The complex aetiology of cerebral palsy

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Abstract | Cerebral palsy (CP) is the most prevalent, severe and costly motor disability of childhood. Consequently, CP is a public health priority for prevention, but its aetiology has proved complex. In this Review, we summarize the evidence for a decline in the birth prevalence of CP in some high-income nations, describe the epidemiological evidence for risk factors, such as preterm delivery and fetal growth restriction, genetics, pregnancy infection and other exposures, and discuss the success achieved so far in prevention through the use of magnesium sulfate in preterm labour and therapeutic hypothermia for birth-asphyxiated infants. We also consider the complexities of disentangling prenatal and perinatal influences, and of establishing subtypes of the disorder, with a view to accelerating the translation of evidence into the development of strategies for the prevention of CP.

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Cerebral palsy (CP) is the most common severe motor disability in children, and its severity is demonstrated by the fact that 40% of children with the condition cannot walk independently[1,2], one-third have epilepsy[3], up to one-third are non-verbal[4,5] and about one-half have some degree of cognitive impairment[2,6–8]. Lifetime costs for a child with CP in the USA have been estimated at just under US$1 million per individual for health expenditures, educational needs, social services and lost economic opportunity[9]. The prevalence, severity and burden of CP make it a public health priority for prevention, and recognition that perinatal exposures and pregnancy complications are strongly linked to the risk of CP provides opportunities for prevention. However, the aetiology of CP has proved complex, making progress in its prevention difficult.

In this Review, we consider the epidemiological observations that provide evidence for the contribution of various developmental pathways to the pathogenesis of CP and for the substantial success in prevention to date. We also consider the complexities of disentangling prenatal and perinatal influences, with a view to accelerating the translation of evidence into clinical approaches to the prevention of CP.

The prevalence of cerebral palsy

In the 1940s, in the USA, two voluntary organizations, the National Society for Crippled Children (later named Easter Seals) and United Cerebral Palsy, initiated two population surveys to determine CP prevalence[10,11]. In Schenectady, New York, the prevalence was 5.9 cases per 1,000 births, whereas in Minneapolis, Minnesota, the prevalence was 1.8 per 1,000 live births[10,11]. These differences in prevalence indicated that defining CP, differentiating CP from other motor disabilities and determining the precise lower limits of severity that delineate cases were all problematic. This difficulty has been repeatedly wrestled with, and numerous international meetings on the definition and classification of CP have been held since 1958 (REFS[12–14]), each leading to changes in the definition of the condition (FIG. 1).

Ongoing population surveillance for CP began in the Nordic countries[15–17]. In the second half of the past century, most reviews concluded that the prevalence of CP (generally expressed in relation to numbers of live births) in industrialized nations was fairly stable at 1.5–2.5 cases per 1,000 live births[18,19], but with a modest increase in the last two decades of the 20th century owing largely to the greatly increased survival of very premature infants as a result of the success of the new technology[19,20].

Estimates of CP prevalence in the 21st century, however, reveal a mixed picture. During the first decade of the century, estimates of CP prevalence were generally higher than in the 20th century in high-income countries (HICs). In the USA, prevalence estimates increased from 2 to as high as 3 cases per 1,000 live births between 2002 and 2012 (REFS[2,21–25]), although the most recent of these surveys showed a slight decline to 2.9 per 1,000 8-year-old children in 2010 from 3.5 in the same surveillance area in 2006 (REF.[26]). However, studies in Australia[3], Europe[27–29], Canada[30], Sweden[31] and Japan[32] have provided evidence for a declining prevalence of CP over time, mostly among low-birthweight and preterm infants (TABLE 1). In China, a decline from 1.6 to

Key points

- Several high-income countries have reported a decline in the prevalence of cerebral palsy (CP); therapeutic hypothermia and magnesium sulfate for neuroprotection might have played a role, but other factors might be important.
- The minimum age at which CP can be reliably diagnosed is controversial; evidence that early diagnosis and intervention improves motor outcome is sparse, but there are hints of benefits for cognitive outcomes.
- No consensus exists about CP subtypes; the general term CP is important for public health and health services planning, but subtypes might have different aetiologies.
- Gestational age and birthweight have been a major focus of CP investigators; to move forward, we must seek a deeper understanding of why these factors convey information about increased risk.
- Preconception factors, including maternal obesity and age, should be considered because they can modify the relationships between CP and other factors that occur later in pregnancy.
- Two-hit and multi-hit models that consider accumulation of risk factors can identify a synergistic increase in the risk of CP, but the time order and clinical relevance of the model components must be established.

1.25 cases per 1,000 children between 1999 and 2017 has been reported[33,34], although ascertainment methods for these reports might have differed from the long-standing registers used in Australia and Europe.

The reported prevalence of CP in South Korea, Japan and India is 2–3 cases per 1,000 live births[35–37], but figures greater than 3 cases per 1,000 live births in Taiwan[38], Egypt[39] and Uganda[40] have been reported in the past few years. Some evidence suggests that rates in rural Africa are much higher[41]. New CP registers are emerging in Bangledesh[42], Mexico[43] and Jordan[44], and hospital-based surveillance is being developed in Vietnam[45].

Major aetiological factors

The first systematic clinical descriptions of CP were authored in the 1840s by the orthopaedic practitioner W. J. Little[46,47]. Little's assertion that nearly all cases of what he called spastic rigidity of newborn children resulted from preterm birth or asphyxia at birth has left an enduring mark on subsequent thinking about the aetiology of CP. Sigmund Freud, in his first career as a child neurologist, cautioned against assuming that these two factors were fully causal[48–50], but only in the latter half of the 20th century did research begin to illustrate the complex nature of these associations.

Nevertheless, Little's insight that the perinatal period was important to the pathogenesis of CP has been supported by subsequent research. Therefore, in this section, we begin by considering the two factors identified by Little before reviewing factors related to preconception, pregnancy and the perinatal period. A comprehensive review of the risk factors for CP is available elsewhere[51].

Birth complications

The obstetric literature from the 20th century is rife with examples of physical trauma in labour, sometimes exacerbated by instrumented deliveries or severe asphyxia in labour and delivery, all of which are capable of causing brain injuries in children that could lead to CP[52]. However, these events were not placed in an appropriate statistical context until the National Collaborative Perinatal Project (NCPP) study of ~50,000 children born during 1959–1966. The NCPP provided compelling evidence that clinical indicators of birth asphyxia (for example, fetal bradycardia, a low Apgar score and delayed time to first breath) occurred in only a minority of children who had CP[53] and rarely led to CP when they occurred. Approximately 70% of children with CP had Apgar scores of ≥7 at 5 min after birth, and 95% of children with a normal birthweight and an Apgar score of 0–3 at 5 min after birth were free from major disability at early school age. These findings made it clear that birth asphyxia was not the dominant cause of CP that many clinicians and the lay public had assumed. A convenience survey of clinicians (largely paediatricians and obstetricians) shortly after the NCPP publications found that the average estimate of the risk of CP after a low Apgar score was 40%, eightfold higher than the 5% risk identified by the NCPP[54,55].

