Boukhris T¹, Sheehy O², Mottron L³, Bérard A¹.

IMPORTANCE: The association between the use of antidepressants during gestation and the risk of autism spectrum disorder (ASD) in children is still controversial. The etiology of ASD remains unclear, although studies have implicated genetic predispositions, environmental risk factors, and maternal depression.

OBJECTIVE: To examine the risk of ASD in children associated with antidepressant use during pregnancy according to trimester of exposure and taking into account maternal depression.

DESIGN, SETTING, AND PARTICIPANTS: We conducted a register-based study of an ongoing population-based cohort, the Québec Pregnancy/Children Cohort, which includes data on all pregnancies and children in Québec from January 1, 1998, to December 31, 2009. A total of 145,456 singleton full-term infants born alive and whose mothers were covered by the Régie de l'assurance maladie du Québec drug plan for at least 12 months before and during pregnancy were included. Data analysis was conducted from October 1, 2014, to June 30, 2015.

EXPOSURES: Antidepressant exposure during pregnancy was defined according to trimester and specific antidepressant classes.

MAIN OUTCOMES AND MEASURES: Children with ASD were defined as those with at least 1 diagnosis of ASD between date of birth and last date of follow-up. Cox proportional hazards regression models were used to estimate crude and adjusted hazard ratios with 95% CIs.

RESULTS: During 904,035.50 person-years of follow-up, 1054 children (0.7%) were diagnosed with ASD; boys with ASD outnumbered girls by a ratio of about 4:1. The mean (SD) age of children at the end of follow-up was 6.24 (3.19) years. Adjusting for potential confounders, use of antidepressants during the second and/or third trimester was associated with the risk of ASD (31 exposed infants; adjusted hazard ratio, 1.87; 95% CI, 1.15-3.04). Use of selective serotonin reuptake inhibitors during the second and/or third trimester was significantly associated with an increased risk of ASD (22 exposed infants; adjusted hazard ratio, 2.17; 95% CI, 1.20-3.93). The risk was persistent even after taking into account maternal history of depression (29 exposed infants; adjusted hazard ratio, 1.75; 95% CI, 1.03-2.97).

CONCLUSIONS AND RELEVANCE: Use of antidepressants, specifically selective serotonin reuptake inhibitors, during the second and/or third trimester increases the risk of ASD in children, even after considering maternal depression. Further research is needed to specifically assess the risk of ASD associated with antidepressant types and dosages during pregnancy.
Severe Congenital Heart Defects Are Associated with Global Reduction of Neonatal Brain Volumes.
von Rhein M¹, Buchmann A², Hagmann C³, Dave H⁴, Bernet V⁵, Scheer I⁶, Knirsch W⁷, Latal B⁸; Heart and Brain Research Group.

OBJECTIVES: To determine neonatal global and regional brain volumes in infants with congenital heart disease (CHD) in comparison with healthy controls and to determine brain growth.

STUDY DESIGN: Prospective cohort study in infants undergoing open-heart surgery for complex CHD. Global and regional volumetric measurements on preoperative cerebral magnetic resonance imaging were manually segmented in children without overt brain lesions.

RESULTS: Preoperative brain volumetry of 19 patients demonstrates reduction in total and regional brain volumes, without any specific regional predilection compared with 19 healthy control infants (total brain volume reduction: 21%, regional brain volume reduction 8%-28%, all P < .001).

CONCLUSIONS: Infants with CHD undergoing bypass surgery have smaller brain volumes prior to surgery without a specific regional predilection. This suggests a fetal origin of reduced brain growth.
Autism and epilepsy: A population-based nationwide cohort study
Sundelin, HEK, Larsson H, Almqvist C, Hultman CM, Tomson T, Ludvigsson JF.
Published online before print June 15, 2016, doi: http://dx.doi.org/10.1212/WNL.0000000000002836 Neurology 10.1212/WNL.0000000000002836

