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Early postnatal Illness severity scores predict neurodevelopmental impairments at 10 years of age in children born extremely preterm

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Abstract

Introduction—A neonatal illness severity score, The Score for Neonatal Acute Physiology-II (SNAP-II), predicts neurodevelopmental impairments at two years of age among children born extremely preterm. We sought to evaluate to what extent SNAP-II is predictive of cognitive and other neurodevelopmental impairments at 10 years of age.

Methods—In a cohort of 874 children born before 28 weeks of gestation, we prospectively collected clinical, physiologic and laboratory data to calculate SNAP-II for each infant. When the children were 10 years old, examiners who were unaware of the child's medical history assessed neurodevelopmental outcomes, including neurocognitive, gross motor, social, and communication functions, diagnosis and treatment of seizures or attention deficit hyperactivity disorder (ADHD),

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academic achievement, and quality of life. We used logistic regression to adjust for potential confounders.

Results—An undesirably high SNAP-II (≥ 30), present in 23% of participants, was associated with an increased risk of cognitive impairment (IQ, executive function, language ability), adverse neurological outcomes (epilepsy, impaired gross motor function), behavioral abnormalities (attention deficit disorder and hyperactivity), social dysfunction (autistic spectrum disorder) and education-related adversities (school achievement and need for educational supports.

In analyses that adjusted for potential confounders, Z-scores ≤ -1 on 11 of 18 cognitive outcomes were associated with SNAP-II in the highest category and 6 of 18 were associated with SNAP-II in the intermediate category. Odds ratios and 95% confidence intervals ranged from 1.4 (1.01, 2.1) to 2.1 (1.4, 3.1). Similarly, 2 of the 8 social dysfunctions were associated with SNAP-II in the highest category, and 3 of 8 were associated with SNAP-II in the intermediate category. Odds ratios and 95% confidence intervals were slightly higher for these assessments, ranging from 1.6 (1.1, 2.4) to 2.3 (1.2, 4.6).

Conclusion—Among very preterm newborns, physiologic derangements present in the first 12 postnatal hours are associated with dysfunctions in several neurodevelopmental domains at 10 years of age. We are unable to make inferences about causality.

Keywords

neurocognitive function; illness-severity scores; physiologic instability; SNAP-II; functional development; brain injury

Introduction

The Score for Neonatal Acute Physiology (SNAP),(1) and a revised version, the SNAP-II,(2) are physiology-based indicators of endogenous mortality risk based on routinely available vital signs and laboratory tests obtained during the first 12 postnatal hours, when clinical/physiologic derangements are less likely to be influenced by medical interventions than derangements that occur later in the hospital course. SNAP-II not only predicts death among very preterm newborns, but also neonatal intraventricular hemorrhage,(3-5) respiratory dysfunction, (3-5) and retinopathy of prematurity.(5-7)

In the ELGAN Study of infants born before 28 weeks gestation, high SNAP-II predicted death, ultrasound-defined morphologic abnormalities of the brain, and low developmental scores at age 2 years.(8, 9) However, neurodevelopmental assessments at age 2 years have limited ability to predict later function, (10-12) and functional abilities at age 10 are qualitatively different and more complex than what can be assessed at age 2 years.(13, 14) Thus, we sought to extend our previous work by examining neurodevelopmental function at age 10 as an outcome associated with high SNAP-II.

The relationship between early indicators of physiologic instability and neurodevelopmental outcomes at school age is not yet known. In this report, we examine the relationship between SNAP-II and dysfunctions at 10 years in a cohort of children born extremely preterm at 14 medical centers in the United States.

Materials and Methods

Participants

The ELGAN study is a multi-center prospective, observational study of the risk of structural and functional neurologic disorders in extremely preterm infants.(15) A total of 1506 infants born before the 28th week of gestation were enrolled during the years 2002-2004 and 1200 survived to 2 years. At age 10 years, 966 of these infants were recruited for an assessment of cognition, executive function, behaviors, and academic achievement. Of these 966 children, 889 (92%) returned for follow up and 874 underwent neurocognitive testing. Enrollment and consent procedures for this follow up study were approved by the institutional review boards of each participating institution. Demographic, pregnancy and newborn variables were examined using a standardized protocol that has been reported by others.(15)

Revised Scores for Neonatal Acute Physiology (SNAP-II)

We collected all physiologic, laboratory and therapy data for the first 12 postnatal hours needed to calculate a SNAP-II.(2) We also identified cut-offs for each week of post-menstrual age at birth that defined the top quartile, top decile, and three categories (<20, 20-29, and ≥30) of SNAP-II.

