

Pediatric Cerebral Palsy Life Expectancy: Has Survival Improved Over Time?

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Abstract

Purpose: The management and treatment of cerebral palsy (CP) presents a challenge despite advancements in nutrition and feeding as well as the management of bronchopulmonary complications and disorders. Relative poorer survival has been observed among CP children and has been associated with intellectual and motor impairments as markers of disease severity and hence excess mortality. However it is unclear if the advancement in treatment parallels survival of these patients. This systematic review is aimed to examine whether or not survival has improved over time, comparing before and after the year 2000.

Materials and methods: We utilized a systematic review design to search literature published between 1966 and 2012. The search terms used were "cerebral palsy and mortality", "cerebral palsy and survival", "cerebral palsy geography", "cognitive impairment" and "motor impairment". We identified 22 articles and performed a literature synthesis to address the research question.

Results: CP survival is influenced motor impairment, intellectual impairment, as well as other contributory factors such as low birth weight, socioeconomic status (SES) and gestational age. The causes of death remain largely respiratory issues and disorders. Survival among CP patients is significantly lower than those of children in the general population. It appears there is no significant difference in survival of CP patients over time despite improvement in treatment and a slight decline in mortality comparing studies published before 2000 with those after 2000.

Conclusions: Motor and intellectual impairment as two major contributing factors to CP survival among children. Additionally, respiratory disorders and issues remain a most significant factor in the causal pathway of CP mortality. Furthermore, the survival of children with CP has not significantly improved over time, despite advancements in respiratory and feeding and nutrition management. The finding in this systematic review is suggestive of aggressive management and treatment of respiratory problems in order to prolong survival of children with CP.

Introduction

Cerebral Palsy is the most common motor disability during childhood with a prevalence range of 1-4 per 1,000 live births for certain age ranges, as gleaned from international studies [1]. In the U.S., an estimated 746,000 children and adults have CP with a prevalence of 3.3 per 1,000 [2]. According to studies from Surveillance of Cerebral Palsy in Europe, prevalence in males is slightly higher than females, at a ratio of 1.33:1 [1]. It is estimated that 70-80% of cases are prenatal, though the majority of these do not have a known cause [1].

Cerebral Palsy (CP) is a developmental disorder affecting cognition and motion (posture and balance) resulting from abnormality of the brain [3]. A small percentage of cases can be caused by hypoxia [3]. In addition to motor function disability, CP can be associated with other conditions including intellectual disability, seizures, impairment of vision, hearing or speech, musculoskeletal disorders, and bronchopulmonary disorders [4,5]. Several factors have been implicated in congenital CP risk, including but not limited to low birth weight, prematurity, infections during pregnancy, maternal steroid use and birth complications [4]. Risk factors for acquired CP include infections, such as meningitis, injury to the brain and cerebrovascular dysfunction [4].

While most cerebral palsies are characterized by some sort of movement dysfunction and/or brain damage, there is a great deal of variety in the kind and severity of symptoms present in an individual, as well as any related conditions. The degree to which functioning is impaired and quality of life is affected varies between individuals as well. Spastic CP is the most common subtype, occurring in 80% of cases [4] and is characterized by abnormally high muscle tension and inability to stretch muscles as well as neuromuscular mobility impairment

resulting from lesions in the brain and motor cortex [4]. Spastic hemiplegia affects one side of the body and is the more ambulatory form [4,6]. Spastic diplegia, the more common form, occurs when the lower extremities are more affected by stiffness and tightness at the lower extremities may cause a scissor gait [4]. Overtime, additional problems such as hip dysplasia can occur [4]. These individuals often have impaired intelligence and vision as well [4]. Spastic quadriplegia is the most severe of the spastic forms and affects all four extremities as well as the trunk and the head [4]. In addition to spastic CP, there is the dyskinetic and hypotonic varieties. Dyskinetic CP is caused by damage to the cerebellum and is illustrated by involuntary movement and low muscle tone, in contrasts with the spastic type [7]. Hypotonic CP is also described by low muscle tone and influences posture maintenance [8]. These subtypes substantially influence life expectancy among these patients, reflecting the severity of cognition and motor dysfunction.

Overall, individuals with CP have a lower life expectancy than the general population, with one study of a California population

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demonstrating a mortality of 90 per 1,000 [9]. Studies on life expectancy and mortality of CP patients have indicated a plethora of different causes of death, including bronchopulmonary disorders, sepsis, seizures and discovered death during sleep. While there is extensive literature on the life expectancy and mortality of CP patients, there is a dearth of literature on how life expectancy has changed over time, specifically a systematic review on the topic. The aim of the current study was to conduct a systematic review of existing studies on life expectancy for CP patients and to describe how survival has changed over time.

