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Las Consecuencias para la Vida de Nacer Muy Prematuro

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Palabras claves

Nacimiento muy prematuro, desarrollo cognitivo, salud mental, calidad de vida, riqueza, relaciones románticas, modelos de desarrollo

Resumen

Alrededor de 15 millones de niños nacen prematuros (<37 sem de gestación) cada año. De éstos, 15% o 2.25 millones son muy prematuros (MPT; <32 sem de gestación). Aquí, revisamos los resultados del desarrollo de bebés MPT en varios dominios desde el motor, cognitivo, y función social hasta salud mental y bienestar a lo largo de la infancia y adolescencia. También son consideradas su adaptación a su curso de vida en términos de relaciones románticas, empleo, y calidad de vida en la adultez. Algunos efectos adversos se reducen a medida que los individuos crecen, y otros se mantienen estables desde la infancia hasta la adultez. Argumentamos que para avanzar en la comprensión de mecanismos de desarrollo y recursos directos de intervención, más efectivamente, los factores sociales deben ser examinados más ampliamente, y los diseños sensibles genéticamente deberían ser tenidos en cuenta con integración de neuroimágenes para probar modelos alternativos de desarrollo. Dado que la evidencia actual está basada casi exclusivamente en estudios de países de altos ingresos, la investigación en países de bajos y medianos ingresos es necesaria en forma urgente.

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INTRODUCCIÓN

Para lograr la Meta de Desarrollo Sostenible 3 (MDS 3 de las Naciones Unidas) para asegurar vidas saludables y promover el bienestar para todos en todas las edades, es crucial determinar la carga global de nacimiento prematuro (Chawanpaiboon et al. 2019). En 2014, 10.6% de nacidos vivos o 14.84 millones de bebés nacieron PT-antes de las 37 semanas de gestación- en todo el mundo. El nacimiento PT es la mayor causa de mortalidad en niños menores de 5 años (Lee et al.2019). En las tres últimas décadas, el mayor progreso en sobrevida se dio para bebés nacidos MPT, o antes de las 32 sem de gestación. Pese a que los MPT dan cuenta del 15% de todos los nacimientos PT, están asociados con los costos más altos por la hospitalización inicial (Petrou et al. 2019) y por el apoyo en salud y educación a largo plazo (Petrou et al. 2013). Dado que en los países de altos ingresos sobreviven actualmente el 95% de los MPT, el foco se ha desplazado desde solo reducir la mortalidad hacia comprender y mejorar los resultados a largo plazo y la calidad de vida. Aquí proveemos un panorama de las consecuencias a lo largo de la vida de nacer MPT y los mecanismos del desarrollo que llevan a resultados adversos motor, psicológico y social.

TERMINOLOGÍA Y EPIDEMIOLOGÍA

La OMD define como nacimiento prematuro a todos aquellos que se producen antes de las 37 semanas completas de gestación. El límite de viabilidad es actualmente alrededor de las 22 semanas, pero la sobrevida a esta EG todavía es rara. Alrededor de 3.3-8.9 % de todos los bebés PT nace extremadamente PT (EPT; <28 sem EG) y alrededor de 9.8-12.8% a las 28-31 sem de gestación, con todos los infantes nacidos antes de las 32 semanas clasificados comos MPT (Chawanpaiboon et al. 2019). Cerca del 20% de los bebés PT nacen moderadamente PT (32-33 sem de gestación), y 60-70% son PT tardíos (PTT; 34-36 semanas de gestación) (Goldenberg et al. 2008).

Los términos PT y bajo PN (BPN; <2500 g) con frecuencia son empleados indistintamente en los estudios de resultados a largo plazo de estos infantes. Aproximadamente 7-10% de todos los bebés nacen con MBP (Wolke 1991) y alrededor de 0.9-1.5% con muy bajo peso de nacimiento (MBN; <1500 g). Los infantes con extremadamente BPN (EBPN) son usualmente clasificados como tales si nacen con <100 g (Hille et al. 2001) o algunas veces <750 o <800 g (Whitfield et al. 1997).

Los infantes adecuados a la EG y pequeños para EG (PEG) son clasificados basados en la relación entre la gestación y PN empleando tablas de crecimiento de población estándar o adapatadas de PN (Zeitlin et al. 2017). Los niños PEG nacen en percentilo <10 o <3 o ≤2 DS debajo de la media para su EG (Zeitlin et al. 2017). Dentro de la población PT, 16-40% de los bebés nacen PEG (percentilo <10).

En números absolutos, la mayoría de los bebés PT nacen en Asia (52.9% de los nacimientos PT globales) y África Sub-Sahariana (28.2%). En contraste, Europa (4.7%) y los estados Unidos (3.3%) dan cuenta de una pequeña fracción de la carga global (Chawanpaiboon et al. 2019).

El parto prematuro puede ser espontáneo (debido a parto prematuro o rotura prematura de membranas) o iniciado clínicamente (sección cesárea o inducción del parto) debido a indicaciones agudas maternas o fetales tales como infección, pobre crecimiento fetal, o elevada presión sanguínea (Goldenberg et al. 2008). Factores asociados con el nacimiento prematuro incluyen los sociodemográficos (ej. raza, pobreza), nutricional (obesidad), genética o microbioma materno, ambientales (ej. fumar) y factores del estilo de vida (ej. tratamiento de fertilidad, edad materna elevada), pero, en 50% de los casos, la causa específica es desconocida (Muglia y Katz 2010).

El número de nacimientos MPT no ha disminuido significativamente, e inclusive ha aumentado en muchos países, mientras que las tasas de mortalidad han disminuido, al menos en países de altos y medianos ingresos (Yeo et al. 2015). Así, el número absoluto de nacidos MPT sobrevivientes está aumentando, generando una preocupación creciente en salud pública.

DESARROLLO DESPUÉS DEL NACIMIENTO MPT

La revisión apunta al desarrollo motor, psicológico, y social desde la infancia hasta la adultez luego de nacer MPT. Por lo tanto, el órgano más considerado es el cerebro. Cuando es posible, el foco está en estudios de alta calidad que (a)sean prospectivos, (b) sean suficientemente robustos (ej., estudios geográficos, epidemiológicos, o multicéntricos), (c) tengan pocos infantes perdidos al seguimiento o bien documentados los faltantes, (d) incluyan grupos de control de término para comparaciones específicas de cohorte, € sean a largo plazo (ej. edad escolar o adultez), (f) incluyan reportes diferenciales de sub-poblaciones (ej., clase social, EPY vs MPT), y (g) estén conducidos por investigadores independientes no involucrados en el cuidado de los infantes bajo investigación y ciegos a la asignación del grupo de estudio (Johnson et al. 2008, Vohr 2007). Se hizo particular énfasis en los estudios que emplean grupos de control contemporáneos, dado que tendencias seculares en scores cognitivos y de conducta han

sido reportados repetidamente (Collishaw et al. 2010, Wolke et al. 1994). Finalmente, enfocamos preominantemente en reportes de de diferencias media o diferencias en proporciones entre individuos MPT y controles de término y, en lo posible, referir a meta-análisis para estimar efecto de tamaños.

Desarrollo Motor y Actividad Física

Las dificultades motoras que siguen al nacimiento MPT van desde retrasos leves, en sentarse o caminar, hasta déficit motor severo, como parálisis cerebral (PC), que permanece como la alteración motora primaria luego del nacimiento MPT (Reid et al. 2016). Otros déficits en coordinación, balance, control motor grueso y fino, e integración visomotora son considerados usualmente como déficits motores sin PC y pueden ser considerados desórdenes del desarrollo de coordinación (DDC) según los criterios del DSM-V (Am. Psychiatr. Assoc. 2013).

Hallazgos de uno de los registros más abarcativos en Victoria, Australia, indican que las tasas de PC han disminuido desde mediados de los 90 en aquellos nacidos MPT (28-31 sem EG), desde 41,5/1000 sobrevivientes neonatales en 1983- 1991 hasta 32.4/1000 sobrevivientes en 2001-2009 (Reid et al. 2016). En contraste, entre los nacidos EPT, las tasas de PC aumentaron hasta el año 2000 con una disminución posterior (92.1, 102.5, y 70.6/1000 sobrevivientes en 1983-1991, 1992-2000, y 2001-2009, respectivamente). Pese a que los nacidos MPT/EPT son solo el 1-2% de todos los nacimientos, ellos hacen una gran contribución a las tasas de niños con PC. Las mejoras para MPT/EPT pueden deberse a considerables cambios en el manejo de los infantes prematuros en las últimas décadas, pero hay poca evidencia de la eficacia de una sola intervención en reducir las tasas de PC (Spittle y Orton 2014).

En cuanto a los déficits motores sin PC, los niños nacidos MPT/MBPN tienen scores de DS -0,57 a -0.88 más bajos que sus pares de término en pruebas estandarizadas de desempeño motor desde la infancia hasta los 15 años de edad (de Kieviet et al. 2009). Estas diferencias tuvieron un moderado a gran efecto de tamaño y se encontraron en una amplia gama de habilidades, incluyendo equilibrio, habilidades con pelota, destreza manual, y desarrollo motor fino y grueso. Mientras que las habilidades motoras mejoraron desde infante hasta niñez, no hubo mejora significativa desde la niñez hasta la adolescencia. Una revisión más reciente que excluyó niños con PC (Edwards et al. 2011) encontró un riesgo mayor para DDC en niños MPT/MBPN, con un OR de 6.29 (IC 95%, 4.37 a 9.05) y un OR de 8.66 (IC 95%, 3.40 a 22.7) para el score en percentilo <5-15 en la Batería de Estudio de Movimiento para Niños (MABC), respectivamente. Mayores diferencias aún de 1.1- 1.6 DS se encontraron entre niños nacidos <26 sem de EG (Marlow et al. 2007).

Sigue habiendo una pregunta importante acerca de si DDC ha disminuido con la mejora del cuidado neonatal. El Estudio Colaborativo del Infante en Victoria (VICS) en Melbourne, Australia, reclutó tres cohortes consecutivas de bebés EPT/EBPN nacidos en 1991.1992, 1997, y 2005 en nuestras cuatro unidades terciarias neonatales en la región (Spittle et al. 2018). Mientras que las tasas de sobrevida aumentaron de 54% en 1991-1992 a 68% en 1997 y se estabilizaron en 2005 en 64%, las tasas de PC permanecieron constantes en 11%, 11%, y 12% respectivamente. En contraste, el déficit motor no-PC aumentó a lo largo del tiempo pese a los avances en el cuidado neonatal, con una prevalencia del 13%, 15%, y 26% entre niños MPT/MBPN, respectivamente (Spittle et al. 2018). Pese a que hubo predictores perinatales independientes consistentes de déficit motor en las tres épocas, incluyendo pobre crecimiento fetal, injuria cerebral, cirugía, y sexo masculino, estos no explicaban el aumento de la tasa de déficit motor en la cohorte 2005. Los autores especularon que otros factores tales como la reducción de la actividad física (AF) pueden haber impactado adversamente en los resultados motores de los niños EPT/EBPN.

En efecto, uno podría esperar que los niños MPT/EPT participen menos en deportes y AF dada su más alta tasa de déficits motores. Sin embargo, según las recomendaciones de la OMS, los individuos nacidos PT son estimulados a participar en AF para mejorar su función pulmonar y aptitud cardiovascular (Spiegler et al. 2019ª). En efecto, un estudio longitudinal reciente desde el nacimiento hasta los 14 años muestra que los niños y adolescentes MPT no se dedican menos a AF o deportes que sus controles de término. Además, la AF fue mayor en adolescentes varones, aquellos de raza blanca, niños de padres con mayor nivel educativo, niños que concurren a eventos deportivos a los 5-7 años, o aquellos que tomaban parte en AF organizada a los 5-7 años (Spiegler et al. 2019b). Entonces, consistente con otros estudios, este estudio encontró que los niños MPT no eran menos predispuestos a ser físicamente activos, pero ellos reducen la participación en deportes hacia la adolescencia de la misma forma que lo hacen los nacidos a término

Desarrollo Cognitivo

Un reciente meta-análisis de 71 estudios de cohorte identificó que los individuos MPT/MBPN tienen scores DS de CI 0.86 (IC 95%, -0.94 a -0.78) más bajos que los controles a la edad de 5-20 años, equiparando a un déficit puntual de 12.9 (Twilhaar et al. 2018ª). Similares tamaños de efectos han sido reportados en otros meta-análisis, con déficits de 10.9 (IC 95%, 9.2 a 12.5) (Bhutta et al. 2002) y 11.9 (IC 95%, 10.47 a 13.42) puntos CI en todos los niños prematuros comparados con controles. Entre Entre las cohortes de MPT, ha sido reportado (Kerr-Wilson et al. 2012)un déficit medio de 13.9 puntos de CI (IC 95%, 11.5 a 16.2). En conjunto, estos estudios indican que el CI en los individuos MPT es, en promedio, DS 0.7 a 0.9 inferior al de sus pares nacidos a término.

En dos meta-análisis, la diferencia media en CI no difirió significativamente en el tiempo, sugiriendo que los resultados cognitivos no han mejorado significativamente pese a los avances en el cuidado neonatal (Kerr-Wilson et al. 2012, Twilhaar et al. 2018b). La única comparación directa de CI en cohortes consecutivas de la misma región geográfica es del grupo del VICS de bebés MPT/MBPN nacidos en 1991-1992, 1997, y 2005. Similar a los hallazgos para PC delineados más arriba, los investigadores encontraron que la diferencia media en CI entre niños MPT y controles no fue significativamente diferente para los nacidos en 2005 comparados con los nacidos en los ´90 a la edad de 8 años. Similarmente, no hubo diferencias significativas en la proporción con déficit cognitivo (CI <-2DS de controles) (Cheong et al. 2017). Entonces, pese a la mejoría del cuidado neonatal y la prevalencia reducida de discapacidades neurosensoriales severas (Doyle et al.), no hay aún evidencia de mejor resultado cognitivo en el tiempo.

Notablemente, todos los meta-análisis encontraron una significativa asociación entre CI y EG (Allotey et al. 2018, Bhutta et al. 2002, Kerr-Wilson et al. 2012, Twilhaar et al. 2018b), indicando un efecto dosis-respuesta de la gestación al nacer sobre el resultado cognitivo. Esta asociación también ha sido mostrada en estudios poblacionales extensos (Poylsen et al. 2013, Wolke et al. 2015b); sin embargo, aún no está claro si ésta es una asociación linear entre nacimientos de todos los prematuros (Bhutta et al. 2002, Kerr-Wilson et al. 2012) o una relación exponencial con aumento del déficit observado en los nacidos antes de las 32 sem de gestación (Jaekel et al. 2013, Wolke et al. 2015b). Está claro, sin embargo, que aquellos nacidos EPT (<26 sem EG) están en mayor riesgo de déficits, con DS de 1.3 a 1.6 en CI en la infancia (Johnson et al.2009, Marlow et al. 2005).