10 year follow up visit

Families willing to participate were scheduled for one visit during which all of the assessments reported here were administered in 3 to 4 hours, including breaks. The assessments were selected to provide the most comprehensive information about neurocognitive and academic function in one testing session. A summary of the neurocognitive assessments used in this study is included as a supplemental table (Supplemental Tables 1a and 1b).

Examiners who were unaware of the child's medical history assessed neurodevelopment in several clinically important domains. While the child was tested, the parent or caregiver completed questionnaires regarding the child's educational, medical, neurological and behavioral status. Questionnaires were also provided to the child's school teacher to obtain teacher-reported behavioral status, as described below.

Neurocognitive and related outcomes

General cognitive ability was assessed with the School-Age Differential Ability Scales–II (DAS-II) Verbal and Nonverbal Reasoning scales.(16) Expressive and receptive language skills were evaluated with the Oral and Written Language Scales (OWLS. (17) Attention and executive function were assessed with both the DAS-II and NEPSY-II (A Developmental NEuroPSYchological Assessment-II).(18, 19) Speed of processing was assessed with NEPSY-II Inhibition Naming. Visual perception was assessed with NEPSY-II Arrows and Geometric Puzzles, while visual motor function was measured with NEPSY-II Visuomotor Precision and Fingertip Tapping. Academic function was assessed with the Wechsler Individual Achievement Test-III (WIAT-III [C]) which provides standard scores in word recognition and decoding, spelling, and numeric operations.(20) Educational outcomes

included receipt of an individual educational plan (IEP), repeating a grade in school, and placement in a remedial class.

Neurological outcomes

Neurological outcomes included the diagnosis of “any” seizures or epilepsy, receipt of anti-epileptic drugs at the time of the assessment, and gross motor function.

Seizure identification was a two stage process. If parents answered “yes” to any of 11 broad questions for possible seizures, they were prompted by the study epileptologist to conduct a structured interview followed by an open-ended interview, both by telephone. The epileptologist then determined whether a reported event was a seizure. A second epileptologist independently reviewed interview responses and similarly rated the event type. When the two physicians' disagreed on the presence of seizures, which occurred in only 3% of the children interviewed, a third epileptologist reviewed the interview responses and made the final determination regarding seizure status.

Gross Motor Function was assessed using the Gross Motor Function Classification System (GMFCS).(21) Children with a GMCFS ≥3 (unable to walk without an assistive mobility device) were considered to have a significant gross motor abnormality.

Social Responsiveness

We used the Social Responsiveness Scale-2 (SRS-2) to identify social impairment and to quantify its severity.(22) This 65-item instrument provides a total score reflecting severity of social deficits in the autism spectrum, as well as five subscale scores for: social awareness, social cognition, social communication, social motivation, and restricted interests and repetitive behavior.

All children were screened by parent report for Autistic Spectrum Disorder (ASD) with the Social Communication Questionnaire (SCQ).(23) Children who screened positive on the SCQ were assessed with the Autism Diagnostic Interview – Revised (ADI-R), and an in-depth parent interview.(24) Children meeting ADI-R modified criteria for ASD were administered the Autism Diagnostic Observation Schedule-2 (ADOS-2). (25, 26) Finally, all children meeting standardized research criteria for ASD on both the ADI-R and ADOS-2 were classified as having ASD.

Behavioral outcomes

Behavioral outcomes were assessed in two ways, by physician diagnosis or treatment for ADHD, and by parental and teacher report of the behavioral status items included in the Child Symptom Inventory-4 (CSI-4).(27, 28) Teachers and parents did not make any DSM-IV diagnosis. Rather, the CSI-4 functioned as a screening tool for determining a behavioral pattern, based on selected behavioral characteristics.

We operationalized the definition of ADHD, using a convention supported by others, to include any 2 of the following 3 ADHD designations: (1) parent report, (2) teacher report, and (3) physician diagnosis. Parent and teacher reports of a designation of ADHD are

reported in Table A. This definition confers a level of agreement sufficient to provide confidence in the child's designation as having ADHD.

