



HHS Public Access

Author manuscript

J Perinatol. Author manuscript; available in PMC 2018 November 29.

Published in final edited form as:

J Perinatol. 2018 July ; 38(7): 908–916. doi:10.1038/s41372-017-0020-8.

Accuracy of the Bayley-II Mental Development Index at 2 Years as a Predictor of Cognitive Impairment at School Age among Children Born Extremely Preterm

Thomas M. O’Shea, MD^a, Robert M. Joseph, PhD^b, Elizabeth N. Allred, MS^{c,d}, H. Gerry Taylor, PhD^e, Alan Leviton, MD^{c,d}, Tim Heeren, PhD^f, Laurie M. Douglass, MD^g, Jean A. Frazier, MD^h, Hernan Jara, PhDⁱ, Karl C. K. Kuban, MD, SMEpi^g, and for the ELGAN Study Investigators

^aDepartment of Pediatrics, University of North Carolina, Chapel Hill, NC, USA

^bDepartment of Psychology and Neuroanatomy, Boston University, Boston, USA

^cDepartment of Neurology, Harvard Medical School, Boston, MA, USA

^dDepartment of Neurology, Neuroepidemiology Unit, Boston Children’s Hospital, Boston, MA, USA

^eDepartment of Pediatrics, Rainbow Babies & Children’s Hospital, University Hospitals Cleveland Medical Center

^fDepartment of Biostatistics, Boston University School of Public Health, Boston, MA, USA

^gDivision of Pediatric Neurology, Department of Pediatrics, Boston Medical Center, Boston, MA, USA

^hDepartment of Psychiatry and Pediatrics, UMASS Medical School/ University of Massachusetts Memorial Children’s Medical Center, Worcester, MA, USA

ⁱDepartment of Radiology, Boston Medical Center, Boston University, Boston, USA

Abstract

Objective—To describe the accuracy of the Bayley Scales of Infant Development-Second Edition (BSID-II) Mental Development Index (MDI) at 2 years of age for prediction of cognitive function at school age of children born extremely preterm.

Design—Study participants were enrolled in the Extremely Low Gestational Age Newborn Study between 2002 and 2004. Two-thirds of surviving children (n=795) were assessed at 2 years with the BSID-II and at 10 years with an intelligence quotient (IQ) test. We computed test characteristics for a low MDI (< 70), including predictive value positive.

Users may view, print, copy, and download text and data-mine the content in such documents, for the purposes of academic research, subject always to the full Conditions of use: http://www.nature.com/authors/editorial_policies/license.html#terms

Contact information for corresponding author: T. Michael O’Shea, MD, MPH, Neonatal-Perinatal Medicine, UNC Hospitals, 4th Floor, Campus Box 7596, Chapel Hill, NC 27599-7596, moshea52@email.unc.edu, **Phone Number:** is 984-974-7826.

None of the authors has relevant financial interests, activities, relationships, or affiliations.

Results—Almost two-thirds of children with a low MDI had a normal IQ (< 70) at 10 years. Concordance between MDI and IQ was highest among children with major motor and/or sensory impairment, and when MDI was adjusted for gestational age.

Conclusion—Most children born extremely preterm with low BSID-II MDI at 2 years have normal intelligence at school age.

Introduction

About 75% of infants born extremely preterm (< 28 weeks of gestation) survive into childhood(1) and about 25% of survivors develop moderate-to-severe cognitive disability.(2–4) Studies of the cognitive outcomes for individuals born extremely preterm have been used to guide clinical care of neonates at the margin of viability,(5, 6) to identify children most in need of special educational resources,(7) and as the evidence base for neonatal intensive care practices.(8–10) Typically, cognitive function is first assessed at 18-24 months using the Bayley Scales of Infant Development (BSID).(11)

Many research studies that have helped to guide current perinatal care have employed the second edition of the BSID (BSID-II) to assessment developmental outcome,(11) and the most frequently met criterion for moderate to severe neurodevelopmental impairment has been a BSID-II Mental Development Index (MDI) more than 2 standard deviations below the mean in the standardization sample, i.e., a score less than 70. Research involving children born with very low birth weight(12, 13) or born very preterm(14, 15) suggests that MDI < 70 is only moderately predictive of IQ < 70 ,(16) and that among extremely low birth weight children without neurosensory impairment, the predictive value is low.(17) The limitations of existing studies of the accuracy of the BSID-II MDI include relatively small samples and short intervals between measurements of MDI and IQ. No study has assessed whether infant or maternal sociodemographic attributes influence the difference between a child's MDI and IQ.

Our objectives were to describe the relationship between MDI < 70 at 2 years adjusted age and cognitive impairment at 10 years of age in a large sample of children born extremely preterm, i.e., the ELGAN Study cohort,(18) and to identify infant or maternal factors that influence the level of agreement between MDI and IQ.

Methods

Participants (Table 1)

The Extremely Low Gestational Age Newborn (ELGAN) Study is a multicenter observational study of the risk of structural and functional neurologic disorders in extremely preterm infants.(18) During the years 2002-2004, women delivering before 28 weeks gestation were asked to enroll in the study. Mothers of 1506 infants born in 14 U.S. hospitals in 5 states gave informed consent for participation. Of 1200 ELGAN Study survivors, 1102 (92%) were evaluated at age 2 years.

At 10 years of age, 966 surviving children, on whom blood specimens were collected in the first weeks of life for assessment of inflammation-related proteins, were recruited. The

families of 889 of these children returned for follow up at 10 years of age. Excluded from the current analysis were 94 children who were not assessed with cognitive measures at both 2 and 10 years of age. The institutional review boards of all participating institutions approved enrollment and consent procedures for this follow-up study.

Demographic and pregnancy variables

After delivery, each mother was interviewed in her native language by a trained research nurse who used a structured data collection form as described in a manual of procedures. This interview was the source of information about mother's pre-pregnancy weight and height, her education, and whether or not she received public health insurance.

