Los scores de severidad de enfermedad neonatal temprana predicen alteraciones del neurodesarrollo a los 10 años de edad en niños nacidos extremadamente prematuros

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ABSTRACT

OBJETIVO: Un score de severidad de enfermedad neonatal, el Score for Neonatal Acute Physiology-II (SNAP-II), predice déficits del neurodesarrollo a los dos años de edad en niños nacidos extremadamente prematuros (EPT). Buscamos evaluar hasta qué punto es predictivo de déficits cognitivos y otros aspectos del neurodesarrollo a los 10 años de edad.

DISEÑO DEL ESTUDIO: En una cohorte de 874 niños nacidos antes de las 28 semanas de gestación, recolectamos datos prospectivos clínicos, fisiológicos y de laboratorio para calcular el SNAP-II en cada niño. Cuando los niños alcanzaron los 10 años de edad, examinadores que desconocían la historia médica del niño evaluaron los resultados en neurodesarrollo, incluyendo funciones neurocognitiva, motora gruesa, social y comunicación, diagnóstico y tratamiento de convulsiones o trastorno por déficit de atención e hiperactividad (ADHD), logro académico y calidad de vida

Empleamos regresión logística para ajustar para potenciales confundidores.

RESULTADOS: Un indeseablemente alto SNAP-II (≥ 30), presente en el 23% de los participantes, estuvo asociado a mayor riesgo de déficit cognitivo (CI, función ejecutiva, habilidades del lenguaje), resultados neurológicos adversos (epilepsia, déficit en función motora gruesa), anormalidades conductuales (ADHD), disfunción social (trastorno del espectro autista) y dificultades relacionadas a la educación (logro en la escuela y necesidad de apoyo educacional). En los análisis que ajustaron para potenciales confundidores, Z-scores ≤-1 en 11 de 18 resultados cognitivos estuvieron asociados con SNAP-II en la categoría más alta, y 3 de 8 estuvieron asociados con una categoría intermedia de SNAP-II. Los Odds ratio y los intervalos de confianza 95% iban desde 1.4 (1.01, 2.1) hasta 2.1 (1.4, 3.1). De la misma forma, 2 de las 8 disfunciones sociales estuvieron asociadas con SNAP-II en la categoría más alta y 3 de 8 se asociaron a SNAP-II en la categoría intermedia. Los Odds ratios y los intervalos de confianza del 95% fueron ligeramente superiores para estas determinaciones yendo desde 1.6 (1.1, 2.4) hasta 2.3 (1.2, 4.6)

CONCLUSIÓN: En los recién nacidos EPT, las alteraciones fisiológicas presentes en las 12 primeras horas postnatales están asociadas con disfunciones en varios dominios del neurodesarrollo a los 10 años de edad. No pudimos hacer inferencias sobre causalidad.

INTRODUCCIÓN

El Score for Neonatal Acute Physiology (SNAP) (1) y una versión revisada, el SNAP-II (2) son indicadores basados en la fisiología del riesgo de mortalidad neonatal endógeno basado en signos vitales rutinariamente disponibles y pruebas de laboratorio obtenidas durante las primeras 12 horas postnatales, cuando los deterioros clínico/fisiológico son menos pasibles de estar influenciados por intervenciones médicas que los trastornos que ocurren más tardíamente durante la estadía hospitalaria. SNAP-II no sólo predice muerte entre los recién nacidos EPT sino también hemorragia intraventricular (3- 5), disfunción respiratoria (3-5) y retinopatía del prematuro (5-7).

En el estudio ELGAN de niños nacidos antes de las 28 semanas de gestación, el SNAP-II elevado predijo muerte, anormalidades morfológicas del cerebro definidas por ultrasonido, y bajos scores del desarrollo a la edad de 2 años (8, 9). Sin embargo, las evaluaciones del neurodesarrollo a los dos años tienen poca capacidad de predecir la función posterior (10- 12) y las capacidades funcionales a la edad de 10 años son cualitativamente diferentes y más complejas que las que pueden ser determinadas a los dos años (13, 14). Entonces, nos propusimos extender nuestro trabajo previo examinando la función del neurodesarrollo a los 10 años como un resultado asociado con SNAP-II alto. La relación entre indicadores tempranos de inestabilidad fisiológica y los resultados en el neurodesarrollo en edad escolar no es conocida aún. En este

reporte, examinamos la relación entre SNAP-II y las disfunciones a los 10 años de edad en una cohorte de niños nacidos EPT en 14 centros médicos en los Estados Unidos.

MATERIALES Y MÉTODOS

Participantes

El estudio ELGAN es un estudio observacional, multicéntrico prospectivo del riesgo de alteraciones neurológicas estructurales y funcionales en infantes EPT (15). Un total de 1506 infantes nacidos antes de la semana 28 de gestación fueron enrolados en el período 2002-2004 y 1200 sobrevivieron a los 2 años. A los 10 años, 966 de estos infantes fueron reclutados para un examen de cognición, función ejecutiva, y logros académicos y del comportamiento. De estos 966 niños, 889 (92%) regresaron para Seguimiento y 874 tuvieron pruebas neurocognitivas. Los procedimientos para enrolamiento y consentimiento informado para este estudio de seguimiento fueron aprobados por el comité institucional de revisión de cada institución participante. Las variables demográficas, de gestación y del recién nacido fueron examinadas utilizando un protocolo estandarizado que ha sido reportado por otros (15).

Scores revisados para fisiología Neonatal aguda (SNAP-II)

Recolectamos todos los datos fisiológicos, de laboratorio y de tratamiento de las primeras 12 horas postnatales requeridos para calcular el SNAP-II (2). También identificamos puntos de corte para cada semana de edad postmenstrual al nacimiento que definían el cuartilo superior, el decilo superior y tres categorías (20, 20-29 y ≥30) del SNAP-II

Visita a Seguimiento a los 10 años

Las familias que aceptaron participar fueron citadas para una visita durante la cual se le harían todas las evaluaciones informadas aquí en 3 a 4 horas, incluyendo pausas. Los exámenes fueron seleccionados para proveer la información más abarcativa acerca de la función neurocognitiva y académica en una sola sesión de pruebas. Un resumen de las pruebas neurocognitivas empleadas en este estudio está incluido como Tabla suplementaria (Tablas suplementarias 1 a y b) (verlas en el archivo original).