Una cuestión clave es si los déficits cognitivos observados en la infancia temprana persisten a lo largo de la vida o si los individuos MPT alcanzan a sus pares a medida que crecen. Los meta-análisis han encontrado típicamente que las diferencias medias en CI no se achican con la edad (Allotey et al. 2018, Twilhaar et al. 2018b). Sin embargo, estos están basados en comparaciones sucesivas transversales más que en un análisis de las trayectorias del desarrollo en el tiempo.

Los estudios que han seguido el desarrollo de individuos MPT/MBPN/EPT desde el nacimiento hasta la adultez no han podido encontrar evidencia de recuperación del desarrollo. El estudio EPICure evaluó el CI en niños EPT a los 2.5, 6, 11, y 19 años de edad junto a un grupo control nacido a término evaluado desde los 6 años de edad. Los déficits en el CI permanecieron estables en el tiempo, pese a que hubo un pequeño pero no significativo achique de la brecha a razón de 0.5 puntos de CI por año, y un déficit de 18 puntos continuaba existiendo a los 19 años de edad (Linsell et al. 2018). Similares resultados han sido reportados para sobrevivientes MBPN/MPT, que tenían CI

significativamente inferior que los controles de término cuando se evaluaron a los 2, 4, 6, 8, y 26 años de edad (Breeman et al. 2015).

Comparando con CI, hay menos reportes de las funciones ejecutivas y de atención hasta la fecha. Los meta-análisis han encontrado déficits pequeños a moderados en la fluencia verbal (DS -0.57), memoria de trabajo (DS -0.36), y flexibilidad cognitiva (DS -0.49) en niños MPT comparados con controles (Aarnoudse-Moens et al. 2009). Diferencias medias estandarizadas de -0.42 a -0.71 para la memoria de trabajo y -0.35 a -0.62 para la velocidad de procesamiento también han sido reportados en niños prematuros comparados con controles (Allotey et al. 2018). Similares tamaños de efecto han sido reportados en niños MPT que tuvieron scores DS 0.51 (IC 95%, -0.58 a -0.44) más bajos que sus controles en 87 mediciones de funciones ejecutivas y DS 0.49 (IC 95%, -0.60 a -0.39) más bajos en pruebas de velocidad de procesamiento (Brydges et al. 2018). También se han observado déficits significativos en cohortes MPT en la adultez (Eryigit Madzwamuse et al. 2015); sin embargo, estas son usualmente más pequeños en tamaño que los déficits en CI. L igual que en los hallazgos para CI, no hay evidencia de funciones ejecutivas mejoradas con la mejora del cuidado neonatal desde los ´90s (Burnett et al. 2018).

Escolaridad y Logro Académico

En meta-análisis del desempeño en pruebas etandarizadas de logros, los niños nacidos PT tienen scores DS 0.71- 0.78 inferiores a los de los controles nacidos a término en matemáticas, DS 0.44-0.67 más bajos en lectura, y DS 0.52-0.56 menor en deletreo (Allotey et al. 2018, Twilhaaa et al. 2018b). En niños nacidos MPT, los scores de matemáticas son DS 0.60 (IC 95%, -0.74 a -0.46) menores que los controles, scores de lectura DS 0.48 (IC 95%, -0.60 a -0.34) menores, y scores de deletreo DS 0.76 (IC 95%, -1.13 a -0.40) más bajos (Aarnoudse-Moens et al.2009).

Estudios poblacionales también encontraron un significativo efecto dosis-respuesta de la EG al nacer sobre los resultados en educación. La asociación rutinaria de datos para 407 503 niños en Escocia reveló que el riesgo de necesidades educativas especiales aumentó a medida que la EG al nacer disminuía para cada semana por debajo de las 40 sem EG, con un OR ajustado de 1.16 (IC 95%, 1.12 a 1.20) para niños nacidos a las 37-39 semanas, OR 1.53 (IC 95%, 1.43 a 1.63) para niños nacidos a 33-36 semanas, OR 2.66 (IC 95%, 2.38ª 2.97) para aquellos nacidos a las 28-32 semanas, y OR 6.92 (IC 95%, 5.58 a 8.58) para niños nacidos a las 24-27 semanas (MacKay et al. 2010).

Un efecto dosis-respuesta del nacimiento antes del término también ha sido reportado en el logro académico (Pettinger et al. 2019, Wolke et al. 2015b). Por ejemplo, la proporción

de niños que no lograron alcanzar un buen nivel en las pruebas de logro escolar a la edad de siete años aumentó a medida que la EG disminuía, con 43% de los niños MPT fallando para tener un buen nivel de logro en la evaluación, comparado con 18% de los niños nacidos a término (RR 1.78; IC 95%, 1.24 a 2.54) (Chan y Quigley 2014).

El nacimiento MPT tiene un efecto deletéreo sobre el aprendizaje, con los niños nacidos MPT presentando desempeño significativamente peor en todas las materias escolares. Sin embargo, déficits marginalmente mayores se encuentran en matemáticas comparados con otras materias (Aarnoudse- Moens et al. 2009, Allotey et al. 2008, Twilhaar et al. 2018b). Esto es debido a que los déficits cognitivos generales de los niños MPT, como las deficiencias en la memoria de trabajo y habilidades visuo-espaciales, más que déficits en habilidades numéricas (Jaekel y Wolke 2014, Simms et al. 2015).

Estos déficits académicos observados en la infancia representan un retraso del desarrollo o déficits persistentes a lo largo de la escolaridad? Twilhaar y colegas (2018ª) no encontraron diferencias significativas en las trayectorias de los niños nacidos MPT y sus controles de término en aritmética, lectura, o deletreo a lo largo de la escuela elemental. Otra investigación de resultados en las pruebas de rendimiento escolar encontró que los niños PT mostraban avances en el rendimiento entre las edades de 7 y 11 años, achicando la brecha levemente con sus pares de término, pero no a las edades 11 y 14 (Odd et al. 2019). Entonces, en general, los niños PT no alcanzan a sus pares, en déficits sustanciales en el rendimiento son evidentes todavía hacia el final de la escolaridad obligatoria.

Al igual que con los resultados cognitivos, basarse en el mejor cuidado neonatal para la mejora de los resultados educativos, no parece traer la respuesta.En las cohortes VICS, el rendimiento en lectura, deletreo, y matemáticas fue significativamente más pobre en niños EPT nacidos en 2005 comparados con los nacidos en los ´90s (Cheong et al.2017). Las razones para el deterioro en el rendimiento académico no son conocidas, pero es claro que las mejoras en el cuidado neonatal necesitan tener paralelo con mejor entrenamiento de maestros y apoyo educacional para niños nacidos PT (Johnson et al. 2015, Pettinger et al. 2019).

Salud Mental

La evaluación de la salud mental en estudios de cohorte ha sido principalmente llevada a cabo en los padres, maestros, o escalas auto-completadas más que con evaluaciones diagnósticas más costosas. Un meta-análisis reciente utilizando estas medidas reveló un pequeño a moderado efecto para síntomas de internalización aumentados (diferencia media estandarizada {DMS} 0.42; IC 95%, 0.26 a 0.58) en niños EPT/EBPN comparados con controles y un pequeño efecto para problemas de externalización (DMS 0.15; IC 95%, 0.02

a 0.28) (Mathewson 2017). Un meta-análisis individual de datos de seis estudios de cohorte en la adultez, también encontró escores más altos para problemas de internalización pero scores más bajos para problemas de externalización entre adultos MPT/MBPN comparados con los controles (Pyhâlâ et al. 2017). Los efectos, sin embargo, fueron usualmente muy pequeños, con diferencias medias en scores z yendo de 0.06 a 0.12.

En la infancia, se ha descripto un fenotipo conductual del PT, caracterizado por un riesgo aumentado para problemas de atención, problemas emocionales, y dificultades con la interacción social, al par que sin riesgo aumentado para conducta agresiva o delictiva (Johnson y Marlow 2011, Mathewson 2017). Esto fue evidenciado primero por un patrón similar de hallazgos en cinco estudios de cohorte (Farooqi et al. 2007, Hille et al. 2001).

A nivel diagnóstico,un meta-análisis de 5 estudios identificó un OR de 3.66 (IC 95%, 2.57 a 5.21) para desórdenes psiquiátricos en niños y adolescentes PT/BPN, con prevalencias estimadas en rango de 21% a 28% (Burnett et al. 2011). El patrón de desórdenes observados en las poblaciones PT indica un riesgo aumentado para ADHD, alteraciones depresivas y de ansiedad, y TEA, al par que sin aumento de desórdenes disruptivos, control-impulso, o de conducta (Johnson y Marlow 2011, Johnson y Wolke 2013).

ADHD es la alteración más común después de nacer PT para lo cual han sido reportados consistentes estimativos de riesgo, con ORs de 3.3 (IC 95%, 2.0 a 5.6) (Allotey et al. 2018) y 3.04 (IC 95%, 2.19 a 4.21) para ADHA en niños y adolescentes MPT (Franz et al. 2018). Las probabilidades son aún mayores para aquéllos nacidos EPT/EBPN (OR, 4.05; IC, 2.38 a 6.87) (Franz et al. 2018). Los niños MPT con altos niveles de síntomas ADHD muestran déficits cognitivos de amplio espectro (James et al. 2018, Retzler et al. 2019), que podrían también dar cuenta por la comorbilidad de los desórdenes psiquiátricos en esta población. En particular, también se ha reportado un riesgo muy aumentado para TEA en poblaciones MPT con una prevalencia de 7% (Agrawal et al. 2018) en MPT y hasta 8% en los nacidos EPT (Johnson et al. 2010).

Hay buena evidencia que los síntomas de internalización evaluados en escalas en MPT persisten hasta la adultez (Mathewson 2017, Pyhâlâ et al. 2017, Van Lieshout et al. 2018b). En contraste, los diagnósticos de desórdenes emocionales se reducen en la adultez, con los EPT/MPT mostrando mejor adaptación emocional de lo que alguna vez se anticipó (Burnett et al. 2014, Jaekel et al. 2018ª, Johnson et al. 2019b). Aún no está claro si esto corresponde a una verdadera disminución o se debe a pérdida del poder estadístico resultante de la pérdida del seguimiento. Los síntomas y diagnósticos de ADHD han sido reportados persistentes hasta la adultez (Breeman et al. 2016ª, Burnett et al.2014).

Desarrollo Social

La principal relación social de un infante es con sus padres. Sin embargo, a medida que los niños crecen, ellos construyen mayores relaciones con sus pares. Hacia el final de la infancia, los niños habrán pasado más horas con sus pares que con sus padres. Entonces, las relaciones padres-hijo y con los pares son revisadas aquí.

Relación parental-niño. Pese a recientes esfuerzos en las políticas de la UCIN para promover el compromiso parental y la proximidad física tan pronto como sea posible, los infantes están con frecuencia en incubadoras por semanas o meses, lo que puede impactar la generación del apego materno (Feldman et al. 2014). Más aún, un nacimiento PT inesperado y el siguiente período de incertidumbre acerca de la sobrevida del bebé pone en alto nivel de estrés a los padres (Singer et al. 1999). Sin embargo, los padres de infantes PT con frecuencia aprender a adaptarse al alto nivel de estrés de los primeros años de vida de su hijo (Schappin et al. 2013).

El apego se refiere a la unión emocional que el infante forma con los cuidadores consistentes quienes son sensibles y responden a sus interacciones sociales (Bowlby 1969). Varias revisiones no encontraron diferencias en el apego seguro-inseguro entre niños PT y de término (Field 1987, van IJzendoorn ey al.1992). En particular, la sensibilidad materna ha sido hallada como el factor mayor para predecir apego seguro (Miljkovitch et al. 2013, Wolke et al. 2014). Un meta-análisis reciente de 34 estudios reportó que pese al estrés inicial y la separación, las madres de los niños PT están tan sensibles en las interacciones con sus niños como las madres de los niños nacidos a término (Bilgin y Wolke 2015). Esto sugiere que la sensibilidad materna similar permite a las madres de infantes PT adaptarse y promover interacciones sensibles (van IJzendoorn et al. 1992).

Mientras que los estilos de apego seguro e inseguro son patrones organizados de manejo de la unión, el apego desorganizado es manifestado por conductas contradictorias, mal-dirigidas, o estereotipadas (Carlson 1998) que están asociadas con la psicopatología del niño (Weinfeld et al. 2000). Pipp-Siegel y colegas (1999) han sugerido que las anormalidades neurológicas pueden conducir a comportamientos similares a aquellos que caracterizan estilos de apego desorganizados, usualmente asociados con situaciones de abuso infantil o abandono. En efecto, hay evidencia que los niños MPT/MBPN son más predispuestos que los niños de término a tener apego desorganizado. Notablemente, esto fue predecible por el déficit neurológico del infante (llanto estresado y retraso del desarrollo) y no relacionado con la parentalidad (sensibilidad materna) (Wolke et al. 2014).

Hay alguna evidencia de que los padres de niños MPT son más frecuentemente sobre-protectores que los padres de niños de término, como lo muestra el ser más controlador en las interacciones de juego madre-niño, aún cuando los investigadores excluyen a niós con déficit neurosensorial (DNS) (Forcada-Guex et al. 2006, Wighman et al. 2007). Similar

sobre-protección ha sido reportada entre adolescentes MBPN (Indredavik et al. 2005) y adultos jóvenes MBPN (Pyhàlà et al. 2011). El mayor control parental de conducta y protección para niños MPT, sin embargo, puede ser parcialmente explicado por los déficits cognitivos y las limitaciones funcionales de los niños PT y por las necesidades adicionales de contexto y guía (Jaekel et al. 2012). Sin embargo, la percepción de los padres sobre la vulnerabilidad de su hijo parece depender mayormente de factores psicológicos del padre (ej., ansiedad, estrés parental) más que de la salud del niño (Tallandini et al. 2014). Más aún, la ansiedad parental ha sido asociada con parentalidad más controladora y menor auto-suficiencia del niño (Schneider et al. 2009), que puede finalmente disminuir su resiliencia (Schwarzer y Warner 2013).

Relación con pares. Un aspecto importante del desarrollo social es la capacidad de relacionar y establecer vínculos con pares. Una revisión sistemática de 23 estudios encontró que los niños y adolescentes MPT tienen niveles más elevados de aislamiento social y problemas con pares que los niños nacidos a término (Ritchie et al. 2015). Más aún, los estudios que incluyeron el auto-reporte del niño encontraron que los niños MPT tienen menos amigos cercanos, pasan menos tiempo con sus amigos, y están menos satisfechos con su red de amistad que sus pares nacidos a término (Heuser et al. 2018, Ritchie et al. 2018). Los niños MPT están más de dos veces predispuestos a la exclusión social y al bullying que los niños de término, y esto con frecuencia persiste desde la escuela elemental a la secundaria (Day et al. 2015, Ritchie et al.2018, Wolke et al. 2015a). Estas pobres relaciones entre los niños MPT son importantes, porque están asociadas con problemas emocionales, déficit de atención e hiperactividad, déficits motores (Day et sal. 2015, Heuser et al. 2018, Ritchie et al. 2018), y el despliegue de más características autistas (ej., mayores tasas de problemas sociales y comunicacionales) (Williamson y Jakobson 2014). Pese a tener menos amigos, la observación directa de las interacciones diádicas entre amigos, uno de los cuales nació PT, encontró que las actividades de amistad y conductas eran similares entre niños nacidos PT y a término, así como la calidad de la relación percibida (Sullivan et al. 2012) Parece que la conducta retraída de los niños MPT puede impedir que formen y mantengan relaciones exitosas con pares.

