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Factores Pronósticos para déficit cognitivo en niños nacidos muy prematuros o con muy bajo peso
Una Revisión sistemática

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IMPORTANCIA

El deficit cognitivo es la forma más común de discapacidad entre los niños nacidos muy prematuros (MPT) a las 32 semanas o menos de EG, o con muy bajo peso de nacimiento (MBPN) de 1250 gramos o menos. Es importante identificar factores que sean buenos predictores del resultado a largo plazo porque la capacidad de predecir el futuro pronóstico ayudará en el cuidado de la salud y el planeamiento y provisión de servicios educativos.

OBJECTIVO

Identificar factores pronósticos para deficit cognitivo en niños nacidos MPT o con MBPN.

REVISIÓN DE EVIDENCIA

Se realizó una revision sistemática utilizando MEDLINE, EMBASE, y PyscINFO para identificar estudios publicados entre el 1º de Enero de 1990 y el 1º de Junio, 2014, reportando modelos de predicción multivariados para neurodesarrollo en niños MPT y MBPN. Se identificaron treinta y un estudios abarcando 98 modelos de factores de riesgo para resultado cognitivo. Dos revisores independientes extrajeron la información clave acerca del diseño del estudio, definición de resultados, selección de factores de riesgo, desarrollo del modelo y reporte y diseño de determinación de sesgos.

HALLAZGOS

Se encontró evidencia de que el sexo masculino, raza/etnia no blanca, bajo nivel de educación parental y bajo peso de nacimiento fueron predictores de déficit cognitivo global en niños menores de 5 años. En niños mayores, sólo se mantuvo la influencia de la educación parental. El sexo masculino también fue predictivo de retraso de lenguaje en la primera infancia, pero no en la infancia media. La EG fue un pobre predictor del resultado cognitivo probablemente debido a un reducido poder de discriminación en cohortes restringidas a un estrecho rango de edad gestacional. El valor pronóstico de injuria cerebral neonatal fue poco claro; sin embargo, los estudios adoptaron estrategias mixtas para manejar niños con discapacidad física o neurosensorial.

CONCLUSIONES Y RELEVANCIA

La influencia de factores de riesgo perinatales sobre el desarrollo cognitivo de MPT o MBPN parece disminuir con el tiempo a medida que los factores ambientales se tornan más importantes. Es difícil aislar los resultados cognitivos de los déficits motores y neurosensorial, y la estrategia para tratar con los chicos no testables tiene implicancias para la predicción de riesgo.

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Este es el primer artículo de revision sistemática abarcativa de factores de riesgo para déficits de neuro desarrollo en niños sobrevivientes MPT (<32 semanas) o MBPN (<1250 gramos). El objetivo de esta revisión fue consolidar la evidencia acerca del riesgo de déficit en los dominios de la cognición, función motora, conducta, audición y visión, para informar en futura investigación pronóstica. El foco de este artículo es identificar factores de riesgo que sean buenos predictores de subóptima función cognitiva, incluyendo habilidades del lenguaje, función ejecutiva y logro académico, así como el CI global

La prematurez tiene un efecto perjudicial sobre todos los dominios del neurodesarrollo. Sin embargo, mientras que la parálisis cerebral (PC) y las alteraciones neurosensoriales como sordera y ceguera pueden tener un efecto severo sobre el desarrollo, los déficits cognitivos son por lejos, las las secuelas más prevalentes en la población MPT y MBPN. El retraso cognitivo ha sido reportado hasta niveles del 40% en la edad escolar entre niños extremadamente prematuros (EPT) nacidos antes de las 28 semanas de EG (1-3)

El score de CI en la edad escolar de niños prematuros sin discapacidad severa ha sido consistentemente más bajo que el de los controles de término y asociado a la EG al nacer (4). Además de estar en mayor riesgo de déficit cognitivo global, los niños MPT o MBPN son más proclives a desempeñarse peor en la atención y función ejecutiva comparados con sus pares de término (5) aún después de ajustar por CI (6-8). También tienen una tasa más alta de problemas del lenguaje tanto en el área expresiva como receptiva que persisten hasta la infancia media (9). Los problemas con el desarrollo cognitivo y lenguaje significan que muchos sobrevivientes MPT o MBPN están en alto riesgo de pobres logros académicos y reducido potencial de ganancias y oportunidades a lo largo de la vida. Una proporción importante requieren educación especial completa, y muchos de ellos en escolaridad común requieren servicios de apoyo especiales académicos, de salud o conductuales. (10) Es posible que exista una relación compleja entre la función cognitiva, factores biológicos y ambientales, y eventos clínicos durante y después del período perinatal de un nacimiento MPT. Para ayudar a promover el óptimo desarrollo, la contribución de todos estos factores de riesgo necesita ser determinada.

El objetivo de esta revisión fue resumir los modelos de predicción publicados de resultado multivariado que intentan identificar la combinación de factores más fuertemente asociada con déficit cognitivo en la primera infancia y más tarde en la niñez.

Métodos

Los métodos para la revisión sistemática general de déficit de neurodesarrollo han sido previamente publicados en un protocolo de revisión, disponible en http://www.crd.york.ac.uk/PROSPERO. El número de registro es CRD42014006943.

Estrategia de búsqueda

Tres estrategias de búsqueda electrónica fueron delineadas en MEDLINE, EMBASE, y PsycINFO (eBoxes 1, 2, y 3 en el Supplement) usando encabezamientos del National

Institutes of Health Medical Subject. Las búsquedas identificaron los artículos publicados entre el 1º de Enero, 1990 y 1º de Junio, 2014, reportando un modelo de predicción multivariado de riesgo para resultado de neurodesarrollo determinado después de los 18 meses de edad en niños MPT o MBPN. No hubo restricción de idioma. Las bibliografías de los artículos incluidos para extracción de datos fueron revisados manualmente para más artículos elegibles.

Criterios de selección

Los artículos fueron incluidos en la selección si cumplían los siguientes criterios: 1) contenían datos originales; 2) la población en estudio nació después del 1º de enero de 1990; 3) la población en estudio tenía 32 semanas de EG o menos o peso de nacimiento de 1250 g o menor y no un grupo altamente selecto (basado en otros criterios clínicos); y 4) un objetivo era realizar un análisis multivariado de factor de riesgo (>2 variables) de un resultado del neurodesarrollo examinado a los 18 meses de edad. Los estudios de factor pronóstico que investigaban el mecanismo causal entre un solo factor predictivo y un resultado para estimar el tamaño del efecto no fueron incluidos en la revisión. Las guías actuales recomiendan no combinar estos dos tipos de estudios porque sus objetivos y estrategias de construcción del modelo difieren y podrían llevar a resultados sesgados al sintetizarlos. (11,12)

Extracción de datos

Todos los artículos identificados por la búsqueda fueron cribados en su título y abstract para la exclusión definida o ver duplicaciones (pantalla 1). Para los restantes artículos, se obtuvo el texto completo, y se aplicaron los criterios de inclusión (pantalla 2) Las dos pantallas fueron realizadas por el primer autor (LL) en primera instancia, pero si había dudas acerca de la elegibilidad de un artículo, era visualizado independientemente por el segundo autor (RM). Si no se podía llegar a una decisión, el artículo era referido al resto del equipo de revisión (JM, JJK y NM). Los artículos no escritos en lengua inglesa incluidos en la revisión fueron completamente traducidos. Los artículos múltiples basados en la misma cohorte de niños tuvieron una revisión del panel (LL y RM) Los artículos que reportaban resultados en la misma área (cognición, función motora, conducta, audición y visión) a la misma edad de evaluación (<5 años y 5 años) fueron examinados en su relevancia para la revisión y sólo un artículo era seleccionado para extracción de datos. Para todos los artículos elegibles para inclusión, ambos revisores (LL y RM) completaron en forma independiente una planilla de extracción de datos y determinaron el riesgo de sesgo en una base de datos (Access 2010; Microsoft Corporation). Estos se validaron en forma cruzada para discrepancias y fueron referidos al resto del equipo de revisión si no se podía alcanzar un acuerdo.

Determinación de riesgo de sesgo

Hay mucha evidencia de que la conducción y reporte de artículos publicados describiendo el desarrollo o validación de modelos de predicción son escasos (13) lo que ha llevado a la creación de herramientas de control de calidad específicas para este tipo de estudios. En esta revisión, la calidad de los estudios fue determinada acorde a la versión modificada de la herramienta Calidad en Estudios Pronósticos (14) que es un set estandarizado de criterios recomendados para usar en revisiones de pronóstico (eTabla 1 en el Suplemento). La herramienta se focaliza en las siguientes 6 áreas de sesgo potencial pertinente a estudios de pronóstico: participación en el estudio, reducción del tamaño del estudio, medición del factor pronóstico, medición del

resultado, medición de confusores y recuento, y el análisis estadístico. Los estudios fueron graduados para cada área de sesgo como Sí, parcialmente o no y fueron clasificados como de bajo a moderado riesgo de sesgo si eran clasificados como Si o parcialmente en las 6 áreas y moderado a alto riesgo de sesgo si era de otra forma.

