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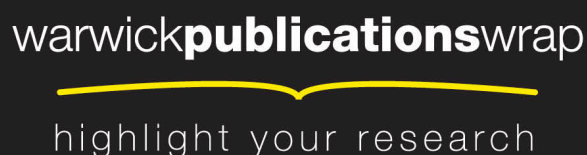
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Neuro-cognitive performance of very preterm or very low birth weight adults at 26 years

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Running head: Adult cognitive profile and preterm birth

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Abstract

Background. Children born very preterm (VP< 32 weeks gestation) and/or with very low birth weight (VBLW< 1500 gr; subsequently VP/VLBW) have been previously reported to have more cognitive impairment and specific executive functioning problems than term children; however, it remains unclear whether these problems persist into adulthood. This study aimed to examine general intelligence (IQ) and executive functioning (EF) of adults born VP/VLBW in comparison to term controls. Additionally, the effects of smallness for gestational age (SGA) and family socio-economic status (SES) at birth were investigated.

Methods. The Bavarian Longitudinal Study is a geographically defined prospective cohort study of neonatal at-risk children born in 1985/86 in Southern Germany. A total of 217 VP/VLBW and 197 controls completed the battery of IQ and EF tests at 26 years of age.

Results. VP/VLBW adults scored significantly lower than controls in IQ and EF. There was a 1.16 standard deviation (SD) unit difference between the VP/VLBW and controls in Full-Scale IQ. VP/VLBW adults were found to have general and multiple cognitive problems rather than specific deficits in EF. SGA was not a significant predictor of cognitive impairment. Family SES had a significant impact on general intelligence in both VP/VLBW and term controls. The SES effects amounted to 1.13 SD units between individuals born into high versus low SES.

Conclusions. No narrowing of cognitive deficits between VP/VLBW and term control adults to previous childhood assessments at 6 years of age was found. VP/VLBW adults do not outgrow their cognitive problems despite many receiving special educational support in childhood. Low family SES at birth has similar additive adverse effects on cognitive performance in VP/VLBW and term offspring.

Keywords: intelligence, executive function, birth weight, prematurity, adulthood

Introduction

Very preterm birth (VP= <32 weeks gestation at birth) and/or very low birth weight (VLBW= <1500 g, VP/VLBW) are associated with poorer general IQ in childhood compared to term controls (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Wolke & Meyer, 1999). In addition, VP/VLBW children more often have problems in executive function (EF) (Mulder, Pitchford, Hagger, & Marlow, 2009) but it is not clear whether these are specific, i.e. in excess of general IQ (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009). Recent studies reported on IQ and EF in VP/VLBW adults (Allen, Cristofalo, & Kim, 2010; Eikenes, Lohaugen, Brubakk, Skranes, & Haberg, 2011; Hack et al., 2002; E. T. M. Hille et al., 2007; Lohaugen et al., 2010; Nosarti et al., 2009; Pyhala et al., 2011; Strang-Karlsson et al., 2010) but there remains controversy whether their cognitive difficulties have improved by adulthood (Hack, 2009) or not (Allen et al., 2010).

Adverse effects of small for gestational age (SGA) birth on cognitive function have also been reported (Gutbrod, Wolke, Soehne, Ohrt, & Riegel, 2000) but these may be childhood limited (Pyhala et al., 2011; Strang-Karlsson et al., 2010). Finally, family socio-economic status (SES) exerts a strong influence on cognitive abilities in both general and preterm populations (Allen et al., 2010; Johnson, 2007). It is however not clear if VP/VLBW children born into low SES families are disproportionally disadvantaged (Sameroff & Chandler, 1975), or, alternatively, at double jeopardy with SES additionally affecting cognitive performance (Breslau, Dickens, Flynn, Peterson, & Lucia, 2006; Escalona, 1982).

Previous findings from VP/VLBW adult studies are inconclusive as they originated from single hospital centers (Eikenes et al., 2011; Hack et al., 2002; Lohaugen et al., 2010; Nosarti et al., 2009), had no term control sample (E. T. M. Hille et al., 2007) or did not consider SGA (Lohaugen et al., 2010) and SES (Pyhala et al., 2011) effects. We report on the follow-up assessment of the Bavarian Longitudinal Study (BLS) at age 26 years : (Q1) Do VP/VLBW

adults show lower cognitive performance (i.e., IQ and EF) compared to term control adults?

(Q2) Do VP/VLBW adults more often have specific EF deficits or multiple cognitive

deficits? (Q3) Do SGA birth and low family SES have additional detrimental effects on

cognitive performance in adulthood?

