**Week 4: Neonatology**

**Neonatal Follow-up**

**Thursday, July 23  4:30-6:00 pm EDT**

**Moderators**
Ricki Goldstein  
Lakshmi Katikaneni

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<thead>
<tr>
<th>EDT</th>
<th>Abstract</th>
<th>Title</th>
<th>Presenting Author</th>
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<td>Introduction &amp; General Information</td>
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<tr>
<td>4:35 pm</td>
<td>3344865</td>
<td>Neurodevelopmental outcome of preterm infants enrolled in the NICHD NRN randomised controlled trial of treatment with myo-inositol</td>
<td>Ira Adams-Chapman</td>
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<td>4:45 pm</td>
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<td>Kaitlin Blackard</td>
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<td>Association of Screen-Time at 6-7 years with Outcomes of Extremely Preterm Infants</td>
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<td>5:15 pm</td>
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<td>Samudragupta Bora</td>
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Note: Schedule subject to change based on presenter availability.
Background: Limited data are available on the neurodevelopmental outcome of preterm infants treated with inositol.

Objective: Evaluate the risk of death or survival with moderate or severe neurodevelopmental impairment (NDI) in preterm infants enrolled in the phase III randomised, placebo controlled trial.

Design/Methods: Infants born between 4/17/2014 - 9/4/2015 who were <28 0/7 weeks gestational age (GA) and survived ≥ 12 hours were eligible for inclusion in the primary study. Infants with major congenital or eye anomalies were excluded.

A follow-up assessment was performed between 22-26 months corrected age by certified examiners. The Bayley Scales of Infant Development (BSID)-IIIIR and a standardized neurosensory examination were completed. Severity of cerebral palsy (CP) was defined by gross motor functional classification level. Moderate/severe NDI is defined by the presence of one or more of the following: BSID III Cognitive or Motor composite <85, moderate/severe CP, blindness, or hearing loss that does not permit the child to communicate despite amplification.

Outcomes were analyzed based on an intention to treat. Chi-square tests were used to analyze categorical data. Poisson regression was used to estimate adjusted relative risks (ARRs) and a generalized linear model with a binomial distribution and identity link was used to estimate adjusted absolute risk difference and 95% confidence interval by treatment group. Outcomes are adjusted for center and GA strata.

Results: Of the 638 infants randomized in the phase III RCT, 539 survived to follow-up, of whom 506 (94%) were seen for the follow-up visit. Inositol treated infants were more likely to die prior to follow-up (20% v 13%; p<.02). The mean corrected age at follow-up was 25.8 ±1.3 weeks. Forty-nine percent of children in both groups met criteria for moderate or severe NDI. In adjusted analyses, there was no difference in the risk of death or survival with moderate/severe NDI for infants in this clinical trial [60% in myo-inositol treated vs 56% in placebo; ARR 1.06 (0.93-1.21; p=0.40)]. Rates of severe IVH (15% v 12%; p=ns); any CP (16% v 15%, p=ns) or moderate/severe CP (9% v 6%, p=ns) did not vary by treatment group.

Conclusion(s): This study represents the largest clinical trial evaluating the ND outcome of extremely prematurely born
Background: Autism Spectrum Disorder (ASD) is more commonly diagnosed in individuals who required care in the Neonatal Intensive Care Unit (NICU) compared to those born healthy at term. We previously showed that analysis of heart rate (HR) and oxygen saturation from pulse oximetry (SpO2) can predict multiple morbidities including acute brain injury in NICU patients (Sullivan et al 2018). Central nervous system dysfunction, in particular imbalance of sympathetic and parasympathetic functions, has been described in children and adults with ASD. Correlation of NICU vital signs patterns and ASD diagnosis has not been described previously.

Objective: Test the hypothesis that HR and SpO2 characteristics add to clinical variables for prediction of ASD.