Newborn variables

Birth weight and gestational age were obtained by medical record review. The gestational age estimates were based on a hierarchy of the quality of available information. Most desirable were estimates based on the dates of embryo retrieval or intrauterine insemination or fetal ultrasound before the 14th week (62%). When these were not available, reliance was placed sequentially on a fetal ultrasound at 14 or more weeks (29%), last menstrual period without fetal ultrasound (7%), and gestational age recorded in the log of the neonatal intensive care unit (1%). The birth weight Z-score is the number of standard deviations the infant's birth weight is above or below the median weight of infants at the same gestational age in a standard data set.(19)

Ultrasound scans

In prior publications we have described how ultrasound images were acquired(20) and how inter-reader agreement was maximized. (21) For the current analyses, we defined white matter damage as moderate/severe ventriculomegaly or echolucency in the periventricular white matter. Radiologists classified the degree of ventriculomegaly using templates of multiple levels of ventriculomegaly and recorded observations about echolucent lesions in 16 white matter zones on each side seen on coronal views. Each scan was read by at least two readers, and if the first two readers disagreed about the presence of white matter damage, the images were sent to a third (tie-breaking) reader who was blinded to the original reports.

Early Cognitive Function at 24 months of age

Assessment with the BSID-II was completed close to 2 years of age, adjusted for gestational age at birth; 77% of children had their exam within the range of 23.5-27.9 months. Certified examiners administered and scored the BSID-II. Only 2% of examiners indicated at the time of the examination that they had more than a limited amount of information about the child. Before testing examiners were told the child's age. After completion of testing they were told the gestational age so that the BSID-II scores could be age-adjusted.

Cognitive Function at ten years of age

For assessment at ten years, cognitive evaluations were administered by child psychologists in a 3- to 4-hour session that included breaks. All psychologist examiners underwent a 1-day

in-person training and verification of fidelity for administration and scoring the test battery. General cognitive ability (or IQ) was assessed with the School-Age Differential Ability Scales–II (DAS-II(22)) Verbal and Nonverbal Reasoning subscales. Executive function was assessed with the DAS-II and the NEUROPSYCHOLOGICAL ASSESSMENT (NEPSY-II).(23) DAS-II Recall of Digits Backward and Recall of Sequential Order measured verbal working memory. NEPSY-II Auditory Attention and Auditory Response Set measured sustained auditory attention, set switching and inhibition. NEPSY-II Inhibition-Inhibition and Inhibition-Switching measured simple inhibition and inhibition in the context of set shifting, respectively. NEPSY-II Animal Sorting measured visual concept formation and mental flexibility. In addition to defining moderate to severe cognitive impairment using IQ alone, we also identified a subgroup with moderate to severe impairment (18.8% of study participants) using latent profile analysis (LPA) applied to measures of IQ and executive function, who on average scored more than two standard deviations below normative expectation across all measures.(24)

Data Analyses

For both the MDI and IQ the standard deviation in the normative sample is 15. Sensitivity, specificity, predictive value positive and predictive value negative were calculated as described previously(25) for three cut-offs: MDI < 55, MDI < 70, and MDI < 85, corresponding to 3, 2, and 1 standard deviations below the mean of 100 in the normative sample. We calculated these test characteristics separately for children with and without major neuromotor and/or sensory impairment, defined as severe gross motor impairment (level 5 on the Gross Motor Function Classification System)(26) and/or severe visual impairment (uncorrectable functional blindness in both eyes).

To compare two test characteristics, we used the 95% confidence interval. If the point estimate for one member of the pair was not included in the 95% confidence interval for the other member, we concluded that the difference was statistically significant at $p < 0.05$. As an overall measure of diagnostic accuracy of cut-offs we computed the diagnostic odds ratio.(27)

To describe the difference in cognitive function between 24 months and 10 years, we calculated the difference between the MDI and the IQ $[(\text{Verbal IQ} + \text{Non-Verbal IQ}) / 2]$ and the exact binomial 95% confidence limits. To evaluate whether maternal or infant attributes influence the relationship of MDI and IQ, we compare this median difference between MDI and IQ for subgroups of study participants with and without the attributes of interest, including fetal growth restriction, male sex, gestational age at birth, neonatal cerebral white matter damage, and lower scores on the motor scale of the BSID-II, i.e., the Psychomotor Development Index, at 2 years adjusted age. For these comparisons we used Kruskal-Wallis tests and defined statistical significance as $p < 0.05$.

Result

Study participants (Table 1)

Children who were eligible for evaluation at 10 years but did not return for evaluation (n=77) were often born to mothers with less than high school education and mothers who were eligible for public assistance, as compared to children included in the current analysis. Children with severe neurosensory impairment (n=60) or who were not tested with both the BSID and DAS (n=94) were more likely to have had cerebral white matter abnormality on neonatal cranial ultrasound and to have had abnormally low PDI at 2 years adjusted age.

Relationship of low MDI at 24 months to cognitive impairment at 10 years (Table 2 and 3)

Of the children with MDI < 55, 53% had IQ > 70 at 10 years of age; and nearly one quarter had an IQ > 85, which is within 1 standard deviation of the mean. Among infants with MDI < 70, 36% had IQ > 85 at school age.

Predictive value positive and diagnostic odds ratio was highest with a cut-off of MDI < 55 (3 standard deviations below the normative mean). Predictive value positive was higher for cognitive outcomes that were based on verbal and nonverbal IQ and executive function combined than for either verbal IQ or non-verbal IQ. Predictive value positive was higher when considering MDI for adjusted age as compared to MDI for actual age.

Among children with moderate to severe gross motor function impairment and/or legal blindness in one or both eyes, the predictive value positive for MDI < 55 was 70% (95% confidence interval: 51%, 84%) and predictive value negative was 75% (95% confidence interval: 54%, 89%), significantly higher than the predictive value positive and predictive value negative among children without major motor and/or sensory impairment. Each of these test characteristics was higher than was found among children without major neuromotor and/or sensory impairment at 10 years of age.