The NCPP reinforced a finding noted by many students of birth asphyxia that the risk of CP is markedly elevated by the presence of abnormal neurological signs in the newborn period, most notably seizures, an inability to suck and breathing difficulties, which together indicate the syndrome of neonatal encephalopathy. This syndrome is often assumed to be the consequence of so-called hypoxic–ischaemic brain damage but can occur in the absence of markers of distress during labour and might even have a closer relationship to pre-labour factors[56,57]. Low Apgar scores, delayed onset of respiration, and seizures might be signs of birth asphyxia, but they are neurological findings themselves and can reflect brain damage that was present before birth. Ellenberg and Nelson have argued that the attribution of CP to birth asphyxia often results from the conflation of the consequences of factors that underlie both CP and birth asphyxia[58,59], and point out that placental pathology and markers of infection often precede abnormal fetal heart patterns[60] and low Apgar scores[61].

Breech vaginal delivery is now avoided in most HICs owing to an assumed risk of birth asphyxia and later CP. The NCPP indeed found an elevated risk of CP for normal-weight babies who were in the breech position in utero, but the risk was the same whether the baby was born vaginally or by Caesarian section[53,62]. Breech position at term can reflect fetal abnormalities that preceded the onset of labour, including abnormal maternal thyroid function[63], fetal growth restriction (FGR), oligohydramnios, gestational diabetes and fetal anomalies[64]. In randomized trials, mortality and short-term morbidity associated with breech presentation were reduced by Caesarian section, but long-term neurodevelopmental outcomes were unaffected[65].

Gestational age and its correlates

Children born preterm account for one-third to one-half of CP diagnoses in HICs, although this proportion is much lower in low-income countries (LICs), where mortality of very preterm babies remains high[40]. The more preterm the newborn baby, the higher the risk of CP; the prevalence of CP reaches ~10% among infants who are born before 28 weeks of gestation, a prevalence that is ~50-fold higher than that among children born at term[66,67].

Apgar score
A scoring system to predict the need of newborn babies for medical attention; the overall score is composed of scores for heart rate, respiratory effort, muscle tone, response to stimulation and skin colouration.

Oligohydramnios
A pregnancy complication characterized by low amniotic fluid levels.

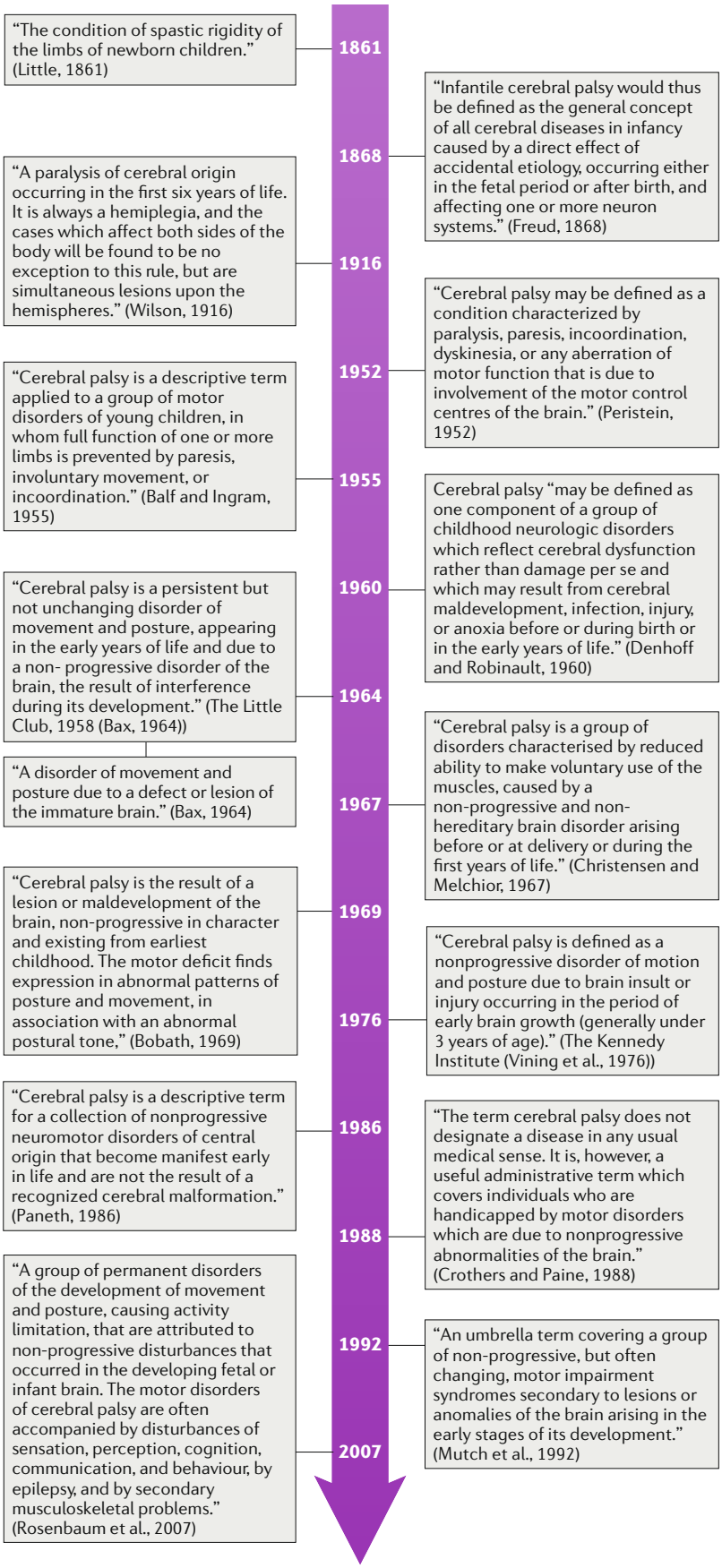

Fig. 1 | **Definitions of cerebral palsy over time.** The definition of cerebral palsy has changed several times since 1861, and the most recent definition was described in 2007.