Methods

Participants

The BLS is a geographically defined prospective whole population sample of children born in Southern Bavaria (Germany) between January 1985 and March 1986 who required admission to one of 17 children's hospitals within the first 10 days after birth (N=7,505; 10.6% of all live births) (Riegel, Ohrt, Wolke, & Osterlund, 1995; Wolke, Schmid, Schreier, & Meyer, 2009). Of this cohort, 682 were born VP/VLBW, 411 of these were eligible for the 26 year follow-up assessment (see Table 1 for sample flow), and 260 (63.3%) participated. Healthy infants who were born in the same obstetric hospitals were recruited as controls. Of the initial 916 control children alive at 6 years, 350 were randomly selected as term controls within the stratification variables sex and family SES to be comparable to the VP/VLBW sample. Of these, 308 were eligible for the 26 year follow-up assessment, and 229 (74.4%) participated (Table 1).

Final sample with all cognitive assessments. Of the 260 VP/VLBW, 43 chose not to participate in cognitive assessments (only provided information via telephone interview and/or questionnaires). As shown in Table 2, the 217 VP/VLBW participants did not differ from adults who dropped out (n=194) in terms of gestational age, birth weight, duration of hospitalization, gender, maternal age, parental marital status, and childhood cognitive scores, but they had fewer prenatal complications and were more often of higher SES. Of the 217 fully assessed VP/VLBW adults, 15 had severe impairments and were not able to participate in cognitive assessments. All had very low IQ scores during childhood (z-scores ranged from

-2.7 to -6.5 SD of the control means). The current cognitive scores of these “proxy” cases were imputed using the z-scores of their childhood IQ assessments.

The control participants who took part in cognitive assessments at the 26 year follow-up (n=197) did not differ from those lost to follow-up (n=112) in terms of neonatal characteristics but they more often had higher SES, older mothers and higher childhood cognitive scores (Table 2).

Ethical approval of this follow-up study was granted by the Ethical Board of the University Hospital Bonn, Germany (reference # 159/09) and all participants gave fully informed written consent. In cases of severe impairment consent was provided by an assigned guardian (usually the parents).

Measures

Cognitive assessments. General cognitive ability was assessed with six subtests of the German version of the Wechsler Adult Intelligence Scale (WAIS III (vonAster, Neubauer, & Horn, 2009)) and converted to age-normed verbal IQ, performance IQ, and Full Scale IQ (FSIQ) scores (see Table S1 for details).

Executive functioning (EF) was assessed with four instruments (Table S1). The Stroop test (Bäumler, 1985) consists of three tasks that assess selective attention, verbal inhibition, and cognitive flexibility (test-retest reliability $r = .90-.96$). The Visual Search and Attention Test (VSAT (Trenerry, Crosson, DeBoe, & Leber, 1990)) measures visual selectivity and attention. The Regensburg Word Fluency Test (RWT (Aschenbrenner, Tucha, & Lange, 2000)) assesses divergent thinking. Lastly, the Rapid Automatized Naming Test (RAN (Wolf & Denckla, 2005)) is a measure of verbal processing speed. Scores of all tests were z-standardized according to the term control group.

Predictors and Confounders. Family SES was computed as a weighted composite score of parents' education and occupation and grouped as low, middle, and high (Bauer, 1988).

Children with birth weights less than the sex specific 10th percentile for gestational age according to a perinatal survey of all Bavarian newborns (Zander, Holzmann, & Selbmann, 1989) were classified as SGA. Multiple birth and prenatal complications (e.g., preeclampsia, anaemia, urinary tract infection, bleeding before 28 weeks) were coded from the standard Bavarian perinatal survey forms (Zander et al., 1989).

Statistical Analysis

SPSS version 22 was used to analyze the data. We compared the VP/VLBW and control samples using Student t-tests for continuous variables and χ^2 tests for categorical variables.

Q1. To assess whether VP/VLBW adults had lower cognitive performance than control adults, first, we calculated unadjusted mean differences and their effect sizes (i.e., Cohen's *d* (Cohen, 1988)). Next, we examined mean differences after controlling for prenatal complications (Anderson, Howard, & Doyle, 2010), SGA (Gutbrod et al., 2000), multiple birth (Chauhan, Scardo, Hayes, Abuhamad, & Berghella, 2010), and family SES (Breslau et al., 2006). Analyses were carried out for the total VP/VLBW sample and for the VP/VLBW sample with proxy cases (*n*=15) excluded.