Objective: To investigate the risk of autism spectrum disorder (ASD) in individuals with epilepsy and in their first-degree relatives to determine shared etiology.
Methods: Through the Swedish Patient Register, we identified 85,201 individuals with epilepsy, as well as all their siblings (n = 80,511) and offspring (n = 98,534). Each individual with epilepsy was compared with 5 controls, matched for age, sex, calendar period, and county, while siblings and offspring were compared with siblings and offspring of controls. We excluded siblings and offspring with epilepsy. Using Cox regression, we calculated hazard ratios (HRs) for future diagnosis of ASD. Logistic regression was applied to calculate odds ratios (ORs) for prior diagnosis of ASD.
Results: During follow-up, 1,381 (1.6%) individuals with epilepsy and 700 (0.2%) controls were diagnosed with ASD. Individuals with epilepsy were therefore at increased risk of future ASD (HR 10.49, 95% confidence interval [CI] 9.55–11.53), with the highest risk seen in individuals diagnosed with epilepsy in childhood. Both siblings (HR 1.62, 95% CI 1.43–1.83) and offspring (HR 1.64, 95% CI 1.46–1.84) of epilepsy patients were at increased risk of ASD. The risk in the offspring was particularly high in mothers with epilepsy (HR 1.91; 95% CI 1.63–2.23). Epilepsy was also associated with a prior diagnosis of ASD (OR 4.56, 95% CI 4.02–5.18).
Conclusions: Individuals with epilepsy are at increased risk of ASD, especially if epilepsy appears in childhood. Further, ASD is more common in the siblings and offspring of individuals with epilepsy, suggesting shared etiology.
Association of the Type of Toy Used During Play With the Quantity and Quality of Parent-Infant Communication


Importance: The early language environment of a child influences language outcome, which in turn affects reading and academic success. It is unknown which types of everyday activities promote the best language environment for children.

Objective: To investigate whether the type of toy used during play is associated with the parent-infant communicative interaction.

Design, Setting, and Participants Controlled experiment in a natural environment of parent-infant communication during play with 3 different toy sets. Participant recruitment and data collection were conducted between February 1, 2013, and June 30, 2014. The volunteer sample included 26 parent-infant (aged 10-16 months) dyads.

Exposures Fifteen-minute in-home parent-infant play sessions with electronic toys, traditional toys, and books.

Main Outcomes and Measures Numbers of adult words, child vocalizations, conversational turns, parent verbal responses to child utterances, and words produced by parents in 3 different semantic categories (content-specific words) per minute during play sessions.

Results: Among the 26 parent-infant dyads, toy type was associated with all outcome measures. During play with electronic toys, there were fewer adult words (mean, 39.62; 95% CI, 33.36-45.65), fewer conversational turns (mean, 1.64; 95% CI, 1.12-2.19), fewer parental responses (mean, 1.31; 95% CI, 0.87-1.77), and fewer productions of content-specific words (mean, 1.89; 95% CI, 1.49-2.35) than during play with traditional toys or books. Children vocalized less during play with electronic toys (mean per minute, 2.9; 95% CI, 2.16-3.69) than during play with books (mean per minute, 3.91; 95% CI, 3.09-4.68). Parents produced fewer words during play with traditional toys (mean per minute, 55.56; 95% CI, 46.49-64.17) than during play with books (mean per minute, 66.89; 95% CI, 59.93-74.19) and use of content-specific words was lower during play with traditional toys (mean per minute, 4.09; 95% CI, 3.26-4.99) than during play with books (mean per minute, 6.96; 95% CI, 6.07-7.97).

Conclusions and Relevance: Play with electronic toys is associated with decreased quantity and quality of language input compared with play with books or traditional toys. To promote early language development, play with electronic toys should be discouraged. Traditional toys may be a valuable alternative for parent-infant play time if book reading is not a preferred activity.
Outpatient Rehabilitation for Medicaid-insured Children Hospitalized With Traumatic Brain Injury
Nathalia Jimenez, Rebecca G. Symons, Jin Wang, Beth H. Ebel, Monica S. Vavilala, Dedra Buchwald, Nancy Temkin, Kenneth M. Jaffe, Frederick P. Rivara
Pediatrics. Volume 137, number 6, June 2016:e20153500
DOI:10.1542/peds.2015-3500

OBJECTIVES: To describe the prevalence of postdischarge outpatient rehabilitation among Medicaid-insured children hospitalized with a traumatic brain injury (TBI) and to identify factors associated with receipt of services.

METHODS: Retrospective cohort of children <21 years, hospitalized for a TBI between 2007 and 2012, from a national Medicaid claims database. Outcome measures were receipt of outpatient rehabilitation (physical, occupational, or speech therapies or physician visits to a rehabilitation provider) 1 and 3 years after discharge. Multivariable regression analyses determined the association of demographic variables, injury severity, and receipt of inpatient services with receipt of outpatient rehabilitation at 1 and 3 years. The mean number of services was compared between racial/ethnic groups.

