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Sobrevida y resultados en el neurodesarrollo en niños nacidos en el límite de la viabilidad

Noelle Younge, M.D., M.H.S., Ricki F. Goldstein, M.D., Carla M. Bann, Ph.D., Susan R. Hintz, M.D., Ravi M. Patel, M.D., P. Brian Smith, M.D., M.P.H., M.H.S., Edward F. Bell, M.D., Matthew A. Rysavy, M.D., Ph.D., Andrea F. Duncan, M.D., Betty R. Vohr, M.D., Abhik Das, Ph.D., Ronald N. Goldberg, M.D., Rosemary D. Higgins, M.D., and C. Michael Cotten, M.D., M.H.S., for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network*

From the Department of Pediatrics, Duke University, Durham (N.Y., R.F.G., P.B.S., R.N.G., C.M.C.), and the Statistics and Epidemiology Unit, RTI International, Research Triangle Park (C.M.B., A.D.) — both in North Carolina; the Department of Pediatrics, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA (S.R.H.); the Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta (R.M.P.); the Department of Pediatrics, University of Iowa, Iowa City (E.F.B., M.A.R.); the Department of Pediatrics, University of Wisconsin, Madison (M.A.R.); the Department of Pediatrics, University of Texas Medical School at Houston, Houston (A.F.D.); the Department of Pediatrics, Women and Infants' Hospital, Brown University, Providence, RI (B.R.V.); and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD (R.D.H.). Address reprint requests to Dr. Younge at the Department of Pediatrics, Duke University, DUMC Box 2739, Durham, NC 27710, or at noelle.younge@duke.edu.

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Abstract

FUNDAMENTOS

Datos reportados en los últimos 5 años indican que las tasas de sobrevida han aumentado entre los niños nacidos en el límite de la viabilidad, pero se sabe menos acerca de cómo este aumento de sobrevida se relaciona con los resultados del neurodesarrollo (ND) en edades tempranas.

METODOS

Comparamos sobrevida y resultados del neurodesarrollo en niños nacidos entre las semanas 22-24 de edad gestacional (EG), evaluados a los 18-22 meses de edad corregida (EC) entre tres épocas: Época 1- años 2000-2003; Época 2- años 2004-2007; y Época 3- años 2008-2011. Los niños nacieron en 11 centros participantes de la red NICHD y NRN (National Institute of Child Health y Human Development Neonatal Research Network). La medida de resultado primaria tuvo tres niveles: sobrevida sin déficit del ND; sobrevida con déficit ND o muerte. Después de ajustar por las diferencias en las características de los niños, incluyendo centro de nacimiento, utilizamos modelos de regresión multinominales generalizados para compara el riesgo relativo de sobrevida sin déficit de ND, sobrevida con déficit del ND y muerte.

RESULTADOS

Los datos de resultado primario estuvieron disponibles para 4274 niños de 4458 (96%) nacidos en los 11 centros. El porcentaje de niños que sobrevivieron aumentó de 30% (424/1391) en la época 1 hasta 36% (487/1348) en la época 3 (p<0.001). El porcentaje de infantes que sobrevivió sin déficit de ND aumentó de 16% (217/1391) en la época 1 a 20% (276/1348) en la época 3 (p= 0.001), mientras que el porcentaje de niños que sobrevivió con déficit del ND no cambió significativamente (15%{207/1391} en la época 1 y 16% {211/1348} en la época 3, p=0.29). Después del ajuste por cambios en las características de base de los niños a lo largo del tiempo, ambas la tasa de sobrevida con déficit de ND (comparada con muerte) y la sobrevida sin déficit de ND (comparada con muerte) aumentaron con el tiempo (RR ajustados, 1.27 [95% intervalo de confianza {IC}, 1.01 a 1.59] y 1.59 [IC 95%, 1.28 a 1.99] respectivamente).

CONCLUSIONES

La tasa de sobrevida sin déficit de ND aumentó entre 2000 y 2011 en esta gran cohorte de niños periviables.

El cuidado de niños en el límite de la viabilidad continúa siendo un gran desafío para la medicina neonatal y perinatal (1). Los infantes nacidos entre las semanas 22 a 24 de gestación con frecuencia mueren o sobreviven con déficits del ND a largo plazo (2-4). El enfoque para la resucitación y el manejo en estas edades gestacionales tempranas varía sustancialmente (1, 5). Los datos reportados durante los últimos cinco años indican que la mortalidad ha declinado entre los infantes extremadamente prematuros (5-9). Investigadores de la Red de Investigación Neonatal (NRN) del Instituto Nacional de salud infantil (NICHD) y desarrollo humano reportaron un descenso en la mortalidad a lo largo de las dos últimas décadas, con las mayores ganancias en sobrevida entre los niños nacidos a las 23 y 24 semanas de gestación después de 2008 (8,9). Dichos estudios generan preguntas acerca del resultado del ND en los infantes sobrevivientes. Estudios de la NRN sobre períodos previos no han mostrado significativa mejoría en los resultados de ND a lo largo del tiempo en bebés periviables (2, 3), y hay preocupación que la mortalidad en descenso en esta población pueda llevar a un mayor número de infantes sobreviviendo con déficits de ND (10, 11). La disponibilidad de datos tanto sobre mortalidad como resultados de ND entre los sobrevivientes es importante para las familias y los clínicos que deben tomar decisiones tempraneasen el cuidado de estos niños de alto riesgo (1).

El objetivo de nuestro estudio fue evaluar los cambios a lo largo del tiempo en la sobrevida y el ND entre infantes nacidos a las 22-24 semanas de EG, al ser examinados a los 18-22 meses de EC (definida como la edad que el infante tendría si hubiera nacido a término). Nuestra hipótesis fue que junto a la tasa de sobrevida, también aumentó la tasa de sobrevida sin déficit del ND desde el año 2000 hasta el 2011.

Métodos

Población en estudio y recolección de datos

Incluímos infantes nacidos a las 22 semanas 0 días hasta 24 semanas 6 días de EG entre el 1º de enero, 2000, y 31de diciembre, 2011, que fueron enrolados en la base de datos de registro genérico de la NICHD NRN. Los datos de 11 centros académicos terciarios que participaron en la NRN durante el tiempo completo del período de estudio fueron incluídos en el análisis. Un total de 427 infantes que no nacieron en los centros fueron excluídos. Los datos de la díada madre-hijo fueron recolectados prospectivamente por personal de investigación entrenados para todos los nacidos vivos, que incluyeron los bebés fallecidos en sala de partos...

La EG fue definida como las semanas completas de gestación, determinadas según el mejor cálculo obstétrico basado en la fecha de última menstruación, factores obstétricos, o ultrasonograma prenatal (o combinación de ellos), o-cuando el dato obstétrico no estuvo disponible- según el examen neonatal que incluía examen de Ballard o Dubowitz (12, 13). Para determinar si hubo cambios en las prácticas de resucitación en el tiempo, evaluamos la proporción de infantes que no recibieron tratamiento activo después del nacimiento, definido como uso de surfactante, intubación endotraqueal, soporte ventilatorio (es decir, presión positiva continua de la vía aérea, ventilación con bolsa y máscara, o ventilación mecánica), compresiones torácicas, epinefrina, o nutrición parenteral (5).

Pequeño para la edad gestacional fue definido como PN debajo del percentilo 10 en las curvas de crecimiento de Olsen (14). Hemorragia intraventricular severa (HIV) fue definida como grado III a IV, según los criterios de Papile et al (15). La presencia de sepsisfue determinada por la presencia de un hemocultivo positivo y fue clasificada como temprana (≤72 hrs) o tardía (> 72 hrs). Retinopatía del prematuro se consideró severa si el infante recibió tratamiento quirúrgico, bevacizumab, o ambos. Enterocolitis necrotizante fue definida como el estadio Bell II a III, según la clasificación de Bell modificada (con scores que van de I a III y más indicando mayor severidad de enfermedad) (16). Los infantes fueron considerados como portadores de DBP si estaban recibiendo oxígeno suplementario a las 36 semanas de edad postmenstrual (EG del bebé al nacer más el tiempo transcurrido postnatal [edad cronológica]).

Generalidades del estudio

Los comités institucionales de revisión de cada uno de los 11 centros aprobaron el protocolo, disponible con el texto completo de este artículo en NEJM.org. Nueve centros requirieron consentimiento informado escrito para el protocolo de seguimiento (dos centros concedieron una excepción), y un centro requirió consentimiento informado escrito para el protocolo intra-hospitalario (10 centros eximieron). El tercer autor, un estadístico en el centro de coordinación de datos, tuvo acceso completo a los datos y realizó el análisis. Todos los autores aseguraron la integridad, exactitud y que los datos fueran completos asi como los análisis y la fidelidad del estudio con el protocolo.

Medidas de resultado

La primera medida de resultado fue un resultado de tres niveles- sobrevida sin déficit de ND, sobrevida con déficit ND, o muerte, determinados a los 18-22 meses de EC con el uso de exámenes neurológicos y de la Escala Bayley de Desarrollo en infantes y niños, segunda edición (Bayley- II), para los niños nacidos entre 2000 y 2005, y tercera edición (Bayley-III), para los bebés nacidos entre 2006 al 2011.Las diferencias entre las dos ediciones están resumidas entre las tablas S1 en el apéndice suplementario, disponible en NEGM.org. Los niños fueron considerados como déficit de ND si tenían por lo menos una de las siguientes condiciones: parálisis cerebral moderada o severa, sistema de clasificación de la función motora gruesa(GMFCS) en un nivel de por lo menos 2 (sobre una escala de 1" déficit leve" a 5 " déficit más severo"), pérdida auditiva profunda, requiriendo amplificación en ambos oídos, déficit visual profundo con una agudeza visual de menos de 20/200 en ambos ojos, o déficit cognitivo, que fue definido como un score de desarrollo mental de menos de 70 (2 desvío estándar de bajo media ± DS de 100± 15 [los scores van desde 50 a 150, con los scores más bajos indicando un mayor grado de retraso madurativo]) (Bayley-II) o un score compuesto cognitivo inferior a 85 (una desviación estándar debajo de media ± DS de 100±15 [los scores van desde 55 a 145, con los scores más bajos indicando un mayor grado de retraso madurativo])-(Bayley-III). Seleccionamos estos puntos de corte para ajustar para la diferencia entre el Bayley –II y Bayley-III en estimar el desempeño cognitivo (17-20), sobre la base de datos que muestran un 97% de concordancia entre el score de desarrollo mental Bayley-II menor de 70 y el score compuesto cognitivo Bayley-III menor de 85% (21). Los scores motores Bayley-II y Bayley-III y los scores de lenguaje Bayley –III no fueron incluidos en la definición para déficit

Dada la potencial discrepancia entre las pruebas Bayley-II y Bayley-III, elegimos el déficit neurosensorial como medida secundaria para comparar los resultados neurológicos a lo largo del tiempo independiente de los scores Bayley. El déficit neurosensorial fue definido como parálisis cerebral moderada o severa, GMFCS de al menos dos, pérdida auditiva profunda, o déficit visual profundo.