Parent-reported Quality of Life

Although health-related quality of life is a complex and sometimes subjective domain, it also conveys information about the biologic impact of exposures on outcomes most important to families. For this reason, we examined five quality of life indicators found in the Pediatric Quality of Life Inventory™ (PedsQL™), including functional assessments of physical, emotional, social, school, and psychological functioning.(29, 30)

Data Analyses

We evaluated the null hypothesis that each measure of neurodevelopmental function at age 10 years was not differentially distributed among children in three SNAP-II categories (< 20, 20-29, and ≥ 30). In the ELGAN cohort, a SNAP-II ≥ 30 correlates roughly with the upper quartile.(8)

To allow for differences in age at the time of the assessment, and to facilitate a comparison to children born at term, we calculated Z-scores using the distributions of values reported in historical normative controls, as described by the authors of the assessments we used.(16, 17, 19, 20)

For assessments of neurocognitive and social function, we created logistic regression models of the risk of a score 1 or more standard deviations below the normative mean for each assessment (*i.e.*, Z-score ≤ -1). These models, which included potential confounders (maternal education, mother's eligibility for government-provided medical insurance, delivery for preeclampsia or fetal indication, gestational age, and birth weight Z-score), allowed us to calculate odds ratios (and 95% confidence intervals) indicating the strength of association between the SNAP-II category and each outcome.

For assessments of educational and neurologic function, behavior, and quality of life, we used a χ^2 trend analysis to test the strength of the relationship between SNAP-II and parent and teacher-reported behavioral abnormalities. Similarly, a χ^2 trend analysis was used for assessments included in the CSI-4.

Results

Sample characteristics (Table 1)

Of the 874 infants in this sample, 53% (N=460) had a SNAP-II below 20, 25% (N=215) had a SNAP-II between 20 and 29, and the remaining 23% (N=199) had a SNAP-II ≥ 30.

The maternal demographic characteristics associated with a SNAP-II ≥ 30 were younger age at delivery, not having a college education, not being married, and eligibility for government-provided (public) medical insurance. Maternal fever during the delivery admission, lower gestational age at birth and lower birth weight were all associated with a SNAP-II >30; fetal growth restriction, however, was not.

Neurocognitive and related outcomes (Supplemental Table 2 and Figures 1 and 2)

Roughly one quarter of all children who had a SNAP-II ≥ 30 had a score 2 or more standard deviations below the normative mean on the DAS-II Verbal, OWLS Listening Comprehension, and OWLS Oral Expression, and WIAT-III Numeric operations assessments. The strength of the association between SNAP-II and both verbal IQ and OWLS, both of which are measures of language function, is strong. Almost one-third of all children with a SNAP-II ≥ 30 had measures of executive function (NEPSY-II) 2 or more standard deviations below the normative mean. In general, the higher the SNAP-II category, the lower the neurocognitive score.

The box and whisker plots (Figure 1) display the distribution of scores on each assessment separately, for each SNAP-II group. The central line in the box indicates the median (50^{th} centile), while the top of the box indicates the 75^{th} centile and the bottom of the box indicates the 25^{th} centile. Children with higher SNAP-IIs had consistently lower scores on the DAS-II, OWLS, WIAT–III and NEPSY-II.

Odds ratios and 95% confidence intervals of a Z-score ≤ 1 displayed in forest plots (Figure 2, top panel) indicate that children with a high SNAP-II were at significantly increased risk of scores one or more standard deviation below the normative mean on almost every cognitive test. In analyses that adjusted for potential confounders, Z-scores ≤ -1 on 11 of 18 cognitive outcomes were associated with SNAP-II in the highest category, and Z-scores ≤ -1 on 6 of 18 were associated with SNAP-II in the intermediate category. Odds ratio's and 95% confidence intervals ranged from 1.4 (1.01, 2.1) to 2.1 (1.4, 3.1) (Figure 2, bottom panel).

Social outcomes (Supplemental Table 3 and Figure 3)

Infants with an undesirable SNAP-II (≥ 20) had modestly increased total and component scores on the SRS, with higher scores reflecting increased social impairment. Fully 10% of boys in both the middle and high SNAP-II groups were considered to have ASD based on a positive Autism Diagnostic Observation Schedule - 2 (ADOS - 2) assessment compared to 4% in the lowest SNAP-II group.

Infants in the middle and high SNAP-II groups were at significantly increased risk on the social motivation subscale of the SRS and a “positive” Social Communication Questionnaire (SCQ), which screens for ASD. In analyses that adjusted for potential confounders, 2 of the 8 social outcomes were associated with SNAP-II in the highest category, and 3 of 8 social outcomes were associated with SNAP-II in the intermediate category. Odds ratio's and 95% confidence intervals ranged from 1.6 (1.1, 2.4) to 2.3 (1.2, 4.6) (Figure 3, bottom panel).

