HHS Public Access

Author manuscript

Pediatr Neurol. Author manuscript; available in PMC 2019 April 01.

Published in final edited form as:

Pediatr Neurol. 2018 April ; 81: 25–30. doi:10.1016/j.pediatrneurol.2017.12.010.

Antecedents of screening positive for attention deficit hyperactivity disorder in 10-year old children born extremely preterm

Alan Leviton, MD,
Boston Children's Hospital and Harvard Medical School, Boston MA, USA

Stephen R Hooper, PhD,
University of North Carolina School of Medicine, Chapel Hill NC, USA

Scott J. Hunter, PhD,
The University of Chicago Medicine Comer Children's Hospital, Chicago IL, USA

Megan N. Scott, PhD,
The University of Chicago Medicine Comer Children's Hospital, Chicago IL, USA

Elizabeth N. Allred, MS,
Boston Children's Hospital and Harvard Medical School, Boston MA, USA

Robert M. Joseph, PhD,
Boston University School of Medicine, Boston MA, USA

T. Michael O'Shea, MD, and
University of North Carolina School of Medicine, Chapel Hill NC, USA

Karl Kuban, MD
Boston Medical Center and Boston University School of Medicine, Boston, MA, USA

for the ELGAN Study Investigators

Abstract

Background—Attention deficit hyperactivity disorder (ADHD) incidence is higher among children born very preterm than among children who are mature at birth.

Methods—We studied 583 ten-year old children born before 28 weeks of gestation whose IQ was above 84 and had a parent-completed Child Symptom Inventory-4 (CSI-4), which allowed classifying the child as having or not having symptoms of ADHD. For 422 we also had a teacher

Corresponding author: Alan Leviton, 84 Sumner Street, Newton MA 02459-1958, alan.leviton@childrens.harvard.edu, telephone: 617 485-7187.

Conflict of interest
Each of the authors declares that she/he has no conflict of interest.

report, and for 583 we also had a parent report of whether or not a physician made an ADHD diagnosis.

Results—The risk profile of screening positive for ADHD based on a parent's report (P) differed from the risk profile based on the teacher's (T) report, while the risk profile according to a physician (MD), and according to any 2 observers (2) closely resembled the parent-report profile. Among the statistically significant risk factors were young maternal age (P, MD, 2), maternal obesity (P, MD, 2), maternal smoking (P, MD, 2), magnesium given at delivery for seizure prophylaxis (P, 2), recovery of *Mycoplasma* sp from the placenta (T, 2), low gestational age (P, 2), low birth weight (T, MD), singleton (P, MD, 2), male (P,T, MD, 2), mechanical ventilation on postnatal day 7 (MD), receipt of a sedative (P, 2), retinopathy of prematurity (P), necrotizing enterocolitis (MD), antibiotic receipt (MD, 2), and ventriculomegaly on brain scan (P, 2).

Conclusion—The multiplicity of risk factors identified can be subsumed as components of four broad themes, low socioeconomic state, immaturity/vulnerability, inflammation, and epigenetic phenomena.

Keywords

Attention Deficit Disorder with Hyperactivity; Infant; Extremely Premature; Epidemiology; Inflammation; Socioeconomic Factors; Epigenetics

Introduction

The lower the gestational age, the higher the rate of attention deficit (hyperactive) disorder (ADHD) [1]. Nevertheless, we are not aware of any study of the epidemiology of ADHD among individuals born extremely prematurely. The ELGAN (Extremely Low Gestational Age Newborn) Study of children born before 28 weeks of gestation provided an opportunity to identify risk factors for ADHD in this high-risk group. When this cohort was evaluated at 10 years of age, parents and teachers completed a Child Symptom Inventory-4 (CSI-4), which provided information about symptoms of ADHD based on DSM-5 criteria. Parents also reported whether a physician had made a diagnosis of ADHD, and whether medication had been prescribed.

Here we explore relationships between prospectively collected information about potential antecedents and a parent's, a teacher's, and a physician's perception of whether or not the child had ADHD symptoms and/or an ADHD diagnosis. We also explore to what extent the antecedent risk factors for ADHD behaviors differed among three sets of observers, (i.e., parents, teachers, and physicians) and combinations of these observers.

