Cerebral palsy: causes and prevention

A study of current knowledge and research funding

William Little Foundation
Cerebral palsy: causes and prevention

A research review by the William Little Foundation

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William Little Foundation
The review of current knowledge was prepared for the William Little Foundation by Dr AnnieBelle J Sassine, a medical researcher at Imperial College London specialising in public health nutrition, epidemiology, statistics, maternal health and pre-term birth.

Dr Sassine collaborated with WLF Chief Executive Jonathan Badger to produce the report on research funding.

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Introduction

The William Little Foundation was established in 1990 (as “the Little Foundation”) by Ian Dawson-Shepherd, the founder of Scope, to fund research into the causes and prevention of cerebral palsy and other developmental disorders. Named after Dr William John Little, the nineteenth century physician who was the first to define the symptoms of infantile cerebral palsy (CP), the Foundation has been fortunate to work with some of the world’s leading researchers into CP and to enable some significant insights into both its causes and its prevention.

While some progress has been made in reducing the onset of CP, the research community is conscious that research has progressed very slowly in the last 20-30 years: we still lack a robust understanding of its causes and only a few therapeutic advances have been made in reducing risk or improving recovery.

While the Foundation has been able to contribute to greater understanding, particularly through the work of Dr Martin Bax and Professor Michael Crawford, it has also become clear to us that there is a lack of a central resource for those with a professional interest or who have been directly affected by CP that defines and describes the vital research that has been and is being undertaken globally. This community has also emphasised the lack of accurate information for the public on the risks of CP.

This review, prepared for the Foundation by Dr AnnieBelle Sassine of Imperial College, London, is a first step towards establishing this resource – highlighting nearly 150 important studies that have had a material impact on our understanding of CP.

As well as identifying what research was either underway or had recently reported, we also intended this review to help us identify the gaps in research
activity based on what we now understand about CP. The second part of this report also reviews the state of funding of CP-related research globally. Both elements are based on publicly available information and data, and there are therefore certain to be gaps. However, the report does provide a sufficient picture to raise concerns for anyone with an interest in combatting CP.

At the heart of the concern is the oft-used observation that, as a comparatively ‘rare’ condition, CP does not merit the research investment of conditions with higher incidence and prevalence. In truth, there is as yet no conclusive measure of CP’s prevalence, not just in the developing world but in the developed world. Moreover, as more babies survive preterm birth due to other medical advances, the incidence of CP may rise in the future. This issue is highlighted by continuing calls by fellow organisations like Action Cerebral Palsy for national CP registers: a call to which the Little Foundation adds its voice. The rarity argument also ignores the disproportionate social cost that is CP’s legacy: the condition is lifelong and frequently involves 24-hour care for those affected. National social and healthcare budgets and those of medical insurance companies for those not supported by a national health service continue to be stretched by the need for ever-increasing provision: CP costs the UK alone £1.6 billion every year. Yet the amount spent annually on research is worryingly small: the figure for the UK is less than £5 million. Our separate funding report looks in more detail at the funding agencies (government and philanthropic) in more detail, revealing a similar picture of cost vs investment disparity worldwide.

If the CP sector is unable to develop the mass of research activity, it is going to need to take a more strategic approach: indeed, we have heard a clear message from the professional community that there is a need for a strong, credible voice, advocate and influencer for CP research into prevention. Our analysis has identified four gaps in research focus where we feel attention could usefully be given in the expectation of a high degree of impact:
1. We need better data on CP prevalence and risk factors, particularly from low- and middle-income countries
2. There is an urgent need for large-scale multi-site prospective collaborative studies looking at maternal nutrition/infection and the risk of CP
3. We need more evidence to show that the origins of CP trace back to the early pregnancy period
4. There is a need for studies to test the relationship between gestational diabetes and CP

This review and its analysis will inform the further evolution of the William Little Foundation’s research strategy and spur our efforts to generate the funds to enable this. We hope you find it similarly helpful.

Lord Hameed of Hampstead
Chair of Trustees
William Little Foundation
Current Knowledge
DEFINITION OF CEREBRAL PALSY

Cerebral palsy (CP) is the most common cause of motor disability in early childhood (1). CP is a lifelong neurological disorder of movement and posture secondary to non-progressive malformations in the developing fetal or infant brain (2, 3). The brain injury may occur in utero (4-9), at birth (10, 11), during the postnatal period (12) or in early childhood (13).

CP is often accompanied by intellectual deficits, disturbances of sensation, perception, and coordination, epilepsy, and secondary musculoskeletal problems (2). Children with CP can also be at risk of non-communicable diseases in adulthood due to lack of physical activity and muscle weakness (14, 15). CP is a very heterogeneous disorder presenting with different clinical types and brain imaging patterns (16). Consequently, motor impairments can vary widely between affected children; however, the poor quality of life and discrimination faced by these children are often similar (17, 18).
PREVALENCE AND TRENDS

The reported incidence of CP can range from 1.5 to more than 4 per 1,000 live births or children of a defined age range based on studies from around the world (1, 19-23). The estimated prevalence from registries has been static over the past three decades with reported incidences ranging between 2-3 per 1,000 live births for the developed world (24-31) and 2 per 1,000 live births for the UK (28, 32). As for low and middle-income countries (LMIC), the data on CP prevalence appear to be very scarce and systematic reviews seem to include data for high-income countries (HIC) mostly (33), although the prevalence of CP in LMIC is suspected to be higher than HIC (22, 23, 34-37).

Extremely preterm birth infants (born before 28 weeks of gestation) are greatly affected by CP, with an estimated prevalence of 40-100 per 1000 live births (24). The increase in the survival of very premature infants has resulted in a modestly increased prevalence of cerebral palsy in developed countries from 1975-1999 that has now subsided (20).

Despite improvements in antenatal, delivery and postnatal care, CP incidence in term infants has not notably changed over the last 30 years (38, 39). In fact, term infants (>37 weeks of gestation) account for 50 to 65% of CP cases although paradoxically preterm birth is a strong risk factor of CP (34, 40-42).

Data from European database (38, 43) in addition to USA (44), Australia (45), and China (46) show that more than 50% of CP cases are among normal birthweight babies (>2500 g). Research on CP has primarily focused on very preterm infants due to the strong association between preterm birth and risk of CP. However, infants born at or after 35 weeks of gestation contribute to two thirds of CP cases and are considered the most under-researched group with the majority of the literature fixating on birth asphyxia as the major cause of CP among this group (45).
TYPES OF CEREBRAL PALSY

CP is a heterogeneous disease presenting with different types. The most common type is spastic CP accounting for 70% of cases and affects muscle control and coordination. It is the result of injury to the motor cortex and the pyramidal regions of the brain that link the motor cortex to the spinal cord, resulting in muscle stiffness and tightness. It includes three subtypes depending on the body area affected: hemiplegia, which affects one side of the body, with the upper body usually more influenced; diplegia which affects the lower extremities of the body (the legs); and quadriplegia which affects all four limbs.

Dyskinetic CP is the second type of CP prevailing in 10-20% of cases. It is responsible for slow and uncontrollable movements of hands, feet, arms or legs that can result in severe changes in muscle tone and posture and can be accompanied by learning disabilities and frequent epilepsy (47, 48).

Ataxic CP (5-10%) is the least common and is characterised by difficulties in balance and coordination and results in shaky movements that can affect writing and speech.

Exhibiting one or more type of CP is classified under Mixed CP (10%).

Rosenbaum et al. in their ground-breaking report that altered the definition of CP advised that classification of CP should be reliable and very specific to the symptoms. Indeed, CP has varying degrees and can range from a minor limp to severe incapability of movement and communication (2).
CAUSES

The epidemiologic risk factors for CP have been substantially investigated with research dating back to the 1970s and the risk pattern differs by CP subtype. The most known risk factors to date are summarised below:

Obstetric mishaps and birth asphyxia

The earliest clinical identification of children with cerebral palsy established two factors: preterm birth and oxygen deprivation during difficult birth.

For a long time, cerebral palsy was thought to happen at birth and was considered a product of obstetric mishap, particularly birth asphyxia. Intrapartum obstetric mishaps include nuchal cord, meconium in the amniotic fluid, mid or high forceps, placental and cord abnormalities such as placental abruption and cord prolapse, most of which are asphyxia-related due to their obstruction of blood oxygen levels to the fetal brain (49). Birth asphyxia in most studies report an attributable risk of less than 10%. Data from the National Collaborative Perinatal Project (NCPP), which studied the relationship of pregnancy and labour events to CP, concluded that pure asphyxial damage was in less than 10% of all CP cases (50, 51). This is further supported by a study conducted in Australia reporting 8% of cases of CP to be attributed to birth asphyxia (52). However, it should be noted that this fraction is more elevated in developing countries with limited access to healthcare. Birth asphyxia is still a major cause of mortality in developing countries and 99% of deaths attributable to intra-partum hypoxia occur in LMIC (53, 54), partly due to lack of access to healthcare or presence of a skilled attendant. A study conducted in Zambia showed that 31% of those who had birth asphyxia showed abnormal neurologic signs (55). Another study from Nepal showed that 18% of birth asphyxia survivors had neonatal encephalopathy (56). However, it would be hard to conclude whether the higher
fraction of CP attributed to birth asphyxia in developing countries is actually true or is an effect of the high prevalence of birth asphyxia reported.

Consequently, different methods to identify fetal hypoxia during labour were introduced in the hope of reducing the incidence of CP, particularly electronic monitoring of fetal heart rate. Although this widely used technique contributed to an increase in surgical deliveries for fetal growth restriction, it failed to reduce the incidence of cerebral palsy at birth over the past three decades (34).

Clark and Hankins stated in their CP trend analysis study, “Despite a five-fold increase in the rate of Caesarean section based, in part, on the electronically derived diagnosis of ‘fetal distress’ cerebral palsy prevalence has remained stable”(39). This was further strengthened in 2004 by Bo Jacobsson and Gudrun Harberg, pioneers in CP research, who concluded that “Evidence suggests that 70 to 80% of cerebral palsy cases are due to prenatal factors and that birth asphyxia plays a relatively minor role (<10%)”(57). In 2007, Martin Bax published ground-breaking results from the European Cerebral Palsy Study about Magnetic Resonance Imaging (MRI) brain findings in 351 CP cases. Half of the CP cases were born at term. The MRI scans showed significant white matter damage of immaturity in 43% of the cases as well as lesions (22.2%) and malformations (9.1%). White matter damage is thought to occur before 34 weeks of gestation and malformations are indicative of earlier cerebral damage. This goes to show that in infants who were born after 34 weeks of gestation, obstetric mishap or perinatal processes couldn’t have caused CP (58). Although prematurity and birth asphyxia are still significant contributors of CP (10, 59), recent evidence suggests that the majority of CP cases are attributable to factors operating earlier in the antenatal period (8, 9, 41, 42, 57, 60-62). The timing of the events and their relationship to the onset of CP is still very complex and not fully understood; nonetheless, intrapartum events are not likely the principal cause of CP, as previously thought.
Gestational age at delivery

Preterm birth has been considered the single largest risk factor for CP (63), manifested by the increased prevalence of CP with declining gestational age at delivery (64, 65). Recent studies show that late term pregnancies, with delivery after 42 weeks may also be at increased risk of CP (66). However, the question to be asked is whether gestation age at delivery is a direct cause for CP or only a reflection of a common antenatal cause? For instance, infants who are born prematurely as well as infants born with cerebral palsy are more likely to have been exposed to fetal inflammation. Could inflammation in this case be the underlying factor causing both preterm birth and CP?