Síntesis de datos y Reporte

Los resultados fueron presentados de acuerdo a las Guías de Items preferidos para el reporte de Revisiones sistemáticas y Meta-análisis (15) Los factores de riesgo estadísticamente significativos ($p < 0.05$) en el modelo final se reportaron para cada estudio. Los estudios se agruparon según el tipo de resultado estudiado (función cognitiva global medida por un test cognitivo general o un score de CI, lenguaje, función ejecutiva y logro académico) y según la edad de examen (<5años y 5 años). Esto es así, porque las evaluaciones en la infancia temprana pueden ser poco confiables y son medidas más crudas del desarrollo cognitivo que descansan en cierto modo sobre la función motora, mientras que las evaluaciones más tarde en la infancia miden el funcionamiento cognitivo de mayor nivel; por lo tanto los factores de riesgo pueden ser distintos. Un factor de riesgo se presentó gráficamente si fue estadísticamente significativo en el modelo final de al menos otros dos estudios (incluyendo estudios con moderado a alto riesgo de sesgo) dentro del área del mismo resultado. Los grupos presentan el número y calidad de todos los estudios que ingresaron cada factor de riesgo en el modelo final y si el factor de riesgo fue informado como un predictor significativo o como no significativo. Dado que no se obtuvieron conclusiones claras acerca de factores de riesgo considerados en el modelo final en sólo 1 ó 2 estudios, los gráficos quedaron truncos en este punto porque no mostraban información.

Resultados

La estrategia de búsqueda para esta revisión sistemática recopiló 44 500 artículos, y después de eliminar los duplicados, la primera pantalla de Título y abstract se realizó sobre 32 283 artículos (Figura 1). En 29 999, el título o el abstract indicaban claramente que el tópico del artículo no era relevante para la pregunta de la revisión o no satisfacían uno de los criterios de inclusión. Los restantes 2284 artículos fueron tamizados en texto completo, aplicando el total de los criterios de inclusión. La elegibilidad no fue clara en 136 (6%) y fueron revisados por un segundo revisor independiente (RM), o se contactó al autor (si la causa de incertidumbre era falta de datos). Después de aplicar los criterios de selección, 91 artículos (de 48 cohortes poblacionales) conteniendo análisis multivariado de factores de riesgo fueron elegibles para la inclusión. Luego de la revisión por el panel, otros 13 artículos fueron excluidos porque reportaban el mismo resultado a la misma edad de evaluación en la misma cohorte que otro artículo con objetivo más relevante. Cinco de los artículos excluidos por superposición de cohorte estaban basados en resultados cognitivos. (8, 16-19). Los 78 artículos remanentes fueron incluidos en la extracción de datos para la revisión sistemática. No fueron identificados más artículos en la revisión manual de las bibliografías. Esta revisión resume los resultados de 31 estudios (20-50) reportando el análisis de factores de riesgo para resultados cognitivos. Estos 31 estudios se basaron en 21 cohortes poblacionales independientes y reportaron un total de 98 modelos de factores de riesgo.

Características del estudio

El principal diseño fue de cohorte prospectiva (n=27). También hubo un estudio transversal (46) y tres trabajos clínicos randomizados (27,42,44). De las 27 cohortes prospectivas, 12 fueron obtenidas de todos los nacidos vivos en una región geográfica definida* y 10 fueron reclutados de una UCIN de un solo centro. † Los estudios fueron conducidos en 12 países incluyendo EE.UU (n=9), Reino Unido (n=4), Países Bajos (n=4), Alemania (n=3), Australia (n=2) , Finlandia (n=2) y Francia (n=2) y un estudio de Austria, Dinamarca, Estonia, Italia y Noruega. La mediana de tamaño muestral fue 219 (rango, 45-3785) y 3 estudios (21,22, 33) tenían más de 1000 participantes. Cuatro estudios (24,26, 38, 50) estuvieron restringidos a niños MPT y 3 estudios (35,44,47) excluyeron nacimientos múltiples. La determinación de riesgo de sesgo clasificó 14 estudios (45%) como de riesgo bajo a moderado y 17 (55%) moderado a alto riesgo de sesgo (Figura 2)

Factores Pronósticos para déficit cognitivo global

Veinte estudios contenían análisis de un factor de riesgo para función cognitiva global o CI (Tablas 1 y 2). Ocho estudios (20-27) examinaron resultados entre las edades de 1.5 y 2.5 años y 12 estudios (28-39) entre los 5 y 13 años. La escala más utilizada antes de los 5 años fue el Indice de Desarrollo Mental de las Escalas Bayley de Desarrollo Infantil versión II (51) o el score Cognitivo compuesto de la versión III (52) en los estudios más recientes. El Indice de Desarrollo Mental examina la cognición a través de la evaluación de percepción sensorial, aprendizaje, memoria, resolución de problemas y lenguaje temprano. La versión más reciente divide las habilidades cognitivas y del lenguaje en dos dominios separados. Hubo mayor variedad en las escalas de medición empleadas en los exámenes a los 5 años ó posterior, siendo la más común el Score de procesamiento mental de la Batería de examen Kauffman para Niños (53) y la escala completa de CI de Weschler para Preescolares y Escala Primaria de Inteligencia revisada (54). Los factores de riesgo significativos en el modelo final de por lo menos un estudio con bajo a moderado riesgo de sesgo y examinado en el modelo final de al menos otros dos estudios se muestran en la Figura 3ª (para niños <5 años y Figura 3B (para niños =ó > de 5 años).

Entre los estudios en los cuales la edad de evaluación fue menor de 5 años (Figura 3ª), los dos estudios más grandes (21-22) con bajo a moderado riesgo de sesgo y por lo menos un estudio con bajo a moderado riesgo de sesgo encontraron los siguientes factores como predictivos de pobre desarrollo cognitivo: sexo masculino, etnia/raza no-blanco, menor nivel de educación parental, menor peso de nacimiento e injuria cerebral durante el período neonatal. Sin embargo, los otros estudios (20, 23, 25, 27) que también examinaron estos factores de riesgo algunas veces contradijeron estos hallazgos, con la excepción de raza/etnia. También se encontró alguna evidencia de que la ausencia de uso de corticoide antenatal y la menor EG no fueron predictivos de menor funcionamiento cognitivo en los menores de 5 años.

La mayoría de los estudios que examinaron la función cognitiva a los 5 años o más tuvieron moderado a alto riesgo de sesgo (Figura 3 B). La asociación entre el nivel de educación parental y el déficit cognitivo fue evidente también en este grupo etario, pero la asociación con sexo masculino disminuyó bastante. Raza/etnia no fue incluido en el modelo final en ninguno de los estudios de niños mayores (o no fue reportada cuando fue utilizada como factor de ajuste en 2 estudios 24-27). Por tanto, no fue

posible determinar si la influencia de este factor prevalecía hacia la infancia media. La mayoría de los estudios a esta edad también encontraron que la más baja EG tenía poco valor pronóstico en un modelo de predicción multivariable)

Factores pronósticos para déficit del desarrollo del Lenguaje

Se encontraron 8 trabajos que reportaron análisis de factores de riesgo para desarrollo de Lenguaje (eTabla 2 en el Suplemento). Cinco estudios (22,25, 40-42) examinaron el resultado entre las edades de 1.5 y 3 años, y 3 estudios (34,37, 43) con moderado a alto riesgo de sesgo examinaron el resultado entre los 5 y 8 años. Hubo mayor heterogeneidad en el tipo de test utilizado para medir habilidades de lenguaje que para cognición. La eFigura en el Suplemento muestra los factores de riesgo encontrados significativos en el modelo final de al menos 1 estudio con bajo a moderado riesgo de sesgo e ingresado en el modelo final de al menos otros dos estudios. Los 5 estudios (22, 25, 40-42) conducidos en niños <5 años incluyeron el sexo masculino en el modelo final y reportaron que esta variable fue predictiva de pobre desarrollo del lenguaje. No fue posible comentar sobre el efecto del sexo masculino en la infancia media porque 2 estudios (34, 37) entre 3 conducidos a los 5 años o más ajustaron para ello pero no informaron sobre los resultados de los factores de ajuste mientras que el tercer estudio (43) no ingresó el sexo en el modelo final porque no fue significativo en el análisis univariado. Tres estudios (22, 40, 43) reportaron que el menor nivel educativo de los padres estaba asociado con pobre desarrollo del lenguaje, y dos estudios (25, 41) reportaron no hallar tal asociación.
También hubo resultados mixtos para el valor pronóstico de ser PEG. No fue posible extraer ninguna conclusión acerca de la injuria cerebral neonatal como factor pronóstico para déficit de lenguaje, posiblemente debido a que los estudios usaron diferentes estrategias para tratar con niños con severo déficit neurosensorial para los cuales los tests standard no pueden emplearse, con algunos incluyendo el menor score posible y otros excluyendo este grupo por completo. Al igual que con la cognición, hubo evidencia de que la EG no fue un fuerte predictor del desarrollo del lenguaje en un modelo multivariado.