Examinadores que desconocían la historia médica del niño evaluaron neurodesarrollo en varios dominios importantes clínicamente. Mientras los niños eran examinados, el padre o el cuidador completaron cuestionarios respecto del estado educativo, médico, neurológico y conductual. También se entregaron cuestionarios al maestro de la escuela del niño para obtener el estado conductual informado por el docente, como se describe más adelante.

Resultados neurocognitivos y relacionados

La capacidad cognitiva general fue determinada con la Escala de habilidad diferencial en la edad escolar (School-Age Differential Ability Scales–II (DAS-II) Verbal and Nonverbal Reasoning scales) verbal y no verbal de razonamiento (16). Habilidades del lenguaje expresivo y receptivo fueron evaluadas con el Oral and Written Language Scales (OWLS) (17). Atención y función ejecutiva fueron investigados con al DAS-II y NEPSY (A Developmental NEuroPSYchological Assessment-II) (18, 19). La velocidad de procesamiento fue determinada con NEPSY-II Inhibition Naming. La percepción visual fue examinada con NEPSY-II Flechas y Puzzles geométricos, mientras que la función visomotora fue medida con NEPSY-II de precisión visomotora y golpeteo de dedos. La función académica se determinó con la escala de Weschler de logro individual (Wechsler Individual Achievement Test-III (WIAT-III (C)), que provee scores estándar en reconocimiento de palabras y decodificación, deletreo y operaciones numéricas (20). Los resultados educativos incluían recepción de un plan educativo individual (PEI), repetir un grado en la escuela o ubicación en escuela de recuperación.

Resultados Neurológicos

Los resultados neurológicos incluyeron el diagnóstico de "cualquier" convulsión o epilepsia, recibir drogas antiepilépticas al momento del examen, y función motora gruesa. La identificación de convulsión fue un proceso en dos etapas.Si los padres respondían "sí" a alguna de las 11 preguntas amplias para posibles convulsiones, eran conducidos por el epileptólogo del estudio para tener una entrevista estructurada seguida de una entrevista a final-abierto, ambas telefónicas. El epileptólogo luego determinaba si el evento reportado era una convulsión. Un segundo epileptólogo revisaba independientemente las respuestas de la entrevista y de la misma manera categorizaba el evento. Cuando los dos médicos disentían sobre la presencia

de convulsiones, que ocurrió sólo en el 3% de los niños entrevistados, un tercer epileptólogo revisó las respuestas de la entrevista e hizo la determinación final en cuanto al estado convulsivo.
La function motora gruesa fue determinada utilizando el Sistema de clasificación de función motora gruesa (GMFCS) (21). Los niños con un GMFCS ≥3 (imposibilitado de caminar sin un dispositivo que asista la movilidad) fueron considerados portadores de una anormalidad motora gruesa significativa.

Respuesta social
Uitlizamos la Escala de Respuesta social-2 (SRS-2) para identificar discapacidad social y cuantificar su severidad (22). Este instrumento de 65 ítems provee un score total que refleja la severidad de los déficits sociales en el espectro autista, así como 5 sub-escalas para sensibilización o conciencia social, cognición social, comunicación social, motivación social, e intereses restringidos y comportamiento repetitivo.
Todos los niños fueron cribados mediante un reporte parental para Trastorno del Espectro Autista (TEA) con el cuestionario de Comunicación Social (SCQ) (23). Los niños con screening positivo en el SCQ eran examinados con la Autism Diagnostic Interview—Revised (ADI-R), y una entrevista más profunda a los padres (24).Los niños que tenían criterio para TEA en el ADI-R modificado recibieron el Autism Diagnostic Observation Schedule-2 (ADOS-II) (25, 26). Finalmente, todos los niños que cumplían los criterios estandarizados de investigación para TEA en ambos ADIR y ADOS-II eran clalsificados como TEA.
Conducta
Los resultados en conducta fueron determinados en dos formas, por diagnóstico médico o tratamiento para ADHD, y por el reporte parental o del maestro de los ítems del estado del comportamiento incluídos en el Inventario de Síntoma del Niño (CSI-4) 27, 28). Los maestros y los padres no hicieron ningún diagnóstico DSM-IV. En cambio, el CSI-4 funcionó como una herramienta de screening para determinar un patrón de comportamiento, basado en características conductuales seleccionadas. La definición de ADHD la operacionalizamos, utilizando una convención apoyada por otros, para incluir 2 de alguna de las siguientes 3 designaciones de ADHD: 1) reporte parental; 2) reporte del maestro y 3) diagnóstico médico. Los reportes de padres y maestros de una designación de ADHD son informados en la Tabla Suplementaria 4 (Ver el original). Esta definición confiere un nivel suficiente de acuerdo para proveer confianza en la designación del niño como paciente ADHD.

Calidad de vida informada por los padres
Pese a que la calidad de vida relacionada con la salud es un área compleja y en algunos casos subjetiva, también aporta información acerca del impacto biológico de exposición a resultados más importantes para las familias. Por esta razón, examinamos 5 indicadores de calidad de vida encontrados en el Pediatric Quality of Life Inventory (PedsQL, Mapi Research Trust, Lyon, France), incluyendo determinaciones funcionales del desempeño físico, emocional, social, escolar y psicológico (29, 30).

Análisis de datos
Evaluamos la hipótesis nula de que cada medida de función del neurodesarrollo a los 10 años no estaba distribuida diferencialmente en 3 categorías de SNAP-II (0-20, 20-29, y ≥30). En la cohorte ELGAN, un SNAP-II ≥30 se correlaciona grosso modo con el cuartilo superior (8). Para permitir diferencias en edad al momento de la evaluación, y para facilitar la comparación con niños nacidos al término, calculamos los scores-Z utilizando las distribuciones de valores informadas en los controles normativos históricos, como describieron los autores de los exámenes que empleamos (16, 17, 19, 20). Para determinaciones de función neurocognitiva y social, creamos modelos de regresión múltiple del riesgo de que un score o más DS debajo de la media normativa para cada determinación (es decir, score Z ≤-1). Estos modelos, que incluían potenciales confundidores (educación materna, madre elegible para seguro médico gubernamental, parto por preeclampsia o indicación fetal, edad gestacional y el score Z del peso de nacimiento) nos permitió calcular odds ratios (y los IC 95%), indicando la fuerza de la asociación entre la categoría del SNAP-II y cada resultado.
Para determinaciones de la función educativa y neurológica, conducta y calidad de vida, utilizamos un anális de tendencia X2 para probar la fuerza de la relación entre SNAP-II, y las anormalidades de conducta reportadas por padres y maestros. También utilizamos un análisis de tendencia X2 para exámenes en el CSI-4.