Design/Methods: We identified all infants in a level 4 NICU from 2009-2015 hospitalized for at least 4 days in the first week after birth who survived to discharge, and then we identified those with eventual diagnosis of ASD. Using archived bedside monitor data collected at 0.5 Hz, we calculated hourly metrics of mean, standard deviation, skewness, kurtosis, and cross correlation of HR and SpO2 and compared them between the ASD cohort and the entire cohort. Three time periods were considered: first week after birth, first 4 weeks after birth, and whole NICU stay. Logistic regression was used to identity HR and SpO2 metrics associated with ASD after correcting for gestational age (GA), birth weight (BW), and sex.

Results: Of 1846 infants discharged from the NICU in the study period that met study criteria (1,157,000 hours of vital sign data), we identified 43 diagnosed with ASD (32,000 hours of data). In the first week after birth, HR was significantly skewed toward more accelerations in infants eventually diagnosed with ASD (Figure 1). In the first 4 weeks after birth, percentage of hourly HR skewness values >1 was about 3% for the entire cohort and about 5-8% for infants with ASD (Figure 2). Considering the whole NICU stay, Figure 3 shows that higher HR skewness values increase the relative risk for eventual ASD diagnosis. Logistic regression analysis showed that HR skewness added to clinical variables to predict ASD risk.

Conclusion(s): In this cohort, HR skewness toward more accelerations throughout the NICU stay (possibly reflecting increased sympathetic tone) is associated with an eventual diagnosis of ASD. If substantiated in larger cohorts of NICU patients, this finding may allow for earlier identification of and interventions for highest risk infants.
Figure 1: First week HR skewness density distribution for ASD and entire cohort. Hourly HR skewness was measured in 1846 NICU patients, 43 of whom were diagnosed with ASD. Density of HR skewness was shifted to the right toward more accelerations in ASD infants.

Figure 2: First 4 week percentage of hourly HR skewness greater than 1 as a function of age in days. In the first 4 weeks after birth, the percentage of hourly HR skewness values greater than 1 was higher in infants eventually diagnosed with ASD as compared to the entire cohort.

Figure 3: Relative risk of ASD based on hourly HR skewness when analyzing entire NICU stay. Skewness of HR toward more accelerations is indicated on x-axis by more positive numbers. Higher HR skewness increases relative risk for eventual ASD diagnosis.

CONTROL ID: 3331011
TITLE: Relationships between retinopathy of prematurity severity and neurodevelopment and vision outcomes
PRESENTER: Jane E. Brumbaugh

AUTHORS (LAST NAME, FIRST NAME): Brumbaugh, Jane E.1; Bell, Edward F.2; Hirsch, Shawn C.12; Crenshaw, Emma G.12; DeMauro, Sara B.3; Adams-Chapman, Ir4; Lowe, Jean R.5; Natarajan, Girija6; Wyckoff, Myra7; Vohr, Betty R.8; Colaizy, Tarah9; Harmon, Heidi9; Watterberg, Kristi L.10; Hintz, Susan R.11; National Institute of Child Health and Human Development, Eunice Kennedy Shriver13

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Background: Severe retinopathy of prematurity (ROP) has been associated with adverse neurodevelopmental and vision outcomes. Relationships between milder forms of ROP and outcomes have not been well delineated.

Objective: To compare neurodevelopment and vision outcomes at 2 years for extremely preterm children with history of no ROP, ROP stage ≤3 without intervention, or ROP with intervention.

Design/Methods: This was a secondary analysis of a randomized controlled trial evaluating the effects of myo-inositol on ROP risk for children born at <28 weeks’ gestation and cared for in the NICHD Neonatal Research Network (4/2014-9/2015). Survivors at 22-26 months’ corrected age underwent comprehensive assessment. Primary outcomes were Bayley Scales of Infant Development (BSID-III) composite scores. Secondary outcomes included non-ROP ophthalmologic morbidities. Outcomes were compared using linear or modified Poisson models with study center as a random effect. Models were adjusted for myo-inositol randomization group, maternal race, gestational age, sex, and severe intracranial hemorrhage. Adjusted risk differences or relative risks with 95% confidence intervals and p-values are reported. Primary outcomes were adjusted for multiple comparisons with a Bonferroni correction.