Factores pronósticos para déficit de funciones ejecutivas

Siete estudios (32, 34, 37, 44-47) con moderado a alto riesgo de sesgo presentaron análisis de factores de riesgo para diferentes aspectos de las funciones ejecutivas (eTabla 3 en el Suplemento), con todos excepto uno basados en edad de examen de 5 a 12 años. El número medio de tests administrados dentro de cada estudio fue 5, y el máximo fue 13. Los factores de riesgo mostrados en la eTabla 3 en el Suplemento fueron significativos en al menos uno de los modelos finales. Fue difícil combinar estos resultados de alguna manera significante debido al pequeño número de estudios utilizando una amplia variedad de tests para medir procesos cognitivos interrelacionados.

Factores pronósticos para bajo logro académico

Cuatro estudios (2 con bajo a moderado riesgo de sesgo {48,50} y dos con moderado a alto riesgo de sesgo {37, 49} realizaron análisis de factores de riesgo para el logro académico (eTabla 4 en el Suplemento) todos basados en edad de examen entre 5 y 12 años. Los 4 estudios presentaron un modelo de habilidad matemática, 2 estudios presentaron un modelo de identificación de letra y palabra y 1 estudio presentó un modelo de escores de lectura. Otra vez, hubo muy pocos estudios e insuficiente superposición de factores de riesgo ingresados a los modelos finales para combinar resultados y obtener alguna conclusión de importancia.

Discusión

En la población MPT o MBPN hubo evidencia fuerte que el sexo masculino fue factor pronóstico de menor desarrollo cognitivo y habilidades de lenguaje en la infancia temprana, un hallazgo apoyado por otros estudios (55-57) que han focalizado exclusivamente en la asociación del sexo del infante con la función cognitiva. Sin embargo, en los estudios conducidos más tarde en la infancia que fueron incluidos en esta revisión, la influencia de sexo sobre la cognición en general estuvo muy disminuida. No pudimos comentar sobre si este hallazgo también era cierto para el desarrollo del lenguaje debido a la falta de estudios examinando niños a los 5 años o más. Hubo similares hallazgos para la raza/etnia no-blanca y menor PN en relación a déficit cognitivo. Ambos factores fueron claramente pronósticos en la infancia temprana, pero no hubo evidencia disponible en la infancia media para raza/etnia, con falta de asociación en los años posteriores para PN. Hubo evidencia que el menor nivel educativo parental fue predictivo de déficit cognitivo apoyado por un reciente estudio (58) en MPT que focalizó sólo en esta hipótesis. Al contrario de los factores relacionados con las características del niño, la influencia de la educación de los padres mostró persistir hasta la infancia media. La evidencia para el valor pronóstico de la educación parental en relación al desarrollo del lenguaje fue débil. La investigación ha mostrado nexos entre raza/etnia no blanca, menor PN y educación parental o estado socioeconómico (59, 60) así que es notable que estos factores fueran predictores independientes en los modelos finales de 4 estudios (21, 22, 24, 26) en el grupo menor de 5 años de edad. Otros estudios (61, 62) han encontrado que el efecto de la raza/etnia está fuertemente mediado por marcadores de deprivación. En esta revisión, el nivel de educación parental emergió como un factor pronóstico del resultado cognitivo, mientras que el nivel socioeconómico parental no lo fue. Este hallazgo puede obedecer a multicolinearidad, o posiblemente un solo marcador del nivel socioeconómico tal como ingreso u ocupación (como ocurrió en muchos estudios de esta revisión) es insuficiente para captar una medida exacta de desventaja social. Combinar una serie de marcadores sociales para componer un score puede ser una mejor estrategia de modelo.

Muchos estudios enfocados exclusivamente en la relación entre injuria cerebral diagnosticada en el período neonatal y la función cognitiva han reportado fuerte relación lineal con el grado de severidad (63, 66). Sin embargo, el valor pronóstico de la injuria cerebral en los modelos multivariados reportados en esta revisión fue mixto. Este resultado es posiblemente causado porque el desarrollo cognitivo y del lenguaje es multifactorial, al revés que el diagnóstico de PC, que está más directamente

relacionado a la injuria cerebral focal, de forma tal que la influencia de factores perinatales se hace menos pronunciada cuando otras variables son ingresadas al modelo. Los hallazgos poco claros pueden también reflejar las diferentes estrategias de modelo adoptadas por los estudios. Algunos estudios excluyeron niños con PC u otro déficit neurosensorial, algunos incluyeron los scores más bajos y otros ajustaron por discapacidad motora. Hubo fuerte evidencia que la EG no fue un robusto predictor del desarrollo cognitivo o del lenguaje en la infancia o niñez media en la población MPT ó MBPN. Pese a que la relación entre mayor EG y mejor cognición está bien establecida a través de todo el espectro de EG desde 25 a 40 semanas, (4) no surge como un predictor importante en estudios individuales con subgrupos pretérmino definidos por EG restringida. Pese a que se observa una fuerte relación positiva con EG cuando se calcula sobrevida sin déficit del desarrollo como índice de todos los nacidos vivos, la asociación se debilita cuando el denominador es sobrevivientes al alta como en todos los estudios de esta revisión. Esto ocurre porque la proporción de niños sobrevivientes aumenta fuertemente con la EG, mientras que la proporción de sobrevivientes con déficit no lo hace.

Nuestro estudio tiene fortalezas y limitaciones. Utilizamos un amplio filtro de búsqueda sin restricción de lenguaje para capturar todos los estudios con análisis exploratorios de factores de riesgo, que es lo recomendado en este tipo de revisión. (67) No se identificaron más artículos en la búsqueda manual de bibliografías, así que es poco probable que hubiera omisiones importantes. Las cohortes del estudio abarcaban un período de 18 años; por tanto, algunos de los factores que afectaban los resultados a principios de los 90 pueden no ser tan relevantes para las poblaciones de PT actuales. También representan poblaciones internacionales diversas, con diferentes métodos de diagnóstico y prácticas clínicas, que pueden explicar el patrón poco claro de resultados para algunos factores. También, los estudios no consideraron los mismos sets de factores candidatos. Modelos múltiples basados en la misma cohorte poblacional fueron un tema mayor, particularmente los estudios sobre función ejecutiva, que con frecuencia realizaban una completa batería de tests. Utilizando reglas estandarizadas, seleccionamos estudios y modelos para la inclusión antes de conducir la síntesis de datos, aunque fue difícil aplicar un set estricto de criterios para cada caso. Otra dificultad en esta revisión fue la enorme variedad de evaluaciones utilizadas, particularmente enre los niños de 5 años ó más.

Conclusiones

En conclusión, hubo evidencia que el sexo masculino, raza/etnia no-blanca, bajo nivel de educación parental y bajo PN fueron predictores significativos de déficit cognitivo global en niños de 18 a 30 meses que nacieron MPT o con MBPN. Después de los 5 años,, el efecto del sexo y PN disminuyeron, el nivel de educación parental todavía era influyente, y no hubo evidencia de efecto duradero de la raza/etnia. Es poco probable que la raza/etnia en sí misma sea un factor causal para déficit cognitivo porque otra investigación ha demostrado una fuerte correlación entre raza/etnia, pobreza y vulnerabilidad social. Hubo evidencia que el sexo masculino fue predictor del desarrollo del lenguaje en la infancia temprana pero no hubo evidencia de que este resultado se mantuviera en la niñez. Hubo hallazgos mixtos en el valor pronóstico de la injuria cerebral durante el período neonatal en el lenguaje y cognición, que puede reflejar los

criterios de selección heterogéneos y métodos de encarar los datos faltantes relacionados a discapacidad severa entre los estudios. Hubo evidencia que entre la población MPT o MBPN la EG tuvo poco valor como factor pronóstico en modelos multivariados prediciendo el riesgo de desarrollo cognitivo o del lenguaje a cualquier edad mayor a los 18 meses. Los hallazgos de esta revisión apoyan la visión de que el efecto de los factores de riesgo perinatales disminuyen a los largo del tiempo a medida que otros factores ambientales y sociales se vuelven más influyentes.

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Síntesis

• El objetivo de esta revisión sistemática fue identificar factores de riesgo que sean robustos predictores de déficit cognitivo en niños nacidos muy prematuros (MPT) o muy bajo peso de nacimiento (MBPN)

• Hubo evidencia que el sexo masculino, raza/etnia no-blanca, nivel educacional parental bajo y menor PN fueron predictores de déficit cognitivo global en niños MPT o MBPN menores de 5 años

• En niños MPT o MBPN de 5 años o más de edad, sólo la influencia de la educación parental se mantuvo en el tiempo, sugiriendo que la influencia de los factores de riesgo perinatales disminuye con el tiempo y los factores ambientales y sociales se vuelven más importantes

• El sexo masculino también fue predictivo de déficits de lenguaje en infantes MPT o MBPN menores de 5 años, pero no hubo evidencia de asociación más allá de esta edad.