RESULTADOS

Características de la muestra

Tabla 1. Características de la muestra en cada estrato de puntuación de SNAP-II

	SNAP-II			Fila
	<20	20-29	≥30	N
Rasgos maternos				
Identidad Racial				
Blanco	53	24	23	546
Negro	50	25	25	222
Otra	57	25	18	96
Hispano				
Si	55	23	22	86
No	52	25	23	785
Edad,años				
<21	48	27	26	113
21-35	52	25	23	584
>35	59	23	17	117
Educación, años				
≤12	49	26	26	353
>12, <16	50	24	26	196
≥ 16	59	24	18	299
Estado civil soltera				
Si	50	25	25	345
No	54	25	21	529
Seguro público				
Si	50	24	26	299
No	54	25	21	561
KBIT Z-score*				
≤ - 1	54	27	19	95
> - 1	52	25	23	730
Características perinatales				
Complicaciones Embarazo				
PE/FI	46	34	19	149
Espontáneo	54	23	23	725
Fiebre				
Si	36	28	36	47
No	54	25	21	797
Sexo				
Masculino	50	26	24	446
Femenino	55	23	22	428
Edad gestacional, semanas				
23-24	24	28	49	183
25-26	53	26	21	296
27	71	20	9	295
Peso al nacer, gramos				
≤ 750	33	29	38	328
751-1000	50	24	16	376
>1000	71	16	10	170
Peso al nacer, score Z				
< -2	53	26	21	53
≥ -2, < -1	42	31	28	118
≥ -1	54	23	22	703
Porcentaje Total	53	25	23	
N	460	215	199	874

Abreviaturas: SNAP-II Escala de calificación de parámetros fisiológicos agudos; KBIT= Prueba de Inteligencia de Kaufman utilizado para obtener estimación rápida de inteligencia.

(Tabla 1- Ver en el original) De los 874 infantes de esta muestra, 53% (n=460) tuvieron un SNAP-II por debajo de 20, 25% (n=215) tuvieron un SNAP-II entre 20 y 29, y el restante 23% (n=199) tuvieron un SNAP-II ≥30. Las características demográficas maternas asociadas a SNAP-II ≥30 fueron menor edad al momento del parto, sin educación superior, no casadas y ser elegibles para seguro médico provisto por el gobierno (público). Fiebre materna durante el parto, menor edad gestacional al nacer y peso más bajo al nacer estuvieron asociadas con SNAP-II ≥30; sin embargo, restricción del crecimiento fetal, no.

Resultados cognitivos y relacionados

(Tabla suplementaria 2 y Figuras 1 y 2- Ver en el original) Alrededor de un cuarto de los niños que presentaron SNAP-II ≥30 tuvieron score en 2 o más DS debajo de la media normativa en las pruebas de DAS-II VERBAL, OWLS comprensión al escuchar, y OWLS expresión oral y WIAT-III operaciones numéricas. La fuerza de la asociación entre SNAP-II y ambos CI verbal y OWLS, ambos medidas de la función del lenguaje, es fuerte. Casi un tercio de todos los niños con un SNAP-II ≥30 tuvo mediciones de función ejecutiva (NEPSY-II) 2 o más DS debajo de la media normativa. En general, a más alta categoría en el SNAP-II, menor score cognitivo. Los gráficos de la Figura 1 (ver en el original) muestran la distribución de los scores en cada evaluación separadamente, para cada grupo SNAP-II. La línea central de la cajuela indica la mediana (centilo 50), mientras que la parte superior de la figura indica el centilo 75 y la base el centilo 25. Los niños con SNAP-II más altos tuvieron consistentemente menores scores en el DAS-II, OWLS, WIAT-III y NEPSY-II. Los odds ratior y los IC 95% de un score Z ≤1 mostrados en los agrupados de la Figura 2- panel superior (ver en el original) indican que los niños con un SNAP-II elevado estaban en un riesgo significativamente aumentado de tener scores 1 ó más DS debajo de la media normativa en casi todos los tests cognitivos. En los análisis de ajuste para potenciales confundidores, los scores Z ≤1 en 11 de 18 resultados cognitivos estuvieron asociados con SNAP-II rn la categoría intermedia. Odds ratios y IC 95% fueron desde 1.4 (1.01, 2.1) hasta 2.1 (1.4, 3.1) (Figura 2, panel inferior- Ver en el original).

Área Social

Tabla Suplementaria 3 y Figura 3-Ver en el original) Los niños con un poco deseable SNAP-II (≥20) tuvieron scores modestamente aumentados en el total y los componentes del SRS, con los scores más elevados reflejando aumento del déficit social. 10 por ciento de los varones en los grupos de rango medio y alto de SNAP-II feron considerados como pacientes TEA basados en un diagnóstico positivo en el ADOS-2 comparados con 4% en el grupo con SNAP-II más bajo. Los niños con SNAP II medio y alto presentaban significativamente mayor riesgo en la sub-escala de motivación social en el SRS y un SCQ "positivo", que tamiza para TEA.En los análisis que ajustaron para potenciales confusores, dos de los ocho resultados sociales estaban asociados con la categoría más alta de SNAP-II y tres de ocho resultados sociales estuvieron asociados con SNAP-II de categoría intermedia. Odds ratios y el IC 95% fueron desde 1.6 (1.1, 2.4) hasta 2.3 (1.2, 4.6) (Figura 3, Panel inferior-Ver en el original)

Areas educacional, neurológica, conductual y calidad de vida

(Tabla 2- Ver en el original)Mientras que aproximadamente 40% de los niños con SNAP-II en la categoría más baja requirieron un plan educativo individual (PEI), 70% requirieron PEI si el SNAP-II era ≥30 y el doble de niños con SNAP-II requería educación de recuperación, comparados con aquellos en la categoría SNAP-II más baja (Tabla 2-Ver en el original). El SANP-II alto estuvo significativamente asociado con recepción de PEI (P 0.oo1) y ubicación en una clase de recuperación (P 0. 001).