Educational, neurologic, behavioral and quality of life outcomes (Table 2)

Whereas approximately 40% of children with a SNAP-II in the lowest SNAP-II category required an individual education plan (IEP), 70% had an IEP if their SNAP-II was ≥ 30, and twice as many children with a SNAP-II ≥ 30 required remedial education, compared to those in the lowest SNAP-II category (Table 2). A high SNAP-II was significantly associated with receipt of an IEP ($p < 0.001$) and placement in a remedial class ($p < 0.001$).

The rate of epilepsy increased significantly with increasing SNAP-II category (p = 0.03) as did the use of seizure medication (p = 0.03) at the time of the assessment.

A high SNAP-II was also associated with a GMFCS ≥3. Almost three times as many infants (8%) with a SNAP-II ≥ 30 and twice as many (6%) with a SNAP-II 20-29 had a GMFCS ≥ 3, compared to those with a score < 20 (3%) (p= 0.007).

By and large, children with high SNAP-IIs had lower quality of life scores on the PedsQL™ inventory. A high SNAP-II was associated with adverse outcomes in 4 out of 5 domains, including physical, social, school, and psychosocial functioning (all p < 0.001).

Because parent and teacher-reported outcomes are less reliable than standardized neurocognitive testing, we did not include adjustments for potential confounders in these analyses. Nonetheless, we view these outcomes as meaningful clinical markers of the derangements we found in neurocognitive testing (Figures 2 and 3).

Behavioral outcomes (Supplemental Table 4)

The association between the diagnosis of ADHD and high SNAP-II appears to be stronger than that of treatment for ADHD and a high SNAP-II. The diagnosis of ADHD was more common among children with higher SNAP-IIs than among children who had lower SNAP-IIs, both by parent report (p=0.03) and teacher report (p=0.003). Associations with other CSI-4-identified behaviors presented in Supplemental Table 4, are viewed largely as exploratory.

Discussion

In this sample of 10-year-old children born before the 28th week of gestation, those who had a SNAP-II ≥ 30 were at increased risk of neurocognitive, behavioral, and social dysfunctions. Children who had a high SNAP-II were also more likely than those with a low SNAP-II to have an IEP, to repeat a grade, to be placed in a remedial class, to be diagnosed or treated for ADHD, ASD, or epilepsy, to need an assistive device to ambulate, and to have diminished quality of life.

The characteristic most strongly associated with a high SNAP-II is gestational age, but within each gestational age group those with a SNAP-II ≥ 30 were at even greater risk of these dysfunctions than those with normal physiologic status.(31) Thus, high SNAPs convey risk information that supplements the risk information conveyed by low gestational age.

Most surprising, however, was the multitude of dysfunctions we found at 10 years among children with early physiologic derangements, even after adjusting for potential confounders. Arguing from Occam's razor, we seek a cohesive explanation for these observations. What characteristic or exposure that differentiates extremely preterm from term infants also differentiates those extremely preterm infants with a high SNAP-II from those with a lower SNAP-II?

Possible explanations for our findings

We offer four explanations for the link between SNAP scores and brain injury in children born extremely preterm. Immaturity may contribute to physiologic instability, increase the risk for neonatal complications, or result in a paucity of endogenous neuroprotectors normally provided by placenta, all of which may be associated with brain injury. In addition, prenatal infection and/or inflammation associated with preterm birth may contribute to brain injury as well.

First, physiologic instability may be in the causal chain between immaturity (and its correlates) and brain injury. Accordingly, SNAP-II could be viewed as a marker or indicator for such risk. While both hypoxemia and hypotension, examples of physiologic instability, have been invoked to account for brain damage in very preterm newborns,(32-39) sufficient support for these claims has yet to be provided.(40-44) Further, despite efforts to improve physiologic stability,(41, 45-52) the rate of neurodevelopmental derangements among extremely preterm infants remains high in numerous studies.(43, 44, 53-57)

Second, high SNAP-II scores are associated with postnatal events such as bacteremia/sepsis, necrotizing enterocolitis, and chronic lung disease,(4, 58) which are associated with adverse brain-related outcomes.(59-62) In this way, SNAP-II could be viewed as a marker for subsequent neonatal adversities. Because these intervening disorders might be in the causal path between high SNAP-II and 10-year outcomes, they are not confounders. Therefore, we did not adjust for them in any of our analyses.