RESULTS: Among 9361 children, only 29% received any type of outpatient rehabilitation therapy during the first year after injury, although 62% sustained a moderate to severe TBI. The proportion of children receiving outpatient therapies declined to 12% in the second and third years. The most important predictor of receipt of outpatient rehabilitation was receipt of inpatient therapies or consultation with a rehabilitation physician during acute care. Compared with children of other racial/ethnic groups, Hispanic children had lower rates of receipt of outpatient speech therapy.

CONCLUSIONS: Hospitalized children who received inpatient assessment of rehabilitation needs were more likely to continue outpatient rehabilitation care. Hispanic children with TBI were less likely than non-Hispanics to receive speech therapy. Interventions to increase inpatient rehabilitation during acute care might increase outpatient rehabilitation and improve outcomes for all children.
Girls and Boys Born before 28 Weeks Gestation: Risks of Cognitive, Behavioral, and Neurologic Outcomes at Age 10 Years
Kuban KCK, Joseph RM, O’Shea TM, et al, on behalf of the Extremely Low Gestational Age Newborn (ELGAN) Study Investigators

Objectives
To compare the prevalence of cognitive, neurologic, and behavioral outcomes at 10 years of age in 428 girls and 446 boys who were born extremely preterm.

Study design
A total of 889 of 966 eligible children previously enrolled in the multicenter Extremely Low Gestational Age Newborns Study from 2002-2004 were evaluated at 10 years of age. Children underwent a neuropsychological battery and testing for autism spectrum disorder (ASD), and parents reported on their child's behavior, development, and seizures.

Results
Of the children, 28% of boys and 21% of girls exhibited moderate to severe impairment on summary measures of cognitive abilities. Boys had a higher prevalence of impairment than girls in nearly all measures of cognition, were more than twice as likely to have microcephaly (15% in boys, 8% in girls), and require more often assistive devices to ambulate (6% in boys, 4% in girls). In contrast, boys and girls had comparable risk for a history of seizure (identified in 10% of the cohort) or epilepsy (identified in 7% of the cohort). The boy-to-girl ratio of ASD (9% in boys, 5% in girls) was lower than expected compared with the overall US autism population.

Conclusions
In this contemporary cohort of children born extremely premature and evaluated at school age, boys had higher prevalence of cognitive, neurologic, and behavioral deficits than girls. The ratio of boys to girls among those with ASD deserves further study as does the perinatal environmental-genetic interactions that might contribute to male preponderance of deficits in this high-risk sample.
Localized Misfolding Within Broca’s Area as a Distinctive Feature of Autistic Disorder
DOI: http://dx.doi.org/10.1016/j.bpsc.2015.11.003

Background
Recent neuroimaging studies suggest that autism spectrum disorder results from abnormalities in the cortical folding pattern. Usual morphometric measurements have failed to provide reliable neuroanatomic markers. Here, we propose that sulcal pits, which are the deepest points in each fold, are suitable candidates to uncover this atypical cortical folding.

Methods
Sulcal pits were extracted from a magnetic resonance imaging database of 102 children (1.5–10 years old) distributed in three groups: children with autistic disorder (n = 59), typically developing children (n = 22), and children with pervasive developmental disorder not otherwise specified (n = 21). The geometrical properties of sulcal pits were compared between these three groups.

Results
Fold-level analyses revealed a reduced pit depth in the left ascending ramus of the Sylvian fissure in children with autistic disorder only. The depth of this central fold of Broca’s area was correlated with the social communication impairments that are characteristic of the pathology.

Conclusions
Our findings support an atypical gyrogenesis of this specific fold in autistic disorder that could be used for differential diagnosis. Sulcal pits constitute valuable markers of the cortical folding dynamics and could help for the early detection of atypical brain maturation.
Creatine Transporter Deficiency: Screening of Males with Neurodevelopmental Disorders and Neurocognitive Characterization of a Case.

OBJECTIVE:
Creatine transporter deficiency (CTD) is an X-linked, neurometabolic disorder associated with intellectual disability that is characterized by brain creatine (Cr) deficiency and caused by mutations in SLC6A8, the Cr transporter 1 protein gene. CTD is identified by elevated urine creatine/creatinine (Cr/Crn) ratio or reduced Cr peak on brain magnetic resonance spectroscopy; the diagnosis is confirmed by decreased Cr uptake in cultured fibroblasts, and/or identification of a mutation in the SLC6A8 gene. Prevalence studies suggest this disorder may be underdiagnosed. We sought to identify cases from a well-characterized cohort of children diagnosed with neurodevelopmental disorders.