La tasa de epilepsia aumentó significativamente con el aumento de categoría de SNAP-II (P= 0.03) al igual que el uso de medicación anticonvulsivante (P= 0.03) en el momento del examen.

Un SNAP-II elevado estuvo también asociado con un GMFCS ≥3. Casi el triple de niños(8%) con SNAP-II ≥30 y el doble (6%) con SNAP-II 20-29 tuvieron un GMFCS ≥3, comparados con aquellos con score 20 (3%) (P=0.007). Los niños con alto SNAP-II tuvieron scores más bajos de calidad de vida en el inventario PedsQL. Un SNAP-II alto estuvo asociado con resultados adversos en 4 de 5 dominios, incluyendo funcionamiento físico, social, escolar y psicosocial (todos P= 0.001). Debido a que los reportes de padres y maestros arrojan resultados menos confiables que los tests neurocognitivos estandarizados, no incluimos ajustes para potenciales confundidores en estos análisis. Sin embargo, vemos estos resultados como significantes marcadores clínicos en las alteraciones que encontramos en las pruebas neurocognitivas. (Figuras 2 y 3)

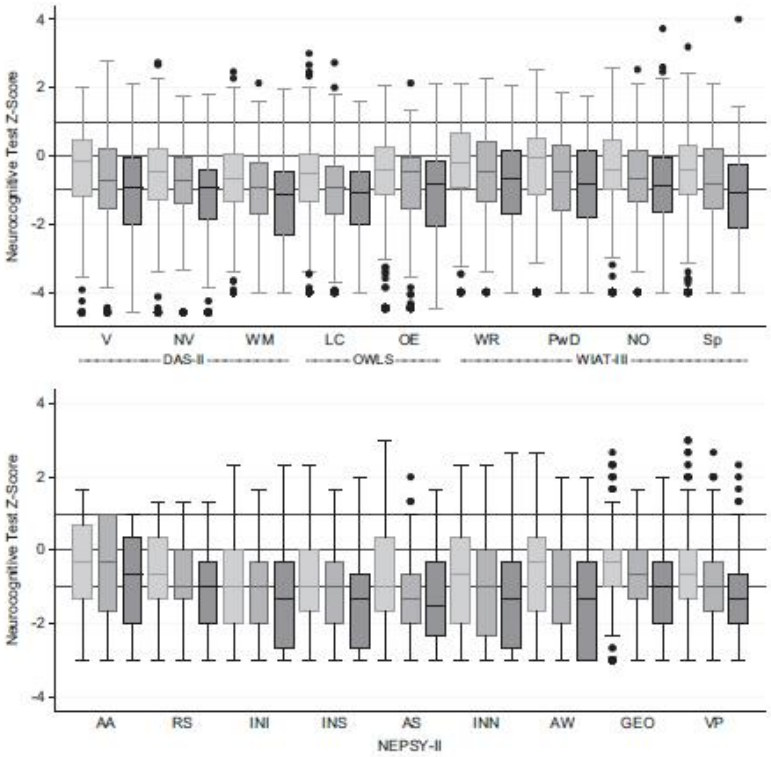

Figura 1. Diagrama de distribución dedatos de cada subtest neurocognitivo relacionado al valor de el SNAP II. Los Z-score estan ajustados a la norma poblacional. Los rectángulos gris muy claro es <25, gris medio > o igual a 25 y <30 y el gris oscuro representa al grupo con SNAP II mayor a 30.Las lineas centrales en cada caja o rectángulo representan la mediana (p50) el borde superior indica el p75 y el inferiro el p25.
AA= Atención auditiva, AS= Clasificación de animales,AW= flechas, GEO= rompecabezas geométricos, INI= Inhibición, INN= Inhibición al denominar, INS= Interruptor de inhibición, LC= Comprensión auditiva, NO= Operaciones Numéricas, NV= Razonamiento no verbal OE= Expresión Oral, PwD=Decodificación, RS= Respuesta Auditiva, Sp= Deletreo, V= Verbal, VP= Precisión visomotora, WM= Memoria de trabajo, WR= Lectura.=

Conducta

(Tabla suplementaria 4- ver en el original) La asociación entre diagnóstico de ADHD y SNAP-II alto parece más fuerte que la existente entre tratamiento por ADHD y alto SNAP-II. El diagnóstico de ADHD fue más común entre los niños con SNAP-II más elevado que entre los niños con SNAP-II más bajo, tanto por reporte parental (P= 0.03) y reporte de la maestra (P= 0.003).Asociaciones con otras conductas identificadas por CSI-4 presentadas en la Tabla suplementaria 4, son consideradas mayormente como exploratorias.

DISCUSION

En esta muestra de niños de 10 años de edad nacidos antes de las 28 semanas de gestación, aquellos que tuvieron un SNAP-II ≥30 estuvieron en mayor riesgo de presentar disfunciones neurocognitivas, conductuales y sociales. También tuvieron mayor tendencia que aquellos con bajo SNAP-II de tener PEI, repetir grados, ser ubicados en clase de recuperación, tener diagnóstico o ser tratado por ADHD, TEA o epilepsia, necesitar un dispositivo de asistencia para caminar, y tener disminuida calidad de vida.

La característica más fuertemente asociada con un alto SNAP-II es la edad gestacional, pero dentro de cada grupo de edad gestacional, aquellos con SNAP-II ≥30 estaban en un riesgo aún mayor de tener estas disfunciones que aquellos con un estado fisiológico normal (31). Entonces, los SNAPs altos reúnen información de riesgo que suplementa la información de riesgo surgida de la edad gestacional.

Más sorprendente, sin embargo, fue la multitud de disfunciones que se encontraron a los 10 años entre niños con tempranos desvíos fisiológicos, aún ajustando por potenciales confundidores. Buscamos una explicación coherente para estas observaciones. Qué característica o exposición que diferencia a los niños EPT de los infantes de término también diferencia a aquellos infantes EPT con alto SNAP-II de aquellos con un SNAP-II más bajo?

