Intelligence of Very Preterm or Very Low Birth Weight Infants in Young Adulthood

Nynke Weisglas-Kuperus, Elysee Hille, ETM, Hugo HJ Duivenvoorden, Martijn MJJ Finken, Jan Maarten JM Wit, Stef van Buuren, Johannes van Goudoever and Pauline MJJ Verloove-Vanhorick

Arch. Dis. Child. Fetal Neonatal Ed. published online 19 Sep 2008;
doi:10.1136/adc.2007.135095

ADC-FNN Online First, published on September 19, 2008 as 10.1136/adc.2007.135095

Intelligence of Very Preterm or Very Low Birth Weight Infants in Young Adulthood

Nynke Weisglas-Kuperus MD PhD[a], Elysee TM Hille PhD[a,b], Hugo J Duivenvoorden PhD[c], Martijn JJ Finken MD[d], Jan Maarten Wit MD PhD[d], Stef van Buuren PhD[b], Johannes B van Goudoever MD PhD[a], S Pauline Verloove-Vanhorick MD PhD[bd], for the Dutch POPS-19 Collaborative Study Group*

Institutional affiliations

a Division of Neonatology, Department of Pediatrics, Erasmus MC - Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands

b Businessunit Prevention and Healthcare, TNO Quality of Life, Leiden, the Netherlands

c Erasmus MC, Department of Medical Psychology & Psychotherapy, NIHES, Rotterdam, the Netherlands

d Department of Pediatrics, Leiden University Medical Center, Leiden, the Netherlands

* Members of the Dutch Collaborative POPS 19 Study Group in Acknowledgements

Correspondence to

N. Weisglas-Kuperus, Erasmus MC - Sophia Children's Hospital, Department of Pediatrics,
Division of Neonatology, Dr. Molewaterplein 60, 3015 GJ Rotterdam, The Netherlands.

Key words

Prematurity, intrauterine and neonatal growth retardation, parental education, intelligence.

Abbreviations

POPS=Project on Premature and Small for gestational age infants, AGA=Appropriate for Gestational Age, IUGR=Intra Uterine Growth Retardation. AGA-NGR=Neonatal Growth Restraint, IQ: =Intelligence Quotient

Length 2547 words

ABSTRACT

Objective
To examine the impact of intrauterine as well as neonatal growth, prematurity, personal and environmental risk factors on intelligence in adulthood in survivors of the early neonatal intensive care era.

Methods
A large geographically based cohort comprised of 94 % of all individuals born alive in the Netherlands in 1983 with a gestational age below 32 weeks and/or a birth weight less than 1,500 gram (POPS-study). Intelligence was assessed in 596 participants at 19 years of age. Intrauterine and neonatal growth were assessed at birth and at 3 months of corrected age. Environmental and personal risk factors were: maternal age, education of the parent, sex and origin.

Results
The cohort's mean IQ was 97.8 (SD 15.6). In multiple regression analysis, participants with high-educated parents had a 14.2 points higher IQ than those with low-educated parents. 1 SD increase in birth weight was associated with 2.6 points higher IQ and a 1-week increase in gestational age with a 1.3 points higher IQ. Persons born to young mothers (<25 yrs) had 2.7 points lower IQ and males had 2.1 points higher IQ than females. The effect on intelligence after early (symmetric) intrauterine growth retardation was more pronounced than after later (asymmetric) intrauterine or neonatal growth retardation. These differences in mean IQ remained when participants with overt handicaps were excluded.

Conclusion
Prematurity as well as the timing of growth retardation are important for later intelligence. Parental education however, best predicted later intelligence in very preterm or very low birth weight infants.

Introduction

Very preterm and very low birth weight survivors are at risk of later handicap.[1] Even those without obvious handicaps may have cognitive problems affecting educational achievement and professional attainment in adulthood. [2-4]

Gestational age at birth (GA) is related to cognitive test scores at school age.[5,6] The immature brain is vulnerable to neonatal complications such as germinal matrix or intraventricular hemorrhage and periventricular leukomalacia as well as more subtle abnormalities such as delayed myelination[7] and reduced brain volume in specific cortical areas.[8] These may have an impact on later cognitive function.