Results: Of the 506 children, 173 (34%) had no ROP, 262 (52%) had ROP stage ≤3 without intervention, and 71 (14%) had ROP with intervention (Figure 1). Maternal race, education, and gestational age differed by ROP status (Table 1). Children with ROP receiving intervention had worse BSID-III motor (p=0.013), cognitive (p=0.001), and language (p=0.007) scores than children with ROP stage ≤3 without intervention (Table 2). There was no difference in motor (p=0.813), cognitive (p=1.000), or language (p=1.000) scores between children with ROP stage ≤3 without intervention and children without ROP. Children with ROP stage ≤3 without intervention had a higher rate of strabismus compared to children without ROP (p=0.040). Children with ROP receiving intervention had a higher rate of prescription lenses (p<0.001) and other vision abnormalities (p=0.044) than children with ROP stage ≤3 without intervention.

Conclusion(s): ROP that regresses without intervention was not associated with adverse neurodevelopmental outcomes at 2 years’ corrected age. In contrast, ROP treated with operative or anti-vascular endothelial growth factor therapy was associated with adverse neurodevelopmental and vision outcomes at 2 years.
Table 1. Maternal and Neonatal Characteristics by ROP Status

Table 2. Neurodevelopment and Vision Outcomes at 22-26 Months' Corrected Age

IMAGE CAPTION:
Figure 1. Flow Chart of Study Subjects

Table 1. Maternal and Neonatal Characteristics by ROP Status

Table 2. Neurodevelopment and Vision Outcomes at 22-26 Months' Corrected Age

CONTROL ID: 3343466
TITLE: Association of Screen-Time at 6-7 years with Outcomes of Extremely Preterm Infants
PRESENTER: Betty R Vohr

AUTHORS (LAST NAME, FIRST NAME): Vohr, Betty R.1; McGowan, Elisabeth C.2; Bann, Carla M.3; Das, Abhik4; Higgins, Rosemary D.5; Hintz, Susan R.6; National Institute of Child Health and Human Development, Eunice Kennedy Shriver

AUTHORS/INSTITUTIONS: B.R. Vohr, Pediatrics, Women & Infants Hospital, Providence, Rhode Island, UNITED STATES;
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A. Das, Biostatistics and Epidemiology, RTI International, Rockville, Maryland, UNITED STATES;
R.D. Higgins, Global and Community Health, George Mason University, Fairfax, Virginia, UNITED STATES;
S.R. Hintz, Pediatrics/Neonatology, Stanford University, Palo Alto, California, UNITED STATES;
Background: Use of screen devices has increased worldwide and extended to young children. The effects of screen time on development and behavior of extreme preterm (EPT) children born < 28 weeks EGA are unknown.

Objective: To determine the effects of high screen time (> 2 hours/day) on cognition, executive function, behavior, social skills, language, and growth of children born EPT at 6-7 years of age.

Results: 176 (43%) of children had > 2 hours/day of screen time and 226 (64%) had a TV or computer in their bedroom. Factors associated with either ↑ screen time or TV/computer in room were ↓ maternal age, non-White race, low maternal education and public insurance. (Table1) In unadjusted analyses children with > 2 hours screen time had lower WISC-IV verbal comprehension, perceptual reasoning and FSIQ, ↑ problems of BRIEF executive function, NEPSY Inhibition, Conners inattention and hyperactivity, (Tables 2 and 3) A TV/Computer in the bedroom was associated with lower IQ, verbal comprehension, perceptual reasoning, and working memory, and increased problems with NEPSY inhibition, Conners inattention and hyperactivity, (Tables 2 & 3) Children with > 2 hours/day screen time were more likely to be overweight (28% vs 15%; p=.002) or obese (15% versus 4%; p<.001). In multivariable regression analyses ↑ screen time was independently associated with ↓ full scale IQ, and ↑ problems with Metacognition, global executive function and regulation, Inhibition, inattention, hyperactivity, and Social Communication Questionnaire Autism scores. A TV or computer in the bedroom was associated with ↓ WISC-IV perceptual reasoning, and ↑ Inhibition problems and hyperactivity. (Table 2 & 3)