ANALISIS ESTADISTICO

Comparamos los resultados entre infantes de tres épocas de año de nacimiento (2000-2003 [época 1], 2004-2007[época 2], 2008-2011[época 3]). El periodo de estudio y las definiciones de época fueron elegidos para ser consistentes con las definiciones en un reporte reciente de la NRN sobre cambios en la mortalidad a lo largo del tiempo (8) y para la consistencia con otros estudios de la NRN sobre resultados ND en infantes en el límite de la viabilidad sobe épocas consecutivas (2,3). Las características demográficas, perinatales, condiciones médicas, tratamientos, y resultados fueron comparados a través de las épocas con el test de chi cuadrado para variables categóricas y test de medianas para las variables continuas. Los resultados fueron estratificados acorde a la época para cada uno de los centros participantes. Un modelo lógico generalizada de múltiple nivel fue realizado para determinar el efecto de la época sobre resultado de 3 niveles categórico, ajustando por edad gestacional, gestación múltiple, raza materna, sexo del infante, y estado de pequeño para la edad gestacional; el centro de nacimientos fue incluido como un efecto aleatorio. Estas covariables fueron seleccionadas para

ajustar por factores basales que pueden influenciar los resultados (22,23). Las variables relacionadas a prácticas de cuidado que pueden haber variado en el tiempo, tales como el uso de corticosteroides antenatales, fueron dejadas fuera del análisis de forma que el efecto temporal no fuera oscurecido. Un enfoque de modelo similar se utilizó para el resultado de déficit neurosensorial. Subgrupos de análisis pre especificados se realizaron acorde a la semana gestacional en la cual nacieron los infantes. Debido a que los cambios en los resultados a lo largo de tiempo podrían reflejar cambios en las prácticas de resucitación, repetimos los análisis ajustados con la muestra limitada a los infantes que recibieron tratamiento activo.

Para determinar más aun el cambio de Bayley-II a Bayley-III llevamos un análisis de sensibilidad para evaluar cambios en resultados a lo largo de los años desde la implementación del Bayley-III. El análisis fue restringido a niños nacidos entre 2003-2011. Utilizamos el año de nacimiento, especificado como una variable continua, en lugar de la época como variable tiempo en el modelo y ajustados por las mismas variables como en el modelo de regresión en el resultado primario.

Todos los análisis fueron desarrollados con el uso del software SAS, versión 9,3 (instituto SAS). Valores de p de 2 colas de menos de 0,05 fueron considerados de significancia estadística. El análisis de resultado primario se considero confirmatorio, y todos los otros análisis reportados fueron tomados como exploratorios y generadores de hipótesis, con los valores de p presentados para propósitos descriptivos. Por lo tanto no se hicieron ajustes para pruebas múltiples.

RESULTADOS

CARACTERISTICAS DE LOS INFANTES Y MATERNAS

Un total de 4458 niños nacieron en los 11 centros participantes durante el período en estudio. El análisis de la cohorte incluyo 4274 infantes (96%) nacidos a las 22 semanas, 1435 (34%) nacidos a las 23 semanas, y 2090 (49%) nacidos a las 24 semanas. El PN, EG, y la distribución del sexo no difirieron significativamente entre épocas, pese a que la proporción de infantes

Tabla 1. Características, Condición medica y Terapias.

Variable	Epoch 1 (2000-2003)	Epoch 2 (2004-2007)	Epoch 3 (2008-2011)	valor p
Todos los niños				
N° total en cohorte	1391	1535	1348	
Promedio del peso al nacer (rango interquartilar) *	600 (533–670)	590 (520–670)	595 (511–680)	0.11
Edad gestacional al nacer - n°/total (%)				
22 sem	241/1391 (17)	274/1535 (18)	234/1348 (17)	0.92
23 sem	496/1391 (36)	489/1535 (32)	450/1348 (33)	0.09
24 sem	654/1391 (47)	772/1535 (50)	664/1348 (49)	0.20
Pequeño par aedad gestacional n°/total (%)	39/1391 (3)	65/1535 (4)	105/1347 (8)	<0.001
Sexo masculino n°/total (%)	759/1391 (55)	834/1535 (54)	702/1348 (52)	0.35
Raza n°/total (%) **				
Negra	642/1385 (46)	708/1521 (47)	608/1322 (46)	0.96
Blanca	695/1385 (50)	747/1521 (49)	639/1322 (48)	0.63
Otra	48/1385 (3)	66/1521 (4)	75/1322 (6)	0.02
Nacimiento múltiple n°/ total (%)	330/1391 (24)	422/1535 (27)	362/1348 (27)	0.049
Glucocorticoides prenatales n°/total (%)				
Alguna dosis	799/1388 (58)	881/1532 (58)	860/1346 (64)	<0.001
Curso completo	398/1386 (29)	511/1527 (33)	593/1342 (44)	<0.001
Antibióticos antenatales n°/total (%) ***	987/1388 (71)	991/1531 (65)	884/1345 (66)	0.001
Cesáreas n°/total (%)	428/1388 (31)	587/1535 (38)	505/1345 (38)	<0.01
Tratamiento no activo, de acuerdo a la edad gestacional. n°/total (%) *				
22 sem	183/241 (76)	213/274 (78)	186/234 (79)	0.65
23 sem	134/496 (27)	150/489 (31)	136/450 (30)	0.39
24 sem	40/654 (6)	32/772 (4)	24/664 (4)	0.07
Total	357/1391 (26)	395/1535 (26)	346/1348 (26)	>0.99
Tratamiento con surfactante n°/total (%)	892/1391 (64)	1009/1533 (66)	889/1348 (66)	0.53
Edad materna promedio (rango intercuartilar) años	25 (21–31)	26 (22–31)	27 (22–32)	<0.001
Educación materna menor que la secundaria n° / total (%)	235/766 (31)	305/1023 (30)	189/792 (24)	0.004
Niños sobrevivientes > 12 hs				
N° total en las cohortes	855	968	865	
Hemorragia intraventricular severa n°7total (%)	236/788 (30)	260/889 (29)	237/824 (29)	0.87
Leucomalacia periventricular n°/total (%)	58/789 (7)	53/889 (6)	58/822 (7)	0.48
Hidrocefalia posthemorragica con colocacion de shunt n°/total (%)	26/854 (3)	10/858 (1)	5/704 (1)	<0.001
Sepsis de inicio precoz n°/total (%)	30/855 (4)	35/967 (4)	19/863 (2)	0.19
Sepsis de inicio tardio n°/total (%)	370/734 (50)	447/834 (54)	331/790 (42)	<0.001
Retinopatia de la Prematuridad Severa n°/total (%)	84/495 (17)	165/535 (31)	126/547 (23)	<0.001
Enterocolitis Necrotizante n°/total (%)				
No cirugía	41/855 (5)	57/968 (6)	47/864 (5)	0.59
Con cirugía	66/855 (8)	87/968 (9)	67/864 (8)	0.52
Cirugía por PDA n°/total (%)	163/855 (19)	187/968 (19)	135/862 (16)	0.08
Ventilación de alta frecuencia n°/total (%)	473/855 (55)	611/966 (63)	547/865 (63)	<0.001
Displasia Broncopulmonar n°/total (%)	372/470 (79)	374/511 (73)	386/536 (72)	0.02
Glucocorticoide postnatal n°/total (%)	298/853 (35)	154/953 (16)	169/861 (20)	<0.001

pequeños para la EG aumento significativamente con el tiempo (Tabla 1). La mediana de edad materna aumento con el tiempo, y la proporción de madres con un nivel de educación inferior al secundario disminuyo. Las tasas de nacimientos múltiples, cesáreas, y uso glucocorticoides antenatales aumento entre las épocas 1 y 3, pese a que la tasa de uso de antibióticos antenatales disminuyo. Las tasas de tratamiento activo no cambiaron significativamente entre épocas. Recibieron tratamiento activo 22% de los infantes nacidos a las 22 semanas (167 de 749), 71% de los nacidos a las 23 semanas (1015 de 1435), y 95% de los nacidos a las 24 semanas (1994 de 2090). La incidencia de hidrocefalia posthemorragica con colocación de válvula, sepsis tardía y DBP disminuyo la época 1 y 3 (Tabla 1). La tasa de uso de corticoides postnatales también disminuyo entre las épocas 1 y 3, pese a que la tasa de ventilación de alta frecuencia aumentó. Los porcentajes de infantes con hemorragia intraventricular severa, leucomalacia intraventricular, sepsis temprana, enterocolitis necrotizante, y ligadura de ductus

arterioso persistente no difirieron significativamente entre épocas. La incidencia de retinopatía del prematuro severa fue más alta en la época 2.

RESULTADOS

El porcentaje de infantes que sobrevivieron sin déficit del ND aumento del 16% (217 de 1319) en la época 1 a 20% (276 de 1348) en la época 3 (p menor a 0.001) (Tabla 2). La tasa de muerte más baja se produjo en la época 3 (64% [861 de 1348 murieron]). Las proporciones de infantes que sobrevivieron con déficit del ND no difirieron significativamente entre épocas. Entre los infantes nacidos a las 22 semanas no hubo cambios significativos en resultados (sobrevida sin déficit ND, sobrevida con déficit ND, y muerte) a lo largo del tiempo. Entre los infantes nacidos a las 23 y 24 semanas la tasa de sobrevida sin déficit del ND aumento entre la época 1 y 3, pero la tasa de sobrevida con déficit del ND no cambio significativamente.