Much research has been devoted to identifying the factors that place preterm infants at the greatest risk of CP; the numerous factors that have been studied include organ immaturity, lack of hormones and growth factors, metabolic factors and environmental toxins, infection and inflammation, physiological instability, medical interventions and pregnancy-related complications[68]. The most strongly associated indicators of CP risk in preterm infants are cranial ultrasonography observations in the first few weeks of life[69]. Lesions that indicate white matter injury — usually seen as echolucency and ventricular enlargement — are associated with a substantially increased risk of CP[70], whereas isolated germinal matrix and ventricular haemorrhage, which are more common than white matter injury in preterm infants, are associated with a much lower risk of CP[71–76].

Mechanical ventilation is widely used for children who are born very preterm and has been linked to CP[70,77]. The effects of mechanical ventilation on risk are confounded, as its use is an indicator of illness severity[78], but animal models and observational studies have provided evidence that mechanical ventilation can cause systemic inflammation and lung damage and can alter blood gas levels in ways that might be detrimental to the perinatal brain[79–81]. Ventilator settings that produce hypocapnia have caused particular concern because they have been associated with brain damage at autopsy and with an increased risk of CP[82–88]. Antenatal administration of steroids during preterm labour to stimulate lung maturation has been associated with a reduced risk of CP[89]; by contrast, postnatal administration of steroids has raised concerns about an increase in CP[90,91].

Intermittent or sustained systemic inflammation in which single[92] or multiple inflammation-related proteins are persistently upregulated[93] in the newborn period has been associated with a twofold to threefold increase in the risk of CP in babies born before 28 weeks of gestation. Studies of infants who are born at a weight ≤1,000 g yield similar evidence[94]. Insufficient blood levels of neurotrophic and/or angiogenic proteins also seem to influence the risk of CP and other neurodevelopmental disorders in some settings. For example, transient hypothyroxinaemia, a common complication of preterm delivery and a correlate of low birthweight[95–98], occurs most often in the smallest and sickest of neonates[96–105], and some observational studies have found that neonatal thyroid hormone deficits are linked to CP, behavioural problems and lower cognitive performance assessed at school age or in adolescence[106–110], although other studies have not[111,112]. For example, a nationwide Dutch cohort study of infants born very preterm and/or with very low birthweights showed that relative hypothyroxinaemia (defined as values >1 s.d. below the mean) was associated with psychomotor developmental delay at 2 years corrected age[109], neurological dysfunction assessed at the age of 5 years, and school failure at age 9 years[113]. A population-representative study of 1,105 children born with a weight of <2,000 g similarly found a fourfold increase in the risk of CP in newborn children with thyroid hormone levels >2.6 s.d. below the state norm compared with children with normal levels after adjustment for gestational age and multiple prenatal, perinatal and

Table 1 | **Trends in the prevalence of cerebral palsy overall and by birthweight or gestational age at delivery**

Location (study)	Prevalence group	Years	Observed prevalence (per 1,000 in specified prevalence group)	95% CI
Northern Alberta, Canada (Robertson et al.[30])	All live births	2008	2.38	2.19–2.57
		2009	2.26	2.10–2.44
		2010	1.89	1.70–2.10
	Birthweight <1,000 g	1985–1988	98.4	59.5–137.4
		2008–2010	40.1	34.5–45.7
	Birthweight 1,000–1,499 g	1985–1988	70.7	43.8–97.6
		2008–2010	22.7	19.3–26.0
	Birthweight 1,500–2,499 g	1985–1988	11.0	7.9–14.1
		2008–2010	6.7	5.9–7.5
	Birthweight ≥2,500 g	1985–1988	1.7	1.6–1.8
		2008–2010	1.3	1.2–1.4
Europe (Sellier et al.[27])	Birthweight <1,000 g	1980	40.9	12.1–97.3
		2005	38.2	26.0–53.8
	Birthweight 1,000–1,499 g	1980	70.9	41.7–110.9
		2005	35.9	26.6–47.2
	Birthweight 1,500–2,499 g	1980	8.5	5.4–12.7
		2005	6.2	4.9–7.8
	Birthweight ≥2,500 g	1980	1.2	0.9–1.5
		2005	0.9	0.8–1.0
Japan (Touyama et al.[32])	All live births	1988–1997	1.8	1.6–2.0
		1998–2007	0.97	0.94–0.99
	Birthweight <1,000 g	1988–1997	65.5	46.1–90.3
		1998–2007	108.7	83.9–138.5
	Birthweight 1,000–1,499 g	1988–1997	89.9	72.2–110.6
		1998–2007	74.6	59.6–92.3
	Birthweight 1,500–1,999 g	1988–1997	28.6	22.0–36.6
		1998–2007	21.0	15.7–27.3
	Birthweight 2,000–2,499 g	1988–1997	2.4	1.6–3.5
		1998–2007	3.0	2.1–4.0
	Birthweight ≥2,500 g	1988–1997	0.6	0.5–0.7
		1998–2007	0.5	0.4–0.7
USA (Durkin et al.[26])	8-year-old children	2006	3.5	3.2–3.9
		2008	3.2	2.9–3.5
		2010	2.9	2.6–3.2
	8-year-old children, excluding those with a documented post-neonatal cause	2006	3.2	2.9–3.5
		2008	3.0	2.7–3.3
		2010	2.6	2.3–2.9
Victoria, Australia (Reid et al.[3])	Gestational age ≥37 weeks	1983–1991	1.2	Not available
		1992–2000	1.2	Not available
		2001–2009	1.0	Not available
	Gestational age 32–36 weeks	1983–1991	5.3	Not available
		1992–2000	3.8	Not available
		2001–2009	4.2	Not available
	Gestational age 28–31 weeks	1983–1991	41.5	Not available
		1992–2000	40.0	Not available
		2001–2009	32.4	Not available
	Gestational age <28 weeks	1983–1991	92.1	Not available
		1992–2000	102.5	Not available
		2001–2009	70.6	Not available

early and late neonatal variables[110]. In a similarly large study of infants born with very low birthweight, transient hypothyroxinaemia was associated with a twofold greater risk of white matter damage, a key antecedent of CP, after adjustment for gestational age and various measures of illness severity[114]. Whether the association between neonatal thyroid hormone deficits and CP is truly causal can be determined only with a randomized trial of thyroid hormone supplementation[95,115].

Similarly, severe maternal iodine deficiency, which presumably leads to maternal and thus fetal hypothyroxinaemia, is associated with cognitive impairments and neurological deficits that resemble CP[116]. Iodine deficiency remains an important remediable cause of cognitive, neurosensory and motor impairment in several parts of the world[117].