Intrauterine growth retardation (IUGR) is known to have negative consequences for academic achievement and professional attainment in term born infants.[9] Less is known about the effect of IUGR on cognitive outcome in preterm infants. In one study IUGR in preterm infants was related to early developmental delay and language problems[10] in another to more need of special education than in appropriate for gestational age (AGA) infants.[11] Weight and head circumference at birth may provide clues for the stage of fetal development in which the growth retardation occurred. Symmetric IUGR, which refers to equally poor weight and head growth, points at a process occurring early to mid pregnancy. Asymmetric IUGR, with relative head sparing, is indicative of growth retardation taking place later in pregnancy. Birth weight irrespective of head circumference predicted learning difficulties in a study of term born children.[12] But it was intrauterine head growth - and not body growth – that was the major determinant of later intelligence in preterm children.[13,14] Effects of IUGR may thus differ between term and preterm born children. In addition, during the neonatal intensive care treatment preterm children may experience neonatal growth restraint and subsequently display a growth pattern similar to IUGR children.[15] Postnatal rather than intrauterine growth is important for early neurodevelopmental outcome.[16] The effect of NGR on later intelligence, however, is unknown.

According to the classification as recently proposed by the World Health Organization [17] later functioning and disability are the result of a dynamic interaction between health, personal and environmental factors. In term born infants environmental and personal factors such as social class at birth explain more of the variation in later cognitive function than intrauterine growth[18,19] and are important for early development in preterm infants.[20,21] The relative contributions of these risk factors on intelligence in adulthood in survivors of the early neonatal intensive care era have not yet been described.

We report a study embedded in the Collaborative Project on Preterm and Small for Gestational Age Infants in the Netherlands (POPS), an ongoing nation-wide follow-up study on the effects of prematurity and dysmaturity on later outcome. In this large geographically based cohort we examined the impact of neonatal conditions such as gestational age, intrauterine and neonatal growth, as well as of environmental and personal factors such as maternal age, parental education, sex and origin on intelligence in adulthood.

Subjects and methods

SUBJECTS

The POPS-cohort comprised of 94 % (n=1338) of all individuals born alive in the Netherlands in 1983 with a gestational age below 32 weeks and/or a birth weight less than 1,500 gram.[22] Of the original cohort, 379 did not survive to their nineteenth year, 312 died in the neonatal period (by definition the first 28 days of life), 51 in the first year of life, and 16 after the first year of life. The remaining 959 were eligible for the current study.

PROCEDURE

Shortly after their 19^{th} birthday subjects were invited to participate in the study. Participation involved cognitive assessment at one of the ten participating centers (eg. Emma Children's Hospital AMC, Amsterdam; University Medical Center , Beatrix Children's Hospital, Groningen; University Hospital Maastricht; University Medical Center St Radboud, Nijmegen Leiden; University Medical Center, Leiden; Erasmus MC - Sophia Children's Hospital, University Medical Center Rotterdam; VU University Medical Center, Amsterdam; Wilhelmina Children's Hospital, UMC; Utrecht Máxima Medical Center, Veldhoven; Isala Clinics, Zwolle). Assessments were carried out by trained nurses; details, logistics and response rate have been reported earlier.[23] The respective medical ethics review boards of the ten participating medical centres all approved the study protocol. All subjects provided written informed consent to participate in the study before assessment started.

OUTCOME

Intelligence was assessed with the computer version of the Multicultural Capacity Test –In termediate Level developed by Bleichrodt. This recently standardized Intelligence test differentiates within the lower half of the IQ spectrum and measures capacity and skills of individuals with secondary education. It derives an Intelligence Quotient (IQ) with a mean of 100 and a standard deviation of 15 in the Dutch norm sample.[24]

RISK FACTORS

Environmental and personal risk factors were: maternal age (in tertiles), highest education of the parents (low [primary school, or junior secondary vocational education], intermediate [general or senior secondary education], high [higher vocational education, or university]), sex (male vs. female) and origin (Caucasian, non-Caucasian). Neonatal factors were gestational age (in weeks), weight (in grams), length (in cm) and head circumference at birth (in cm) and at 3 months of corrected age. Weight, length and head circumference were expressed as standard deviation scores (SDS) to adjust for (gestational) age and sex.[25,26] Subjects with a birth weight and/or length <-2SD were labelled IUGR. Symmetric IUGR was defined as both birth size and head circumference ≤-2 SD below the mean for the infant's gestational age. Asymmetric IUGR was defined as birth size ≤-2 SD and head circumference >-2SD. Those with weight and length above – 2SD at birth as well as at 3 months were labelled appropriate for gestational age (AGA). Infants with weight and length above – 2SD at birth and with weight and/or length <-2SD at 3 months were labelled neonatal growth restraint (AGA-NGR)[15].