Methods

Participants

The enrollment and consent procedures for all aspects of this multi-center prospective, observational study of the risk of structural and functional neurologic disorders in extremely preterm infants [2] were approved by the institutional review boards of all participating institutions. At age 10-years, 889 children had a neurocognitive assessment [3], while a

parent completed questionnaires regarding the child's medical and neurological status and behavior, including the Child Symptom Inventory-4 Parent Checklist (CSI-4)[4]. Parents also completed a questionnaire that asked the following two questions. Since age 2 years, have you been told by a doctor or other health professional that your child has or has had attention deficit or hyperactivity (ADD or ADHD)? Does your child currently take or has your child taken since age 2 years any daily medications for attention deficit or hyperactivity (ADD or ADHD)?

Of the children assessed, 583 had a DAS IQ ≥ 85 and a parent report about ADHD. They constitute the sample for this report. Of these children, 422 also had a teacher report. Additional details about data collected for this report can be found in the Supplementary Material.

Data analysis

We evaluated the null hypothesis that ELGANs who screen positive for a diagnosis of ADHD have the same demographic, pregnancy and perinatal characteristics as their peers who screen negative. We limited our attention to the entity of ANY ADHD, and not individual subtypes (*i.e.*, inattentive, hyperactive-impulsive, and combined forms) for three reasons. First, we did not have information from the physician about diagnostic details, only that s/he did or did not make a diagnosis of ADHD. Second, the relatively small numbers of children in each subgroup (inattentive, hyperactive-impulsive, and combined), appreciably limited power and did not allow robust analyses. Third, we are supported by a literature emphasizing a unitary concept of ADHD [5], and factor analyses that have a heavy "common factor" loading [6, 7].

Because including children with a low IQ [8] might lead us to identify the antecedents of low IQ as well as the antecedents of ADHD, we limited our analyses to children whose IQ was 85 or above. We began with univariable analyses (Supplementary Material Tables), and then selected likely candidates for multivariable analyses. Because postnatal phenomena can be influenced by antepartum phenomena, we created multinomial logistic regression models in which risk factors are ordered in a temporal pattern, so that the earliest occurring predictors/covariates of any ADHD at age 10 years are entered first and are not displaced by later occurring covariates [9]. For these time-oriented logistic regression risk models, we categorized sets of antecedents/covariates by the time they occur, or are identified (e.g., antenatal, early postnatal, and later postnatal). We used a step down procedure seeking a parsimonious solution without interaction terms. These models allowed us to calculate odds ratios and 95% confidence intervals. Results are displayed as forest plots for any ADHD according to a parent, teacher, physician, any two, or by receipt of medication.

Results

We limited these analyses to the 583 children for whom we had a parent-completed CSI-4 and whose DAS verbal and non-verbal scores were both ≥ 85. The CSI-4 does not make a diagnosis of ADHD. Rather, it screens children. Parent reports screened18% (104/583) of children as positive for ADHD (ADHD-SP), while teachers screened 14% (60/422) as ADHD-SP.

The supplement provides tables and text describing what we found on univariable analyses. Based on these findings we constructed time-oriented risk models that evaluate risk factors in the order they occur or are first identified (Table 1). What we call the first epoch consists of maternal demographic and pregnancy characteristics, while the second epoch consists of perinatal exposures and characteristics first identified at the time of birth, and the third epoch includes exposures and characteristics from the first postnatal month.

The risk factor patterns for ADHD-SP based on parent report and physician diagnosed ADHD have similarities, while the pattern for teacher-identified ADHD-SP is unlike that of either parent or physician. Consequently, the pattern for any two reporters closely approximates that of parent and physician. As expected, the pattern associated with prescribed medication most closely resembles that of physician-identified ADHD.

The risk profile associated with parent-reported ADHD-SP has 9 variables, 3 from the first epoch (*i.e.*, low maternal age at delivery, pre-pregnancy maternal obesity, and smoking during pregnancy), 3 from the second epoch (magnesium for seizure prophylaxis, male sex and singleton) and 3 from the third epoch (receipt of a sedative, ventriculomegaly, and pre-threshold retinopathy of prematurity). The risk profile associated with teacher-reported ADHD-SP has only 3 variables (recovery of *Mycoplasma* sp from the placenta parenchyma, male sex, and low birth weight). The risk profile associated with physician diagnosed ADHD shares 3 variables with the parent-reported ADHD-SP profile (low maternal age and mother's pre-pregnancy obesity, singleton) and has 3 third epoch variables that are not part of the parent-reported or teacher-reported profiles (mechanical ventilation on day 7, antibiotic receipt during weeks 2-4, and "surgical" necrotizing enterocolitis).

Discussion

The major findings of this study are that the risk profiles differ by who identified the ADHD-SP, and that both antenatal and postnatal risk factors are probably important.