Preconception and early gestation

Genetics. Familial clustering of CP has been described: three studies since 2007 have indicated that the relative risk of CP for the sibling of a child with CP is four[118], five[119] and nine[120], respectively. However, even these relative risks translate to a small absolute risk of CP of 1–2%. Copy number variants and mutations in single genes have been implicated in CP, but these findings are limited by small numbers of patients, genetic heterogeneity and a paucity of validation studies[121]. Whole-exome sequencing has revealed several potentially disease-causing gene variants, but functional and pathway studies are needed to validate these findings[122].

Among the most studied genetic risk factors is *APOE* genotype. *APOE* encodes apolipoprotein E (ApoE), a lipid transport protein that is abundant in the brain; the *APOE*ε4* allele has been associated with several neurological conditions, most notably Alzheimer disease. Studies of *APOE* genotype and the risk of CP have produced a variety of results. The *APOE*ε4* allele has been associated with an elevated relative risk of CP in one Brazilian study[123] and two studies conducted in the USA[124,125], one of which also indicated an elevated risk among carriers of the *APOE*ε2* allele. In a large, population-based study conducted in Norway, the *APOE*ε4* allele was associated with an increased severity of CP[126], whereas the *APOE*ε2* or *APOE*ε3* alleles and the s59007384 polymorphism in the *TOMM40* gene (which is located on chromosome 19 close to *APOE*) were associated with reduced severity of CP[127]. However, in a second Brazilian study, an elevated risk of CP was associated only with the *APOE*ε2* allele[128], and a Norwegian family study identified *APOE*ε3* to be the *APOE* allele most closely linked with CP[129]. Furthermore, three much larger studies — two conducted in Australia[130,131] and one in China[132] — found no association of any *APOE* allele with the risk of CP.

In a review published in 2009 (REF.[133]), an association between certain thrombophilia-related genes and CP caused by intrauterine strokes was suggested, but the literature on this area is sparse. A subsequent Australian study of candidate maternal or fetal thrombophilia-related genes that included 587 children with CP and their mothers and 1,154 healthy mother and child pairs identified no significant association of CP with these genes or any others studied after correction for multiple comparisons[131]. A nested case–control study conducted in California, USA, that was intended to replicate the previously identified links between several polymorphisms and CP in 127 affected children indicated an association of CP with the inducible nitric oxide synthase (iNOS)-231 T allele (which is involved in inflammation) and the *APOE*ε4* allele. Both associations were statistically significant at the 0.04–0.05 level, but neither remained significant after adjustment for multiple comparisons[125].

Multiple births. The prevalence of CP among twins is fourfold higher than among singletons[134,135], and this excess is greater for higher-order multiples[136,137]. Nearly all of this excess risk is accounted for by the lower gestational age and lower birthweights associated with multiple births[138,139], but the risk of CP is slightly higher even for full-term multiple births than for singletons born at term[140–142]. CP in one twin is associated with a greatly increased risk of CP in their co-twin: in one analysis of >20,000 twin sets in Norway, the twin of a child with CP had a 15-fold higher risk of CP than singletons[120]. Despite this elevated risk, fewer than 12% of twin sets are concordant for CP[143]. In the only two published series of identical twins, concordance for CP was 18–40%[144,145].

Little is known about the factors that contribute to disparate susceptibility to CP between co-twins, although factors such as birth order, birthweight discordance, gender and chorionicity have been examined[145–148]. Monochorionic placentation is thought to convey a higher risk than dichorionic placentation[149], as for the risk of congenital anomalies[150], but information on zygosity and chorionicity is rarely known for children with CP, making this thesis difficult to investigate in most databases. Genetics could have a role, but other factors are more strongly associated; for example, the death of a co-twin in utero is associated with a substantially higher risk of CP in the surviving twin[139,151,152].

Socio-economic status and correlates. Several studies have demonstrated that children who are socially disadvantaged are at higher risk of CP than those who are not[138,139,153–157]. For example, a higher prevalence of CP has been identified among African-American children than among other children[138,139], but this observation was only partially explained by differences in level of maternal education and was largely a function of higher rates of preterm birth among socially disadvantaged women[26,154]. However, although multiple indicators of social disadvantage are associated with an increased risk of CP, these relationships seem to be moderated or mediated by differences in gestational age, birthweight and/or their correlates (for example, maternal obesity[139,153,154], which is more common among women of lower socio-economic status[158–161]).

Analysis of a database of 6 million births in California, USA, revealed a dose–response relationship between pre-pregnancy obesity and CP: the relative risk of CP for the children of mothers classed as morbidly obese (2.7) was significantly higher than for those whose mothers were classed as obese (1.3)[162]. Large studies conducted

Hypocapnia
A condition characterized by low blood levels of carbon dioxide.

Chorionicity
Whether twins share the same placenta (monochorionic) or each have their own placenta (dichorionic).

in South Carolina (USA)[163], Norway and Denmark[164], and Sweden[25] produced similar results. In the Swedish study, the association was limited to infants born at term. Putative mechanisms for this consistent finding include the excess inflammation seen in obesity[165,166], placental dysfunction[167,168] and thyroid hormone deficits[169,170]. However, maternal obesity does not seem to be associated with an increased risk of CP among children who are born before the 28th week of gestation[171].

Pregnancy and congenital anomalies

Fetal growth restriction and maternal pre-eclampsia. Several studies have identified associations of CP with FGR in infants born at term or near term[172–174], in infants born late or moderately preterm[174] or in infants born at any gestational age[175]. The most definitive data come from the pooling of several national CP registers referred to as Surveillance of Cerebral Palsy in Europe, which revealed a significant fourfold to sixfold excess risk of CP among infants with FGR who were born at 32–42 weeks of gestation[176]. This finding is consistent with evidence from an Australian reconstructed population cohort study in which being small for gestational age and pregnancy-induced hypertension were associated with a twofold to ninefold increase in the risk of CP among all infants born after 27 weeks of gestation[175].

FGR and maternal pre-eclampsia have both been associated with a reduced risk of CP in studies of children born with low birthweight[177,178]. However, birthweight is inextricably linked with gestational maturity, which is strongly associated with CP; therefore, studies of children with a birthweight below a specified threshold will include growth-restricted newborn babies from more mature gestational age strata, who have a lower risk of CP than infants of lower gestational ages[179]. Population-wide studies that include infants of all gestational ages do not reproduce this anomaly[118,176,180].