VIDA ADULTA

Personalidad

Comparado con controles nacidos a término, los adultos nacidos MPT son menos extrovertidos (Eryigit- Madzwamuse et al. 20155, Pesonen et al.2008), más agradables y cautelosos (Hertz et al. 2013), Pesonen et al. 2008), más tímidos y aislados (Eryigit-Madzwamuse et al. 2015), Johnson et al.2019b), y menos predispuestos a conductas criminales y de riesgo, tales como fumar y uso de drogas ilícitas y de alcohol (Eryigit-

Madzwamuse et al.2015, Hack et al. 2002, Hille et al. 2008). Los adultos nacidos MPT reportan niveles más altos de formas neuróticas y autísticas que los nacidos a término (Allin et al. 2006, Eryigit- Madzwamuse et al. 2015, Hertz et al. 2013). La personalidad socialmente retraída de los adultos MPT o las experiencias adversas con pares pueden hacer más difícil para ellos formar y mantener relaciones.

Relaciones sociales

La vida social de los adultos nacidos MPT han sido investigadas típicamente en estudios de cohorte y en los estudios del registro de Escandinavia. En un meta-análisis de 21 estudios incluyendo 4.4 millones de participantes, adultos PT/BPN fueron menos proclives a formar relaciones románticas (OR, 0.72; IC 95%, 0.64 a 0.81), a haber tenido relaciones sexuales (OR, 0.43; IC 95%, 0.31 a 0.61), o haberse convertido en padres (OR, 0.77; IC 95%, 0.65 a 0.91) comparados con adultos nacidos a término (Mendonça et al. 2019). No se encontraron diferencias acorde al sexo o a edad, sugiriendo que los individuos nacidos PT/BPN son menos proclives a cumplir estos hitos hacia los 30 años en la vida adulta.

Las dificultades sociales son importantes porque están asociadas con resultados adversos (Umberson et al. 2010), tales como menos riqueza, aislamiento social, y menor salud física y mental (Jaekel et al. 2018a), y ellos siempre preocupan a sus padres (Wolke et al. 2017). La prematuridad está también asociada con una pérdida de fertilidad intergeneracional: No solo los adultos nacidos PT son menos proclives a ser padres, sino que sus padres también mostraron menos `probabilidades de tener otros niños luego del nacimiento de un bebé PT (Alenius et al. 2018). Pese a tener menos amigos (Baumann et al. 2016), Darlow et al. 2013), la calidad del apoyo social de los pares fue percibida como buena en los adultos nacidos PT/BPN al igual que aquellos nacidos a término. Más aún, cuando los adultos PT tienen pareja romántica, la calidad de la relación fue percibida levemente más positiva que en sus pares de término (Mendonça et al. 2019).

Marcadores de riqueza

En un meta-análisis de 23 estudios incluyendo 5.9 millones de participantes, los adultos nacidos PT/BPN se encontraron con calificaciones educativas más bajas (OR, 0.74; IC, 0.69 a 0.80), menores tasas de empleo (OR, 083; IC 95%, 0.74 a 0.92), y mayor recepción de beneficios sociales (OR, 1.25; IC 95% 1.09 a 1.42) que los adultos nacidos a término (Bilgin et al. 2018). Estas asociaciones fueron consistentes a través de diferentes regiones geográficas y edad, y se encontró un efecto dosis-respuesta de la EGpara las calificaciones educativas, en cual adultos nacidos PMT fueron 18% menos probables de tener altas calificaciones que los nacidos a término y los adultos MPT fueron un 40% menos capaces de obtener altas calificaciones. Pese a que estudios previos reportaron que los adultos

prematuros eran menos dispuestos a vivir independientemente (Baumann et al. 2016, Kajantie et al. 2008), la vida independiente no fue significativamente menor en este meta-análisis (Bilgin et al. 2018). Esto puede obedecer a que los países escandinavos tienen un sistema de bienestar y prácticas culturales que apoyan la vida independiente de la gente joven (D´Onofrio et al. 2013), reduciendo el impacto adverso del nacimiento PT en la transición a la vida adulta. Es necesario investigar en otras partes del mundo.

Calidad de vida

La calidad de vida relacionada a la Salud (HRQoL en inglés) se refiere al impacto subjetivo de la salud sobre el estado general de bienestar del individuo psicológico, social y físico (Horsman et al. 2003). HRQoL permite la comparación de los efectos o consecuencias de diferentes exposiciones o tratamientos a través de todas las condiciones médicas (ej., cábcer hasta nacimiento PT). Es muy útil cuando deben tomarse decisiones difíciles acerca de la dirección a tomar cuando hay limitación en la fuente de recursos de salud (Wolke 3026).

Una revisión sistemática en 2008 identificó 15 estudios que habían comparado HRQoL en pre-escolar (6 estudios), edad escolar (1), adolescencia (4), y adultez temprana (4) entre individuos EPT/MPT/MBPN y controles nacidos a término (Zwicker y Harris 2008). HRQoL fue más baja en individuos nacidos PT en los años pre-escolares, según el reporte parental. En la adolescencia, los padres reportaron menor HRQoL en participantes EPT/MPT/MBPN que en los controles de término, pero no hubo diferencias en los auto-reportes. Más aún, en la adultez tenmprana (18-23 años), no se encontraron diferencias significativas entre grupos, pese a que los adultos EPT/MPT/MBPN tendieron a reportar levemente menos funcionamiento físico y general (Zwicker y Harris 2008).

Estos resultados necesitan ser interpretados cautelosamente por un número de razones. Primeramente, se encontraron diferentes observaciones cuando se emplearon reportes parentales versus auto-reportes, con los padres reportando HRQoL inferior a la de los participantes propiamente dichos (Baumann et al 2016, Zwicker y Harris 2008). Consistente con la teoría de la comparación social, los padres pueden tener una visión más amplia de sus hijos comparados con sus pares, mientras que sus hijos pueden compararse a sí mismos con una selección de pares de la misma edad con los cuales interactúan. Además, los estudios que incluyen solo auto-reportes excluyen a quienes con DND, que muy posiblemente no puedan completar estas escalas.Esto introduce sesgo a favor de las no diferencias de grupo. Entonces, los estudios deberían incluir tanto auto-reportes y reportes parentales (Baumann et al. 2016). Tercero, los estudios de toda la población de sobrevivientes PT tienen pérdida al Seguimiento, siendo los más propensos al abandono los DND, los socialmente vulnerables, y aquellos que pertenecen a minorías étnicas (Hille

et al. 2005; Wolke et al. 1995, 2009). Estos grupos son más propensos a tener menor HRQoL (Wolke 2016). Cuarto, las varias mediciones de HRQoL son muy diferentes en sus escalas. Algunas solo agregan ítems en subescalas, mientras que otras determinan utilidades (ej., scores de utilidad de multi-atributos que representan las medias de preferencias de la comunidad desde 0.00 {preferiría estar muerto} a 1.00 {Salud perfecta}). Entonces, las comparaciones de los estudios son solo estrictamente posibles si se utilizan las mismas medidas. Finalmente, el nivel de HRQoL está influenciado por variaciones en la filosofía de tratamiento neonatal en las diferentes regiones (Breeman et al. 2016b), por diferencias culturales, y por la felicidad general de la nación (Verrips et al. 2008).

Tres estudios de cohorte de sobrevivientes EBPN/MPT/MBPN en Alemania (Baumann et al. 2016), los Países Bajos (Van Lunenburg et al. 2013), y Canadá (Saigal et al. 2016) que siguieron niños hasta la adultez usaron idéntica medida de HRQoL. Una comparación de estos tres estudios (Wolke 2016) encontró que, primeramente, la HRQol de individuos EBPN fue, en promedio, inferior a la de los individuos MPT/MBPN, que a su vez reportaron inferior HRQoL que los RN normales en la adolescencia y adultez. Segundo, HRQoL no mejoró con la edad en los individuos EBPN o MPT/MBPN. Una comparación previa de tres cohortes en la adolescencia, al menos en los grupos EBPN de Alemania y Canadá, encontraron similares niveles de HRQoL (Verrips et al. 2008). Tercero, DND es un factor mayor que reduce la HRQoL hasta bien entrada la adultez. Considerando la estabilidad de estas diferencias comparada con individuos PN normal,parece que cualquiera sean los servicios que los individuos MPT/MBPN recibieron desde la adolescencia temprana en adelante no hicieron diferencia en su HRQoL en la adultez (Wolke 2016).

MECANISMOS DEL DESARROLLO

Comprender por qué los sobrevivientes MPT tienen más problemas del ND y por qué algunos déficits persisten a lo largo del tiempo mientras que otros muestran plasticidad es importante, no solamente por el avance teórico sino también para informar el desarrollo las intervenciones. Aquí exploramos los mecanismos potenciales del desarrollo para ayudar a explicar las consecuencias en el curso de la vida de nacer PT.

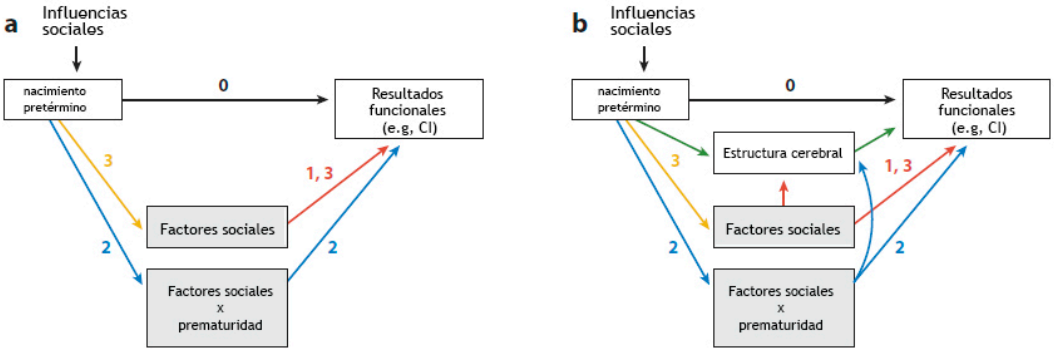

Figura 1

a) Modelos de pruebas alternativas que relacionan el efecto del nacimiento pretérmino en el resultado funcional.
Modelo 0: El nacimiento prematuro tiene un efecto principal sobre el resultado funcional ignorando otras influencias
Modelo 1: Los factores sociales tiene un efecto principal sobre el resultado además de el nacimiento prematuro.
Modelo 2: Los factores sociales moderan los efectos del nacimiento prematuro. en el resultado funcional
Modelo 3: Los factores sociales median los efectos del nacimiento prematuro en el resultado funcional
b)Los modelos 0 a 3 pueden explorar cómo los efectos únicos o conjuntos afectan el desarrollo cerebral como mediador neural
Abreviatura: CI, coeficiente de inteligencia.

Influencias ambientales

La mayoría de los estudios prospectivos han usado un simple modelo de efecto principal para investigar la asociación de diferencias perinatales al nacer y resultados adversos del desarrollo (ver Figura 1ª, Modelo 0). Este enfoque es limitado porque falla en tomar en cuenta otras influencias importantes que pueden operar entre el nacimiento y resultados posteriores. A modo de ilustración, consideramos tres factores: nivel socioeconómico (NSE), calidad del paternaje, e influencias traumáticas de los pares. Estos factores están ubicados en diferentes estratos en el modelo ecológico de Bronfenbrenner (1989) y pueden operar de diferentes maneras en conjunción con el nacimiento MPT y las complicaciones asociadas.

Primeramente, estos factores pueden tener un efecto principal en el desarrollo de niños MPT (ver Figura 1a, Modelo 1). Por ejemplo, NSE puede ser un factor adicional para predecir el resultado de ND. También significa que los efectos del bajo NSE son los mismos para niños nacidos MPT y a término, y son aditivos. Si el bajo NSE tiene efectos de detrimento del resultado que se está considerando, entonces el bajo NSE debería ser considerado un factor de riesgo. Inversamente, si el alto NSE tiene efectos benéficos, podría ser considerado un factor protector (Luthar et al. 2000).

Alternativamente, NSE puede ser un moderador de la asociación entre nacimiento MPT y el resultado de interés (Figura 1a, Modelo 2). Esto significa, por ejemplo, que el bajo NSE tiene un nivel significativamente más amplio en niños MPT (ej., son más vulnerables a los efectos del NSE que los niños nacidos a término), consistentes con un modelo de diátesis-

estrés (Ellis et al. 2011). Más aún, si el NSE alto provee protección contra los efectos de nacer MPT y los niños alcanzan el nivel de funcionamiento de aquellos nacidos a término, entonces esto podría ser considerado resiliencia: la capacidad de recuperarse después de la exposición al riesgo (ej., nacer MPT) (Taylor et al. 2019).

Consideremos los modelos de efecto principal y de moderación dentro del contexto de hallazgos en los estudios de cohorte. Haber nacido en una familia de alto NSE versus una de bajo NSE tiene un efecto similar sobre el niño (Wolke y Meyer 1999) y el CI adulto (Eryigit Madzwamuse et al. 2015) en poblaciones MPT y de término. El efecto del NSE sobre el CI es comparable al efecto de nacer MPT versus término en el efecto de tamaño sobre CI (Eryigit Madzwamuse et al. 2015). Expresado de manera diferente, tener una madre cuyo más alto grado educativo fue en la escuela elemental o secundaria tiene el mismo efecto adverso sobre el CI como haber sufrido daño cerebral severo o enfermedad pulmonar crónica (Benavente-Fernández et al. 2019). Estos hallazgos son consistentes con un modelo de efecto principal sin indicación de un efecto de interacción (Figura 1a, Modelo 1).Entonces, no sorprende que el NSE es reportado como una de las principales influencias sobre los resultados cognitivos en niños MPT (Breeman et al. 2017, Linsell et al. 2015). Es, sin embargo, desconcertante que, para 2018, solo 15 de 70 estudios incluidos en un meta-análisis de nacimiento MPT y CI consideraron algún marcador de NSE (Twilhaar et al. 2018b).