Material and Methods

Literature search

The aim of this systematic review was to examine published literature in determining whether or not CP mortality has improved over time. Since the methodology used in this study involves synthesis of literature, there was no formal IRB approval. Utilizing the PubMed search engine, we examined articles published between 1966 and mid 2012 to determine whether or not cerebral palsy survival has improved over time (Figure 3). We compared studies conducted and published before and after 2000. Our search criteria included, (A.) peer reviewed studies published in the English language only, (B.) studies with sufficient sample size to have the power (80%) to determine the factors that may be associated with survival, (C.) This review included the most recent publication from a single institution if more than one article was published from the same sample in the same subject. This systematic review excluded papers that presented an abstract without a body text. We also excluded conference proceedings in order to avoid preliminary findings bias. The search terms used were “cerebral and palsy”, “cerebral palsy and mortality”, “cerebral palsy and survival”, “cerebral and palsy and geography”, “cognitive and impairment” and “motor and impairment”.

Sample size and patient population

With the above search terms, we first identified (k=30) articles on cerebral palsy and mortality, then narrowed our search to cerebral palsy in children and mortality (k=22). Eventually this systematic review included 8 articles in the synthesis of results.

This systematic review involves patients from original studies diagnosed with CP treated and followed for the disease. The samples from the original articles were studied in several countries in the world including Australia, United States (California), United Kingdom and Sweden.

Data quality

We examined the quality of all the articles prior to their inclusion in this systematic review. These assessments included study aims and objectives (Were the aims/objectives clearly stated?), outcome measures (Were the primary and secondary end points measured in a way to relate with the aim of study?), power and sample size estimation (Did the authors formally calculate the sample size needed for the study as well as present a power statement?), bias and confounding assessment as well as the adjustment for search confounding (Were bias identified and confounding assessed and controlled for?). Furthermore, studies were examined for design (retrospective, case control, perspective) as well as follow up period and loss to follow up (<10%). We also examined whether or not consecutive patients were studied as well as whether randomization or matching were used. Studies with poor quality, because of their effect on inference, were excluded from the

final results synthesis. Finally, the type of analysis used was assessed to see whether or not it was appropriate for the aim of the study.

Data synthesis

The synthesis of the results of this review was performed by identifying the common themes with respect to factors associated with cerebral palsy mortality. With this approach, we examined the number of patients dead or alive in each of the study samples in order to assess the proportion of those dying relative to those alive. We also used the hazard ratio to examine the force or risk of dying given the type of CP and other factors (cognitive impairment and loco-motor dysfunction), and compared these parameters before and after 2000 in order to determine whether or not survival has improved over time.

Results

The purpose of this systematic review was to assess the existing body of literature on mortality and life expectancy for pediatric patients with cerebral palsy in order to determine if survival has improved over time. This review revealed that children with cerebral palsy are more likely to have a higher mortality than the general population. In terms of age progression, Singer et al. [10] found that mortality rate was very high until age 15, with excess death rates at 20/1000 and above, and then decreased from 15 to 50 until it later reached a steady rate. Previously, Blair et al. [11] showed CP patients to have a standardized mortality ratio (SMR) of 4 to 5 times that of the general populations for ages 15-40. In a study by Hemming et al. [12], the percentage of individuals in a CP cohort surviving to the age of 20 was much less than the general population. A number of indicators for excess mortality have been reported. One of the most common is the severity of motor and intellectual impairment, with life expectancy decreasing as severity increases. The presence of multiple impairments also showed lower survivability. Shorter gestational age and lower birth weight demonstrated greater survival. Overall, the literature indicates that there has been little improvement in life expectancy for those with CP. However, some advances have been seen with the implementation of certain treatments. Therefore it is not fully understood why survival has not paralleled improvement in treatments.

