1. Association of Child Poverty, Brain Development, and Academic Achievement
Nicole L. Hair, PhD; Jamie L. Hanson, PhD; Barbara L. Wolfe, PhD; Seth D. Pollak, PhD

**IMPORTANCE:** Children living in poverty generally perform poorly in school, with markedly lower standardized test scores and lower educational attainment. The longer children live in poverty, the greater their academic deficits. These patterns persist to adulthood, contributing to lifetime-reduced occupational attainment.

**OBJECTIVE:** To determine whether atypical patterns of structural brain development mediate the relationship between household poverty and impaired academic performance.

**DESIGN, SETTING, AND PARTICIPANTS:** Longitudinal cohort study analyzing 823 magnetic resonance imaging scans of 389 typically developing children and adolescents aged 4 to 22 years from the National Institutes of Health Magnetic Resonance Imaging Study of Normal Brain Development with complete sociodemographic and neuroimaging data. Data collection began in November 2001 and ended in August 2007. Participants were screened for a variety of factors suspected to adversely affect brain development, recruited at 6 data collection sites across the United States, assessed at baseline, and followed up at 24-month intervals for a total of 3 periods. Each study center used community-based sampling to reflect regional and overall US demographics of income, race, and ethnicity based on the US Department of Housing and Urban Development definitions of area income. One-quarter of sample households reported the total family income below 200% of the federal poverty level. Repeated observations were available for 301 participants.

**EXPOSURE:** Household poverty measured by family income and adjusted for family size as a percentage of the federal poverty level.

**MAIN OUTCOMES AND MEASURES:** Children’s scores on cognitive and academic achievement assessments and brain tissue, including gray matter of the total brain, frontal lobe, temporal lobe, and hippocampus.

**RESULTS:** Poverty is tied to structural differences in several areas of the brain associated with school readiness skills, with the largest influence observed among children from the poorest households. Regional grey matter volumes of children below 1.5 times the federal poverty level were 3 to 4 percentage points below the developmental norm \( P < .05 \). A larger gap of 8 to 10 percentage points was observed for children below the federal poverty level \( P < .05 \). These developmental differences had consequences for children’s academic achievement. On average, children from low-income households scored 4 to 7 points lower on standardized tests \( P < .05 \). As much as 20% of the gap in test scores could be explained by maturational lags in the frontal and temporal lobes.

**CONCLUSIONS AND RELEVANCE:** The influence of poverty on children’s learning and achievement is mediated by structural brain development. To avoid long-term costs of impaired academic functioning, households below 150% of the federal poverty level should be targeted for additional resources aimed at remediating early childhood environments.

2.
OBJECTIVE: To investigate the effect of gestational age, particularly late preterm birth (34–36 weeks gestation) and early term birth (37–38 weeks gestation) on school performance at age 7 years.

DESIGN: Population-based prospective UK Millennium Cohort Study, consisting of linked educational data on 6031 children.

METHODS: School performance was investigated using the statutory Key Stage 1 (KS1) teacher assessments performed in the third school year in England. The primary outcome was not achieving the expected level (level 2) of general performance in all three key subjects (reading, writing and mathematics). Other outcomes investigated subject-specific performance and high academic performance (level 3).

RESULTS: 18% of full-term children performed below the expected KS1 general level, and risk of poor performance increased with prematurity: compared to children born at full-term, there was a statistically significant increased risk of poor performance in those born very preterm (<32 weeks gestation, adjusted RR 1.78, 95% CI 1.24 to 2.54), moderately preterm (32–33 weeks gestation, adjusted RR 1.71, 95% CI 1.15 to 2.54) and late preterm (34–36 weeks gestation, adjusted RR 1.36, 95% CI 1.09 to 1.68). Early term children performed statistically significantly worse in 4 out of 5 individual subject domains than full-term children, but not in the primary outcome (adjusted RR 1.07, 95% CI 0.94 to 1.23).

CONCLUSIONS: Late preterm, and to a lesser extent, early term birth negatively impact on academic outcomes at 7 years as measured by KS1 assessments.

Altered Gray Matter Volume and School Age Anxiety in Children Born Late Preterm

Cynthia E. Rogers, MD1; Deanna M. Barch, PhD; Chad M. Sylvester, MD, PhD; David Pagliaccio, MS; Michael P. Harms, PhD; Kelly N. Botteron, MD; and Joan L. Luby, MD

Objectives: To determine if late preterm (LP) children differ from full term (FT) children in volumes of the cortex, hippocampus, corpus callosum, or amygdala and whether these differences are associated with anxiety symptoms at school-age.

Study design: LP children born between 34 and 36 weeks gestation and FT children born between 39 and 41 weeks gestation from a larger longitudinal cohort had magnetic resonance imaging scans at school-age. Brain volumes, cortical surface area, and thickness measures were obtained. Anxiety symptoms were assessed using a structured diagnostic interview annually beginning at preschool-age and following the magnetic resonance imaging.