Third, elevated SNAP-II scores may convey information about immaturity/vulnerability, such as that attributable to a paucity of placenta-provided endogenous protectors (63), which are known to have beneficial neurotrophic effects on development. Consider that all babies of the same gestational age are not equally mature or vulnerable. From this perspective, SNAP-II provides additional information about physiologic maturation, serving as a marker for processes that are developmentally regulated, including the ability to synthesize growth factors and other proteins capable of protecting the brain.(63) SNAP-II has been correlated with corticospinal tract development, independent of both gestational age and postnatal risk factors, lending support to the theory argument that SNAP-II provides information about neurotrophic effects on brain maturation.(64)

Finally, systemic inflammation, which may be developmentally-regulated, puts the newborn brain at increased risk of multiple disturbances.(65-68) Although systemic inflammation differentiates very preterm from term newborns,(69) early physiologic derangements and first day of life elevations of circulatory inflammation-related proteins, in general, were not associated with systemic inflammation in the ELGAN Study.(70) The rate of maternal fever, which is associated with both chorioamnionitis and early-onset sepsis,(71, 72) however, was increased among those with a SNAP-II ≥ 30. Nonetheless, while preterm infants exposed to chorioamnionitis tend to have higher SNAP-IIs than children not so exposed,(73) the evidence that chorioamnionitis contributes to brain damage in very preterm newborn is mixed.(74-77).

Strengths and limitations

Our study has several strengths. First, we included a large number of infants, making it unlikely that we have missed important associations due to lack of statistical power, or that we claimed associations that might reflect the instability of small numbers. Second, we selected infants based on gestational age, not birth weight, in order to minimize confounding due to factors related to fetal growth restriction.(78) Third, we collected all of our data prospectively. Fourth, attrition at neurocognitive assessment was only modest. The weaknesses of our study are those of all observational studies. We are unable to distinguish between causation and association as explanation for what we found.

Conclusion

SNAP-II provides information that supplements the risk information conveyed by gestational age, and conveys important information about infants' vulnerability to neurodevelopmental adversities 10 years later. We view the multiplicity of neurodevelopmental dysfunctions associated with a high SNAP-II as support for SNAP-II as a marker for immaturity/vulnerability. Support for or against this view could come from studies that evaluate the relationship between SNAP-II and developmentally-regulated biomarkers.

Because no other group has evaluated the relationship between SNAP during the first 12 postnatal hours in very preterm newborns and their function 10 years later, we view our assessments as exploratory. We offer 95% confidence intervals of odds ratios to illustrate the range of values that might be expected when attempts are made to replicate our findings, or test associations between SNAPs and later function in somewhat different ways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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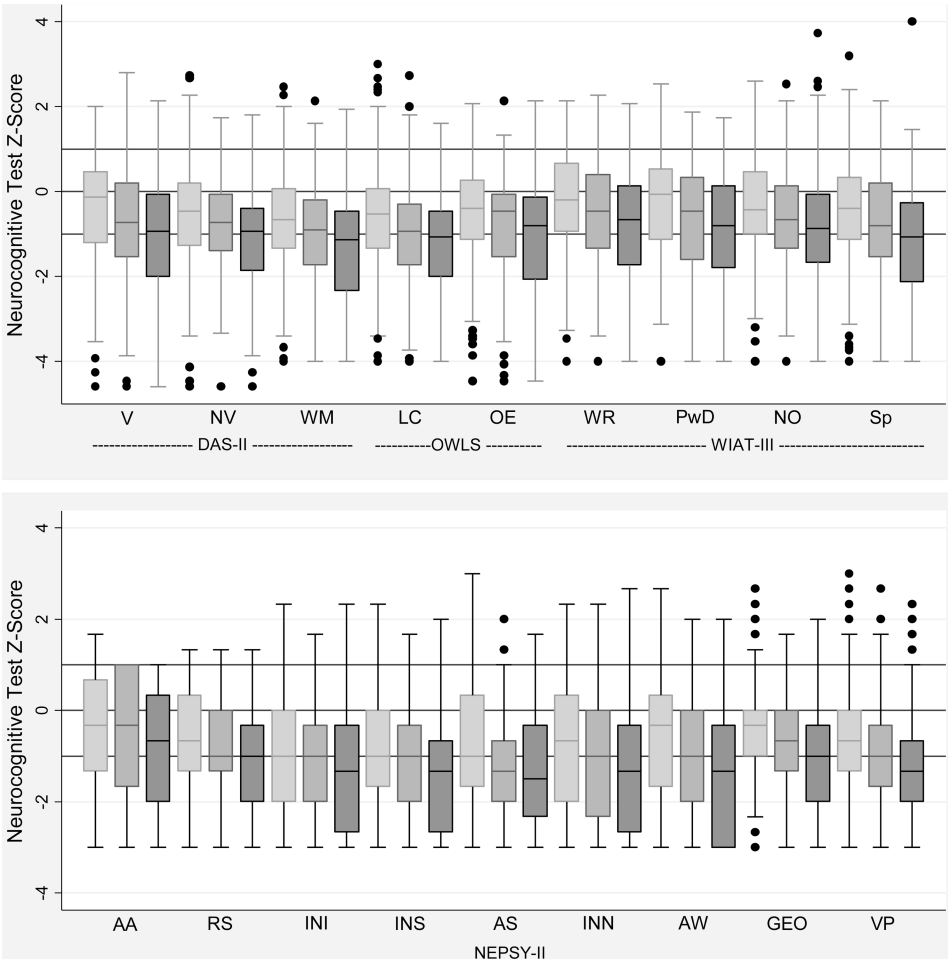