Antenatal factors

Congenital anomalies and genetic variants, characterised by brain and cortical malformations, have been strongly linked to certain types of CP (67-70), as evidenced by birth defects occurring in 14-50% of CP children (70-72). Consequently, genetic risk factors, particularly chromosomal abnormalities, have been implicated in the aetiology of CP (16, 73-75), with the most recent evidence identifying disease-causing mutant genes in 14% of CP cases (76).

Non-genetic antenatal factors also play a major role. Multiple pregnancies (twin/triplets) (77, 78), untreated maternal hypothyroidism and thrombophilia (79-82), advanced maternal age (>35 years) (83), high parity, obesity (84), and preeclampsia (85-89). However further research is still required to confirm these relations.

The link between hypothyroidism as a risk factor for CP is becoming more established. Three large studies (England, Netherlands, USA) conducted on premature infants showed a strong association between low neonatal thyroid levels and adverse neurodevelopment outcomes (85-89). However, the link...
between hypothyroidism and risk of CP may be mediated by iodine deficiency. Iodine deficiency is a main contributor to hypothyroidism through its effect on thyroid hormones (T3 and T4), which are necessary for normal brain and nervous system development during pregnancy (90). There is increasing evidence for the link between iodine deficiency and neurological impairment/brain damage, which is thought to resemble CP (91-100).

Furthermore, a study conducted by Ahlin et al. showed that non-infectious risk factors such as not living with the baby’s father and gestational diabetes were strong independent predictors of CP, particularly spastic CP (101). A recent study conducted in Israel showed an increased risk of neuropsychiatric disease (including CP) in mothers who developed gestational diabetes during their pregnancy (102). In a study from Pakistan, authors reported that lack of antenatal care was associated with a high risk for spastic CP (103). Karen Nelson’s study showed that fetal growth restriction was another potential risk factor associated with the risk of CP in term babies born to mothers with normal blood pressure (4).

There is increasing evidence about the role of infection and the onset of CP. Intrauterine infection or inflammation has been strongly linked to CP (104). In fact, a case-control study conducted on term babies found that mothers who were exposed to severe infection during their pregnancy were 15 times more likely to give birth to babies born with spastic CP. The latest systematic review published by Cochrane reports that bacterial and viral infections during pregnancy may also have a role, further backed up by studies showing that urinary tract infections can impose a risk for CP (8, 105-107).

Other antenatal factors include placental vascular disorders and abnormalities, which were also shown to be associated with CP (104).

Bax et al. in their European MRI study of cerebral palsy (EMCP) discussed how nutritional, genetic, and inflammatory factors can lead to inadequate placental development, which predisposes the fetus to increased risk of hypoxic
ischemic events which in turn lead to white matter damage in the brain. Intriguingly, they uncovered all lesions detectable by MRI scans originated well before the time of birth. The authors emphasized that interventions around the time of birth might not decrease the risk of CP as cerebral damage would have already occurred (58).

Additionally, a recently published article (2019) explored associations between fetal exposure to maternal infection and the risk of autism, depression, and bipolar disorder in around 1,800,000 children followed up longitudinally up to 41 years. Results of the study showed that exposure to maternal infection during pregnancy increased the risk of autism and depression among children. This study is particularly important, given that CP is also a neurodevelopment disorder and often accompanied by co-morbidities such as behavioural and cognitive difficulties. This further emphasizes the need to understand the role of maternal infection in the onset of CP, particularly with increasing evidence hinting that CP could be the product of an ischemic prenatal stroke (108, 109). Stroke is the result of disrupted blood flow and inflammation resulting in a hypoxic region and scarring. Infection and nutritional imbalances are known to favour ischemia and inflammation (110-112).

This all plausibly suggests that CP may not be, as commonly perceived, a product of obstetric mishap.

**Perinatal factors**

Perinatal factors include placental damage approaching labour, birth asphyxia, and perinatal infection. Chorioamnionitis, defined as the inflammation of the fetal membranes due to a bacterial infection, has been consistently associated with CP in term infants (7, 8, 104, 113-115). In a recent meta-analysis, term/near-term babies born to mothers who were diagnosed with histologic chorioamnionitis had 4.3 times the risk of CP compared to babies born to normal healthy controls (116).
Placental abruption, characterized by the separation of the placenta from the inner wall of the uterus prior to birth, has also been linked to CP, possibly due to the loss of oxygen transfer to the fetus (7, 104). Factors related to the mode of delivery have been also implicated, in particular emergency Caesarean section as a risk factor for spastic CP (101).

**Neonatal events**

Events in the neonatal period have been also linked to the development of CP. These include acute intrapartum hypoxia, intraventricular haemorrhage, periventricular leukomalacia, meconium aspiration, neonatal stroke, seizures, sepsis, fetal infection, and particular syndromes and chromosomal abnormalities (57, 71, 103, 117, 118). Most neonatal events have been attributed to a higher risk of dyskinetic CP such as admittance to NICU, Apgar score, and neonatal seizures (101, 103) However, many cases of spastic CP have been also linked to neonatal risk factors; small head circumference has been associated with hemiplegic spastic CP (101) whilst neonatal infection in babies born at term was a strong and independent predictor of spastic diplegia and quadriplegia (107).

Although these neonatal events may occur independently, recent evidence shows that neonates who are exposed to an inadequate intrauterine environment could be highly susceptible to such subsequent intrapartum events- a so-called ‘double-hit model’ (5, 119).

**Nutrition**

One of the first pioneers in cerebral palsy research was Professor Paul Polani at Guy’s Hospital, he was an expert in medical genetics. His early works on CP concluded the absence of a specific genetic cause, suggesting rhesus haemolytic
disease as a potential risk factor, and leaving behind the possibility of infection and inadequate nutrition as plausible culprits (120).

Studies investigating the role of maternal nutrition in CP development in the offspring are very limited, despite considerable evidence linking maternal nutrition to brain development in pregnancy. Crawford et al. discovered that the brain is made up of essential omega-3 docosahexaenoic acid (DHA) and omega-6 arachidonic acid (ARA) (121-123), a finding that triggered numerous supplementation trials to assess the effect of essential fatty acids on preterm birth and brain development (124-128). Results from the FOSS trial conducted at Chelsea and Westminster Hospital showed that male infants born to mothers who were supplemented with brain-specific fatty acids ARA, DHA, and EPA had significantly larger total brain volumes, grey matter, corpus callosum and cortical volumes compared to the placebo groups. These MRI findings suggest a protective potential for essential fatty acids against hypoxic ischaemic injury, which normally attacks the grey matter area (129).

The lack of information on the role of nutrition in the onset of CP is quite surprising given that cerebral palsy is characterized by lesions in the developing brain. A review of supplementary trials in nutritionally-deficient populations that involved the supplementation of DHA, Vitamin D, folic acid, and/or iodine concluded that these may prevent many brain and central nervous system malfunctions (130).

One study in 1998 investigated the role of maternal diet during pregnancy in the development of CP using a semi quantititative food-frequency questionnaire administered by mothers of infants with CP (N=91) and matched controls (N=246). Results showed that maternal diet rich in fish and modest meat intake during pregnancy might reduce the risk of CP (131). The authors highlighted the need for future large multi-center cohort studies to assess the relationship between pregnancy diet and CP, which might be very difficult, as it would require a birth cohort of 100,000 over a period of at least 4 years (131).
In 2013, a study was published showing a link between impaired maternal immune system within 5 years before pregnancy and risk of cerebral diseases in the offspring (106). The authors stated that they were unable to account for the possible confounding effect of dietary factors, which have been shown to affect the immune system (106).

These studies, along with findings from the FOSS trial and Bax et al.’s study, suggest a strong role for brain specific fatty acids in neuroprotection and possibly preventive measures against neurodevelopmental disorders.
The identification of potential risk factors in the onset of CP has lead to the development of many preventive strategies stretching from antenatal to postnatal period (104, 132).

For antenatal and intrapartum interventions, treatment of pregnant women with magnesium sulfate (MgSO$_4$) for fetal neuroprotection significantly decreased the risk of CP by 32% based on 5 randomized controlled trials (RCTs) with a total of 6145 children (104). This intervention was considered of high-quality evidence of effectiveness. In fact, Karin Nelson’s observational study in 1995 showed that exposure to MgSO$_4$ was significantly lower in very low birth weight (VLBW) born with CP compared to VLBW controls (133). In April 2020, results from a multi-centre trial were published by a research group in Denmark who studied the effect of antenatal magnesium sulphate on cerebral palsy in infants born preterm. Findings showed that magnesium sulphate given to mothers before 32 weeks of pregnancy decreased the risk of moderate to severe CP in children (134).

There was medium-quality evidence for the harmful effect of giving prophylactic antibiotics to women in preterm labour with intact membranes as opposed to not giving antibiotics. Another ineffective and rather harmful intervention was the immediate delivery of women with suspected fetal growth restriction. They were at higher risk of CP than women whose birth was delayed (104). There is not enough evidence on the effectiveness of giving antenatal corticosteroids or antihypertensive drugs in the reduction of CP (104).

Very recently, a pre-clinical study in Australia supported by the Cerebral Palsy Alliance Research Foundation (CPARF), showed that low platelet count might weaken blood vessels in the brain and increase susceptibility to stroke and subsequent CP. The authors suggest that platelet monitoring may be an effective preventive measure against CP (135).
Hartman et al. just published a study in Cell Reports showing that MRI with hierarchal region splitting may help provide insight to selected newborns with salvageable lesions that can be responsive to human neural stem cell transplant and prevent cerebral infarct. Although these results are promising showing MRI as an important biomarker tool, clinical trials are required to confirm the success of stem cell interventions (136).