• Hay necesidad de estudios de buena calidad y bien conducidos de pronóstico en la población MPT o MBPN, particularmente en niños mayores, entre los cuales la base de evidencia es débil.

Review

Prognostic Factors for Poor Cognitive Development in Children Born Very Preterm or With Very Low Birth Weight
A Systematic Review

Louise Linsell, BSc, MSc; Reem Malouf, MSc, MD; Joan Morris, MA, MSc, PhD; Jennifer J. Kurinczuk, BSc, MBChB, MSc, MD; Neil Marlow, BA, MBBS, MRCP, MD

IMPORTANCE Cognitive delay is the most common form of impairment among children born very preterm (VPT) at 32 weeks or less or with very low birth weight (VLBW) of 1250 g or less. It is important to identify factors that are robust predictors of long-term outcome because the ability to predict future prognosis will assist in health care and educational service planning and provision.

OBJECTIVE To identify prognostic factors for poor cognitive development in children born VPT or with VLBW.

EVIDENCE REVIEW A systematic review was conducted using MEDLINE, EMBASE, and PyscINFO databases to identify studies published between January 1, 1990, and June 1, 2014, reporting multivariable prediction models for neurodevelopment in VPT or VLBW children. Thirty-one studies comprising 98 risk factor models for cognitive outcome were identified. Two independent reviewers extracted key information on study design, outcome definition, risk factor selection, model development, and reporting and conducted a risk-of-bias assessment.

FINDINGS There was evidence that male sex, nonwhite race/ethnicity, lower level of parental education, and lower birth weight were predictive of global cognitive impairment in children younger than 5 years. In older children, only the influence of parental education was sustained. Male sex was also predictive of language impairment in early infancy, but not in middle childhood. Gestational age was a poor predictor of cognitive outcome, probably because of a reduced discriminatory power in cohorts restricted to a narrow gestational age range. The prognostic value of neonatal brain injury was unclear; however, studies adopted mixed strategies for managing children with physical or neurosensory disability.

CONCLUSIONS AND RELEVANCE The influence of perinatal risk factors on cognitive development of VPT or VLBW children appears to diminish over time as environmental factors become more important. It is difficult to isolate cognitive outcomes from motor and neurosensory impairment, and the strategy for dealing with untestable children has implications for risk prediction.

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This is the first article from a comprehensive systematic review of risk factor analyses for poor neurodevelopmental outcomes in very preterm (VPT) (≤32 weeks) or very low birth weight (VLBW) (≤1250 g) survivors. The objective of this comprehensive review was to consolidate the evidence on the risk of impairment in the domains of cognition, motor function, behavior, hearing, and vision, to inform future prognostic research. The focus of this first article is to identify risk factors that are robust predictors of impaired cognitive function, including language skills, executive function, and academic attainment, as well as global IQ.

Prematurity has a pervasive effect on all neurodevelopmental domains. However, while cerebral palsy (CP) and neurosensory disorders such as deafness and blindness can have a severe effect on development, cognitive impairments are by far the most prevalent sequelae in the VPT or VLBW population. Cognitive delay has been reported to be as high as 40% at school age among extremely preterm (EPT) children born at less than 28 weeks' gestation.[1-3] The IQ scores at school age of preterm children without severe disability have consistently been found to be lower than those of their term control subjects and related to gestational age (GA) at birth.[4]

In addition to being at increased risk of global cognitive impairment, VPT or VLBW children are more likely to perform less well on tests of attention and executive function compared with their full-term peers,[5] even after adjusting for IQ.[6-8] They also have a higher rate of language problems in both the expressive and receptive domains that persists into middle childhood.[9] Problems with cognitive and language development mean that many VPT or VLBW survivors are at high risk of poor academic attainment and reduced lifelong earning potential and life chances. A significant proportion require full-time specialist education, and most of those in mainstream education require specialist academic, health, or behavioral support services to aid their transition through school.[10]

There is likely to be a complex relationship between cognitive function, biological and environmental factors, and clinical events during and after the perinatal period of a VPT birth. To help promote optimal development, the contribution of all these factors to risk needs to be determined. The objective of this review article was to summarize published multivariable outcome prediction models that aim to identify the combination of factors most strongly associated with cognitive impairment in early infancy and later childhood.

At a Glance

- The objective of this systematic review was to identify risk factors that are robust predictors of cognitive impairment in children born very preterm (VPT) or with very low birth weight (VLBW).
- There was evidence that male sex, nonwhite race/ethnicity, lower level of parental education, and lower birth weight were predictive of global cognitive impairment in VPT or VLBW children younger than 5 years.
- In VPT or VLBW children 5 years and older, only the influence of parental education was sustained, suggesting that the influence of perinatal risk factors diminishes over time and that environmental and social factors become more important.
- Male sex was also predictive of language impairment in VPT or VLBW infants younger than 5 years, but there was no evidence of an association beyond this age.
- There is a need for good-quality, well-conducted studies of prognosis in the VPT or VLBW population, particularly in older children, among whom the evidence base is weak.

Methods

The methods for the overall systematic review of poor neurodevelopment have been previously published in a review protocol, available at http://www.crd.york.ac.uk/PROSPERO. The registration number is CRD42014006943.

Search Strategy

Three electronic search strategies were devised in MEDLINE, EMBASE, and PsycINFO databases (eBoxes 1, 2, and 3 in the Supplement) using the National Institutes of Health Medical Subject Headings. The searches identified any journal articles published between January 1, 1990, and June 1, 2014, reporting a multivariable risk prediction model for a neurodevelopmental outcome assessed after age 18 months in VPT or VLBW children. No language restrictions were made. The bibliographies of all articles included for data extraction were hand searched for further eligible articles.

Eligibility Criteria

Articles were included in the review if they satisfied the following eligibility criteria: (1) they contained original data; (2) the study population was born after January 1, 1990; (3) the study population was 32 weeks' GA or younger or with birth weight of 1250 g or less and not a highly select group (based on other clinical criteria); and (4) one objective was to perform a multivariable risk factor analysis (>2 variables) of a neurodevelopmental outcome assessed after 18 months of age. Explanatory prognostic factor studies that investigated the causal pathway between a single prognostic factor and an outcome to estimate effect size were not included in the review. Current guidelines recommend not combining these 2 distinct types of study because their objectives and model-building strategies differ and could lead to biased results if synthesized.[11,12]

Data Extraction

All articles identified by the search strategies were screened on title and abstract for definite exclusions and duplicates (screen 1). For the remaining articles, the full text was retrieved, and the inclusion criteria were applied (screen 2). The 2 screens were performed by the first author (L.L.) in the first instance, but if there was uncertainty about the eligibility of an article, it was screened independently by the second author (R.M.). If a decision could not be reached, the article was referred to the rest of the author review team (J.M., J.J.K., and N.M.). Non–English-language articles included in the review were fully translated. Multiple articles based on the same cohort of children underwent a panel review (by L.L., R.M., and N.M.). Articles reporting the same outcome domain (cognition, motor function, behavior, hearing, and vision) at the same age at assessment (<5 years and ≥5 years) were assessed on relevance to the review, and only one article was selected for data extraction. For all articles eligible for inclusion, both reviewers (L.L. and R.M.) independently completed a full data extraction form and risk-of-bias assessment on a customized database (Access 2010; Microsoft Corporation). These

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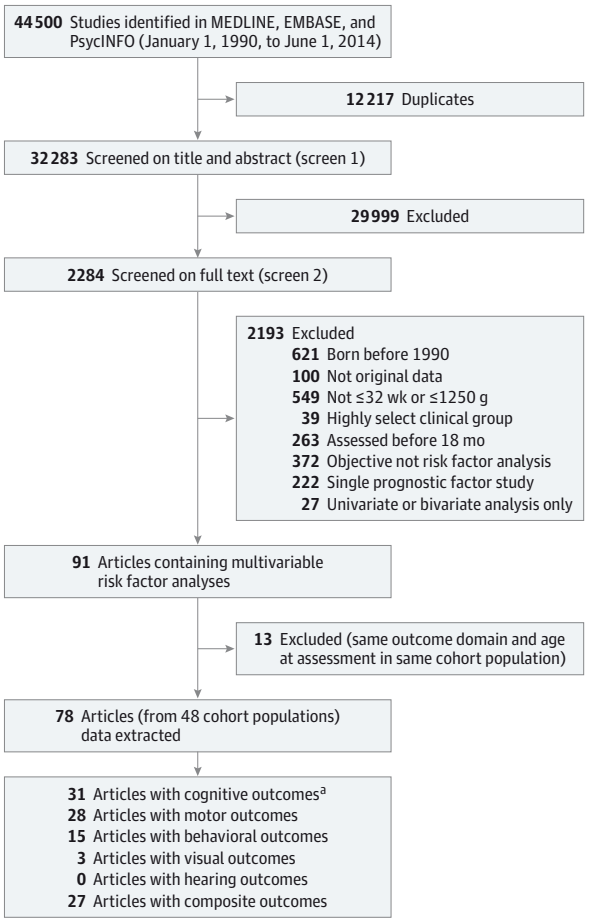
Figure 1. Flow Diagram



[a] Reviewed in this article.

were cross-validated for discrepancies and were referred to the rest of the author review team if agreement could not be reached.

