influence of additional predictors of cognitive performance for VPT and FT children, measures of child sex, family social risk, and neonatal WMA were introduced into the analysis. The fitted model parameters are reported in Model 2. As shown in Table 3, the restricted log-likelihood value for Model 2 was reduced from \(-3,113.36\) in Model 1 to \(-3,077.86\), suggesting that the addition of these factors improved model fit. No substantial influence on estimated standard deviations of random-intercept or random-slope was observed.

Moderate to severe WMA were associated with significantly lower IQ scores \((p < .001)\). Model 2 demonstrated that at any given age, VPT children with moderate to severe WMA scored on average 18.06 points below VPT children with no WMA at term equivalent age. Mild WMA were also associated with lower IQ scores, with affected VPT children scoring on average 4.09 points below their VPT peers with no WMA, at any given age. This effect, however, failed to reach statistical significance \((p = .15)\).

A significant effect of family social risk \((p < .05)\) was also found. This suggested that, across both birth groups, the IQ score of any given child decreased by an average of 2.8 points in the presence of one family social risk factor and decreased by another 2.8 points among those with two or more family social risk factors. A marginally significant effect of birth group remained \((p = .12)\), implying residual effects of VPT birth, with VPT children at any given age scoring an average of 4.19 IQ points below their FT peers, over and above decrements in IQ attributable to the presence of WMA.

The final model (Model 3) was extended to test for interactions between model variables. The effects of family social risk and WMA remained similar to Model 2, with moderate to severe WMA having the greatest negative impact on cognitive performance. A significant fixed effect of sex \((p < .05)\) was also found. All possible interactions between age, birth group, sex, family social risk, and WMA were tested, however, the only significant interaction found was that between age and sex \((p < .05)\). These results must be interpreted with the acknowledgment that upon fitting the models to the data, cognitive performance at age 4 years represented the origin, as this was the first data point. Thus, the Age \(\times\) Sex interaction implies that across both groups, female children scored on average 3.46 IQ points higher than male children at the origin (age 4 years). This sex difference, however, was not constant across childhood as a significant effect of age suggests a positive estimated slope for males over time \((\beta = .32, SE = .13, p < .05)\). Specifically, this effect suggests that across birth groups, males on average showed a 3.2-point increase in IQ with each additional year, from 4 to 12 years. The estimated slope for females, although slightly negative, was small and nonsignificant \((\beta = -.09, SE = .14, p = .50)\). Figure 2 illustrates the predicted mean performance for male and female children, in each birth group. Although the trajectories for VPT children are shown to be lower than that of FT children, as no evidence of an Age \(\times\) Birth Group interaction was found, their slopes are identical.

To further illustrate the implications of the final fitted model and to graphically demonstrate the influence of family social risk and WMA on VPT and FT children’s cognitive development over time, a series of predicted mean growth curve comparisons were calculated from the estimated coefficients presented in Model 3. The results of this analysis are summarized in Figures 3 and 4.

**Influence of Family Social Risk on Cognitive Development**

Figure 3 illustrates predicted mean growth trajectories for VPT and FT children exposed to varying degrees of family social risk. Across both birth groups, family social risk is shown to have a cumulative negative effect on children’s cognitive performance, with children born into families with two or more identified family social risk factors found to have a predicted mean cognitive trajectory that was 5.6 IQ points lower than children born into families not characterized by any such risk factors. Although family social risk is shown to negatively impact the cognitive trajectories of both VPT and FT children, it is clear that the combination of VPT birth and high family social risk is particularly detrimental, with VPT children exposed to two or more family social risk factors having the lowest trajectory.
Influence of WMA on Cognitive Development

Figure 4 illustrates the predicted mean growth trajectories for VPT children with varying degrees of neonatal neurological risk relative to FT children. Neonatal WMA were associated with poorer cognitive performance across childhood, with a marked decrement in cognitive performance for those with moderate to severe WMA. The average growth curve trajectory for VPT children with mild WMA was 4 IQ points lower than VPT children without WMA and 8 IQ points below that of FT born children. The average growth curve trajectory for VPT children with moderate to severe WMA, at term, is shown to be 18 IQ points below VPT children without WMA and 22 IQ points below FT born children. Although the model predicts a higher trajectory for VPT children without WMA, a 4.2-IQ point decrement remains evident when compared to the FT trajectory, signifying potential residual effects of preterm birth on cognitive outcome.