Q2. In order to test whether VP/VLBW adults had specific EF deficits, we compared mean EF scores of VP/VLBW and control samples in multivariate analyses of variance (MANOVA) controlling for FSIQ in addition to prenatal complications, SGA birth, multiple birth and family SES. Any differences that remain significant after adjusting for FSIQ indicates specific EF deficits in the VP/VLBW sample. Next, we estimated the amount of variance in EF measures explained by FSIQ. We also investigated whether VP/VLBW adults more often had multiple cognitive problems compared to term adults. Multiple cognitive problems were defined by the number of cognitive outcome measures (out of 10) with a score below the 10th percentile.

Q3. To examine whether SGA status was an additional predictor of cognitive performance we conducted a 2 (VP/VLBW vs controls) by 2 (SGA versus normal birth weight) MANOVA (VP/VLBW–SGA (n=85), VP/VLBW–normal birth weight (n=132), control–SGA (n=19), and control–normal birth weight samples (n=178)). Finally, to examine the impact of family SES and its interaction with birth status (VP/VLBW versus control) on each cognitive outcome measure we used MANOVA and reported effect sizes (i.e., partial eta square).

Results

Compared to controls, VP/VLBW adults were by definition born at earlier gestation and weighed less, had more medical complications, were more often multiple births, SGA, and had lower IQ scores during childhood; they were also of lower SES (Table 2). The VP/VLBW and controls did not differ in sex distribution and maternal characteristics. However, more VP/VLBW (40.1%) than term adults (24.4%) were still living with their parents at 26 years ($\chi^2=11.62$, $df=1$, $p<0.01$). The current sample (both VP/VLBW and controls) differed systematically from the original population in terms of family SES, therefore, further analyses were performed on a weighted, population representative sample.^a

Q1: Do VP/VLBW adults have lower cognitive performance (IQ and EF) in comparison to term control adults?

VP/VLBW adults scored significantly lower than controls on all measures. The magnitude of differences between VP/VLBW and controls (Cohen's d) ranged from 0.83 to 0.96 for IQ measures and from 0.46 to 0.78 for EF measures (Table S2). Exclusion of proxy cases (n=15) from the VP/VLBW sample did not substantially alter the findings.

There were on average 0.90 to 1.27 SD units difference between the VP/VLBW and term adults' IQ scores in adjusted models (Figure 1 – Panel A). These differences were reduced to

^a The inverse of the sample fraction in each family SES category (i.e., proportional weighting) was used for the VP/VLBW and control group separately to adjust the frequency of family SES categories in the current sample.

0.73 to 1.09 SD when proxy cases were excluded from the VP/VLBW sample (Figure 1- Panel B). The differences in EF measures ranged from 0.59 SD units to 0.88 SD units with the exception of the VSAT (1.15 SD units difference); the EF differences were overall, apart from VSAT, smaller than the differences in the IQ comparisons. Removing proxy cases did not change the pattern but slightly reduced the differences.

In Appendix Table S3 findings for VP/VLBW adults <29 weeks gestation and ≥29 weeks gestation are reported. These indicate a tendency of poorer cognitive outcomes with decreasing gestation.

Q2: Do VP/VLBW adults more often have specific EF deficits or alternatively, multiple cognitive deficits?

All EF differences between the VP/VLBW and control samples disappeared after adjusting for FSIQ except for the difference in VSAT ($F(1, 405) = 6.29, p < .05$). FSIQ explained 46% to 59% of variance in the VP/VLBW sample (Table S4). Analyses were repeated after proxy cases were excluded but findings remained the same. The variance explained by the FSIQ in the control sample's EF scores ranged from 3% to 17%.

This suggested that VP/VLBW adults may more often have multiple rather than specific cognitive problems. Only 27.3% of the VP/VLBW sample did not have any cognitive deficits whereas 28.7% had deficits in 6 or more areas of cognition (Figure 2). In contrast, 51.5% of the control sample had no cognitive deficits and only 4% were found to have cumulative deficits in 6 or more areas. Thus, if term adults had any cognitive problems, these were mainly in one or two specific areas while they were more likely to be multiple in VP/VLBW adults ($\chi^2=56.32, df=6, p<0.001$).

Q3: Do SGA birth and low family SES have additional detrimental effects on cognitive performance?

The comparisons showed no significant effect of SGA and no interaction between SGA and preterm status. We repeated comparisons only between the VP/VLBW-SGA and VP/VLBW – normal birth weight samples, still no significant SGA impact was found.