STATISTICAL ANALYSIS

Multiple imputation was applied to adjust for missing values (correcting for positive selection bias)[23, 27]. This simulation-based approach creates a number of imputed (completed) data sets by "filling in" plausible values for the missing data. The imputations are based on a model that uses information from other variables to achieve optimal estimates. Only imputations for the missing values between the lowest and highest values of the measured outcome variable are valid. Uncertainty about the model estimates is reflected in differences between imputations in the different completed data sets. Realistic complete data estimates can be attained through pooling results from the completed data sets. We used the MICE (Multivariate Imputation by Chained Equations) software program[28] to create five imputed datasets, based on the neonatal, environmental and personal factors mentioned above and all available outcome-specific data at ages 5, 10, 14 and 19 years of age. We applied predictive mean matching to create multiple imputations. Confidence intervals for the outcomes were estimated through pooling of the multiple imputations. [29]

Group differences for categorical variables were analyzed with Anova. Multiple regression analyses were performed to analyse the importance of the factors simultaneously. We assessed whether environmental and personal factors, the severity and timing of growth retardation (expressed as birth weight SDS and as asymmetric, symmetric IUGR or AGA-NGR) and GA were risk factors for intelligence at 19 years of age. Analyses were performed firstly with physical and cognitive handicaps included and secondly with handicaps excluded. The unstandardized regression coefficient (symbolized by B), including 95% confidence intervals (95% CI) and the standardized regression coefficient (β) are presented. Data were analysed with the SPSS 12.1 software program.

Results

Of the survivors 12.6% was handicapped and had moderate to severe problems in cognitive or neurosensory functioning[27], 596 of the 959 (62.1%) participated in the assessments[23] and 562 (94.3%) completed the Intelligence test (IQ) at a mean age of 19.3 years (SD 0.2 years).

Characteristics of the study group in relation to IQ are shown in TABLE 1. The mean IQ at 19 years of age was 97.8 (SD 15.6, 95% CI 96.5-99.1). 4.3% had an IQ < 70. Mean maternal age was 27 years (SD 4.8), gestational age was 31 weeks (SD 2.5). At birth mean weight 1314 grams (SD 283), mean weight SDS –0.9 (SD 1.6), mean length SDS –0.8 (SD 1.6) and mean head circumference SDS –0.6 (SD 1.4). At 3 months of age mean weight SDS was –1.3 (SD 1.5) and mean length –1.3 (SD1.4). Maternal age at birth was missing in 12, parental education in 18, origin in 6, gestational age in 1, length and head circumference at birth in 134 and 80 respectively and weight, length and head circumference at 3 months of age in 48, 73 and 85 of the 562 participants respectively. Due to co linearity, stepwise multiple regression analyses were done for birth weight and gestational age (FIGURE 1) and for asymmetric and symmetric IUGR and AGA-NGR (TABLE 2) separately.

TABLE 1 Characteristics of the study group before and after multiple imputation in relation to IQ at age 19

Characteristics			**Before MI**	**After MI**	**Intelligence (IQ)**			
		n	%	%	Mean	[SD]	95% CI	
Environmental and personal factors								
Maternal age at birth	<25 yrs.	174	31.6	34.9	94.9	15.0	94.2	95.7
	25-30 yrs.	214	38.9	38.0	99.5	16.0	99.1	99.9
	> 30 yrs	162	29.5	27.1	99.2	15.3	98.7	99.6
Parental education	Low	172	32.0	38.9	92.2	14.3	91.2	93.2
	Intermediate	208	38.2	36.2	98.6	15.0	98.2	99.0
	High	162	29.8	24.9	106.2	14.7	105.7	106.7
Sex	Male	255	45.4	51.8	98.8	16.6	98.5	99.2
	Female	307	54.6	48.2	96.7	14.4	96.4	97.1
Origin	Caucasian	496	89.2	85.3	98.1	15.6	97.8	98.3
	non Caucasian	60	10.8	14.7	96.5	15.2	95.8	97.1
Neonatal factors								
Gestational age	<32 weeks	413	73.6	70.5	98.4	15.9	98.1	98.7
	>=32 weeks	148	28.4	29.5	96.4	14.9	96.0	96.9
Growth	AGA	274	56,5	53.7	99.7	15.7	98.7	100.7
	AGA-NGR	79	16,3	17.3	95.5	15.8	93.6	97.4
	Assym. IUGR	46	9,5	12.1	97.4	14.6	96.7	98.1
	Sym. IUGR	86	17.2	16.9	94.6	14.9	94.0	95.2