Risk-of-Bias Assessment

Overwhelming evidence shows that the conduct and reporting of published articles describing the development or validation prediction models are poor,[13] which has led to the creation of quality assessment tools specific for these types of studies. In this review, the quality of studies was assessed according to a modified version of the Quality in Prognosis Studies tool,[14] which is a standardized set of criteria recommended for use in reviews of prognosis (eTable 1 in the Supplement). The tool focuses on the following 6 areas of potential bias pertinent to studies of prognosis: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and statistical analysis. Studies were graded as yes, partly, or no for each bias domain and were classified as having a low to moderate risk of bias if they were graded as yes or partly in all 6 bias domains and moderate to high risk of bias otherwise.

Data Synthesis and Reporting

The results were presented in accord with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[15] Risk factors that were statistically significant ($P < .05$) in the final model were reported for each study. Studies were grouped according to the type of outcome studied (global cognitive function measured by a general cognitive test or IQ score, language, executive function, and academic attainment) and according to the age at assessment (<5 years and ≥5 years). This is because assessments in early infancy can be unreliable and are more crude measurements of cognitive development that rely to some extent on motor function, whereas assessments in later childhood measure higher-order cognitive functioning; therefore, risk factors may differ. A risk factor was presented graphically if it was statistically significant in the final model of at least 1 study with low to moderate risk of bias and was included in the final model of at least 2 other studies (including studies with moderate to high risk of bias) within the same outcome domain. The plots display the number and quality of all studies that entered each risk factor into the final model and whether the risk factor was reported as a significant predictor or as nonsignificant. Because no clear conclusions could be made about risk factors considered in the final model of only 1 or 2 studies, the graphs were truncated at this point because they become noninformative.

Results

The search strategy for the comprehensive systematic review retrieved 44 500 articles, and after removing duplicates, the first screen on title and abstract was performed on 32 283 articles (**Figure 1**). For 29 999, the title or abstract clearly indicated that the topic of the article was not relevant to the review question or did not satisfy one of the inclusion criteria. The remaining 2284 articles were screened on full text, applying the full set of eligibility criteria. Eligibility was unclear in 136 (6%), and were reviewed by the second independent reviewer (R.M.), or the author was contacted (if uncertainty was because of missing information). After applying the eligibility criteria, 91 articles (from 48 cohort populations) containing multivariable risk factor analyses were eligible for inclusion. Following panel review, a further 13 articles were excluded because they reported the same outcome domain at the same age at assessment in the same cohort as another article with a more relevant objective. Five of the articles excluded because of cohort overlap were based on cognitive outcomes.[8,16-19] The remaining 78 articles were included in the data extraction for the comprehensive systematic review. No further articles were identified in the hand search of bibliographies. This review article summarizes the results of the 31 studies[20-50] reporting risk factor analyses for cognitive outcomes. These 31 studies were based on 21 independent cohort populations and reported a total of 98 risk factor models.

Study Characteristics

The main study design was prospective cohort (n = 27). There was also one cross-sectional study[46] and 3 randomized clinical trial populations.[27,42,44] Of the 27 prospective cohorts, 12 were ascertained from all live births in a geographically defined region,* and 10 were recruited from a single-center neonatal intensive care unit.† Studies were conducted in 12 countries, including the United States (n = 9), United Kingdom (n = 4), Netherlands (n = 4), Germany (n = 3), Aus-

*References 20, 23, 25, 26, 29-31, 33, 36, 38, 40, 50
†References 28, 32, 34, 37, 39, 41, 43, 45, 47, 49

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tralia (n = 2), Finland (n = 2), and France (n = 2) and 1 study each from Austria, Denmark, Estonia, Italy, and Norway. The median sample size was 219 (range, 45-3785), and 3 studies[21,22,33] had more than 1000 participants. Four studies[24,26,38,50] were restricted to EPT children, and 3 studies[35,44,47] excluded multiple births. The risk-of-bias assessment classified 14 studies (45%) as low to moderate risk of bias and 17 studies (55%) as moderate to high risk of bias (**Figure 2**).

Prognostic Factors for Global Cognitive Impairment

Twenty studies contained a risk factor analysis for general cognitive function or IQ (**Table 1** and **Table 2**). Eight studies[20-27] assessed outcome between ages 1.5 and 2.5 years and 12 studies[28-39] between ages 5 and 13 years. The most common assessment used before age 5 years was the Mental Development Index from the Bayley Scales of Infant Development version II[51] or the Cognitive Composite Score from version III[52] in the more recent studies. The Mental Development Index assesses cognition through evaluation of sensory perception, knowledge, memory, problem solving, and early language. The more recent version splits cognitive and language skills into separate domains. There was more variety in measurement scales used in assessments at age 5 years and older, with the most common being the Mental Processing Composite Score from the Kaufman Assessment Battery for Children[53] and the full-scale IQ from Wechsler's Preschool and Primary Scale of Intelligence–Revised.[54] Risk factors that were found to be significant in the final model of at least 1 study with low to moderate risk of bias and examined in the final model of at least 2 other studies are shown in **Figure 3**A (for children <5 years) and Figure 3B (for children ≥5 years).

Among studies in which the age at assessment was younger than 5 years (Figure 3A), the 2 largest studies[21,22] with low to moderate risk of bias and at least 1 other study with low to moderate risk of bias found the following factors to be predictive of poorer cognitive development: male sex, nonwhite race/ethnicity, lower level of parental education, lower birth weight, and brain injury during the neonatal period. However, the other studies[20,23,25,27] that also examined these risk factors sometimes contradicted these findings, with the exception of race/ethnicity. There was also some evidence that the absence of antenatal corticosteroid use and lower GA were not predictive of poorer cognitive function in children younger than 5 years.

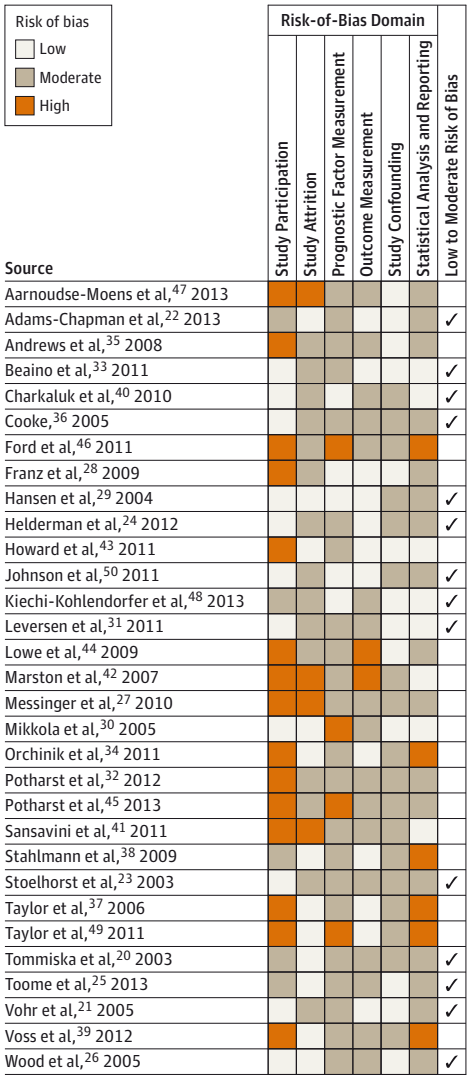
Most of the studies examining cognitive function at 5 years and older had moderate to high risk of bias (Figure 3B). The association between level of parental education and cognitive impairment was also evident in this age group, but the association with male sex was greatly diminished. Race/ethnicity was not entered into the final model in any of the studies among older children (or was not reported when it was used as an adjustment factor in 2 studies[34,37]). Therefore, it was not possible to determine whether the influence of this factor prevailed into middle childhood. Most studies in this age group also found that younger GA had little prognostic value in a multivariable prediction model.

Prognostic Factors for Impaired Language Development

Risk factor analyses for language development were conducted in 8 studies (eTable 2 in the Supplement). Five studies[22,25,40-42] assessed outcome between ages 1.5 and 3 years, and 3 studies[34,37,43] with moderate to high risk of bias assessed outcome between ages 5 and 8 years. There was more heterogeneity in the types of tests used to measure language skills compared with cognition. The eFigure in the Supplement shows the risk factors that were found to be significant in the final model of at least 1 study with low to moderate risk of bias and entered into the final model of at least 2 other studies.