Results: LP children (n = 21) had a smaller percentage of total, right parietal, and right temporal lobe gray matter volume than FT children (n = 87). There were no differences in hippocampal, callosal, or amygdala volumes or cortical thickness. LP children also had a relative decrease in right parietal lobe cortical surface area. LP children had greater anxiety symptoms over all assessments. The relationship between late prematurity and school-age anxiety symptoms was mediated by the relative decrease in right temporal lobe volume.

Conclusions: LP children, comprising 70% of preterm children, are also at increased risk for altered brain development particularly in the right temporal and parietal cortices. Alterations in the right temporal lobe cortical volume may underlie the increased rate of anxiety symptoms among these LP children. These findings suggest that LP delivery may disrupt temporal and parietal cortical development that persists until school-age with the right temporal lobe conferring risk for elevated anxiety symptoms.
The long-term consequences of preterm birth: What do teachers know?
Samantha Johnson; Camilla Gilmore; Ian Gallimore; Julia Kaekel; Dieter Wolke

AIM: The knowledge and information needs of education professionals were assessed to determine how prepared they feel to support the growing number of preterm children entering schools today.

METHOD: In a national survey, 585 teachers and 212 educational psychologists completed the Preterm Birth-Knowledge Scale (PB-KS) to assess knowledge of outcomes following preterm birth. Total scores (range 0–33) were compared between groups and the impact of demographic characteristics on knowledge was analysed. Training and information needs were also assessed.

RESULTS: Teaching staff (mean 14.7, SD 5.5) had significantly lower knowledge scores than educational psychologists (mean 17.1, SD 5.0; p<0.001); both had significantly lower scores than neonatal clinicians surveyed previously (mean 26.0, SD 3.6; p<0.001). Education professionals’ poorest areas of knowledge related to the most frequent adverse outcomes following preterm birth. Only 16% of teaching staff had received training about preterm birth and more than 90% requested more information. Having a special educational needs role and being employed at least 16 years were associated with higher knowledge scores.

INTERPRETATION: Education professionals have poor knowledge of the needs of children born preterm and most feel ill-equipped to support them in school. As teachers have primary responsibility for providing long-term support for children born preterm, this is of significant public health and educational concern.

PLAY Project Home Consultation Intervention Program for Young Children With Autism Spectrum Disorders: A Randomized Controlled Trial
Richard Solomon, MD; Laurie A. Van Egeren, PhD; Gerald Mahoney, PhD; Melissa S. Quon Huber, PhD; Perri Zimmerman, MBA

OBJECTIVE: To evaluate the effectiveness of the Play and Language for Autistic Youngsters (PLAY) Project Home Consultation model, in combination with usual community services (CS), to improve parent-child interaction, child development, and autism symptomatology in young children with autism spectrum disorders (ASDs) compared with CS only.

METHODS: Children (N 5 128) with autism or PDD-NOS (DSM-4 criteria) aged 2 years 8 months to 5 years 11 months and recruited from 5 disability agencies in 4 US states were randomized in two 1-year cohorts. Using videotape and written feedback within a developmental framework, PLAY consultants coached caregivers monthly for 12 months to improve caregiver-child interaction. CS included speech/language and occupational therapy and public education services. Primary outcomes included change in parent-child interactions, language and developmental, and autism-related diagnostic category/symptoms. Secondary outcomes included parent stress and depression and home consultant fidelity. Data were collected pre- and post-intervention.

RESULTS: Using intent-to-treat analysis (ITT), large treatment effects were evident for parent and child interactional behaviors on the Maternal and Child Behavior Rating Scales. Child language and developmental quotient did not differ over time by group, although functional development improved significantly. PLAY children improved in diagnostic categories on the Autism Diagnostic Observation Schedule (ADOS). PLAY caregivers’ stress did not increase, and depressive symptomatology decreased. Home consultants administered the intervention with fidelity.

CONCLUSIONS: PLAY intervention demonstrated substantial changes in parent-child interaction without increasing parents’ stress/depression. ADOS findings must be interpreted cautiously because results do not align with clinical experience. PLAY offers communities a relatively inexpensive effective intervention for children with ASD and their parents.
5.

**Increasing Incidence of the Neonatal Abstinence Syndrome in U.S. Neonatal ICUs**

Veeral N. Tolia, M.D.; Stephen W. Patrick, M.D., M.P.H.; Monica M. Bennett, Ph.D.; Karna Murthy, M.D.; John Sousa, B.S.; P. Brian Smith, M.D., M.P.H., M.H.S.; Reese H. Clark, M.D.; and Alan R. Spitzer, M.D.

**BACKGROUND:** The incidence of the neonatal abstinence syndrome, a drug-withdrawal syndrome that most commonly occurs after in utero exposure to opioids, is known to have increased during the past decade. However, recent trends in the incidence of the syndrome and changes in demographic characteristics and hospital treatment of these infants have not been well characterized.

**METHODS:** Using multiple cross-sectional analyses and a deidentified data set, we analyzed data from infants with the neonatal abstinence syndrome from 2004 through 2013 in 299 neonatal intensive care units (NICUs) across the United States. We evaluated trends in incidence and health care utilization and changes in infant and maternal clinical characteristics.