AGA=Appropriate for Gestational Age. IUGR=Intra Uterine Growth Retardation. AGA-NGR=Neonatal Growth Restraint

FIGURE 1 presents differences in mean IQ for gestational age and birth weight SDS, environmental and personal factors in multiple regression analyses. A high parental education was the best predictor for IQ at 19 years of age (β 0.39), followed by birth weight SDS (β 0.27), gestational age (β 0.22), maternal age at birth > 25 yrs (β 0.08 and 0.07) and sex (β 0.07). Participants with high-educated parents had a 14.2 points higher IQ than those with low-educated parents. A 1 SD increase in birth weight was associated with a 2.6 points higher IQ, and a 1-week increase in gestational age with a 1.3 points higher IQ. Persons born to mothers aged 25-30 years had a higher IQ than those born to younger mothers (mean difference 2.7 points). Men had a higher IQ than women (mean difference 2.1 points). Comparable results were obtained when multiple regression analyses were repeated with handicaps excluded.

TABLE 2 presents differences in mean IQ for asymmetric and symmetric IUGR, AGA-NGR, and environmental and personal factors in multiple regression analyses. Handicaps included, subjects born after symmetric IUGR lost 5.8 (β 0.14) those born after asymmetric IUGR lost 3.7 (β 0.08)**,** and those with PGR lost 4.1 IQ points (β 0.10)**.** Handicaps excluded, these losses were 5.3, 3.6 and 3.2 IQ points, (β 0.13, β 0.08, β 0.08) respectively.

TABLE 2 Differences in mean IQ for AGA. IUGR and AGA-NGR

Characteristics		**Intelligence (IQ)**							
		Handicaps included				*Handicaps excluded*			
		B	**95% CI**		**β**	**B**	**95%CI**		**β**
Gestational age	Weeks	0.5	-0.1	1.0	0.07	0.4	-0.1	0.9	0.07
Growth	AGA	-			-	-			-
	AGA-NGR	-4.1	-6.6	-1.5	-0.10	-3.2	-6.3	-0.1	-0.08
	Asym. IUGR	-3.7	-7.1	-0.4	-0.08	-3.6	-6.7	-0.6	-0.08
	Sym. IUGR	-5.8	-9.1	-2.5	-0.14	-5.3	-8.5	-2.1	-0.13

The unstandardized regression coefficient (B), 95% confidence interval (95% CI) and the standardized regression coefficient (β) of the neonatal factors, adjusted for influence environmental and personal factors in the model (e.g. maternal age at birth, parental education, sex and origin).

Discussion

In our cohort the mean IQ was 97.8 (SD 15.6) on a very recently standardized test. This good outcome at young adulthood in these survivors from the early neonatal intensive care era is in agreement with the recent Canadian study of Saigal et al[4] and might largely be attributed to the favorable socioeconomic circumstances. All families had access to health care and could benefit from the Dutch social service system, 85 % were of Caucasian origin and parental education was high in 25%. Parental education best predicted later intelligence. Adjusted for the influence of all other variables, participants born of high-educated parents scored almost 1 SD in mean IQ points higher than those born of low-educated parents, reflecting probably genetic as well as educational influences. Persons born to mothers aged 25-30 years had a higher IQ than those born to younger or older mothers. This U-shaped effect of maternal age on intelligence is in line with findings from other developmental studies in non-premature populations.[30] Maternal age reflects both socioeconomic and personal age-related factors such as experience and physical endurance. In the POPS study, as in most other follow-up studies, at an early age, the handicap risk was significantly greater for boys than for girls.[31] For intelligence this male disadvantage had disappeared at 19 years of age. Since we performed multiple imputations this cannot be explained by the fact that the males followed had higher maternal education and socioeconomic level than those lost to follow up and might be catching up. Genetic conditions may account for up to 72% of the variance of the differences in intelligence.[32] In children at high biological risk however these genetic factors might be overshadowed by environmental factors.[33] In these children an optimal environment can compensate for a cognitive delay.[20,21]