El NSE refleja una multitud de factores, incluyendo factores sociales, familiares,y de paternaje (Wolke 2019), que necesitan ser desagregados. Si queremos abrir la caja negra de cómo estos factores influencian el desarrollo, necesitamos medirlos con el mismo detalle con que se ha hecho en cuanto a las complicaciones perinatales (Wolke 2019), lo cual requiere mayor colaboración entre disciplinas en el diseño de los estudios de seguimiento. Consideremos el paternaje, un factor fuertemente asociado con NSE (Sherman y Harris 2012) y el logro académico. Wolke y colegas (2013) encontraron que los efectos de la sensibilidad de la parentalidad evaluada a los 6 años de edad fueron moderados por el estado al nacer (ej., MPT versus término): los niños MPT fueron fuerte y adversamente afectados por padres poco sensibles, mientras que padres muy sensibles fue observado como conductor hacia logro académico casi a la par con los niños nacidos a término (Ver Figura 2). Entonces, los efectos de nacer MPT sobre los resultados académicos son moderados por la parentalidad sensible. Esto sigue un modelo de estrés-diátesis e indica potencialidad de resiliencia en los resultados académicos para aquéllos nacidos MPT (ver Figura 1, Modelo 2).

Otra interacción (Ver Figura 1ª, Modelo 2) argumenta que las variaciones en las características del niño pueden alterar la susceptibilidad a las influencias ambientales (ej., la

sensibilidad a las influencias negativas y positivas). Esta susceptibilidad diferencial propone que ciertas influencias ambientales tales como la parental pueden llevar a peores resultados bajo condiciones de pobreza parental y mejores resultados bajo condiciones de buena parentalidad en individuos susceptibles comparados con no susceptibles (Ellis y Del Giudice 2019, Ellis et al. 2011). Hay poca razón para sugerir que nacer MPT pueda estar relacionado con sensibilidad a la ventaja (ej., sensibilidad aumentada a experiencias positivas) (Belsky y Pluess 2013). Desde una perspectiva evolutiva,la mayoría de estos infantes no hubieran sobrevivido sin el cuidado neonatal moderno. En efecto, cuando el modelo estrés diátesis versus la teoría de susceptibilidad diferencial (TSD) fue testeado en niños MBPN, hubo poca evidencia para TSD, pero hubo apoyo para el modelo de estrés-diátesis (Jaekel et al. 2015). Entonces, hay evidencia creciente que nacer MPT hace que los niños sean más vulnerables a los factores de riesgo ambientales (Poehlmann et al. 2015, Van lieshout et al. 2018a, Wolke 2018).

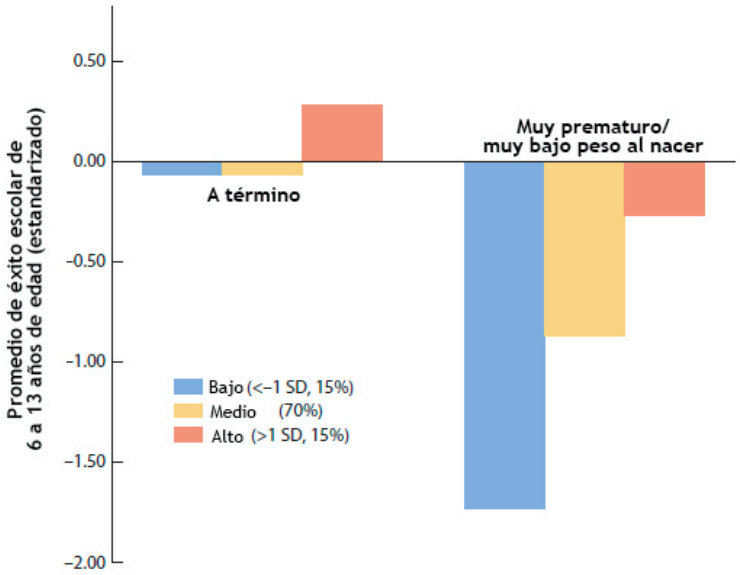

Figura 2

Efecto de la crianza sensible (baja, media o alta) a los 6 años sobre el éxito escolar a los 13 años. Variación por muy prematuro (VP) / muy bajo peso al nacer (VLBW) versus a término. Abreviatura: SD, Desviación Estándar. Adaptado con permiso de Wolke et al. (2013)

Un tercer modelo considera a los factores ambientales como mediadores entre el nacimiento MPT y resultados posteriores (Ver Figura 1, Modelo3). Los niños MPT, como se revisa aquí, están en riesgo aumentado para problemas emocionales en la adolescencia. De manera similar, está bien documentada que los niños que están expuestos al trauma, tal como ser hostigados por sus pares, están en mayor riesgo de problemas emocionales (Wolke y Lereyra 2015, Zwierzynska et al. 2013). Una investigación reciente notó que una parte mayor del efecto de nacer EPT/MPT sobre los problemas emocionales fue explicado por los niños EPT/MPT siendo más de dos veces susceptibles de ser hostigados en la

escuela que sus paresnacidos a término, lo cual a su vez explicó el exceso de problemas emocionales en la adolescencia. Entonces, el hostigamiento medió completamente los efectos de nacer EPT/MPT sobre los problemas emocionales (Wolke et al. 2015a).

Influencias Genéticas

Nacer PT es un evento ambiental que inicia una cascada de mayores intervenciones ambientales (ej., cuidado en UCIN). En todos los niños, los genes están envueltos en el desarrollo cognitivo y conductual. Entonces, diseños genéticamente sensibles que van desde estudios en gemelares hasta el uso de estudios de asociación en todo el genoma basados en escores de riesgo poligénicos pueden ser usados para determinar lacontribución genética a los resultados del desarrollo. Los efectos de los genes son dependientes de ser expresados o si factores ambientales (ej., complicaciones neonatales o injuria cerebral) compartidos o no, reducen su expresión. En efecto, en niños MPT, cualquiera de los efectos genéticos aditivos fueron opacados por factores ambientaqles compartidos en pares gemelares (Koeppen- Schomerus et al. 2000). Más del 85% de la variación en los escores cognitivos a los 2 años de edad fue explicado por el ambiente; entonces, los efectos genéticos pueden estar muy reducidos comparados con nacer a término, al menos en el desarrollo temprano.

Los diseños en gemelares pueden ayudar aún más para probar nexos causales utilizando gemelares discordantes para un factor de riesgo. Groen- Blokhuis y colegas (2011) probaron tres modelos usando pares gemelares monocigóticos y dicigóticos e individuos no relacionados discordantes en cuanto al PN. Sus hallazgos mostraron claramente que el MBPN significativamente predijo más problemas de atención, aún entre niños que eran genéticamente idénticos. Desafortunadamente, mientras los bebés pueden ser discordantes para PN, la gestación raramente varía, así que los efectos de la gestación no pueden ser testeados dentro de esos diseños. Futura investigación incluyendo escores poligénicos puede servir para evaluar cómo el nacer PT como evento ambiental puede reducir los efectos genéticos.

El Cerebro

Nacer MPT le confiere al cerebro un insulto para el desarrollo normal del cerebro (ej., desarrollo interrumpido), y hy con frecuencia el riesgo adicional de una injuria adquirida (ej., hemorragia) (Volpe 2009).En los límites de la viabilidad (22-24 sem EG), el cerebro consiste enteramente de sustancia blanca. En las siguientes 16 semanas, la sustancia gris se expande rápidamente, con un dramático aumento del área de la superficie del cerebro por

medio del plegado cortical (Hûppi et al. 1996, Kapellou et al. 2006). Cuando los bebés nacen prematuramente, este patrón de crecimiento es interrumpido debido a alteraciones en los patrones de crecimiento, injuria directa a la sustancia blanca (Constable et al. 2008, Inder et al. 2005, Miller et al. 2005), o razones indeterminadas. Cuanto más temprano el nacimiento, mayor la disrupción; además, los varones son más afectados que las mujeres (Kapellou et al. 2006, Vasileiadis et al. 2009). Esto lleva a la construcción de un cerebro diferente al de los niños de término, con distribución alterada de la sustancia gris y blanca en múltiples regiones indicando reorganización de las estructuras cortical y subcortical relacionadas al volumen del cerebro, distribución del volumen, microestructura y conectividad (Ball et al. 2013). Estas alteraciones son detectables aún en la edad adulta en muchas áreas (Bâuml et al. 2015, Meng et al. 2016).

Avances recientes en neuroimágenes han tomado dos direcciones. Primeramente, los investigadores han desarrollado incubadores RNM-compatibles con dispositivos integrados para la cabeza que permiten el escaneo secuencial del cerebro en desarrollo mientras los infantes están en cuidado intensivo neonatal (Hintz y O´Shea 2008). Segundo, la disponibilidad de rutina de RNM permite el estudio de diferencias anatómicas, y, más recientemente, estudios de RNM funcional están mejorando nuestro entendimiento de las diferencias en la activación y conectividad del área cerebral en niños y adultos PT (Nosarti 2013).

Una vía de investigación crucial será determinar cómo los cambios en eñ desarrollo del cerebro debido al nacimiento MPT están asociados con los resultados funcionales tales como el desarrollo cognitivo, emocional, o social (Montagna y Nosarti 2016) (ver Figura 1b). Tales resultados pueden estar relacionados con alteraciones anatómicas (Nosarti et al. 2008), alteraciones de toda la red (Kelly et al. 2015, Meng et al. 2016), o alteraciones específicas tales como el cerebro anterior colinérgico (Grothe et al. 2017) y pueden ser potencialmente tratables. Los primeros estudios fueron prometedores y mostraron asociaciones sgnificativas entre el desarrollo temprano del cerebro estudiado durante el período neonatal y el retraso del desarrollo 2 años más tarde (Kapelloy et al. 2006). Sin embargo, más de una década después, las comparaciones entre la costosa RNM versus la utilidad del ultrasonido cranial son sorprendentes. La RNM predijo losresultados motores adversos levemente mejor que el ultrasonido, pero ambos métodos fueron nada sensibles y no predijeron los problemas cognitivos a la edad de 18-24 meses (Edwards et al. 2018). Un leve efecto benéfico de la RNM fue encontrado en que a los padres les gustaba ver el cerebro completo, lo cual reducía sus ansiedades más de lo que lo hacía el ultrasonido. Sin embargo, una sola RNM en el Reino Unido cuesta aproximadamente 300 libras más que un ultrasonido de rutina. Los factores sociales han mostrado que alteran el desarrollo del cerebro y deben ser considerados en los estudios (Kim et al. 2018). Más aún la medición

del tamaño de la cabeza en los primeros años de vida está altamente correlacionado con el crecimiento del cerebro y es predictivo del desarrollo cognitivo posterior (Jaekel et al. 2018b). Entonces, es importante considerar qué medidas son requeridas para que la ciencia básica avance en el conocimiento de los mecanismos del desarrollo y cuáles son suficientes para el seguimiento de rutina (Doyle et al. 2014).

En resumen, para comprender de qué manera el nacer MPT lleva a resultados adversos, es necesario contar con medición detallada de influencias ambientales. Más aún, para diferentes resultados y factores ambientales, pueden aplicar diferentes mecanismos y modelos. Comprender cómo el nacimiento MPT altera el desarrollo del cerebro y cómo las experiencias ambientales tales como el trauma o el paternaje llegan al cerebro puede ayudar a comprender los mecanismos neurales subyacentes a diversos resultados fenotípicos.

CONCLUSIONES Y DIRECCIONES FUTURAS

Primero, nacer MPT tiene una amplia gama de efectos adversos sobre el desarrollo motor y psicológico y el bienestar a lo largo de la vida. La Figura 3 resume los efectos del nacimiento MPT/MBPN sobre el funcionamiento en varias áreas revisadas aquí. Muestra el tamaño aproximado de los efectos reportados en estudios en la niñez y la adultez. Los tamaños de efecto son definidos como pequeños (OR1.48 o invertido 0.67; d de Cohen entre medias,0.2), moderados (OR, 3.45 o 0.29; d de Cohen, 0.5), o grandes (OR, 9 0 0.11; d de Cohen, 0.8) (Chen et al. 2010).

Los mayores efectos adversos de nacer MPT comparados con nacer de término se encuentran para PC, DDC, CI y TEA. Mientras que los tamaños de efecto son grandes, PC se encuentra en menos del 5% de los nacidos MPT/MBPN y TEA en 7-8%, pero DDC y, en particular, bajo CI (<-2DS) son encontradas en hasta un 25% de los niños MPT. Entonces, el DDC y CI son las mayores

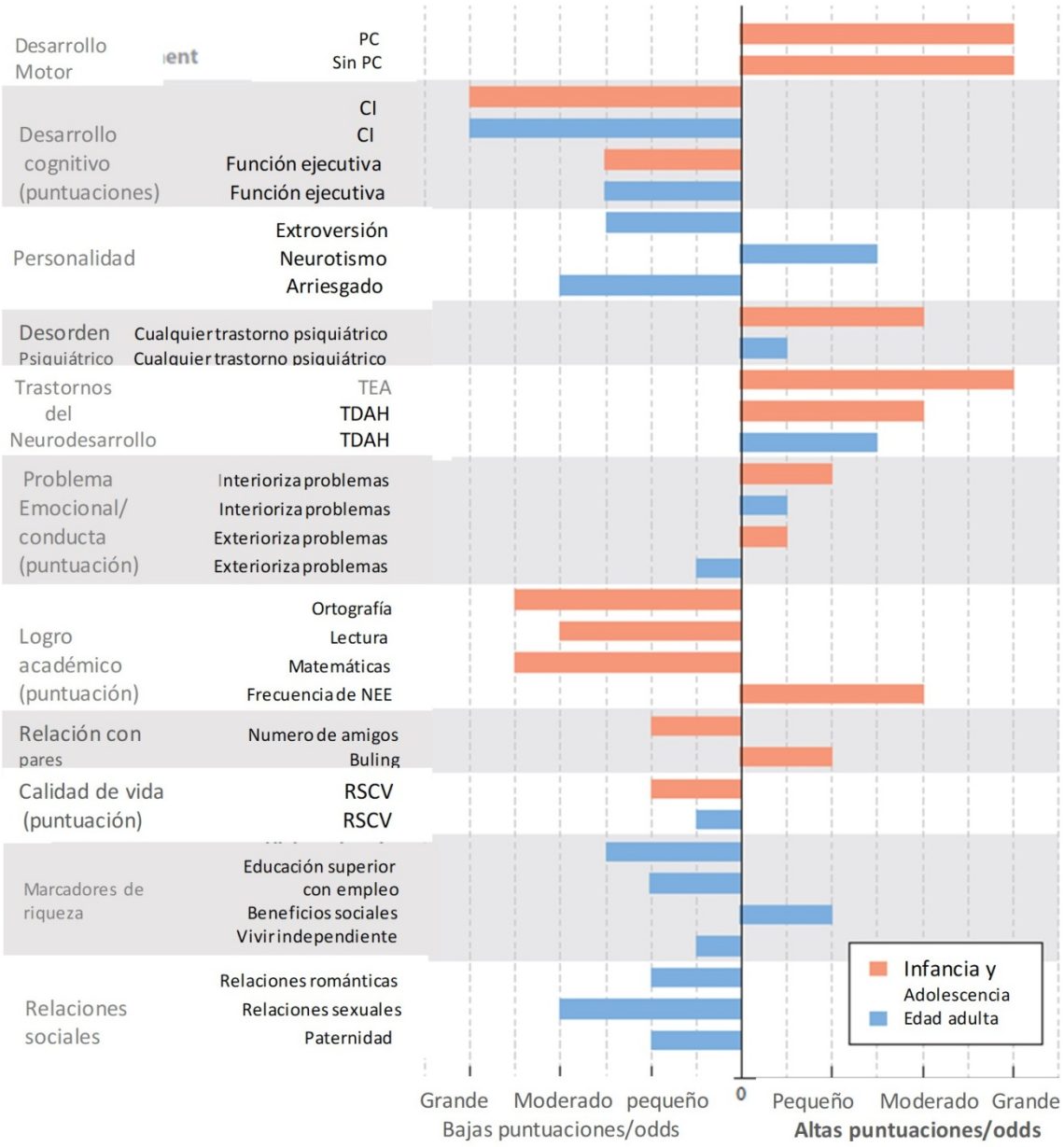

Figura 3

Efecto aproximado del tamaño del impacto del nacer muy prematuro sobre resultados a largo plazo (comparado con nacidos a término; cero es la línea vertical) Resultados de valoraciones en la infancia y adolescencia se muestran en rojo y resultados en edad adulta en azul. Abreviaturas: TEA, trastorno del espectro autista; TDAH, trastorno déficit atención e hiperactividad; PC, parálisis cerebral; RSCV, relación salud calidad de vida; CI, coeficiente intelectual, NEE, necesidad de educación especial.

secuelas de nacer MPT. Nacer MPT tiene efectos moderados sobre el logro académico- en particular, scores más bajos en matemáticas y deletreo- mayores necesidades educativas especiales en la escuela, y riesgo aumentado de algún desorden psiquiátrico en la niñez, especialmente ADHD. Más aún, tamaños de efecto moderados se encontraron para las funciones ejecutivas y la personalidad, tal como ser menos extrovertido, más neurótico, y menos propenso a involucrarse en conductas de riesgo. Pequeños tamaños de efecto se

encontraron para los problemas de internalización y externalización, relaciones con pares, hostigamiento, HRQoL en la niñez. Mientras que los tamaños de efecto son pequeños para esto último, estos usualmente afectan una gran proporción de individuos MPT. Las relaciones con los padres son poco afectadas en cuanto a la sensibilidad parental, y los efectos de sobreprotección son pequeños o pueden ser explicados porque los MPT/MBPN tienen mayores necesidades de encuadre debido a CI menor.