**RESULTS:** Among 674,845 infants admitted to NICUs, we identified 10,327 with the neonatal abstinence syndrome. From 2004 through 2013, the rate of NICU admissions for the neonatal abstinence syndrome increased from 7 cases per 1000 admissions to 27 cases per 1000 admissions; the median length of stay increased from 13 days to 19 days (P<0.001 for both trends). The total percentage of NICU days nationwide that were attributed to the neonatal abstinence syndrome increased from 0.6% to 4.0% (P<0.001 for trend), with eight centers reporting that more than 20% of all NICU days were attributed to the care of these infants in 2013. Infants increasingly received pharmacotherapy (74% in 2004-2005 vs. 87% in 2012-2013, P<0.001 for trend), with morphine the most commonly used drug (49% in 2004 vs. 72% in 2013, P<0.001 for trend).

**CONCLUSIONS:** From 2004 through 2013, the neonatal abstinence syndrome was responsible for a substantial and growing portion of resources dedicated to critically ill neonates in NICUs nationwide.

6.

**Deletion of the MC4R Gene in a 9-Year-Old Obese Boy**

Lesley Turner, BSc, MD, FRCPC; Anne Gregory, BSc (Hons), MD; Laurie Twells, BA, MSc, PhD; Deborah Gregory, BN, MSc, PhD; and Dimitri J. Stavropoulos, BSc, MSc, PhD, FCCMG

**BACKGROUND:** The most common monogenic form of obesity is caused by mutations in the melanocortin 4 receptor (MC4R) gene. More than 150 mutations have been reported in the MC4R gene, the majority being point mutations. Most individuals with MC4R gene mutations have early-onset obesity, hyperphagia, and increased longitudinal growth.

**METHODS:** A 9-year-old Caucasian boy was referred to genetics for obesity, food-seeking behavior, and developmental delay. History and physical exam were not consistent with Prader Willi syndrome, but revealed several minor anomalies. Owing to significant obesity and hyperphagia, a Prader Willi syndrome methylation test and a microarray were requested.

**RESULTS:** Methylation testing for Prader Willi syndrome was normal. Microarray analysis revealed two changes: (1) A 2.6-Mb deletion at chromosome 18q21.31 was identified and contained several OMIM genes, including the MC4R gene, and (2) an 0.87-Mb duplication at chromosome region 16p13.3 was found and contained one gene. Parental samples revealed that the boy’s father had the same deletion and duplication. This case appears to be the first with a deletion of 18q21.31 encompassing the MC4R gene presenting with features of hyperphagia and obesity.
CONCLUSIONS: Haploinsufficiency of the MC4R gene either through whole gene deletion or nonsense or missense mutations is associated with a significant risk of obesity. The case emphasizes both the role of the MC4R gene in obesity as well as the importance of looking for chromosomal microdeletions/duplications as a cause of obesity in children with minor anomalies or developmental delay.

Association of Gln27Glu and Arg16Gly Polymorphisms in Beta2-Adrenergic Receptor Gene with Obesity Susceptibility: A Meta-Analysis
Hongxiu Zhang; Jie Wu; Lipeng Yu

BACKGROUND: The beta2-adrenergic receptor (ADRB2) gene polymorphism has been implicated in susceptibility to obesity, but study results are still controversial.

OBJECTIVE: The present meta-analysis is performed to determine whether there are any associations between the Gln27Glu (rs1042714) or the Arg16Gly (rs1042713) polymorphisms in ADRB2 and obesity susceptibility.

METHODS: The PubMed (1950–2014), Embase (1974–2014), and China National Knowledge Infrastructure (CNKI, 1994–2014) databases were searched using the search terms (“Beta2-adrenergic receptor”, “b2-adrenergic receptor” or “ADRB2”), “polymorphism,” and “obesity”. Fixed- or random-effects pooled measures were determined on the bias of heterogeneity tests across studies. Publication bias was examined by Egger’s test and the modified Begg’s test.

RESULTS: Eighteen published articles were selected for meta-analysis. Overall analyses showed that rs1042714 (Gln27Glu) was associated with significantly increased obesity risk in the heterozygote model (Gln/Glu vs. Gln/Gln: OR: 1.16, 95% CI: 1.04–1.30, I² = 49%, P = 0.009) and the dominant model (Gln/Glu + Glu/Glu vs. Gln/Gln: OR: 1.2, 95% CI: 1.00–1.44, I² = 55%, P = 0.04), whereas no significant association was found in the other models for rs1042714. Also, no significant association was found between the rs1042713 (Arg16Gly) gene polymorphism and the risk of obesity in all genetic models. In addition, neither rs1042713 (Arg16Gly) nor rs1042714 (Gln27Glu) showed any significant association with obesity susceptibility when the population were stratified based on gender.