In our study neonatal factors at first sight had relatively little impact on intelligence in comparison with parental education. One SD more in birth weight resulted in 2.6 IQ points more and one week in gestational age in 1.3 IQ points more. Compared with infants born at 36 weeks, however those born at 26 weeks have on average 13.0 lower IQ points. Our findings in this respect compare to those of a recent meta-analysis of intelligence in school-aged children who were born very preterm, with a 10.9 mean IQ points differences between the very preterm and the controls.[5]

The effect on intelligence in premature infants after early symmetric IUGR was more pronounced than after asymmetric IUGR. Due to an increased risk of handicaps during neonatal intensive care treatment, however the effect of NGR on intelligence was more serious than of asymmetric IUGR. In this study we were unable to differentiate the small "normal" from the IUGR children. Moreover neonatal data were collected at a time when cerebral ultrasound was not routinely available. Neonatal complications such as cerebral hemorrhage or periventricular leukomalacia may result in overt handicaps that can be diagnosed at an early age. However, very preterm and very low birth weight infants develop cognitive problems in the absence of overt handicaps or neuroimaging abnormalities.[34,35] To study these more subtle effects we performed analyses in which participants with overt cognitive or neurosensory handicaps were excluded. The effect of neonatal growth restraint became less pronounced. Yet, the timing of the growth retardation remained a significant predictor of intelligence, suggesting that overt neonatal cerebral brain damage leading to overt handicaps does not explain these differences in IQ. This study has not the potential to identify the precise mechanisms underlying these differences in IQ. Neonatal factors contributing to neurobehavioral deficits may include the vulnerability of the immature brain both before and after birth, multiple clinical problems specific to prematurity, stressful environmental conditions and multiple painful procedures. Moreover, neonatal hospital stay might hamper the quality of infant-parent interaction.[36]

We conclude that neonatal factors such as gestational age at birth, intrauterine and neonatal growth are of predictive value. The effect on intelligence after early (symmetric) intrauterine growth retardation is more pronounced than after later (asymmetric) intrauterine or neonatal growth restraint. Environmental factors however, especially parental education, best predict later intelligence. In our study parental education was relatively high. The good outcome at young adulthood in these survivors from the early neonatal intensive care era seems therefore partly due to the favorable socioeconomic circumstances of the study group growing up in the Dutch society, that is representative for most Western societies. Even very preterm children with normal IQ, however are at risk for neuropsychological deficits that might result in learning and behavioral problems. In our study compared with the general Dutch population, although the mean IQ in our cohort was only 2.2 IQ points lower, twice as many young adults born very preterm and/or with a very low birth weight were poorly educated (24% vs. 12.8%) and three times as many were neither employed nor in school (7.6% vs. 2.6%) at 19 years of age.[27] Today we are witnessing an increase in number of preterm births in many countries in the Western world. Prevention of preterm birth should therefore have high priority. An optimal environment during fetal life as well as during neonatal intensive care treatment is warranted to prevent neonatal complications and growth restraint. After discharge early intervention programs should focus on the prevention of neurocognitive deficits and promote the parent child relationship. In addition support for children growing up in less favorable socioeconomic circumstances is needed.

Contributors
N Weisglas-Kuperus drafted the paper and together with ETM Hille created the study design. ETM Hille coordinated the data collection. N Weisglas-Kuperus, S.van Buuren and HJ Duivenvoorden analyzed the data. JB van Goudoever, MJJ Finken, JM Wit and SP Verloove-Vanhorick contributed to the interpretation. SP Verloove-Vanhorick initiated and directed the POPS study as a whole and the follow-up study at age 19 in particular. All authors contributed to the drafting and the revision of this manuscript.