The organizations that provide guidance about making a diagnosis of ADHD recommend observation in two settings [10], or gathering information from both a classroom teacher and from parents [11]. In the ELGAN Study cohort, the kappa for parent and teacher agreement about ADHD-SP (regardless of subtype) was 0.23, which indicates only a "fair level" of agreement [12]. This might reflect nothing more than the different settings in which teacher and parent see the child. It is also possible that the teacher completing the report has seen the child only when the child is medicated, whereas the parent and the physician has seen the child when not medicated. Then again, parents and teachers might really differ in the behaviors they consider acceptable. We explored the possibility that each behavioral set has a relatively unique risk profile.

We now review the individual risk factors identified, documenting which of these risk factors have been reported by others, and which are new. Then we offer a synthesis of all our findings.

Socio-economic information

Three of the maternal (antenatal) risk factors for parent-identified ADHD-SP (young age at the time of delivery, pre-pregnancy obesity, pregnancy smoking) convey information about socio-economic status, a well-known correlate of ADHD [13], as well as inflammation [14], and epigenetic phenomena phenomena [15, 16].

Magnesium for seizure

Even though antenatal magnesium exposure can be neuroprotective [17], here receipt of magnesium for seizure prophylaxis is likely a surrogate for preeclampsia and fetal growth restriction, risk factors for ADHD among children born at term [18].

Male

Both parents and teachers identified ADHD-SP more commonly among boys than among girls. Indeed, in one study of children born preterm, fully 84% of the children with ADHD were boys [1]. One group of authors postulated a “female protective effect against attention-deficit/hyperactivity disorder” [19].

Singleton

Among children born at term, however, singletons had higher rates than twins of ADHD symptoms in three studies [20–22], lower rates in one study [23], and no difference in one study [24]. We did not find any other assessment of the relationship between twinning and ADHD among children born very preterm.

Gestational age and birth weight

Attention problems and diagnoses of ADHD are more common in preterm and low birthweight children than in their term-born peers [1, 25–27]. Even among children not selected by gestational age or birthweight, low birthweight has been identified as an ADHD antecedent [28, 29].

Any sedative

Because very preterm newborns in the intensive care nursery are exposed to stressful and painful procedures during neonatal intensive care, they are often given analgesics and sedatives. Both fentanyl [30] and midazolam [31] exposure have been associated with brain imaging abnormalities and poorer outcomes. What remains unclear is the magnitude of the contribution from confounding by indication [32].

For example, recipients of these drugs are more likely than others to have remained on the ventilator for extended periods of time and to have had bowel disease requiring surgery. Both of these exposures were associated in the ELGAN Study with prolonged inflammation [33, 34] and developmental adversities [35, 36].

Ventriculomegaly

To our knowledge, no report other than ours identifies ventriculomegaly as an antecedent of attention problems. We emphasize that our sample for these analyses consists only of

children whose IQ was ≥ 85, thus eliminating intellectual disability or low cognitive abilities (sometimes associated with ventriculomegaly) as the primary reason for these limitations.

Retinopathy of Prematurity (ROP)

Prethreshold ROP had been the intensity of disease that prompted surgical intervention when these data were collected. Since then, "plus disease," defined as abnormal dilation and tortuosity of the blood vessels, is now the primary indication for laser treatment [37]. Consequently, both of these ROP variables probably provide similar risk information.

We are not aware of any report that identified ROP as an antecedent of ADHD. The most plausible explanations for their co-occurrence in any child invoke exposure to a common antecedent, such as relative hyperoxia [38], or a common vulnerability associated with especially low gestational age [39].

Mechanical ventilation on day 7

The mechanical ventilation variable likely conveys information that is similar to the variable for receipt of sedative described above. We are not aware of any report of mechanical ventilation or bronchopulmonary dysplasia (a correlate of mechanical ventilation) as risk factors for ADHD.

Antibiotic treatment during weeks 2-4

The antibiotic variable conveys information about bacteremia, as well as low gestational age [40]. Thus, this variable can convey information not only about inflammation, but also immaturity/vulnerability (above and beyond that conveyed by low gestational age and related variables).

Necrotizing enterocolitis (NEC)

The NEC variable might also carry information about inflammation [34], although it might also convey information about anesthetic-induced developmental neurotoxicity [41, 42]. We are aware of only one report of NEC placing the very preterm newborn at increased of an impairment of selective attention [43].

An echolucent image, the ultrasound image of periventricular leukomalacia

We found only one report of an association between periventricular leukomalacia and an impairment of selective attention in children born extremely preterm [43].

Synthesis

In an effort to synthesize what might appear to be disparate isolated findings, we offer the following four broad themes.