Comparison of MDI at 24 months and IQ at 10 years (Figure 1; Table 4)

The distribution of the difference in 2-year and 10-year scores (IQ - MDI) was skewed to the right, with a mean value of 5 (95% confidence limits: 3, 6.5). Children born to mothers with pre-pregnancy obesity, males, and children with lower motor skills at 2 years adjusted age, exhibited greater increase in cognitive tests scores between 2 and 10 years.

Discussion

In this cohort of children born extremely preterm over half of those classified as having cognitive impairment at 2 years, based on their having a low MDI, did not have cognitive impairment at 10 years. Even children with very low MDI (< 55), were more likely than not to have IQ > 70 at 10 years of age. The value of MDI for prediction of cognitive impairment at 10 years of age was higher when using MDI for adjusted age, rather than MDI for actual age. In addition, predictive value positive was higher for a cognitive outcome that included tests of executive function than for verbal or nonverbal IQ alone. As has been reported by others,(17) the predictive accuracy of the MDI was higher among children with motor and/or sensory impairment as compared to children without these impairments. Several maternal

and infant factors that have been previously associated with lower MDI, such as pre-pregnancy maternal obesity, male sex, and impaired motor skills at two years, were associated with greater increase in cognitive scores between 2 and 10 years.

Predictive Value of the BSID

Although the BSID has been used widely as a cognitive assessment for infants, the BSID-II manual states that “the BSID-II is not to serve as an intelligence test for young children.” (28) While MDI correlates moderately well with IQ,(16) our findings indicate that cognitive impairment identified with the BSID-II frequently does not persist through school age among infants born extremely preterm. One explanation is that the BSID-II might overestimate the degree of impairment; another is that cognitive functioning might improve after infancy. It follows that evaluations at school age, when intelligence and other aspects of cognitive function can be assessed, are essential in order to provide a more valid description of the long-term outcomes of individuals born extremely preterm.

Our finding that extremely preterm infants with low MDI more often than not did not have cognitive impairment at 10 years of age agrees with a study of children born with extremely low birth weight, in which only 37% of those with MDI < 70 at 20 months had IQ < 70 at 8 years.(17) Our results also agree with a study of children born before 30 weeks of gestation in which 50% of those with MDI < 70 at 2 years had IQ < 70 at 4 years. However our primary finding contrasts with that of two studies of children born with very low birth weight,(12, 13) and a study of infants born before 31 weeks of gestation,(14) in which the predictive value positives for MDI < 70 were 0.75 or greater. In studies that described a higher predictive value positive than reported here, IQ was measured at 5 years of age or less, so that the interval between testing with the BSID and IQ testing was less than the interval in the present study. In addition, studies showing high predictive value involved infants of greater birth weight and gestational age, and thus, lower rates severe neonatal illnesses. Such illness can slow developmental trajectory early in life but typically resolve during early childhood. Of the five prior studies of the BSID in very low birth weight children, very preterm, or extremely low birth weight, 1 used the first edition of the BSID, 2 used the second edition, and 2 used the third edition. Although the three scales are correlated with each other,(29) (and Figure 1 of Lowe et al(30)) it is possible that some of the discrepancy across studies is attributable to use of different versions of the BSID.

When using the BSID to evaluate children born prematurely, typical practice is to subtract from the child's age the number of days between the date of the infant's birth and the expected date of birth.(31) This adjustment for the degree of prematurity results in a higher MDI score, and thus would be expected to increase the specificity and predictive value positive. Our study provides empiric support for this supposition and emphasizes the importance of adjustment for degree of prematurity when the goal of assessment is to obtain the most valid indication of the child's eventual cognitive ability.

A low MDI was more predictive of cognitive impairment defined using tests of both executive function and IQ, as compared to cognitive impairment based only on IQ. The basis of this finding is unclear but may reflect a higher sensitivity of measures of executive function to complications of preterm birth compared with IQ.(32)

Factors associated with predictive value of the BSID

A larger increase in test scores between 2 and 10 years was found among children born to mothers with pre-pregnancy obesity, male children, and children with impaired motor skills at 2 years. Each of these factors is associated with lower cognitive function.(4, 17, 33, 34) In contrast to a prior study of extremely low birth weight children, we did not find that children with severe brain ultrasound abnormality were less likely to improve from an MDI below 70 to an IQ above 70.(17) As was found in an Australian cohort of extremely low birth weight children,(35) ELGAN Study males exhibited a greater increase in scores on cognitive assessments between 2 years and 10 years, even though they have a higher rate of cognitive impairment at 10 years.(36) Male sex is associated with a higher risk of neonatal morbidities,(37) such as chronic lung disease, that have the potential for delaying development but often resolve during infancy. Conversely, early life risk factors for cognitive impairment that do not tend to resolve, such as fetal growth restriction,(38) cerebral white matter damage,(39) and social disadvantage,(4, 40) were not associated with improvement in cognitive assessment scores between 2 and 10 years.

Two other risk factors for impaired early cognitive function, maternal pre-pregnancy obesity(4, 41) and impaired infant motor function,(17) also were associated with a greater increase in scores on cognitive assessments between 2 years and 10 years. It is plausible that the influence of these factors on brain development diminishes after infancy or that these factors prompt increased utilization of early intervention.(42)

Strengths and Limitations

Strengths of this study include a relatively large sample size, diversity of the sample with respect to sociodemographic attributes, and assessments by individuals who were not aware of children's prior tests results or medical histories. Study participants who did not return for evaluation were more likely to have indicators of lower socioeconomic status, such as eligibility for public health insurance. The resulting selection bias most likely led to our overestimating the cognitive abilities of the sample. A potential limitation of this study is that early assessments were completed with the second edition of the BSID (BSID-II), rather than the third edition (BSID-III), which is widely used in contemporary trials.(43–45) By simultaneously assessing children with the two editions, we(46) and others(30, 47, 48) have found that average scores on the BSID-III are higher than those on the BSID-II, suggesting that the BSID-III underestimates the degree of developmental delay.(47) However, consensus is lacking on a strategy for making scores from the BSID-II and BSID-III more comparable.(11, 49)

