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Lasting Effects of Preterm Birth and Neonatal Brain Hemorrhage at 12 Years of Age

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Abstract

Objectives—To compare cognitive, language, behavioural and educational outcomes of preterm children to term controls, and to evaluate the impact of neonatal brain injury, indomethacin and environmental risk factors on intellectual function at 12 years.

Methods—375 children born in 1989–1992 with birth weight 600–1250g enrolled in the Indomethacin Intraventricular Hemorrhage (IVH) Prevention Trial and 111 term controls were evaluated at 12 years of age. Neuropsychometric testing, neurological exam, and interviews on educational needs were completed. Severe brain injury was defined as the presence of grade 3–4 IVH, periventricular leukomalacia or severe ventriculomegaly on cranial ultrasound.

Results—On the Wechsler Scales of Intelligence for Children, the preterm cohort obtained a mean full scale IQ of 87.9 ± 18.3 , verbal IQ of 90.8 ± 18.9 , and performance IQ of 86.8 ± 17.9 . Preterm children obtained scores 6–14 points lower than term controls on all psychometric tests after adjustment for socio-demographic factors. On the Clinical Evaluation of Language Fundamentals (test of basic language skills), 22–24% of preterm children scored in the abnormal ranges (<70) as opposed to 2–4% of controls. Preterm children with and without brain injury required more school services (76% and 44% vs. 16%), and support in reading (44% and 28% vs. 9%), writing (44% and 20% vs. 4%), and mathematics (47% and 30% vs. 6%) compared to controls. Preterm children also displayed more behaviour problems than their term counterparts. Severe neonatal brain injury was the strongest predictor of poor intelligence (mean difference -22.1 ; CI $-28.1, -16.2$). Antenatal steroids, higher maternal education, and 2-parent family were associated with better cognition, whereas minority status incurred a disadvantage. Indomethacin did not affect intellectual function among preterm children.

Conclusion—Preterm children born in the early 1990s, especially those with severe brain injury, demonstrate serious deficits in their neuropsychological profile, which translates into increased use of school services at 12 years.

Keywords

Very low birth weight; prematurity; cognition; language; school outcomes

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Introduction

One of the challenges of modern perinatal care for preterm infants is achieving optimal survival while simultaneously limiting the rate of neurodevelopmental handicap. High grade intraventricular hemorrhage (IVH) is a complication which has been shown to contribute to long-term disabilities associated with preterm birth (1,2).

Studies extending into adolescence show that preterm children, despite normal intelligence, continue to exhibit higher rates of neurodevelopmental disabilities compared to their term peers resulting in poorer academic and social functioning, and higher educational needs (3-18). The majority of these cohorts represent children born in the late 70s and early 80s, prior to the extensive use of antenatal steroids and surfactant therapy.

We have previously shown that indomethacin lowers the incidence and decreases the severity of IVH in preterm infants (19). Follow-up studies of this cohort were reassuring with regards to the safety of indomethacin on developmental outcomes (2,20,21). Furthermore, a gender-mediated effect of indomethacin on cognitive and language skills was identified (22). Preterm boys assigned to indomethacin performed better in cognitive and verbal tasks in comparison to preterm placebo controls.

The objective of this study was to describe cognitive, language, and behavioural outcomes along with educational placement of preterm children at 12 years of chronological age in comparison to term controls. The contributions of indomethacin, early neonatal insults and later social risk factors on cognitive and verbal outcomes were examined. It was hypothesized that preterm children would continue to exhibit significant deficits on all neuropsychological domains compared to term controls, preterm boys randomized to indomethacin would continue to demonstrate a benefit in cognitive and verbal skills compared to placebo preterm subjects at age 12, and severe brain injury would be the strongest predictor of long-term cognitive function.

Methods

Participants

Between 09/05/1989 and 08/31/1992, 505 infants with a birth weight of 600 to 1250 g admitted by 6 hours of age to Women and Infants' Hospital (Providence, RI), Maine Medical Center (Portland, ME), and Yale New Haven Hospital (New Haven, CT) were enrolled after parental consent to a prospective trial on early administration of low-dose indomethacin to prevent IVH. Details of the newborn protocol have been described elsewhere (19,23). Of the 505 infants, 432 did not have IVH around 6 hours and 431/432 were randomized to the Primary IVH Prevention Trial (19); 61 infants with grade 1–2 IVH were part of the Secondary IVH Prevention Trial (23); 12 with grade 3–4 IVH were also offered neurodevelopmental follow-up. All are included in our total cohort. Unless otherwise specified, results pertain to the total cohort.

For the 12-year assessment, 111 term controls were also evaluated. They were recruited from the local community or randomly selected from a telemarketing list of 10,000 families. Term controls were frequency-matched to the preterm group on zip-code, age, gender, maternal education, and race.

Procedure

The institutional review boards of the 3 participating centers approved all protocols related to the Multicenter Randomized Indomethacin IVH Prevention Trial. Informed consents were obtained from parents of all children at the 12-year visit.