To our knowledge, there has been no study that tested the effect of nutritional interventions during pregnancy on the prevention of CP. There has been however a double blind RCT conducted by the University of Oxford (the DOLPHIN trial), which investigated the role of a nutrition supplement in 40 children with suspected CP in the UK (1 month-18 months). Based on the rationale that phosphatidylcholine is the most abundant brain phospholipid that comprises choline (uridine-5-monophosphate (UMP) and the long-chain polyunsaturated fatty acid DHA, the treatment group received a supplement containing DHA, choline and uridine. The trial did not find significant differences in cognitive and language performances between the supplemented and placebo groups (137).

As part of her PhD thesis at Imperial College London, Dr. Xia Zheng conducted a mice experiment to test the effect of DHA-enriched diet on improving outcomes of hypoxic ischemic encephalopathy (HIE) brain damage. Although her results showed improvement in DHA levels in pup brains of the DHA-enriched diet group, there was no neuroprotective effect through reduction of inflammation and apoptosis. However, she discusses that the lack of neuroprotective effect could be attributed to the insufficient sample size and low dose of DHA in the DHA enhanced diet in the study.

This further highlights the crucial need for studies investigating the role of nutrition, specifically brain-specific fatty acids and key nutrients such as choline, their dosage and the timing of interventions in the prevention of cerebral damage. Importantly, a recently published review provided compelling evidence for the synergistic role of DHA and choline in ensuring brain and eye health and authors
suggested a prenatal screening for DHA (138) and choline status to ensure maternal nutrient needs are met prior to pregnancy (139).
SUMMARY

The current state of evidence on CP suggests a plausible role of prenatal infection in the onset of CP. Preterm birth is still a powerful independent risk factor for CP, but recent trend analysis for CP prevalence indicates that almost half of the cases of CP occur in babies born at term. Despite improvements in fetal monitoring and the consequent dramatic increase in the rates of Cesarean Sections, the rate of CP among term babies has not decreased and the MRI scans on infants with CP suggest that the timing of lesions traces back to the prenatal period. Consequently, the long-term focus on obstetric mishap should be shifted to prenatal factors, particularly fetal exposure to infection and/or inadequate maternal nutrition.

This brief review highlights important research gaps worth pursuing to increase our understanding in CP, which the evidence now indicates is preventable.

In view of the COVID-19 pandemic, children and adults living with cerebral palsy are at higher risk for severe illness due to their susceptibility to chronic diseases, compromised immune systems and their compromised mental well-being. The Center for Disease Control has listed people with neurological disorders such as cerebral palsy as vulnerable and advised that they should be shielded and isolated. This is particularly dangerous, as people living with cerebral palsy require special care and therapy and already feel neglected and secluded from society. One could only imagine the toll of the COVID-19 pandemic on an already fragile group of people who are fighting a daily health, mental, and social battle. The British Medical Journal recently published a commentary on the socioeconomic gradient in health and the covid-19 outbreak, in which the writers narrate the story of a 17 year old boy with cerebral palsy in Hubei who was found dead after being left alone at home for 6 days because his single father was quarantined in a health facility for suspected covid-19 infection (140).
Even before the COVID-19 crisis, people with cerebral palsy and their families lead a very difficult life- the pandemic has further exposed the frailty and disproportionate burden affecting those living with lifelong neurologic diseases. Today, more than ever, our world necessitates human solidarity and strong multidisciplinary collaboration to protect our most vulnerable not only from diseases and viruses but also from the detrimental effects of suffering and depression that accompany them.
RESEARCH GAPS

Prevalence and risk factor data from LMICs

More research is required for LICs, which have different epidemiological features of cerebral palsy. A study in Uganda showed that preterm birth was a minor contributor to CP compared to postnatal infections (such as malarial infections) that contributed to 25% of all cases of CP (36, 141). In India, the reported CP prevalence is said to be 3 per 1,000 live births (142). This is particularly important as some studies from low and middle-income countries show a prevalence of CP ranging from 4.4 to 10 per 1,000 live births or children (143, 144).

Maternal nutrition and infection

The role of nutrition in the development of cerebral diseases has not been clearly investigated. Large prospective studies with assessment of diet intake preconception up until delivery are necessary. Studies looking at the potential relationship between maternal lipid and micronutrient status (choline, iodine) in early pregnancy and the risk of CP are also needed. However, these will require vast collaborations to reach large sample sizes of more than 100,000 women due to the low incidence rate of CP (2 per 1,000 live births) and the cost could be extortionately high. Nutritional factors, as opposed to other risk factors such as age, BMI, parity, obstetric history, cannot be accessed via medical records. Retrospective studies tracing back the nutrition of mothers who gave birth to CP children is also rather difficult, hence the need for prospective studies. Alternatively, the synergistic effect of supplementation trials with brain-specific fatty acids and cofactors (choline and B12) and iodine on the suppression on inflammation and the prevention of cerebral damage should be the next steps. It would be worth starting in LMICs where incidence rate is much higher and would require a smaller
sample size. Fish and marine sources are rich in DHA, choline and iodine, deficiencies of which have been implicated in brain damage. The results will be crucial to inform public health policy and could potentially help prevent neurological impairment.

The cost of these trials, though prohibitively expensive, would be worth it if brain damage can be avoided by a simple intervention such as increasing intake of marine and fish sources or supplementation.

**Origins in early pregnancy**

The timing of the brain lesions is still not fully elucidated and although many studies show that the aetiology of CP has its origins in the prenatal period, it is crucial to identify specific time periods after which cerebral damage might become irreversible. This will be crucial for all preventive interventions.

**Gestational diabetes and CP**

Many charity websites give strong claims linking gestational diabetes in pregnancy to increased risk of CP; however, these claims are not backed up by proper scientific studies that were powered to test this specific association. Although some studies show an increased risk of CP with gestational diabetes in certain populations such as mothers with obesity, the results cannot be generalisable without the warrant of longitudinal or case/control studies to prove the validity of these claims.
PIONEERS IN CP RESEARCH

There are many researchers who have been working on identifying causes of cerebral palsy for more than 20 years:

— Allan Colver, Emeritus Professor Community Child Health at the Institute of Health & Society at Newcastle University, UK. His research mainly focuses on child health; he co-founded the North of England Collaborative Cerebral Palsy Survey and established a database of children with Autism Spectrum Disorder. He also coordinated a European Commission / Wellcome Trust-funded study (SPARCLE) across Europe of children with cerebral palsy (18, 145).

— Fiona Stanley, Distinguished Research Professor at the School of Paediatrics and Child Health, University of Western Australia. An epidemiologist of many years’ standing, she has specialised in public health, child and maternal health and cerebral palsy. She has published many joint papers with the other Australian scientists listed below, particularly around trends, prevalence, and risk factors of CP in Australia (4, 31, 41, 45, 71, 118, 146, 147).

— Nadia Badawi, Professor in the Faculty of Medicine & Health, University of Sydney and Chair of the Cerebral Palsy Alliance. With a research focus into new-born encephalopathy as well as prevention, best intervention and ultimately a cure for cerebral palsy, she is currently very much the public face of the CP research community in Australia

— Sarah McIntyre, Senior Research Fellow at the Cerebral Palsy Alliance, University of Sydney. Her research focus is population-based aetiology research for cerebral palsy, neonatal encephalopathy and congenital anomalies with the long-term aim of identifying avenues for prevention of neurodisability.
— Hayley Smithers-Sheedy, NHMRC Early Career Fellow at the Sydney Medical School, The University of Sydney. Her research focus is epidemiology, congenital infection, neurodevelopmental disability and consumer involvement in research.

— Eve Blair, Adjunct Associate Professor, Telethon Kids Institute, School of Paediatrics and Child Health, University of Western Australia. Her research on cerebral palsy has had a tangible effect on the approach of the Australian courts and litigation compensation, providing a more evidence-based pathway to assessing causation. Her research has included population-based studies and cerebral palsy registers.

— Dinah Reddihough, Professor at the Murdoch Children’s Research Institute in Victoria where she heads the Developmental Disability & Rehabilitation Research Group. Her primary research interest is childhood disability, particularly CP, and she was responsible for founding the Australasian Academy of Cerebral Palsy & Developmental Medicine.

— Linda Watson and the Australian Cerebral Palsy Register Group. They are all researchers from various universities and research institutes in Australia and usually share authorship on most studies.

— Karin Nelson, Scientist Emeritus, Clinical Neurosciences Program at the Division of Intramural Research, National Institute of Neurological Disorders and Stroke (NINDS), the National Institutes of Health, USA (50, 62, 117, 133).

— Bo Jacobsson, Professor in the Department of Obstetrics and Gynecology, Institute of Clinical Sciences, University of Gothenburg, who, with Kate Himmelmann and Paul Uvebrant (below), is among the pioneers in research on CP in Sweden. They have various joint papers focusing on aetiology, risk factors, trends, and consequences in Sweden (27, 38, 57, 148, 149).
Kate Himmelmann, Adjunct University Lecturer in the Department of Pediatrics at the University of Gothenburg’s Institute of Clinical Sciences.

Paul Uvebrant, Professor in the Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg.

Kerr Graham, Professor at the Murdoch Children’s Research Institute in Victoria, Australia. He is an international leader in orthopaedic management of cerebral palsy (10, 34).

Martin Bax, Retired Consultant Paediatrician, Division of Paediatrics, Obstetrics and Gynaecology, Imperial College, London. He is one of the famous pioneers in CP who revised the definition and classification of CP and conducted a study on MRI scans for children in CP which revealed brain damage dating to prenatal period (3, 58, 150).

Nigel Paneth, Professor of Epidemiology, Biostatistics and Pediatrics at Michigan State University, USA. He is particularly interested in the causes and prevention of childhood neurodevelopmental handicap, particularly CP. His studies look at the epidemiology of CP (20).

Peter Pharoah, Emeritus Professor at the Department of Public Health and Policy at the University of Liverpool. His research has focused on identifying risk factors for CP and epidemiology of CP in England and Wales (12, 28, 78, 145, 151).

Peter Rosenbaum, Professor of Pediatrics and co-founder of the CanChild Centre for Childhood Disability Research at McMaster University in Ontario Canada. His study on the definition and classification of CP has been cited by 3,406 articles (2).