Conclusion(s): These data provide evidence that high screen time >2 hours/d and having a TV or computer in the bedroom may contribute further to the outcomes of EPT children, and are independently associated with cognitive, executive function, behavior and health challenges.
## Table 1: Number of words recalled with each condition (Non-Analytic Communication) vs. Total number of words recalled with each condition (Analytic Communication).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Words Recalled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Analytic Communication</td>
<td>56.7 ± 11.1</td>
</tr>
<tr>
<td>Analytic Communication</td>
<td>68.5 ± 10.9</td>
</tr>
<tr>
<td>Total Recall</td>
<td>125.2 ± 22.0</td>
</tr>
</tbody>
</table>

## Table 2: Summary of Social Communication Questionnaire.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Social Communication Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Analytic Communication</td>
<td>5.5 ± 1.4</td>
</tr>
<tr>
<td>Analytic Communication</td>
<td>6.5 ± 0.8</td>
</tr>
<tr>
<td>Total Recall</td>
<td>12.0 ± 2.2</td>
</tr>
</tbody>
</table>

## Table 3: Linear Regression Model of Continuous (SAL) Interactions by Social Communication.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Social Communication Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Analytic Communication</td>
<td>5.5 ± 1.4</td>
</tr>
<tr>
<td>Analytic Communication</td>
<td>6.5 ± 0.8</td>
</tr>
<tr>
<td>Total Recall</td>
<td>12.0 ± 2.2</td>
</tr>
</tbody>
</table>

## Image Caption:

No specific image caption is provided.
Background: Adults born extremely preterm (EP, <28 weeks’ gestation) or extremely low birthweight (ELBW, <1000 g birthweight) have higher blood pressure than term-born controls, but differences in other cardiometabolic risk factors are not well described.

Objective: To compare a comprehensive cardiovascular risk profile between young adult EP/ELBW and term-born controls at 25 years of age.

Design/Methods: Prospective longitudinal study of all EP/ELBW survivors born in 1991-92 in the state of Victoria, Australia, recruited at birth, and contemporaneous term-born controls. At age 25 years, variables including anthropometry, adiposity, blood pressure, exercise tolerance, fasting plasma glucose, insulin resistance, serum lipids, C-reactive protein (CRP), and vascular endothelial indices were measured, and smoking status obtained from history. A score of 1 was assigned based on the best three quartiles for the various variables obtained from the controls, and a score of zero assigned for the worst quartile. Values for the individual variables were summed, along with the score of 1 for non-smoking status, with a maximum possible score of 14. A higher score indicated a more favorable cardiovascular risk profile. Multivariable logistic regression models were used to determine differences in proportions with individual measures in the favourable quartiles between EP/ELBW and control groups, adjusting for sex and allowing for clustering within families for multiple births. Overall cardiovascular risk profiles were contrasted between groups by the Mann-Whitney U Test.

Results: Data were obtained from 165 adults born EP/ELBW, and 131 controls at 25 years of age, although not all had values for all variables. Compared with controls, adults born EP/ELBW had strong evidence for unfavorable distributions of abdominal visceral fat, blood pressure, and exercise tolerance, weaker evidence for unfavorable distributions of fasting plasma glucose and high-density lipoprotein cholesterol, and little evidence for differences in other individual variables (Table). There was strong evidence that the cardiovascular risk profiles were less favorable in the adults born EP/ELBW than in the controls (Figure).

Conclusion(s): Compared with controls born at term, 25-year-olds born EP/ELBW had unfavorable cardiovascular risk profiles. Longer term follow-up is critical to determine the cardiovascular sequelae of adults born EP/ELBW.
**CONTROL ID:** 3378399

**TITLE:** Comparison of longitudinal follow-up at 2, 5 and 8 years in preterm infants <30 weeks’ gestation.

**PRESENTER:** Iris Esmee van der Horst

**AUTHORS (LAST NAME, FIRST NAME):** van der Horst, Iris E.¹; van Beek, Pauline E.¹; Wetzer, Josse A.¹; Verheijen, Anne C.¹; Thijsse, Guusje J.¹; Van Och, Anne F.¹; Blom, Renée¹; Katgert, Titia¹; Vugs, Brigitte A.¹; Andriessen, Peter¹