All 5 studies[22,25,40-42] conducted in children younger than 5 years included male sex in the final model and reported that this variable was predictive of poor language development. It was not possible to comment on the effect of male sex in middle childhood because 2 studies[34,37] among 3 conducted at age 5 years and older adjusted for it but did not report the results for adjustment factors while the third study[43] did not enter sex into the final model because it was not significant in the univariate analysis. Three studies[22,40,43] reported that lower level of parental education was associated with poor language development, and 2 studies[25,41] reported no such association. There were also mixed findings for the prognostic value of children being small for GA. It was not possible to draw any conclusions about neonatal brain injury as a prognostic factor for language impairment, possibly because studies used different strate-

Figure 2. Risk-of-Bias Assessment



Shown are 31 studies comprising 98 risk factor models for cognitive outcome.

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Table 1. Summary of Studies Reporting Risk Factor Analyses for Global Cognitive Impairment in Children Born Very Preterm or With Very Low Birth Weight Assessed at Younger Than 5 Years

Source (Study Identifier)	Country and Recruitment Period	Age at Assessment, y	GA, wk/ BW, g	Design and Participants	Survivors Assessed, No. (%)[a]	Outcome Measure, Continuous Unless Otherwise Specified	Method for Dealing With Untestable Children	Significant Risk Factors for Poorer Outcome at $P < .05$ in Final Model
Tommiska et al,[20] 2003 (A)	Finland 1996-1997	1.5	<1000g	PC of infants born and treated in a single-center NICU (Helsinki) and enrolled for the national routine FUP	78 (94)	MDI score from BSID-II	Excluded if severe developmental problem (n = 3) or exhaustion (n = 2)	No. of days from January 1, 1996, to birth
Vohr et al,[21] 2005 (B)	United States 1993-1998	1.5-1.8	<33 wk and <1000 g	PC of infants admitted to the NICU of 12 centers participating in the multicenter NICHD NRN routine FUP	3785 (80)	MDI score from BSID-II (<70 vs ≥70), blinded assessment	Excluded if test not completed (n = 118)	Birth epoch (1993-1994 vs 1995-1996), lower BW, BPD, any high-frequency ventilation, IVH 3-4, male sex, lower maternal education, no private insurance, multiple pregnancy, nonwhite race/ethnicity, outborn,[b] PVL, PN corticosteroid use
Adams-Chapman et al,[22] 2013 (C)	United States 2006-2008	1.5-1.8	<1000 g	PC of infants admitted to the NICU of 20 centers participating in the multicenter NICHD NRN routine FUP	1477 (91)	Cognitive Composite Score from BSID-III, blinded assessment	Assigned a score of 54 if severely delayed (n = 39)	Lower BW, black race/ethnicity, dysfunctional feeding, GMFCS≥2, non-English speaking, male sex, lower maternal education, MV days, multiple pregnancy, NEC 2-3, no private insurance, IVH 3-4 or PVL
Stoelhorst et al,[23] 2003 (D)[c]	Netherlands 1996-1997	2	<32 wk	PC of all live births in 3 Dutch health regions comprising 9% of the population	146 (62)	MDI score from BSID-I	Assigned a score of 50 if severely disabled (n = 3), otherwise excluded (n = 5)	Male sex, lower maternal age, non-Dutch, PN corticosteroid use, SGA
Helderman et al,[24] 2012 (E)	United States 2002-2004	2	<28 wk	PC of all live births in 14 centers in 5 states (ELGAN study)	921 (77)	MDI score from BSID-II (<55 and 55-69 vs ≥70), blinded assessment	Excluded if GMFCS ≥1 (n = 83)	BW <−2 SDs, BMI >30, male sex, lower maternal education, nonwhite race/ethnicity
Toome et al,[25] 2013 (F)	Estonia 2007	2	<32 wk	PC of all live births in Estonia enrolled in the national neonatal research routine FUP	155 (99)	Cognitive Composite Score from BSID-III (<70 vs ≥70)	Assigned a score of −4 SDs below the mean (No. not reported)	IVH 3-4 or PVL 2-4, NEC 2-3
Wood et al,[26] 2005 (G)	United Kingdom and Republic of Ireland 1995	2.5	<26 wk	PC of all live births in the United Kingdom and Republic of Ireland (EPICure study)	196 (64)	MDI score from BSID-II	Excluded if MDI <55 or functional motor disability (n = 52)	Afro-Caribbean race/ethnicity, no AN corticosteroid use, BPD, male sex, lower maternal education, PROM
Messinger et al,[27] 2010 (H)[d]	United States 1999-2001	2.5	<1000 g	Infants admitted to the NICU of 12 centers participating in the multicenter NICHD NRN routine FUP and enrolled in a glutamine supplementation RCT	539 (47)	MDI score from BSID-II	Excluded if test uncompleted (No. not reported)	BW ≤750 g, higher maternal income, higher MDI at 18 mo

Abbreviations: AN, antenatal; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BPD, bronchopulmonary dysplasia; BSID, Bayley Scales of Infant Development[51]; BW, birth weight; ELGAN, Extremely Low Gestational Age Newborns; FUP, follow-up; GA, gestational age; GMFCS, Gross Motor Functional Classification System[68]; IVH, intraventricular hemorrhage; MDI, Mental Developmental Index from the BSID; MV, mechanical ventilation; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NICHD NRN, National Institute of Child Health and Human Development Neonatal Research Network; PC, prospective cohort; PN, postnatal; PROM, prolonged rupture of membranes; PVL, periventricular leukomalacia; RCT, randomized clinical trial; SGA, small for gestational age.

[a] Percentage of survivors assessed for outcome measure specified.

[b] Born outside of the hospital where they were admitted to the NICU.

[c] Two models for motor skills reported, with the model based on 2-year outcome included and the model based on 1.5-year outcome not included.

[d] Several models for cognitive function fitted, with the full model adjusting for 18-month MDI and Behavior Rating Scale total score included.

gies to deal with children with severe neurosensory impairment for whom standard assessments could not be used, with some imputing the lowest possible score and others excluding this group completely. As with cognition, there was evidence that GA was not a strong predictor of language development in a multivariable model.

Prognostic Factors for Impaired Executive Function

Seven studies[32,34,37,44-47] with moderate to high risk of bias presented risk factor analyses for different aspects of executive function (eTable 3 in the Supplement), with all except one based on age at assessment of 5 to 12 years. The median number of tests

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Table 2. Summary of Studies Reporting Risk Factor Analyses for Global Cognitive Impairment in Children Born Very Preterm or With Very Low Birth Weight Assessed at 5 Years and Older

Source (Study Identifier)	Country and Recruitment Period	Age at Assessment, y	GA, wk/ BW, g	Design and Participants	Survivors Assessed, No. (%)[a]	Outcome Measure, Continuous Unless Otherwise Specified	Method for Dealing With Untestable Children	Significant Risk Factors for Poorer Outcome at $P < .05$ in Final Model
Franz et al,[28] 2009 (I)[b]	Germany 1996-1999	4.6-7	<30 wk and <1500 g	PC study of infants admitted to a single-center level 3 NICU (Ulm University)	219 (83)	MPC from KABC, blinded assessment	Assigned a score of 30 if minimal speech and a score of 20 if minimal sensory or motor achievements elicited	Lower BW SDS, smaller HC SDS gain (discharge to 5 y), IVH or PVH ≥3, lower maternal education, MV days, PVL
Hansen et al,[29] 2004 (J)[c]	Denmark 1994-1995	5	<28 wk or <1000 g	PC of all live births in Denmark ascertained from all 18 neonatal care units and the Danish Medical Birth Register (ETFOL Study)	247 (94)	FIQ from WPPSI-R (continuous score and <70 vs ≥70), blinded assessment	Excluded if test not completed (n = 5); children with CP, visual disability, first language not Dutch, or >27 wk GA excluded from analysis of continuous score (n = 110)	Model 1 (continuous score): BPD, lower parental education; Model 2 (<70 vs ≥70): BPD, IVH 3-4, or PVL
Mikkola et al,[30] 2005 (K)[c]	Finland 1996-1997	5	<1000 g	PC of all live births in Finland enrolled for the national routine FUP	172 (83)	FIQ from WPPSI-R (continuous score and <70 vs ≥70)	Excluded if cognitively impaired and unable to cooperate (n = 9), excluded if test not completed (n = 12)	Model 1 (continuous score): no AN corticosteroid use, IVH 3-4, male sex, multiparity, multiple pregnancy, lower parental SES, vaginal delivery; Model 2 (<70 vs ≥70): no AN corticosteroid use, BPD, hospital area, perforated NEC
Leversen et al,[31] 2011 (L)[d]	Norway 1999-2000	5	<28 wk or <1000 g	PC of all live births in Norway	248 (67)	FIQ from WPPSI-R	Excluded if CP, blind, deaf, or autistic (n = 33); excluded if test not completed (n = 25)	Model 1 (GA <28 wk): lower maternal education, preeclampsia, ROP >2; Model 2 (GA ≥28 wk): male sex
Potharst et al,[32] 2012 (M)[e]	Netherlands 2002-2004	5	<30 wk or <1000 g	PC study of infants admitted to a single-center NICU (Amsterdam)	102 (68)	FIQ from WPPSI-III	Excluded if too disabled to be tested (n = 4)	Behavior problems at 2 y, lower MDI at 2 y, lower parental education, parental foreign country of birth, sepsis, or meningitis
Beaino et al,[33] 2011 (N)	France 1997	5	<33 wk	PC of all live births in 9 French regions comprising one-third of all births (EPIPAGE study)	1503 (62)	MPC from KABC (<70 and 70-84 vs ≥85), blinded assessment	Excluded if moderate to severe neurosensory disability (n = 70), excluded if test not completed (n = 239)	Breastfed at discharge, cystic PVL or IPH, GA ≤28 wk, IVH grade 3/echodensities/VD, lower parental SES, SGA, ≥3 siblings
Orchinik et al,[34] 2011 (O)[f]	United States 2001-2003	5	<28 wk or <1000 g	PC of infants admitted to a single-center NICU (Ohio) participating in the multicenter NICHD NRN routine FUP	142 (72)	WJ-III COG Brief Intellectual Ability <10th centile, blinded assessment	Assigned a score of 40 if too low functioning to comply with test demands	GA <25 wk, infection (sepsis, NEC, or meningitis), IVH 3-4/PVL/ VD, neurosensory disorder or MDI <70 at 20 mo
Andrews et al,[35] 2008 (P)[c]	United States 1996-1999	5-8	<32 wk	PC of infants admitted to a single-center NICU (Alabama) participating in the multicenter NICHD NRN routine FUP, multiple births excluded	259 (69)	WISC-IV or DAS if <6 y or unable to complete the WISC-IV (continuous score and <70 vs ≥70)	Excluded if test not completed (n = 2)	Model 1 (continuous score): younger GA, PVL; Model 2 (<70 vs ≥70): no history of PROM, younger GA
Cooke,[36] 2005 (Q)	England 1991-1992	7	<32 wk	PC of all live births in all 8 hospitals in the Liverpool postal district	280 (77)	WISC-III (<89 vs ≥89, mean of the group)	Excluded if not free of major disability and not attending mainstream school (n = 29)	Younger GA, smaller HC at 7 y, PDA