Segundo, algunos efectos adversos se reducen a lo largo del desarrollo, y otros persisten desde la infancia hasta la adultez. La inteligencia y las funciones ejecutivas ninguna o muy poca mejoría con la edad. Las dificultades sociales observadas en la infancia en términos de síntomas de TEA y relaciones con pares continúan siendo observadas en la adultez, manifestándose por una personalidad retraída y menor compromiso en conductas normales de tomar riesgo. En general, elriesgo de desórdenes psiquiátricos parece disminuir en la adultez (ver Figura 3). Las dificultades motoras, cognitivas, emocionales y sociales parecen contribuir a las dificultsades que algunos individuos MPT tienen en la transición a la adultez, incluyendo menos participación en la educación superior, menos posibilidad de estar empleado, y mayor posibilidad de recibir beneficios sociales. Es muy notable su menor predisposición a generar relaciones románticas y sexuales y de tener hijos. Entonces, más adultos MPT que de término pueden tener menor soporte social y financiero una vez que sus padres fallecen, lo cual tiene importantes implicancias para un futuro apoyo del estado.

Tercero, los individuos MPT que tienen un déficit significativo en algún área (Ej., CI) con frecuencia tienen problemas en otros dominios (ej., logro académico, relaciones sociales). Entonces, hay comorbilidad frecuente, y, para una minoría de niños y adultos MPT, los problemas son complejos, requiriendo apoyo de servicios médicos, psicológicos, y educación, Sin embargo, aún los niños nacidos a término raramente no tienen ningún problema (Wolke y Meyer 1999), y entonces es importante recordar que, pese a las frecuentes probabilidades de resultados adversos, la mayoría de los niños y adultos MPT desarrollan adaptaciones sin mayores problemas.

Cuarto, pese a la significativa disminución en mortalidad y PC para bebés nacidos MPT, aún no hay evidencia de que esto haya sido equiparado por mejores resultados del desarrollo en las áreas aquí revisadas.

Una multitud de desafíos enfrentan los futuros investigadores, la práctica y la intervención. Mucho de la investigación observacional sobre los efectos de nacer MPT puede ser demasiado simplista, fallando en llegar más allá en factores médicos asociados con nacer MPT. La ciencia del desarrollo tiene mucho para contribuir para ayudar a develar qué factores a lo largo de la vida pueden incrementar el riesgo, proveer protección o

resiliencia, o los mediadores asociados con los resultados en la vida. Esto es poco probable que sea logrado por una sola profesión o un solo estudio longitudinal, que con frecuencia tiene un poder estadístico limitado. Requiere colaboración interdisciplinaria y reunir estudios de cohorte y registro en todo el mundo. Tales colaboraciones en curso incluyen la iniciativa APIC (http://www.apic-preterm.org) y un extenso proyecto con fondos de la Unión Europea, RECAP PT(http://www.recap-preterm.eu). Los diseños inclusivos para neuroimágenes y genética deberían ser tenidos en cuenta en las próximas cohortes.

El uso de medidas centrales entre estudios de cohorte (Doyle et al. 2014) podría permitir la directa comparación sobre si los cambios en el cuidado neonatal entre cohortes consecutivas han conducido a cambios en los resultados del desarrollo. Esto debe incluir mediciones del ambiente social, tal como relaciones parentales y con pares, porque los cambios pueden ser debidos tanto a los cambios sociales como a los avances en el cuidado neonatal.

La prevención primaria del nacimiento PT en sí mismo es necesaria, pero tales esfuerzos han tenido poco éxito hasta la fecha. Entonces, un desafío clave es minimizar los efectos adversos del nacimiento PT sobre el cerebro durante el cuidado neonatal y promover el desarrollo después del alta. Dado que la escolaridad es uno de los mayores factores que afectan los resultados a lo largo de la vida, nuevas intervenciones excediendo los 2 años de edad deberían testearse, incluyendo nuevos recursos para mejorar el apoyo educacional para niños nacidos PT (http://www.pretermbirth.info; Johnson et al. 2015, 2019a).

Finalmente, los reportes sobre resultados del desarrollo en niños MPT hasta la adultez provienen exclusivamente de países de altos ingresos. Sin embargo, la mayoría de los niños PT nacen en ámbitos transicionales o de bajos ingresos (Chawanpaiboon et al. 2019), y no tenemos idea cómo se desempeñan en la vida. Esta escasez de investigación en países de bajos ingresos debe ser resuelta.

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ANNUAL REVIEWS

Annual Review of Developmental Psychology

The Life Course Consequences of Very Preterm Birth

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Abstract

Around 15 million children are born preterm (<37 weeks of gestation) every year. Of these, 15% or 2.25 million are born very preterm (VP; <32 weeks of gestation). Here, the developmental outcomes of VP babies in diverse domains from motor, cognitive, and social function to mental health and well-being throughout childhood and adolescence are reviewed. Their life course adaptation in terms of romantic relationships, employment, and quality of life into adulthood is also considered. Some adverse effects reduce as individuals age, and others remain remarkably stable from childhood into adulthood. We argue that to advance understanding of developmental mechanisms and direct resources for intervention more effectively, social factors need to be assessed more comprehensively, and genetically sensitive designs should be considered with neuroimaging integrated to test alternative developmental models. As current evidence is based almost exclusively on studies from high-income countries, research from low- and middle-income countries is urgently needed.

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INTRODUCTION

To achieve the United Nations' Sustainable Development Goal 3 to ensure healthy lives and promote well-being for all at all ages, it is crucial to address the global burden of preterm birth (Chawanpaiboon et al. 2019). In 2014, 10.6% of live births or 14.84 million babies were born preterm—before 37 weeks of gestation—worldwide. Preterm birth is the leading cause of child mortality under age five (Lee et al. 2019). In the past three decades, the largest improvement in survival has been for babies born very preterm (VP), or before 32 weeks of gestation. Although VP births account for only 15% of all preterm births, they are associated with the highest costs both for initial hospitalization (Petrou et al. 2019) and for health and educational support in the long term (Petrou et al. 2013). As up to 95% of VP babies now survive in high-income countries, focus has shifted from solely reducing mortality to understanding and improving long-term outcomes and quality of life. Here we provide an overview of the life course consequences of VP birth and the developmental mechanisms leading to adverse motor, psychological, and social outcomes.

Very preterm (VP): <32 weeks of gestation

Extremely preterm (EP): variable; ranging from gestation <28 weeks or <26 weeks

Moderate preterm (MP): 32–33 weeks of gestation

Late preterm (LP): 34–36 weeks of gestation

Low birthweight (LBW): birthweight <2,500 g

TERMINOLOGY AND EPIDEMIOLOGY

The World Health Organization defines preterm birth as all births before 37 completed weeks of gestation. The limit of viability is currently around 22 weeks, but survival at this gestational age is still rare. About 3.3–8.9% of all preterm babies are born extremely preterm (EP; <28 weeks of gestation) and about 9.8–12.8% at 28–31 weeks of gestation, with all infants born before 32 weeks classified as VP (Chawanpaiboon et al. 2019). Up to 20% of preterm babies are born moderate preterm (MP; 32–33 weeks of gestation), and 60–70% are late preterm (LP; 34–36 weeks of gestation) (Goldenberg et al. 2008).

The terms preterm and low birthweight (LBW; <2,500 g) are often used interchangeably in studies of the long-term outcomes of these infants. Approximately 7–10% of all babies are born

with LBW (Wolke 1991) and around 0.9–1.5% with very low birthweight (VLBW; <1,500 g). Extremely low birthweight (ELBW) infants are usually labeled as such if born <1,000 g (Hille et al. 2001) or sometimes <750 or <800 g (Whitfield et al. 1997).

Appropriate for gestational age and small for gestational age (SGA) infants are classified based on the relationship between gestation and birthweight using standard population or customized birthweight growth charts (Zeitlin et al. 2017). SGA children are born in the <10th or <3rd percentile or ≤2 standard deviations (SDs) below the mean for their gestational age (Zeitlin et al. 2017). Within the preterm population, 16–40% of babies are born SGA (<10th percentile).

In absolute numbers, most preterm babies are born in Asia (52.9% of global preterm births) and sub-Saharan Africa (28.2%). In contrast, Europe (4.7%) and the United States (3.3%) account for just a small fraction of the global burden (Chawanpaiboon et al. 2019).

Preterm labor may be spontaneous (due to spontaneous preterm labor or prelabor rupture of membranes) or clinician initiated (cesarean section or induction of labor) due to acute maternal or fetal indications such as infection, poor fetal growth, or high blood pressure (Goldenberg et al. 2008). Factors associated with preterm delivery include sociodemographic (e.g., race, poverty), nutritional (e.g., obesity), maternal genetic or microbiome, environmental (e.g., smoking), and lifestyle factors (e.g., fertility treatment, increasing maternal age), but still, in 50% of cases, the specific cause is unknown (Muglia & Katz 2010).

The number of VP births has not significantly decreased, and has even increased in many countries, while mortality rates have decreased, at least in high- and middle-income countries (Yeo et al. 2015). As such, the absolute number of survivors born VP is increasing, presenting a growing public health concern.

Very low birthweight (VLBW): birthweight <1,500 g

Extremely low birthweight (ELBW): birthweight <1,000 g

Appropriate for gestational age: the fetus/newborn has a weight corresponding to their gestational age (e.g., above the 10th percentile on standard weight charts)

Small for gestational age (SGA): the fetus/infant has a weight below that expected for their gestational age (e.g., below the 10th percentile on standard weight charts)

Term: ≥37 weeks of gestation

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DEVELOPMENT AFTER VERY PRETERM BIRTH

This review focuses on motor, psychological, and social development from infancy to adulthood following VP birth. Thus, the major organ considered is the brain. Whenever possible, the focus is on high-quality studies that (*a*) are prospective, (*b*) are sufficiently powered (e.g., geographical, epidemiological, or multicenter studies), (*c*) have few infants lost to follow-up or good documentation of dropouts, (*d*) include full-term control groups for cohort-specific comparisons, (*e*) are long term (i.e., into school age or adulthood), (*f*) include differential reports of subpopulations (e.g., social class, EP versus VP), and (*g*) are conducted by independent researchers not involved in the care of the infants under investigation and blind to study group allocation (Johnson et al. 2008, Vohr 2007). Particular emphasis is placed on studies using contemporaneous control groups, as secular trends in cognitive and behavioral scores have been repeatedly reported (Collishaw et al. 2010, Wolke et al. 1994). Finally, we focus predominantly on reports of mean differences or differences in proportions between VP individuals and term-born controls and, where possible, refer to meta-analyses to estimate effect sizes.

Motor Development and Physical Activity

Motor difficulties following VP birth range from mild delays, such as in sitting or walking, to severe neuromotor impairment, such as cerebral palsy (CP), which remains the primary motor disorder following VP birth (Reid et al. 2016). Other deficits in coordination, balance, gross and fine motor control, and visuomotor integration are usually referred to as motor impairments without CP and may be considered developmental coordination disorder (DCD) according to DSM-V criteria (Am. Psychiatr. Assoc. 2013).

Findings from one of the most comprehensive CP registries in Victoria, Australia, indicate that CP rates have decreased since the mid-1990s in those born VP (28–31 weeks of gestation), from 41.5/1,000 neonatal survivors in 1983–1991 to 32.4/1,000 in 2001–2009 (Reid et al. 2016). In contrast, among EP births, CP rates increased until 2000 with a decrease thereafter (92.1, 102.5, and 70.6/1,000 neonatal survivors in 1983–1991, 1992–2000, and 2001–2009, respectively). Although VP/EP births are just 1–2% of all births, they make a large contribution to the rates of children with CP. The improvements for VP/EP births may be due to considerable change in the management of preterm infants over recent decades, but there is little evidence for the efficacy of any single intervention in reducing CP rates (Spittle & Orton 2014).

Regarding motor impairments without CP, children born VP/VLBW had scores −0.57 to −0.88 SD lower than term-born peers on standardized tests of motor performance from infancy to 15 years of age (de Kieviet et al. 2009). These differences were of a moderate to large effect size and were found in a wide range of skills, including balance, ball skills, manual dexterity, and fine and gross motor development. While motor skills improved from infancy to childhood, no significant improvement was found from childhood into adolescence. A more recent review excluding children with CP (Edwards et al. 2011) found a higher risk for DCD in VP/VLBW children, with an odds ratio (OR) of 6.29 (95% CI, 4.37 to 9.05) and an OR of 8.66 (95% CI, 3.40 to 22.07) for scoring in the <5th or 5th–15th percentile on the Movement Assessment Battery for Children (MABC), respectively. Even larger differences of 1.1–1.6 SD have been found among children born <26 weeks of gestation (Marlow et al. 2007).