Funding
The organizations mentioned in the acknowledgements that sponsored the study had no involvement in study design, data collection, analysis, interpretation of the data, or in the writing of the report.POPS-19 was supported by grants from the Netherlands Organization for Health Research and Development (ZonMw), Edgar Doncker Foundation, Foundation for Public Health Fundraising Campaigns, Phelps Foundation, Swart-van Essen Foundation, Foundation for Children's Welfare Stamps, TNO Quality of Life, Netherlands Organization for Scientific Research (NWO), Dutch Kidney Foundation, Sophia Foundation for Medical Research, Stichting Astmabestrijding and the Royal Effatha Guyot group. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication

Competing interest
None declared.

Ethical approval
Institutional review boards in all centres gave approval.

Acknowledgements
We thank the young adults and their parents for their generosity in participating in our ongoing studies for the last 19 years, R. Brand for his statistical advise, W. Resing, R. van den Berg and N. Bleichrodt for their advise in the use of the MCT and J.J. Hagoort for editing the English text.

* Members of the Dutch POPS-19 Collaborative Study Group:
TNO Quality of Life, Leiden (ETM Hille, CH de Groot, H Kloosterboer-Boerrigter, AL den Ouden, A Rijpstra, SP Verloove-Vanhorick, JA Vogelaar, coordinating center); Emma Children's Hospital AMC, Amsterdam (JH Kok, A Ilsen, M van der Lans, WJC Boelen-van der Loo, T Lundqvist, HSA Heymans); University Medical Center Groningen, Beatrix Children's Hospital, Groningen (EJ Duiverman, WB Geven, ML Duiverman, LI Geven, EJLE Vrijlandt); University Hospital Maastricht, Maastricht (ALM Mulder, A Gerver); University Medical Center St Radboud, Nijmegen (LAA Kollée, L Reijmers, R Sonnemans); Leiden University Medical Center, Leiden (JM Wit, FW Dekker, MJJ Finken); Erasmus MC - Sophia Children's Hospital, University Medical Center Rotterdam (N Weisglas-Kuperus, MG Keijzer-Veen, AJ van der Heijden, JB van Goudoever); VU University Medical Center, Amsterdam (MM van Weissenbruch, A Cranendonk, HA Delemarre-van de Waal, L de Groot, JF Samsom); Wilhelmina Children's Hospital, UMC, Utrecht (LS de Vries, KJ Rademaker, E Moerman, M Voogsgeerd); Máxima Medical Center, Veldhoven (MJK de Kleine, P Andriessen, CCM Dielissen-van Helvoirt, I Mohamed); Isala Clinics, Zwolle (HLM van Straaten, W Baerts, GW Veneklaas Slots-Kloosterboer, EMJ Tuller-Pikkemaat); Royal Effatha Guyot Group, Zoetermeer (MH Ens-Dokkum); Association for Parents of Premature Babies (GJ van Steenbrugge).

What is already known on this topic

Very preterm and very low birth weight infants are at risk of cognitive deficits at school age. Disability and functioning has been recently defined by the World Health Organization as a dynamic interaction between neonatal, personal and environmental factors. In very preterm and very low birth weight infant the relative contributions of these factors on cognitive function in adulthood have not yet been described.

WHAT THIS STUDY ADDS

Prematurity as well as the timing of growth retardation are important for later intelligence. Parental education however, best predicted later intelligence in very preterm or very low birth weight infants.