Peter Uldall, Emeritus Professor of Child Neurology at the Department of Pediatrics and Adolescent Medicine at The University of Copenhagen, Denmark. His research interests focus on the causes and consequences of cerebral palsy (29, 30, 82).
KEY ORGANISATIONS

UK NGOs with CP Interest

F: Family support
R: Research

— Aberdeen & District Cerebral Palsy Association [F]
— Action Cerebral Palsy [F, R]
— Action Medical Research [R]
— Adult Cerebral Palsy Hub [F]
— Bedford & District Cerebral Palsy Society [F]
— Bliss [F, R]
— Bobath Centre for Children with Cerebral Palsy [F, R]
— Boparan Charitable Trust [F]
— Brain Charity [F]
— Brain Injury Hub [F]
— Brain Injury Rehabilitation Trust / Disabilities Trust [F, R]
— Brainstars [F]
— Brainwave [F]
— British Institute for Brain-Injured Children [F]
— Castang Foundation [R]
— Caudwell Children [F]
— Cerebra [R]
— Cerebral Palsy Africa [F]
— Cerebral Palsy Midlands [F]
— Cerebral Palsy Northamptonshire [F]
— Cerebral Palsy Plus [F]
— Cerebral Palsy Scotland [F, R]
— Cerebralpalsy.org.uk / Bridge McFarland LLC [F]
— Chailey Heritage Foundation [F]
— Cheyne Charity [F]
— Child Brain Injury Trust [F]
— Children Today Charitable Trust [F]
— Contact (Contact-a-Family) [F]
— Council for Disabled Children [F]
— CP Sport [F]
— CPotential [F]
— Cumbria Cerebral Palsy [F]
— Dame Vera Lynn Children’s Charity [F]
— Dreams Come True [F]
— Elifar Foundation [F]
— Family Fund [F]
— Footsteps Centre [F]
— Freddie Farmer Foundation [F]
— Great Ormond Street Hospital [R]
— International Cerebral Palsy Society [R]
— Lincolnshire Cerebral Palsy Society [F]
— Liverpool Cerebral Palsy Society [F]
— Merlin's Magic Wand [F]
— National Network of Parent Carer Forums [F]
— NewLife [F, R]
— NICE [F]
— Paces [F]
— Rainbow Centre for Conductive Education [F]
— Roald Dahl's Marvellous Children's Charity [F]
— Scope [F]
— Sequal Trust [F]
— Shropshire Cerebral Palsy Society [F]
— Sky Badger [F]
— Starlight Children's Foundation [F]
— Sparks / GOSH Charity [R]
— Stars Foundation For Cerebral Palsy [F]
— Stick ’n Step [F]
— Stockport Cerebral Palsy Society [F]
— Tree of Hope [F]
— WellChild [F, R]
— Whoopsadaisy [F]

**International NGOs with CP Interest**

**Australia**  
Cerebral Palsy Alliance  
Steptember

**Australia/USA**  
Cerebral Palsy Alliance Research Foundation

**Canada**  
Brain Canada  
CanChild  
CHILD-BRIGHT Network  
Kids Brain Health Network  
Ontario Federation for Cerebral Palsy Research Fund

**France**  
Fondation Paralysie Cérébrale / Fondation Motrice

**India**  
ADAPT – India
Amrit Foundation of India
Indian Institute of Cerebral Palsy
Rehabilitation Council of India

Italy
Cerebral Palsy European Community Association

S Africa
Malamulele Onward
The Paige Project – South Africa
United Cerebral Palsy Association of South Africa

Singapore
Cerebral Palsy Alliance of Singapore

Switzerland
Naked Heart Foundation

USA
Brain Injury Association of America
Brain Trauma Foundation
Cerebral Palsy Group
Cerebral Palsy Guidance
Cerebral Palsy Guide
Cure CP
Graham’s Foundation
Holton’s Heroes
Hope for HIE
March of Dimes
Reaching for the Stars
Save Babies Through Screening Foundation
The Baby Alex Foundation
The Cerebral Palsy Foundation
The Silverlining Brain Injury Charity
United Cerebral Palsy
Interested Bodies – UK Research

— Medical Research Council
— Wellcome Trust
— British Academy of Childhood Disability
— British Association of Perinatal Medicine
— British Maternal & Fetal Medicine Society
— Academic Paediatrics Association
— UK Child Health Research Collaboration
— Royal College of Paediatrics & Child Health
— Royal College of Obstetricians & Gynaecologists
— UK Clinical Research Collaboration
— Economic & Social Research Council
— UK Research & Innovation
— Innovate UK
— Research England
— British Academy of Childhood Disability

Interested Bodies – International Research

— Australasian Academy of Cerebral Palsy & Developmental Medicine
— American Academy for Cerebral Palsy & Developmental Medicine
— International Alliance of Academies of Childhood Disability
— European Academy of Childhood Disability
— International Alliance for Pediatric Stroke
— International Pediatric Stroke Study
— Cerebral Palsy Alliance Research Institute
— CP Quest
— IMPACT for CP
— International Cerebral Palsy Genomics Consortium
— Centre of Research Excellence in Cerebral Palsy
— European Academy of Childhood Disability
— National Organization for Rare Disorders

Centres of Research – UK

— Department of Public Health, University of Liverpool
— National Perinatal Epidemiology Unit, Radcliffe Infirmary, University of Oxford
— Department of Public Health, University of Oxford
— Department of Community Child Health, Alder Hey Children's NHS Foundation Trust, Liverpool
— Institute of Health & Society, Newcastle University
— Department of Paediatric Neurosciences, Evelina Children's Hospital, Guy's & Saint Thomas' NHS Foundation Trust
— School of Nursing & Midwifery, Queen's University Belfast
— Centre for the Economics of Mental Health, Institute of Psychiatry
— Department of Clinical Sciences, Brunel University
— Division of Paediatrics, Obstetrics & Gynaecology, Imperial College
— FSID Unit of Paediatric & Perinatal Epidemiology, University of Liverpool
— Saving Newborn Lives / Save the Children, International Perinatal Care Unit, Institute of Child Health, London
— Institute of Child Health, Royal Hospital for Children, Bristol
— Department of Paediatrics & Neonatal Medicine, Hammersmith Hospital, London
— Institute of Nursing & Health Research, Ulster University, Belfast
— York District Hospital, York
— Academic Unit of Paediatrics, University of Leeds
— MRC Centre for Causal Analyses in Translational Epidemiology, University of Bristol
— MRC-Dunn Human Nutrition Unit, University of Cambridge

Centres of Research – International

— National Institute of Neurological Disorders and Stroke
— Eunice Kennedy Shriver National Institute of Child Health and Human Development
— Waisman Center, University of Wisconsin-Madison – USA
— University of Alabama at Birmingham – USA
— Division of Birth Defects & Developmental Disabilities, National Center on Birth Defects & Developmental Disabilities, Centers for Disease Control & Prevention – USA
— Institute of Allied Health Sciences, College of Medicine, National Cheng Kung University – Taiwan
— Institute of Public Health, College of Medicine, National Cheng Kung University – Taiwan
— College of Public Health, University of South Florida – USA
— Washington University in St. Louis – USA
— Department of Epidemiology, College of Human Medicine, Michigan State University – USA
— Hackensack Meridian School of Medicine, Seton Hall University
— CanChild Centre for Childhood Disability Research, McMaster University – Canada
— Developmental Disability & Rehabilitation Research, Murdoch Children’s’ Research Institute, The Royal Children's Hospital, Victoria – Australia
— College of Human Medicine, Michigan State University – USA
— Department of Neurology, Université Libre de Bruxelles – Belgium
— Department of Rehabilitation Medicine, VU University Medical Center, Amsterdam – The Netherlands
— Department of Physical Medicine, Rehabilitation & Pediatrics, Feinberg Northwestern School of Medicine, Rehabilitation Institute of Chicago – USA
— Department of Rehabilitation Medicine, Erasmus MC, University Medical Centre, Rotterdam – The Netherlands
— Department of Epidemiology & Biostatistics, Erasmus Medical Centre, Rotterdam - The Netherlands
— Department of Pediatrics, Erasmus Medical Centre, Rotterdam – The Netherlands
— RTI International, N Carolina – USA
— National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control & Prevention – USA
— Klinik für Kinder und Jugendmedizin, University of Lübeck – Germany
— INSERM, UMR 1027, Paul Sabatier University, Toulouse – France
— Department of Paediatrics, Queen Silvia Children's Hospital, Göteborg University – Sweden
— Laboratory of Medical Biology, University Hospital of Grenoble – France
— AUSL Viterbo – Italy

— National Institute of Public Health, University of Southern Denmark, Copenhagen – Denmark

— School of Public Health, Peking University Health Science Center, Beijing – China

— School of Public Health, Fudan University, Shanghai – China

— Department of Community Health Sciences, University of Calgary – Canada

— Department of Neurology, Assiut University – Egypt

— Department of Neurology, El Azhr University – Egypt

— Department of Neurology, Sohag University, Sohag – Egypt

— National Centre for Maternal & Infant Health, Beijing Medical University – China

— Department of Pediatrics, Göteborg University – Sweden

— Robinson Research Institute, University of Adelaide – Australia

— Department of Paediatric Neurology, Adelaide Women’s & Children’s Hospital, School of Pediatrics & Reproductive Health, University of Adelaide – Australia

— School of Pediatrics & Reproductive Health, University of Adelaide – Australia

— South Australian Clinical Genetics Service, SA Pathology (at Women’s and Children’s Hospital), Adelaide – Australia

— School of Molecular & Biomedical Science, University of Adelaide – Australia

— Department of Pediatric Rehabilitation, Women’s and Children’s Hospital, Adelaide – Australia