CONCLUSION: Our meta-analysis revealed that the rs1042714 (Gln27Glu) polymorphism is associated with obesity susceptibility. However, our results do not support an association between rs1042713 (Arg16Gly) polymorphisms and obesity in the populations investigated. This conclusion warrants confirmation by more case-control and cohort studies.

A prospective cohort study investigating gross motor function, pain, and health-related quality of life 17 years after selective dorsal rhizotomy in cerebral palsy
Kristina Tedroff, Kristina Löwing, Eva Åström

AIM: The aim of this study is to evaluate the long-term effects of selective dorsal rhizotomy (SDR), 15 to 20 years after surgery in patients with cerebral palsy.

METHOD: Eighteen children (four females, 14 males; mean age at SDR 4y 7mo, SD 1y 7mo) with bilateral spastic cerebral palsy (CP), were prospectively assessed after SDR. This study focuses on the outcome 15 to 20 years after the procedure. The assessments include the Modified Ashworth Scale for spasticity, the Gross Motor Function Measure (GMFM-88), the Wilson Mobility Scale, The Health-Related Quality of Life Health Survey, SF-36v2, and the Brief Pain Inventory.

RESULTS: The effect of normalized muscle tone in lower extremities after SDR was sustained after a median of 17 years. The best gross motor function capacity, according to the GMFM score, was seen at the 3-year follow-up,
thereafter a gradual decline followed. Half of the individuals reported low intensity pain and interference. Compared to a norm sample the physical health component of SF-36v2 was slightly lower and the mental health component slightly higher.

**INTERPRETATION**: The spasticity-reducing effect of SDR does not improve long-term functioning, nor prevent contractures, but it can possibly reduce the pain often experienced by individuals with CP.

8.

**Avascular necrosis as a complication of the treatment of dislocation of the hip in children with cerebral palsy.**

Koch, A.; Jozwiak, M.; Idzior, M.; Molinska-Glura, M.; Szulc, A

We investigated the incidence and risk factors for the development of avascular necrosis (AVN) of the femoral head in the course of treatment of children with cerebral palsy (CP) and dislocation of the hip. All underwent open reduction, proximal femoral and Dega pelvic osteotomy. The inclusion criteria were: a predominantly spastic form of CP, dislocation of the hip (migration percentage, MP > 80%), Gross Motor Function Classification System, (GMFCS) grade IV to V, a primary surgical procedure and follow-up of > one year.

There were 81 consecutive children (40 girls and 41 boys) in the study. Their mean age was nine years (3.5 to 13.8) and mean follow-up was 5.5 years (1.6 to 15.1). Radiological evaluation included measurement of the MP, the acetabular index (AI), the epiphyseal shaft angle (ESA) and the pelvic femoral angle (PFA). The presence and grade of AVN were assessed radiologically according to the Kruczynski classification.

Signs of AVN (grades I to V) were seen in 79 hips (68.7%). A total of 23 hips (18%) were classified between grades III and V.

Although open reduction of the hip combined with femoral and Dega osteotomy is an effective form of treatment for children with CP and dislocation of the hip, there were signs of avascular necrosis in about two-thirds of the children. There was a strong correlation between post-operative pain and the severity of the grade of AVN.

9.

**Health and Functioning of Families of Children With Special Health Care Needs Cared for in Home Care, Long-term Care, and Medical Day Care Settings**

Carmen Caicedo, PhD, RN

**Objectives**: To examine and compare child and parent or guardian physical and mental health outcomes in families with children with special health care needs who have medically complex technology dependent needs in home care, long-term care (LTC), and medical day care (MDC) settings. The number of children requiring medically complex technology-dependent care has grown exponentially. In this study, options for their care are home care, LTC, or MDC. Comparison of child and parent/guardian health outcomes is unknown.

**Methods**: Using repeated measures data were collected from 84 dyads (parent/guardian, medically complex technology-dependent child) for 5 months using Pediatric Quality of Life Inventory Generic Core Module 4.0 and Family Impact Module Data analysis: x2, RM-ANCOVA.

**Results**: There were no significant differences in overall physical health, mental health, and functioning of children by care setting. Most severely disabled children were in home care; moderately disabled in MDC; children in vegetative state LTC; however, parents perceived children’s health across care setting as good to excellent. Parents/guardians from home care reported the poorest physical health including being tired during the day, too
tired to do the things they like to do, feeling physically weak, or feeling sick and had cognitive difficulties, difficulties with worry, communication, and daily activities. Parents/guardians from LTC reported the best physical health with time and energy for a social life and employment.

**Conclusions:** Trends in health care policy indicate a movement away from LTC care to care in the family home where data indicate these parents/guardians are already mentally and functionally challenged.

10.

**Neurobehavioral Concerns Among Males with Dystrophinopathy Using Population-Based Surveillance Data from the Muscular Dystrophy Surveillance, Tracking, and Research Network**

Kristin Caspers Conway, PhD; Katherine D. Mathews, MD; Pangaja Paramsothy, PhD; Joyce Oleszek, MD; Christina Trout, MSN; Ying Zhang, PhD; Paul A. Romitti, PhD

**OBJECTIVE:** To describe the occurrence of selected neurobehavioral concerns among males with a dystrophinopathy and to explore the associations with corticosteroid or supportive device use.