Implications and conclusions

Our findings suggest that caution is appropriate when interpreting findings from clinical trials involving extremely preterm neonates when the BSID is used to ascertain cognitive impairment. For example, in a trial of caffeine for extremely low birth weight neonates, caffeine treatment was associated with a lower risk of MDI < 70 at 18 months adjusted age, but was not associated with a lower risk of IQ < 70 at 5 years of age. (10, 50)

The BSID's relatively low predictive value positive also is relevant to prognostic predictions for extremely preterm fetuses.(11) Hack and her colleagues have expressed concern that decisions to not provide intensive care for extremely preterm infants in the delivery room might be "biased by reported high rates of cognitive impairments based on the use and presumptive validity of the BSID II MDI."(17) A hopeful message can be taken from our finding that among infants with a very low MDI (< 55) at two years of age, over one-half had a normal IQ (> 70) and almost one quarter had an IQ 85 at school age.

Acknowledgments

This study was supported by the National Institute of Neurological Disorders and Stroke (grants 5U01NS040069-05 and 2R01NS040069-09) and the Office of the Director of the National Institutes of Health ((1UG3OD023348-01).

The authors also gratefully acknowledge the contributions of their subjects, and their subjects' families, as well as those of their colleagues listed below.

Project Lead for ELGAN-2: Julie V. Rollins, MA

Site Principal Investigators

Baystate Medical Center, Springfield, MA: Bhahvesh Shah, MD; Rachana Singh, MD, MS

Boston Children's Hospital, Boston, MA: Linda Van Marter, MD, MPH and Camilla Martin, MD, MPH; Janice Ware, PhD

Tufts Medical Center, Boston, MA: Cynthia Cole, MD; Ellen Perrin, MD

University of Massachusetts Medical School, Worcester, MA: Frank Bednarek, MD; Jean Frazier, MD

Yale University School of Medicine, New Haven, CT: Richard Ehrenkranz, MD; Jennifer Benjamin, MD

Wake Forest University, Winston-Salem, NC: T. Michael O'Shea, MD, MPH

University of North Carolina, Chapel Hill, NC: Carl Bose, MD; Diane Warner, MD, MPH

East Carolina University, Greenville, NC: Steve Engelke, MD

Helen DeVos Children's Hospital, Grand Rapids, MI: Mariel Poortenga, MD; Steve Pastyrnak, PhD

Sparrow Hospital, East Lansing, MI: Padu Karna, MD; Nigel Paneth, MD, MPH; Madeleine Lenski, MPH

University of Chicago Medical Center, Chicago, IL: Michael Schreiber, MD; Scott Hunter, PhD; Michael Msall, MC

William Beaumont Hospital, Royal Oak, MI: Danny Batton, MD; Judith Klarr, MD

Site Study Coordinators

Baystate Medical Center, Springfield, MA: Karen Christianson, RN; Deborah Klein, BSM, RN

Boston Children's Hospital, Boston MA: Maureen Pimental, BA; Collen Hallisey, BA; Taryn Coster, BA

Tufts Medical Center, Boston, MA: Ellen Nysten, RN; Emily Neger, MA; Kathryn Mattern, BA

University of Massachusetts Medical School, Worcester, MA: Lauren Venuti, BA; Beth Powers, RN; Ann Foley, EdM

Yale University School of Medicine, New Haven, CT: Joanne Williams, RN; Elaine Romano, APRN

Wake Forest University, Winston-Salem, NC: Debbie Hiatt, BSN (deceased); Nancy Peters, RN; Patricia Brown, RN; Emily Anusinha, BA

University of North Carolina, Chapel Hill, NC: Gennie Bose, RN; Janice Wereszczak, MSN; Janice Bernhardt, MS, RN

East Carolina University, Greenville, NC: Joan Adams (deceased); Donna Wilson, BA, BSW

Nancy Darden-Saad, BS, RN

Helen DeVos Children's Hospital, Grand Rapids, MI: Dinah Sutton, RN; Julie Rathbun, BSW, BSN

Sparrow Hospital, East Lansing, MI: Karen Miras, RN, BSN; Deborah Weiland, MSN

University of Chicago Medical Center, Chicago, IL: Grace Yoon, RN; Rugile Ramoskaite, BA; Suzanne Wiggins, MA; Krissy Washington, MA; Ryan Martin, MA; Barbara Prendergast, BSN, RN

William Beaumont Hospital, Royal Oak, MI: Beth Kring, RN

Psychologists

Baystate Medical Center, Springfield, MA: Anne Smith, PhD; Susan McQuiston, PhD

Boston Children's Hospital: Samantha Butler, PhD; Rachel Wilson, PhD; Kirsten McGhee, PhD; Patricia Lee, PhD; Aimee Asgarian, PhD; Anjali Sadhwani, PhD; Brandi Henson, PsyD

Tufts Medical Center, Boston MA: Cecelia Keller, PT, MHA; Jenifer Walkowiak, PhD; Susan Barron, PhD

University of Massachusetts Medical School, Worcester MA: Alice Miller, PT, MS; Brian Dessureau, PhD; Molly Wood, PhD; Jill Damon-Minow, PhD

Yale University School of Medicine, New Haven, CT: Elaine Romano, MSN; Linda Mayes, PhD; Kathy Tsatsanis, PhD; Katarzyna Chawarska, PhD; Sophy Kim, PhD; Susan Dieterich, PhD; Karen Bearrs, PhD

Wake Forest University Baptist Medical Center, Winston-Salem NC: Ellen Waldrep, MA; Jackie Friedman, PhD; Gail Hounshell, PhD; Debbie Allred, PhD

University Health Systems of Eastern Carolina, Greenville, NC: Rebecca Helms, PhD; Lynn Whitley, PhD Gary Stainback, PhD

University of North Carolina at Chapel Hill, NC: Lisa Bostic, OTR/L; Amanda Jacobson, PT; Joni McKeeman, PhD; Echo Meyer, PhD