— Department of Physical Medicine & Rehabilitation, Michigan Medicine, University of Michigan – USA
Department of Epidemiology & Public Health Medicine, Royal College of Surgeons in Ireland – Ireland
Department of Anthropology, University of Michigan – USA
Department of Neurology, Boston University – USA
Discipline of Paediatrics & Child Health, Children's Hospital Westmead and Sydney Medical School, University of Sydney – Australia
Division of Maternal-Fetal Medicine, Department of Gynecology-Obstetrics, Johns Hopkins University School of Medicine – USA
Department of Neurology, Children’s National Medical Center, Washington – USA
Departments of Neurology & Pediatrics, University of California, San Francisco – USA
Department of Global Public Health & Primary Care, University of Bergen – Norway
Department of Pediatrics, Haukeland University Hospital, Bergen – Norway
Department of Public Health & Primary Health Care, University of Bergen – Norway
Medical Birth Registry of Norway, Norwegian Institute of Public Health, Bergen – Norway
Department of Clinical Medicine, Section for Pediatrics, University of Bergen – Norway
Department of Obstetrics & Gynaecology, Seoul National University College of Medicine – South Korea
Department of Obstetrics & Gynecology, Soroka University Medical Center, Ben Gurion University of the Negev, Beer Sheva – Israel
Center of Clinical Research, Faculty of Health Sciences, Ben Gurion University of the Negev – Israel
Telethon Kids Institute, University of Western Australia, Perth – Australia
— Department of Epidemiology, College of Human Medicine, Michigan State University – USA
— National Center on Birth Defects & Developmental Disabilities, Centers for Disease Control & Prevention, Atlanta, Georgia – USA
— Surveillance of Cerebral Palsy in Europe – Italy
— Department of Paediatrics & Child Psychiatry, University of Göteborg – Sweden
— Western Australian Research Institute for Child Health, Princess Margaret Hospital for Children, Perth – Australia
— Departments of Pediatric Neurology, Montreal Children’s Hospital, McGill University – Canada
— Department of Human Development, Michigan State University – USA
— National Neurosciences Centre, Kolkata – India
— Department of Pediatrics & Child Health, Makerere University, Kampala – Uganda
— School of Public Health, College of Health Sciences, Makerere University – Uganda
— Department of Women's & Children's Health, Karolinska Institutet – Sweden
— Department of Public Health, Karolinska Institutet – Sweden
— Department of Neuropaediatrics, Astrid Lindgren Children's Hospital, Stockholm – Sweden
— IMC/ThEMAS-RHEOP, Grenoble University Hospital – France
— School of Medicine, LDS Hospital, University of Utah – USA
— Department of Paediatrics, University of Melbourne – Australia
— Grace Centre for Newborn Care, Sydney Children's Hospital Network, Sydney – Australia
— Developmental Medicine, The Royal Children's Hospital, Melbourne – Australia
— March of Dimes Birth Defects Foundation, California Birth Defects Monitoring Program, Oakland – USA
— Department of Epidemiology, Institute of Public Health, University of Aarhus – Denmark
— National Health & Medical Research Council Research Unit in Epidemiology & Preventive Medicine, University of Western Australia, Nedlands – Australia
— Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore – USA
— Neal Hodgson Woodruff School of Nursing and Rollins School of Public Health, Emory University, Atlanta – USA
— Department of Pediatrics, All India Institute of Medical Sciences, New Delhi – India
— MRC Maternal & Infant Health Care Strategies Research Unit, University of Pretoria – South Africa
— Measurement & Health Information Systems, World Health Organisation, Geneva – Switzerland
— Human Resources for Health, World Health Organisation, Geneva – Switzerland
— Department of Pediatrics, Saint Louis University, Saint Louis – USA
— Department of Statistics & Epidemiology, RTI International, N Carolina – USA
— University Teaching Hospital, Lusaka – Zambia
— Center for Research for Mothers & Children, National Institute of Child Health & Human
— Development, Bethesda – USA
— Department of Pediatrics, University of Alabama at Birmingham, Birmingham – USA
— Department of Paediatrics, Institute of Medicine, Kathmandu – Nepal
— Department of Paediatrics, Nepal Medical College, Kathmandu – Nepal
— Department of Obstetrics & Gynaecology, Institute for the Health of Women & Children, Perinatal Centre, Sahlgrenska University Hospital, Göteborg – Sweden
— Department of Neurology & Pediatrics, University of Vermont – USA
— Department of Pediatrics (Neonatology), Wake Forest University Health Sciences, N Carolina – USA
— Neuroepidemiology Unit, Children’s Hospital of Boston – USA
— Department of Pediatrics (Newborn Medicine & Pediatric Neurology), Floating Hospital for Children at Tufts Medical Center, Boston – USA
— Perinatal Neuroepidemiology Unit, Departments of Gynecology and Pediatrics, Hannover Medical School – Germany
— INSERM U149 Research Unit on Perinatal Health & Women's Health, Villejuif – France
— Hôpital Charles Nicolle, Rouen – France
— Research Unit on Epidemiology & Public Health, INSERM U558, Toulouse – France
— Hôpital Jeanne de Flandre, Lille – France
— Hôpital Antoine Béclère, Paris – France
— Hôpital Mère-Enfant, Nantes – France
— Hôpital Hautepierre, Strasbourg – France
— Hôpital Saint-Jacques, Besançon – France
— CHU Montpellier, Montpellier – France
— Hôpital Universitaire, Nancy – France
— Department of Pediatrics, Izaak Walton Killam Health Centre, Halifax – Canada
— Departments of Pediatrics, Obstetrics & Gynaecology, Perinatal Epidemiology Research Unit, Dalhousie University, Halifax – Canada
— Department of Paediatric Rehabilitation, Medical University of Bialystok – Poland
— Paediatric Department, Kolding Hospital, Kolding – Denmark
— Department of Child Neurology, University Children's Hospital, Tübingen – Germany
— Registre des Handicaps de l’Enfant et Observatoire Périnatal, ThEMAS, Technologies de l’Imagerie de la Modélisation et de la Cognition, Grenoble – France
— Langley Porter Neuropsychiatric Institute, San Francisco – USA
— Department of Paediatrics, Monash University, Melbourne – Australia
— Oregon Institute of Occupational Health Sciences, Oregon Health & Science University, Portland – USA
— Institute of Child Health, Neurology & Genetics, College of Medicine, University of Arizona – USA
— Centre for Applied Genomics, The Hospital for Sick Children, Toronto – Canada
— Department of Pediatrics, University of Alberta, Edmonton – Canada
— Holland Bloorview Kids Rehabilitation Hospital, Department of Paediatrics, University of Toronto, Toronto – Canada
— Human Genome Sequencing Center, Baylor College of Medicine, Houston – USA
— Center for Developmental Health, Curtin University of Technology, Perth – Australia
— Department of Medicine, Pontifícia Universidade Católica de Goiás, Goiânia – Brazil

— Departments of Pediatrics and Pediatric Neurology, Laboratory for Molecular Biology, and Units of Pediatric Hematology, Human Genetics and Child Development, HaEmek Medical Center, Afula – Israel

— Pediatric Department, Rigshospitalet, Copenhagen – Denmark

— Department of Pediatrics, Janeway Health Centre, St. John's – Canada

— Developmental Pediatrics, BC Children's Hospital, Vancouver – Canada
Research Funding
GLOBAL OVERVIEW

Medical research is a powerful tool as it informs public health policy and can drive health, social, and economic benefits. The purpose of this analysis is to assess the state of funding for CP research globally from key government and charity health funders in countries where most of CP research is generated.

Cerebral palsy’s pooled prevalence is 2 to 3 per 1,000 live births (1, 19-22, 28). This prevalence is suggested to be higher in some low- and middle-income countries (LMICs) (37, 141). As a lifelong problem with poor quality of life (2, 34, 145, 152-155). CP and its associated comorbidities place a huge economic burden on families and the healthcare systems. In 2003, the United States’ Centers for Disease Control & Prevention (CDC) estimated the annual total lifetime costs for CP in the USA to be $11.5 billion, with each CP case costing $1.2 million (156).

The causes of CP are still not fully elucidated; obstetric mishaps were thought to be the major contributors for CP for a long time, although recent studies now show that prenatal factors such as maternal infection may contribute to the cerebral damage in CP and that CP may in fact be preventable. That there is now plausibility that CP may be preventable is as a result of the ground-breaking study led by Professor Martin Bax and part-funded by the Little Foundation, which found all lesions identifiable by MRI had been initiated well before the time of birth (58).

This insight, alongside the low quality of life, extortionate costs of medical and social care, and the healthcare economic burden attributed to CP, should place it on the top priority list for medical research (18, 157-161). However, our analysis demonstrates that this is not necessarily the case.
KEY OBSERVATIONS

— Most CP research is funded by high-income countries, and less so by low and middle-income countries

— The countries that report the largest funding of CP-related research are the USA (£17.9m), Canada (£5.5m), the UK (£4.6m) and Australia (£3.9m) – 2014 figures

— Australia spends the highest proportion of its annual health research budget on CP research – 0.42%

— The CP-related research spend of £4.6m in the UK in 2014 represented 0.23% of all UK Health Research supported by government and charity. The 2018 CP-related research spend of £5.65m in the UK represented 0.22% of total spend, representing a decrease in CP-related spending over the past 4 years.

— In 2014, 24% (£1.1m) of CP research in the UK was spent on understanding the causes (aetiology) and only 0.3% was spent on prevention research

— Compared to 2014, the 2018 attributable research funding to aetiology of CP decreased to 17% (£1m) of CP, whilst the prevention-related research increased to 7 %.
<table>
<thead>
<tr>
<th>Country</th>
<th>Funding for CP-related Research</th>
<th>GBP Equivalent</th>
<th>% of total health research spend on CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>AUS $7,100,000&lt;sup&gt;1&lt;/sup&gt;</td>
<td>3,919,023</td>
<td>0.42%&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Canada</td>
<td>CAN $8,870,281</td>
<td>5,474,815</td>
<td>0.24%</td>
</tr>
<tr>
<td>UK</td>
<td>GBP £4,601,129&lt;sup&gt;3&lt;/sup&gt;</td>
<td>4,603,129</td>
<td>0.23%</td>
</tr>
<tr>
<td>USA</td>
<td>US $21,904,363&lt;sup&gt;4&lt;/sup&gt;</td>
<td>17,979,320</td>
<td>0.07%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Table 1 - Global leaders in CP-related research funding in 2014

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<sup>1</sup> Encompasses NHMRC, CPARF, and ARC total funding for CP research (government and charity spend)
<sup>2</sup> Based on NHMRC 2013-2014 NHMRC research spending in National Health Priority Areas and NHMRC CP funding for 2013
<sup>3</sup> Based on UKCRC Health Research Analysis Data of 2014, which includes government and charity spend
<sup>4</sup> Based on 2013 NIH funding -wide actual funding for Research, Condition and Disease Categories (RCDC), CPARF, NSF funding in the USA
<sup>5</sup> Based on the reported NIH total health expenditure (2013) of US$26,081.3 million from Viergever et al.
GEOGRAPHICAL SPREAD

United Kingdom

Health Research Analysis 2014

Every five years, the UK clinical research collaboration (UKCRC) releases a dataset of all health research, including grants from charity and government funders. We searched the term “cerebral palsy” in the abstract for recent research grants included, and we retrieved 31 grants from different funding agencies; 9 from the Action Medical Research (AMR), 12 from the Department of Health (DoH), 4 from the Medical Research Council (MRC), 3 from the Wellcome Trust (9.7%) and the remaining 3 were from Sparks, the Engineering and Physical Sciences Research Council (EPSRC) and Chief Scientist Office (CSO) in Scotland.

Total funding between 2010-2015 was £16,197,600. The Department of Health (DoH) contributed £5,797,433, followed by the Wellcome Trust with £3,860,176 worth of funding, and £3,823,833 from the MRC. The latest UKHRA report for funding data in 2014 estimated a total funding of £ 4.6 million in 2014 for CP research. The DoH in England and Wales contributed 37% of the total expenditure on CP research, followed by the MRC (30%), Wellcome Trust (17%), AMR (7%), EPRC (4%), SPARKS (3%), and CSO Scotland (3%).
Figure 1 - Funding amount and proportions for cerebral palsy research in UK (2014) according to the various funding organisations. Total funding is £4.6m. Graph generated based on data from the UKCRC Health Research Analysis Public Dataset 2014.