Family SES had a significant effect on verbal IQ ($F_{SES}=28.32$, $p<0,001$, $\eta^2=0.123$), performance IQ ($F_{SES}=12.58$, $p<0,001$, $\eta^2=0.059$), and FSIQ ($F_{SES}=25.08$, $p<0,001$, $\eta^2=0.110$) after controlling for preterm birth. There was no interaction between preterm birth and family SES, rather there was an additive impact of family SES (Figure 3). Regarding EF measures, family SES had a significant main effect on 3 out of 7 measures, VSAT ($F_{SES}=7.34$, $p<0,001$, $\eta^2=0.035$), Stroop task 3 ($F_{SES}=6.44$, $p<0.05$, $\eta^2=0.031$), and RWT ($F_{SES}=10.31$, $p<0,001$, $\eta^2=0.049$).

Discussion

This study showed that VP/VLBW adults performed poorer than term controls in all aspects of general IQ and EF with moderate to large effect sizes (Cohen's d 0.46-0.96). These results indicate similar cognitive deficits as in childhood and these have remained to be multiple rather than specific problems (Wolke & Meyer, 1999). SGA did not add to the prediction of cognition in adulthood. Being born into a low or middle SES compared to a high SES family had additive detrimental effects on general cognitive performance of VP/VLBW and term controls.

The strengths of this study are that twenty six years later, 63.3% of the eligible VP/VLBW sample could be reached and 52.8% had a full cognitive assessment. Systematic dropout occurred due to social factors similarly in the VP/VLBW and control sample. Social factors are the major reason for dropout in longitudinal studies (Hille et al., 2005; Dieter Wolke et al., 2009). To correct for social factors, we used weights based on the frequency of family SES to reflect the original population distribution. The large sample size allowed for robust

estimations of differences between VP/VLBW and term adults recruited in the same obstetric hospitals. The longitudinal nature of our study allowed us to include adults who were non-testable due to severe cognitive impairment (proxy cases) thus enabling a true estimate of the overall burden of VP/VLBW birth (Wolke, Ratschinski, Ohrt, & Riegel, 1994). Furthermore, we standardized test scores according to same aged term adults to control for the Flynn effect, i.e. secular trends of rising IQ scores (Flynn, 1987). The limitation of this study is that we used an abbreviated version of the WAIS. However, this version of the WAIS has been reported to be highly correlated ($r=0.97$ for FSIQ) with the full version of the WAIS (Lohaugen et al., 2010; Ryan & Ward, 1999).

Even after adjusting for confounding factors, IQ differences between the VP/VLBW and controls were between 0.90 and 1.27 SD units as it was in the 6 years follow up with a range from 0.7 to 1.4 SD units (Wolke & Meyer, 1999). Therefore, the current results indicate no narrowing of cognitive deficits of VP/VLBW born individuals compared to controls over a 20 year period. The IQ differences in the current study were slightly larger than the differences reported in previous studies with other samples of adolescents and young adults (Bhutta et al., 2002; Hack et al., 2002; Lohaugen et al., 2010; Nosarti et al., 2009; Pyhala et al., 2011). This may be partly explained by inclusion of non-testable VP/VLBW adults, who had significant cognitive impairment since childhood, in the current but not in most previous studies (Eikenes et al., 2011; Pyhala et al., 2011; Strang-Karlsson et al., 2010). Inclusion of all adults is necessary to gain true population estimates of cognitive abilities. Furthermore, standardizing the scores according to the control group avoided score inflation seen due to the Flynn effect and thus guarded against under-estimations of cognitive deficits (Wolke et al., 1994). Finally, pre-pregnancy, prenatal-, peri- and neonatal complications variations across study samples might additionally help to explain differences in results (Anderson et al., 2010).

Our results support previous findings that VP/VLBW adults have problems in cognitive flexibility, inhibition, visual selectivity, attention, word fluency, and processing speed (Pyhala et al., 2011; Strang-Karlsson et al., 2010). However, these differences were smaller than those reported for FSIQ and most of them disappeared once controlled for FSIQ. Thus little evidence for specific EF deficits in VP/VLBW adults was found, rather, consistent with our previous follow-up in childhood at 6 years of age (Wolke & Meyer, 1999), VP/VLBW adults more often suffer from multiple cognitive problems.