Helen DeVos Children's Hospital, Grand Rapids, MI: Steve Pastyrnak, PhD

Sparrow Hospital, Lansing, MI: Joan Price, EdS; Megan Lloyd, MA, EdS

University of Chicago Medical Center, Chicago, IL: Susan Plesha-Troyke, OT; Megan Scott, PhD

William Beaumont Hospital, Royal Oak, MI: Katherine M. Solomon, PhD; Kara Brooklier, PhD; Kelly Vogt, PhD

This study was supported by from the Office of the Director, National Institutes of Health (1UG3OD023348-01), the National Institute of Neurological Disorders and Stroke (5U01NS040069-05 and 2R01NS040069-09), and the National Institute of Child Health and Human Development (5P30HD018655-28). Dr. Frazier has the following disclosures: serving on the data safety monitoring board for Forest Pharmaceuticals and receiving research support from Alcobra, Janssen Pharmaceuticals, Neuren, and SyneuRX International. No funds from these entities were used to support this project, and none of these entities reviewed or commented on this study. All other authors declare that they have no financial or ethical conflicts of interest. The authors gratefully acknowledge the contributions of the research participants and their families, as well as those of their colleagues.

Abbreviations

BSID Bayley Scales of Infant Development

MDI Mental Development Index

SD	standard deviation
ELGAN	Extremely Low Gestational Age Newborn
IQ	Intelligent quotient
DAS-II	Differential Ability Scales–II
NEPSY-II	NEuroPSYchological Assessment-II

References

- O'Shea TM, Allred EN, Dammann O, Hirtz D, Kuban KCK, Paneth N, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. *Early Human Development*. 2009; 85(11):719–25. [PubMed: 19765918]
- Serenius F, Kallen K, Blennow M, Ewald U, Fellman V, Holmstrom G, et al. Neurodevelopmental Outcome in Extremely Preterm Infants at 2.5 Years After Active Perinatal Care in Sweden. *Jama-Journal of the American Medical Association*. 2013; 309(17):1810–20.
- Johnson S, Fawke J, Hennessy E, Rowell V, Thomas S, Wolke D, et al. Neurodevelopmental Disability Through 11 Years of Age in Children Born Before 26 Weeks of Gestation. *Pediatrics*. 2009; 124(2):E249–E57. [PubMed: 19651566]
- Helderman JB, O'Shea TM, Kuban KCK, Allred EN, Hecht JL, Dammann O, et al. Antenatal Antecedents of Cognitive Impairment at 24 Months In Extremely Low Gestational Age Newborns. *Pediatrics*. 2012; 129(3):494–502. [PubMed: 22331342]
- Tyson JE, Parikh NA, Langer J, Green C, Higgins RD, National Institute of Child H. et al. Intensive care for extreme prematurity—moving beyond gestational age. *N Engl J Med*. 2008; 358(16):1672–81. [PubMed: 18420500]
- Marrs CC, Pedroza C, Mendez-Figueroa H, Chauhan SP, Tyson JE. Infant Outcomes after Periviable Birth: External Validation of the Neonatal Research Network Estimator with the BEAM Trial. *Am J Perinatol*. 2015
- Marlow N. Measuring neurodevelopmental outcome in neonatal trials: a continuing and increasing challenge. *Arch Dis Child Fetal Neonatal Ed*. 2013; 98(6):F554–8. [PubMed: 23839983]
- Morris BH, Oh W, Tyson JE, Stevenson DK, Phelps DL, O'Shea TM, et al. Aggressive vs. conservative phototherapy for infants with extremely low birth weight. *New England Journal of Medicine*. 2008; 359(18):1885–96. [PubMed: 18971491]
- Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med*. 2001; 344(26):1966–72. [PubMed: 11430325]
- Schmidt B, Roberts R, Davis P, Doyle L, Barrington K, Ohlsson A, et al. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med*. 2007; 357(19):1893–902. [PubMed: 17989382]
- Kilbride HW, Aylward GP, Doyle LW, Singer LT, Lantos J. Prognostic neurodevelopmental testing of preterm infants: do we need to change the paradigm? *J Perinatol*. 2017; 37(5):475–9. [PubMed: 28252658]
- Munck P, Niemi P, Lapinleimu H, Lehtonen L, Haataja L, Group PS. Stability of cognitive outcome from 2 to 5 years of age in very low birth weight children. *Pediatrics*. 2012; 129(3):503–8. [PubMed: 22371467]
- Ross G, Lipper EG, Auld PA. Consistency and change in the development of premature infants weighing less than 1,501 grams at birth. *Pediatrics*. 1985; 76(6):885–91. [PubMed: 4069857]
- Bode MM, D'Eugenio DB, Mettelman BB, Gross SJ. Predictive validity of the Bayley, Third Edition at 2 years for intelligence quotient at 4 years in preterm infants. *J Dev Behav Pediatr*. 2014; 35(9):570–5. [PubMed: 25370298]
- Spencer-Smith MM, Spittle AJ, Lee KJ, Doyle LW, Anderson PJ. Bayley-III Cognitive and Language Scales in Preterm Children. *Pediatrics*. 2015; 135(5):e1258–65. [PubMed: 25896835]