Entre los niños sobrevivientes no encontraron diferencias significativas en la incidencia de ND y déficit neurosensorial entre épocas (Tabla 3). La incidencia de déficit visual profundo disminuyo significativamente a 2 de 484 infantes (menos 1%) en la época 3, pero las tasas de otros componentes individuales del déficit del ND fueron similares en el tiempo. Sobrevida y resultado de ND variaron entre centros (fig 1).

De los 4274 infantes con datos para el resultado primario, 4227 tuvieron datos completos de todas las variables incluidas en el modelo general de regresión (46 infantes fueron excluidos porque faltaron datos de la raza y un infante fue excluido porque faltaba el dato porque era pequeño para la edad gestacional). Después de ajustar por las características basales, encontramos que tanto la tasa de sobrevida del ND vs muerte y la tasa de sobrevida sin déficit del ND vs muerte aumentaron entre la época 1 y 3 y entre la época 2 y 3 (Tabla 4). El aumento en la tasa de sobrevida sin déficit del ND no fue significativamente superior al de la sobrevida con déficit del ND. Nuestros hallazgos fueron similares cuando limitamos el análisis a los infantes que recibieron tratamiento activo.

Después de excluir el score de Bayley de nuestros resultados, encontramos que la tasa de sobrevida con déficit Neurosensorial vs muerte y la tasa de sobrevida son déficit Neurosensorial vs muerte aumento en el tiempo, pero el aumento en la tasa de sobrevida con déficit neurosensorial no difirió significativamente del aumento de la tasa de sobrevida sin déficit neurosensorial (Tabla 4).

Entre los infantes nacidos a las 23 semanas, tanto la tasa de sobrevida sin déficit ND vs muerte y la tasa de sobrevida sin déficit ND vs. Sobrevida con déficit ND aumentaron entre las épocas 1 y 3 (Tabla 4). Entre los niños nacidos a los 24 semanas, la tasa de sobrevida con déficit del ND vs muerte y la tasa de sobrevida sin déficit del ND vs muerte aumentaron el tiempo, pero estas tasas de aumento no difirieron significativamente. No hubo cambio significativo en los resultados entre los infantes nacidos a las 22 semanas. Sin embargo, los intervalos de confianza del 95% fueron amplios, lo cual refleja el pequeño tamaño muestral en este grupo de edad gestacional.

En los análisis de sensibilidad para evaluar cambios en resultados entre infantes elegibles del Bayley III (es decir, bebes que nacieron entre 2006-2011), en quienes se empleo el año de nacimiento en lugar de la época del modelo de regresión, encontramos que la tasa de sobrevida sin déficit ND vs muerte aumento desde 2006 al 2011 (riesgo relativo ajustado, 1,08 x cada año de aumento; y ISE 95%, 1,04 a 1,13). La tasa de sobrevida con déficit del ND vs muerte también aumento (Riesgo relativo ajustado 1,08; intervalo de confianza 95%, 1,03 a 1,13). La tasa de sobrevida sin déficit de ND vs sobrevida con déficit ND no cambio significativamente en el tiempo (riesgo relativo ajustado, 1,00; intervalo de confianza 95%, 0,96 a 1,05).

DISCUSIÓN

Nuestro estudio mostró un aumento de la tasa de sobrevida sin déficit del ND desde 2000 al 2011 en una gran cohorte de niños nacidos en el límite de la viabilidad en un consorcio de centro de cuidados terciarios académicos de la EEUU. Una caída significativa en la mortalidad

durante el periodo de estudio estuvo acompañada por aumentos relativos en la tasa de sobrevida con déficit del ND y la tasa de sobrevida sin déficit del ND. El aumento en la tasa de sobrevida no estuvo asociado con un aumento desproporcionado en la tasa de sobrevida con déficit del ND; más vale la tasa de sobrevida sin déficit ND y la tasa de sobrevida con déficit del ND aumentaron similarmente (riesgo relativo ajustado, 1,27; intervalo de confianza 95%, 0,99 a 1,65). Estos hallazgos son importantes para guiar la consejería y la toma de decisiones con respecto al nacimiento en el límite de la viabilidad. El pronóstico continúa siendo reservado; en la época más reciente la mortalidad fue 64%, y 43 % de los sobrevivientes tuvieron déficit ND.

Tabla 2. Supervivencia y Neurodesarrollo 18-22 meses de edad corregida.

Resultado	Epoch 1 (2000-2003)		Epoch 2 (2004-2007)		Epoch 3 (2007-2011)		valor p
	no./total no.	% (95% CI)*	no./total no.	% (95% CI)*	no./total no.	% (95% CI)*	
Todos los niños							
Supervivientes sin alteración del neurodesarrollo	217/1 391	16 (14- 18)	250/1535	16 (15-18)	274/1348	20 (18- 23)	0.001
Supervivientes con alteración del neurodesarrollo	207/1 391	15 (13- 17)	209/1535	14 (12-15)	211/1348	16 (14- 18)	0.29
Muertos	967/1 391	70 (67- 72)	1074/1535	70 (68-72)	863/1348	64 (61- 66)	<0.001
Supervivientes sin alteración del neurodesarrollo	345/1 380	25 (22- 27)	391/1533	26 (23-28)	395/1348	29 (27- 32)	0.01
Supervivientes con alteración del neurodesarrollo	73/1 380	5 (4- 7)	68/1533	4 (3-5)	92/1348	7 (5- 8)	0.01
Nacidos a las 22 semanas							
Supervivientes sin alteración del neurodesarrollo	2/241	1 (0- 3)	4/274	1 (1-4)	3/234	1 (0- 4)	0.80
Supervivientes con alteración del neurodesarrollo	4/241	2 (0- 4)	9/274	3 (2-6)	5/234	2 (0- 5)	0.46
Muertos	235/241	98 (95- 99)	261/274	95 (92-97)	226/234	97 (93- 98)	0.39
Nacidos a las 23 semanas							
Supervivientes sin alteración del neurodesarrollo	34/496	7 (5- 9)	55/489	11 (9-14)	59/450	13 (10- 17)	0.005
Supervivientes con alteración del neurodesarrollo	63/496	13 (10- 16)	41/489	8 (6-11)	51/450	11 (9- 15)	0.08
Muertos	399/496	80 (77- 84)	393/489	80 (77-84)	340/450	76 (72- 79)	0.11
Nacidos a las 24 semanas							
Supervivientes sin alteración del neurodesarrollo	181/654	28 (24- 31)	191/772	25 (22-28)	214/664	32 (29- 36)	0.007
Supervivientes con alteración del neurodesarrollo	140/654	21 (18- 25)	159/772	21 (18-24)	155/664	23 (20- 27)	0.44
Muertos	333/654	51 (47- 55)	422/772	55 (51- 58)	295/664	44 (41- 48)	<0.001

Tabla 3. Neurodesarrollo entre niños sobrevivientes a los 18-22 meses de edad corregida.

Resultado	Epoch 1 (2000–2003)	Epoch 2 (2004–2007)	Epoch 3 (2008–2011)	valor p
		*no./total no. (%)**		
Discapacidad del neurodesarrollo	207/424 (49)	209/459 (46)	211/487 (43)	0.25
Discapacidad Neurosensorial	73/413 (18)	66/457 (14)	92/487 (19)	0.18
Paráliisis Cerbral moderada o severa	62/423 (15)	50/458 (11)	56/487 (11)	0.19
Parálisis cerebral severa.	34/424 (8)	25/459 (5)	26/487 (5)	0.18
Discapacidad visual profunda.	10/424 (2)	7/457 (2)	2/484 (<1)	0.04
Pérdida auditiva severa	17/421 (4)	16/457 (4)	14/487 (3)	0.63
Discapacidad Cognitiva	194/417 (47)	204/457 (45)	195/480 (41)	0.19
Discapacidad Cognitiva solamente.**	123/417 (29)	141/457 (31)	119/480 (25)	0.10

***El número de niños evaluados bajo escala de Bailey y del desarrollo fue 421 para Epoch 1, 458 para Epoch2, y 480 para Epoch3. El número de niños bajo examen neurológico fue 424 para Epoch 1, 4458 para Epoch2 y 487 para Epoch 3.**
****La discacpacidad cognitiva solamente indica que los niños con discapacidad cognitiva pero sin parálisis cerebral severa o moderada, discapacidad visual o perdidad auditiva profunda**

Las mejoras en la sobrevida y en los resultados del ND que observamos pueden reflejar avances en el cuidado obstétrico y neonatal. Observamos descensos en las tasas de uso de glucocorticoides neonatales, sepsis tardía, hidrocefalia posthemorragica con colocación de shunt, DBP en el tiempo, cada una de las cuales ha estado asociado independientemente con resultados adversos del ND (24-27). El manejo perinatal proactivo ha estado asociado con mejores resultados entre los infantes extremadamente prematuros incluyendo una tasa aumentada de sobrevida y tasas sin cambio o reducida de discapacidad entre los sobrevivientes (5,20, 28-30). En nuestro estudio, las tasas de nacimiento por cesárea y de glucocorticoides antenatales aumentaron con el tiempo. La mejoría en los resultados no pareció deberse a cambios en el uso de tratamiento activos para los niños, porque las tasas de tratamiento activo fueron similares entre épocas y los hallazgos del estudio no cambiaron significativamente cuando restringimos el análisis a los bebes que recibieron tratamiento activo. Los cambios en las características maternas pueden haber contribuido a la mejora de los resultados, porque la edad materna y el nivel de educación aumentaron en el tiempo. Estudios previos de sobrevida y

resultados del ND entre bebes extremadamente prematuros han mostrado resultados mixtos con reporte de tasas de déficit del ND aumentados (10,11), sin cambios (2, 3,31), o disminuidas en el tiempo (32,33). Muchos de estos estudios incluyeron primariamente infantes más maduros, y no queda claro si los resultados pueden ser extrapolados a la población en el límite de la viabilidad. Comparar los resultados del ND entre estudios en esta población sería complicado por los datos dispersos y diferencias en la selección de muestras, en los criterios utilizados para definir déficit, y la edad al seguimiento. Estudios del Reino Unido, Suecia y Japón publicados en 2012 y 2013, mostraron tasas del déficit del ND del 34% (46 de 136 niño), 41% (56 de 138), y 47% (130 de 279) respectivamente, entre infantes sobrevivientes nacidos entre las 22 y 24 semanas, al ser evaluados a los 2 ½ a 3 años de edad corregida, al comparar con una tasa del 46% (627 de 1370), en nuestro estudio (20,31,34). Entre niños nacidos a las 24 semanas, las tasas de déficit del ND fueron más altas en nuestro estudio (44%) que en estos tres estudios (30 a 37%). No queda claro cuanta de esta variación es debida a diferencias en la muestra, diseño del estudio, características de los niños o practicas de cuidado. Encontramos variación en los resultados por centros; esta observación es consistente con los hallazgos de otros estudios publicados en el 2015 y 2004 que evaluaban niños extremadamente prematuros (5,22).