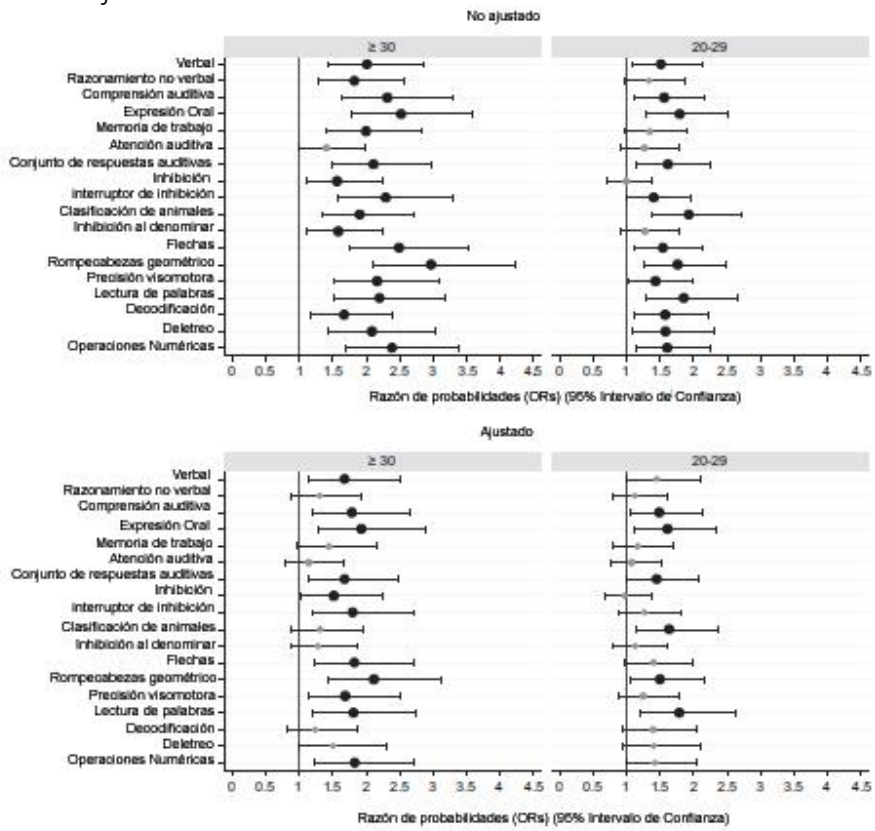

Figura 2. Razón de probabilidades (ORs) e intervalo de confianza 95% de un Z. score menor o igual a - 1 en cada evaluación neurocognitiva DAS-II y NEPSY-II a los 10 años asociado al valor de SNAP-II (mayor o igual a 30 o entre 20 y 29). Los valores de ORs están ajustados en el panel inferiro de acuerdo a años de educación materna, indicación del parto (fetal o preeclampsia), edad gestacional y peso al nacer.

Posibles explicaciones para nuestros hallazgos

Ofrecemos cuatro explicaciones para el nexo entre scores de SNAP y daño cerebral en niños nacidos EPT. La inmadurez puede contribuir a la inestabilidad fisiológica, aumentar el riesgo de complicaciones neonatales o resultar en escasez de neuroprotectores normalmente provistos por la placenta, todos los cuales pueden estar asociados con la injuria cerebral. Además, la infección y/o inflamación prenatal asociada al nacimiento pretérmino pueden contribuir también al daño cerebral.

Primero, la inestabilidad fisiológica puede estar en la cadena causal entre la inmadurez (y sus correlatos) y daño cerebral. Acorde a esto, SNAP-II podría ser visto como un marcador o indicador para dicho riesgo. Mientras que tanto hipoxemia como hipotensión, ejemplos de inestabilidad fisiológica, han sido invocados para dar cuenta del daño cerebral en niños EPT (32, 39), todavía falta aportar suficiente evidencia para estas aseveraciones (40-44). Además, a pesar de los esfuerzos para mejorar la estabilidad fisiológica (41, 45-52) la tasa de desvíos del neurodesarrollo entre niños EPT permanece elevada en numerosos estudios (43, 44, 53-57).

Segundo, scores SNAP-II elevados están asociados con eventos postnatales tales como bacteriemia/sepsis, enterocolitis necrotizante, y enfermedad pulmonar crónica (4, 58) que están asociados con resultados adversos relativos al cerebro (59-62). En esta forma, SNAP-II podría ser visto como un marcador para subsiguientes adversidades neonatales. Dado que estos desórdenes podrían estar en el paso causal entre SNAP-II elevado y los resultados a los 10 años, no son confundidores. Por lo tanto, no ajustamos para ellos en ninguno de nuestros análisis.

Tercero, scores SNAP-II elevados pueden expresar información acerca de inmadurez/vulnerabilidad, tal como la atribuible a la escasez de protectores endógenos provistos por la placenta (63) que se sabe tienen efectos beneficiosos neurotróficos sobre el desarrollo. Considerar que todos los bebés de la misma edad gestacional no son igualmente maduros o vulnerables. Desde esta perspectiva, SNAP-II provee información adicional acerca de la maduración fisiológica, sirviendo como un marcador para procesos que están regulados por el desarrollo, incluyendo la capacidad de sintetizar factores de crecimiento y otras proteínas capaces de proteger el cerebro(63). SNAP-II ha sido relacionado con el desarrollo del tracto corticoespinal, independiente tanto de la edad gestacional como de factores de riesgo postnatales, prestando apoyo a la teoría que SNAP-II provee información acerca de los efectos neurotróficos sobre la maduración del cerebro (64).

Finalmente, la inflamación sistémica, que puede ser regulada por el desarrollo, pone al cerebro del recién nacido en riesgo aumentado de múltiples alteraciones (65-68). Pese a que la inflamación sistémica diferencia a los niños EPT de los de término (69), los descalabros fisiológicos tempranos y la elevación en el primer día de vida de proteínas relacionadas con la inflamación en la circulación, en general no fueron asociadas con la inflamación sistémica en el estudio ELGAN (70). La tasa de fiebre materna, que está asociada a corioamnionitis y sepsis temprana (71, 72), sin embargo, estuvo aumentada en aquellos con SNAP-II ≥ 30. Pese a esto, mientras que los bebés pretérmino expuestos a corioamnionitis tienden a presentar SNAPs-II más altos que los niños no expuestos (73) la evidencia de que la corioamnionitis contribuye al daño cerebral en recién nacidos EPT es variable (74-77).