16. dos Santos E, de Kieviet J, Konigs M, van Elburg R, Oosterlaan J. Predictive value of the Bayley Scales of Infant Development on development of very preterm/very low birth weight children: a meta-analysis. *Early Hum Dev.* 2013; 89:487–96. [PubMed: 23597678]
17. Hack M, Taylor HG, Drotar D, Schluchter M, Cartar L, Wilson-Costello D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. *Pediatrics.* 2005; 116(2):333–41. [PubMed: 16061586]
18. O'Shea TM, Allred EN, Dammann O, Hirtz D, Kuban KC, Paneth N, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. *Early Hum Dev.* 2009; 85(11):719–25. [PubMed: 19765918]
19. Yudkin PL, Aboualfa M, Eyre JA, Redman CWG, Wilkinson AR. New Birth-Weight and Head Circumference Centiles for Gestational Ages 24 to 42 Weeks. *Early Human Development.* 1987; 15(1):45–52. [PubMed: 3816638]
20. Teele R, Share J. *Ultrasonography of infants and children.* Philadelphia: Saunders; 1991.
21. Kuban K, Adler I, Allred EN, Batton D, Bezinque S, Betz BW, et al. Observer variability assessing US scans of the preterm brain: the ELGAN study. *Pediatr Radiol.* 2007; 37(12):1201–8. [PubMed: 17901950]
22. Elliott CD. *Differential ability scales.* second. San Antonio, TX: The Psychological Corporation; 2007.
23. Korkman M, Kirk U, Kemp S. *NEPSY-II, second edition: Clinical and interpretive manual.* 2007
24. Heeren T, Joseph RM, Allred EN, O'Shea TM, Leviton A, Kuban KCK. Cognitive functioning at age 10 years among children born extremely preterm: A latent profile approach. *Pediatr Res.* 2017
25. Fowlie PW. Towards safer diagnosis in clinical practice - understanding and using diagnostic tests in the neonatal unit more appropriately. *Semin Fetal Neonatal Med.* 2005; 10(1):83–90. [PubMed: 15698973]
26. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol.* 1997; 39(4):214–23. [PubMed: 9183258]
27. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol.* 2003; 56(11):1129–35. [PubMed: 14615004]
28. Bradley-Johnson S. Cognitive assessment for the youngest children: A critical review of tests. *Journal of Psychoeducational Assessment.* 2001; 19:19–44.
29. Goldstein D, Folgle E, Weiber J, O'Shea T. Comparison of the Bayley scales of infant development 2nd ed. Bayley scales of infant development with premature infants. *J Psychoed Assess.* 1995; 13:391–6.
30. Lowe JR, Erickson SJ, Schrader R, Duncan AF. Comparison of the Bayley II Mental Developmental Index and the Bayley III cognitive scale: are we measuring the same thing? *Acta Paediatrica.* 2012; 101(2):E55–E8. [PubMed: 22054168]
31. Black MM, K. *Essentials of Bayley Scales of Infant Development-II Assessment.* New York, NY: John Wiley & Sons, Inc; 2000.
32. Orchinik LJ, Taylor HG, Espy KA, Minich N, Klein N, Sheffield T, et al. Cognitive outcomes for extremely preterm/extremely low birth weight children in kindergarten. *J Int Neuropsychol Soc.* 2011; 17(6):1067–79. [PubMed: 21923973]
33. Pugh SJ, Richardson GA, Hutcheon JA, Himes KP, Brooks MM, Day NL, et al. Maternal Obesity and Excessive Gestational Weight Gain Are Associated with Components of Child Cognition. *J Nutr.* 2015; 145(11):2562–9. [PubMed: 26423736]
34. Kuban KJ, RM, O'Shea TM, Allred EN, Heeren T, Douglass L, Stafstrom CE, Jara H, Frazier JA, Hirtz D, Leviton A. Extremely Low Gestational AGE newborn (ELGAN) Study Investigators Girls and boys born before 28 weeks gestation: Risks of cognitive, behavioral, and neurological outcomes at age 10 years. *J Pediatr.* 2016 Mar 19. [E pub ahead of print].
35. Roberts G, Anderson PJ, Doyle LW. The stability of the diagnosis of developmental disability between ages 2 and 8 in a geographic cohort of very preterm children born in 1997. *Archives of Disease in Childhood.* 2010; 95(10):786–90. [PubMed: 19828882]

36. Kuban KC, Joseph RM, O'Shea TM, Allred EN, Heeren T, Douglass L, et al. Girls and Boys Born before 28 Weeks Gestation: Risks of Cognitive, Behavioral, and Neurologic Outcomes at Age 10 Years. *J Pediatr*. 2016; 173:69–75. e1. [PubMed: 27004675]
37. Stevenson DK, Verter J, Fanaroff AA, Oh W, Ehrenkranz RA, Shankaran S, et al. Sex differences in outcomes of very low birthweight infants: the newborn male disadvantage. *Arch Dis Child Fetal Neonatal Ed*. 2000; 83(3):F182–5. [PubMed: 11040165]
38. Streimish IG, Ehrenkranz RA, Allred EN, O'Shea TM, Kuban KCK, Paneth N, et al. Birth weight- and fetal weight-growth restriction: Impact on neurodevelopment. *Early Human Development*. 2012; 88(9):765–71. [PubMed: 22732241]
39. O'Shea TM, Kuban KCK, Allred EN, Paneth N, Pagano M, Dammann O, et al. Neonatal cranial ultrasound lesions and developmental delays at 2 years of age among extremely low gestational age children. *Pediatrics*. 2008; 122(3):E662–E9. [PubMed: 18762501]
40. Whitaker AH, Feldman JF, Lorenz JM, Shen S, McNicholas F, Nieto M, et al. Motor and cognitive outcomes in nondisabled low-birth-weight adolescents - Early determinants. *Archives of Pediatrics & Adolescent Medicine*. 2006; 160(10):1040–6. [PubMed: 17018463]
41. van der Burg JW, Allred EN, Kuban K, O'Shea TM, Dammann O, Leviton A. Maternal obesity and development of the preterm newborn at 2 years. *Acta Paediatr*. 2015; 104(9):900–3. [PubMed: 25982514]
42. Watkins S, Jonsson-Funk M, Brookhart MA, Rosenberg SA, O'Shea TM, Daniels J. Preschool motor skills following physical and occupational therapy services among non-disabled very low birth weight children. *Matern Child Health J*. 2014; 18(4):821–8. [PubMed: 23820671]
43. Juul SE, Mayock DE, Comstock BA, Heagerty PJ. Neuroprotective potential of erythropoietin in neonates; design of a randomized trial. *Matern Health Neonatol Perinatol*. 2015; 1:27. [PubMed: 27057344]
44. Ballard RA, Keller RL, Black DM, Ballard PL, Merrill JD, Eichenwald EC, et al. Randomized Trial of Late Surfactant Treatment in Ventilated Preterm Infants Receiving Inhaled Nitric Oxide. *J Pediatr*. 2016; 168:23–9.e4. [PubMed: 26500107]
45. Vaucher YE, Peralta-Carcelen M, Finer NN, Carlo WA, Gantz MG, Walsh MC, et al. Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. *N Engl J Med*. 2012; 367(26):2495–504. [PubMed: 23268664]
46. Silveira RC, Filipouski G, Goldstein D, O'Shea T, Procianoy R. Agreement between Bayley Scales Second and Third Edition Assessments of Very Low Birth Weight Infants. *Archives of Pediatrics & Adolescent Medicine*. 2012
47. Anderson PJ, De Luca CR, Hutchinson E, Roberts G, Doyle LW. Underestimation of Developmental Delay by the New Bayley-III Scale. *Archives of Pediatrics & Adolescent Medicine*. 2010; 164(4):352–6. [PubMed: 20368488]
48. Johnson S, Moore T, Marlow N. Using the Bayley-III to assess neurodevelopmental delay: which cut-off should be used? *Pediatr Res*. 2014; 75(5):670–4. [PubMed: 24492622]
49. Aylward GP. Continuing issues with the Bayley-III: where to go from here. *J Dev Behav Pediatr*. 2013; 34(9):697–701. [PubMed: 24217027]
50. Schmidt B, Anderson PJ, Doyle LW, Dewey D, Grunau RE, Asztalos EV, et al. Survival Without Disability to Age 5 Years After Neonatal Caffeine Therapy for Apnea of Prematurity. *Jama-Journal of the American Medical Association*. 2012; 307(3):275–82.