This issue particularly affects studies of pre-eclampsia and CP. A study conducted in Australia showed that pre-eclampsia seems to provide a strong protective effect against CP in infants with low birthweights, but that no association with CP is observed in a sample defined by truncation of gestational age rather than of birthweight[181]. Confounding of FGR with gestational age seems to be reduced, if not completely avoided[182], by selecting samples of preterm infants on the basis of truncated gestational age rather than truncated birthweight, a practice that is becoming more common[183] but is still not universal[184].

Infection. Maternal infections can lead to CP by transmission of pathogens to the fetus (even without a detectable maternal inflammatory response[185]) and by induction of persistent systemic inflammation that can sensitize the brain to subsequent insults[186–188]. Infections such as toxoplasmosis, rubella, cytomegalovirus and herpes simplex virus during pregnancy have been associated with increased risks of CP[189–191], but these agents account for only a small fraction of CP cases in HICs. A subtype of CP that is associated with microcephaly has been reported as a result of perinatal mother-to-child chikungunya virus infection[192]. Zika virus infection in utero can damage the fetal brain[193], but the magnitude of the contribution of Zika virus to CP is not yet understood. To date, seven case-series and one cohort study have examined whether children with clinical evidence of congenital Zika virus infection exhibit early indicators of motor dysfunction and epilepsy; in total, 54% of these children had seizures and all of them were judged to have abnormal motor development after follow-up periods of 3–12 months[194].

The presence of several nonspecific indicators of infection, such as maternal fever[195–197], maternal receipt of antibiotics[198] and chorioamnionitis[197,199,200], close to the time of delivery have been linked to an increased risk of CP. Infections earlier in pregnancy have often been associated with CP as well[201–204], but not all studies agree[205].

Birth defects. Two lines of evidence indicate that developmental aberrations similar to those that cause birth defects are involved in an appreciable fraction of CP cases. First, imaging studies of children with CP have shown that cerebral malformations, which are often unsuspected before CT or MRI, are not infrequent. One systematic review of the topic showed that such malformations were found in 10% of children with CP, mostly in children who were born at term[206]. Several different brain developmental defects seem capable of producing CP, especially neuronal migration disorders[207], such as schizencephaly[208] and polymicrogyria[209]. Interestingly, cytomegalovirus infection might underlie these neuronal migration disorders in some instances[191,210]. In general, the brain malformations involved seem to arise from a wide variety of genetic and environmental insults, are not rare in CP and can be congenital or acquired[211]. Intrauterine infections are associated with congenital anomalies; the most recently identified association is with Zika virus infection[212,213]. A detailed review of the development of these abnormalities is available elsewhere[51].

The second line of evidence is the frequent presence of malformations outside the nervous system in children with CP. The NCPP showed that such malformations are observed threefold more often in children with CP than in healthy children, a finding that has been confirmed in subsequent studies[214–216]. Hypertensive disorders of pregnancy are associated with congenital malformations, in particular congenital heart defects[217,218], as are indicators of thyroid dysfunction[219–221]; each of these factors are associated with FGR, CP and other neurodevelopmental disorders (possibly reflecting mitochondrial dysfunction[222]). A study conducted in Australia found that 53% of children with CP and severe FGR who were born at or near term had a major birth defect[180].

Perinatal risk factors

Perinatal stroke. Perinatal stroke, which occurs between late gestation and 28 days after birth, might account for as much as half of hemiplegic CP in infants born at term[223,224], whereas children with other CP subtypes often have multifocal or more diffuse injury. The most common form of perinatal stroke is thrombosis in the arterial distribution, usually in the middle cerebral artery, but periventricular venous infarction can

Schizencephaly
A birth defect characterized by abnormal clefts in the cerebral hemispheres of the brain.

Polymicrogyria
A birth defect characterized by abnormal ridges and folds in the brain.

contribute[225,226]. Most perinatal strokes are ischaemic, but haemorrhagic strokes can occur, sometimes as a complication of ischaemic injury[227].

The causes of perinatal stroke are largely unknown. Perinatal stroke can be a complication of congenital heart disease[228] and bacterial or viral meningitis[229]. Placental factors such as chorioamnionitis[199], prolonged rupture of membranes[230] and placental thrombosis[231] have also been implicated. Pre-eclampsia and FGR are also risk factors[223]. Genetic predispositions to thrombophilia have been described above.

Kernicterus. Neonatal jaundice is the most common complication of the newborn period, usually caused by unconjugated hyperbilirubinaemia[232]. Unconjugated bilirubin crosses the blood–brain barrier in the first days of life and can damage several parts of the brain, particularly the basal ganglia and acoustic nuclei. The yellow staining seen at autopsy in this condition is the origin of the neuropathological term kernicterus. Symptoms of bilirubin-associated encephalopathy in newborn babies include lethargy, impaired tone, cyanosis, vomiting and absence of the suck reflex[233]. Chronic bilirubin encephalopathy manifests as aberrant processing disorders (particularly hearing impairment) and CP.

CP that results from kernicterus is typically choreoathetotic or dystonic, indicating damage to extrapyramidal structures[233]. In preterm infants, kernicterus can occur with bilirubin levels that would not pose risks to infants born at term. Kernicterus was once a common cause of CP[234,235], but in HICs, the number of cases of CP associated with kernicterus has declined substantially owing to prevention and better management of newborn hyperbilirubinaemia. Kernicterus remains a notable cause of CP in LICs[236,237].

Prevention of cerebral palsy

Magnesium sulfate

Case–control studies conducted in the 1990s suggested that magnesium sulfate ($MgSO_4$), which is administered in pregnancy to treat pre-eclampsia and in preterm labour to slow contractions, reduces the risk of CP in infants born preterm[238–240]. Modest support for this hypothesis was provided by some cohort studies[240] but not others[241,242]. A concern in all such observational studies was confounding by indication[78] — the possibility that recipients of $MgSO_4$ were at an inherently lower risk of CP, given that maternal pre-eclampsia has been associated with a lower risk of CP in studies of infants with truncated birthweights[178,243–245]. However, the benefit of $MgSO_4$ was clearly demonstrated by the BEAM trial, in which the risk of CP in infants born before 32 weeks of gestation and who were randomly assigned to receive $MgSO_4$ during labour was nearly 40% lower than among infants of the same gestational age who received placebo[246,247]. Two meta-analyses of randomized trials converge on an estimated 30% reduction in the risk of CP as a result of $MgSO_4$ administration[248–250]. A similar reduction was reported in a meta-analysis of observational studies[251].