Motor impairment as a contributory factor

As stated, survival is lower with more severe impairment, including motor impairment. Hutton et al. [13] found a 20 year survival of 99% for those without severe functional disabilities compared to the 50% found for those that were severely physically disabled. Crichlan et al. [14] observed that those with the hemiplegic type of CP, in which one side is affected and ambulation is slightly better than other types, fared better in survival according to Kaplan-Meier Survival Curve. There was a hazard ratio (HR) of 3.3 when all other types were compared to the hemiplegic group, implying a survival advantage for the hemiplegic group. In Williams et al. [15], there were no deaths with individuals that had less than four limb involvement with their CP. A more reliable example of motor impairment as an indicator of survival is exhibited in a study by Hemming et al. [12], which observed motor impairment to be the best indicator of survival based on estimated hazard ratios for ages 2-20 years. Severe lower limb impairment had the highest ratio of 5.01, with a higher ratio indicating it as a better predictor of mortality. In Hutton et al. [16], severe motor disability was associated with a 30 year survival of 42% and survival decreased with increasing severity. Blair et al. [11] found risk of mortality increasing by 39% for each increase in severity categorization. Hutton et al. [17] observed those

with a severe manual disability had a 24.9 times higher risk of dying than those that did not and it was 21.9 times higher for those with a severe ambulatory disability compared to those that did not. Reid et al. [18] demonstrated that the strongest independent predictor of mortality was non-independent ambulation, with an adjusted hazard ratio of 6.2. Another convincing indication of how risk of expiration increases with increasing motor dysfunction comes from Westbom et al. [19]. The estimated survival at 19 years of age was 60% in children with a GMFCS level V, or children with the most severe gross motor function impairments while all children in the cohort with GMFCS level I and II survived, along with 96% of all children in the cohort.

Intellectual impairment as a contributory factor

Like motor function, more severe intellectual impairment is related to excess mortality. Cohen et al. [20] found a correlation between functional outcome and intellectual functioning. Crichlan et al. [14] indicated severe mental retardation to be a strong predictor of decreased survival as the hazard ratio of severe retardation to the lesser categories was 4.7. Blair et al. [11] demonstrated that those with profound intellectual disability, 23% were estimated to die by age 5 and 50% by age 18. This comes in contrast to the 10% and 24% of severe intellectual disability and pales in comparison to the 1.1% and 2.8% of those with higher intellectual functioning. This study found intellectual function a better predictor of mortality than motor functioning, as risk doubled with each increased categorization of severity and a mortality risk ratio of 2.14. Hutton et al. [17] observed that of those with severe cognitive disability in their cohort, 63% live to age 35, compared to 98% without severe disabilities. This study illustrated that the risk of dying was 18.3 times as likely for those with severe cognitive impairment compared those without. Reid et al. [18] showed intellectual ability to be a good predictor of mortality, with a hazard ratio of 3.0. However, it was not as reliable a predictor as independent ambulation. Hemming et al. [12] found intellectual ability to be the second best risk indicator, with a proportional hazard ratio of 3.91. This goes along with Hutton et al. [17] in finding intellectual ability to increase risk of death less so than motor dysfunction. In this same vein, Baird et al. [21] suggested that motor function is a better risk indicator than non-motor indicators such as cognitive ability.

Other contributory factors

The body of literature also indicated other contributory factors beyond severity of motor or cognitive impairment. One such factor is birth weight. Hemming et al. [12] observed that in the 1980's, survival of those born with low birth weight was significantly better than those born at normal birth weight ($P<.01$). The study also found significant interaction between socioeconomic status and birth weight as those born in affluent areas experienced a birth weight effect 2.2 times greater than the effect felt by those born in deprived areas. Hutton et al. [13] found that subjects with birth weight <2500 g had 20 year survival of 92% while those with a weight greater than that had a survival of 87%. However, later, Hutton et al. [16] saw a different result, as normal birth weight did not experience a cohort effect but the 10 year survival of low birth weight infants decreased between 1966 and 1989 from 97% to 89%. Hutton et al. [22] reiterated the economic status to birth weight effect relationship, as it was noted that children of normal birth weight (≥ 2500 g) born into affluent families have poorer survival than those from less affluent families while children of low birth weight fare better in affluence. In addition to birth weight, gestational age proved to be a risk factor as well. Hemming et al. [12] observed that survival

of children born pre-term was significantly ($P<.01$) better than that of children born at term. In line with this, Hutton et al. [13] found subjects with gestational age of less than 37 weeks had 20 year survival of 93% while those greater than 37 weeks had a 20 year survival of 85%. Hemming et al. [23] illustrated that the proportions of severe motor or cognitive impairments increased with increasing gestational age, such as a 20% to 50% between weeks 30 and 40 for cognitive impairment. Most recently, Reid et al. [18] showed term birth to be a risk factor for mortality, with a hazard ratio of 1.8. Finally, another examined risk factor was pre or postnatal acquisition of CP. Hutton et al. [17] concluded that survival rates of those with postneonally acquired cerebral palsy, though lower, were not significantly different from those with cerebral palsy not acquired postneonally. Baird et al. [21] echoed this in concluding mortality for children with a postnatal cause is also not significantly different from those with presumed prenatal and perinatal causation ($p=0.58$). Similarly, Hutton et al. [16] demonstrated that early onset CP had better survival than late onset but the difference was not significant.