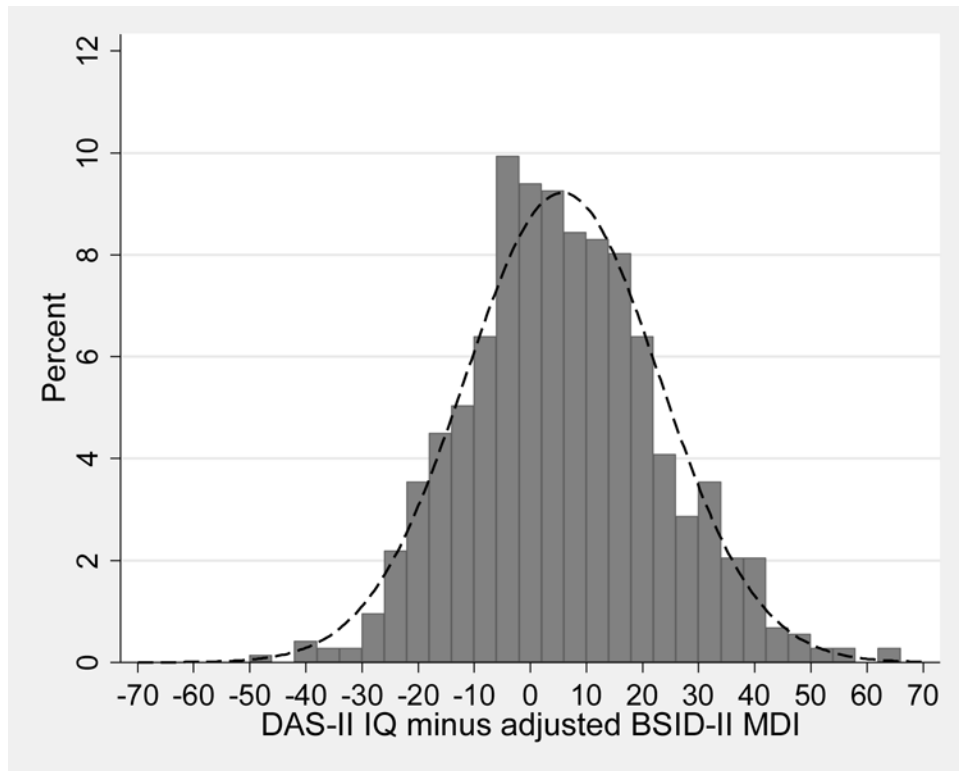


Figure 1. Frequency distribution for DAS IQ at 10 years minus BSID MDI at 2 years. The overlying normal curve is calculated using the mean and standard deviation of the difference.

Table 1

Sample characteristics for children eligible for assessment at 10 years of age (n=966). These are column percents.

Factor	Level	Returned for 10-year assessment		
		Yes		No
		Major Impairment		
		Yes	No	
Maternal education	12	40	47	55
	13-15	22	22	26
	16	38	23	19
Public insurance	Yes	35	39	60
Pre-pregnancy body mass index	30	22	27	18
Region in which child was born	New England	40	42	44
	North Carolina	30	23	25
	Lake Michigan	30	35	31
Sex	Male	50	44	44
Gestational age	23-24	18	38	14
	25-26	46	41	60
	27	37	21	26
Birth weight Z-score	< -2	6	8	1
	-2, < -1	13	14	14
	-1,	81	78	84
White matter abnormality ^{††}	Yes	11	28	9
Psychomotor Development Index at 2 years	< 55	10	47	25
	55-69	15	20	11
	70-84	22	15	23
	85	53	18	42
Total sample		735	154	77

* Major impairment was defined as either severe gross motor impairment (level 5 on the Gross Motor Function Classification System) or severe visual impairment (uncorrectable functional blindness in both eyes).

^{††} White matter abnormality: ventriculomegaly and or a hypoechoic lesion on cranial ultrasound during the NICU stay.

Abbreviations: DAS – Differential Ability Scales

Table 2

The percent of children who had an MDI at age 2 years in the range listed at the top of the column who also had the standard score of the DAS components at age 10 years listed on the left. These are column percents.