**METHODS:** Medical record abstraction of neurobehavioral concerns was conducted for 857 affected males from 765 families, born since 1982 and followed through 2011, and enrolled in the population-based Muscular Dystrophy Surveillance, Tracking, and Research Network. Cumulative probabilities for attention-deficit hyperactivity disorder (ADHD), behavior problems, and depressed mood were calculated from Kaplan-Meier estimates for the subsample of oldest affected males (n = 765). Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for corticosteroid and supportive device use were estimated from Cox regression models with time-dependent covariates.

**RESULTS:** Of the 857 affected males, 375 (44%) had at least 1 of the 3 selected neurobehavioral concerns; a similar percentage (45%) was found among the 765 oldest affected males. The estimated cumulative probabilities among these oldest affected males were 23% for ADHD, 43% for behavior problems, and 51% for depressed mood. Corticosteroid (HR = 2.35, 95% CI = 1.75–3.16) and mobility device (HR = 1.53, 95% CI = 1.06–2.21) use were associated with behavior problems. Use of a mobility device (HR = 3.53, 95% CI = 2.13–5.85), but not corticosteroids, was associated with depressed mood. ADHD was not significantly associated with corticosteroid or mobility device use. Respiratory assist device use was not examined due to low numbers of users before onset of neurobehavioral concerns.

**CONCLUSION:** Selected neurobehavioral concerns were common among males with a dystrophinopathy. Reported associations highlight the importance of increased monitoring of neurobehavioral concerns as interventions are implemented and disease progresses.
Other Key Articles on Developmental Disabilities

2015

1. Incidental Detection of Cancer Predisposition Gene Copy Number Variations by Array Comparative Genomic Hybridization

J. Austin Hamm, MD; Fady M. Mikhail, MD, PhD; Dana Hollenbeck, MPH, MS, CGC; Meagan Farmer, MS, CGC; and Nathaniel H. Robin, MD

We describe 2 pediatric patients who presented to medical genetics clinic for evaluation and were incidentally found via array comparative genomic hybridization to have pathogenic copy number variations of cancer predisposition genes. We subsequently reviewed 3554 previous array comparative genomic hybridization results to estimate the frequency of similar incidental findings.

2. A Cluster-Randomized Trial to Reduce Cesarean Delivery Rates in Quebec

Nils Chaillet, Ph.D., Alexandre Dumont, M.D., Ph.D., Michal Abrahamowicz, Ph.D., Jean-Charles Pasquier, M.D., Ph.D., Francois Audibert, M.D., Patricia Monnier, M.D., Ph.D., Haim A. Abenhaim, M.D., M.P.H., Eric Dubé, M.Sc., Marylène Dugas, Ph.D., Rebecca Burne, M.Sc., and William D. Fraser, M.D.

BACKGROUND: In Canada, cesarean delivery rates have increased substantially over the past decade. Effective, safe strategies are needed to reduce these rates.

METHODS: We conducted a cluster-randomized, controlled trial of a multifaceted 1.5-year intervention at 32 hospitals in Quebec. The intervention involved audits of indications for cesarean delivery, provision of feedback to health professionals, and implementation of best practices. The primary outcome was the cesarean delivery rate in the 1-year postintervention period.

RESULTS: Among the 184,952 participants, 53,086 women delivered in the year before the intervention and 52,265 women delivered in the year following the intervention. There was a significant but small reduction in the rate of cesarean delivery from the preintervention period to the postintervention period in the intervention group as compared with the control group (change, 22.5% to 21.8% in the intervention group and 23.2% to 23.5% in the control group; odds ratio for incremental change over time, adjusted for hospital and patient characteristics, 0.90; 95% confidence interval [CI], 0.80 to 0.99; P = 0.04; adjusted risk difference, −1.8%; 95% CI, −3.8 to −0.2). The cesarean delivery rate was significantly reduced among women with low-risk pregnancies (adjusted risk difference, −1.7%; 95% CI, −3.0 to −0.3; P = 0.03) but not among those with high-risk pregnancies (P = 0.35; P = 0.03 for interaction). The intervention group also had a reduction in major neonatal morbidity as compared with the control group (adjusted risk difference, −0.7%; 95% CI, −1.3 to −0.1; P = 0.03) and a smaller increase in minor neonatal morbidity (adjusted risk difference, −1.7%; 95% CI, −2.6 to −0.9; P<0.001). Changes in minor and major maternal morbidity did not differ significantly between the groups.

CONCLUSIONS: Audits of indications for cesarean delivery, feedback for health professionals, and implementation of best practices, as compared with usual care, resulted in a significant but small reduction in the rate of cesarean delivery, without adverse effects on maternal or neonatal outcomes. The benefit was driven by the effect of the intervention in low-risk pregnancies.
3.