Causes of death

In addition to contributory factors for mortality, causes of death were also evaluated as part of survival studies. A unifying aspect of the studies was the indication of broncopulmonary disorders as a direct cause of death. For instance Evans et al. [24], obtained 73 death certificates of infants with CP and found that only 22% had cerebral palsy listed as the underlying cause while 28% had a respiratory related underlying cause of death. Strauss et al. [25] went in depth on the topic of cause of death and adds another dimension to it by looking at CP patients risk for cancer. It was shown that in each age group he examined, the total number of cancer deaths was substantially higher than expected in the general population, as indicated by significantly larger standardized mortality rates (SMR). Eighteen children aged less than 15 years died from brain cancer, which was 44% of all deaths under 15 in the study cohort. This was greater than the 0.68 expected in the general population, $SMR=26$. Also, digestive tract cancer was higher and breast cancer deaths were three times higher than the researchers expected in this population. Surprisingly, this study found a smaller proportion of respiratory related deaths than expected. However, Reddihough et al. [26] and Baird et al. [21] observed respiratory problems, such as pneumonia, to be most commonly reported.

Treatments

Some studies looked at survival in response to specific treatments. With scoliosis and spinal deformities being conditions associated with CP, Tsirikos et al. [9] examined survival in a cohort that underwent spinal fusion surgery. While 12.5% of the cohort experied, the mean survival for this group of pediatric patients with spastic CP and severe involvement who underwent spinal fusion was 11.2 years. Proportional hazard regression analysis was used to identify variables that best predicted survival time and found that degree of preoperative thoracic kyphosis angle and length of Intensive Care Unit (ICU) stay following surgery were best, as determined by beta coefficients (β), Wald statistics, and significance levels for the analysis. Another common aspect of CP is musculoskeletal spasticity, for which there are some treatments. A treatment examined by Krach et al. [27] is intrathecal baclofen (ITB). The study observed that survival at 8 years of follow-up was 92% (SD 1.9%) in the ITB cohort and 82% (SD 2.4%) in the non-ITB cohort ($p<0.001$). Another important issue with CP patients is feeding, and Strauss et al. [28] examines survival for those that need a feeding tube.

The study found that gastrostomy feeding was associated with a 2.3 times higher mortality than the reference group which could be fed orally. Westbom et al. [19] backed this finding by indicating a nine-fold increased risk of dying for those that were tube-fed. This study suggested that gastrointestinal tube feeding indicates the fragility of the patient, which could explain its association with increased mortality.

Survival over time

Overall, the body of literature reveals that survival has changed little in recent history. Figure 1 shows the proportion of a study cohort that died during the study period for studies published in different years. This figure shows a rise and fall in the percentage of a cohort that died during the study period. It peaks during the early 2000's and has since fallen, but still fluctuates greatly between studies. Also, the proportion that died in recent studies is generally not lower than the proportion in much earlier studies. However, caution should be taken with the interpretation of this figure as the cohort size, characteristics, demographics and other factors vary between studies. Over time, there has been consistency in cause of death and contributory factors. For instance, Evans et al. [24] found respiratory distress to be a common direct cause of death and this were reiterated by Reid et al. [18]. Several studies found respiratory related issues to be a common cause of death. Furthermore, there was consistency in the contributory factors for excess mortality. Severity of motor and intellectual function has often been mentioned. For instance, Evans et al. [5] found that severe motor and intellectual sub-normality were good predictors of survival and this remained the case over two decades later, as Baird et al. [21] indicated that the main predictive factor was severity of impairment of functional ability. However, there has been some progress, especially

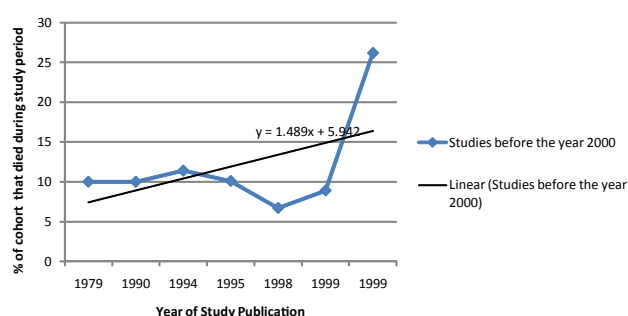


Figure 1: This figure shows the percentage of each study cohort that dies during the study period for each study published in a given year, for studies before the year 2000. A linear regression line was created for the data.