(continued)

administered within each study was 5, and the maximum was 13. The risk factors listed in eTable 3 in the Supplement were significant in at least 1 of the final models. It was difficult to combine these results in any meaningful way because of the small number of studies using a wide variety of tests to measure interrelated cognitive processes.

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Table 2. Summary of Studies Reporting Risk Factor Analyses for Global Cognitive Impairment in Children Born Very Preterm or With Very Low Birth Weight Assessed at 5 Years and Older (continued)

Source (Study Identifier)	Country and Recruitment Period	Age at Assessment, y	GA, wk/ BW, g	Design and Participants	Survivors Assessed, No. (%)[a]	Outcome Measure, Continuous Unless Otherwise Specified	Method for Dealing With Untestable Children	Significant Risk Factors for Poorer Outcome at $P < .05$ in Final Model
Taylor et al,[37] 2006 (R)[c,g]	United States 1992-1995	8	<1000 g	PC of infants admitted to a single-center NICU (Ohio) participating in the multicenter NICHD NRN routine FUP	204 (86)	MPC from KABC (continuous and <1 SD below mean of control group), blinded assessment	Excluded if untestable because of severe developmental impairments (n = 10)	Model 1 (continuous score): longer neonatal hospital stay, NEC, NRI >3, PVL, VD; Model 2 (<70 vs ≥70): longer neonatal hospital stay, NRI >3, PVL, VD
Stahlmann et al,[38] 2009 (S)	Germany 1997-1999	7-9	<27 wk	PC of all live births in all 8 perinatal centers in Schleswig-Holstein	75 (82)	MPC from KABC or equivalent (<70 vs ≥70), blinded assessment[h]	Assigned a score of <70 if untestable because of extremely limited capacities	IVH 3-4/PVL
Voss et al,[39] 2012 (T)	Germany 1993-1998	10-13	<1000 g	PC study of infants admitted to a single-center NICU (Hannover)	148 (87)	HAWIK-III composite IQ score	Assigned a score of 39 (40 is the lowest possible score)	HC increase <6 mm per wk, IVH 3-4/PVL, immigrant status, parenteral nutrition >41 d

Abbreviations: AN, antenatal; BPD, bronchopulmonary dysplasia; BSID, Bayley Scales of Infant Development[51]; BW, birth weight; CP, cerebral palsy; DAS, Differential Ability Scales[69]; EPIPAGE, Etude Epidemiologique sur les Petits Ages Gestationnels; ETFOL, Ekstrem Tidlig Født Og Lavvægtig (Danish National Study in Infants With Extremely Low Gestational Age and Birth Weight; FIQ, Full-scale IQ from WPPSI-R; FUP, follow-up; GA, gestational age; HAWIK, Hamburg Wechsler Intelligence Test for Children[70]; HC, head circumference; IPH, intraparenchymal hemorrhage; IVH, intraventricular hemorrhage; KABC, Kaufman Assessment Battery for Children[53]; MDI, Mental Developmental Index from the BSID; MPC, Mental Processing Composite Score from the KABC; MV, mechanical ventilation; NEC, necrotizing enterocolitis; NICHD NRN, National Institute of Child Health and Human Development Neonatal Research Network; NICU, neonatal intensive care unit; NRI, Neonatal Risk Index; PC, prospective cohort; PROM, prolonged rupture of membranes; PVH, periventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; SDS, standard deviation score; SES, socioeconomic status; SGA, small for gestational age; VD, ventricular dilatation; WISC, Wechsler Intelligence Scale for Children[71]; WJ-III COG, Woodcock-Johnson Tests of Cognitive Abilities, Third Edition[72]; WPPSI-R, Wechsler's Preschool and Primary Scale of Intelligence–Revised.[54]

[a] Percentage of survivors assessed for outcome measure specified.

[b] Two models for cognitive function reported; the same perinatal factors fitted with change in weight variables added to the first model and change in head circumference variables added to the second model. Perinatal factors are included in Figure 3B as significant if $P < .05$ in both models and nonsignificant if $P \geq .05$ in both models and otherwise are not included.

[c] Two models for cognitive function reported, with one based on dichotomous outcome and the other based on continuous outcome. Risk factors are included in Figure 3B as significant if $P < .05$ in both models and nonsignificant if $P \geq .05$ in both models and otherwise are not included.

[d] Two models for cognitive function reported for each gestational age group (<28 weeks and ≥28 weeks). Risk factor was considered significant if $P < .05$ in either model.

[e] Two models for FIQ at 5 years reported, with one including 2-year developmental assessments and the other including 3-year developmental assessments. The former model is reported as 2-year assessments, which are more routine in general practice.

[f] Each risk factor was fitted separately and adjusted for sex, race/ethnicity, parental SES, and months in school at testing (the article did not report the results for the adjustment factors).

[g] Each risk factor was fitted separately and adjusted for sex, race/ethnicity, parental SES, family stressors, and family resources (the article did not report the results for the adjustment factors).

[h] Seven children were tested with an equivalent instrument (HAWIK, Snijders-Oomen Nonverbal Intelligence Test, or the Culture Fair Intelligence Tests).

Prognostic Factors for Poor Academic Attainment

Four studies (2 studies[48,50] with low to moderate risk of bias and 2 studies[37,49] with moderate to high risk of bias) performed risk factor analyses for academic attainment (eTable 4 in the Supplement), all based on age at assessment between 5 and 12 years. All 4 studies presented a model on mathematical ability, 2 studies presented a model on letter and word identification, and 1 study presented a model on reading scores. Again, there were too few studies and insufficient overlap in the risk factors entered into the final models to combine the results and draw any meaningful conclusions.

Discussion

For the VPT or VLBW population, there was fairly strong evidence that male sex was a prognostic factor for poorer cognitive development and language skills in early infancy, a finding supported by other studies[55-57] that have focused exclusively on the association of infant sex with cognitive function. However, in the studies conducted later in childhood that were included in this review, the influence of sex on general cognition was largely diminished. We were unable to comment on whether this finding was also true for language development because of the lack of studies assessing children at 5 years and older. There were similar findings for nonwhite race/ethnicity and lower birth weight in relation to cognitive impairment. Both factors were clearly prognostic in early infancy, but no evidence was available in middle childhood for race/ethnicity, with a lack of association in later years for birth weight. There was evidence that a lower level of parental education was predictive of cognitive impairment, supported by a recent study[58] in an EPT population that focused solely on this hypothesis. Unlike factors related to infant characteristics, the influence of parental education appeared to persist into middle childhood. Evidence for the prognostic value of parental education in relation to language development was weak.