Figure 2 displays the distribution of funding according to area of research. The largest amount was for aetiology, £1,122,402 (24.4%) followed by detection and diagnosis £997,806 (21.7%), treatment evaluation £828,521 (18%), underpinning £551,792 (12%), treatment and development £484,990 (10.5%), disease management £336,915 (7.3%), health services £264,942 (5.8%), and prevention £15,769 (0.3%).
The funding agencies discovered to date and described below are divided into charitable and governmental according to their source of funding:
To obtain a complete picture of government funding for CP research, we accessed the UK Research & Innovation (UKRI) portal (https://gtr.ukri.org/) and identified 254 projects from the portal’s “cerebral palsy” keyword search. Of these, 199 were found upon further review to be unrelated to CP but related to other diseases such as Alzheimer’s. We excluded one Medical Research Council (MRC) grant from 1997. Consequently, we identified 54 active and closed projects (either directly related to CP or indirectly via risk factors such as pre-term birth, low birthweight or stroke), with a collective value of £28.7 million, funded between 2005-2019 by 5 research councils.

Of the funding bodies, the Medical Research Council (MRC) accounts for more than half of the CP-related projects, followed by the Engineering & Physical Sciences Research Council (EPSRC), and Innovate UK. The remaining 5.7% of the projects were equally distributed between the Economic & Social Research Council (ESRC), Biotechnology & Biological Sciences Research Council (BBSRC), and the Arts & Humanities Research Council (AHRC) (Figure 3).
Figure 3 - Distribution of CP projects by UKRI institutions (n=54 projects).

Figure 4 shows the total funding for each of the UKRI institutions for the 2005-2019 periods. The MRC was the biggest funder for CP research followed by the EPSRC.

Figure 4 - Total funding for CP research by various UKRI institutions for 2005-2019. Pie chart compiled from data available via UKRI research council portal for government-funded projects.
Figure 5 represents the total funding for the 54 identified projects that are related to CP. The funding received by UKRI institutions for CP research (2005-2019) is sporadic and does not reflect a regular and general upward trend, although it highlights boom years (2006, 2010, 2016). Except for 2008, where no grant was awarded, the MRC seem to be consistently funding new projects annually.

![Figure 5 - Total funding for cerebral palsy-related research by UK Research and Innovation (2005–2019): Medical Research Council (MRC), The Engineering and Physical Sciences Research Council (EPSRC), and Innovate UK.](image)

**UK Department of Health / National Institute for Health Research**

The NIHR is the largest national clinical research funder in Europe, with a reported 2015-2016 budget of over £1 billion. The advertised funding opportunities through their website do not include cerebral palsy under their specialties; however, they do include neurological disorders and mental health. We identified 50 research projects using the term ‘cerebral palsy’ on the NIHR database that stores the portfolio of studies funded by each of their research programmes between 1997-2019 via the link: [https://www.journalslibrary.nihr.ac.uk/eme/#/](https://www.journalslibrary.nihr.ac.uk/eme/#/).

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7 The funding amounts are in British pounds and correspond to the amount allocated to each grant at the start year. Chart was compiled from data available via UKRI research council portal for government-funded projects (2005-2019).
It should be noted that these projects are strictly restricted to academic institutions and not to UK clinical research collaborations. Out of the 50, 20 projects were unrelated to CP (thyroid cancer, cardiac arrest, hyperacute stroke system, oesophageal reflux, Alzheimer’s Disease, intracerebral haemorrhage, dementia, cardiac disease, epilepsy, stenting) and 13 projects were indirectly related to CP (preterm birth, neonatal health, seizures, neurodisability) and 17 research projects were related to CP. Furthermore, none of the NIHR-funded projects were in the fields of aetiology or prevention research. Figure 6 shows the total NIHR funding for the 30 research projects directly or indirectly related to CP, which amounts to £25,036,579. Unlike research council funding, total NIHR funding for CP research has increased from 2005 to 2019, peaking in 2014 and 2018. However, the number of projects specifically related to CP have decreased since 2014 (Figure 6).

Figure 6 - Total funding for cerebral palsy-related research by NIHR (2005–2019), by specificity to CP research.

The funding amounts are in British pounds and correspond to the amount allocated to each grant at the start year. Chart was compiled from data available via journals library portal for portfolio of NIHR funded studies (2005-2019).
Foundations / Charities

Action Medical Research

Action Medical Research has funded a considerable number of studies related to CP, mostly to studies exploring interventions for babies/children living with CP. Current research interests focus on advancements in ultrasound scans for identification of early hip problems for children with CP, technology-based approaches for hand and arm rehabilitation and surgical interventions to improve mobility. Their areas of interest include, but are not limited to, preterm birth (in collaboration with Borne Charity), stillbirth, birth asphyxia, and autism. Data from the UKCRC/HRA showed that AMR funded 9 CP research grants in 2014, contributing a total of £342,736 for CP research, 40% of which was spent on aetiology of CP (£136,620).

Cerebra

Cerebra – For Brain Injured Children & Young People is a UK research charity with a focus on research to improve life opportunities for children with brain conditions, autism, ADHD, Down’s syndrome, learning disabilities, cerebral palsy, epilepsy and developmental delay. One research priority is to “identify women at risk of experiencing complications in pregnancy and preventing or minimising the impact of those complications on mother and baby.” Annual research expenditure is circa £660k, mainly supporting academic chairs in UK/European universities. Their Thousand Women Study has collected over 2,000 blood samples from women during pregnancy, with associated demographic and clinical information, creating an internationally unique resource for research into the obstetric causes of preterm birth.
**Sparks**

Sparks is a children’s medical research charity that does not receive any government funding and currently supporting over £5 million-worth of research, with cerebral palsy being one of their historic priorities. The UKCRC report of 2015 shows one CP grant funded by Sparks in 2009 for £223k. In 2014, the total estimated spend for CP research by Sparks was £114k, which accounted for 3% of the total amount spent on CP research. 51% of this funding was spent on aetiology (£57,696) and 6.5% on prevention of CP (£7,436). Their current funding opportunities do not include CP, however, instead focusing on other paediatric medical diseases.

**Castang Foundation**

The Castang Foundation was established by a bequest in 1986 to fund research for cerebral palsy, subsequently funded by private donations. The Foundation funds research on cerebral palsy and other disability-causing neurological conditions in partnership with other organisations – including The Little Foundation. Primary research interests include basic science for the understanding of the causes of disability, and effectiveness of interventions to improve quality of life. Their latest grant scheme is in collaboration with BACD (see below) and the award covers £60,000 funding for UK research projects lasting 12-18 months that have the potential of changing the lives of children with neurodisability.

**British Academy of Childhood Disability**

The BACD is an organisation for professionals working on childhood disability. It is affiliated with the British Association of Community Child Health, part of the Royal College of Paediatrics & Child Health, and is the UK branch for the
European Academy of Childhood Disability. The academy offers two annual awards for UK-based research, the Castang Award (see above) and the Paul Polani Award (in association with the Royal College of Paediatrics & Child Health) – amounting to £15,000 for research projects on paediatric neurodisability.

*Wellcome Trust*

The Wellcome Trust is a private research charity based in London, managing an investment portfolio of £25.9 billion, which funds their work. They do not have a specific funding scheme for cerebral palsy. We searched their database of grants awarded using the keyword search term ‘cerebral palsy’ and only one grant was retrieved. The grant was for the development of a neonatal brain health index (DELPHI) with the aim of recognising patterns of brain activity to detect the severity of brain injury- this was an Innovator Award for recognising brain injury from babies’ brainwaves. Although not included in their database, the 10-year SPARCLE study by Allan Colver about the quality of life of children with cerebral palsy across Europe was partially funded by the Wellcome Trust. We looked at Ethos Library to identify CP-related doctoral theses funded by the Wellcome Trust and only one was retrieved. The UKHRA report of 2014 data showed that the Wellcome Trust contributed to 17% of the total amount spent on CP research, equivalent to £781,687, out of which £182,323 was spent on aetiology (23.3%) and none on prevention.
Europe

European Commission

The European Commission, the executive of the European Union, is one of the largest public funders of health research in the world. A search of their current funding opportunities for research revealed no specifically CP-related schemes. However, historically, the Commission has funded many CP-related projects. Through their Erasmus+ Programme, which aims to increase awareness and education, they have funded 59 CP-related projects, one of which was a multi-country training programme for improving the wellbeing of persons with cerebral palsy through inclusive feeding and physical activity (€255,489).

Our search through the Cordis database, of all EU-funded CP-related research projects (via https://cordis.europa.eu) yielded 43 projects, 7 of which started before 2005 and 2 of which did not have available budget information. The total EU contribution for CP-related research between 2005 and 2019 was €62,624,825. Figure 7 shows the total yearly spend for CP-research. Although there is more consistent funding after 2013, with more money spent on CP-related research, there is no evidence of an overall increasing trend. The peak year was 2015, followed by 2017 and 2006.
Figure 7 - Total funding for cerebral palsy-related research by European Commission (2005–2019).

Funding amounts are in Euros and correspond to the amount allocated to each grant at the start year. Chart was compiled from data available via the Cordis database of the European Commission.

We also searched the Horizon 2020 Framework Programme for current calls. We did not find CP-specific calls; however, there were a few for neurodegenerative diseases.

Nevertheless, the European Commission’s Joint Research Centre, having invested over €1m in supporting its development, took on responsibility in 2016 for coordinating the work of the Surveillance of Cerebral Palsy in Europe network, managing its Central Registry, funding development of several CP registries across Europe and ensuring European-level collaboration amongst medical professionals, researchers and policy makers.

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8 Surveillance of Cerebral Palsy in Europe (SCPE) was established in 1998 as a collaboration of professionals and researchers working with cerebral palsy (CP) registries, bringing together paediatricians, paediatric neurologists, epidemiologists and therapists from across Europe. The aim is to disseminate knowledge about CP through epidemiological data, to develop best practice in monitoring trends in CP, to raise standards of care for individuals with CP, to inform for service planning, and to provide a framework for collaborative research. It is a non-profit NGO funded by the European Union Health Programme.
Australia

Australia is at the forefront of global funders of research relating to cerebral palsy in terms of commitment, with the highest reported proportion of annual national health research budgets (0.42%) devoted to this area. There is a comparatively thriving environment of scientific societies, research charities and government-funded research councils prepared to invest in research both in and outside Australia.

Government

*National Health Medical Research Council*

NHMRC is Australia’s primary distributor of federal medical research funding and has an annual appropriation of AUS $829 million. It has increased its funding for CP research over 2000 - 2014 (Figure 8) and sponsored 125 grants with circa AUS $53 million over that period.
The ARC is the “is the primary source of advice to the Government on investment in the national research effort” and is other major distributor of government research funds, with a budget of c. AUS $800 million. It administers the National Competitive Grants Programme and is responsible for the Excellence in Research programme. Details could be found of only 6 grants relating to CP research, making its total of AUS $1,542,000 the lowest of the 3 key funders of CP research in Australia (162).
Australasian Academy of Cerebral Palsy & Developmental Medicine

The Academy was founded in 2002 to provide “multi-disciplinary scientific education for health professionals and to promote excellence in research and best practice clinical care for children and adults with cerebral palsy and developmental conditions”. However, unlike its US counterpart, it does not have a research grant programme although its members make up the bulk of grant recipients from both government research councils and NGOs.