Contributions of Biological and Social Risk on Cognitive Development in Children Born VPT

To illustrate the joint effects of WMA and family social risk on the cognitive development of VPT born children, the final model was refitted with dichotomous indicators of cerebral WMA risk (mild to severe WMA = 1, no WMA = 0) and family social risk (≥ 2 family social risk factors = 1, ≤ 1 family social risk factor = 0). The model was fitted to the data from the full sample; however, predictions were based only on the VPT series. Predicted trajectories were generated for four different
combinations of risk, including low risk (no WMA, low family social risk factor), medium risk (WMA-only), medium risk (high family social risk-only), and high risk (WMA + high family social risk).

Predicted mean growth trajectories in accordance with the refitted model are displayed in Figure 5 and illustrate a number of important findings. First, VPT children with no WMA and low family social risk had the highest average cognitive trajectory. Second, high family social risk in the absence of WMA lowered the average cognitive growth curve trajectory for VPT children by 4.7 IQ points in the absence of WMA, illustrating the cognitive risks associated with raising a VPT born child in a high-risk family environment. Third, WMA in the absence of high family social risk further lowered the cognitive performance of VPT children, with the average cognitive trajectory of VPT children with WMA on term MRI shown to be 7.4 IQ points lower than that of low-risk VPT children. However, when these risk factors were both present, the adverse effects on cognitive function were increased, with the average cognitive trajectory of high-risk (WMA + high family social risk) VPT born children predicted to be 12 IQ points below that of low-risk (no WMA, low family social risk) VPT children. Thus, combining biological and family social risk served to increase the magnitude of the effect substantially, in an additive manner.

**Discussion**

This study extends on previous research concerned with the long-term cognitive development of children born VPT. Of the few longitudinal studies that extend beyond early childhood, methodological differences, and limitations made it unclear whether VPT children’s general cognitive abilities improved, deteriorated, or remained stable over time. This prospective longitudinal study addressed this important question by growth curve modeling to examine trajectories of cognitive development in VPT born children (≤32 weeks gestation) and typically developing FT children over an extended period of time from age 4 to 12 years. Strengths of the study included the large sample size, repeated cognitive assessment across childhood, the consistency of cognitive measures used, and the examination of both neurological and social risk processes. The main study findings and implications are discussed below.

**Cognitive Development in VPT and FT Born Children**

Consistent with previous research, children born VPT scored below FT children on standardized tests of general intellectual functioning (Anderson & Doyle, 2008; Bhutta et al., 2002; Kerr-Wilson et al., 2012; Marlow, 2004; Vohr, 2010), with the VPT cohort scoring 9–12 points below the FT cohort across all age assessments. This range of mean differences is very similar to the figure reported in Bhutta et al.’s (2002) meta-analysis of 15 studies of school-aged VPT and FT children, which found an overall weighted mean IQ difference of 10.9 points. It is also consistent with Kerr-Wilson et al.’s (2012) more recent meta-analysis of 27 studies of school-age children, which reported an overall IQ difference between FT and preterm children of 11.94 points.