Figure 1.

[1]. Box-and-whisker plots of each neurocognitive subtest by SNAP-II. All subtest Z-scores are adjusted to population norms. Key: light gray is < 25, medium gray is ≥ 25, < 30, dark gray is ≥ 30. The central line in the box indicates the median (50th centile), while the top of the box indicates the 75th centile and the bottom of the box indicates the 25th centile. V=Verbal, NV=Nonverbal reasoning, WM=Working memory, LC=Listening comprehension, OE=Oral expression, WR=Word reading, PwD=Pseudoword decoding, NO=Numerical operations, Sp=Spelling, AA=Auditory attention, RS= Auditory response set, INI= Inhibition inhibition, INS= Inhibition switching, AS= Animal sorting, INN= Inhibition naming, AW=Arrows, GEO=Geometric puzzles, VP=Visuomotor precision.

[1]Odds ratios whose lower bound is to the right of the 1.0 vertical line are statistically significant at the $p < 0.05$ level.

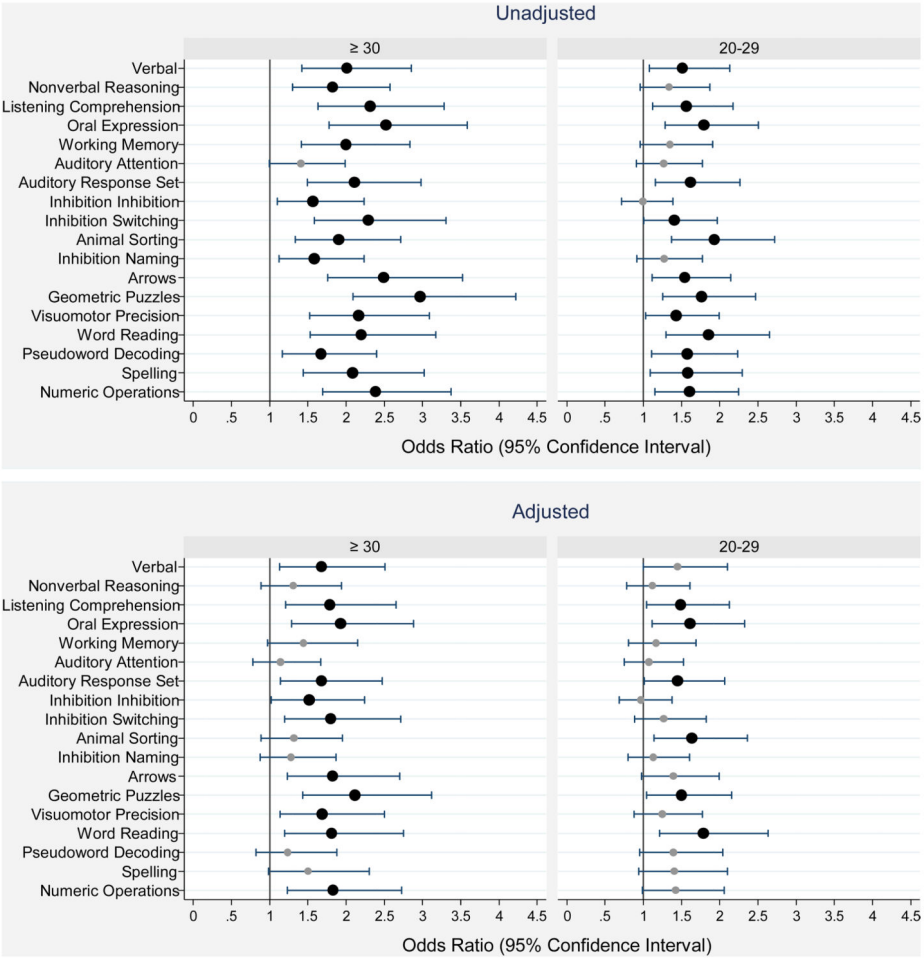

Figure 2.

[1]. Forest plots of odds ratios (ORs) and 95% confidence intervals of a Z-score ≤ -1 on each DAS-II and NEPSY-II neurocognitive assessment at age 10 associated with a SNAP-II ≥ 30 or a SNAP-II between 20 and 29. Odds ratios in the top panel are unadjusted while those in the bottom panel are adjusted for maternal education (≤ 12 and > 12, < 16 years), public insurance, delivery for preeclampsia or fetal indication, gestational age (23-24 and 25-26 weeks) and birth weight Z-score (< -2 and ≥ -2, < -1).

[1]Odds ratios whose lower bound is to the right of the 1.0 vertical line are statistically significant at the $p < 0.05$ level.

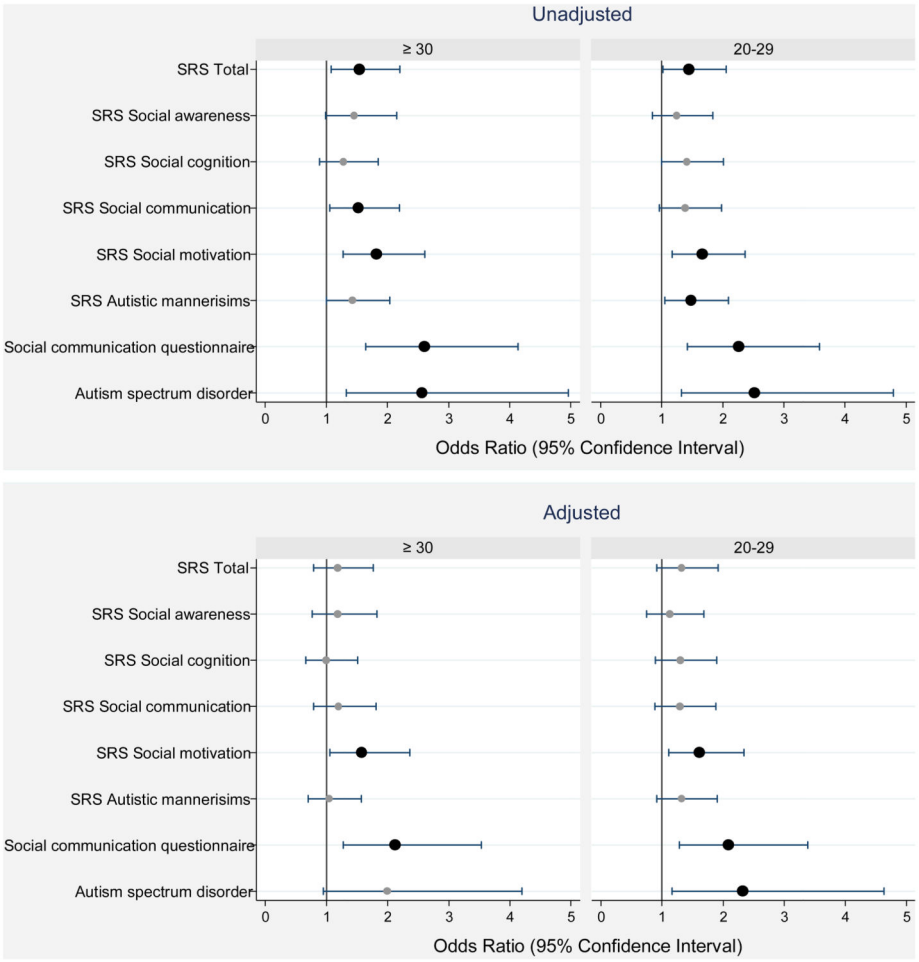

Figure 3.