Foundations / Charities

Cerebral Palsy Alliance

The Cerebral Palsy Alliance was established 75 years ago and has a remit “to help babies, children, teenagers and adults living with neurological and physical disabilities lead the most comfortable, independent and inclusive lives possible.” In addition to this focus on the quality of life of those affected by CP, and with an annual income of c. AUS $110 million, it is one of the 3 main drivers of CP research in Australia via its associated Cerebral Palsy Alliance Research Foundation (see below).

The Alliance manages Australia’s National Cerebral Palsy Register, expected to be one of the largest in the world and which has contributed significantly to our current understanding of CP prevalence, trends and risk factors.

Cerebral Palsy Alliance Research Foundation
Launched in Australia initially in 2005, subsequently in 2015 in the USA, by the Cerebral Palsy Alliance, “to fund the best CP research around the world”. Total funding from CPARF was close to AUS $22,000,000 covering 102 grants, with 32.3% allocated to the formation of Cerebral Palsy Alliance Research Institute at the University of Sydney, 16.8% allocated to strategic grants for prevention and cure, and 50.9% allocated to competitive grants to cover doctoral scholarships and fellowships for CP research (162).

A recent review on the available funding for CP between 2005-2015 concluded that funding lacked consistency throughout the years and equivalence across the three funding bodies; overall, competitive funding from NHMRC and CPARF has improved. However, the NHMRC has sporadic annual awards, resulting in an irregular pattern of funding. The review’s authors highlighted the need for a consistent funding pattern from NHMRC and increased funding from the federal government in order to meet its acknowledged research priorities of prevention and cure of CP (162).

Following the review’s publication in 2016, the Federal Government’s Ministry of Health in June 2018 granted AUS $2 million in additional funding for the Cerebral Palsy Alliance’s Research Institute to address issues related to early diagnosis and treatment of CP, clinical trials in high risk infants, and new therapies to prevent CP during pregnancy (163).
United States of America

Government

National Institutes of Health

The main key funder for cerebral palsy research in the USA is the National Institutes of Health (NIH), a national medical research agency that is part of the U.S. Department of Health & Human Services. Although there are no specific program announcements or requests for applications to address CP research gaps particularly, the NIH has conducted workshops and set strategic plans to identify gaps in CP research and prioritise specific areas.

A recently published review by Wu et al. assessed the state of NIH funding for CP research from 2001 to 2013 (164). Results showed an increasing linear trend of funding for NIH-sponsored CP research, amounting to a total of $392.8 million, with an annual average of $30 million. The grants were awarded to 188 organisations across 43 US states. The funding was provided by 20 different NIH institutes, with 76% coming from the National Institute of Neurological Disorders and Stroke (NINDS) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). $1.4 million was spent on 80 scientific meetings, and the remaining amount was spent on different research categories: 55% for clinical research ($215 million), 48% for basic research ($187 million), 11% for development of new technologies ($45 million) and 7% for translational research ($26.3 million). The biggest area of research was attributed to central nervous system development and mechanisms of injury (over $100 million) followed by research on muscle function and structure (around $90 million). In contrast, around $35 million was spent on basic and clinical research
to identify risk factors for CP. The review highlighted the crucial need for continued funding for the development of effective strategies for the prevention and treatment of CP (164).

CP has gained remarkable visibility recently in N America. In 2017, both the NICHD and NINDS put a 5-year strategic plan to tackle gaps in CP research. Two workshops were held, and high priority recommendations were set to increase advances in basic and translational research, clinical research, and workforce development. The prenatal period was a particular focus area, with particular focus given to improving the understanding of the fundamental mechanisms of the brain-spine-muscle axis and molecular pathways of injury, establishing biomarkers of genetic, structural, and functional basis that drive impairment, and identifying critical periods of brain and motor development (165). In 2013, according to the NIH’s review of funding for research condition and diseases categories, the estimated worldwide total spend on CP research was $18 million.

*National Science Foundation (NSF)*

The NSF is an independent agency that accounts for 25% of federal support to US academic institutions for research – their sole beneficiaries. Although there are no specific research projects tailored to tackle the issue of CP, an analysis of available funding via Grantome showed 115 grants granted by the NSF for CP-related topics. Their range of funding is very wide, from thousands to millions, and granted to US academic institutions only. Many of the grants support workshops and conferences. In 2014, the estimated total funding by the NSF for CP research was $3,354,363, none of which was spent on either prevention or aetiology.
American Academy for Cerebral Palsy & Developmental Medicine

As with the Australian Academy of Cerebral Palsy & Developmental Medicine (above), the AACPDM’s mission is: “to provide multidisciplinary scientific education for health professionals and promote excellence in research and services for the benefit of people with and at risk for cerebral palsy and other childhood-onset disabilities. Originating from the CP Advisory Medical Council, it has a multi-disciplinary membership of over 1,000 health professionals (paediatricians, neurologists, surgeons, rehabilitators, therapists, nurses, special educators, engineers, and scientists). It accepts donations from the public and companies (e.g. Amazon) and partners with medical research charities. It works closely with the NIH and, together, have established the NINDS/AACPDM Common Data Elements (CDEs) for Cerebral Palsy online resource to help standardize data collection and assessment in research.

The Academy hosts annual conferences – in 2019 jointly with the International Alliance of Academies of Childhood Disability – which includes the World CP Register and Surveillance Congress It also collaborates with the Cerebral Palsy Alliance with medium-scale research grant programmes:

— Transformative practice grants for its membership – focused on the translation of evidence-based strategies into practice
— Clinical research grants up to $25,000 - open to non-members for high impact projects on CP or childhood-onset disability
— International meeting development grants up to $50,000 – for newly-formed organisations that aim to develop seminars related to early identification and treatment of individuals with childhood-acquired disability (166).
— Junior investigator research grants up to $15,000 – aimed at fostering the scientific development of the next generation of scientists.
Foundations / Charities

*Cerebral Palsy Alliance Research Foundation*

The CPARF was recently (2015) founded in New York for US grants (2015) as a complementing organisation to the CPARF in Australia, mentioned above, but without its international funding remit. The grants cover up to $180,000 on projects that fit into the foundation’s priorities for expanding CP research in the US: aetiology, prevention, causal pathways, early identification and intervention, and cure. The areas of research differ each year and the 2019-targeted areas are technology innovations, regenerative medicine using stem cells, genetics and reduction of pain (167). The money comes from private donations and, in some instances, government agencies, such as the $2 million grant by the Australian Ministry of Health. In 2014, the Foundation’s estimated annual research spend was £550,000.

*Cerebral Palsy Foundation*

Based in New Jersey, the CPF, formerly known as the United Cerebral Palsy Research & Educational Foundation, was founded in 1955 and is the nation’s principal non-government agency sponsoring research and education for cerebral palsy. It is funded by private donors and corporate supporters such as Apple and Microsoft.

The foundation has funded many research projects related to the cause, cure of CP and evidence-based care for children affected by cerebral palsy and related developmental disabilities. Currently, it has no grant schemes to offer; however, it is funding animal trials conducted by researchers at the Kennedy Krieger...
Institute and John Hopkins which are looking at the effectiveness of anti-inflammatory medication in reducing perinatal white matter inflammation.

*Cure CP*

Cure CP is a non-profit organisation based in Atlanta, Georgia, founded by two families who had children with CP. It pursues a unique approach, directing all funding to support research focused on regenerative medicine. It secures its funding through private donations and supporters such as investment banks (Merrill Lynch/Goldman Sachs) and other private companies. CP Cure mainly supports clinical trials and research studies related to regenerative medicine (https://curecp.org/studies-we-support/) such as grants given to Duke University School of Medicine for the use of cord blood stem cells to treat children with spastic CP and University of Texas, also looking at stem cells from cord blood for children with CP. It also contributed to other clinical trials and to the Cerebral Palsy Summit annual meetings. There is no detail available on the scale of its grant-making, while its annual income reported via GuideStar appears to be below $200k.

*Bill & Melinda Gates Foundation*

Although there are no thematic grants for CP in particular, the foundation recently awarded the University of San Diego a grant worth $219,675 for the testing of 3 new drug candidates for the potential to protect new-borns against brain injury and cerebral palsy.

A notable facet of the Gates Foundation’s approach has been to seek resolution to major issues by investing at scale on the basis of critical mass, such as with their investment in the Global Polio Eradication Initiative. Based on the accumulated knowledge of many years of research and the certainty of the
required approach, the Foundation’s investment of circa $3 billion was designed to improve and accelerate vaccination programmes globally – leading to polio’s near eradication.
Canada

RAND Europe’s 2008 report Health and Medical Research in Canada10 observes that “one of the most interesting aspects of the Canadian health research system is the use of endowment funding, a system more commonly associated with university funding. The Canadian Health Services Research Foundation (CHSRF) is mainly funded by endowments from the major federal funders of health or services research: the then Medical Research Council of Canada (MRCC, now the Canadian Institutes of Health Research [CIHR]); Health Canada (the federal healthcare funder); and the Social Sciences & Humanities Research Council (SSHRC).” Other funding agencies include the Canadian Foundation for Innovation, Canadian Research Chairs, Networks of Centres of Excellence and the Natural Science & Engineering Research Council.

They observe that “the higher education sector spends more than the federal government, and nearly as much as industry, on health R&D.” Proportions of investment in health research in 2005 were: 24% business enterprise, 25.6% higher education and 25% government, with 62% of all research activity being undertaken in the higher education sector and 34% in the business sector. The NGO/charity sector was reported as contributing circa 8-9% of Canada’s R&D funding.

Total health research expenditure in 2018 is reported as $4.13 billion11, an increase from 2014’s $3.71 billion.

Government

**Canadian Institutes of Health Research**

The CIHR is the largest single funder of health R&D in Canada, being responsible for circa 60% of all federal spend and circa 12% of national R&D funding\textsuperscript{12}. It spends approximately $1 billion each year to support health research. There are 13 CIHR institutes that set the research priorities and offer grants. We conducted a search of CIHR's public funding database, which comprises bilingual (English and French) information on successful grant applications, studentships and fellowships using the following keywords: “cerebral palsy” and “la paralysie cérébrale” via: https://webapps.cihr-irsc.gc.ca/decisions/

Grants were included if their abstracts indicated specific focus on CP, its risk factors, or its effects and implications. A total of 106 CP-related programs were retrieved between 2008 and 2019, almost all for Canadian researchers. The total amount spent by the CIHR between 2008-2018 on CP-related research was $31,458,810. Research related to the aetiology of CP accounted for $6,192,529, research for the prevention of CP amounted to $4,520,997, early detection and diagnosis research, $719,566. The remaining $20 million was spent on muscle rehabilitation, orthopaedic and mobility-related interventions, treatments to improve quality of life and lifestyle of CP affected children, and social support.