The first, low socioeconomic status and perhaps genetic contributions, too, are conveyed by three maternal characteristics (*i.e.*, young age at the time of delivery, pre-pregnancy obesity, pregnancy smoking) [13].

The second theme is endogenous vulnerability/immaturity [26]. The most obvious of the variables conveying such information are low gestational age and low birthweight. On the other hand, each of the postnatal variables also has the potential to carry this information because each occurs most commonly in the least mature. This applies to receipt of a sedative, ventriculomegaly, ROP, mechanical ventilation on day 7, receipt of an antibiotic, and NEC.

The third major theme is inflammation [44]. Among the variables that are likely to carry information about inflammation are maternal obesity [14], maternal smoking during pregnancy [45, 46], ventriculomegaly [47], ROP [48], mechanical ventilation on day 7 [33], NEC [34], and of course, recovery of *Mycoplasma* sp from the placenta parenchyma, and receipt of an antibiotic.

The fourth major theme is epigenetic phenomena [49]. The variables likely to convey this information include maternal obesity [50], maternal smoking during pregnancy [51], magnesium for seizure prophylaxis (as a surrogate for preeclampsia) [52], and ROP (via its association with fetal growth restriction) [53]. Epigenetic processes have been invoked to explain the relationships between impaired development and social status [54], endogenous immaturity [55], and inflammation [56].

Strengths and limitations

Our study has several strengths. First, it is comprised of a large number of infants. Second, infants were selected according gestational age criteria and not birth weight, thereby minimizing confounding associated with fetal growth restriction 16). Third, all antecedent data were collected years before ascertainment of ADHD-SP. Fourth, attrition was modest.

Our study also has several limitations. First, we were not able to obtain teacher assessments of 252 children. Although these children do not appear to have had neonatal characteristics that differ from children whose teacher provided a report, their absence reduces the power and has the potential to be a source of bias. Second, the CSI-4, which we used to identify children who screened positive for ADHD based on the parent's or teacher's report, has not been adequately compared to other ADHD assessment instruments [57]. Third, our reliance on assessments of behaviors is not in keeping with the claims of others that a neurobiologic perspective should be preferred [58]. Fourth, we did not have any information about family history of ADHD or about alleles of selected genes and so could not assess familial contributions or gene-environment interactions.

Conclusion

The risk profiles of 10-year old children born before the 28th week of gestation identified by parents appear to differ from the risk profile of their peers identified as ADHD by teachers. This raises the possibility that the parents and teachers identified different phenotypes, each with its own risk profile. The multiplicity of risk factors identified can be subsumed as components of four broad themes, low socioeconomic state, immaturity/vulnerability, inflammation, and epigenetic phenomena.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors express their gratitude to the children and their families who participated in this study. They also gratefully acknowledge the contributions of the ELGAN Study Investigators, listed below.

Boston Children's Hospital, Boston MA

Janice Ware, Taryn Coster, Brandi Henson, Rachel Wilson, Kirsten McGhee, Patricia Lee, Aimee Asgarian, Anjali Sadhwani

Tufts Medical Center, Boston MA

Ellen Perrin, Emily Neger, Kathryn Mattern, Jenifer Walkowiak, Susan Barron

University of Massachusetts Medical School, Worcester MA

Jean Frazier, Lauren Venuti, Beth Powers, Ann Foley, Brian Dessureau, Molly Wood, Jill Damon-Minow

Yale University School of Medicine, New Haven, CT

Richard Ehrenkranz, Jennifer Benjamin, Elaine Romano, Kathy Tsatsanis, Katarzyna Chawarska, Sophy Kim, Susan Dieterich, Karen Bearrs

Wake Forest University Baptist Medical Center, Winston-Salem NC

T. Michael O'Shea, Nancy Peters, Patricia Brown, Emily Ansusinha, Ellen Waldrep, Jackie Friedman, Gail Hounshell, Debbie Allred

University Health Systems of Eastern Carolina, Greenville, NC

Stephen C. Engelke, Nancy Darden-Saad, Gary Stainback

North Carolina Children's Hospital, Chapel Hill, NC

Diane Warner, Janice Wereszczak, Janice Bernhardt, Joni McKeeman, Echo Meyer

Helen DeVos Children's Hospital, Grand Rapids, MI

Steve Pastyrnak, Wendy Burdo-Hartman, Julie Rathbun, Sarah Nota, Teri Crumb,

Sparrow Hospital, Lansing, MI

Madeleine Lenski, Deborah Weiland, Megan Lloyd

University of Chicago Medical Center, Chicago, IL

Scott Hunter, Michael Msall, Rugile Ramoskaite, Suzanne Wiggins, Krissy Washington, Ryan Martin, Barbara Prendergast, Megan Scott

William Beaumont Hospital, Royal Oak, MI

Judith Klarr, Beth Kring, Jennifer DeRidder, Kelly Vogt

Funding

This research was supported by the National Institute of Neurological Diseases and Stroke (5U01NS040069-05S1 and 2R01NS040069 - 06A2), the National Institute of Child Health and Human Development (5P30HD018655-34), and the Office of the National Institutes of Health Director (1UG3OD023348-01).