Prenatal and neonatal data were retrieved from the study database. Bronchopulmonary dysplasia (BPD) was defined as oxygen requirement and abnormal chest x-ray at 28 days after birth (24). Severe brain injury was defined as the presence of either grade 3–4 IVH, periventricular leukomalacia (PVL), or grade 2 and above ventriculomegaly. School psychologists blinded to the participants' perinatal history conducted neuropsychological testing. Mean standard score was 100 with a standard deviation of 15. Participants with significant impairments who could not be tested received the test's lowest standard score. Cognitive functioning was evaluated with the Wechsler Intelligence Scale for Children-III (WISC-III) (25), which yields Verbal and Performance IQ (VIQ and PIQ), and a composite Full Scale IQ (FSIQ) score. Four factor indices are derived from the results of the subtests: the Verbal Comprehension Index provides an estimate of verbal reasoning, the Perceptual Organization Index evaluates nonverbal problem-solving skills, the Freedom from Distractibility Index measures working memory, and the Processing Speed Index appraises the rapidity to process visual information. The Peabody Picture Vocabulary Test-Revised (PPVT-R)(26) was administered to evaluate receptive listening vocabulary. The rapid naming composite of the Comprehensive Test of Phonological Processing (CTOPP)(27) measured efficiency of phonological information retrieval from long-term memory. The Clinical Evaluation of Language Fundamentals (CELF)(28) served to examine receptive and expressive language (syntax, semantics, and verbal language memory). The Developmental test of Visual-Motor Integration (VMI)(29) measured visual perception and motor planning. Reading skills were determined using the Test of Word Reading Efficiency (TOWRE)(30) and the Gray Silent Reading Test (GSRT)(31). In the TOWRE, participants are asked to rapidly read a list of real words and pronounceable non-words. The task evaluates phonemic decoding and word deciphering accuracy and fluency. Finally, the GSRT taps reading comprehension. Caretakers filled out the Child Behaviour Checklist (CBCL)(32), a questionnaire designed to describe social competencies and emotional/behavioural issues of children. T-scores above 69 (98th percentile) were considered clinically significant for behaviour problems. Scores were derived for withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behaviour, aggressive behaviour, and the presence of any behaviour problem.

A standard neurologic examination was completed. Major neurosensory impairment was defined as the presence of any of the following: abnormal neurologic examination including cerebral palsy, hearing aids, blind services, ventriculo-peritoneal shunts, or seizures. Updated sociodemographic information was provided by the primary caretakers. Details on special health care needs, school resources, and Individualized Educational Plan (IEP) participation were collected. In the United States, an IEP is a written plan that addresses educational needs of children who struggle with their academic curriculum.

Statistical analysis

Neuropsychological outcomes were compared between preterm and term subjects (total cohort) with adjustment for potential confounders (male gender, maternal age at birth < 20, maternal years of education, minority status by maternal report and household structure). Between-group mean differences and odds ratio with 95% confidence intervals were computed using linear or logistic regression. To determine whether male gender modulated the effect of prematurity on outcomes, an interaction term between the two exposure factors was created. Comparative analyses between preterm and term controls were repeated after exclusion of children with severe brain injury. Multiple regression analysis was used to identify perinatal and social factors that predicted VIQ and FSIQ scores and requirement for an IEP at 12 years. Independent variables were selected based on the scientific literature. Because the primary trial was designed to examine the effect of indomethacin in preterm infants without early brain injury, analyses were repeated with restriction to the 327 children enrolled in the Primary IVH

Prevention Trial to examine the treatment-by-gender effect (interaction between indomethacin and male gender). Analyses were conducted with SAS 9.1.

Results

At 12 years of chronological age, 375 preterm children were evaluated, of whom 179 (47.7%) were assigned prophylactic indomethacin. Neonatal characteristics of the 375 preterm children included gestational age of 28 ± 2 weeks (range 23–34 weeks) and birth weight 961 ± 174 g, with 25% small for gestational age ($<10^{\text{th}}$ percentile). Thirty-four percent received antenatal steroids, 9% had severe brain injury, and 46% had BPD. Preterm participants and non-participants at 12 years were comparable with regards to gestational age, birth weight, gender, antenatal steroids, BPD, severe brain injury, maternal age at birth, minority status, and rates of neurosensory disabilities prior to the visit (not shown). Maternal, infant and child characteristics of the preterm children with ($n=34$) and without brain injury ($n=337$) and term controls ($n=111$) are shown in table 1. Proportions surviving were lower for preterm infants with brain injury than those with none. Maternal social characteristics were similar among all groups. Abnormal neurosensory findings were, as expected, more prevalent in the preterm cohort, especially among those with severe brain injury.

Tables 2 and 3 present the general intelligence (WISC-III), spoken and written language (PPVT-R, CTOPP, CELF, TOWRE, GRST), visual-motor coordination (VMI), and behaviour (CBCL) findings. WISC-III mean IQ scores for the total preterm cohort compared to term controls are shown in Table 2. Although on average preterm children obtained IQ and factor index scores within the normal ranges, they lagged behind term controls by 9 to 14 points. The proportion of preterm children scoring in the abnormal ranges (<70) approximated 11–16% on the different IQ scales. IQ scores did not differ between males and females, regardless of prematurity status (not shown).

There were 337 preterm subjects available for comparisons after exclusion of preterm children with severe brain injury. Mean full-scale, verbal, and performance IQ scores for the preterm cohort without brain injury were 92.4 ± 17.3 , 88.5 ± 16.5 , and 89.6 ± 16.7 respectively, with 10%, 8%, and 13% scoring in the abnormal ranges. Mean differences between preterm children without brain injury and term controls narrowed, but remained significant on all scales (table 2).

On spoken and written language testing (table 3), the total preterm cohort consistently scored lower than the term group. Differences between the two were less pronounced on tests of lower-level language skills (phonological processing, phonemic (non-word) decoding and sight word reading). However, preterm subjects exhibited significant difficulties with higher-level language skills including syntax, semantics, and verbal language memory with more than 20% performing in the abnormal ranges on the CELF. Moreover, one quarter of preterm children obtained scores <70 on reading comprehension (31). No interaction was identified between gender and prematurity (not shown). The analyses were repeated with restriction to children without severe brain injury. Risk of scoring in the abnormal ranges on language testing was comparable between preterm without severe brain injury and term children on phonological processing (CTOPP) (table 3). However, preterm children without brain injury still manifested deficits compared to term controls on vocabulary, basic language and basic reading skills.