Canadian, British, American and Australian obstetric societies and bodies have issued clinical practice guidelines that recommend $MgSO_4$ for fetal neuroprotection in the setting of imminent preterm birth at <32–34 weeks of gestation[252]. Implementation of these guidelines might be a contributor to the reduction in CP prevalence among children who have low birthweights in many HICs[3]. Nevertheless, $MgSO_4$ can cause maternal adverse effects[248], such as respiratory depression, hypotension and confusion, and questions remain about the optimal timing of administration[253], dosage[253,254] and duration[255,256], and modifiers of therapeutic efficacy (for example, maternal obesity)[257,258].

Therapeutic hypothermia

A series of randomized trials with consistent results have shown that lowering of body and/or head temperature by 2°C for 48 h, beginning in the first few hours after birth, can reduce the risk of and mortality from CP in children who are born after 36 weeks of gestation and who have hypoxic–ischaemic encephalopathy[259,260]. All trials enrolled infants with signs of encephalopathy and indicators of fetal and immediate neonatal distress that are thought to reflect asphyxia. Therapeutic hypothermia is now used internationally[261,262] and has become the standard of care in many centres in HICs. Trials are underway to determine the safety and efficacy of cooling therapy in low-income and middle-income countries (LMICs)[263] and in infants whose treatment was delayed beyond the first few hours. Whether head cooling would be effective in infants with neonatal encephalopathy that is not associated with evidence of hypoxia or ischaemia is an open question.

Among infants who are born at term or late preterm and who have moderate to severe encephalopathy, hypothermia improves survival and neurodevelopmental outcomes, including the development of CP, at 18 months of age[257], but CP is not eliminated altogether by this treatment. Children with severe newborn encephalopathy remain at increased risk of severe neurodevelopmental impairment despite the treatment[264]. Preterm birth and comorbid exposure to clinical or histological chorioamnionitis (or the correlates of each) are associated with a reduced response to hypothermia[265].

Attempts to combine cooling with adjunctive therapies to provide additional benefits are underway[266,267]. For example, 1,000 U/kg erythropoietin administered intravenously in three doses (immediately after birth, at 24 h and 1 week later) in conjunction with hypothermia is well tolerated and produces plasma concentrations that are neuroprotective in animals. However, a large efficacy trial is needed to determine whether this add-on therapy improves outcomes in infants undergoing hypothermia[268].

Investigational therapies

Various other therapies for CP have been tested and are under investigation. Caffeine is one of the most commonly prescribed medications in neonatal intensive care units as a treatment for apnoea[269]. A Canadian multicentre trial of caffeine in premature infants with apnoeic episodes indicated a reduction in the risk of motor and cognitive impairment with the treatment. The finding was statistically significant at 18 months[270] but not at 5 years[271].

Melatonin treatment in combination with hypothermia has been compared with hypothermia alone in one small trial ($n = 15$ in each arm) in infants with birth asphyxia[272]. The results hinted that melatonin improved survival during 6 months of follow-up and lowered the risk of seizures and indicators of white matter injury assessed at 2 weeks after birth. A trial of melatonin in preterm birth before 28 weeks of gestation is ongoing[273].

Erythropoietin has been studied in four randomized trials in infants born very preterm or who are very small. The treatment seemed to reduce the proportion of children with Bayley Mental Development Index scores <70 at follow-up, but the treatment did not affect the risk of CP[274].

Finally, stem cell therapies for CP are also under investigation. These studies are not yet at a sufficiently advanced stage to discern the effects of the treatment on CP[275,276], but evidence from small studies hints at benefits for some children[277].

Early diagnosis and intervention

The age at which a CP diagnosis is validly, reliably and fully ascertained by ruling out transient or progressive motor problems is controversial. Long-standing evidence indicates that a proportion of motor problems detected before the age of 1 year (for example, developmental delay, coordination problems and transient dystonia) resolve by school age without intervention[278–282] and that a small fraction of motor disability in children of school age is the result of progressive motor pathology (for example, in metabolic disorders[283]), neither of which fits the current model of CP. Clinical prediction models and neuroimaging have been used to diagnose CP before the age of 2 years, but further research is necessary.

Clinical prediction studies

Few studies have repeatedly assessed CP status over the first several years of childhood among the general population. Evidence from two studies suggests that a diagnosis of CP at or before a child's first birthday is unreliable[280,281]. In the largest study to date, which included 37,000 children, 45% of those who were diagnosed with definite CP at their first birthday 'outgrew' their motor problems by the age of 7 years[280], and fewer than 3% of infants who were thought to have probable CP at age 1 year had CP at age 7 years. It is important to distinguish between CP diagnosed at an early age solely on the basis of neurological findings and CP accompanied by clear evidence of a disability. Thus, a diagnosis made after ~2 years of age is more reliable[284], particularly when the motor problems are disabling (for example, an inability to walk five steps unaided or a need for physical assistive devices). However, in a study of children who were born preterm and weighed <2,000 g at birth, diagnosis of non-disabling CP was not a stable diagnosis until after 6 years of age[285]. This instability of diagnosis at the milder end of CP probably explains why some, but not all, CP registers conduct regular clinical reassessments at the age of 5 years to ensure diagnostic accuracy[286].

Claims that accurate identification of children who are at high risk of CP is possible at just a few months of age are increasing in the literature. However, clinical prediction studies have often assessed CP in combination with other disorders or used other proxies for a diagnosis of CP, such as an interim clinical diagnosis of a high risk of CP before a true diagnosis is confirmed[287,288]. A review published in 2017 concluded that CP could be diagnosed on the basis of the absence of so-called jittery movements in infancy[287], but the conclusions were based largely on expert opinion, most of the reviewed studies defined CP in combination with other motor problems, and none included data beyond the age of 2 years (see the appendix in the review[287]). The use of various definitions of 'high risk of CP' has hampered direct comparisons between studies. For example, of 12 studies that focused on motor dysfunction (see a review of these studies[288]), the outcome assessed in 6 was CP 'or other disorders', and in 5 the clinical decision relied on clinical impressions, intelligence or development quotients; in only 1 of the 12 was CP assessed alone. In addition, the majority of these studies do not include follow-up of children at or beyond 2 years of age, and most are not population-based or geographically representative of the general population or a targeted high-risk group.

In some studies in Australia and Europe, use of the General Movements Assessment in high-risk patients has indicated a high sensitivity and specificity for the prediction of a high risk of CP. These findings have prompted the Australian investigators to recommend widespread adoption into clinical practice[289]. However, given that decisions about diagnostic tests should be made on the basis of patient benefits[289], we feel that additional research is needed, as do others[290]. Indeed, although some evidence indicates that early detection and intervention can improve some cognitive outcomes[291], the improvements observed in motor dysfunction are much more modest[287,291], and the evidence for a benefit is limited by a dearth of high-quality trials[292].