References

1. Sucksdorff M, Lehtonen L, Chudal R, Suominen A, Joelsson P, Gissler M, et al. Preterm Birth and Poor Fetal Growth as Risk Factors of Attention-Deficit/Hyperactivity Disorder. Pediatrics. 2015; 136:e599–608. [PubMed: 26304830]
2. O'Shea TM, Allred EN, Dammann O, Hirtz D, Kuban KC, Paneth N, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. Early Hum Dev. 2009; 85:719–25. [PubMed: 19765918]
3. Joseph RM, O'Shea TM, Allred EN, Heeren T, Hirtz D, Jara H, et al. Neurocognitive and Academic Outcomes at Age 10 Years of Extremely Preterm Newborns. Pediatrics. 2016; 137 pii: e20154343.
4. Sprafkin J, Gadow KD, Salisbury H, Schneider J, Loney J. Further evidence of reliability and validity of the Child Symptom Inventory-4: parent checklist in clinically referred boys. Journal of clinical child and adolescent psychology : the official journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53. 2002; 31:513–24.
5. Heidbreder R. ADHD symptomatology is best conceptualized as a spectrum: a dimensional versus unitary approach to diagnosis. Attention deficit and hyperactivity disorders. 2015; 7:249–69. [PubMed: 25957598]
6. Martel MM, von Eye A, Nigg J. Developmental differences in structure of attention-deficit/hyperactivity disorder (ADHD) between childhood and adulthood. International journal of behavioral development. 2012; 36:279–92. [PubMed: 25635150]
7. Bernfeld J. ADHD and factor analysis: are there really three distinct subtypes of ADHD? Applied neuropsychology Child. 2012; 1:100–4. [PubMed: 23428296]
8. Frazier TW, Demaree HA, Youngstrom EA. Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. Neuropsychology. 2004; 18:543–55. [PubMed: 15291732]
9. Frazier JA, Wood ME, Ware J, Joseph RM, Kuban KC, O'Shea M, et al. Antecedents of the child behavior checklist-dysregulation profile in children born extremely preterm. J Am Acad Child Adolesc Psychiatry. 2015; 54:816–23. [PubMed: 26407491]
10. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th. DSM-5; 2013.
11. American Academy of Pediatrics. Clinical Practice Guideline. Diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. Pediatrics. 2000; 105:1158–70. [PubMed: 10836893]
12. Leviton A, Hunter SJ, Scott MN, Hooper SR, Joseph RM, O'Shea TM, et al. Observer variability identifying attention deficit hyperactivity disorder in 10-year old children born extremely preterm. Acta Paediatr. 2017
13. Russell G, Ford T, Rosenberg R, Kelly S. The association of attention deficit hyperactivity disorder with socioeconomic disadvantage: alternative explanations and evidence. Journal of child psychology and psychiatry, and allied disciplines. 2014; 55:436–45.
14. van der Burg JW, Allred EN, McElrath TF, Fichorova RN, Kuban K, O'Shea TM, et al. Is maternal obesity associated with sustained inflammation in extremely low gestational age newborns? Early Hum Dev. 2013; 89:949–55. [PubMed: 24090868]
15. Knopik VS, Maccani MA, Francazio S, McGeary JE. The epigenetics of maternal cigarette smoking during pregnancy and effects on child development. Development and psychopathology. 2012; 24:1377–90. [PubMed: 23062304]
16. Neri C, Edlow AG. Effects of Maternal Obesity on Fetal Programming: Molecular Approaches. Cold Spring Harbor perspectives in medicine. 2016; 6:a026591.
17. Zeng X, Xue Y, Tian Q, Sun R, An R. Effects and Safety of Magnesium Sulfate on Neuroprotection: A Meta-analysis Based on PRISMA Guidelines. Medicine. 2016; 95:e2451. [PubMed: 26735551]
18. Silva D, Colvin L, Hagemann E, Bower C. Environmental risk factors by gender associated with attention-deficit/hyperactivity disorder. Pediatrics. 2014; 133:e14–22. [PubMed: 24298003]
19. Taylor MJ, Lichtenstein P, Larsson H, Anckarsater H, Greven CU, Ronald A. Is There a Female Protective Effect Against Attention-Deficit/Hyperactivity Disorder? Evidence From Two