METHOD:
Urine screening for CTD was performed on a cohort of 46 males with autism spectrum disorder (ASD) and 9 males with a history of non-ASD developmental delay (DD) classified with intellectual disability.

RESULTS:
We identified 1 patient with CTD in the cohort based on abnormal urine Cr/Crn, and confirmed the diagnosis by the identification of a novel frameshift mutation in the SLC6A8 gene. This patient presented without ASD but with intellectual disability, and was characterized by a nonspecific phenotype of early language delay and DD that persisted into moderate-to-severe intellectual disability, consistent with previous descriptions of CTD.

CONCLUSION:
Identification of patients with CTD is possible by measuring urine Cr and Crn levels and the current case adds to the growing literature of neurocognitive deficits associated with the disorder that affect cognition, language and behavior in childhood.
OBJECTIVE:
Life-long adverse effects of childhood maltreatment on mental health are well established, but effects on child-to-adulthood cognition and related educational attainment have yet to be examined in the general population. We aimed to establish whether different forms of child maltreatment are associated with poorer cognition and educational qualifications in childhood/adolescence and whether associations persist to midlife, parallel to associations for mental health.

METHOD:
Cognitive abilities at ages 7, 11, and 16 years (math, reading, and general intellectual ability) and 50 years (immediate/delayed memory, verbal fluency, processing speed) were assessed using standardized tests, and qualifications by age 42 were self-reported. Information on childhood maltreatment (neglect and abuse: sexual, physical, psychological, witnessed), cognition, and mental health was available for 8,928 participants in the 1958 British Birth Cohort.

RESULTS:
We found a strong association of child neglect with cognitive deficits from childhood to adulthood. To illustrate, the most neglected 6% of the population (score ≥4) had a 0.60 (95% CI = 0.56-0.68) SD lower cognitive score at age 16 and a 0.28 (95% CI = 0.20-0.36) SD deficit at age 50 years relative to the non-neglected participants (score = 0) after adjustment for confounding factors and mental health, and they also had increased risk of poor qualifications (i.e., none/low versus degree-level). Childhood neglect and all forms of abuse were associated with poorer child-to-adulthood mental health, but abuse was mostly unrelated to cognitive abilities.

CONCLUSION:
The study provides novel data that child neglect is associated with cognitive deficits in childhood/adolescence and decades later in adulthood, independent of mental health, and highlights the lifelong burden of child neglect on cognitive abilities and mental health.
Planned Out-of-Hospital Birth and Birth Outcomes.
Snowden JM1, Tilden EL, Snyder J, Quigley B, Caughey AB, Cheng YW.

BACKGROUND:
The frequency of planned out-of-hospital birth in the United States has increased in recent years. The value of studies assessing the perinatal risks of planned out-of-hospital birth versus hospital birth has been limited by cases in which transfer to a hospital is required and a birth that was initially planned as an out-of-hospital birth is misclassified as a hospital birth.

METHODS:
We performed a population-based, retrospective cohort study of all births that occurred in Oregon during 2012 and 2013 using data from newly revised Oregon birth certificates that allowed for the disaggregation of hospital births into the categories of planned in-hospital births and planned out-of-hospital births that took place in the hospital after a woman's intrapartum transfer to the hospital. We assessed perinatal morbidity and mortality, maternal morbidity, and obstetrical procedures according to the planned birth setting (out of hospital vs. hospital).

RESULTS:
Planned out-of-hospital birth was associated with a higher rate of perinatal death than was planned in-hospital birth (3.9 vs. 1.8 deaths per 1000 deliveries, P=0.003; odds ratio after adjustment for maternal characteristics and medical conditions, 2.43; 95% confidence interval [CI], 1.37 to 4.30; adjusted risk difference, 1.52 deaths per 1000 births; 95% CI, 0.51 to 2.54). The odds for neonatal seizure were higher and the odds for admission to a neonatal intensive care unit lower with planned out-of-hospital births than with planned in-hospital birth. Planned out-of-hospital birth was also strongly associated with unassisted vaginal delivery (93.8%, vs. 71.9% with planned in-hospital births; P<0.001) and with decreased odds for obstetrical procedures.

CONCLUSIONS:
Perinatal mortality was higher with planned out-of-hospital birth than with planned in-hospital birth, but the absolute risk of death was low in both settings. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.).