A major question remains as to whether DCD has decreased with improved neonatal care. The Victorian Infant Collaborative Study (VICS) in Melbourne, Australia, recruited three consecutive cohorts of EP/ELBW babies born in 1991–1992, 1997, and 2005 from four tertiary neonatal units in the region (Spittle et al. 2018). While survival rates increased from 54% in 1991–1992 to 68% in 1997 and stabilized in 2005 at 64%, CP rates remained constant at 11%, 11%, and 12%, respectively. In contrast, non-CP motor impairment increased over time despite advances in neonatal care, with a prevalence of 13%, 15%, and 26% among EP/ELBW children, respectively (Spittle et al. 2018). Although there were consistent independent perinatal predictors of motor impairment across the three epochs, including poorer fetal growth, brain injury, surgery, and male sex, these did not explain the increased rate of motor impairment in the 2005 cohort. The authors speculated that other factors such as reduced physical activity (PA) may have adversely impacted motor outcomes in the EP/ELBW children.

Indeed, one might expect that VP/EP children participate less in sports and PA given their higher rate of motor impairments. However, according to World Health Organization recommendations, individuals born preterm are encouraged to participate in PA to improve lung function and cardiovascular fitness (Spiegler et al. 2019a). Indeed, a recent longitudinal study from birth to 14 years shows that VP children and adolescents did not engage less in PA or sports than term-born controls. Rather, PA was higher in male adolescents, those of white ethnicity, children of more highly educated parents, children taken to live sporting events at 5–7 years, or those who took part in organized PA at 5–7 years (Spiegler et al. 2019b). Thus, consistent with other studies, this study found that VP children are not less likely to be physically active, but they reduce participation in sports by adolescence just as term-born children do.

Cognitive Development

A recent meta-analysis of 71 cohort studies identified that VP/VLBW individuals had IQ scores 0.86 SD (95% CI, −0.94 to −0.78) lower than controls at age 5–20 years, equating to a 12.9-point deficit (Twilhaar et al. 2018a). Similar effect sizes have been reported in other meta-analyses, with

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deficits of 10.9 (95% CI, 9.2 to 12.5) (Bhutta et al. 2002) and 11.9 (95% CI, 10.47 to 13.42) IQ points in all preterm children compared with controls. Among VP cohorts, a mean deficit of 13.9 (95% CI, 11.5 to 16.2) IQ points has been reported (Kerr-Wilson et al. 2012). Together, these studies indicate that IQ in VP individuals is, on average, 0.7 to 0.9 SD lower than term-born peers.

In two meta-analyses, the mean difference in IQ did not differ significantly over time, suggesting that cognitive outcomes have not improved significantly despite advances in neonatal care (Kerr-Wilson et al. 2012, Twilhaar et al. 2018b). The only direct comparison of IQ in consecutive cohorts from the same geographical region is from the VICS group for EP/ELBW babies born in 1991–1992, 1997, and 2005. Similar to the findings for CP outlined above, researchers found that the mean difference in IQ between EP children and controls was not significantly different for births in 2005 compared with births in the 1990s at age 8 years. Similarly, there was no significant difference in the proportion with cognitive impairment (IQ <-2 SD of controls) (Cheong et al. 2017). Thus, despite improved neonatal care and reduced prevalence of severe neurosensory disabilities (Doyle et al. 2010), there is no evidence yet of improved cognitive outcome over time.

Notably, all meta-analyses found a significant association between IQ and gestational age (Allotey et al. 2018, Bhutta et al. 2002, Kerr-Wilson et al. 2012, Twilhaar et al. 2018b), indicating a dose-response effect of gestation at birth on cognitive outcome. This association has also been shown in large, population-based studies (Poulsen et al. 2013, Wolke et al. 2015b); however, it is not yet clear whether this is a linear association among births at all preterm gestations (Bhutta et al. 2002, Kerr-Wilson et al. 2012) or an exponential relationship with increasing deficit observed in those born before 32 weeks of gestation (Jaekel et al. 2013, Wolke et al. 2015b). It is clear, however, that those born EP (<26 weeks of gestation) are at highest risk for impairments, with deficits of 1.3 to 1.6 SD in IQ in childhood (Johnson et al. 2009, Marlow et al. 2005).

A key question is whether cognitive deficits observed in early childhood persist across the life span or whether VP individuals catch up to their peers as they age. Meta-analyses have typically found that mean differences in IQ do not narrow with age (Allotey et al. 2018, Twilhaar et al. 2018b). However, these are based on successive cross-sectional comparisons rather than an analysis of developmental trajectories across time.

Studies that have tracked the development of VP/VLBW/EP individuals from birth through adulthood have failed to find evidence of developmental catch-up. The EPICure study assessed IQ in EP children at 2.5, 6, 11, and 19 years of age alongside a term-born control group assessed from 6 years of age. Deficits in IQ remained stable over time, although there was a small but statistically not significant narrowing of the gap by 0.5 IQ points per year, and an 18-point deficit remained at 19 years of age (Linsell et al. 2018). Similar results have been reported for VLBW/VP survivors, who had significantly lower IQ than term-born controls when assessed at 2, 4, 6, 8, and 26 years of age (Breeman et al. 2015).

Compared with IQ, there are fewer reports of attention and executive functions to date. Meta-analyses have found small to moderate deficits in verbal fluency (−0.57 SD), working memory (−0.36 SD), and cognitive flexibility (−0.49 SD) in VP children compared with controls (Aarnoudse-Moens et al. 2009). Standardized mean differences of −0.42 to −0.71 for working memory and −0.35 to −0.62 for processing speed have also been reported in preterm children compared with controls (Allotey et al. 2018). Similar effect sizes have been reported in VP children who had scores 0.51 SD (95% CI, −0.58 to −0.44) lower than controls on 87 measures of executive functions and 0.49 SD (95% CI, −0.60 to −0.39) lower on tests of processing speed (Brydges et al. 2018). Significant deficits have also been observed in VP cohorts in adulthood (Eryigit Madzwamuse et al. 2015); however, these are usually smaller in size than deficits in IQ. Similar to the findings for IQ, there is no evidence of improved executive functions with improved neonatal care since the 1990s (Burnett et al. 2018).

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Schooling and Academic Attainment

In meta-analyses of performance on standardized achievement tests, preterm-born children have scores 0.71–0.78 SD lower than term-born controls in mathematics, 0.44–0.67 SD lower in reading, and 0.52–0.56 SD lower in spelling (Allotey et al. 2018, Twilhaar et al. 2018b). In children born VP, mathematics scores are 0.60 SD (95% CI, −0.74 to −0.46) lower than controls, reading scores 0.48 SD (95% CI, −0.60 to −0.34) lower, and spelling scores 0.76 SD (95% CI, −1.13 to −0.40) lower (Aarnoudse-Moens et al. 2009).

Population-based studies have also found a significant dose-response effect of gestation at birth on educational outcomes. Routine data linkage for 407,503 children in Scotland revealed that the risk of special educational needs increased as gestational age at birth decreased for each week of gestation below 40 weeks, with an adjusted OR of 1.16 (95% CI, 1.12 to 1.20) for children born at 37–39 weeks, OR 1.53 (95% CI, 1.43 to 1.63) for children born at 33–36 weeks, OR 2.66 (95% CI, 2.38 to 2.97) for those born at 28–32 weeks, and OR 6.92 (95% CI, 5.58 to 8.58) for children born at 24–27 weeks (MacKay et al. 2010).

A dose-response effect of birth at all gestations prior to term has also been reported in academic attainment (Pettinger et al. 2019, Wolke et al. 2015b). For example, the proportion of children who failed to reach a good level of achievement at age seven in school attainment tests increased as gestational age at birth decreased, with 43% of VP children failing to have a good level of achievement in assessment, compared with 18% of children born at full term (relative risk 1.78; 95% CI, 1.24 to 2.54) (Chan & Quigley 2014).

VP birth has a pervasive effect on learning, with children born VP having significantly poorer performance in all school subjects. However, marginally greater deficits are found in mathematics compared with other subjects (Aarnoudse-Moens et al. 2009, Allotey et al. 2018, Twilhaar et al. 2018b). This is due to VP children's general cognitive deficits, such as impairments in working memory and visuospatial skills, rather than deficits in numerical skills (Jaekel & Wolke 2014, Simms et al. 2015).

Do academic deficits observed in childhood represent a developmental delay or persistent deficits across schooling? Twilhaar and colleagues (2018a) found no significant differences in the trajectories of VP children and term-born controls in arithmetic, reading, or spelling throughout elementary school. Another investigation of results on school attainment tests found that preterm children showed gains in attainment between ages 7 and 11, closing the gap slightly with term-born peers, but not at ages 11 and 14 (Odd et al. 2019). Thus, overall, preterm children do not catch up with their peers, and substantial deficits in achievement are still evident at the end of compulsory schooling.

As with cognitive outcomes, relying on improved neonatal care for improving educational outcomes does not appear to hold the answer. In the VICS cohorts, achievement in reading, spelling, and mathematics was significantly poorer in EP children born in 2005 compared with those born in the 1990s (Cheong et al. 2017). The reasons for the deterioration in academic performance are not known, but it is clear that improvements in neonatal care need to be paralleled with improved teacher training and educational support for children born preterm (Johnson et al. 2015, Pettinger et al. 2019).

Mental Health

The assessment of mental health in cohort studies has mainly been carried out using parent, teacher, or self-completed rating scales rather than costly diagnostic evaluations. A recent meta-analysis using these measures revealed a small to moderate effect for increased internalizing symptoms [standardized mean difference (SMD) 0.42; 95% CI, 0.26 to 0.58] in EP/ELBW children

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compared with controls and a small effect for externalizing problems (SMD 0.15; 95% CI, 0.02 to 0.28) (Mathewson 2017). An individual participant data meta-analysis of six cohort studies in adulthood similarly found higher scores for internalizing problems but lower scores for externalizing problems among VP/VLBW adults compared with controls (Pyhälä et al. 2017). The effects, however, were usually very small, with mean differences in z-scores ranging from 0.06 to 0.12.

In childhood, a preterm behavioral phenotype has been described, characterized by an increased risk for attention problems, emotional problems, and difficulties with social interaction, alongside no increased risk for aggressive or delinquent behavior (Johnson & Marlow 2011, Mathewson 2017). This was first evidenced by a similar pattern of findings in five cohort studies (Farooqi et al. 2007, Hille et al. 2001).

At the diagnostic level, a meta-analysis of five studies identified an OR of 3.66 (95% CI, 2.57 to 5.21) for psychiatric disorders in preterm/LBW children and adolescents relative to full-term controls, with prevalence estimates that ranged from 21% to 28% (Burnett et al. 2011). The pattern of disorders observed in preterm populations indicates an increased risk for attention-deficit/hyperactivity disorder (ADHD), depressive and anxiety disorders, and autism spectrum disorder (ASD), alongside no increased risk for disruptive, impulse-control, or conduct disorders (Johnson & Marlow 2011, Johnson & Wolke 2013).

ADHD is the most common disorder after VP birth for which fairly consistent risk estimates have been reported, with ORs of 3.3 (95% CI, 2.0 to 5.6) (Allotey et al. 2018) and 3.04 (95% CI, 2.19 to 4.21) for ADHD in VP children and adolescents (Franz et al. 2018). The odds are even higher for those born EP/ELBW (OR, 4.05; 95% CI, 2.38 to 6.87) (Franz et al. 2018). VP children with high levels of ADHD symptoms show wide-ranging cognitive deficits (James et al. 2018, Retzler et al. 2019), which might also account for the comorbidity of psychiatric disorders in this population. In particular, a highly increased risk for ASD has also been reported in VP populations, with a prevalence of 7% among children born VP (Agrawal et al. 2018) and up to 8% among those born EP (Johnson et al. 2010).

There is good evidence that internalizing symptoms assessed in rating scales in VP persist into adulthood (Mathewson 2017, Pyhälä et al. 2017, Van Lieshout et al. 2018b). In contrast, diagnoses of emotional disorders reduce by adulthood, with EP/VP survivors showing better emotional adaptation than once anticipated (Burnett et al. 2014, Jaekel et al. 2018a, Johnson et al. 2019b). Whether this is a true decline or due to reduced statistical power resulting from loss from follow-up is not yet clear. Conversely, both ADHD symptoms and diagnoses have been found to persist into adulthood (Breeman et al. 2016a, Burnett et al. 2014).

Social Development

An infant's main social relationship is with their parents. However, as children grow up, they increasingly build relationships with peers. By the end of childhood, children will have spent many more hours with peers than with their parents. Thus, parent-child and peer relationships are reviewed here.

Parent-infant relationship. Despite recent efforts of neonatal infant care unit (NICU) policies to promote parental involvement and physical proximity as early as possible, infants are often in incubator care for weeks or months, which may impact maternal attachment formation (Feldman et al. 2014). Furthermore, an unexpected preterm birth and the ensuing period of uncertainty over their infant's survival can place high levels of stress on parents (Singer et al. 1999). However, parents of preterm infants often learn to cope with the higher stress over the first years of their offspring's life (Schappin et al. 2013).

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Attachment refers to the emotional bond that the infant forms with consistent caregivers who are sensitive and responsive in their social interactions (Bowlby 1969). Several reviews found no differences in secure-insecure attachment between preterm and term-born children (Field 1987, van IJzendoorn et al. 1992). In particular, maternal sensitivity has been found to be a major factor in predicting secure attachment (Miljkovitch et al. 2013, Wolke et al. 2014). A recent meta-analysis of 34 studies reported that despite the initial stress and separation, mothers of preterm children were as sensitive in their interactions with their children as mothers of term-born children (Bilgin & Wolke 2015). This suggests that similar maternal sensitivity allows mothers of preterm infants to adapt to and promote sensitive interactions (van IJzendoorn et al. 1992).

While secure and insecure attachment styles are organized patterns of dealing with reunion, disorganized attachment is manifested by contradictory, misdirected, or stereotypical behaviors (Carlson 1998) that are associated with child psychopathology (Weinfield et al. 2000). Pipp-Siegel and colleagues (1999) have suggested that neurological abnormalities can lead to behaviors similar to those that characterize disorganized attachment styles, usually associated with situations of child abuse or neglect. Indeed, there is evidence that VP/VLBW children are more likely than term-born children to have disorganized attachment. Notably, this was predicted by the infant's neurological impairment (distressing cry and developmental delay) and unrelated to parenting (maternal sensitivity) (Wolke et al. 2014).

There is some evidence that parents of VP children are more often overprotective than parents of term-born children, as indicated by being more controlling in mother-infant play interactions, even when researchers exclude children with neurosensory impairment (NSI) (Forcada-Guex et al. 2006, Wightman et al. 2007). Similar overprotection has been reported among VLBW adolescents (Indredavik et al. 2005) and VLBW young adults (Pyhälä et al. 2011). Higher parental control behavior and protection for VP children, however, may be partly explained by VP children's cognitive deficits and functional limitations and additional needs for framing and guidance (Jaekel et al. 2012). However, parents' perception of their child's vulnerability appears to depend mostly on parents' psychological factors (e.g., anxiety, parental stress) rather than the child's health (Tallandini et al. 2014). Indeed, parental anxiety has been associated with more controlling parenting and children's lower self-efficacy (Schneider et al. 2009), which may ultimately impair their resiliency (Schwarzer & Warner 2013).