DAS-II at 10 years	Uncorrected MDI at age 2 years				Row N	
	<55	55-69	70-84	85		
Verbal Reasoning	<55	13	3	0.5	0.6	31
	55-69	21	6	2	1	55
	70-84	28	27	14	7	137
	85	37	63	83	91	512
Non-Verbal Reasoning	<55	7	1	0.5	0	15
	55-69	15	8	4	0	47
	70-84	36	29	16	11	166
	85	43	62	79	89	507
Working Memory	<55	16	4	1	2	40
	55-69	12	9	1	2	41
	70-84	28	20	13	5	119
	85	44	67	85	91	531
Maximum number of children	173	172	207	183	735	

DAS-II at 10 years	Corrected MDI at age 2 years				Row N	
	<55	55-69	70-84	85		
Verbal Reasoning	<55	22	6	4	0.5	31
	55-69	25	17	8	2	55
	70-84	29	28	28	11	137
	85	24	49	59	87	512
Non-Verbal Reasoning	<55	13	3	1	0.2	15
	55-69	23	10	6	3	47
	70-84	34	30	34	14	166
	85	30	57	59	83	507
Working Memory	<55	30	6	4	1	40

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

DAS-II at 10 years	Corrected MDI at age 2 years	Row N			
		< 55	55-69	70-84	85
55-69	12	12	9	2	41
70-84	29	25	24	9	119
85	29	58	63	87	531
Maximum number of children	79	69	179	408	735

Abbreviations: MDI – Mental Development Index; DAS – Differential Ability Scales

Table 3

Measures of the ability of a low MDI at age 2 years to predict DAS standard scores and cognitive function at 10 years of age among children who did not have a major neuromotor or sensory impairment.

	Percent Impaired at age 10		Row N	Performance impairment at age 2 (95% confidence interval) predicting impairment at age 10			
	Adjusted MDI < 55 at age 2 (n=79)	Adjusted MDI 55 at age 2 (n=656)		PVP	PVN	Sens	Spec
DAS Verbal < 70	47	7	86	47 (36, 58)	93 (90, 94)	43 (32, 54)	94 (91, 95)
DAS Non-verbal < 70	35	5	62	35 (25, 47)	95 (93, 96)	45 (32, 58)	92 (90, 94)
Mod/Sev Impairment*	63	14	139	63 (53, 74)	86 (84, 89)	36 (28, 45)	95 (93, 97)

	Percent Impaired at age 10		Row N	Performance impairment at age 2 (95% confidence interval) predicting impairment at age 10			
	Adjusted MDI < 70 at age 2 (n=148)	Adjusted MDI 70 at age 2 (n=587)		PVP	PVN	Sens	Spec
DAS Verbal < 70	36	6	86	36 (28,44)	94 (92,96)	62 (50, 72)	85 (82,88)
DAS Non-verbal < 70	25	4	62	25 (18,33)	96 (46,72)	60 (46,72)	84 (80,86)
Mod/Sev Impairment*	48	12	139	48 (40,56)	88 (86, 91)	51 (42, 59)	87 (84,90)

	Percent Impaired at age 10		Row N	Performance impairment at age 2 (95% confidence interval) predicting impairment at age 10			
	Adjusted MDI < 85 at age 2 (n=327)	Adjusted MDI 85 at age 2 (n=408)		PVP	PVN	Sens	Spec
DAS Verbal < 70	23	2	86	23 (19, 28)	98 (95, 99)	88 (80, 94)	61 (57, 65)
DAS Non-verbal < 70	15	3	62	15 (12, 20)	97 (95, 98)	81 (69, 90)	59 (55, 63)
Mod/Sev Impairment*	36	5	139	36 (31, 42)	95 (92, 97)	85 (78, 90)	64 (61, 69)

* Impairment based on LPA analysis of IQ and EF

Abbreviations: MDI – Mental Development Index; DAS – Differential Ability Scales; Mod/Sev – moderate/severe; PVP – predictive value positive; PVN – predictive value negative; Sens – sensitivity; Spec – specificity; LPA – latent profile analysis; IQ – intelligence quotient; EF – executive function

Table 4

Difference between IQ at 10 years of age and MDI at 2 years adjusted age (95% confidence limits).

Factor	Level	Median (95% CI)*	N	p-value**
Maternal education	12	6 (2.5, 9)	294	0.20
	13-15	4 (-1.5, 8)	165	
	16	4 (2, 6)	276	
Public insurance	Yes	6.25 (4, 9.5)	254	0.16
	No	4 (1.5, 6)	481	
Pre-pregnancy BMI	30	9 (3.5, 13)	155	0.01
	< 30	4 (2, 5.5)	555	
ELGAN site at birth	New England	4.5 (1, 7)	296	0.92
	North Carolina	4.25 (2, 8)	218	
	Lake Michigan	5.5 (2.5, 9)	221	
Sex	Male	6.5 (4, 9)	369	0.01
	Female	3 (1, 5.5)	366	
Gestational age	23-24	7 (3, 13)	129	0.14
	25-26	3.5 (1, 6)	337	
	27	5.5 (2, 9)	269	
Birth weight Z-score	< -2	6.5 (-5, 12.5)	41	0.41
	-2, < -1	2.5 (0.15, 7.5)	98	
	-1	5 (3.5, 7)	325	
White matter abnormality (VM and/or EL)	Yes	4.25 (-0.5, 10)	80	0.67
	No	5 (3, 6.5)	655	
PDI at 2 years	< 55	11.75 (5.5, 16)	70	0.0001
	55-69	16 (6.5, 21)	107	
	70-84	9 (5.5, 11)	158	
	85	1 (-0.5, 3)	384	
Weight Z-score at 2 years	< -2	6.25 (-0.5, 16)	36	0.56
	-2, < -1	5.5 (0, 9)	115	
	-1	4 (2, 6)	563	
Weight Z-score at 10 years	< -2	5.75 (-5.5, 11)	46	0.82
	-2, < -1	6.25 (3.5, 9)	144	
	-1	4.5 (2.5, 6)	538	
Total sample		5 (3, 6.5)	735	