Although both preterm and term groups performed below standard references on the visual-motor integration test (table 3), preterm children had lower scores than their term peers.

On the CBCL, preterm children (total cohort) were 5 times more likely to have at least one behaviour problems than term controls (21.7% vs 4.7%). Figure 1 illustrates the proportion of preterm and term children scoring in the abnormal ranges on selected CBCL subscales and

exhibiting at least one behaviour problem. Parents of preterm children with brain injury reported more attention, thought and social problems than parents of term controls. Parents of preterm children without brain injury also reported increased attention deficit compared to term controls.

Table 4 displays use of educational services. Whereas 10% of term controls had an IEP, this proportion increased to 35% among preterm children without brain injury and to 76% for children with severe brain injury. A significant proportion of preterm students required additional support in reading, writing, and mathematics. Nevertheless, the majority (88%) of preterm children free of neonatal brain injury were enrolled in a regular classroom.

On multivariate linear regression, severe brain injury was the strongest predictor of verbal and full-scale IQs in the total preterm cohort (table 5). Presence of this neonatal complication led to a 20-point deficit on the VIQ and FSIQ scores. Antenatal steroids had some beneficial effect on FSIQ (3.7-point increase; 95% CI 0.3 to 7.1). The remainder of the variance was in part explained by social determinants, namely maternal education (2-point increase in IQ scores for each additional year of maternal education), household structure (5-point decrease if single-parent family), and race (8-point decrease if member of a minority group). Logistic regression on requirement for an IEP showed a protective effect of antenatal steroids (OR 0.5; 95% CI 0.3–0.8) whereas severe brain injury (OR 5.2; 95% CI 1.8–15.0) and maternal education less than high school (OR 2.4; 95% CI 1.2–5.1) increased the likelihood of having an IEP.

Indomethacin Effect in Preterm Children

All analyses were repeated to examine the effect of indomethacin on test scores among preterm children enrolled in the primary trial (table 6). IQ scores did not differ between preterm children randomized to indomethacin and those assigned to placebo. This finding remained after stratification by gender (not shown). Furthermore, there was no difference between the indomethacin and saline groups on any of the language scores. A treatment-by-gender effect was not identified. Post-hoc analyses were conducted on the subset of preterm children enrolled in the primary trial who did not develop severe brain injury (n=319) to examine the effect of indomethacin on neuropsychological outcomes. No significant differences in test scores were detected (not shown). The current study was powered at 95% to detect a 6-point difference.

Discussion

In this study of neuropsychological outcomes at 12 years of age of a cohort of children born in the early 1990s, preterm children continued to lag behind term controls on all measures of intellectual function, even after exclusion of those with severe brain injury. Severe brain injury was the most important predictor of adverse cognitive sequelae. However, this study did not demonstrate a beneficial effect of indomethacin on 12-year outcomes.

Preterm children in our cohort, despite a mean FSIQ within the normal range, still scored almost 1 standard deviation below normal term controls. Even after exclusion of children with severe brain injury, an 11-point difference remained and was clinically significant. However, the absence of serious findings on cranial ultrasound does not preclude significant brain injury that could only be visible with magnetic resonance imaging (MRI), which was not widely available during the indomethacin trial. Hence, a subset of preterm children categorized as without severe brain injury on cranial ultrasound scanning may have had unrecognized neonatal cerebral insults that could explain, among other things, the 8–13% rate of very low IQ scores and the 10% rate of major neurosensory impairment. In addition, other biological and environmental factors also contribute to long-term neurodevelopmental outcomes.

Almost 25% of the total preterm cohort experienced difficulties in spoken and written language comprehension as measured by the receptive component of the CELF and the GSRT. In contrast, lower level skill such as access to phonological information was almost comparable to term peers after excluding children with severe brain injury. We previously demonstrated with functional MRI that preterm children compared to term controls activated different regions of the cerebral cortex on language-based tasks at age 8 years (33). Neural pathways subserving semantic processing in preterm children were the same as those involved in phonological processing in term controls. The more preterm children exhibited patterns of brain activity similar to term controls on semantic processing tasks, the better was their verbal comprehension index score. Furthermore, indomethacin seemed to have a positive effect in preterm boys on development of brain signaling during phonological processing as the neural activation pattern was similar to term boys (34). This was not observed among preterm girls or boys randomized to saline. In the current study, however, gender and indomethacin effects were not detected. Finally, imaging studies conducted on a subset of the 12-year cohort showed that preterm children engaged alternative neural pathways during phonological processing, which suggests developmental compensatory mechanisms (35). This could explain the encouraging results observed in the current study in phonological processing.

Overall, parents of preterm 12 year old children reported more attention, thought, and social problems than parents of term controls. A number of studies have also indicated higher prevalence of anxiety and depression, withdrawn personality, and hyperactivity (3,10-14,16,36,37), which was not observed in our cohort.

Although our findings pertain to a group of children born more than 15 years ago, trends over time suggest that the gap in neuropsychological skills between preterm and term children has remained relatively constant (4,6,7,9,13,17). With increasing survival of children born prematurely (1,38), the prevalence of children with minor to major cognitive impairment continues to rise. This translates into a higher economic burden on the school system as illustrated by the high proportion of preterm students with brain injury (76%) and without brain injury (44%) requiring special educational services. Parents, educators, and physicians must continue to carefully monitor the academic progress of preterm teens and ensure appropriate learning supports, especially among families of lower socio-economic status, who are at higher risk of having unmet service needs (10).