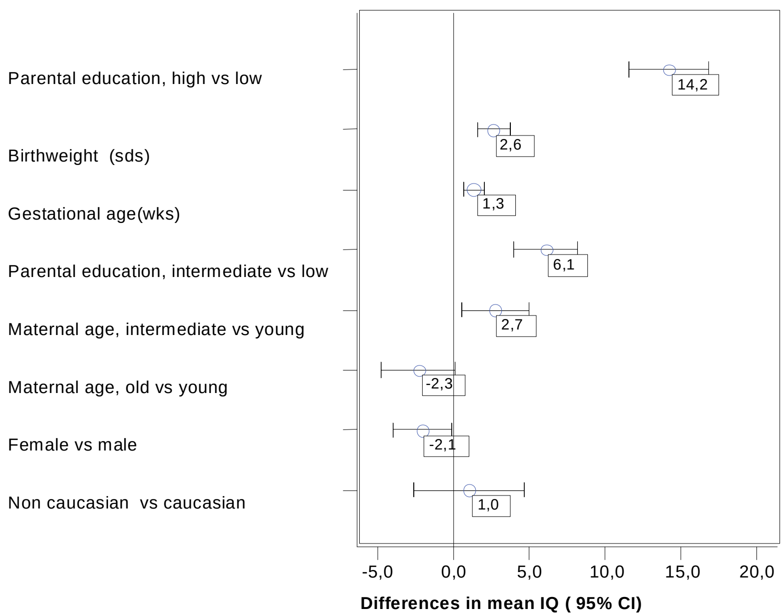
References

1. Veen S, Ens-Dokkum MH, Schreuder AM, Verloove-Vanhorick SP, Brand R, Ruys JH. Impairments, disabilities, and handicaps of very preterm and very-low-birthweight infants at five years of age. The Collaborative Project on Preterm and Small for Gestational Age Infants (POPS) in The Netherlands. Lancet 1991;338(8758):33-6.
2. Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E, Klein N. Outcomes in young adulthood for very-low-birth-weight infants. N Engl J Med 2002;346(3):149-57.
3. Cooke RW. Health, lifestyle, and quality of life for young adults born very preterm. Arch Dis Child 2004;89(3):201-6.
4. Saigal S, Stoskopf B, Streiner D, Boyle M, Pinelli J, Paneth N, et al. Transition of extremely low-birth-weight infants from adolescence to young adulthood: comparison with normal birth-weight controls. Jama 2006;295(6):667-75.
5. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. Jama 2002;288(6):728-37.
6. Cooke RW. Perinatal and postnatal factors in very preterm infants and subsequent cognitive and motor abilities. Arch Dis Child Fetal Neonatal Ed 2005;90(1):F60-3.
7. Huppi PS, Schuknecht B, Boesch C, Bossi E, Felblinger J, Fusch C, et al. Structural and neurobehavioral delay in postnatal brain development of preterm infants. Pediatr Res 1996;39(5):895-901.
8. Peterson BS, Anderson AW, Ehrenkranz R, Staib LH, Tageldin M, Colson E, et al. Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. Pediatrics 2003;111(5 Pt 1):939-48.
9. Strauss RS. Adult functional outcome of those born small for gestational age: twenty-six-year follow-up of the 1970 British Birth Cohort. Jama 2000;283(5):625-32.
10. Gutbrod T, Wolke D, Soehne B, Ohrt B, Riegel K. Effects of gestation and birth weight on the growth and development of very low birthweight small for gestational age infants: a matched group comparison. Arch Dis Child Fetal Neonatal Ed 2000;82(3):F208-14.
11. Kok JH, den Ouden AL, Verloove-Vanhorick SP, Brand R. Outcome of very preterm small for gestational age infants: the first nine years of life. Br J Obstet Gynaecol 1998;105(2):162-8.
12. O'Keeffe MJ, O'Callaghan M, Williams GM, Najman JM, Bor W. Learning, cognitive, and attentional problems in adolescents born small for gestational age. Pediatrics 2003;112(2):301-7.
13. Frisk V, Amsel R, Whyte HE. The importance of head growth patterns in predicting the cognitive abilities and literacy skills of small-for-gestational-age children. Dev Neuropsychol 2002;22(3):565-93.
14. Bergvall N, Iliadou A, Johansson S, Tuvemo T, Cnattingius S. Risks for low intellectual performance related to being born small for gestational age are modified by gestational age. Pediatrics 2006;117(3):e460-7.
15. Finken M, Dekker F, de Zegher F, Wit J. Long-term height gain of prematurily born children with neonatal growth restraint; parallelism with the growth pattern of children born small-for-gestational-age. Pediatrics 2006:in press.
16. Latal-Hajnal B, von Siebenthal K, Kovari H, Bucher HU, Largo RH. Postnatal growth in VLBW infants: significant association with neurodevelopmental outcome. J Pediatr 2003;143(2):163-70.
17. World Health Organization Classification of Functioning DaH. ICF International Classification of Functioning, Disability and Health. Geneva, Switzerland: World Health Organization, 2001.
18. Jefferis BJ, Power C, Hertzman C. Birth weight, childhood socioeconomic environment, and cognitive development in the 1958 British birth cohort study. Bmj 2002;325(7359):305.
19. Sommerfelt K, Andersson HW, Sonnander K, Ahlsten G, Ellertsen B, Markestad T, et al. Cognitive development of term small for gestational age children at five years of age. Arch Dis Child 2000;83(1):25-30.
20. Fletcher JM, Landry SH, Bohan TP, Davidson KC, Brookshire BL, Lachar D, et al. Effects of intraventricular hemorrhage and hydrocephalus on the long-term neurobehavioral development of preterm very-low-birthweight infants. Dev Med Child Neurol 1997;39(9):596-606.
21. Weisglas-Kuperus N, Baerts W, Smrkovsky M, Sauer PJ. Effects of biological and social factors on the cognitive development of very low birth weight children. Pediatrics 1993;92(5):658-65.
22. Verloove-Vanhorick SP, Verwey RA, Brand R, Gravenhorst JB, Keirse MJ, Ruys JH. Neonatal mortality risk in relation to gestational age and birthweight. Results of a national survey of preterm and very-low-birthweight infants in the Netherlands. Lancet 1986;1(8472):55-7.
23. Hille ET, Elbertse L, Gravenhorst JB, Brand R, Verloove-Vanhorick SP. Nonresponse bias in a follow-up study of 19-year-old adolescents born as preterm infants. Pediatrics 2005;116(5):e662-6.
24. Bleichrodt N, Berg R. Multiculturele Capaciteiten Test Middelbaar niveau (MCT-M): Handleiding. Amsterdam: NOA, 2000.
25. Niklasson A EA, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977–1981). Acta Paediatr Scand 1991 1991;80:756-62.
26. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, et al. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47(3):316-23.