Exosome-mediated inflammasome signaling after central nervous system injury
Juan Pablo de Rivero Vaccari; Frank Brand III; Stephanie Adamczak; Stephanie W. Lee; Jon Perez-Barcena; Michael Y. Wang; M. Ross Bullock; W. Dalton Dietrich; and Robert W. Keane

Neuroinflammation is a response against harmful effects of diverse stimuli and participates in the pathogenesis of brain and spinal cord injury (SCI). The innate immune response plays a role in neuroinflammation following CNS injury via activation of multiprotein complexes termed inflammasomes that regulate the activation of caspase 1 and the processing of the pro-inflammatory cytokines IL-1β and IL-18. We report here that the expression of components of the nucleotide-binding and oligomerization domain (NOD)-like receptor protein-1 (NLRP-1) inflammasome, apoptosis speck-like protein containing a caspase recruitment domain (ASC), and caspase 1 are significantly elevated in spinal cord motor neurons and cortical neurons after CNS trauma. Moreover, NLRP1 inflammasome proteins are present in exosomes derived from CSF of SCI and traumatic brain-injured patients following trauma. To investigate whether exosomes could be used to therapeutically block inflammasome activation in the CNS, exosomes were isolated from embryonic cortical neuronal cultures and loaded with short-interfering RNA (siRNA) against ASC and administered to spinal cord-injured animals. Neuronal-derived exosomes crossed the injured blood–spinal cord barrier, and delivered their cargo in vivo, resulting in knockdown of ASC protein levels by approximately 76% when compared to SCI rats treated with scrambled siRNA. Surprisingly, siRNA silencing of ASC also led to a significant decrease in caspase 1 activation and processing of IL-1β after SCI. These findings indicate that exosome-mediated siRNA delivery may be a strong candidate to block inflammasome activation following CNS injury.

4.

Transition outcomes for young adults with Disabilities
Sue C. Lina; Mei-Ling Ting Lee; and Terry A. Adirimc

PURPOSE: Transition to adulthood can be very challenging for children with special health care needs (CSHCN) especially for those with disabilities who experience functional limitations in activities at home, in school, and in the community. The study examined the transition outcomes in areas of health, education, and independent living for young adult with special health care needs (YASHCN) with disabilities.

METHOD: The study is a secondary data analysis of the 2007 Survey of Adult Transition and Health (SATH). Multivariate logistic regression analysis assessed the association between having disabilities and the transition outcomes.

RESULTS: Overall, YASHCN with disabilities reported favorable health related transition outcomes with improved access to primary care, care coordination, and physician engagement in transition discussions and connection to mentors. Furthermore, YASHCN with disabilities had higher odds of receiving Medicaid or other insurance for low income or disabilities as an adult (AOR = 5.26, 95% CI = 3.74, 7.04). However, they were less likely to report having control over personal finances, making friends, and obtaining a high school diploma.

CONCLUSION: The findings suggest that YASHCN with disabilities may be among the small proportion of CSHCNs who had a positive transition to adult health care services. However, transition outcomes related to independent living still need more improvements.
5. "Complex" attention-deficit hyperactivity disorder, more norm than exception? Diagnoses and comorbidities in a developmental clinic.
Koolwijk I, Stein DS, Chan E, Powell C, Driscoll K, Barbaresi WJ.

OBJECTIVE: Current recommendations for evaluation and diagnosis of attention-deficit hyperactivity disorder (ADHD) are meant for primary care settings and may not adequately address the needs of children seen in subspecialty developmental-behavioral pediatric settings who may have higher rates of comorbid developmental, learning, and psychiatric disorders. The authors sought to characterize the diagnostic complexity of school-aged children diagnosed with ADHD after comprehensive multidisciplinary evaluation in a subspecialty developmental-behavioral pediatric clinic.

METHODS: The authors conducted a retrospective medical record review of 144 patients aged 7 to 11 years who were consecutively evaluated by an interdisciplinary team (developmental-behavioral pediatrician, psychologist, educator) in a school-age clinic within a developmental-behavioral pediatrics tertiary care center from January 1, 2009 to December 31, 2009.

RESULTS: After comprehensive evaluation, rates of ADHD diagnosis increased from 32.6% (n = 47) preevaluation to 54.2% (n = 78) postevaluation (p < .0001). Rates of learning disorders among children receiving a final diagnosis of ADHD increased from 2.6% (n = 2) preevaluation to 50% (n = 39) postevaluation. (p < .0001). Among children receiving a final diagnosis of ADHD, 73.1% (n = 57) were diagnosed with at least 1 comorbid psychiatric, developmental, or learning disorder.

CONCLUSIONS: Among school-aged children diagnosed with ADHD in a developmental-behavioral pediatric subspecialty setting, a comprehensive evaluation including developmental, neuropsychological, and educational assessments yielded high rates of comorbid psychiatric, developmental, and learning disorders. This supports the need to provide comprehensive interdisciplinary assessment for such children to ensure the identification and treatment of not only the core symptoms of ADHD but also the comorbidities that may otherwise go unrecognized and therefore not optimally treated.