Prophylactic indomethacin, which lowers cerebral blood flow in animal studies, did not adversely affect the neuropsychological outcomes at 12 years and is consistent with prior reports of this cohort at younger ages (2,20,21). A treatment-by-gender effect favoring male preterm subjects randomized to early indomethacin was not identified, which suggests that the early advantage of the medication may diminish with increasing age as other variables, particularly environmental factors, become more important. As hypothesized, severe brain injury constituted the most important predictor of adverse long-term outcomes. Lower birth weight did not convey additional risk of poor cognitive performance after neonatal morbidities were added in the model. This indicates that the effect of birth weight may be mediated by associated morbidities. Contrary to other studies, we did not find lung injury to be predictive of long-term outcomes (4,6). BPD at 28 days may not have been a sufficiently sensitive measure compared to total days on oxygen or chronic lung disease at 36 weeks post-conception. Our results continue to support the influence of socio-economic factors on cognitive development with increasing age (4,18). However, we cannot distinguish at this time whether the social risks we examined directly influence IQ or are proxy measures of other indicators such as maternal IQ, quality of the home and school environment, or peer influences, which are also associated with later cognitive function (39).

To our knowledge, this is the largest US follow-up study with 375 preterm and 111 term subjects to extend to 12 years of age. The retention rate of 85% was high and the large sample size achieved allowed us to examine simultaneously the effects of multiple risk factors on outcomes. The assessment was comprehensive and covered several domains of neuropsychological abilities.

Limitations inherent to long-term cohort studies include both the lack of early MRI studies and attrition bias: children from socially and economically disadvantaged families are more likely to be lost (40,41). Therefore, our results may underestimate the true prevalence of adverse outcomes.

Conclusion

Preterm children manifest delays in cognitive abilities compared to term controls at 12 years of age. Severe brain injury remains a significant predictor of poor long-term outcomes, along with unfavorable social factors. Preterm survivors continue to require multiple educational supports at 12 years of age. These findings indicate that extended efforts to prevent serious brain injury in preterm infants are needed.

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Abbreviations

BPD, Bronchopulmonary dysplasia
 CBCL, Child Behavior Checklist
 CELF, Clinical Evaluation of Language Fundamentals
 CTOPP, Comprehensive Test of Phonological Processing
 FSIQ, Full Scale IQ
 GSRT, Gray Silent Reading Test
 IEP, Individualized Educational Plan
 IVH, Intraventricular hemorrhage
 PIQ, Performance IQ
 PPVT-R, Peabody Picture Vocabulary Test
 PVL, Periventricular leukomalacia
 SGA, Small-for-gestational age
 TOWRE, Test of Word Reading Efficiency
 VIQ, Verbal IQ
 VMI, Visual-Motor Integration
 WISC, Wechsler Intelligence Scale for Children

References

1. Institute of Medicine. Preterm Birth: Causes, Consequences, and Prevention. National Academies Press; Washington, DC: 2006.
2. Vohr BR, Allan WC, Westerveld M, Schneider KC, Katz KH, Makuch RW, et al. School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. *Pediatrics* 2003;111(4 Pt 1):e340–6. [PubMed: 12671149]
3. Botting N, Powls A, Cooke RW, Marlow N. Attention deficit hyperactivity disorders and other psychiatric outcomes in very low birthweight children at 12 years. *J Child Psychol Psychiatry* 1997;38(8):931–41. [PubMed: 9413793]