There was, however, evidence for a specific deficit in visual selectivity and executive attention (VSAT). Indeed, in our previous follow-up at 6 years (Wolke & Meyer, 1999), similar specific deficits were found in processing simultaneous information to solve tasks such as visual spatial recognition. This is a pattern replicated by others in adulthood (Pyhala et al., 2011) who found that differences in visuospatial encoding attenuated but remained significant after controlling for FSIQ while differences in lower level EF tasks such as word fluency disappeared. There are two possible explanations: Firstly, VP/VLBW adults may have specific impairments of visual short-term memory storage capacity. Secondly, VP/VLBW adults may have general problems with higher-order EF activities that require complex processing and attention skills beyond the effect of general cognitive ability. This is consistent with a workload model proposing that with increasing workload of cognitive tasks lower gestation groups perform exponentially more poorly (Jaekel, Baumann, & Wolke, 2013). Future research on VP/VLBW samples may structure outcome assessments by workload requirements and investigate the specific role of visual short-term memory storage capacity.

There is considerable evidence that SGA influences neuro-development during childhood (Walker & Marlow, 2008). We previously reported that SGA has adverse effects on cognitive performance in childhood although less so than gestation (Gutbrod et al., 2000). By

adulthood, VP/VLBW individuals may have outgrown the effects of SGA on cognitive function (Pyhala et al., 2011; Strang-Karlsson et al., 2010). In light of current knowledge, we conclude that SGA effects on cognition may be childhood limited.

Finally, family SES had a strong impact on adult IQ. This was found for both VP/VLBW and term controls. Although there was no evidence that VP/VLBW adults were disproportionately disadvantaged by family SES, they experienced double jeopardy (Breslau et al., 2006; Escalona, 1982). For example, as shown in Figure 3, the gap between low family SES VP/VLBW adults and high family SES controls was on average 2.25 SD units. Moreover, being born VP/VLBW into a family with high SES was compensatory but high SES VP/VLBW adults, on average, only reached mean IQ-scores comparable to term children raised in low SES families. The impact of family SES on IQ was slightly higher in adulthood than previously found in childhood in this same cohort (Wolke & Meyer, 1999). This is likely to be the result of the cumulative exposure to factors such as child rearing, family relationships, access to resources and education associated with family of origin SES that contribute to cognitive development over time (Lawson, Makoli, & Goodman, 2013). This suggests that SES effects increase over time and age of studied individuals needs to be taken into account when effects of family SES are evaluated across studies.

Conclusion

Our findings suggest no narrowing of cognitive deficits by adulthood between VP/VLBW and term controls. VP/VLBW children, as a group, do not outgrow their general cognitive deficits by adulthood despite most receiving formal or informal educational support at school age (Saigal et al., 2003). Furthermore, being born into a low SES family is associated with double jeopardy for VP/VLBW adults. Overall, VP/VLBW have multiple rather than specific cognitive problems aton. However, 27% of VP/VLBW grew up without any cognitive deficits and SGA had no adverse impact on cognition by adulthood indicating considerable

plasticity of the brain to fetal growth restriction. Future research may identify whether multiple cognitive deficits are correlated to alterations in brain structure and altered connectivity patterns recently described (Bauml et al., 2014; Eikenes et al., 2011; Nosarti et al., 2009) and what neonatal and environmental factors may help some VP/VLBW to overcome the odds (Jaekel, Pluess, Belsky, & Wolke, 2014; Wolke, Jaekel, Hall, & Baumann, 2013).

Supporting Information

Additional supporting information may be found in the online version of this article.

Table S1: Detailed description of cognitive assessments

Table S2: Descriptives of outcome variables

Table S3: Descriptives for VP/VLBW < 29 weeks, VP/VLBW & \geq 29 weeks, and term controls.

Table S4: Regression results for EF outcomes

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Key points

- Very preterm and/or very low birth weight (VP/VLBW) adults performed much poorer than term adults in all aspects of IQ and executive functioning (EF) indicating that they don't outgrow their cognitive deficits.
- The cognitive problems were often multiple rather than specific EF deficits.
- SGA did not add to prediction of cognitive ability in adulthood suggesting that the effect of SGA on cognition is childhood limited.
- Family SES at birth had a strong impact on general cognitive ability (IQ) of both VP/VLBW and term adults creating a double jeopardy for VP/VLBW adults when it is low.

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Figure 1. Forest plot comparing the total VP/VLBW sample (n=217) to term controls (n=197) (Panel A) and the VP/VLBW sample excluding the proxy cases (n=202) to term controls (Panel B).