Fortalezas y limitaciones

Nuestro studio tiene varias fortalezas. Primero, inlcuimos un gran número de infantes, hacienda poco probable que hayamos perdido importantes asociaciones debido a falta de poder estadístico, o que hayamos mostrado asociaciones que podrían reflejar la inestabilidad del número pequeño. Segundo, seleccionamos infantes basados en la edad gestacional, no peso de nacimiento, para minimizar confundir debido a factores relacionados con la restricción del crecimiento fetal (78). Tercero, recolectamos todos nuestros datos prospectivamente. Cuarto, la deserción en el examen neurocognitivo fue solamente modesta. Las debilidades de nuestro estudio son aquellas comunes a todos los estudios observacionales. No podemos distinguir entre asociación y cusalidad como explicación para los hallazgos.

Tabla 2. Características educacionales, neurológicas, conductuales y de calidad de vida.

Características		SNAP-II			fila	Valor de p
		<20	20-29	>30	N	
Caracaterísticas Educacionales						
[illegible]	Si	44	80	70	<70	<0.001
[illegible]	Si	16	21	22	161	0.053
[illegible]	Si	15	24	31	184	< 0.001
Diagnósticos médicos						
Convulsión	Si	10	14	13	102	0.14
Epilepsia	Si	6	9	11	65	0.03
TDAH	Si	19	27	30	204	0.002
Recibe medicación frecuentemente por:						
Convulsiones	Si	3	5	11	46	0.03
TDAH	Si	15	20	19	144	< 0.001
Trastorno de déficit de atención con hiperactividad TDAH						
Definición Operacional	2 de 3	14	19	21	148	0.02
Trastorno de la Motricidad gruesa						
GMF GS	> 3	3	6	8	44	.007
Inventario Pediatrico de Calidad de vida (Ped IQl)						
Desempeño	<70	14	22	23	153	<0.001
físico	>70, <85	13	15	19	124	
Desempeño	<70	25	32	26	239	0.62
emocional	>70, <85	26	22	25	212	
Desempeño	<70	20	28	36	221	<0.001
social	>70, <85	16	20	15	155	
Desempeño	<70	31	47	48	345	<0.001
escolar	>70, <85	24	22	25	203	
Desempeño	<70	25	36	38	26.4	<0.001
psicosocial	>70,<85	30	27	30	249	
medinos columna N		480	215	199	87.4	

CONCLUSION

SNAP-II prove información que suplementa la información de riesgo expresada por la edad gestacional,y transmite información importante acerca de la vulnerabilidad de los infantes a las adversidades del neurodesarrollo 10 años más tarde. Vemos la multiplicidad de disfunciones de neurodesarrollo asociadas a SNAP-II alto como un apoyo del SNAP-II como marcador de inmadurez/vulnerabilidad. Apoyo a favor o en contra de esta visión podría venir de estudios que evalúen la relación entre SNAP-II y biomarcadores regulados por el desarrollo.

Debido a que ningún otro grupo ha evaluado la relación entre SNAP en las primeras doce horas de vida postnatal en niños EPT y su función10 años más tarde, vemos nuestras investigaciones como exploratorias. Ofrecemos intervalos de confianza del 95% de odds ratios para ilustrar el rango de valores que podrían esperarse cuando se hagan intentos de replicar nuestros hallazgos, o de probar asociaciones entre SNAPs y función posterior en alguna forma diferente.

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ORIGINAL ARTICLE

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

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OBJECTIVE: 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.

STUDY DESIGN: 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), 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.

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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 twenty-eighth week of gestation were enrolled during the years 2002 to 2004 and 1200 survived to 2 years. At age 10 years, 966 of these infants were recruited for an

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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 the 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 to 29 and $\geqslant 30$) 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 h, 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 supplementary Table (Supplementary Tables 1a and b).

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 $\geqslant 3$ (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 Supplementary Table 4. 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, Mapi Research Trust, Lyon, France), 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 to 29, and $\geqslant 30$). In the ELGAN cohort, a SNAP-II $\geqslant 30$ 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 s.d. below the normative mean for each assessment (that is, *Z*-score $\leqslant -1$). 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 $\geqslant 30$.

The maternal demographic characteristics associated with a SNAP-II $\geqslant 30$ 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.

Table 1. Sample characteristics among in each Score for Neonatal Physiology (SNAP-II) stratum

	SNAP-II			*Row*
	< 20	*20–29*	*⩾ 30*	N
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[a]				
⩽ −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
Sex				
Male	50	26	24	446
Female	55	23	22	428
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

Abbreviation: SNAP-II, Score for Neonatal Acute Physiology-II. [a]KBIT - Kaufman Brief Intelligence Test used to obtain a quick estimate of intelligence These are row percents.

Neurocognitive and related outcomes

(Supplementary 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 s.d.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 (fiftieth centile), while the top of the box indicates the seventy-fifth centile and the bottom of the box indicates the twenty-fifth 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 s.d. 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

(Supplementary 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 with 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, two of the eight social outcomes were associated with SNAP-II in the highest category and three of eight 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