[1]. Forest plots of odds ratios (ORs) and 95% confidence intervals of a T score ≥ 60 on the Social Responsiveness Scale (SRS-2) subtests, and of documented characteristics of ASD based on the Autism Diagnostic Observation Schedule-2 (ADOS-2) at age 10 associated with a SNAP-II ≥ 30 or a SNAP-II between 20 and 29. Odds ratios in the top panel are unadjusted while those in the bottom panel are adjusted for gestational age (23-24 and 25-6 weeks), birth weight Z-score (< -2 and ≥ -2, < -1), delivery for maternal or fetal indications, and maternal fever with 48 hours of delivery.

[1]Odds ratios whose lower bound is to the right of the 1.0 vertical line are statistically significant at the $p < 0.05$ level.

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Table 1

Sample characteristics among in each Score for Neonatal Physiology (SNAP-II) stratum. These are row percents.

		SNAP-II			Row N
		< 20	**20-29**	**≥ 30**	
Maternal characteristics					
Racial identity	White	53	24	23	546
	Black	50	25	25	222
	Other	57	25	18	96
Hispanic	Yes	55	23	22	86
	No	52	25	23	785
Age, years	< 21	48	27	26	113
	21-35	52	25	23	584
	> 35	59	23	17	117
Education, years	≤ 12	49	26	26	353
	> 12, < 16	50	24	26	196
	≥ 16	59	24	18	299
Single marital status	Yes	50	25	25	345
	No	54	25	21	529
Public insurance	Yes	50	24	26	299
	No	54	25	21	561
KBIT Z-score[1]	≤ -1	54	27	19	95
	> -1	52	25	23	730
Perinatal characteristics					
Pregnancy complication	PE/FI	46	34	19	149
	Spontaneous	54	23	23	725
Fever	Yes	36	28	36	47
	No	54	25	21	797
Newborn characteristics					
Sex	Male	50	26	24	446
	Female	55	23	22	428

		SNAP-II			Row N
		< 20	20-29	≥ 30	
Gestational age (weeks)	23-24	24	28	49	183
	25-26	53	26	21	296
	27	71	20	9	295
Birth weight, grams	≤ 750	33	29	38	328
	751-1000	50	24	16	376
	> 1000	71	16	10	170
Birth weight Z-score	< -2	53	26	21	53
	≥ -2, < -1	42	31	28	118
	≥ -1	54	23	22	703
Overall row percent		53	25	23	
Maximum column N		460	215	199	874

[1] KBIT - Kaufman Brief Intelligence Test used to obtain a quick estimate of intelligence

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Table 2

Educational, neurologic, behavioral and quality of life characteristics. The percent of children in each Score for Neonatal Physiology (SNAP-II) stratum who also had the characteristics listed on the left at 10 years. Column percents.

Characteristic		SNAP-II			Row N	p-Value[I]
		< 20	20-29	≥ 30		
Educational characteristics						
Had an IEP	Yes	44	60	70	470	< 0.001
Repeated a grade	Yes	16	21	22	161	0.053
Placed in a remedial class	Yes	15	24	31	184	< 0.001
Physician diagnoses						
Any seizure	Yes	10	14	13	102	0.14
Epilepsy	Yes	6	9	11	65	0.03
ADHD	Yes	19	27	30	204	0.002
Currently receiving medication for:						
Seizures	Yes	3	5	11	45	0.03
ADHD	Yes	13	20	19	144	< 0.001
Attention deficit hyperactivity disorder						
Operational definition of ADHD	Any 2 of 3	14	19	21	148	0.02
Gross Motor function derangement						
GMFCS[II]	≥ 3	3	6	8	44	.007
Peds QL© inventory						
Physical functioning	< 70	14	22	23	153	< 0.001
	≥ 70, < 85	13	15	19	124	
Emotional functioning	< 70	25	32	26	229	0.62
	≥ 70, < 85	26	22	25	212	
Social functioning	< 70	20	28	36	221	< 0.001
	≥ 70, < 85	18	20	15	155	
School functioning	< 70	31	47	48	345	< 0.001
	≥ 70, < 85	24	22	25	203	

Characteristic		SNAP-II			Row N	p-Value[I]
		< 20	20-29	≥ 30		
Psychosocial functioning	< 70	25	36	38	264	< 0.001
	≥ 70, < 85	30	27	30	249	
Maximum column N		460	215	199	874	

[I] χ^2_{trend}

[II] Gross Motor Function Classification System