En el subgrupo de análisis realizado según la semana gestacional en que nacieron los bebés, encontramos que la tasa de sobrevida sin déficit del ND aumento en el tiempo entre los bebes nacidos a las 23 y 24 semanas. Sin embargo, solo 1% de los niños nacidos a las 22 semanas sobrevivió sin déficit del ND en cada época. Entre los 167 infantes nacidos a las 22 semanas que recibieron tratamiento activo después de nacer 9 (5%) sobrevivieron son déficit del ND.

Las mejores mediciones de resultados del ND para infantes prematuros continúan siendo debatidas. Nuestra definición de déficit de ND incluyo medida de la función motora, déficit sensorial, retraso cognitivo, que es consistente con la definición utilizada en otros estudios. Los clínicos y la familia deberían notar que es factible que haya variación sustancial en el funcionamiento a largo plazo de niños clasificados como portadores del ND en la infancia temprana. Pese a que la determinación temprana del ND es importante para la identificación a tiempo de niños en riesgo para déficit neurológicos a largo plazo o retraso madurativo, su capacidad para predecir la función más adelante es limitada (35,37). Muchos niños se acoplaran a sus pares para la edad escolar, mientras otros tendrán déficit persistente. A la inversa algunos niños sin déficit del ND en la infancia temprana manifestaran déficit en la edad escolar (37,38). El Bayley II y el Bayley III han mostrado correlacionarse con los resultados cognitivos más tardíos, pero dan cuenta de solo una minoría de la variación en el funcionamiento cognitivo tardío (35, 36,39). Las tasas reportadas de déficit de edad escolar entre niños que nacieron extremadamente prematuros son generalmente más bajas que las reportadas en la infancia temprana, pero los estudios están limitados por los pequeños tamaños muestrales y los resultados heterogéneos (35, 37,40). Es necesario investigación adicional para comprender mejor los resultados a largo plazo entre niños en el límite de la viabilidad.

Nuestro análisis estuvo complicado por la transición del Bayley II y Bayley III durante el periodo de estudio. Los estudios incluyendo niños extremadamente prematuros han mostrado que los scores compuestos cognitivos del Bayley III son como en promedio, 10 a 11 puntos más altos que los scores del índice de desarrollo mental Bayley II (17,18). Para solucionar esta limitación, definimos el déficit cognitivo utilizando un score conservador el Bayley III menor que 85, que es un desvío estándar menor del score medio de 100. Johnson et al (21) observaron 97% de concordancia entre el score de desarrollo mental Bayley II menor de 70 y el score compuesto cognitivo del Bayley III menor a 85. Más aun, mostramos un aumento en la tasa de sobrevida sin déficit neurosensorial en el tiempo, con el déficit neurosensorial definido por los mismos componentes que el déficit del ND con la exclusión de los scores Bayley. Finalmente, cuando evaluamos los cambios en los resultados en los años desde la implementación del Bayley III, los resultados fueron consistentes.

Nuestro estudio tiene limitaciones adicionales. Los datos representan un grupo selecto de infantes nacidos en un subgrupo de centros académicos y pueden ser no generalizables a otras

poblaciones. Más aun, no corregimos para pruebas múltiples, lo cual aumenta la probabilidad de que algunas de las diferencias significativas que observamos en nuestro análisis de resultados secundario puedan haber ocurrido por azar. Hay una pequeña chance de que los cambios de los resultados en el tiempo reflejen sobo variaciones aleatorias.

En conclusión, nuestro estudio demostró un pequeño pero significativo aumento en la tasa de sobrevida sin déficit del ND a los 18- 22 meses de edad corregida entre niños nacidos en el límite de la viabilidad. Pese a las mejoras en el tiempo, la incidencia de muerte, déficit del ND, y otros resultados adversos permanece alto en esta población.

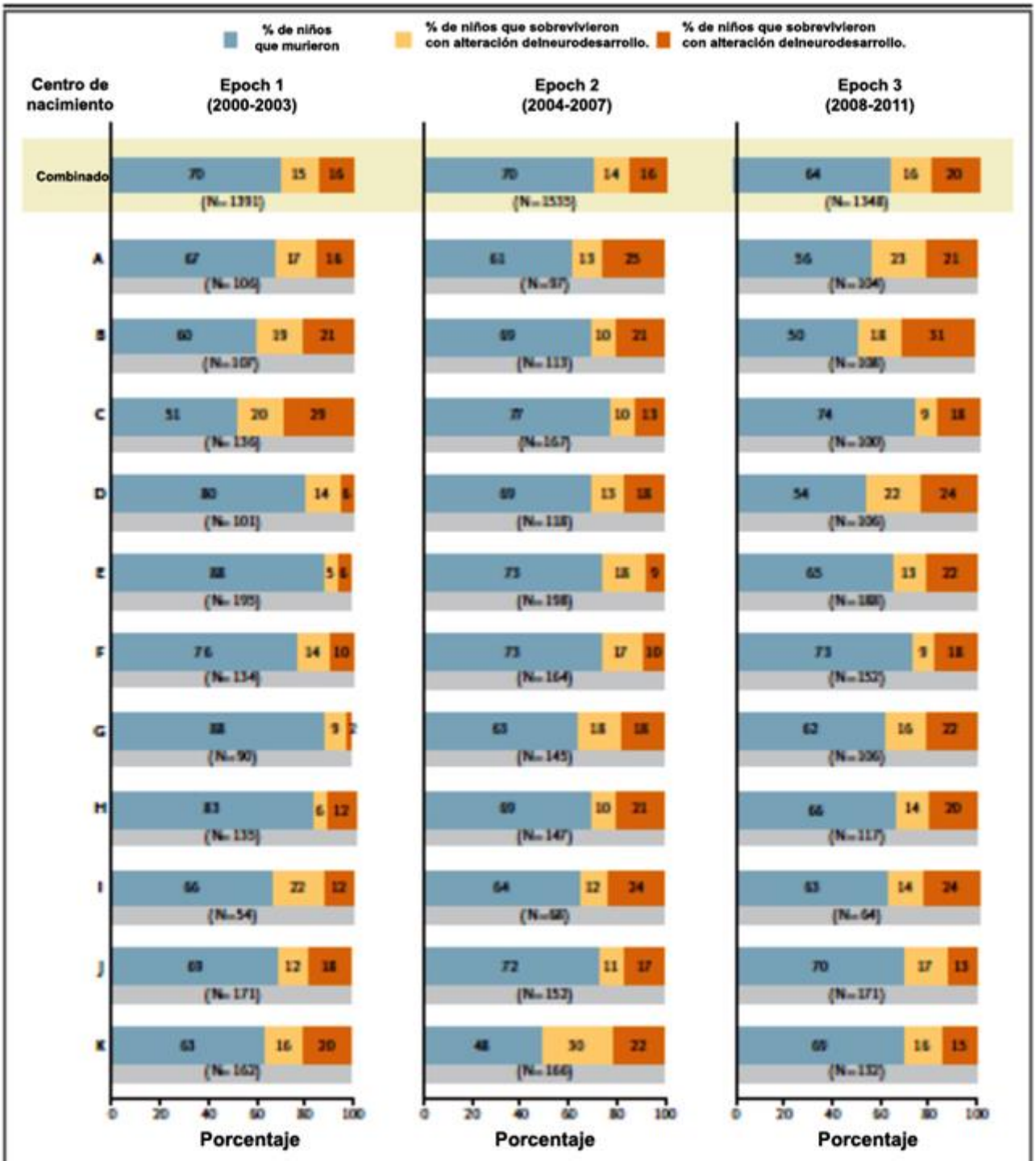

Figura 1. Mortalidad y Neurodesarrollo a los 18-22 meses de dad corregida por centro y Epoch.
Se muestran las tasas de muerte, supervivencia con y sin alteraciones del neurodesarrollo en los 11 centros incluidos en el análisis. Las tasas fueron ajustadas por edad gestacional al nacer,, sexo, raza, gstaciones múltiples y pequeños para edad gestacional.

Tabla 4. Supervivencia y resultado neurológico a los 18-22 ms de edad corregida.