Peer relationships. An important aspect of social development is the ability to relate to and form relationships with peers. A systematic review of 23 studies found that VP children and adolescents have higher levels of social withdrawal and peer problems than children born at term (Ritchie et al. 2015). Furthermore, studies that included the child's own self-report found that VP children have fewer close friends, spend less time with friends, and are less satisfied with their friendship network than their term-born peers (Heuser et al. 2018, Ritchie et al. 2018). VP children are also more than twice as likely to be socially excluded and bullied than term-born children, and this often persists from elementary to secondary school (Day et al. 2015, Ritchie et al. 2018, Wolke et al. 2015a). Poor peer relationships among VP children are important, as they are associated with emotional problems, inattention and hyperactivity, motor deficits (Day et al. 2015, Heuser et al. 2018, Ritchie et al. 2018), and the display of more autistic features (i.e., higher rates of social and communication problems) (Williamson & Jakobson 2014). Despite having fewer friends, direct observation of dyadic interactions between friends, one of whom was born preterm, found that friendship activities and behaviors are similar between children born preterm and at term, as well as their perceived relationship quality (Sullivan et al. 2012). It appears that VP children's withdrawn behavior may hinder them in forming and maintaining successful peer relationships.

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ADULT LIFE

Personality

Compared with term-born controls, adults born VP are less extraverted (Eryigit-Madzwamuse et al. 2015, Pesonen et al. 2008), more agreeable and cautious (Hertz et al. 2013, Pesonen et al. 2008), more shy and withdrawn (Eryigit-Madzwamuse et al. 2015, Johnson et al. 2019b), and less prone to criminal and risk-taking behaviors, such as smoking and illicit drug and alcohol use (Eryigit-Madzwamuse et al. 2015, Hack et al. 2002, Hille et al. 2008). VP-born adults report higher levels of neuroticism and more autistic features than term-born controls (Allin et al. 2006, Eryigit-Madzwamuse et al. 2015, Hertz et al. 2013). VP adults' socially withdrawn personality or adverse peer experiences may make it more difficult for them to form and maintain social relationships.

Social Relationships

The social lives of adults born VP have typically been investigated in cohort studies and Scandinavian registry studies. In a meta-analysis of 21 such studies including 4.4 million participants, preterm/LBW adults were less likely to form romantic partnerships (OR, 0.72; 95% CI, 0.64 to 0.81), to have had sexual intercourse (OR, 0.43; 95% CI, 0.31 to 0.61), or to have become parents (OR, 0.77; 95% CI, 0.65 to 0.91) compared to adults born at term (Mendonça et al. 2019). No differences according to sex or age were found, suggesting that individuals born preterm/LBW are less likely to accomplish these milestones by their late thirties in adult life.

Social difficulties are important as they are associated with adverse outcomes (Umberson et al. 2010), such as less wealth, social isolation, and poorer physical and mental health (Jaekel et al. 2018a), and they often worry parents (Wolke et al. 2017). Prematurity is also associated with a cross-generational fertility loss: Not only are adults born preterm less likely to become parents, but their parents were also less likely to have further children after the birth of a preterm child (Alenius et al. 2018). Despite having fewer friends (Baumann et al. 2016, Darlow et al. 2013), the quality of social support from peers was perceived as being as good in adults born preterm/LBW as in those born at term. Furthermore, when preterm adults had a romantic partner, the quality of this relationship was perceived as slightly more positive than in term-born peers (Mendonça et al. 2019).

Markers of Wealth

In a meta-analysis of 23 studies including 5.9 million participants, adults born preterm/LBW were found to have lower educational qualifications (OR, 0.74; 95% CI, 0.69 to 0.80), lower employment rates (OR, 0.83; 95% CI, 0.74 to 0.92), and greater receipt of social benefits (OR, 1.25; 95% CI, 1.09 to 1.42) than adults born at term (Bilgin et al. 2018). These associations were consistent across different geographical regions and age, and a dose-response effect of gestational age was found for educational qualifications, in which adults born LMP were 18% less likely than term-born adults to have higher educational qualifications, and VP adults were 40% less likely. Although previous studies reported that preterm adults were less likely to live independently (Baumann et al. 2016, Kajantie et al. 2008), independent living was not significantly lower in this meta-analysis (Bilgin et al. 2018). This may be because Scandinavian countries have a welfare system and cultural practices that support young people's independent living (D'Onofrio et al. 2013), reducing the adverse impact of preterm birth on the transition into adult life. Investigation in other parts of the world is required.

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Quality of Life

Normal birthweight (NBW): birthweight >2,499 g

Health-related quality of life (HRQoL) refers to the subjective impact of health on an individual's overall psychological, social, and physical well-being (Horsman et al. 2003). HRQoL allows for the comparison of the effects or consequences of different exposures or treatments across all medical conditions (e.g., from cancer to preterm birth). This is helpful when difficult decisions have to be made about where to direct limited health budget resources (Wolke 2016).

A systematic review in 2008 identified 15 studies that had compared HRQoL at preschool (6 studies), at school age (1), in adolescence (4), and in early adulthood (4) between EP/VP/VLBW individuals and term-born controls (Zwicker & Harris 2008). HRQoL was lower in individuals born preterm in the preschool years, according to parent report. In adolescence, parents reported lower HRQoL for EP/VP/VLBW participants than term-born controls, but no differences were found in self-reports. Furthermore, in early adulthood (18–23 years), no significant differences were found between groups, although EP/VP/VLBW adults tended to report slightly less physical and overall functioning (Zwicker & Harris 2008).

These results need to be interpreted cautiously for a number of reasons. Firstly, different findings were found when parent versus self-reports were used, with parents reporting lower HRQoL than the participants themselves (Baumann et al. 2016, Zwicker & Harris 2008). Consistent with social comparison theory, parents may take a wider view of their offspring compared to all same-aged peers, while their offspring may compare themselves to a selection of same-aged peers they interact with. Secondly, studies that include only self-reports exclude those with severe NSI, who are less likely to be able to complete these scales. This introduces bias in favor of no group differences. Thus, studies should include both self-reports and parent reports (Baumann et al. 2016). Thirdly, whole-population studies of VP survivors have loss to follow-up, with those with NSI, those who are socially deprived, and those from ethnic minorities more likely to drop out (Hille et al. 2005; Wolke et al. 1995, 2009). These groups are more likely to have lower HRQoL (Wolke 2016). Fourthly, the various measures of HRQoL are very different in their scaling. Some just add items in subscales, while others determine utilities [i.e., multi-attribute utility scores that represent mean community preferences ranging from 0.00 (rather be dead) to 1.00 (perfect health)]. Thus, comparisons of studies are strictly only possible if the same measures are used. Finally, level of HRQoL is influenced by variations in neonatal treatment philosophy across different regions (Breeman et al. 2016b), by cultural differences, and by the general happiness of the nation (Verrips et al. 2008).

Three cohort studies of ELBW/VP/VLBW survivors in Germany (Baumann et al. 2016), the Netherlands (van Lunenburg et al. 2013), and Canada (Saigal et al. 2016) that had followed children into adulthood used an identical measure of HRQoL. A comparison of these three studies (Wolke 2016) found that, firstly, HRQoL of ELBW individuals was, on average, lower than that of VP/VLBW individuals, who in turn reported lower HRQoL than normal birthweight (NBW) adolescents and adults. Secondly, HRQoL did not improve with age in ELBW or VP/VLBW individuals. A previous comparison of the three cohorts in adolescence, at least in the German and Canadian ELBW groups, had found similar levels of HRQoL in adolescence (Verrips et al. 2008). Thirdly, NSI is a major factor that reduces HRQoL well into adulthood. Considering the stability of these differences compared to NBW individuals, it appears that whatever services ELBW or VP/VLBW individuals received from early adolescence onwards made no difference to their HRQoL in adulthood (Wolke 2016).

DEVELOPMENTAL MECHANISMS

Understanding why VP survivors have more developmental problems and why some impairments persist across time while others show plasticity is important, not just for theoretical advancement

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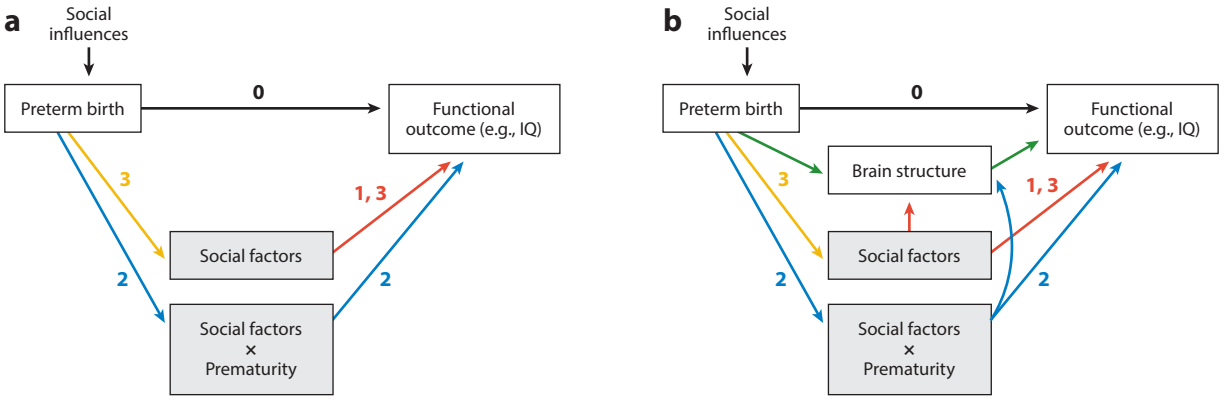

Figure 1

(*a*) Testing alternative models of the effect of preterm birth on functional outcome. Model 0: Preterm birth has a main effect on functional outcome ignoring other influences. Model 1: Social factors have a main effect on functional outcome in addition to preterm birth. Model 2: Social factors moderate the effects of preterm birth on functional outcome. Model 3: Social factors mediate the effect of preterm birth on functional outcome. (*b*) Models 0 to 3 may explore how single or joint effects impact brain development as a neural mediator. Abbreviation: IQ, intelligence quotient.

but also for informing the development of interventions. Here we explore potential developmental mechanisms to help explain the life course consequences of VP birth.

Environmental Influences

Most prospective studies have used a simple main effect model investigating the association between perinatal differences at birth and adverse developmental outcomes (see **Figure 1*a***, Model 0). This approach is limited as it fails to take account of other important influences that may operate between birth and later outcomes. For illustration, we consider three such factors: socioeconomic status (SES), parenting quality, and traumatic peer influences. These factors are located in different layers in Bronfenbrenner's (1989) ecological model and may operate in different ways in conjunction with VP birth and associated complications.

Firstly, these factors may have a main effect on VP children's development (see **Figure 1*a***, Model 1). For example, SES may be an additional factor predicting developmental outcome. It also means that the effects of low SES are the same for children born VP and at term, and are additive. If low SES has detrimental effects on the outcome under consideration, then low SES would be considered as a risk factor. Conversely, if high SES has beneficial effects, then it could be considered a protective factor (Luthar et al. 2000).

Alternatively, SES may be a moderator of the association between VP birth and the outcome of interest (**Figure 1*a***, Model 2). This means, for example, that low SES has a significantly larger effect in VP children (i.e., they are more vulnerable to the effects of SES than children born at term), consistent with a diathesis-stress model (Ellis et al. 2011). Furthermore, if high SES provides protection against the effects of VP birth and children reach the level of functioning of those born at term, then this would be considered resilience: the ability to bounce back after exposure to risk (i.e., VP birth) (Taylor et al. 2019).

Let us consider the main effect and moderation models within the context of findings from cohort studies. Being born into a high-SES versus low-SES family has a similar effect on child (Wolke & Meyer 1999) and adult IQ (Eryigit Madzwamuse et al. 2015) in VP and term-born populations. The effect of SES on IQ is comparable to the effect of being born VP versus term in

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effect size on IQ (Eryigit Madzwamuse et al. 2015). Expressed differently, having a mother whose highest educational attainment was at elementary or secondary school has the same adverse effect on IQ as having suffered severe brain damage or chronic lung disease (Benavente-Fernández et al. 2019). These findings are consistent with a main effect model with no indication of an interaction effect (**Figure 1*a***, Model 1). It is thus no surprise that SES is reported as one of the major influences on cognitive outcomes in VP children (Breeman et al. 2017, Linsell et al. 2015). It is, however, disconcerting that, by 2018, only 15 of 70 studies included in a meta-analysis of VP birth and IQ considered some marker of SES (Twilhaar et al. 2018b).

SES reflects a multitude of factors, including social, family, and parenting factors (Wolke 2019), that need to be unpacked. If we wish to unlock the black box of how these factors influence development, we need to measure them in as much detail as we have perinatal complications (Wolke 2019), which will require greater collaboration across disciplines in the design of follow-up studies. Let us consider parenting, a factor strongly associated with SES (Sherman & Harris 2012) and academic achievement. Wolke and colleagues (2013) found that the effects of sensitivity of parenting assessed at 6 years of age were moderated by birth status (i.e., VP versus term): VP children were strongly and adversely affected by low sensitive parenting, while very sensitive parenting was found to lead to academic attainment nearly on par with children born at term (see **Figure 2**). Thus, the effects of VP birth on academic outcomes are moderated by sensitive parenting. This follows a diathesis-stress model and indicates potential resiliency in academic outcomes for those born VP (see **Figure 1**, Model 2).

Another interaction (see **Figure 1*a***, Model 2) argues that variations in child characteristics may alter susceptibility to environmental influences (i.e., the sensitivity to both negative and positive influences). This differential susceptibility proposes that certain environmental influences such as parenting can lead to poorer outcomes under conditions of poor parenting and better outcomes

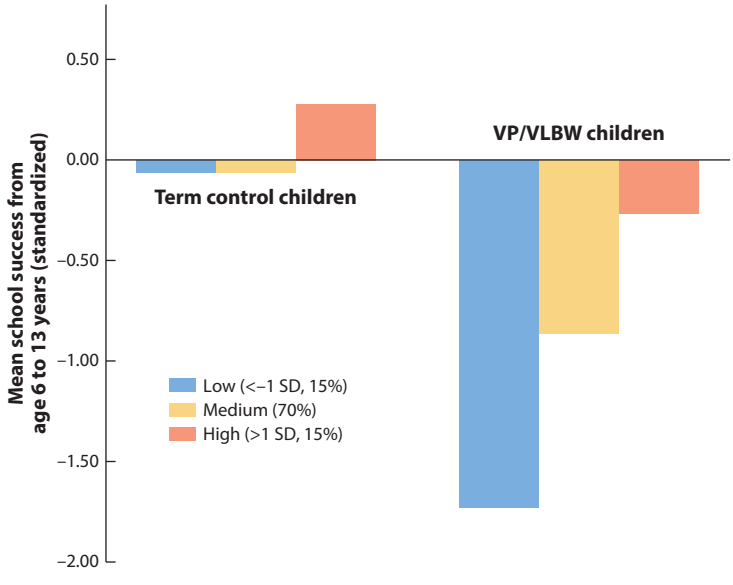

Figure 2

Effect of sensitive parenting (low, medium, or high) at 6 years of age on school success at 13 years of age. Variation by very preterm (VP)/very low birthweight (VLBW) versus term-born status. Abbreviation: SD, standard deviation. Adapted with permission from Wolke et al. (2013).