Legend. The mean differences derived from multiple linear regressions (i.e., regression weight of birth status) in SD units and their 95% confidence intervals showing VP/VLBW (error bars) and term controls (zero line). A mean difference less than zero indicates weaker performance of the VP/VLBW sample. Mean differences are adjusted for prenatal complications, SGA, multiple birth, and family SES and computed in a weighted, population representative sample. *Stroop task 1: reading color words; Stroop task 2: naming color lines; Stroop task 3: naming color of the color words; VSAT: Visual Search & Attention Test; RWT: Regensburg Word Fluency Test; RAN- objects and RAN-numbers: Rapid Automatized Naming Test objects and number scales.*

Figure 2. Relative frequency of multiple cognitive problems of VP/VLBW adults in comparison to their term controls.

Legend. The number of cognitive outcome measures (out of 10) with a score below the 10th percentile of control distribution were counted in weighted, population representative control sample, VP/VLBW total sample, and VP/VLBW sample excluding proxy cases.

- VP/VLBW sample – total (n=217)
- VP/VLBW sample – excluding proxy cases (n=202)
- Control sample (n=197)

Figure 3. Full Scale IQ (FSIQ) mean scores with 95% CI for the VP/VLBW and term controls born into low, medium, and high family SES.

Legend. Full Scale IQ (FSIQ) means with their 95% confidence intervals in SD units are presented for VP/VLBW sample – total and term controls by family SES categories (low, medium, and high) adjusted for prenatal complications, SGA, and multiple birth; and computed in a weighted, population representative sample.

Control sample (n=197)
VP/VLBW sample (n=217)

Figure 1.

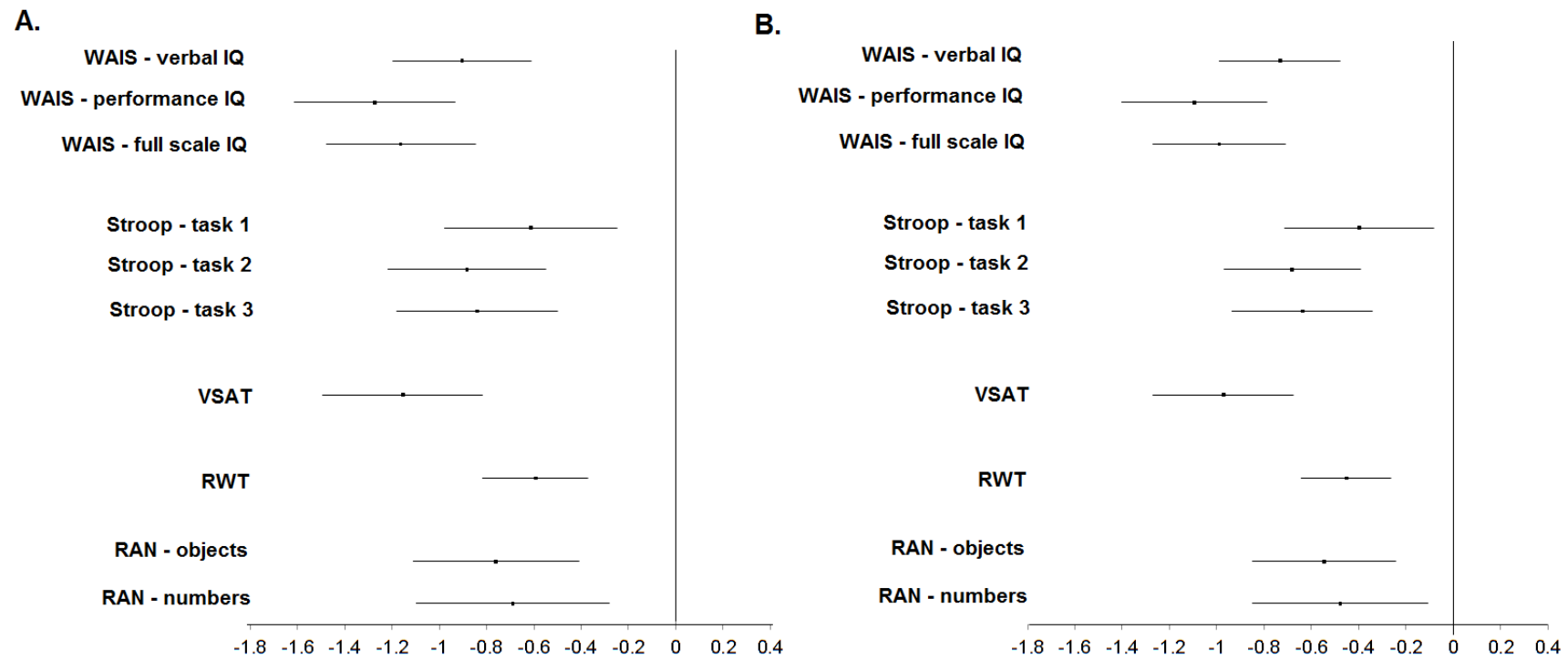


Figure 2.