Although as a group the VPT children in the study appeared to perform within the lower end of the normal cognitive range, the consistent IQ differences found between VPT and FT children raise
considerable concerns for the long-term cognitive and academic consequences of VPT birth. Additionally, as studies have tended to focus on mean group differences, little acknowledgment has been given to the potential for individual variability, an important consideration given the heterogeneous nature of development in both VPT and FT populations (Stålnacke et al., 2015). In this study, the examination of observed trajectories of estimated IQ scores revealed reasonable levels of inter- and intra-individual variability, which were more pronounced in the VPT group. Also apparent when examining the observed IQ trajectories was that, while some VPT children were performing very poorly, many were functioning at levels comparable to FT children. Additionally, although the overall trend showed stability over time, VPT children demonstrated variability in their individual trajectories, with some children showing improvements and others showing declines between ages 4 and 12 years. The importance of acknowledging individual patterns of cognitive development was recently highlighted by Stålnacke et al. (2015) who found that, although in general preterm children showed stability in cognitive functioning from 5.5 to 18 years, groups of preterm individuals also showed changes in function over this time. Findings of this nature highlight the importance of taking into account change at both the individual and group level and understanding factors that influence a particular child’s developmental path.

Informative longitudinal research and analysis is essential in understanding the true impact of preterm birth on long-term cognitive outcomes and determining whether VPT children are most likely to experience a developmental lag or a persistent pattern of cognitive impairment. The linear mixed effects growth curve analysis carried out in this study estimated the rates of change at the individual and group level and indicated little evidence for change in cognitive functioning over time, with the average cognitive trajectory for both FT and VPT children being stable from 4 to 12 years.

Stability of cognitive impairments in VPT children has been reported previously (Allin et al., 2008; Saigal et al., 2000), however several prospective longitudinal studies have also found evidence of change in cognitive functioning over time (Botting et al., 1998; Isaacs et al., 2004; Koller et al., 1997; O’Brien et al., 2004). Brien et al.’s (1998) study of VLBW children found significant declines in IQ scores from age 6 to 12 years; however, their FT comparison group showed a comparable IQ decline, resulting in a similar discrepancy between the two groups at each time point. O’Brien et al. (2004) later reported significant declines in IQ scores alongside increased requirements for remedial educational support in VPT children (<33 weeks gestation) from 8 to 15 years. Moreover, Isaacs et al. (2004) found that such declines were evident in VPT children who were neurologically normal at age 8 years. Unlike the current study, O’Brien et al. (2004) and Isaacs et al. (2004) both lacked a FT born comparison group. Additionally, as these studies only assessed children at two time points, the full nature of changes in cognitive problems across childhood was unclear. Despite these limitations and although the current study found no substantial evidence of cognitive decline in VPT born children from 4 to 12 years, further follow-up into adolescence is needed to fully evaluate VPT children’s long-term cognitive trajectories.

The stable and low trajectory demonstrated by VPT children within the current study is troubling and implies that it is not realistic to assume that a VPT child will recover from early cognitive delays with age. These children need to be continually monitored across childhood, with their birth status acknowledged throughout the school-age years. Early cognitive interventions should also be considered as it would appear unlikely that many of these children will reach a level of cognitive functioning that is comparable to FT born children, without some level of assistance. The earlier these interventions are implemented, the more likely that an optimal cognitive outcome will be reached.

Influence of Sex on Cognitive Development

The growth curve analysis also revealed small differences in the cognitive trajectories of male and female children. Findings showed that at age 4, females obtained slightly higher IQ scores than
males, but with age this gap narrowed, with males showing comparable performance to females by age 12. Given that a difference in slope was not found between the two birth groups, as indicated by a nonsignificant Age × Group interaction, this initial decrement and then increase in general cognitive functioning for male children is difficult to interpret and cannot be solely attributed to either birth group.