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under conditions of good parenting in susceptible compared to nonsusceptible individuals (Ellis & Del Giudice 2019, Ellis et al. 2011). There is little reason to suggest that VP birth may be related to vantage sensitivity (i.e., increased sensitivity to positive experiences) (Belsky & Pluess 2013). From an evolutionary perspective, most of these infants would not have survived without modern NICU care. Indeed, when a diathesis-stress model versus differential susceptibility theory (DST) was tested in LBW children, there was little evidence for DST, but there was support for the diathesis-stress model (Jaekel et al. 2015). Thus, there is increasing evidence that VP birth makes children more vulnerable to environmental risk factors (Poehlmann et al. 2015, Van Lieshout et al. 2018a, Wolke 2018).

A third model considers environmental factors as mediators between VP birth and later outcomes (see **Figure 1**, Model 3). VP children, as reviewed here, are at higher risk for emotional problems in adolescence. Similarly, it is well documented that children who are exposed to trauma, such as being bullied by peers, are at higher risk for emotional problems (Wolke & Lereya 2015, Zwierzynska et al. 2013). A recent investigation noted that a major part of the effect of EP/VP birth on emotional problems was explained by EP/VP children being more than twice as likely to be bullied than their term-born peers, which in turn explained the excess of emotional problems in adolescence. Thus, bullying completely mediated the effects of EP/VP birth on emotional problems (Wolke et al. 2015a).

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Genetic Influences

Preterm birth is an environmental event that sets off a cascade of further environmental interventions (i.e., NICU care). In all children, genes are involved in cognitive and behavioral development. Thus, genetically sensitive designs ranging from twin studies to the use of genome-wide association studies based on polygenic risk scores may be used to determine genetic contributions to developmental outcomes. Effects of genes are dependent on whether they can be expressed or whether shared or nonshared environmental factors (e.g., neonatal complications or brain injury) reduce their expression. Indeed, in VP children, any additive genetic effects were overshadowed by shared environmental factors in twin pairs (Koeppen-Schomerus et al. 2000). More than 85% of the variance in cognitive scores at 2 years of age was explained by shared environment; thus, genetic effects may be much reduced compared to birth at term, at least in early development.

Twin designs can further help test causal links using twin pairs that are discordant for a risk factor. Groen-Blokhuis and colleagues (2011) tested three models using monozygotic and dizygotic twin pairs and unrelated individuals discordant for birthweight. Their findings showed clearly that LBW significantly predicted higher attention problems, even among children who were otherwise genetically identical. Unfortunately, while babies can be discordant for birthweight, gestation rarely varies, so effects of gestation cannot be tested within such designs. Future research including polygenic scores may serve to evaluate how VP birth as an environmental event may reduce genetic effects.

The Brain

VP birth confers an insult to normal brain development (i.e., interrupted development), and there is often the superimposed risk of acquired brain injury (e.g., hemorrhage) (Volpe 2009). At the limits of survival (22–24 weeks of gestation), the brain consists entirely of white matter. In the following 16 weeks, gray matter expands rapidly, with a dramatic increase in brain surface area through cortical folding (Hüppi et al. 1996, Kapellou et al. 2006). When babies are born

prematurely, this pattern of growth is disrupted due to alterations in growth patterns, direct injury to the white matter (Constable et al. 2008, Inder et al. 2005, Miller et al. 2005), or undetermined reasons. The earlier the birth, the greater the disruption; in addition, boys are affected more than girls (Kapellou et al. 2006, Vasileiadis et al. 2009). This leads to building a different brain than in term births, with altered gray and white matter distribution in multiple regions indicating reorganization of cortical and subcortical structures relating to brain volume, volume distribution, microstructure, and connectivity (Ball et al. 2013). These alterations are still detectable in adulthood in many areas (Bäuml et al. 2015, Meng et al. 2016).

Recent advances in neuroimaging have taken two directions. Firstly, researchers have developed MRI-compatible incubators with integrated head coils that allow for sequential scanning of the developing brain while infants are in neonatal intensive care (Hintz & O'Shea 2008). Secondly, the routine availability of MRI allows the study of anatomical differences, and, more recently, functional MRI studies are improving our understanding of differences in brain area activation and connectivity in preterm children and adults (Nosarti 2013).

A crucial research pathway will be to determine how changes in brain development due to VP birth are associated with functional outcomes such as cognitive, emotional, or social development (Montagna & Nosarti 2016) (see **Figure 1*b***). Such outcomes may be related to anatomical alterations (Nosarti et al. 2008), whole network alterations (Kelly et al. 2015, Meng et al. 2016), or specific alterations such as in the cholinergic forebrain (Grothe et al. 2017) and may be potentially treatable. Early studies were promising and showed significant associations between early brain development assessed during the neonatal period and delayed development 2 years later (Kapellou et al. 2006). However, more than a decade on, comparisons of costly MRI versus the utility of cranial ultrasound are sobering. In a recent study, MRI predicted adverse motor outcomes slightly better than ultrasound, but both methods were insensitive and neither predicted cognitive problems at age 18–24 months (Edwards et al. 2018). A mild beneficial effect of MRI was found in that parents liked seeing the whole brain, which reduced their anxieties more than an ultrasound did. However, a single MRI in the United Kingdom costs approximately £300 more than a routine ultrasound. Social factors have been found to alter brain development and have to be considered in studies (Kim et al. 2018). Furthermore, simply measuring head size in the first years of life is highly correlated with brain growth and is predictive of later cognitive development (Jaekel et al. 2018b). Thus, it is important to consider what measures are required for basic science to advance knowledge of developmental mechanisms and which are sufficient for routine follow-up (Doyle et al. 2014).

In summary, to understand how VP birth leads to adverse outcomes, it is necessary to have more detailed measurement of environmental influences. Furthermore, for different outcomes and environmental factors, different mechanisms and models may apply. Understanding how VP birth alters brain development and how environmental experiences such as trauma or parenting get into the brain may help us understand the neural mechanisms underlying diverse phenotypic outcomes.

CONCLUSIONS AND FUTURE DIRECTIONS

First, VP birth has a wide range of adverse effects on motor and psychological development and well-being across the life span. **Figure 3** summarizes the effects of VP/VLBW birth on functioning across the various domains reviewed here. It shows the approximate size of the effects as reported across studies in childhood and adulthood. Effect sizes are defined as small (OR, 1.48 or inverted 0.67; Cohen's d between means, 0.2), moderate (OR, 3.45 or 0.29; Cohen's d, 0.5), or large (OR, 9 or 0.11; Cohen's d, 0.8) (Chen et al. 2010).

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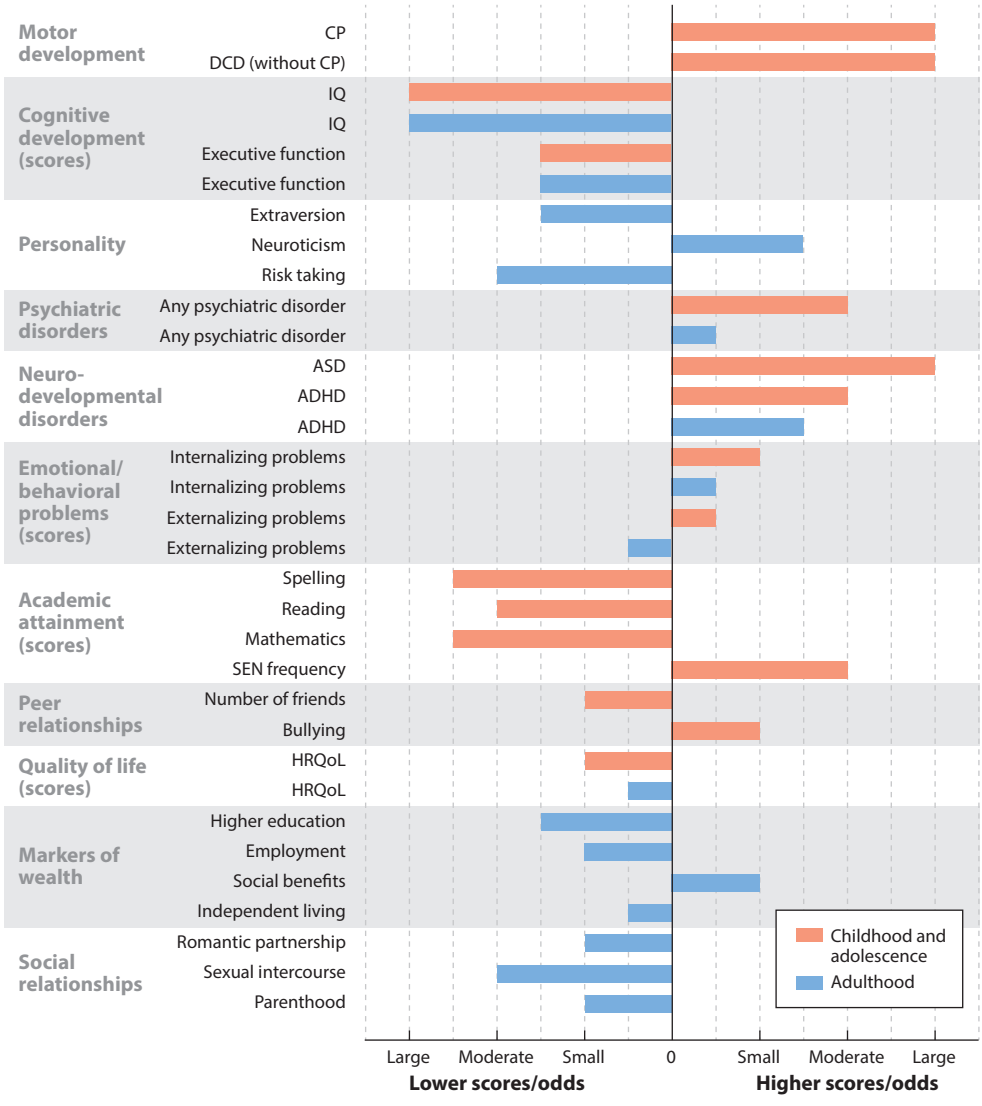

Figure 3

Approximate effect sizes for the impact of very preterm birth on long-term outcomes (compared with birth at term; zero vertical line). Outcomes assessed in childhood and adolescence are shown in red and outcomes assessed in adulthood in blue. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CP, cerebral palsy; DCD, developmental coordination disorder; HRQoL, health-related quality of life; IQ, intelligence quotient; SEN, special educational needs.

The largest adverse effects of VP compared to full-term birth are found for CP, DCD, IQ, and ASD. While the effect sizes are large, CP is found in less than 5% of VP/VLBW births and ASD in 7–8%, but DCD and, in particular, low IQ (<−2 SD) are found in up to 25% of VP children. Thus, DCD and IQ are the major sequelae of VP birth. VP birth has moderate effects on academic attainment—in particular, lower mathematics and spelling scores—higher special educational needs in school, and increased risk of any psychiatric disorder in childhood,

especially ADHD. Furthermore, moderate effect sizes were found for executive functions and personality, such as being less extraverted, more neurotic, and less likely to engage in risk-taking behavior. Small effect sizes were found for internalizing and externalizing problems, relationship with peers, bullying, and HRQoL in childhood. While the effect sizes are small for the latter, these usually affect a large proportion of VP individuals. Relationships with parents are little affected in regards to parental sensitivity, and the effects for overprotection are small or may be explained by VP/VLBW having higher needs for framing due to lower IQ.

Second, some adverse effects reduce across development, and others persist from childhood into adulthood. Intelligence and executive functioning show no or very little improvement with age into adulthood. Social difficulties noticed in childhood in terms of ASD symptoms and relationships with peers are still found in adulthood, manifesting in a withdrawn personality and less engagement in normative risk-taking behaviors. Overall, the risk of psychiatric disorders seems to reduce by adulthood (see **Figure 3**). Motor, cognitive, emotional, and social difficulties are likely to contribute to the difficulties some VP individuals have in the transition to adulthood, including being less likely to participate in higher education, less likely to be employed, and more likely to receive social benefits. Most notable is their decreased likelihood of forming romantic and sexual relationships and having children themselves. Thus, more VP than full-term adults may have lower social and financial support once their parents are gone, which has important implications for future public support.

Third, VP individuals who have a significant deficit in one domain (e.g., IQ) often have problems in other domains (e.g., academic achievement, social relationships). Thus, comorbidity is frequent, and, for a minority of VP children and adults, the problems are complex, requiring support from medical, psychological, and education services. However, even term-born children rarely have no problems at all (Wolke & Meyer 1999), and thus it is important to remember that, despite the often increased odds of adverse outcome, most VP children and adults develop adaptively without major problems.

Fourth, despite the significant decrease in mortality and CP for babies born VP, there is as yet no evidence that this has been matched by improved developmental outcomes across the domains reviewed here.

A multitude of challenges face future researchers, practice, and intervention. Much of the observational research on the effects of VP birth may be too simplistic, failing to go beyond medical factors associated with VP birth. Developmental science has much to contribute to help unravel what factors across life may increase risk further, provide protection or resilience, or mediate the association with life outcomes. This is unlikely to be achieved by a single profession or single longitudinal study, which is often limited in statistical power. It requires interdisciplinary collaboration and bringing together cohort and registry studies across the world. Such ongoing collaborations include the APIC initiative (**http://www.apic-preterm.org**) and a large European Union–funded project, RECAP Preterm (**http://www.recap-preterm.eu**). Neuroimaging and genetically sensitive designs should also be considered for future cohort studies.

The use of core measures across cohort studies (Doyle et al. 2014) would allow for direct comparison of whether changes in neonatal care across consecutive cohorts have led to changes in developmental outcomes. This must include measures of the social environment, such as parent and peer relations, as changes may be due as much to social changes as to advances in neonatal care.

Primary prevention of preterm birth itself is needed, but such efforts have met with little success to date. Thus, a key challenge is to minimize adverse effects of VP birth on the brain during neonatal care and to promote development after discharge. As schooling is one of the major factors affecting life course outcomes, new interventions extending beyond the first 2 years should be

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trialed, including new resources to improve educational support for children born preterm (**http://www.pretermbirth.info**; Johnson et al. 2015, 2019a).

Finally, reports on developmental outcomes of VP children into adulthood come exclusively from high-income countries. However, the vast majority of preterm children are born in transitional or low-income settings (Chawanpaiboon et al. 2019), and we have no idea how they fare in life. This paucity of research in low-income countries needs to be addressed.

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