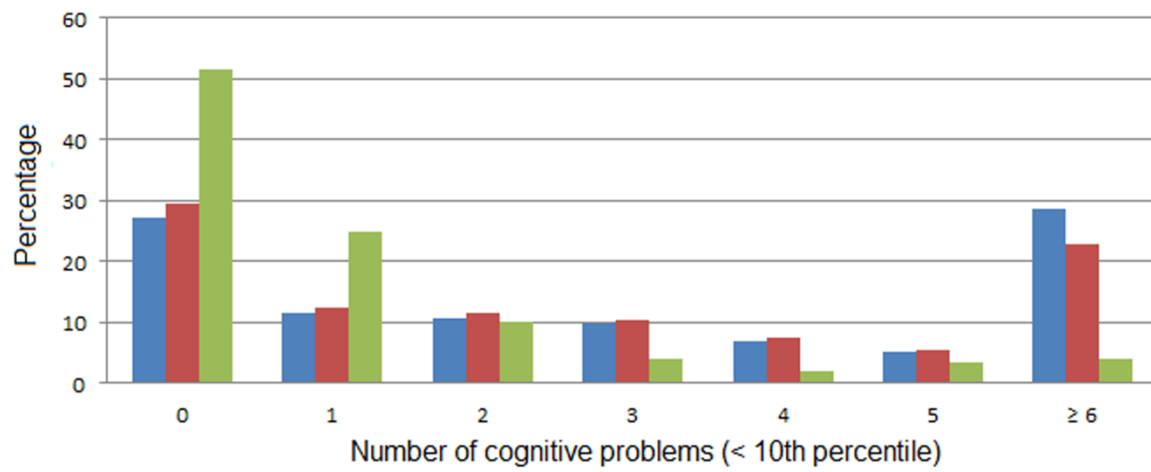


Figure 3.

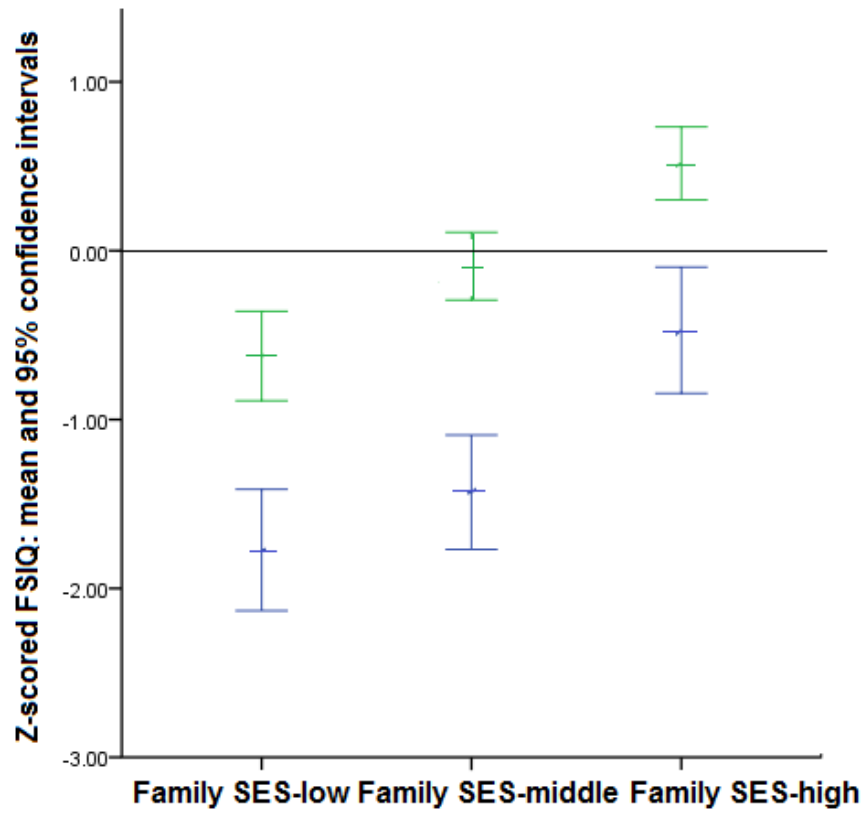


Table 1. The BLS cohort and the current sample.