**Canadian Foundation for Healthcare Improvement**

The CFHI (formerly the Canadian Health Services Research Foundation) is a federally funded organisation focused on the spread of innovative practices and working “shoulder-to-shoulder with our partners to deliver better patient care

\textsuperscript{12} Health Canada is the country’s other main funder of medical research, but with a public health remit.
more efficiently.” Its annual budget is c. $17 million CAN. It appears to fund no explicitly CP-related programmes but does support others focused on obstetric practice: i.e. taking a multi-institutional approach to maternal and foetal health.

Foundations / Charities

*Ontario Federation for Cerebral Palsy Research Fund*

The OFCP offers a CP-specific funding scheme for the support of high-quality research in Canada. Projects with an estimated budget of $50,000.00 or less, per year, over a three-year term are eligible for the award. Based on their research inventory, they have previously funded 23 CP-related grants, 4 out of which were related to aetiology of CP and 2 to prevention.

*Kids Brain Health Network*

KBHN (formerly NeuroDevNet) is part of the National Centres of Excellence programme, part government/part philanthropy funded, “as a network of researchers and clinicians seeking to understand brain development, with the specific goal of mobilizing this knowledge to improve the lives of children living with neurodevelopmental disabilities and their families.” It funds collaborative research, with a focus on early diagnosis.

Current research funding opportunities include an open funding competition to identify “an innovative approach to diagnosis, treatment or support for caregivers raising children with neurodisabilities”. Recent grant awards vary between $90k CAN and $200k CAN. The organisation also runs a programme
of developmental neuroscience research training awards funded in association with Brain Canada.

Importantly, the Network is also the originator and funder of the Canadian Cerebral Palsy Register in 2007, which is already providing important epidemiological data as a way to determine prevalence and describe CP in Canada’s population. It is currently evolving to incorporate quality-of-life questions.

**Brain Canada**

Brain Canada describes itself as “the national convenor of the community of those who support and advance brain research” and drives the Canada Brain Research Fund, a $260 million CAN initiative established in 2011 in collaboration with Health Canada and a number of major philanthropic institutions. To date this Fund has supported 6 CP-related research projects with a collective value of $1.9 million CAN.

**CanChild**

CanChild is a research organisation housed at McMaster University, with a focus on children and youths with disabilities, with an annual income of circa $700k CAN. Its recent Childhood Cerebral Palsy Integrated Neuroscience Discovery Network (CP-NET) project seeks to connect families affected by CP to a national, multi-disciplinary community of research scientists to improve the understanding of CP with regard to causes, prevention and rehabilitation, with a particular focus on hemiplegic CP.
CHILD-BRIGHT Network

CHILD-BRIGHT Network is a research organisation hosted by McGill University that, using a family- and child-focused approach, “creates novel interventions to optimize development, promote health outcomes, and deliver responsive and supportive services for children with brain-based developmental disabilities”. Their research studies new diagnostic tests, therapies, service models, and technologies “to optimize the physical and mental health of … children”.

While one of its 3 research themes is early intervention, current projects do not include a CP element. However, 3 historical CP-related projects (looking at brain repair and improving early diagnosis) are reported, albeit without details of the scale of their funding.
Globally

This section highlights other countries that have reported CP-related research and funding.

India

The Indian Council of Medical Research (ICMR) is one of the biggest research funding agencies, with a reported USD 140.3 million spent on health research in 2011 (168). However, there is no information available on CP specific grants or previous awards, except for one grant. Other potential funding agencies are Biotechnology Industry Research Assistance Council (BIRAC). A search through their multiple institutional archived awards showed one grant related to CP children. The Indian Department of Science and Technology (DST) is also a major health research funder; however, there is little information about the funding and grant schemes for all CP-research in India. Nevertheless, there is evidence of CP-related research projects in India, albeit with no detail yet available on focus, scale or institutions (169).

China

The main funder for CP research in China is the National Natural Science Foundation of China (NSFC). A search for all CP-related articles showed that most projects are supported by the NSFC. The Ministry of Health also contributes to some CP research (46); however, neither organisation provides information about the current and past state of funding for CP-related research.
Japan

The Japan Society for Promotion of Science (JSPS) and Japan Science & Technology Agency (JST) are the two main funding agencies for health research in Japan, with an estimated spending in 2011 and 2012 of USD 472.5 million and USD 338.5 million respectively (168). The Kaken Database of Grants-in-Aid for Scientific Research reports on 11 CP-related research projects funded between 1985 and 2018 with a collected value of ¥32.9 million (£253,355 equivalent). Although there is no website information on the amount and number of grants spent on CP-related research, they have funded numerous studies, mostly on rehabilitation and medical outcomes of children with CP.

The research/medical ‘interested parties’ community is served by the Japan Cerebral Palsy Study Group, administered (and we assume funded) by UMIN, Japan’s University/Hospital Medical Information Network, with an annual conference. However, member/participants (and their institutions) are not identifiable and, thus, it is difficult to define their research and the scale of its funding.

South Korea

CP-related research in Korea is predominantly funded through governmental agencies. The Korea National Institute of Health (KNIH) and the Korean National Research Foundation (NRF) are the two main public funding organisations for health research. While there is no information available on their contribution to CP research, a search of the Korea Education & Research Information’s Research Information Service System database reveals details of 775 CP-related research papers published between 1983 and 2019 – albeit with no details of the scale of funding. Published studies from Korea report funding from the NRF, Korea Centers for Disease Control & Prevention (KCDC) and
Allergan Korea Ltd, a pharmaceutical company that supported the newly introduced Korean Database of Cerebral Palsy.

Singapore

In Singapore, the main health funding agency is the Singapore National Medical Research Council (NMRC). A search through Singapore government integrated grant management system using the keyword “cerebral palsy” yielded two awarded grants, one in 2010 and the other in 2016, with no information on the amount of the award. The Cerebral Palsy Alliance of Singapore (CPAS), KK Women's & Children's Hospital (KKH) and the National University Hospital launched Singapore's first cerebral palsy registry in September 2017 (170).

South Africa

CP research in Africa overall is limited as little has been published. Although there are quite a few studies generated from South Africa, there doesn’t seem to be a clear funding scheme for CP. The South African Medical Research Council, which is the main funder for health research, does not have available information on funding for CP. In fact, a review on CP in Africa highlighted a crucial need for studies on prevalence, spectrum of cerebral palsy, and main aetiologies in the African context.
Brazil

The publicly funded\textsuperscript{13} São Paulo Research Foundation (FAPESP) is one of the country’s leading funding agencies for health research (2012 estimate is USD 154.2 million, more recently over USD 500 million in support of c. 11k project proposals) (168). We searched the grant and scholarship database using the keyword “cerebral palsy”, which yielded a total of 81 CP-related research grants and scholarships, without available data on the amount given.

It is worth noting that FAPESP has signed a bilateral agreement with UK Research & Innovation (see above) “to welcome, encourage and support applications that may cut across their national boundaries and involve international collaborative teams”.

Argentina

The Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) (English: National Scientific and Technical Research Council) is one of the main funding agencies for health research in Argentina. Cuts in government funding means, however, that overall the Council is having to reduce the number of early-stage researchers it has historically funded.

There is no explicit research policy around CP, but the term “cerebral palsy / parálisis cerebral” yielded details of a total of 6 grants without available information on the amount of funding given – none are focused on either aetiology or prevention.

\textsuperscript{13} São Paulo State’s constitution mandates 1% of monthly revenue to the Foundation:

https://www.nature.com/articles/d42473-018-00281-z
CONCLUSIONS

The results of the analysis of available funding for CP research shows that the United States’ NIH is still the largest and most consistent contributor. The funding for CP research in Australia has also increased, particularly due to the founding of the CPARF, now one of the main funders for CP research. In the UK, government-based funding for CP from the UKRI has not been increasing, whilst funding from the NIHR has improved over the years, although not directly related to CP.

Results of this review also show that only two philanthropically funded organisations in the UK have a specific call for CP research, with The Little Foundation being unique in focusing on CP prevention. Results of the health research analysis report from the UKCRC show that, in general, the total estimate for health relevant research in the UK was £2bn in 2014. Funding for neurological research, which includes CP, appeared to have had the greatest decrease, falling from 11.6% in 2004/05 to 9.0% per cent in 2014 (Figure 9) (171).
Among the reasons given for the lack of investment in CP research is the condition’s comparative rarity. Two things militate against this: the inconsistent nature and lack of CP registers globally in all probability masks the true prevalence of CP – particularly in the less developed world; and the social cost of caring for those affected by CP is growing, while incidence is not decreasing among those not affected by pre-term birth.

The increasing evidence that CP may be preventable has not yet been paralleled by an increase in funding for the prevention and identification of risk factors for CP. There is a strong need for substantial future investment by government and philanthropic agencies to prioritise and increase funding for CP-related research projects and to increase funding for work on prevention.

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14 Image reproduced from “UK Health Research Analysis 2014 (UK Clinical Research Collaboration, 2015)” in accordance with Creative Commons Attribution 4.0 International (CC BY 4.0) License.
The cost of cerebral palsy

As a lifelong condition with poor quality of life, CP and its associated co-morbidities place a huge burden on families as well as the health and social care systems. The high lifetime costs for a child born with the condition, combined with the size of the CP-affected population, underline the case for prevention to be a public health priority.

The average lifetime cost per person, based on research studies in the United States in 2003 (172) and Denmark in 2009 (159), and an estimate reported by the Chief Medical Officer of England in 2014 (173), is at least £690,595. These estimates include health expenditure, educational needs, social services and lost economic opportunity, but exclude legal claims and compensation pay-outs.

In the absence of a national CP register we cannot be precise about the life expectancy of those affected by CP, nor about their overall number in the UK population. The generally accepted lifespan is 30-70 years (159), while the CP population is believed to be similar to those with multiple sclerosis and Parkinson’s disease at between 100,000 and 120,000. Thus, assuming an average lifespan of 50 years, the annual cost to the UK economy of mitigating CP is £1.4-1.6 billion and may be significantly more.

Compensation payments arising from litigation against the NHS amounted to a further liability of £390m between 2012 and 2015 (174).

If prevention research holds out a reasonable prospect of reducing the incidence of CP, it is clear that significant and durable savings can be made.
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