Research has shown links among nonwhite race/ethnicity, lower birth weight, and parental education or socioeconomic status (SES),[59,60] so it is notable that these factors were independent predictors in the final models of the 4 studies[21,22,24,26] in the age group younger than 5 years. Other studies[61,62] have found that the effect of race/ethnicity is strongly mediated by markers of deprivation. In

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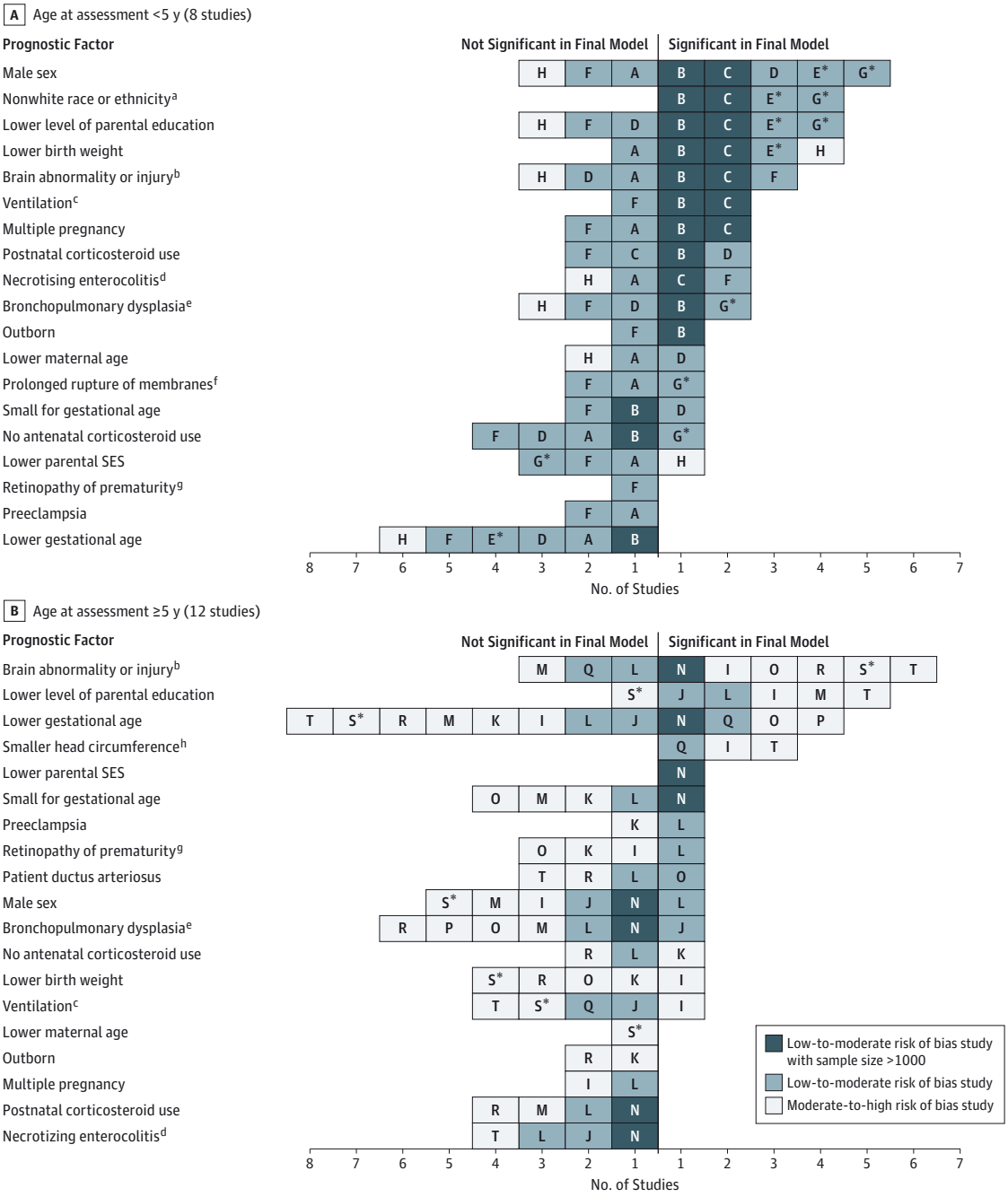
Figure 3. Evidence Synthesis of Risk Factors for Global Cognitive Impairment in Children Born Very Preterm or With Very Low Birth Weight



Prognostic factors are presented if significant ($P < .05$) in the final model of at least 1 study with low-to-moderate risk of bias and entered into the final model of at least 3 studies (across all ages). A through T indicate study identifiers listed in Table 1 and Table 2 (* denotes an extremely preterm cohort); SES, socioeconomic status.

[a] Nonwhite (B and E), black (C), or Afro-Caribbean (G).

[b] Intraventricular hemorrhage or periventricular leukomalacia (B, C, D, F, H, I, L, M, O, S, and T), periventricular leukomalacia or ventricular dilatation (R), intraventricular hemorrhage grades 2 to 4 (A), parenchymal lesion (Q), intraventricular hemorrhage grades 1 to 3, echodensities, ventricular dilatation, cystic periventricular leukomalacia, or intraparenchymal hemorrhage (N).

[c] Any high-frequency (B), any mechanical ventilation (J), or mechanical ventilation days (C, F, I, Q, S, and T).

[d] Perforated necrotizing enterocolitis (A), necrotizing enterocolitis stages 2 to 3 (C and F), surgical or radiograph diagnosed (J), bowel perforation or necrotizing enterocolitis (T), or not specified (H, L, and N).

[e] Oxygen requirement at 36 weeks' gestational age (B, D, F, G, J, L, M, N, O, and R) or not specified (H and P).

[f] More than 24 hours before labor (G) or not specified (A and F).

[g] Stage 3 to 4 (I, K, and L), at least stage 3 with laser therapy (F), or stage 4 to 5 or treatment with cryotherapy or laser therapy (O).

[h] Increase in head circumference from discharge to 5 years (I), occipitofrontal circumference 7-year centile (Q), or increase in head circumference less than 6 mm per week (T).

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the present review, level of parental education emerged as a prognostic factor of cognitive outcome, whereas parental SES did not. This finding may be because of multicollinearity, or possibly a single marker of parental SES such as income or occupation (as used in most studies in the review) is insufficient to capture an accurate measure of social disadvantage. Combining a range of social markers into a composite score may be a more effective modeling strategy.

Many studies that have focused exclusively on the relationship between brain injury diagnosed in the neonatal period and subsequent cognitive function have reported strong linear trends with grade of severity.[63-66] However, the prognostic value of brain injury in the multivariable models reported in this review was mixed. This result is possibly because cognitive and language development is multifactorial, unlike a diagnosis of CP, which is more directly related to focal brain injury, so that the influence of perinatal factors becomes less pronounced when other variables are entered into a model. The unclear findings may also reflect the different modeling strategies adopted by the studies. Some studies excluded children with CP or other neurosensory impairment, some imputed lowest scores, and others adjusted for motor disability.

There was strong evidence that GA was not a robust predictor of cognitive and language development in infancy or in middle childhood in the VPT or VLBW population. Although the relationship between older GA and improved cognition is well established across the whole spectrum of GA from 25 to 40 weeks,[4] it does not emerge as an important predictor in individual studies with preterm subgroups defined by restricted GA. Although a strong positive relationship with GA is seen when survival without neurodevelopmental impairment is calculated as a function of all live births, the association weakens when the denominator is survivors at discharge, as with all the studies included in this review. This occurs because the proportion of surviving children rises steeply with GA, while the proportion of impaired survivors does not.

Our study has strengths and limitations. We used a broad search filter with no language restriction to capture all studies with exploratory risk factor analyses, which is recommended in this type of review.[67] No further articles were identified in the hand-search of bibliographies of all studies included, so it is unlikely that there were any major omissions. The study cohorts spanned an 18-year period; hence, some of the factors affecting outcome in the early 1990s may not be so relevant to current preterm populations. They also represent diverse international populations, with differing methods of ascertainment and clinical practices, which may explain the unclear pattern of the results for some factors. Also, studies did not all consider the same sets of candidate factors. Multiple models based on the same cohort population were a major issue, particularly studies on executive function, which often performed a whole battery of tests. Using standard rules, we selected studies and models for inclusion before data synthesis was conducted, although it was difficult to apply a strict set of criteria for each case. Another difficulty in this review was the sheer variety of assessments used, particularly among children 5 years and older.

Conclusions

In conclusion, there was evidence that male sex, nonwhite race/ethnicity, lower level of parental education, and lower birth weight were significant predictors of global cognitive impairment in children 18 to 30 months old who were born VPT or with VLBW. After age 5 years, the effect of infant sex and birth weight diminished, level of parental education was still influential, and there was no evidence on the lasting effect of race/ethnicity. It is unlikely that race/ethnicity itself is a causal factor for cognitive impairment because other research has demonstrated a strong correlation between race/ethnicity, poverty, and social disadvantage. There was evidence that male sex was predictive of language development in early infancy, but no evidence that this result was sustained into childhood. There were mixed findings on the prognostic value of brain injury during the neonatal period on language and cognition, which may reflect the heterogeneous selection criteria and methods of dealing with missing data related to severe disability across the studies. There was evidence that within the VPT or VLBW population GA had little value as a prognostic factor in multivariable models predicting the risk of cognitive or language development at any age older than 18 months. The findings of this review lend support to the view that the effect of perinatal risk factors diminishes over time as other environmental and social factors become more influential.

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