<i>Sample</i>	<i>N</i>
<u>VP/VLBW Sample</u>	
Initial sample	682
Refused from the beginning	7
Died in hospital	172
Died between discharge and 26 years	12
Non-German speakers	43
Not traceable/abroad	37
Remaining eligible sample for 26 years assessments	411
No contact or refused for 26 years assessment	151
Participated at 26 years assessments:	260
Partial assessment (phone interview or questionnaire only)	43
Remaining sample with cognitive assessments ^a	217
<u>Control Sample</u>	
Initial sample	350
Died between 6 and 26 years	2
Not traceable/abroad	40
Remaining eligible sample for 26 years assessments	308
No contact or refused for 26 year assessment	79
Participated at 26 years assessments:	229
partial assessment (telephone interview, questionnaires only)	32
Remaining sample with cognitive assessments	197

^a Of this sample, 15 were proxy cases due to cognitive impairment.

Table 2. Comparison of VP/VLBW and term controls that were assessed in adulthood and those who dropped out.

	ADULT SAMPLE			DROP-OUT SAMPLE			
	VP/VLBW (n=217)	Control (n=197)	p- value ^a	VP/VLBW (n=194)	p- value ^b	Control (n=112)	p- value ^c
Gestation (weeks)	30.35 (2.53)	39.67 (1.16)	<.001	30.73 (2.05)	ns	39.57 (1.25)	ns
Birth weight (g), (SD)	1310.74 (320.03)	3370.81 (452.2)	<.001	1292.40 (293.47)	ns	3399.73 (436.62)	ns
SGA (N, %)	85 (39.2%)	18 (9.1%)	<.001	91 (46.9%)	ns	13 (11.6%)	ns
Multiples (N, %)	57 (26.3%)	7 (3.6%)	<.001	46 (23.7%)	ns	5 (4.5%)	ns
Complication scores							
Pre-pregnancy	1.39 (0.81)	1.15 (0.80)	<.01	1.28 (0.86)	ns	1.06 (0.77)	ns
Prenatal	2.17 (1.16)	0.75 (0.91)	<.001	2.64 (1.26)	<.001	0.91 (0.95)	ns
Perinatal	4.66 (1.40)	2.12 (1.50)	<.001	4.48 (1.43)	ns	2.14 (1.52)	ns
Neonatal	9.38 (2.70)	0.39 (0.64)	<.001	9.33 (2.73)	ns	0.38 (0.67)	ns
Hospitalization in days	76.22 (34.51)	6.96 (2.90)	<.001	79.06 (38.79)	ns	7.72 (4.70)	ns
Severe sensory-motor impairment at 56m (N, %)^d	13 (6.0%)	1 (0.5%)	<.001	8 (4.1%)	ns	1 (0.9%)	ns

Female (N, %)	103 (47.5%)	103 (52.3%)	ns	96 (49.5%)	ns	51 (45.5%)	ns
Family SES at birth (N, %)			<.01		<.01		<.001
SES-high	48 (22.0%)	69 (35.0%)		34 (17.6%)		23 (20.5%)	
SES-middle	102 (47.0%)	83 (41.1%)		71 (36.6%)		40 (35.7%)	
SES-low	67 (30.7%)	45 (22.8%)		89 (46.1%)		49 (43.8%)	
Maternal age (years)	28.94 (4.73)	29.26 (4.66)	ns	27.98 (5.30)	ns	27.68 (4.96)	<.01
Married/Cohabiting (N, %)	200 (93.9%)	192 (97.5%)	ns	166 (87.4%)	ns	106 (96.4%)	ns
Griffiths 5m ^e	96.19 (21.41)	107.60 (10.85)	<.001	94.81 (19.42)	ns	104.44 (10.52)	<.05
Griffiths 20m	92.65 (21.17)	107.06 (6.46)	<.001	91.11 (21.04)	ns	105.11 (6.87)	<.05
CDI 56m ^f	83.37 (24.75)	102.33 (13.44)	<.001	78.94 (23.36)	ns	98.60 (13.85)	<.05

Note. Means and SD if not other indicated; ^a compares adult VP/VLBW and control samples; ^b compares adult VP/VLBW and drop-out VP/VLBW samples; ^c compares adult control and drop-out control samples; ^d includes CP grade 3 or 4, blindness and/or non-correctable hearing problems at 56 months; ^e Griffiths Mental Development Scale score at 5 months; ^f a composite index score of cognitive and language ability at 56 month.