Influence of Family Social Risk on Cognitive Development

As expected, high family social risk was a significant predictor of poorer cognitive performance for both VPT and FT born children. Numerous studies have documented the association between family social risk factors such socioeconomic adversity, poverty, maternal academic underachievement, and poor cognitive development in children raised in these contexts (Bradley & Corwyn, 2002; Duncan et al., 1994; Hackman & Farah, 2009; Noble et al., 2005; Wong & Edwards, 2013). This study found that high family social risk in the first 2 years of life had an adverse impact on the cognitive outcomes of VPT and FT children, highlighting the importance of the early home environment for optimal cognitive development. The increased prevalence of VPT birth among lower SES families is thus problematic as social risk appears to compound the early biological risk associated with preterm birth (Blumenshine et al., 2010; Kramer et al., 2000; Wong & Edwards, 2013).

Influence of WMA on Cognitive Development

The majority of VPT born children in this study had WMA, with 58% subject to mild abnormalities and 17% with moderate to severe abnormalities on term MRI. WMA were a strong predictor of cognitive impairment across childhood, with the severity of abnormalities influencing the magnitude of long-term effects. Although the nature of the association between WMA and cognitive impairment is complex, the importance of cerebral white matter connectivity for adaptive cognitive development is increasingly recognized. WMA have been shown to affect between 50% and 70% of VPT infants, and have been found to be one of the strongest predictors of cognitive and motor impairments (Inder, Anderson, et al., 2003; Inder, Wells, et al., 2003; Iwata et al., 2012; Woodward et al., 2006, 2009, 2012). This study provides further support for the potential utility of neonatal MRI in helping to identify children who do and do not need monitoring and intervention support.

Limitations and Future Research

Although this study had a number of methodological strengths, some limitations must also be acknowledged. First, although the attrition rates across the length of the study were exceptionally low, the sample size utilized was relatively small for the statistical analysis that was conducted. Upon dividing children into different categories, the proportions of children representing each combination of characteristics became relatively small,
potentially reducing the statistical power of the analyses. Second, although consistency in the use of cognitive measures was a strength of this study, in order to administer age-appropriate assessments two different versions of the Wechsler Intelligence scales were used to estimate IQ across childhood. This may have made it more difficult to detect subtle differences in the effects of preterm birth on IQ. Additionally, short forms were used to minimize time and allow opportunities for other domain measures. Sattler and Dumont (2004) acknowledged that short forms can be used to obtain an estimate of a child’s intellectual status in instances when a precise IQ is not required and that the attained score must be explicitly documented as an estimate of the child’s FSIQ. Short forms have also been reported to amplify the effects of any administrative errors that may take place during the test while giving excessive weight to each of the subtests included in the form (Sattler & Dumont, 2004). Nonetheless, short forms are a common research practice and the use of repeated measures over time goes someway to mitigating the limitations of the use of an abbreviated measure. The next step would be to consider these IQ trajectories alongside measures of more specific cognitive skills and school functioning.

Conclusions

Children born VPT were found to be at an increased risk of cognitive impairment across childhood and were consistently shown to perform below FT comparison children on standardized tests of general intellectual functioning. Overall, levels of cognitive function were stable from age 4 to 12 years, with VPT children appearing unlikely to recover from early delays with time. Although it is clear that on average VPT children perform below their FT born peers, many of these children had positive outcomes and were performing as well as FT children. That being said, evidence to date would suggest that one should not assume a VPT child will grow out of their cognitive problems with time or underestimate the assistance that many of these children will require during their schooling careers. The hazardous combination of neurological and family social risk emphasized the importance of acknowledging not only a VPT infant’s medical condition but also their home environment. It is imperative to follow this study group further into adolescence to fully evaluate patterns of cognitive development over time and continue to work toward understanding whether VPT birth commonly results in temporary cognitive delays or more persistent impairments.

References


StataCorp. (2011). *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP.


**Supporting Information**

Additional supporting information may be found in the online version of this article at the publisher’s website:

**Table S1.** Summary of Longitudinal Analyses of the Cognitive Development of Children Born Very Preterm

**Table S2.** Maximum Likelihood Estimates (SE) From Mixed Effects Models Fitted to Children’s Cognitive Growth Data (IQ Score Trajectories): Supplementary Analysis Including Nonlinear Effect of Age