4. Botting N, Powls A, Cooke RW, Marlow N. Cognitive and educational outcome of very-low-birthweight children in early adolescence. *Dev Med Child Neurol* 1998;40(10):652–60. [PubMed: 9851233]
5. Hack M, Taylor HG, Klein N, Mercuri-Minich N. Functional limitations and special health care needs of 10- to 14-year-old children weighing less than 750 grams at birth. *Pediatrics* 2000;106(3):554–60. [PubMed: 10969102]
6. Taylor HG, Minich N, Bangert B, Filipek PA, Hack M. Long-term neuropsychological outcomes of very low birth weight: associations with early risks for periventricular brain insults. *J Int Neuropsychol Soc* 2004;10(7):987–1004. [PubMed: 15803562]
7. Saigal S, Hoult LA, Streiner DL, Stoskopf BL, Rosenbaum PL. School difficulties at adolescence in a regional cohort of children who were extremely low birth weight. *Pediatrics* 2000;105(2):325–31. [PubMed: 10654950]
8. Doyle LW, Casazal D. Outcome at 14 years of extremely low birthweight infants: a regional study. *Arch Dis Child Fetal Neonatal Ed* 2001;85(3):F159–64. [PubMed: 11668155]
9. Rickards AL, Kelly EA, Doyle LW, Callanan C. Cognition, academic progress, behavior and self-concept at 14 years of very low birth weight children. *J Dev Behav Pediatr* 2001;22(1):11–8. [PubMed: 11265918]
10. D'Angio CT, Sinkin RA, Stevens TP, Landfish NK, Merzbach JL, Ryan RM, et al. Longitudinal, 15-year follow-up of children born at less than 29 weeks' gestation after introduction of surfactant therapy into a region: neurologic, cognitive, and educational outcomes. *Pediatrics* 2002;110(6):1094–102. [PubMed: 12456905]
11. Johnson A, Bowler U, Yudkin P, Hockley C, Wariyar U, Gardner F, et al. Health and school performance of teenagers born before 29 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2003;88(3):F190–8. [PubMed: 12719391]
12. Gardner F, Johnson A, Yudkin P, Bowler U, Hockley C, Mutch L, et al. Behavioral and emotional adjustment of teenagers in mainstream school who were born before 29 weeks' gestation. *Pediatrics* 2004;114(3):676–82. [PubMed: 15342838]
13. Grunau RE, Whitfield MF, Fay TB. Psychosocial and academic characteristics of extremely low birth weight (< or =800 g) adolescents who are free of major impairment compared with term-born control subjects. *Pediatrics* 2004;114(6):e725–32. [PubMed: 15576337]
14. Dahl LB, Kaarensen PI, Tunby J, Handegard BH, Kvernmo S, Ronning JA. Emotional, behavioral, social, and academic outcomes in adolescents born with very low birth weight. *Pediatrics* 2006;118(2):e449–59. [PubMed: 16882786]
15. Farooqi A, Hagglof B, Sedin G, Gothefors L, Serenius F. Chronic conditions, functional limitations, and special health care needs in 10- to 12-year-old children born at 23 to 25 weeks' gestation in the 1990s: a Swedish national prospective follow-up study. *Pediatrics* 2006;118(5):e1466–77. [PubMed: 17079547]
16. Farooqi A, Hagglof B, Sedin G, Gothefors L, Serenius F. Mental health and social competencies of 10- to 12-year-old children born at 23 to 25 weeks of gestation in the 1990s: a Swedish national prospective follow-up study. *Pediatrics* 2007;120(1):118–33. [PubMed: 17606569]
17. Samuelsson S, Finnstrom O, Flodmark O, Gaddlin PO, Leijon I, Wadsby M. A longitudinal study of reading skills among very-low-birthweight children: is there a catch-up? *J Pediatr Psychol* 2006;31(9):967–77. [PubMed: 16510770]
18. 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. *Arch Pediatr Adolesc Med* 2006;160(10):1040–6. [PubMed: 17018463]
19. Ment LR, Oh W, Ehrenkranz RA, Philip AG, Vohr B, Allan W, et al. Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. *Pediatrics* 1994;93(4):543–50. [PubMed: 8134206]
20. Ment LR, Vohr B, Oh W, Scott DT, Allan WC, Westerveld M, et al. Neurodevelopmental outcome at 36 months' corrected age of preterm infants in the Multicenter Indomethacin Intraventricular Hemorrhage Prevention Trial. *Pediatrics* 1996;98(4 Pt 1):714–8. [PubMed: 8885951]

21. Ment LR, Vohr B, Allan W, Westerveld M, Sparrow SS, Schneider KC, et al. Outcome of children in the indomethacin intraventricular hemorrhage prevention trial. *Pediatrics* 2000;105(3 Pt 1):485–91. [PubMed: 10699097]
22. Ment LR, Vohr BR, Makuch RW, Westerveld M, Katz KH, Schneider KC, et al. Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. *J Pediatr* 2004;145(6):832–4. [PubMed: 15580211]
23. Ment LR, Oh W, Ehrenkranz RA, Phillip AG, Vohr B, Allan W, et al. Low-dose indomethacin therapy and extension of intraventricular hemorrhage: a multicenter randomized trial. *J Pediatr* 1994;124(6): 951–5. [PubMed: 8201485]
24. Bancalari E, Abdenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. *J Pediatr* 1979;95(5 Pt 2):819–23. [PubMed: 385815]
25. Wechsler, D. Wechsler Scale of Intelligence for Children - Third Edition. Psychological Corp; New York, NY: 1991.
26. Dunn, L.; Dunn, L. PPVT: Peabody Picture Vocabulary Test - Revised Form. Circle Pines; MN: 1981.
27. Wagner, RK.; Torgesen, JK.; Rashotte, CA. Comprehensive Test of Phonological Processing. PRO-ED; Austin, Texas: 1999.
28. Semel, E.; Wiig, EH.; Secord, WA. Clinical Evaluation of Language Fundamentals. Vol. 3rd ed.. The Psychological Corporation Harcourt Brace Co; San Antonio: 1995.
29. Beery, KE. The Beert-Buktenica Developmental Test of Visual-Motor Integration. Parsippany; NJ: 1997.
30. Wagner, RK.; Torgesen, JK.; Rashotte, CA. Test of Word Reading Efficiency. PRO-ED; Austin, Texas: 1999.
31. Wiederholt, JL.; Blalock, G. Gray Silent Reading Tests. PRO-ED; Austin, Texas: 2000.
32. Achenbach, TM. Manual for the Child Behavior Checklist/4–18 and 1991 Profile. University of Vermont Department of Psychiatry; Burlington, VT: 1991.
33. Peterson BS, Vohr B, Kane MJ, Whalen DH, Schneider KC, Katz KH, et al. A functional magnetic resonance imaging study of language processing and its cognitive correlates in prematurely born children. *Pediatrics* 2002;110(6):1153–62. [PubMed: 12456913]
34. Ment LR, Peterson BS, Meltzer JA, Vohr B, Allan W, Katz KH, et al. A functional magnetic resonance imaging study of the long-term influences of early indomethacin exposure on language processing in the brains of prematurely born children. *Pediatrics* 2006;118(3):961–70. [PubMed: 16950986]
35. Ment LR, Peterson BS, Vohr B, Allan W, Schneider KC, Lacadie C, et al. Cortical recruitment patterns in children born prematurely compared with control subjects during a passive listening functional magnetic resonance imaging task. *J Pediatr* 2006;149(4):490–8. [PubMed: 17011320]
36. Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Fayers P, Brubakk AM. Psychiatric symptoms and disorders in adolescents with low birth weight. *Arch Dis Child Fetal Neonatal Ed* 2004;89(5):F445–50. [PubMed: 15321968]
37. 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. [PubMed: 12169077]
38. Joseph KS, Kramer MS, Allen AC, Cyr M, Fair M, Ohlsson A, et al. Gestational age- and birthweight-specific declines in infant mortality in Canada, 1985–94. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. *Paediatr Perinat Epidemiol* 2000;14(4):332–9. [PubMed: 11101020]
39. Sattler, JM. Assessment of Children Cognitive Applications. Vol. 4th ed.. Jerome M. Sattler, Publisher, Inc; San Diego, CA: 2001.
40. 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. [PubMed: 16263980]
41. Callanan C, Doyle L, Rickards A, Kelly E, Ford G, Davis N. Children followed with difficulty: how do they differ? *J Paediatr Child Health* 2001;37(2):152–6. [PubMed: 11328470]