**AUTHORS/INSTITUTIONS:** I.E. van der Horst, P.E. van Beek, J.A. Wetzer, A.C. Verheijen, G.J. Thijsse, A.F. Van Och, R. Blom, T. Katgert, B.A. Vugs, P. Andriessen, Máxima Medical Centre, Veldhoven, NETHERLANDS;

**CURRENT CATEGORY:** Neonatology

**CURRENT SUBCATEGORY:** Neonatal Follow-up

**KEYWORDS:**

**SESSION TITLE:** Neonatal Follow-up | Neonatal Follow-up

**SESSION TYPE:** Platform/Webinar

**ABSTRACT BODY:**

**Background:** Neurodevelopmental assessment at 2 years is frequently used as a primary outcome of clinical trials in very preterm infants. The issue, however, is whether outcome at 2 years adequately reflects long-term outcome. The objective of this study was to evaluate neurodevelopmental impairment (NDI) in preterm infants <30 weeks’ gestation at
Design/Methods: A retrospective single-center cohort study was conducted in Máxima Medical Centre, between 1990-2010. In total, 625 infants (Figure 1) were seen at (the corrected age of) 2, 5 and 8 years. The primary outcome was NDI, a composite outcome based on cognitive score (Bayley Scales of Infant and Toddler Development, Wechsler Preschool Primary Scale of Intelligence, Wechsler Intelligence Scale for Children or Revision Amsterdam Child Intelligence test, depending on age of assessment), neurological assessment and visual and hearing impairment. NDI was classified as mild if the cognitive scores were between -1 and -2 SD from the norm score (100, SD 15), squints or refractive errors, hearing loss not sufficient to require aids or mild motor disorder not classified as cerebral palsy (CP); as moderate if cognitive scores between -2 and -3 SD, functionally impaired vision, hearing loss requiring aids or unilateral CP; as severe if cognitive score > -3 SD, blindness, hearing loss despite aids or bilateral CP.

Results: The NDI classification of infants at 2, 5 and 8 years is shown in Table 1. The distributions of NDI are comparable at different time points. The (within subject) relation between NDI at 2, 5 and 8 years is shown in Table 2. Of the infants with no NDI at 2 years, 27% had an mild or moderate impairment at 8 years. Of the infants with a severe NDI at 2 years, only 41% still had a severe NDI at 8 years. Of the infants assessed at 2 years, 61% (370/608) remained in the same NDI category at 8 years, 20% (124/608) moved to a better category and 19% (114/608) moved to a worse category. Of the infants assessed at 5 years, 71% (436/614) remained in the same NDI category at 8 years, 15% (92/614) moved to a better category and 14% (86/614) moved to a worse category.

Conclusion(s): Although most clinical trials use neurodevelopmental assessment at 2 years as primary outcome, this study challenges the value of this. Follow-up programmes or clinical trial outcome measurements in very preterm infants should extend towards school life.

Table 1: NDI at 2, 5 and 8 years of age

<table>
<thead>
<tr>
<th>Age</th>
<th>No.</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>2 years</td>
<td>625</td>
<td>100</td>
</tr>
<tr>
<td>5 years</td>
<td>614</td>
<td>100</td>
</tr>
<tr>
<td>8 years</td>
<td>608</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2: Relationship between NDI outcome at 2, 5 and 8 years

<table>
<thead>
<tr>
<th>NDI at 8 years</th>
<th>NDI at 5 years</th>
<th>NDI at 2 years</th>
<th>NDI at 8 years</th>
<th>NDI at 5 years</th>
<th>NDI at 2 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Total</td>
<td>NDI at 8 years</td>
<td>NDI at 5 years</td>
<td>NDI at 2 years</td>
<td>NDI at 8 years</td>
<td>NDI at 5 years</td>
</tr>
<tr>
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<td>----------------</td>
</tr>
<tr>
<td>Mild</td>
<td>370</td>
<td>Mild</td>
<td>196</td>
<td>Mild</td>
<td>105</td>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
<td>124</td>
<td>Moderate</td>
<td>60</td>
<td>Moderate</td>
<td>37</td>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
<td>114</td>
<td>Severe</td>
<td>55</td>
<td>Severe</td>
<td>32</td>
<td>Severe</td>
</tr>
<tr>
<td>Total</td>
<td>608</td>
<td>Total</td>
<td>371</td>
<td>Total</td>
<td>193</td>
<td>Total</td>
</tr>
</tbody>
</table>