6. Effect of Delayed Cord Clamping on Neurodevelopment at 4 Years of Age: A Randomized Clinical Trial.

IMPORTANCE: Prevention of iron deficiency in infancy may promote neurodevelopment. Delayed umbilical cord clamping (CC) prevents iron deficiency at 4 to 6 months of age, but long-term effects after 12 months of age have not been reported.

OBJECTIVE: To investigate the effects of delayed CC compared with early CC on neurodevelopment at 4 years of age.

DESIGN, SETTING, AND PARTICIPANTS: Follow-up of a randomized clinical trial conducted from April 16, 2008, through May 21, 2010, at a Swedish county hospital. Children who were included in the original study (n = 382) as full-term infants born after a low-risk pregnancy were invited to return for follow-up at 4 years of age. Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) and Movement Assessment Battery for Children (Movement ABC) scores (collected between April 18, 2012, and July 5, 2013) were assessed by a blinded psychologist. Between April 11, 2012, and August 13, 2013, parents recorded their child's development using the Ages and Stages
Questionnaire, Third Edition (ASQ) and behavior using the Strengths and Difficulties Questionnaire. All data were analyzed by intention to treat.

**INTERVENTIONS:** Randomization to delayed CC (≥180 seconds after delivery) or early CC (≤10 seconds after delivery).

**MAIN OUTCOMES AND MEASURES:** The main outcome was full-scale IQ as assessed by the WPPSI-III. Secondary objectives were development as assessed by the scales from the WPPSI-III and Movement ABC, development as recorded using the ASQ, and behavior using the Strengths and Difficulties Questionnaire.

**RESULTS:** We assessed 263 children (68.8%). No differences were found in WPPSI-III scores between groups. Delayed CC improved the adjusted mean differences (AMDs) in the ASQ personal-social (AMD, 2.8; 95% CI, 0.8-4.7) and fine-motor (AMD, 2.1; 95% CI, 0.2-4.0) domains and the Strengths and Difficulties Questionnaire prosocial subscale (AMD, 0.5; 95% CI, >0.0-0.9). Fewer children in the delayed-CC group had results below the cutoff in the ASQ fine-motor domain (11.0% vs 3.7%; P = .02) and the Movement ABC bicycle-trail task (12.9% vs 3.8%; P = .02). Boys who received delayed CC had significantly higher AMDs in the WPPSI-III processing-speed quotient (AMD, 4.2; 95% CI, 0.8-7.6; P = .02), Movement ABC bicycle-trail task (AMD, 0.8; 95% CI, 0.1-1.5; P = .03), and fine-motor (AMD, 4.7; 95% CI, 1.0-8.4; P = .01) and personal-social (AMD, 4.9; 95% CI, 1.6-8.3; P = .004) domains of the ASQ.

**CONCLUSIONS AND RELEVANCE:** Delayed CC compared with early CC improved scores in the fine-motor and social domains at 4 years of age, especially in boys, indicating that optimizing the time to CC may affect neurodevelopment in a low-risk population of children born in a high-income country.

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**Effectiveness of a Telehealth Service Delivery Model for Treating Attention-Deficit/Hyperactivity Disorder: A Community-Based Randomized Controlled Trial**

Kathleen Myers, MD, MPH, MS, Ann Vander Stoep, PhD, Chuan Zhou, PhD, Carolyn A. McCarty, PhD, Wayne Katon, MD

**OBJECTIVE:** To test the effectiveness of a telehealth service delivery model for the treatment of children with attention-deficit/hyperactivity disorder (ADHD) that provided pharmacological treatment and caregiver behavior training.

**METHOD:** The Children’s ADHD Telemental Health Treatment Study (CATTs) was a randomized controlled trial with 223 children referred by 88 primary care providers (PCPs) in 7 communities. Children randomized to the experimental telehealth service model received 6 sessions over 22 weeks of combined pharmacotherapy, delivered by child psychiatrists through videoconferencing, and caregiver behavior training, provided in person by community therapists who were supervised remotely. Children randomized to the control service delivery model received treatment with their PCPs augmented with a telepsychiatry consultation. Outcomes were diagnostic criteria for ADHD and oppositional defiant disorder (ODD) and role performance on the Vanderbilt ADHD Rating Scale (VADRS) completed by caregivers (VADRS-Caregivers) and teachers (VADRS-Teachers) and impairment on the Columbia Impairment Scale-Parent Version (CIS-P). Measures were completed at 5 assessments over 25 weeks.

**RESULTS:** Children in both service models improved. Children assigned to the telehealth service model improved significantly more than children in the augmented primary care arm for VADRS-Caregiver criteria for inattention (c²[4] ¼ 19.47, p < .001), hyperactivity (c²[4] ¼ 11.91, p ¼ .02), combined ADHD (c²[4] ¼ 14.90, p ¼ .005), ODD (c²[4] ¼ 10.05, p ¼ .04), and VADRS-Caregiver role performance (c²[4] ¼ 12.40, p ¼ .01) and CIS-P impairment (c²[4] ¼ 20.52, p < .001). For the VADRS-Teacher diagnostic criteria, children in the telehealth service model had significantly more improvement in hyperactivity (c²[4] ¼ 11.28, p ¼ .02) and combined ADHD (c²[4] ¼ 9.72, p ¼ .045).
CONCLUSION: The CATTS trial demonstrated the effectiveness of a telehealth service model to treat ADHD in communities with limited access to specialty mental health services.