Neuroimaging studies

We have discussed the use of neuroimaging in detail in a previous review[293], in which we concluded that neuroimaging is not required for diagnosis of CP because the disorder is based on clinical findings, and the principal contribution of imaging is to the understanding of CP aetiology and pathogenesis. We also concluded that imaging studies were less informative than they could be, largely because study designs were rarely based on generalizable samples.

Since this previous review, several population-based neuroimaging studies have provided evidence that the occurrence of white matter injury has declined and that of grey matter injury has increased, whereas the prevalence of malformations in children with CP remained about the same. However, the authors of a review of these studies[294] concluded that a dearth of standardized protocols and terminology were probably responsible for the heterogeneity of these findings (for example, there was no minimum or standard age at assessment).

The well-designed Generation R study of a geographically representative sample from the Netherlands,

published in 2017, highlighted a diverse array of research questions that can be addressed by merging neuroimaging with developmental neuroscience and epidemiology[295]; an example is an ongoing effort to develop growth curves of optimal brain development. Nevertheless, studies of selected populations continue to be more common, and these types of studies were considered in a 2018 systematic review of early MRI for detection of motor outcomes at term-corrected age in children born preterm[296]. This review identified a high sensitivity and specificity of MRI for detection of CP or other motor problems, but the findings were difficult to generalize because not all participants had CP, and few studies were of unselected, sequentially recruited, representative infants. Instead, most were carried out in tertiary centres with high-risk patients, and recruitment rates of eligible infants were as low as 17% in some settings. Consequently, further research is needed to establish the effect of sample composition[297] and the clinical relevance of MRI in early identification of CP.

Complexities in cerebral palsy epidemiology

Accumulation and interaction of insults

CP can often be the result of combined insults, but not all insults are equally influential and some probably have context-specific effects; the importance of timing and co-occurrence of different insults is unclear, although several examples have been studied. The combination of antenatal inflammation with postnatal systemic inflammation is associated with an increased risk of CP in children born before 28 weeks of gestation[298], as are combinations of postnatal systemic inflammation and high or low levels of proteins that are related to angiogenesis and thyroid dysfunction[299,300]. FGR and/or very preterm birth seem to make infants particularly susceptible to multiple-hit phenomena that involve white matter injury and its correlates because these infants tend to have more vigorous postnatal inflammatory responses than do other infants[301–303]. Chronic placental inflammation followed by acute fetal inflammation followed by neonatal illness is similarly associated with cerebral white matter injury in infants who are born before 32 weeks of gestation[304].

Additional evidence that accumulation of insults is involved in CP comes from a population-based study of infants with birthweights <2 kg with risk factors associated with ventilator use. This study showed that the risk of CP increased incrementally with addition of three ventilatory risk factors: hyperoxia, hypocapnia and ventilation for longer than expected for gestational age. The presence of one ventilatory risk factor was associated with an 11% risk of CP, two risk factors were associated with a 35% risk and three risk factors were associated with a 57% risk[88]. In a study of over 200,000 pregnancies, pre-eclampsia, neonatal infection, presumed birth asphyxia and neonatal illness were cumulatively associated with an increased risk of CP[213]. Similarly, a study of nearly 6,000 infants with very low birthweights in Taiwan indicated a strong interaction between sepsis and postnatal hypoxic–ischaemic events. Infants with sepsis alone had a 10% risk of CP, but adding one, two, three or four events increased the risk of CP to 17%, 27%, 40% and 55%, respectively[305].

Hidden from view

Although a small fraction of CP is caused by obvious postnatal events, such as meningitis or head trauma, at least 90% of the factors that predispose infants to CP in HICs are no longer operative and are often no longer detectable after the perinatal period. Furthermore, many prenatal causes are often hidden from view because the inflammatory stimuli that seem to contribute to preterm birth, the silent strokes and the hormonal changes operate under the cover of amnion and uterus. However, a firm diagnosis of CP cannot usually be made until the child's nervous system is mature enough to display the motor deficits that describe CP, usually at about the age of 2 years. By the time a child is diagnosed with CP, the history of the pregnancy and the perinatal period can be reconstructed only from medical records and maternal recall, which are useful but have limitations (for example, recall bias and reliance on clinical notes). Prospective data collection can improve the precision of data about exposures, but to date, few prospective preconception or pregnancy cohort studies have included follow-up of children to school age or beyond to assess neurodevelopmental outcomes. Consequently, delivery and neonatal factors have received much consideration, partly because of the dearth of quality evidence about earlier antecedents of CP. This bias has important implications because pre-pregnancy and early pregnancy risk factors (such as body weight) and their correlates can influence the capacity for delivery-related and postnatal factors to provide information about the risk of CP (for example, maternal age)[306].

One disorder or many?

The relationships between clinical entities that are used as diagnoses and established pathophysiological pathways vary greatly. Some disorders are defined by abnormalities at the molecular level, such as sickle cell anaemia, but many are defined by their clinical appearance[307] and often represent the common end point of various pathophysiological changes. Use of such disease entities often continues despite recognition of their heterogeneity because the entity is useful in clinical management; for example, whether a stroke was ischaemic or thrombotic matters little for the rehabilitation of a patient.

As discussed above, the term CP includes entities that are apparently caused by multiple pathways, yet the single term persists. Some epidemiologists have referred to 'cerebral palsies'[308] and the current definition refers to a group of disorders to indicate the heterogeneity[309,310], but this usage has not taken hold in clinical settings, largely because the traditional phenomenological entity and its observable subdivisions are clinically useful for prognosis and management. Novel classification schemes based on topography have not consistently improved reliability in describing CP subtypes[311]; therefore, the field has moved away from classification according to the underlying impairment and towards a focus on functioning[312–315]. What this trend means for aetiological research remains to be seen.

The temptation, which is consistent with the current emphasis on precision medicine, is to divide the condition into narrower subdivisions that are more likely to be aetiologically homogeneous. However, when a clinical entity is fairly uncommon, as is the case for CP, creating finer and finer subdivisions makes investigation of aetiology very difficult. Even in the collaborative perinatal project, which included 50,000 participants, analysis did not consider much beyond the diagnosis of CP itself; the only difference emphasized was that between children with birthweights above and below 2,500 g (REFS[53,316,317]). Two initiatives could help to overcome this difficulty: one is the newly initiated integration of Danish and Norwegian birth cohorts (referred to as MOBAND)[318], which aggregates the medical records from 200,000 well-studied pregnancies and births and links them to the national CP registers of those countries, and the other is the Global Pregnancy 'CoLaboratory'[319] (CoLab; see Related links), a network of investigators from multiple population-based register and cohort studies who seek to facilitate standardization of data collection instruments and study designs and to enable data sharing to solve complex questions about major pregnancy complications and their sequelae. However, no consensus has been reached on the kinds of subdivisions (for example, gestational age at birth, type of motor abnormality or distribution of affected limbs) that would lead to the greatest aetiological insight[318].