Control ID: 3385282

Title: Visuospatial Outcomes and Cortical Thickness Correlates in Very Low Birthweight Adults: A Prospective
National Cohort Study
PRESENTER: Samudragupta Bora

AUTHORS (LAST NAME, FIRST NAME): Bora, Samudragupta1; Melzer, Tracy R.2; Horwood, John2; Darlow, Brian2; Woodward, Lianne J.3

AUTHORS/INSTITUTIONS: S. Bora, Mothers, Babies and Women’s Health, Mater Research Institute, Faculty of Medicine, The University of Queensland, South Brisbane, Queensland, AUSTRALIA; T.R. Melzer, J. Horwood, B. Darlow, University of Otago, Christchurch, NEW ZEALAND; L.J. Woodward, University of Canterbury, Christchurch, NEW ZEALAND;

CURRENT CATEGORY: Neonatology
CURRENT SUBCATEGORY: Neonatal Follow-up
KEYWORDS: Neurodevelopment, Preterm Birth, Brain.
SESSION TITLE: Neonatal Follow-up | Neonatal Follow-up
SESSION TYPE: Platform | Webinar

ABSTRACT BODY:

Background: Visuospatial impairments without any major underlying vision or general cognitive problems are a common outcome associated with very preterm birth. While these impairments are well-documented from early childhood through adolescence, limited data exist for adulthood.

Objective: To 1) describe the motor and nonmotor-dependent visuospatial outcomes of a national cohort of adults born very low birthweight; and 2) identify the concurrent cranial lobar cortical thickness correlates of severe visuospatial impairment.

Design/Methods: Data were drawn from a 28-year prospective follow-up study of all surviving infants born very low birthweight (<1,500 grams) in New Zealand during 1986. Sample retention was 77% (250/323 survivors), with data from 225 participants available for current analysis. Individuals were studied alongside a comparison group of 100 age-matched, full-term born adults recruited at age 22 years. Visuospatial outcomes were assessed using the Wechsler Adult Intelligence Scale Block Design (motor task), Benton Judgment of Line Orientation (nonmotor task), and Brixton Spatial Anticipation Test (nonmotor task). Mild impairment was defined as scores <1 SD and severe impairment as scores <2 SD of the comparison group mean. Of the 250 very low birthweight participants, 150 underwent cranial magnetic resonance imaging on 3T General Electric HDxt scanner, with usable data available for 142. Cortical thickness was estimated for each hemisphere across the four lobes using FreeSurfer Version 6.0.

Results: Figure 1 shows the between-group differences in standardized scores. As shown in Figure 2, very low birthweight adults exhibited an increased risk of visuospatial impairments relative to their full-term peers across both motor (18%–28% vs. 1%–14%; P<.001) and nonmotor (9%–19% vs. 3%–8%; P≤.01) domains. After adjusting for age, sex, and vision, cortical thickness of frontal (Exp[B]=1.74, 95% CI=1.08–2.82) and parietal (Exp[B]=0.37, 95% CI=0.14–0.96) lobes in the right hemisphere were associated with severe visuospatial impairment. Jointly these variables explained 14% (Nagelkerke R²) of variance and accurately classified 82% of cases.

Conclusion(s): Findings of this study are novel in demonstrating visuospatial impairments as a consequence of very low birthweight persisting into adulthood, although rates appear to be lower than in childhood and adolescence. Regional vulnerabilities of the brain were identified that may adversely impact the visuospatial outcomes in this high-risk population.

Figure 1: Visuospatial Assessment Scores of Very Low Birthweight and Full-Term Adults
**Figure 2:** Visuospatial Impairments of Very Low Birthweight and Full-Term Adults

**IMAGE CAPTION:**

**Figure 1:** Visuospatial Assessment Scores of Very Low Birthweight and Full-Term Adults

**Figure 2:** Visuospatial Impairments of Very Low Birthweight and Full-Term Adults