TABLE 1

Characteristics of the 12-Year-Old Cohort

	Preterm		Term
	Brain injury	No brain injury	
Number of subjects at inception *	58	408	-
Proportion surviving to NICU discharge, No (%)	42/58 (72%)	398/408 (98%) ⁺	-
Proportion surviving to 12 years, No (%)	39/58 (67%)	395/408 (97%) ⁺	-
Follow-up at 12 years (%)	34/39 (87%)	337/395 (85%)	111
Child characteristics			
Male sex, No (%)	21 (62%)	181 (54%)	51 (46%)
Social factors			
Maternal years at birth, mean (SD)	27.5 (5.6)	27.5 (6.1)	29.3 (6.0)
Maternal years of education, mean (SD)	13.8 (2.7)	13.4 (2.3)	14.3 (2.8)
Maternal education < High school, No (%)	3/34 (9%)	38/336 (11%)	9/111 (8%)
Single parent household, No (%)	11/34 (32%)	115/332 (35%)	31/111 (28%)
Minority status by maternal report, No (%)	8/34 (24%)	100/337 (30%)	34/111 (31%)
Neurosensory impairment			
Abnormal neurologic examination, No (%)	17/34 (50%)	23/337 (7%) ⁺	0
Cerebral palsy, No (%)	17/34 (50%)	17/337 (5%) ⁺	0
Ventriculo-peritoneal shunt, No (%)	7/34 (21%)	1/337 (0.3%) ⁺	0
Seizure disorder, No (%)	6/33 (18%)	5/327 (1.5%) ⁺	0
Hearing aids, No (%)	4/33 (12%)	8/323 (2.5%) ⁺	0
Blind services, No (%)	5/32 (16%)	4/325 (1.2%) ⁺	0
Any neurosensory impairment, No (%)	21/34 (62%)	34/333 (10%) ⁺	0
Glasses, No (%)	15/33 (46%)	109/327 (33%)	33/111 (30%)
Mean age at assessment, mean (SD), years	12.2 (0.4)	12.2 (0.4)	12.7 (0.8)

* Some children died or were discharged prior to near-term cranial ultrasound and could not be classified into the 2 subgroups (brain injury vs. no brain injury).

⁺ Preterm children with brain injury vs. no brain injury, p-value < 0.05 (Fisher's exact test)

Comparisons of WISC-III scores between preterm and term children at 12 years of chronological age

TABLE 2

IQ	Preterm N=375		Term N=111	Adjusted Mean Difference or Odds Ratio (95%CI) - All children included		Adjusted Mean Difference or Odds Ratio (95%CI) - Children with severe brain injury excluded [*]
	n	Mean (SD)		n	Mean (SD)	
WISC-III						
Verbal IQ	369	90.8 (18.9)	103.9 (16.0)	111	103.9 (16.0)	-8.9 (-12.0, -5.7) ⁺
Performance IQ	367	86.8 (17.9)	103.1 (15.7)	111	103.1 (15.7)	-12.7 (-15.9, -9.5) ⁺
Full Scale IQ	366	87.9 (18.3)	103.8 (15.7)	111	103.8 (15.7)	-11.7 (-14.7, -8.7) ⁺
Verbal comprehension	369	92.3 (18.6)	104.3 (15.4)	108	104.3 (15.4)	-8.1 (-11.2, -4.9) ⁺
Perceptual organization	367	86.9 (17.7)	102.9 (15.8)	111	102.9 (15.8)	-12.8 (-16.0, -9.6) ⁺
Freedom of distractibility	367	89.9 (16.8)	101.7 (16.4)	110	101.7 (16.4)	-8.3 (-11.5, -5.1) ⁺
Processing speed	361	94.5 (19.9)	108.5 (16.7)	108	108.5 (16.7)	-10.0 (-13.7, -6.3) ⁺
Subtest scaled score						
Information	368	8.7 (3.8)	10.7 (3.6)	110	10.7 (3.6)	-1.3 (-2.0, -0.6) ⁺
Similarities	369	8.9 (3.5)	11.1 (3.1)	111	11.1 (3.1)	-1.5 (-2.1, -0.9) ⁺
Arithmetic	366	7.7 (3.4)	10.3 (3.6)	111	10.3 (3.6)	-2.0 (-2.7, -1.3) ⁺
Vocabulary	365	8.8 (3.8)	10.7 (3.0)	110	10.7 (3.0)	-1.2 (-1.9, -0.6) ⁺
Comprehension	368	7.8 (3.9)	10.3 (3.3)	111	10.3 (3.3)	-1.7 (-2.4, -1.0) ⁺
Digit span	369	8.4 (3.2)	10.0 (3.0)	110	10.0 (3.0)	-1.0 (-1.6, -0.4) ⁺
Picture completion	368	8.0 (3.4)	10.1 (2.9)	111	10.1 (2.9)	-1.7 (-2.4, -1.0) ⁺
Coding	365	8.4 (3.8)	10.6 (3.4)	110	10.6 (3.4)	-1.4 (-2.1, -0.6) ⁺
Picture arrangement	367	7.9 (3.8)	10.5 (3.5)	111	10.5 (3.5)	-2.0 (-2.7, -1.3) ⁺
Block design	368	7.7 (3.9)	11.2 (3.7)	111	11.2 (3.7)	-2.7 (-3.5, -2.0) ⁺
Object assembly	367	7.0 (3.5)	9.7 (3.0)	111	9.7 (3.0)	-2.1 (-2.8, -1.5) ⁺
Symbol search	363	9.1 (4.3)	12.4 (3.5)	109	12.4 (3.5)	-2.6 (-3.4, -1.7) ⁺
WISC-III, No (%)						
Verbal IQ <70		42/369 (11.4%)	1/111 (0.9%)		14.0 (1.9, 105.1) ⁺⁺	11.1 (1.4, 87.6) ⁺⁺
Performance IQ <70		61/367 (16.6%)	0		-	-
Full Scale IQ <70		52/366 (14.2%)	0		-	-