Specificity is problematic for all symptom-based case definitions[320], and mis-specification of heterogeneous syndromes as singular entities can mask important findings about aetiology[321], including evidence of therapeutic benefits[322]. Subtypes of a syndrome can be established in three ways. The first is to demonstrate different risk profiles. The second is to establish that the underlying morbid anatomy or pathophysiology differs. The third is to demonstrate that a subset of a disorder can be prevented (as in the case of kernicteric brain damage prevented by control of bilirubin blood levels). In reality, none of these strategies alone will provide a definitive answer about subtypes of CP because some similarities and differences in the antecedents, neuroanatomy and efficacy of interventions are observed across subtypes.

Several lines of evidence indicate that environmental and maternal characteristics are differentially associated with different subtypes of CP. Some studies have provided evidence that social status[323] and maternal body weight[324] are associated with increased risk of hemiplegia, but not other CP subtypes. Consideration of maternal age also influences which factors are most strongly associated with increased risk of different types of CP[306]. Stratification of infants according to postnatal occurrence of persistent systemic inflammation seems to provide different information about the risk factors associated with quadriplegia[299,300], but not other CP subtypes, among children who are born before the 28th week of gestation. The CP risk factor profiles for different subtypes among infants with FGR also differ from those for infants with normal growth[325], especially for children with CP who have FGR and are born at term, among whom rates of congenital birth defects are very high[180]. Some evidence indicates that patterns of childhood growth differ according to CP subtype[326]. Finally, the antecedents of the severest forms of CP seem to differ from those of less severe motor disorders[327], and in some studies the profile of comorbid neurodevelopmental disorders differs by CP subtype (for example, the co-occurrence of intellectual disability and epilepsy seems to be more likely to develop among children who develop hemiplegia than among children who develop other types of CP)[328,329].

Despite this evidence, without agreement on reliable definitions of CP subtypes, the findings are difficult to interpret and hard to replicate across populations with different background prevalence of contributing factors. Integration of findings from hypothesis-driven clinical studies and preclinical studies is most likely to inform about the appropriate subdivision of neurodevelopmental syndromes that are rooted in pregnancy.

Future directions

Large public health interventions (for example, improved access to clean water, hygiene and other interventions that focus on common infections before, during and between pregnancies) combined with rigorous emphasis on hypothesis-driven data collection in LMICs could probably teach us a lot about CP aetiology. A similar focus on periconception modifiable risk factors that influence the early gestation milieu that contributes to increased risk of CP would be informative in LICs and HICs — for example, a focus on alleviating social disadvantage. Overall, there is a pressing need to understand how the environment influences brain development, how it affects placentation and later placental functioning while the brain grows, and why specific environmental factors seem to raise the risk of CP and precipitating pregnancy disorders.

Current knowledge of the pathogenesis of CP during embryogenesis and placentation rests largely on evidence from models in cell lines and embryos and on downstream placental histopathology and related clinical syndromes[330–332]. However, we do not know whether these methods represent in vivo pathogenesis or how to translate emerging preclinical information into population-level benefits. Maternal and fetal blood-based profiling and imaging techniques are much less informative about pregnancy disorders before the 15th gestational week[333,334], which seems to be a key aetiological window[333,335–337]. Emerging technologies, such as trophoblast retrieval and isolation from the cervix[338,339], might provide relevant information about early placental development and function in ongoing pregnancies, but large follow-up studies are needed to discern the relevance to CP and its correlates. Single biomarkers are unlikely to be very useful clinically for large sections of the general population, but molecular profiling to establish the timing and order of processes that disrupt physiological homeostasis during pregnancy might prompt better thinking about aetiology and prevention. For example, consideration of key concepts from physiology, such as homeostasis, regulated systems

and redundancy, as major intellectual tools to understand aetiology might improve our capacity to formulate and test hypotheses[340] (details of specific examples are available elsewere[341–343]).

Infection and other inflammation-inducing exposures before and after very preterm birth are associated with an increased risk of CP via complex pathways[92–94,298,344]. Some evidence suggests that the risk of CP and comorbid brain disorders is decreased by administration of exogenous proteins that reduce neuroinflammation, possibly by controlling the regulation of systemic inflammation and neuropoietin signalling[116,345,346]; however, meticulously designed, hypothesis-driven preclinical and clinical studies will be needed to translate these observations into population-wide benefits[322,347].

We cannot overstate the importance of preterm delivery and FGR[348], which are themselves heterogeneous syndromes[349,350], in the CP risk profile, but large studies of infants born at term, which account for approximately half of all CP diagnoses, might enable easier identification of antecedents, in part because the number of indicators of different pathological processes increases as the gestational age at delivery decreases and, consequently, so does the complexity[351–353]. Population-based studies of pregnancies at all gestational ages will continue to be the most helpful. CP registers and emerging consortiums that focus on standardized data collection, analysis and sharing to study complex pregnancy disorders (for example, CoLab) are beginning to enable the kind of research necessary to examine these possibilities more closely[354,355].

Conclusions

We know that the aetiological factors involved in most cases of CP operate between conception and a few weeks after birth, yet identifying preventable causes of CP has proved difficult. Several risk factors have been identified, but they overlap and interact with each other in ways that are not easy to dissect. Nevertheless, important to keep in mind is that the young 21st century has witnessed the development of two preventive measures for CP: $MgSO_4$ treatment for mothers at risk of preterm delivery, and head and/or body cooling for infants born at term with neonatal encephalopathy.

The ongoing formation of large national databases of data from unselected pregnancies in combination with multidisciplinary collaboration to integrate these resources for the study of complex diseases in pregnancy gives hope for new discoveries; these data include real-time surveys of exposures in pregnant women, and biological specimens such as archived serum, urine and newborn blood spots. This information is invaluable when accompanied by follow-up information about the presence or absence of CP in the offspring, or when linked to records of CP. If the modest information about pregnancy that is currently available from maternal recall and medical records years later can be supplemented with data sources that provide clear information about exposures to infections, nutrients, environmental toxins, allergens and many other phenomena during pregnancy, our limited knowledge could give way to an era in which the widespread prevention of CP is a feasible goal.

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