Representative Twin Samples. J Am Acad Child Adolesc Psychiatry. 2016; 55:504–12 e2. [PubMed: 27238069]

20. Ehringer MA, Rhee SH, Young S, Corley R, Hewitt JK. Genetic and environmental contributions to common psychopathologies of childhood and adolescence: a study of twins and their siblings. Journal of abnormal child psychology. 2006; 34:1–17. [PubMed: 16465480]
21. Moilanen I, Linna SL, Ebeling H, Kumpulainen K, Tamminen T, Piha J, et al. Are twins' behavioural/emotional problems different from singletons'? European child & adolescent psychiatry. 1999; 8(Suppl 4):62–7. [PubMed: 10654135]
22. van den Oord EJ, Koot HM, Boomsma DI, Verhulst FC, Orlebeke JF. A twin-singleton comparison of problem behaviour in 2-3-year-olds. Journal of child psychology and psychiatry, and allied disciplines. 1995; 36:449–58.
23. Levy F, Hay D, McLaughlin M, Wood C, Waldman I. Twin sibling differences in parental reports of ADHD, speech, reading and behaviour problems. Journal of child psychology and psychiatry, and allied disciplines. 1996; 37:569–78.
24. Robbers SC, van Oort FV, Polderman TJ, Bartels M, Boomsma DI, Verhulst FC, et al. Trajectories of CBCL attention problems in childhood. European child & adolescent psychiatry. 2011; 20:419–27. [PubMed: 21713506]
25. Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics. 2009; 124:717–28. [PubMed: 19651588]
26. O'Shea TM, Downey LC, Kuban KK. Extreme prematurity and attention deficit: epidemiology and prevention. Frontiers in human neuroscience. 2013; 7:578. [PubMed: 24065904]
27. Halmoy A, Klungsoyr K, Skjaerven R, Haavik J. Pre- and perinatal risk factors in adults with attention-deficit/hyperactivity disorder. Biological psychiatry. 2012; 71:474–81. [PubMed: 22200325]
28. Mick E, Biederman J, Prince J, Fischer MJ, Faraone SV. Impact of low birth weight on attention-deficit hyperactivity disorder. J Dev Behav Pediatr. 2002; 23:16–22. [PubMed: 11889347]
29. Galera C, Cote SM, Bouvard MP, Pingault JB, Melchior M, Michel G, et al. Early risk factors for hyperactivity-impulsivity and inattention trajectories from age 17 months to 8 years. Archives of general psychiatry. 2011; 68:1267–75. [PubMed: 22147844]
30. McPherson C, Haslam M, Pineda R, Rogers C, Neil JJ, Inder TE. Brain Injury and Development in Preterm Infants Exposed to Fentanyl. The Annals of pharmacotherapy. 2015; 49:1291–7. [PubMed: 26369570]
31. Duerden EG, Guo T, Dodbiba L, Chakravarty MM, Chau V, Poskitt KJ, et al. Midazolam dose correlates with abnormal hippocampal growth and neurodevelopmental outcome in preterm infants. Ann Neurol. 2016; 79:548–59. [PubMed: 26754148]
32. Sjoding MW, Luo K, Miller MA, Iwashyna TJ. When do confounding by indication and inadequate risk adjustment bias critical care studies? A simulation study. Crit Care. 2015; 19:195. [PubMed: 25925165]
33. Bose CL, Laughon MM, Allred EN, O'Shea TM, Van Marter LJ, Ehrenkranz RA, et al. Systemic inflammation associated with mechanical ventilation among extremely preterm infants. Cytokine. 2013; 61:315–22. [PubMed: 23148992]
34. Martin CR, Bellomy M, Allred EN, Fichorova RN, Leviton A. Systemic inflammation associated with severe intestinal injury in extremely low gestational age newborns. Fetal Pediatr Pathol. 2013; 32:222–34. [PubMed: 23002960]
35. Laughon M, O'Shea MT, Allred EN, Bose C, Kuban K, Van Marter LJ, et al. Chronic lung disease and developmental delay at 2 years of age in children born before 28 weeks' gestation. Pediatrics. 2009; 124:637–48. [PubMed: 19620203]
36. Martin CR, Dammann O, Allred EN, Patel S, O'Shea TM, Kuban KC, et al. Neurodevelopment of extremely preterm infants who had necrotizing enterocolitis with or without late bacteremia. J Pediatr. 2010; 157:751–6.e1. [PubMed: 20598317]
37. Davitt BV, Wallace DK. Plus disease. Survey of ophthalmology. 2009; 54:663–70. [PubMed: 19665743]