IQ	Preterm N=375		Term N=111		Adjusted Mean Difference or Odds Ratio (95%CI) - All children included	Adjusted Mean Difference or Odds Ratio (95%CI) - Children with severe brain injury excluded [‡]
	n	Mean (SD)	n	Mean (SD)		

Adjustement for male gender, maternal age < 20, maternal years of education, minority status, single-parent household.

* Severe brain injury: grade 3 and 4 IVH, PVL, grade 2 and above ventriculomegaly

⁺ P-value < 0.005

⁺⁺ p-value <0.05

TABLE 3

Comparisons of neuropsychological scores between preterm and term children at 12 years of chronological age

	Preterm N=375		Term N=111		Adjusted Mean Difference or Odds Ratio (95%CI) - All children included	Adjusted Mean Difference or Odds Ratio (95%CI) - Children with severe brain injury excluded *
	n		n			
LANGUAGE						
PPVT-R, mean (SD)	361	92.0 (25.2)	110	105.4 (20.9)	-11.4 (-16.2, -6.6) ⁺	-8.7 (-12.8, -4.5) ⁺
PPVT-R <70, No (%)		48/361 (13.3%)		4/110 (3.6%)	5.0 (1.6, 15.3) ⁺⁺	4.3 (1.3, 14.5) ⁺⁺
CTOPP, mean (SD)	336	93.6 (21.4)	111	100.8 (15.6)	-5.6 (-9.9, -1.2) ⁺⁺	-3.3 (-7.3, 0.8)
Rapid naming total		45/336 (13.4%)		4/111 (3.6%)	3.8 (1.3, 10.8) ⁺⁺	2.6 (0.9, 7.8)
Rapid naming <70, No (%)						
CELF, mean (SD)						
Expressive	331	85.8 (19.8)	110	99.53 (15.1)	-11.7 (-15.4, -8.0) ⁺	-9.9 (-13.4, -6.4) ⁺
Receptive	331	86.9 (21.0)	110	102.66 (17.7)	-13.7 (-17.7, -9.8) ⁺	-11.7 (-15.4, -7.9) ⁺
Total	330	85.4 (20.0)	110	100.71 (16.1)	-13.2 (-16.9, -9.5) ⁺	-11.2 (-14.7, -7.7) ⁺
CELF, No (%)						
Expressive <70		74/331 (22.4%)		3/110 (2.7%)	13.2 (3.8, 45.9) ⁺	11.1 (3.1, 39.8) ⁺
Receptive <70		73/331 (22.1%)		4/110 (3.6%)	8.8 (3.0, 26.0) ⁺	7.4 (2.4, 22.5) ⁺
Total <70		78/330 (23.6%)		3/110 (2.7%)	13.7 (4.0, 46.8) ⁺	11.7 (3.3, 41.3) ⁺
TOWRE, mean (SD)						
Sight word efficiency	339	93.7 (16.7)	111	101.2 (11.9)	-5.7 (-8.9, -2.5) ⁺	-4.0 (-7.0, -1.0) ⁺⁺
Phonemic decoding	339	91.6 (18.3)	109	100.2 (14.0)	-6.6 (-10.2, -3.0) ⁺	-5.0 (-8.4, -1.6) ⁺⁺
TOWRE, No (%)						
Sight word efficiency < 70		34/339 (10.0%)		0/109	-	-
Phonemic decoding < 70		44/339 (13.0%)		1/109 (0.9%)	17.6 (2.3, 134.7) ⁺	14.4 (1.8, 117.5) ⁺⁺
Gray Silent Reading Test, mean (SD)	361	88.6 (24.8)	109	104.3 (22.4)	-12.8 (-17.7, -8.0) ⁺	-11.2 (-16.0, -6.4) ⁺
Gray Silent Reading Test <70, No (%)		91/361 (25.2%)		5/109 (4.6%)	7.1 (2.7, 18.4) ⁺	5.9 (2.2, 15.5) ⁺
PERCEPTUAL-MOTOR SKILLS						
VMI, mean (SD)	352	82.4 (14.0)	107	91.5 (13.7)	-8.3 (-11.2, -5.3) ⁺	-7.1 (-9.9, -4.2) ⁺

	Preterm N=375	n	Term N=111	Adjusted Mean Difference or Odds Ratio (95%CI) - All children included	Adjusted Mean Difference or Odds Ratio (95%CI) - Children with severe brain injury excluded [*]
VMI <70, No (%)	57/352 (16.2%)		2/107 (1.9%)	9.5 (2.3, 39.7) ⁺	7.3 (1.7, 31.1) ⁺⁺

Adjustement for male gender, maternal age < 20, maternal years of education, minority status, single-parent household.