27. Hille T, Weisglas-Kuperus N, van Goudoever J, Jacobusse G, Ens-Dokkum M, de Groot L, et al. Functional Outcomes and Participation in Young Adulthood for Very Preterm and Very Low Birthweight Infants:the Dutch POPS-study at 19 years of age. Pediatrics, in press 2007.
28. van Buuren S BH, Knook DL. . Multiple imputation of missing blood pressure covariates in survival analysis. Stat.Med. 1999;18(6):681-94.
29. Rubin D. Multiple imputation for nonresponse in surveys. New York: John Wiley & Sons, 1987.
30. Vreugdenhil HJ, Lanting CI, Mulder PG, Boersma ER, Weisglas-Kuperus N. Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age. J Pediatr 2002;140(1):48-56.
31. Verloove-Vanhorick SP, van Zeben-van der Aa DM, Verwey RA, Brand R, Ruys JH. The male disadvantage in very low birthweight infants: does it really exist? Eur J Pediatr 1989;149(3):197-202.
32. Deary IJ, Spinath FM, Bates TC. Genetics of intelligence. Eur J Hum Genet 2006;14(6):690-700.
33. Koeppen-Schomerus G, Eley TC, Wolke D, Gringras P, Plomin R. The interaction of prematurity with genetic and environmental influences on cognitive development in twins. J Pediatr 2000;137(4):527-33.
34. Cooke RW, Abernethy LJ. Cranial magnetic resonance imaging and school performance in very low birth weight infants in adolescence. Arch Dis Child Fetal Neonatal Ed 1999;81(2):F116-21.
35. Stewart AL, Rifkin L, Amess PN, Kirkbride V, Townsend JP, Miller DH, et al. Brain structure and neurocognitive and behavioural function in adolescents who were born very preterm. Lancet 1999;353(9165):1653-7.
36. Perlman JM. Neurobehavioral deficits in premature graduates of intensive care--potential medical and neonatal environmental risk factors. Pediatrics 2001;108(6):1339-48.

.

FIGURE 1. Differences in mean IQ for gestational age and birth weight SDS, environmental and personal factors in multiple regression analyses


Parental education, high vs low
Birthweight (sds)
Gestational age(wks)
Parental education, intermediate vs low
Maternal age, intermediate vs young
Maternal age, old vs young
Female vs male
Non caucasian vs caucasian
14,2
2,6
1,3
6,1
2,7
-2,3
-2,1
1,0
-5,0
0,0
5,0
10,0
15,0
20,0
Differences in mean IQ (95% CI)