38. Reich B, Hoeber D, Bendix I, Felderhoff-Mueser U. Hyperoxia and the Immature Brain. Dev Neurosci. 2016; 38:311–30. [PubMed: 28152539]
39. Hadi AM, Hamdy IS. Correlation between risk factors during the neonatal period and appearance of retinopathy of prematurity in preterm infants in neonatal intensive care units in Alexandria, Egypt. Clin Ophthalmol. 2013; 7:831–7. [PubMed: 23674885]
40. Leviton A, O'Shea TM, Bednarek FJ, Allred EN, Fichorova RN, Dammann O. Systemic responses of preterm newborns with presumed or documented bacteraemia. Acta Paediatr. 2012; 101:355–9. [PubMed: 22085230]
41. Mann GE, Kahana M. The uncomfortable reality … We simply do not know if general anesthesia negatively impacts the neurocognitive development of our small children. International journal of pediatric otorhinolaryngology. 2015; 79:1379–81. [PubMed: 26143125]
42. Sinner B, Becke K, Engelhard K. General anaesthetics and the developing brain: an overview. Anaesthesia. 2014; 69:1009–22. [PubMed: 24829066]
43. Anderson PJ, De Luca CR, Hutchinson E, Spencer-Smith MM, Roberts G, Doyle LW. Attention problems in a representative sample of extremely preterm/extremely low birth weight children. Developmental neuropsychology. 2011; 36:57–73. [PubMed: 21253991]
44. Allred EN, Dammann O, Fichorova RN, Hooper SR, Hunter SJ, Joseph RM, et al. Systemic Inflammation during the First Postnatal Month and the Risk of Attention Deficit Hyperactivity Disorder Characteristics among 10 year-old Children Born Extremely Preterm. Journal of neuroimmune pharmacology: the official journal of the Society on NeuroImmune Pharmacology. 2017
45. Goncalves RB, Coletta RD, Silverio KG, Benevides L, Casati MZ, da Silva JS, et al. Impact of smoking on inflammation: overview of molecular mechanisms. Inflamm Res. 2011; 60:409–24. [PubMed: 21298317]
46. Lee J, Taneja V, Vassallo R. Cigarette smoking and inflammation: cellular and molecular mechanisms. J Dent Res. 2012; 91:142–9. [PubMed: 21876032]
47. Leviton A, Allred EN, Fichorova RN, Kuban KC, Michael O'Shea T, Dammann O. Systemic inflammation on postnatal days 21 and 28 and indicators of brain dysfunction 2years later among children born before the 28th week of gestation. Early Hum Dev. 2016; 93:25–32. [PubMed: 26735345]
48. Lee J, Dammann O. Perinatal infection, inflammation, and retinopathy of prematurity. Semin Fetal Neonatal Med. 2012; 17:26–9. [PubMed: 21903492]
49. Walton E, Pingault JB, Cecil CA, Gaunt TR, Relton CL, Mill J, et al. Epigenetic profiling of ADHD symptoms trajectories: a prospective, methylome-wide study. Molecular psychiatry. 2016
50. Cordero P, Li J, Oben JA. Epigenetics of obesity: beyond the genome sequence. Current opinion in clinical nutrition and metabolic care. 2015; 18:361–6. [PubMed: 26049633]
51. Pagani LS. Environmental tobacco smoke exposure and brain development: the case of attention deficit/hyperactivity disorder. Neurosci Biobehav Rev. 2014; 44:195–205. [PubMed: 23545330]
52. van Dijk M, Oudejans CB. STOX1: Key player in trophoblast dysfunction underlying early onset preeclampsia with growth retardation. Journal of pregnancy. 2011; 2011:521826. [PubMed: 21490791]
53. Lee JW, VanderVeen D, Allred EN, Leviton A, Dammann O. Pre-threshold retinopathy in premature infants with intra-uterine growth restriction. Acta Paediatr. 2015; 104:27–31. [PubMed: 25196981]
54. Naumova OY, Hein S, Suderman M, Barbot B, Lee M, Raefski A, et al. Epigenetic Patterns Modulate the Connection Between Developmental Dynamics of Parenting and Offspring Psychosocial Adjustment. Child development. 2016; 87:98–110. [PubMed: 26822446]
55. Cruickshank MN, Oshlack A, Theda C, Davis PG, Martino D, Sheehan P, et al. Analysis of epigenetic changes in survivors of preterm birth reveals the effect of gestational age and evidence for a long term legacy. Genome medicine. 2013; 5:96. [PubMed: 24134860]
56. Claycombe KJ, Brissette CA, Ghribi O. Epigenetics of inflammation, maternal infection, and nutrition. J Nutr. 2015; 145:1109S–15S. [PubMed: 25833887]