^{*} Severe brain injury: grade 3 and 4 IVH, PVL, grade 2 and above ventriculomegaly

⁺ p-value < 0.005

⁺⁺ p-value <0.05

TABLE 4

Comparisons of educational resource use between preterm and term children at 12 years chronological age

	Preterm		Term
	Brain injury N=34	No brain injury N=337	N=111
Special services through an Individualized Educational Plan (IEP), n (%)	25/33 (76%)	117/334 (35%)	11/110 (10%) ^{*+}
Classroom setting			
Regular classroom, n (%)	23/34 (68%)	295/335 (88%)	108/111 (97%) ^{*+}
Special classroom, n (%)	11/34 (32%)	40/335 (12%)	3/111 (3%) ^{*++}
Educational services			
Remedial instruction in reading, n (%)	15/34 (44%)	93/336 (28%)	10/111 (9%) ^{*+}
Remedial instruction in writing, n (%)	15/34 (44%)	68/336 (20%)	4/111 (4%) ^{*+}
Remedial instruction in math, n (%)	16/34 (47%)	100/335 (30%)	7/111 (6%) ^{*+}
Physical therapy, n (%)	17/34 (50%)	26/335 (8%)	0
Occupational therapy, n (%)	16/34 (47%)	29/335 (9%)	0
Speech and language therapy, n (%)	17/34 (50%)	38/335 (11%)	2/110 (2%) ^{*++}
Behaviour management, n (%)	3/34 (9%)	33/335 (10%)	8/111 (7%)
Number of educational services			
None, n (%)	8/34 (24%)	189/335 (56%)	93/111 (84%)
1–2, n (%)	7/34 (20%)	53/335 (16%)	12/111 (11%)
3 and more, n (%)	19/34 (56%)	93/335 (28%)	6/111 (5%) [∫]
Repeated a grade, n (%)	8/33 (24%)	73/333 (22%)	10/110 (9%) ^{*+}

* Term cohort vs. preterm cohort: p-value < 0.005

+ Term cohort vs preterm cohort excluding children with brain injury: p-value < 0.005

++ p-value < 0.05

∫ Chi-square for trend across all services categories (term vs. preterm, term vs. preterm excluding children with brain injury) p-value < 0.005

TABLE 5

Multivariate regression analysis of verbal and full scale IQ among preterm children

Variables in model	Verbal IQ	Full Scale IQ
	Mean difference (95% CI) N=355	Mean difference (95% CI) N=347
Birth weight (100 g increment)	0.1 (−1.0, 1.3)	0.5 (−0.5, 1.6)
Small for gestational age	−2.1 (−6.1, 2.0)	−0.4 (−4.3, 3.4)
Male gender (vs. female)	0.5 (−2.9, 3.9)	−0.7 (−4.0, 2.5)
Antenatal steroids	3.0 (−0.6, 6.6)	3.7 (0.3, 7.1) *
BPD	−3.1 (−7.0, 0.9)	−2.4 (−6.1, 1.4)
Severe brain injury	−19.9 (−25.9, −13.9) *	−22.1 (−28.1, −16.2) *
Maternal age < 20 (vs. ≥ 20)	−0.5 (−5.7, 4.7)	−0.4 (−5.4, 4.6)
Maternal years of education (1 year increment)	2.3 (1.6, 3.1) *	2.0 (1.3, 2.7) *
Single-parent household (vs. two-parent household)	−5.3 (−9.1, −1.6) *	−5.9 (−9.4, −2.3) *
Minority status by maternal report (white non-hispanic vs. others)	−8.9 (−12.9, −4.8) *	−8.4 (−12.2, −4.5) *
Model adjusted R²	0.29	0.31

*
p-value < 0.05

TABLE 6
Neuropsychological test results by treatment group (n=327)

	INDOMETHACIN Mean (SD)	PLACEBO Mean (SD)	Adjusted Mean Difference* (95% CI)
WISC-III			
Verbal IQ	91.9 (18.2)	92.0 (17.6)	-1.2 (-4.6, 2.3)
Performance IQ	86.4 (17.5)	88.5 (17.5)	-3.2 (-6.8, 0.5)
Full-Scale IQ	88.3 (18.1)	89.4 (17.0)	-2.3 (-5.7, 1.2)
LANGUAGE			
PPVT-R	93.2 (23.4)	93.2 (24.6)	-1.2 (-6.0, 3.6)
CTOPP	92.7 (20.7)	95.4 (20.9)	-2.6 (-7.4, 2.3)
CELF – Total language score	85.6 (19.5)	87.1 (19.5)	-2.1 (-6.1, 1.9)
TOWRE - Phonemic decoding	91.4 (17.7)	91.9 (16.9)	-0.9 (-4.6, 2.9)
TOWRE - Sight word efficiency	93.1 (16.2)	94.8 (15.4)	-1.8 (-5.3, 1.7)
Gray Silent Reading Test	89.0 (24.8)	90.3 (24.4)	-2.3 (-7.4, 2.9)

* Adjustment for maternal education, minority, single-parent household Indomethacin-by-gender effect: p-value > 0.05.