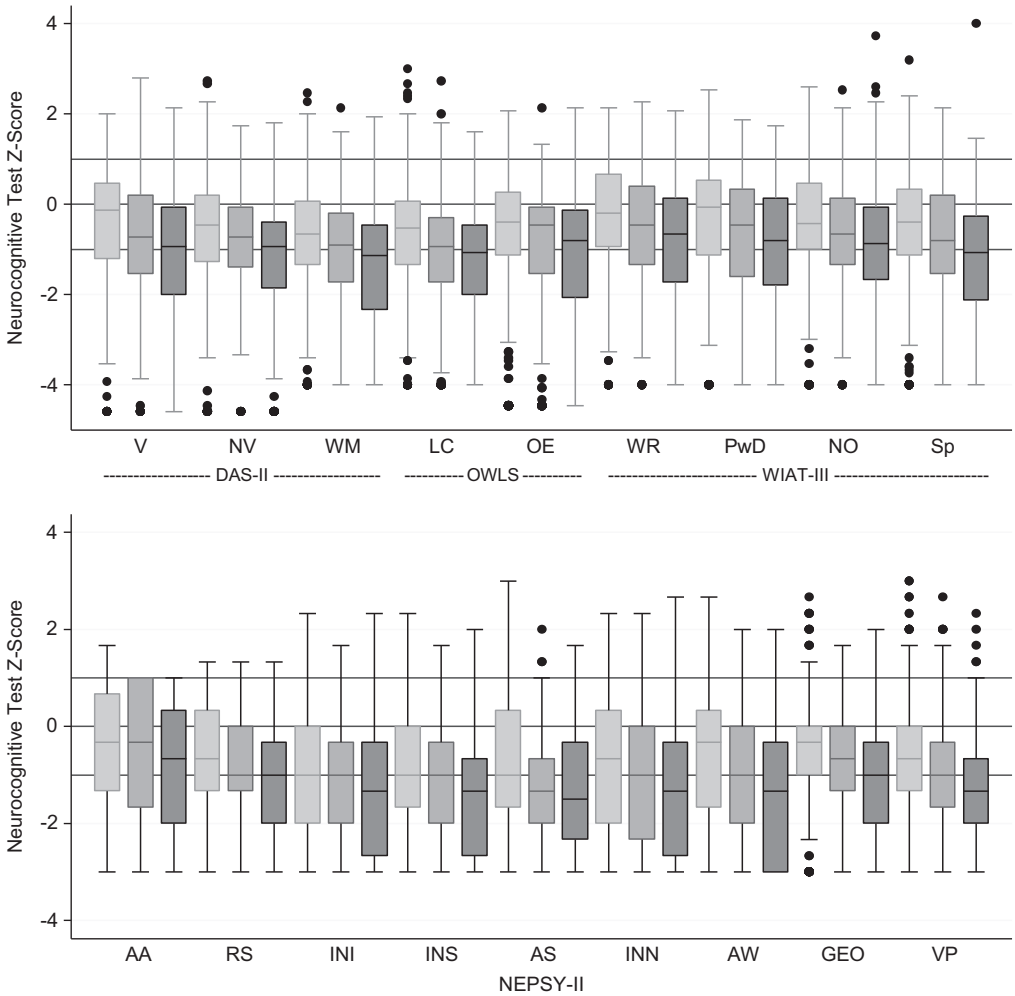
(Table 2) Whereas ~40% of children with a SNAP-II in the lowest SNAP-II category required an individual education plan (IEP), 70% had an IEP if their SNAP-II was ⩾30 and twice as many children with a SNAP-II ⩾30 required remedial education, compared with those in the lowest SNAP-II category (Table 2). 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 with 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).



[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 1. Box-and-whisker plots of each neurocognitive subtest by SNAP-II. All subtest *Z*-scores are adjusted to population norms. Light gray is < 25, medium gray is $\geqslant 25$, < 30, dark gray is $\geqslant 30$. The central line in the box indicates the median (fiftieth centile), while the top of the box indicates the seventy-fifth centile and the bottom of the box indicates the twenty-fifth centile. AA, auditory attention; AS, animal sorting; AW, arrows; GEO, geometric puzzles; INI, inhibition inhibition; INN, inhibition naming; INS, inhibition switching; LC, listening comprehension; NO, numerical operations; NV = nonverbal reasoning, OE, oral expression; PwD, pseudoword decoding;RS, auditory response set; Sp, spelling; V, verbal; VP, visuomotor precision; WM, working memory; WR, word reading.

Behavioral outcomes

(Supplementary 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 Supplementary Table 4, are viewed largely as exploratory.

DISCUSSION

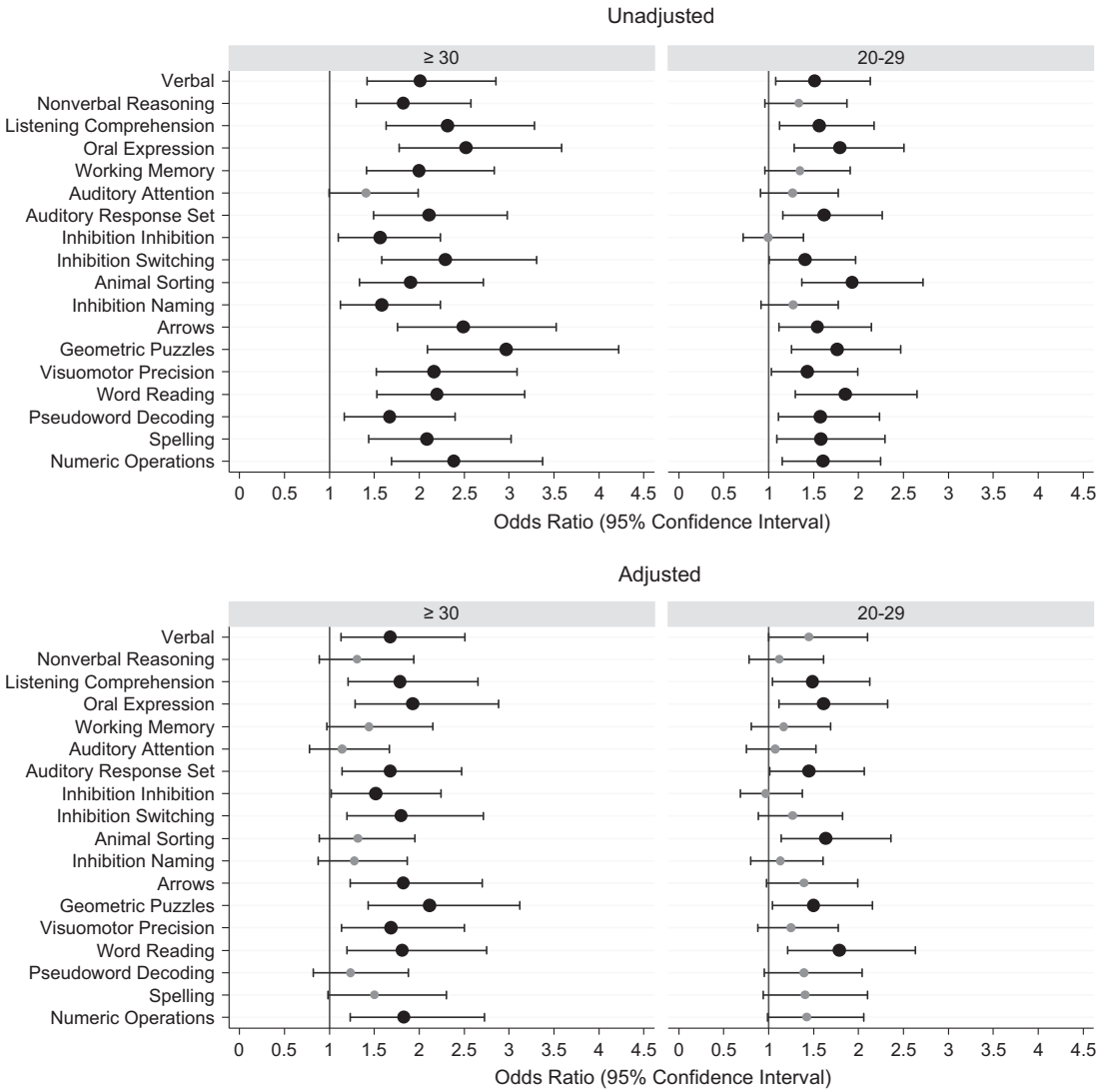
In this sample of 10-year-old children born before the twenty-eighth week of gestation, those who had a SNAP-II $\geqslant 30$ were at increased risk of neurocognitive, behavioral and social dysfunctions. Children who had a high SNAP-II were also more likely than those with a low SNAP-II to have an IEP, 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 $\geqslant 30$ 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