Resultado	Riesgo Relativo Ajustado (IC 95%)	
	Epoch 3 (2008–2011) vs. Epoch 2 (2004–2007)	Epoch 3 (2008–2011) vs. Epoch 1 (2000–2003)
Todos los niños		
Supervivientes sin alteraciones del Neurodesarrollo vs muerte	1.52 (1.22–1.88)	1.59 (1.28–1.99)
Supervivientes con alteraciones del Neurodesarrollo vs muerte	1.43 (1.14–1.79)	1.27 (1.01–1.59)
Supervivientes sin alteraciones del Neurodesarrollo s supervivientes con alteración del neurodesarrollo	1.08 (0.83–1.40)	1.27 (0.99–1.65)
Supervivientes sin alteración Neurosensorial vs muerte.	1.39 (1.15–1.68)	1.44 (1.18–1.75)
Supervivientes con alteracion neurosensorial vs muerte.	1.93 (1.38–2.70)	1.54 (1.11–2.15)
Supervivientes sin alteración Neurosensorial vs supervivientes con alteración neurosensorial.	0.72 (0.51–1.02)	0.93 (0.66–1.32)
Nacidos a las 22 sem		
Supervivientes sin alteraciones del Neurodesarrollo vs muerte	0.74 (0.16–3.47)	1.30 (0.21–8.08)
Supervivientes con alteraciones del Neurodesarrollo vs muerte	0.63 (0.20–1.97)	1.30 (0.34–5.02)
Supervivientes sin alteraciones del neurodesarrollo vs supervivientes con alteraciones del neurodesarrollo.	1.13 (0.17–7.41)	0.99 (0.11–9.34)
Nacidos a las 23 sem		
Supervivientes sin alteraciones del Neurodesarrollo vs muerte	1.29 (0.86–1.94)	2.31 (1.46–3.66)
Supervivientes con alteraciones del Neurodesarrollo vs muerte	1.53 (0.98–2.40)	1.07 (0.71–1.62)
Supervivientes sin alteraciones del neurodesarrollo vs supervivientes con alteraciones del neurodesarrollo.	0.86 (0.49–1.50)	2.17 (1.23–3.83)
Nacidos a las 24 sem		
Supervivientes sin alteraciones del Neurodesarrollo vs muerte	1.63 (1.26–2.11)	1.46 (1.12–1.90)
Supervivientes con alteraciones del Neurodesarrollo vs muerte	1.46 (1.11–1.92)	1.34 (1.01–1.78)
Supervivientes sin alteraciones del neurodesarrollo vs supervivientes con alteraciones del neurodesarrollo.	1.12 (0.83–1.51)	1.08 (0.79–1.47)
Niños que recibieron tratamiento activo		
Supervivientes sin alteraciones del Neurodesarrollo vs muerte	1.55 (1.24–1.93)	1.64 (1.30–2.06)
Supervivientes con alteraciones del Neurodesarrollo vs muerte	1.44 (1.14–1.81)	1.30 (1.03–1.64)
Supervivientes sin alteraciones del neurodesarrollo vs supervivientes con alteraciones del neurodesarrollo.	1.08 (0.83–1.40)	1.26 (0.97–1.65)

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Survival and Neurodevelopmental Outcomes among Periviable Infants

Noelle Younge, M.D., M.H.S., Ricki F. Goldstein, M.D., Carla M. Bann, Ph.D., Susan R. Hintz, M.D., Ravi M. Patel, M.D., P. Brian Smith, M.D., M.P.H., M.H.S., Edward F. Bell, M.D., Matthew A. Rysavy, M.D., Ph.D., Andrea F. Duncan, M.D., Betty R. Vohr, M.D., Abhik Das, Ph.D., Ronald N. Goldberg, M.D., Rosemary D. Higgins, M.D., and C. Michael Cotten, M.D., M.H.S., for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network*

ABSTRACT

BACKGROUND

Data reported during the past 5 years indicate that rates of survival have increased among infants born at the borderline of viability, but less is known about how increased rates of survival among these infants relate to early childhood neurodevelopmental outcomes.

METHODS

We compared survival and neurodevelopmental outcomes among infants born at 22 to 24 weeks of gestation, as assessed at 18 to 22 months of corrected age, across three consecutive birth-year epochs (2000–2003 [epoch 1], 2004–2007 [epoch 2], and 2008–2011 [epoch 3]). The infants were born at 11 centers that participated in the National Institute of Child Health and Human Development Neonatal Research Network. The primary outcome measure was a three-level outcome — survival without neurodevelopmental impairment, survival with neurodevelopmental impairment, or death. After accounting for differences in infant characteristics, including birth center, we used multinomial generalized logit models to compare the relative risk of survival without neurodevelopmental impairment, survival with neurodevelopmental impairment, and death.

RESULTS

Data on the primary outcome were available for 4274 of 4458 infants (96%) born at the 11 centers. The percentage of infants who survived increased from 30% (424 of 1391 infants) in epoch 1 to 36% (487 of 1348 infants) in epoch 3 (P<0.001). The percentage of infants who survived without neurodevelopmental impairment increased from 16% (217 of 1391) in epoch 1 to 20% (276 of 1348) in epoch 3 (P=0.001), whereas the percentage of infants who survived with neurodevelopmental impairment did not change significantly (15% [207 of 1391] in epoch 1 and 16% [211 of 1348] in epoch 3, P=0.29). After adjustment for changes in the baseline characteristics of the infants over time, both the rate of survival with neurodevelopmental impairment (as compared with death) and the rate of survival without neurodevelopmental impairment (as compared with death) increased over time (adjusted relative risks, 1.27 [95% confidence interval {CI}, 1.01 to 1.59] and 1.59 [95% CI, 1.28 to 1.99], respectively).

CONCLUSIONS

The rate of survival without neurodevelopmental impairment increased between 2000 and 2011 in this large cohort of periviable infants. (Funded by the National Institutes of Health and others; ClinicalTrials.gov numbers, NCT00063063 and NCT00009633.)

From the Department of Pediatrics, Duke University, Durham (N.Y., R.F.G., P.B.S., R.N.G., C.M.C.), and the Statistics and Epidemiology Unit, RTI International, Research Triangle Park (C.M.B., A.D.) — both in North Carolina; the Department of Pediatrics, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA (S.R.H.); the Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta (R.M.P.); the Department of Pediatrics, University of Iowa, Iowa City (E.F.B., M.A.R.); the Department of Pediatrics, University of Wisconsin, Madison (M.A.R.); the Department of Pediatrics, University of Texas Medical School at Houston, Houston (A.F.D.); the Department of Pediatrics, Women and Infants' Hospital, Brown University, Providence, RI (B.R.V.); and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD (R.D.H.). Address reprint requests to Dr. Younge at the Department of Pediatrics, Duke University, DUMC Box 2739, Durham, NC 27710, or at noelle.younge@duke.edu.

*A complete list of investigators and participating sites in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network is provided in the Supplementary Appendix, available at NEJM.org.

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Care of periviable infants remains a great challenge in neonatal and perinatal medicine.[1] Infants born between 22 and 24 weeks of gestation often die or survive with long-term neurodevelopmental impairment.[2-4] The approach to resuscitation and management at these early gestational ages varies substantially.[1,5]

Data reported during the past 5 years indicate that mortality has declined among extremely premature infants.[6-9] Investigators at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) reported a decrease in mortality over the past two decades, with the greatest gains in survival seen among infants born at 23 and 24 weeks of gestation after 2008.[8,9] Such studies raise questions about neurodevelopmental outcomes in surviving infants. NRN studies over previous periods have not shown significant improvement in neurodevelopmental outcomes over time among periviable infants,[2,3] and there is concern that declining mortality in this population may lead to a greater number of infants surviving with neurodevelopmental impairment.[10,11] The availability of data on both mortality and neurodevelopmental outcomes among survivors is important for families and clinicians making early care decisions for these high-risk infants.[1]

The objective of our study was to evaluate changes over time in survival and neurodevelopmental outcomes among infants born at 22 to 24 weeks of gestation, as assessed at 18 to 22 months of corrected age (with corrected age defined as the age the infant would be if born at term). We hypothesized that in addition to the rate of survival, the rate of survival without neurodevelopmental impairment also increased from 2000 through 2011.

Methods

Study Population and Data Collection

We included infants born at 22 weeks 0 days to 24 weeks 6 days of gestation between January 1, 2000, and December 31, 2011, who were enrolled in the generic database registry of the NICHD NRN. Data from the 11 academic tertiary care centers that participated in the NRN for the entire duration of the study period were included in the analysis. A total of 427 infants who were not born at the centers were excluded. Data for mother–infant dyads were collected prospectively by trained research personnel for all live births, which included infants who died in the delivery room. Gestational age was defined as completed weeks of gestation, as determined according to the best obstetrical estimate that was based on the last menstrual period, obstetrical factors, or prenatal ultrasonogram (or a combination thereof), or — when obstetrical dating was unavailable — according to neonatal assessment that included the Ballard or Dubowitz examination.[12,13] To assess whether there were changes in resuscitation practices over time, we evaluated the proportion of infants who did not receive active treatment after birth, which was defined by the use of surfactant, endotracheal intubation, ventilatory support (i.e., continuous positive airway pressure, bag-mask ventilation, or mechanical ventilation), chest compressions, epinephrine, or parenteral nutrition.[5] Small for gestational age was defined as birth weight below the 10th percentile on Olsen growth curves.[14] Severe intraventricular hemorrhage was defined as grade III to IV, according to the criteria of Papile et al.[15] The presence of sepsis was determined by a positive blood culture and was classified as early onset (≤72 hours) or late onset (>72 hours). Retinopathy of prematurity was considered to be severe if the infant received surgical treatment, intravitreal bevacizumab, or both. Necrotizing enterocolitis was defined as Bell's stage II to III, according to the modified Bell's classification (with scores ranging from I to III and higher scores indicating greater severity of disease).[16] Infants were considered to have bronchopulmonary dysplasia if they were receiving supplemental oxygen at 36 weeks of postmenstrual age (the infant's gestational age at birth plus the time elapsed since birth [chronological age]).

Study Oversight

The institutional review boards at each of the 11 centers approved the protocol, available with the full text of this article at NEJM.org. Nine centers required written informed consent for the follow-up protocol (2 centers granted a waiver), and 1 center required oral informed consent for the in-hospital protocol (10 centers granted a waiver). The third author, a statistician at the data coordinating center, had full access to the data and performed the analysis. All the authors vouch for the integrity, accuracy, and completeness of the data and analyses and for the fidelity of the study to the protocol.

OUTCOME MEASURES

The primary outcome measure was a three-level outcome — survival without neurodevelopmental impairment, survival with neurodevelopmental impairment, or death, as assessed at 18 to 22 months of corrected age. Neurodevelopmental outcomes were assessed at 18 to 22 months of corrected age with the use of neurologic examinations and the Bayley Scales of Infant and Toddler Development, second edition (Bayley-II), for infants born between 2000 and 2005, and third edition (Bayley-III), for infants born between 2006 and 2011. Differences between the two editions are summarized in Table S1 in the Supplementary Appendix, available at NEJM.org. Infants were considered to have neurodevelopmental impairment if they had at least one of the following conditions: moderate or severe cerebral palsy, Gross Motor Function Classification System level of at least 2 (on a scale of 1 [mild impairment] to 5 [most severe impairment]), profound hearing loss requiring amplification in both ears, profound visual impairment with visual acuity of less than 20/200 in both eyes, or cognitive impairment, which was defined as a Mental Developmental Index score of less than 70 (two standard deviations below the mean ±SD score of 100±15 [scores range from 50 to 150, with the lower scores indicating a greater degree of developmental delay]) (Bayley-II) or a Cognitive Composite score of less than 85 (one standard deviation below the mean ±SD score of 100±15 [scores range from 55 to 145, with the lower scores indicating a greater degree of developmental delay]) (Bayley-III). We selected these cutoff points to adjust for the difference between Bayley-II and Bayley-III in estimating cognitive performance,[17-20] on the basis of data showing 97% agreement between a Bayley-II Mental Developmental Index score lower than 70 and a Bayley-III Cognitive Composite score lower than 85.[21] Bayley-II and Bayley-III motor scores and Bayley-III language scores were not included in the definition for neurodevelopmental impairment.