CLINICAL TRIAL REGISTRATION INFORMATION—Children’s Attention Deficit Disorder With Hyperactivity (ADHD)Telemental Health Treatment Study; http://clinicaltrials.gov; NCT00830700.

8.

Fatigue is a major issue for children and adolescents with physical disabilities
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AIM: This study aimed to investigate fatigue, and its correlates, in children and adolescents with physical disabilities.

METHOD: Sixty-five young people aged 8 to 17 years (35 males, 30 females; mean age 13y 2mo, SD 2y 8mo) with mild to moderate physical disabilities (Gillette Functional Assessment Questionnaire levels 7–10) were recruited. Self-reported fatigue was measured using the PedsQL Multidimensional Fatigue Scale. Physical activity was measured using 7-day hip-worn accelerometer. Associations between fatigue, physical activity, and socio-demographic characteristics were examined using analysis of covariance, with significance ($\alpha$) set at 0.05. Results were compared with normative data from other paediatric populations.

RESULTS: Among children with physical disabilities, fatigue was associated with being physically inactive ($F$-statistic=4.42, $p=0.040$), female ($F=4.37$, $p=0.042$), and of low socio-economic status ($F=3.94$, $p=0.050$). Fatigue was not associated with age, weight status, or functional impairment. Young people with physical disabilities experienced high levels of fatigue compared with other paediatric health populations, and comparable to the paediatric cancer population.

INTERPRETATION: Fatigue is an important issue for young people with physical disabilities. Clinicians and researchers working with this group should be mindful that fatigue is likely to impact on an individual’s ability to undertake new treatment regimens or interventions. Interventions aimed at reducing fatigue are warranted. Increasing physical activity might play a role in reducing fatigue.

9.

b-Blockers and Angiotensin Converting Enzyme Inhibitors: Comparison of Effects on Aortic Growth in Pediatric Patients with Marfan Syndrome
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OBJECTIVES: Angiotensin converting enzyme inhibitors (ACEI) have been shown to decrease aortic growth velocity (AGV) in Marfan syndrome (MFS). We sought to compare the effect of b-blockers and ACEI on AGV in MFS.

STUDY DESIGN: We retrospectively reviewed all data from all patients with MFS seen at Arkansas Children’s Hospital between January 1, 1976 and January 1, 2013. Generalized least squares were used to evaluate AGV over time as a function of age, medication group, and the interaction between the 2. A mixed model was used to compare AGV between medication groups as a function of age, medication group (none, b-blocker, ACEI), and the interaction between the 2.

RESULTS: A total of 67 patients with confirmed MFS were identified (34/67, 51% female). Mean age at first encounter was 13 _ 10 years, with mean follow-up of 7.6 _ 5.8 years. There were 839 patient encounters with a
median of 10 (range 2-42) encounters per patient. AGV was nearly normal in the b-blocker group, and was less than either the ACEI or untreated groups. The AGV was higher than normal in ACEI and untreated groups (P < .001 for both).

CONCLUSIONS: b-blocker therapy results in near-normalization of AGV in MFS. ACEI did not decrease AGV in a clinically significant manner.

10.

Sociodemographic Attributes and Spina Bifida Outcomes
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BACKGROUND: A National Spina Bifida Patient Registry (NSBPR) was begun in 2009 to help understand the natural history of spina bifida (SB) and the effects of treatments provided by SB clinics. We used the NSBPR to explore the relationship of sociodemographic characteristics with SB outcomes.

METHODS: Using NSBPR data collected in 2009 to 2012, we examined the unadjusted association between demographic characteristics and 4 SB outcomes: bowel continence, bladder continence, mobility, and presence of pressure sores. We then developed multivariable logistic models to explore these relationships while controlling for SB clinic, SB type, and level of lesion.

RESULTS: Data were available on 2054 patients <22 years of age from 10 SB clinics. In the multivariable models, older age groups were more likely to have continence and pressure sores and less likely to be community ambulatory. Males and patients without private insurance were less likely to be continent and community ambulatory. Non-Hispanic blacks were less likely to be continent. Level of lesion was associated with all outcomes; SB type was associated with all but pressure sores; and all outcomes except community ambulation showed significant variation across clinic sites.

CONCLUSIONS: Sociodemographic attributes are associated with SB outcomes. In particular, males, non-Hispanic blacks, and patients without private insurance have less favorable outcomes, and age has an impact as well. These characteristics need to be considered by clinicians who care for this patient population and factored into case-mix adjustment when evaluating variation in clinical and functional outcomes among different SB clinics.