57. Collett BR, Ohan JL, Myers KM. Ten-year review of rating scales. V: scales assessing attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2003; 42:1015–37. [PubMed: 12960702]

58. Carmichael JA, Kubas HA, Carlson HL, Fitzer KR, Wilcox G, Lemay JF, et al. Reconsidering “inattention” in attention-deficit hyperactivity disorder: implications for neuropsychological assessment and intervention. Applied neuropsychology Child. 2015; 4:97–105. [PubMed: 25748971]

Table

Time-oriented risk models of any ADHD according to the reporter. These are odds ratios and 95% confidence intervals comparing children identified by parents, teachers, physicians, any two of these reporters, and by receipt of medication for ADHD to children not identified as having any ADHD according to any of these criteria. In time-oriented risk models, risk factors are organized in temporally ordered epochs. Predictors/covariates of the outcome (*e.g.*, report of ADHD) in the earliest epoch are entered first and are NOT displaced by covariates in later epochs. Each epoch here is based on including the variables from the previous epochs. The final models with all variables included at one time are in Supplement Table K.

		Parent	Teacher	Physician	Any 2	ADHD Rx
Epoch 1						
Maternal age	< 21	**2.3 (1.1, 4.7)**		**2.3 (1.3, 4.3)**	**2.7 (1.4, 5.3)**	**3.3 (1.8, 6.2)**
Mother's BMI	≥ 30	**2.4 (1.4, 4.3)**		**1.7 (1.1, 2.8)**	**2.8 (1.6, 4.8)**	**1.7 (1.00, 3.0)**
Smoked during preg	Yes	**2.2 (1.1, 3.3)**		**2.0 (1.2, 3.5)**	**2.1 (1.1, 3.9)**	
Mycoplasma	Yes		**2.5 (1.1, 5.9)**		**2.2 (1.01, 4.7)**	
Epoch 2						
Magnesium for sz	prophylaxis	**1.7 (1.1, 2.5)**			**1.5 (1.02, 2.2)**	
Sex	Male	**1.9 (1.2, 3.2)**	**3.3 (1.8, 6.1)**	**1.6 (1.05, 2.5)**	**2.0 (1.2, 3.3)**	**1.8 (1.1, 2.9)**
Singleton	Yes	**2.5 (1.4, 4.6)**		**1.8 (1.1, 3.1)**	**2.6 (1.3, 5.0)**	
Gestational age, wks	23–24	**2.1 (1.2, 3.6)**			**2.2 (1.2, 4.0)**	**1.8 (1.03, 3.2)**
Birthweight, grams	≤ 750		**2.4 (1.3, 4.4)**	**2.1 (1.3, 3.3)**		
Epoch 3						
Any sedative d 1–28	Yes	**3.0 (1.8, 5.1)**			**1.9 (1.1, 3.4)**	
Ventriculomegaly **	Yes	**3.2 (1.5, 6.7)**			**2.7 (1.2, 6.0)**	
ROP: pre-threshold‡‡	Yes	**2.0 (1.02, 4.0)**				
Mech ventilation Day 7	Yes			**2.1 (1.2, 3.6)**		**2.3 (1.3, 4.3)**
Antibiotic, week 2–4	Yes			**3.5 (1.6, 7.6)**	**3.6 (1.3, 9.5)**	**2.9 (1.2, 6.6)**
NEC	IIIb			**3.3 (1.1, 9.6)**		
Echolucent lesion **	Yes				**3.5 (1.1, 11)**	
ROP: plus disease	Yes				**2.6 (1.2, 5.7)**	
Epoch 4						
M-CHAT positive†	Yes					**2.2 (1.1, 4.4)**

	Parent	Teacher	Physician	Any 2	ADHD Rx
Model N	547	422	560	546	560

** Alone or with other ultrasound scan abnormalities

Satisfied ET-ROP criteria for ablative surgery (pre-threshold disease)

† Among those with GMFCS < 1 and no vision or hearing abnormality