Given the potential discrepancy between Bayley-II and Bayley-III assessments, we chose neurosensory impairment as a secondary outcome to compare neurologic outcomes over time independent of Bayley scores. Neurosensory impairment was defined as moderate or severe cerebral palsy, Gross Motor Function Classification System level of at least 2, profound hearing loss, or profound visual impairment.

STATISTICAL ANALYSIS

We compared outcomes among infants in three birth-year epochs (2000–2003 [epoch 1], 2004–2007 [epoch 2], and 2008–2011 [epoch 3]). The study period and epoch definitions were chosen to be consistent with the definitions in a recent NRN report on changes in mortality over time[8] and for consistency with previous NRN studies of neurodevelopmental outcomes in periviable infants over consecutive epochs.[2,3] Demographics, perinatal characteristics, medical conditions, therapies, and outcomes were compared across epochs with the use of chi-square tests for categorical variables and median tests for continuous variables. Outcomes were stratified according to epoch for each of the participating centers. Multilevel generalized logit modeling was conducted to determine the effect of epoch on the three-level categorical outcome, with adjustment for gestational age, multiple gestation, maternal race, sex of the infant, and small-for-gestational-age status; birth center was included as a random effect. These covariates were selected to adjust for baseline factors that may influence outcomes.[22,23] Variables related to care practices that may have changed over time, such as the use of antenatal glucocorticoids, were left out of the analysis so that the temporal effect would not be obscured. A similar modeling approach was used for the outcome of neurosensory impairment. Prespecified subgroup analyses were performed according to the gestational week in which the infants were born. Because changes in outcomes over time could reflect changes in resuscitation practices, we repeated the adjusted analyses with the sample limited to infants who received active treatment.

To further address the change from Bayley-II to Bayley-III, we performed a sensitivity analysis to evaluate changes in outcomes over the years since the implementation of Bayley-III. The analysis was restricted to infants born between 2006 and 2011. We used birth year, specified as a continuous variable, in place of epoch as the time variable in the model and adjusted for the same variables as in the regression model of the primary outcome.

All analyses were performed with the use of SAS software, version 9.3 (SAS Institute). Two-sided P values of less than 0.05 were considered to indicate statistical significance. The primary outcome analysis was considered to be confirma-

tory, and all other reported analyses were deemed exploratory and hypothesis generating, with P values presented for descriptive purposes. Thus, no adjustments were made for multiple testing.

RESULTS

INFANT AND MATERNAL CHARACTERISTICS

A total of 4458 infants were born at 11 participating centers during the study period. The analysis cohort included 4274 infants (96%) for whom data on the primary outcome were available. The cohort comprised 749 infants (18%) born at 22 weeks, 1435 infants (34%) born at 23 weeks, and 2090 infants (49%) born at 24 weeks. Birth weight, gestational age, and infant sex distributions did not differ significantly across epochs, although the proportion of infants who were small for their gestational age increased significantly over time (Table 1). The median maternal age increased over time, and the proportion of mothers with an education level less than high school decreased. The rates of multiple births, cesarean sections, and antenatal glucocorticoid use increased between epoch 1 and epoch 3, although the rate of antenatal antibiotic use decreased. Rates of active treatment did not change significantly across epochs. Active treatment was received by 22% of the infants (167 of 749) born at 22 weeks, by 71% (1015 of 1435) born at 23 weeks, and by 95% (1994 of 2090) born at 24 weeks.

The incidence of posthemorrhagic hydrocephalus with shunt placement, late-onset sepsis, and bronchopulmonary dysplasia decreased between epoch 1 and epoch 3 (Table 1). The rate of postnatal glucocorticoid use also decreased between epoch 1 and epoch 3, although the rate of high-frequency ventilation increased. The percentages of infants with severe intraventricular hemorrhage, periventricular leukomalacia, early-onset sepsis, necrotizing enterocolitis, and ligation of a patent ductus arteriosus did not differ significantly across epochs. The incidence of severe retinopathy of prematurity was highest in epoch 2.

OUTCOMES

The percentage of infants who survived without neurodevelopmental impairment increased from 16% (217 of 1391) in epoch 1 to 20% (276 of 1348) in epoch 3 (P<0.001) (Table 2). The rate of death was lowest in epoch 3 (64% [861 of 1348 infants died]). The proportions of infants who survived with neurodevelopmental impairment did not differ significantly across epochs. Among infants born at 22 weeks, there was no significant change in outcomes (survival without neurodevelopmental impairment, survival with neurodevelopmental impairment, and death) over time. Among infants born at 23 and 24 weeks, the rate of survival without neurodevelopmental impairment increased between epoch 1 and epoch 3, although the rate of survival with neurodevelopmental impairment did not differ significantly.

Among surviving infants, we found no significant difference in the incidence of neurodevelopmental impairment or neurosensory impairment across epochs (Table 3). The incidence of profound visual impairment declined significantly to 2 of 484 infants (<1%) in epoch 3, but the rates of other individual components of neurodevelopmental impairment were similar over time. Survival and neurodevelopmental outcomes varied across centers (Fig. 1).

Of the 4274 infants with data on the primary outcome, 4227 infants had complete data on all of the variables included in the generalized logit regression model (46 infants were excluded because of missing data on race and 1 infant was excluded because of missing data on small-for-gestational-age status). After adjusting for baseline characteristics, we found that both the rate of survival with neurodevelopmental impairment versus death and the rate of survival without neurodevelopmental impairment versus death increased between epoch 1 and epoch 3 and between epoch 2 and epoch 3 (Table 4). The increase in the rate of survival without neurodevelopmental impairment was not significantly greater than that of survival with neurodevelopmental impairment. Our findings were similar when we limited the analysis to infants who received active treatment.

After we excluded the Bayley score from our outcomes, we found that both the rate of survival with neurosensory impairment versus death and the rate of survival without neurosensory impairment versus death increased over time, but the increase in survival rate with neurosensory impairment did not differ significantly from the increase in survival rate without neurosensory impairment (Table 4).

Among the infants born at 23 weeks, both the rate of survival without neurodevelopmental impairment versus death and the rate of survival without neurodevelopmental impairment versus survival with neurodevelopmental impairment in-

Table 1. Infant Characteristics, Medical Conditions, and Therapies.

Variable	Epoch 1 (2000–2003)	Epoch 2 (2004–2007)	Epoch 3 (2008–2011)	P Value*
All infants				
Total no. in cohort	1391	1535	1348	
Median birth weight (interquartile range) — g	600 (533–670)	590 (520–670)	595 (511–680)	0.11
Gestational age at birth — no./total no. (%)				
22 wk	241/1391 (17)	274/1535 (18)	234/1348 (17)	0.92
23 wk	496/1391 (36)	489/1535 (32)	450/1348 (33)	0.09
24 wk	654/1391 (47)	772/1535 (50)	664/1348 (49)	0.20
Small for gestational age — no./total no. (%)	39/1391 (3)	65/1535 (4)	105/1347 (8)	<0.001
Male sex — no./total no. (%)	759/1391 (55)	834/1535 (54)	702/1348 (52)	0.35
Race — no./total no. (%)†				
Black	642/1385 (46)	708/1521 (47)	608/1322 (46)	0.96
White	695/1385 (50)	747/1521 (49)	639/1322 (48)	0.63
Other	48/1385 (3)	66/1521 (4)	75/1322 (6)	0.02
Multiple birth — no./total no. (%)	330/1391 (24)	422/1535 (27)	362/1348 (27)	0.049
Antenatal glucocorticoids — no./total no. (%)‡				
Any receipt	799/1388 (58)	881/1532 (58)	860/1346 (64)	<0.001
Full course	398/1386 (29)	511/1527 (33)	593/1342 (44)	<0.001
Antenatal antibiotics — no./total no. (%)§	987/1388 (71)	991/1531 (65)	884/1345 (66)	0.001
Cesarean delivery — no./total no. (%)	428/1388 (31)	587/1535 (38)	505/1345 (38)	<0.01
No active treatment, according to gestational age at birth — no./total no. (%)¶				
22 wk	183/241 (76)	213/274 (78)	186/234 (79)	0.65
23 wk	134/496 (27)	150/489 (31)	136/450 (30)	0.39
24 wk	40/654 (6)	32/772 (4)	24/664 (4)	0.07
Total	357/1391 (26)	395/1535 (26)	346/1348 (26)	>0.99
Surfactant treatment — no./total no. (%)	892/1391 (64)	1009/1533 (66)	889/1348 (66)	0.53
Median maternal age (interquartile range) — yr	25 (21–31)	26 (22–31)	27 (22–32)	<0.001
Maternal education less than high school — no./total no. (%)	235/766 (31)	305/1023 (30)	189/792 (24)	0.004
Infants surviving >12 hr‖				
Total no. in cohort	855	968	865	
Severe intraventricular hemorrhage — no./total no. (%)	236/788 (30)	260/889 (29)	237/824 (29)	0.87
Periventricular leukomalacia — no./total no. (%)	58/789 (7)	53/889 (6)	58/822 (7)	0.48
Posthemorrhagic hydrocephalus with shunt placement — no./total no. (%)	26/854 (3)	10/858 (1)	5/704 (1)	<0.001
Early-onset sepsis — no./total no. (%)	30/855 (4)	35/967 (4)	19/863 (2)	0.19
Late-onset sepsis — no./total no. (%)	370/734 (50)	447/834 (54)	331/790 (42)	<0.001
Severe retinopathy of prematurity — no./total no. (%)	84/495 (17)	165/535 (31)	126/547 (23)	<0.001
Necrotizing enterocolitis — no./total no. (%)				
No surgery	41/855 (5)	57/968 (6)	47/864 (5)	0.59
With surgery	66/855 (8)	87/968 (9)	67/864 (8)	0.52
Surgery for patent ductus arteriosus — no./total no. (%)	163/855 (19)	187/968 (19)	135/862 (16)	0.08
High-frequency ventilation — no./total no. (%)	473/855 (55)	611/966 (63)	547/865 (63)	<0.001
Bronchopulmonary dysplasia — no./total no. (%)	372/470 (79)	374/511 (73)	386/536 (72)	0.02
Postnatal glucocorticoids — no./total no. (%)	298/853 (35)	154/953 (16)	169/861 (20)	<0.001