[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.

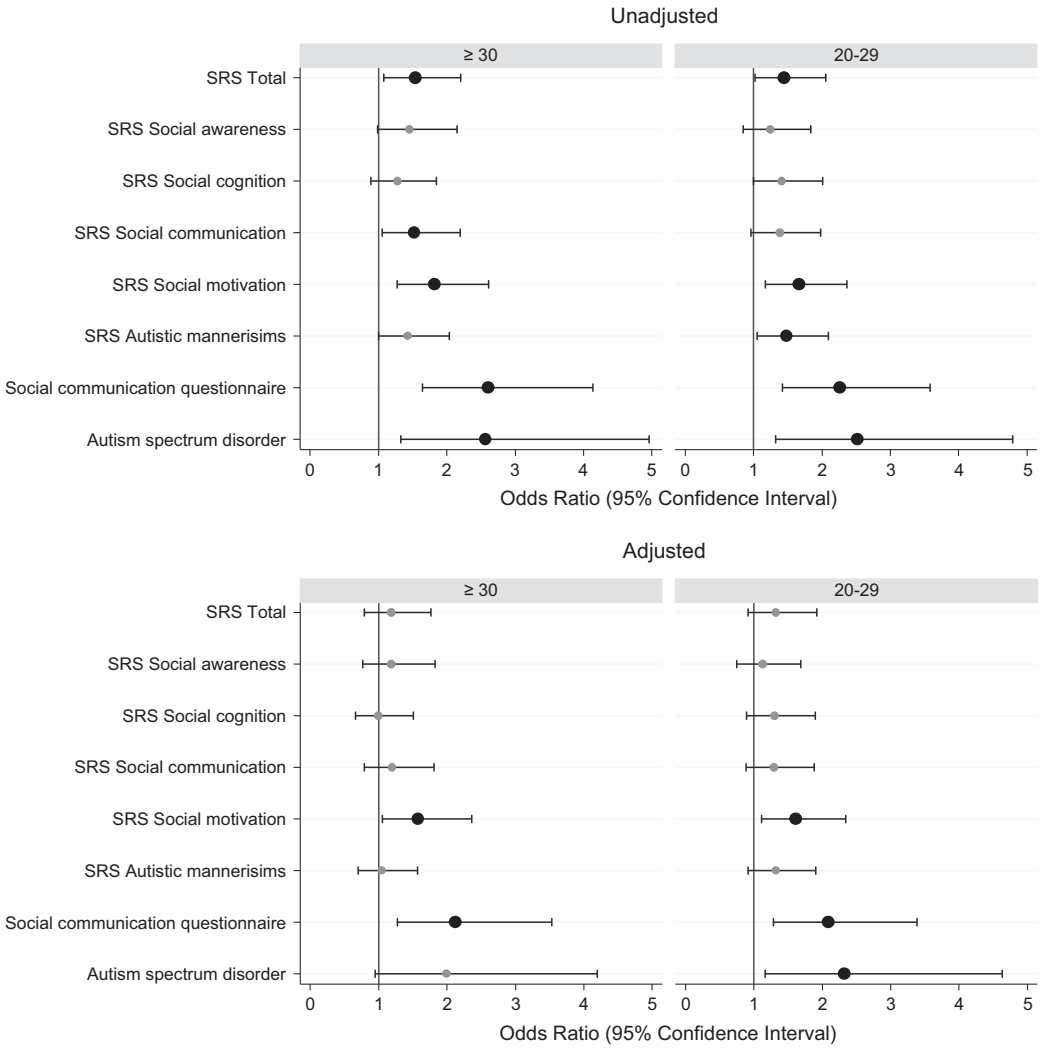
Figure 2. Forest plots of odds ratios (ORs) and 95% confidence intervals of a *Z*-score $\leqslant -1$ on each DAS-II and NEPSY-II neurocognitive assessment at age 10 associated with a SNAP-II $\geqslant 30$ or a SNAP-II between 20 and 29. Odds ratios in the top panel are unadjusted, while those in the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

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



[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. Forest plots of odds ratios (ORs) and 95% confidence intervals of a T-score $\geqslant 60$ 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 $\geqslant 30$ 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 to 24 and 25–6 weeks), birth weight *Z*-score (< -2 and $\geqslant -2$, < -1), delivery for maternal or fetal indications, and maternal fever with 48 h of delivery.

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 $\geqslant 30$. 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

Table 2. Educational, neurologic, behavioral and quality of life characteristics

Characteristic		*SNAP-II*			*Row*	P-*value*[a]
		< 20	*20–29*	*⩾ 30*	*N*	
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[b]	⩾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	
Psychosocial functioning	< 70	25	36	38	264	< 0.001
	⩾ 70, < 85	30	27	30	249	
Maximum column N		460	215	199	874	

Abbreviations: ADHD, attention deficit hyperactivity disorder; GMFCS, Gross Motor Function Classification System; SNAP-II, Score for Neonatal Acute Physiology-II. 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. [a]χ^2 trend. [b]Gross Motor Function Classification System.

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.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Journal of Perinatology website (http://www.nature.com/jp)