* P values were determined using chi-square tests for categorical variables and median tests for continuous variables.
† Race was determined by investigators on the basis of chart abstraction using categories specified in the study manual of operation (black, white, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or more than one race).
‡ Any receipt of antenatal glucocorticoids was defined as a full or partial course during the current pregnancy for the purpose of accelerating fetal maturity. A full course was defined as two doses of betamethasone (12 or 24 hours apart) or four doses of dexamethasone (≥6 hours apart).
§ Receipt of antenatal antibiotics was defined as receipt of any antibiotic preceding birth during the hospital admission in which delivery occurred.
¶ Active treatment was defined as the use of surfactant, endotracheal intubation, ventilatory support (i.e., continuous positive airway pressure, bag-mask ventilation, or mechanical ventilation), chest compressions, epinephrine, or parenteral nutrition.
‖ Data on medical conditions and therapies were available for infants surviving more than 12 hours and undergoing the applicable examination (e.g., sonogram for intraventricular hemorrhage).

creased between epoch 1 and epoch 3 (Table 4). Among the infants born at 24 weeks, both the rate of survival with neurodevelopmental impairment versus death and the rate of survival without neurodevelopmental impairment versus death increased over time, but the rates of increase did not differ significantly. There was no significant change in outcomes among the infants born at 22 weeks. However, the 95% confidence intervals for these estimates were wide, which reflects the small sample size in this gestational age group.

In the sensitivity analyses to evaluate changes in outcomes among the infants eligible for the Bayley-III examination (i.e., infants who were born between 2006 and 2011), in which birth year was used in place of epoch in the regression model, we found that the rate of survival without neurodevelopmental impairment versus death increased from 2006 to 2011 (adjusted relative risk, 1.08 per 1-year increase; 95% confidence interval [CI], 1.04 to 1.13). The rate of survival with neurodevelopmental impairment versus death also increased (adjusted relative risk, 1.08; 95% CI, 1.03 to 1.13). The rate of survival without neurodevelopmental impairment versus survival with neurodevelopmental impairment did not change significantly over time (adjusted relative risk, 1.00; 95% CI, 0.96 to 1.05).

DISCUSSION

Our study showed an increase in the rate of survival without neurodevelopmental impairment from 2000 through 2011 in a large cohort of periviable infants born at a consortium of U.S. academic tertiary care centers. A significant decline in mortality over the study period was accompanied by relative increases in both the rate of survival with neurodevelopmental impairment and the rate of survival without neurodevelopmental impairment. The increase in the rate of survival was not associated with a disproportionate increase in the rate of survival with neurodevelopmental impairment; rather, the rate of survival without neurodevelopmental impairment and the rate of survival with neurodevelopmental impairment increased similarly (adjusted relative risk, 1.27; 95% CI, 0.99 to 1.65). These findings are important for guiding counseling and decision making with respect to periviable birth. Prognosis continues to be guarded; in the most recent epoch, mortality was 64%, and 43% of surviving infants had neurodevelopmental impairment.

The improvements in survival and neurodevelopmental outcomes that we observed may reflect advances in obstetrical and neonatal care. We observed declines in the rates of postnatal glucocorticoid use, late-onset sepsis, posthemorrhagic hydrocephalus with shunt placement, and bronchopulmonary dysplasia over time, each of which has been independently associated with adverse neurodevelopmental outcomes.[24-27] Proactive perinatal management has been associated with better outcomes among extremely premature infants, including an increased rate of survival and unchanged or reduced rates of disability among survivors.[5,20,28-30] In our study, the rates of cesarean delivery and antenatal glucocorticoid use increased over time. The improvement in outcomes was unlikely to be due to changes in the use of active treatment for infants, because the rates of active treatment were similar across epochs and the study findings did not change significantly when we restricted the analysis to infants who received active treatment. Changes in maternal characteristics may have contributed to the improvement in outcomes, because maternal age and level of education increased over time.

Previous studies of survival and neurodevelopmental outcomes among extremely premature infants have shown mixed results, with reports of increased,[10,11] unchanged,[2,3,31] or decreased rates of neurodevelopmental impairment over time.[32,33] Many of these studies involved primarily more mature infants, and it is unclear whether the results can be extrapolated to the periviable population. Comparing neurodevelopmental outcomes across studies in this population would be complicated by sparse data and differences in sample selection, criteria used to define impairment, and age at follow-up. Studies from the United Kingdom, Sweden, and Japan, published in 2012 and 2013, showed rates of neurodevelopmental impairment of 34% (46 of 136 infants), 41% (56 of 138), and 47% (130 of 279), respectively, among surviving infants born at 22 to 24 weeks, as evaluated at 2.5 to 3 years of corrected age, as compared with a rate of 46% (627 of 1370) in our study.[20,31,34] Among infants born at 24 weeks, rates of neurodevelopmental impairment were higher in our study (44%) than in these three studies (30 to 37%). It is unclear how much of

Table 2. Survival and Neurodevelopmental Outcomes at 18 to 22 Months of Corrected Age.

Outcome	Epoch 1 (2000–2003)		Epoch 2 (2004–2007)		Epoch 3 (2008–2011)		P Value†
	no./total no.	*% (95% CI)**	*no./total no.*	*% (95% CI)**	*no./total no.*	*% (95% CI)**	
All infants‡							
Survival without neurodevelopmental impairment	217/1391	16 (14–18)	250/1535	16 (15–18)	276/1348	20 (18–23)	0.001
Survival with neurodevelopmental impairment	207/1391	15 (13–17)	209/1535	14 (12–15)	211/1348	16 (14–18)	0.29
Death	967/1391	70 (67–72)	1076/1535	70 (68–72)	861/1348	64 (61–66)	<0.001
Survival without neurosensory impairment	340/1380	25 (22–27)	391/1533	26 (23–28)	395/1348	29 (27–32)	0.01
Survival with neurosensory impairment	73/1380	5 (4–7)	66/1533	4 (3–5)	92/1348	7 (6–8)	0.01
Infants born at 22 wk							
Survival without neurodevelopmental impairment§	2/241	1 (0–3)	4/274	1 (1–4)	3/234	1 (0–4)	0.80
Survival with neurodevelopmental impairment§	4/241	2 (1–4)	9/274	3 (2–6)	5/234	2 (1–5)	0.46
Death	235/241	98 (95–99)	261/274	95 (92–97)	226/234	97 (93–98)	0.39
Infants born at 23 wk							
Survival without neurodevelopmental impairment	34/496	7 (5–9)	55/489	11 (9–14)	59/450	13 (10–17)	0.005
Survival with neurodevelopmental impairment	63/496	13 (10–16)	41/489	8 (6–11)	51/450	11 (9–15)	0.08
Death	399/496	80 (77–84)	393/489	80 (77–84)	340/450	76 (71–79)	0.11
Infants born at 24 wk							
Survival without neurodevelopmental impairment	181/654	28 (24–31)	191/772	25 (22–28)	214/664	32 (29–36)	0.007
Survival with neurodevelopmental impairment	140/654	21 (18–25)	159/772	21 (18–24)	155/664	23 (20–27)	0.44
Death	333/654	51 (47–55)	422/772	55 (51–58)	295/664	44 (41–48)	<0.001

* Unadjusted binomial confidence intervals were determined with use of the Wilson method.
† P values were determined using chi-square tests.
‡ Included are 4274 infants who had data available on the primary outcome.
§ Among the 27 surviving infants born at 22 weeks, the median (interquartile range) gestational age was 22 weeks 5 days (22 weeks 4 days to 22 weeks 6 days) and birth weight was 570 g (510 to 620).

Table 3. Neurodevelopmental Outcomes among Infants Surviving to 18 to 22 Months of Corrected Age.

Outcome	Epoch 1 (2000–2003)	Epoch 2 (2004–2007)	Epoch 3 (2008–2011)	P Value†
		*no./total no. (%)**		
Neurodevelopmental impairment	207/424 (49)	209/459 (46)	211/487 (43)	0.25
Neurosensory impairment	73/413 (18)	66/457 (14)	92/487 (19)	0.18
Moderate or severe cerebral palsy	62/423 (15)	50/458 (11)	56/487 (11)	0.19
Severe cerebral palsy	34/424 (8)	25/459 (5)	26/487 (5)	0.18
Profound visual impairment	10/424 (2)	7/457 (2)	2/484 (<1)	0.04
Profound hearing loss	17/421 (4)	16/457 (4)	14/487 (3)	0.63
Cognitive impairment	194/417 (47)	204/457 (45)	195/480 (41)	0.19
Cognitive impairment alone‡	123/417 (29)	141/457 (31)	119/480 (25)	0.10

* The number of children who underwent a Bayley Scales of Infant and Toddler Development examination was 421 in epoch 1, 458 in epoch 2, and 480 in epoch 3. The number of children who underwent a neurologic examination was 424 in epoch 1, 458 in epoch 2, and 487 in epoch 3.
† P values were determined using chi-square tests.
‡ Cognitive impairment alone indicates infants with cognitive impairment but without moderate or severe cerebral palsy, profound visual impairment, or profound hearing impairment.

this variation is due to differences in sample ascertainment, study design, infant characteristics, or care practices. We found variation in outcomes by center; this observation is consistent with the findings from other studies published in 2015 and 2004 that assessed extremely premature infants.[5,22]

In the subgroup analysis performed according to the gestational week in which the infants were born, we found that the rate of survival without neurodevelopmental impairment increased over time among infants born at 23 weeks and 24 weeks. However, only 1% of infants born at 22 weeks survived without neurodevelopmental impairment in each epoch. Among the 167 infants born at 22 weeks who received active treatment after birth, 9 (5%) survived without neurodevelopmental impairment.

The best measures of neurodevelopmental outcomes in premature infants continue to be debated. Our definition of neurodevelopmental impairment included measures of motor function, sensory impairment, and cognitive delay, which is consistent with the definition used in other studies. Clinicians and families should note that there is likely to be substantial variation in the long-term functioning of children classified as having neurodevelopmental impairment in early childhood. Although early neurodevelopmental assessment is important for the timely identification of children at risk for long-term neurologic impairment or developmental delay, its capacity to predict later functioning is limited.[35-37] Many children will catch up to their peers by school age, whereas other children will have persistent impairment. Conversely, some children without signs of neurodevelopmental impairment in early childhood will have impairments that manifest at school age.[37,38] Bayley-II Mental Developmental Index and Bayley-III Cognitive Composite scores have been shown to correlate with later cognitive outcomes but account for only a minority of the variance in later cognitive functioning.[35,36,39] Reported rates of impairment at school age among children who were born extremely premature are generally lower than those reported in early childhood, but studies have been limited by small sample sizes and heterogeneous results.[35,37,40] Additional research is needed to better understand long-term outcomes among periviable infants.

Our analysis was complicated by the transition from Bayley-II to Bayley-III during the study period. Studies involving extremely premature infants have shown that Bayley-III Cognitive Composite scores are, on average, 10 to 11 points

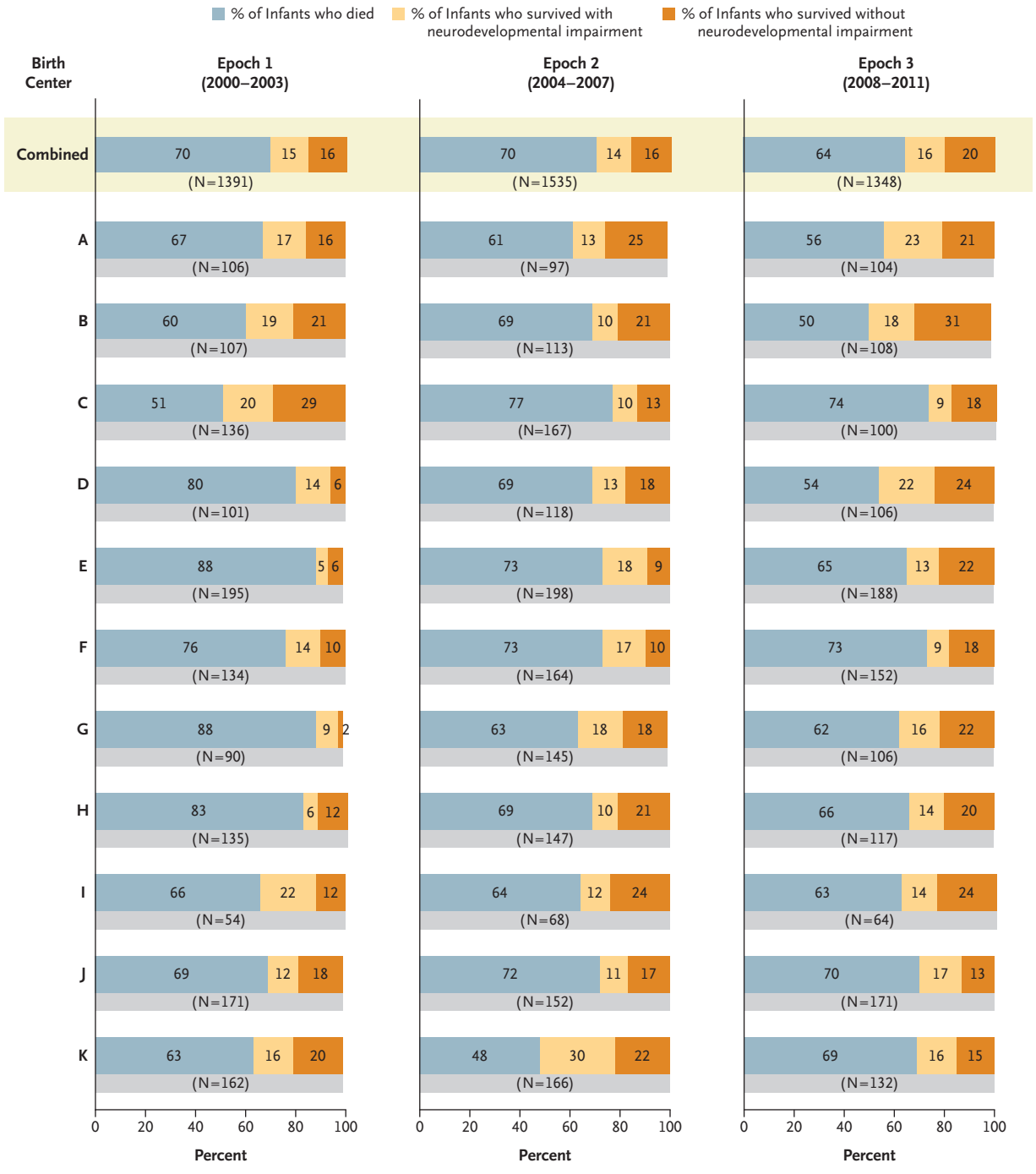

Figure 1. Mortality and Neurodevelopmental Outcomes at 18 to 22 Months of Corrected Age by Birth Epoch and Center.

Shown are the rates of death, survival with neurodevelopmental impairment, and survival without neurodevelopmental impairment at the 11 centers that were included in the analysis. The rates were adjusted for gestational age at birth, multiple gestation, sex, race, and small-for-gestational-age status. Because of rounding, percentages may not total 100.

Table 4. Survival and Neurodevelopmental Outcomes at 18 to 22 Months of Corrected Age.

Outcome	Adjusted Relative Risk (95% CI)*	
	Epoch 3 (2008–2011) vs. Epoch 2 (2004–2007)	Epoch 3 (2008–2011) vs. Epoch 1 (2000–2003)
All infants†		
Survived without neurodevelopmental impairment vs. died	1.52 (1.22–1.88)	1.59 (1.28–1.99)
Survived with neurodevelopmental impairment vs. died	1.43 (1.14–1.79)	1.27 (1.01–1.59)
Survived without neurodevelopmental impairment vs. survived with neurodevelopmental impairment	1.08 (0.83–1.40)	1.27 (0.99–1.65)
Survived without neurosensory impairment vs. died	1.39 (1.15–1.68)	1.44 (1.18–1.75)
Survived with neurosensory impairment vs. died	1.93 (1.38–2.70)	1.54 (1.11–2.15)
Survived without neurosensory impairment vs. survived with neurosensory impairment	0.72 (0.51–1.02)	0.93 (0.66–1.32)
Infants born at 22 wk‡		
Survived without neurodevelopmental impairment vs. died	0.74 (0.16–3.47)	1.30 (0.21–8.08)
Survived with neurodevelopmental impairment vs. died	0.63 (0.20–1.97)	1.30 (0.34–5.02)
Survived without neurodevelopmental impairment vs. survived with neurodevelopmental impairment	1.13 (0.17–7.41)	0.99 (0.11–9.34)
Infants born at 23 wk§		
Survived without neurodevelopmental impairment vs. died	1.29 (0.86–1.94)	2.31 (1.46–3.66)
Survived with neurodevelopmental impairment vs. died	1.53 (0.98–2.40)	1.07 (0.71–1.62)
Survived without neurodevelopmental impairment vs. survived with neurodevelopmental impairment	0.86 (0.49–1.50)	2.17 (1.23–3.83)
Infants born at 24 wk¶		
Survived without neurodevelopmental impairment vs. died	1.63 (1.26–2.11)	1.46 (1.12–1.90)
Survived with neurodevelopmental impairment vs. died	1.46 (1.11–1.92)	1.34 (1.01–1.78)
Survived without neurodevelopmental impairment vs. survived with neurodevelopmental impairment	1.12 (0.83–1.51)	1.08 (0.79–1.47)
Infants receiving active treatment‖		
Survived without neurodevelopmental impairment vs. died	1.55 (1.24–1.93)	1.64 (1.30–2.06)
Survived with neurodevelopmental impairment vs. died	1.44 (1.14–1.81)	1.30 (1.03–1.64)
Survived without neurodevelopmental impairment vs. survived with neurodevelopmental impairment	1.08 (0.83–1.40)	1.26 (0.97–1.65)

* Comparisons were adjusted for gestational age (defined as completed weeks of gestation), multiple gestation, sex, race, small-for-gestational-age status, and birth center (random effect). Gestational age was not included in 22-, 23-, and 24-week subgroup analyses.
† Data on survival and neurodevelopmental outcomes were available for 4227 infants (46 infants were excluded because of missing data on race, and 1 infant was excluded because of missing data on small-for-gestational-age status).
‡ Data on survival and neurodevelopmental outcomes were available for 737 infants.
§ Data on survival and neurodevelopmental outcomes were available for 1417 infants.
¶ Data on survival and neurodevelopmental outcomes were available for 2073 infants.
‖ Data on survival and neurodevelopmental outcomes were available for 3158 infants.

higher than the Bayley-II Mental Developmental Index scores.[17,18] To address this limitation, we defined cognitive impairment using a conservative Bayley-III Cognitive Composite score lower than 85, which is one standard deviation below the mean score of 100. Johnson et al.[21] observed 97% agreement between a Bayley-II Mental Developmental Index score lower than 70 and a Bayley-III Cognitive Composite score lower than 85. Furthermore, we showed an increase in the rate of survival without neurosensory impairment over time, with neurosensory impairment defined by the same components as neurodevelopmental impairment with the exclusion of the Bayley

scores. Finally, when we evaluated changes in outcomes in the years since the implementation of Bayley-III, the results were consistent.

Our study has additional limitations. The data represent a select group of infants born in a subset of academic centers and may not be generalizable to other populations. Furthermore, we did not correct for multiple testing, which increases the probability that some of the significant differences that we observed in our secondary outcomes analyses may have occurred by chance. There is a small chance that the changes in outcomes over time reflect random variation alone.

In conclusion, our study showed a small but significant increase in the rate of survival without neurodevelopmental impairment at 18 to 22 months of corrected age among periviable infants. Despite improvements over time, the incidence of death, neurodevelopmental impairment, and other adverse outcomes remains high in this population.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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