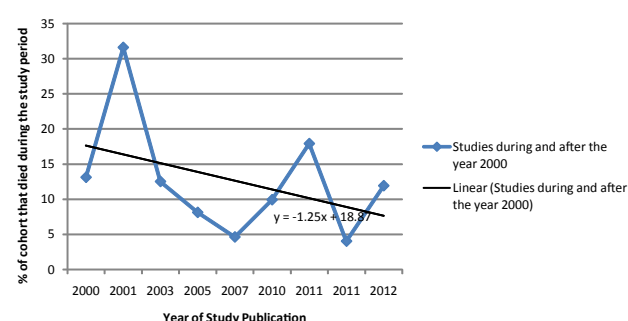
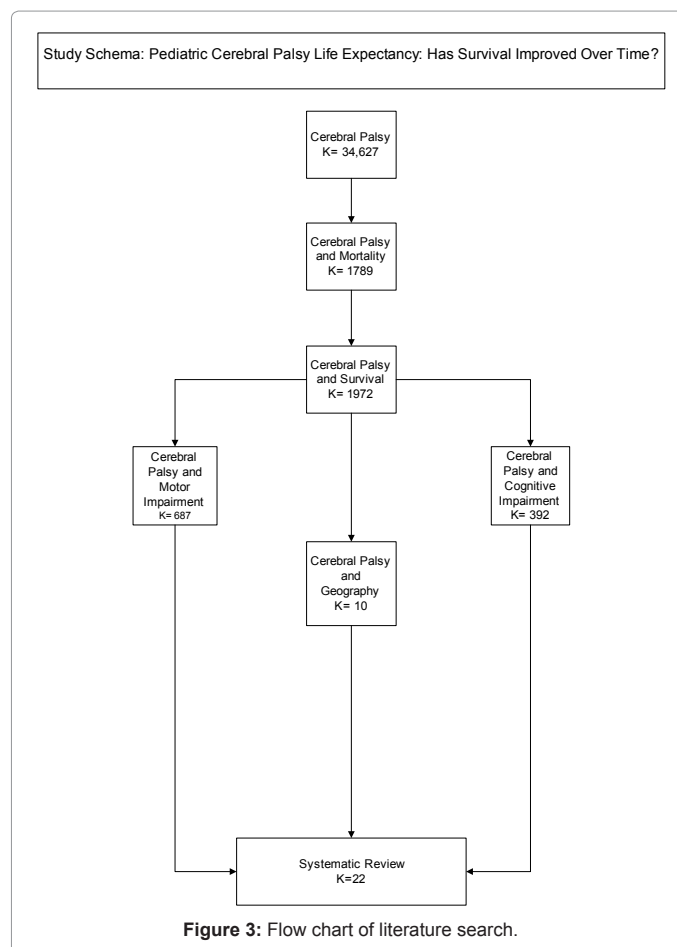


Figure 2: This figure shows the percentage of each study cohort that dies during the study period for each study published in a given year, for studies after the year 2000. A linear regression line was created for the data.



with certain treatments. Tsirikos et al. [9] found that spinal fusion surgery for scoliosis associated with CP prolonged survival. Krach et al. [27] found that intrathecal baclofen, a drug used to treat the spasticity associated with CP, led to greater life expectancy. An area where progress is lacking is nutritional/feeding issues, because studies found that a gastrointestinal feeding tube was associated with lower life expectancy (Figure 2).

Discussion

This study was proposed to examine whether or not pediatric CP survival has improved over time. To address this question, we performed as systematic review using published literature between 1966 and 2012. There a few relevant findings in this systematic review. First, cerebral palsy survival is influenced by motor impairment, intellectual impairment, as well as other contributory factors such as low birth weight, gestational age, feeding and socioeconomic status (SES). Secondly, the causes of death remain largely respiratory issues and disorders. Thirdly, survival among cerebral palsy patients is significantly lower than those of children in the general population. Finally, it appears there is no significant difference in survival of CP patients over time despite improvement in treatment and a slight decline in mortality comparing studies published before 2000 with those after 2000.

This systematic review has indicated that motor impairment, intellectual impairment, low birth weight, gestational age as well as SES tend to influence survival of children with cerebral palsy. Our systematic

review found that in cohort studies, children with severe intellectual or motor impairment were the ones with the least survival. Our findings agree with previously published literature on the impact of cerebral palsy severity, which is directly defined by motor impairment and intellectual deterioration as major contributing factors to mortality [11-21]. While there are factors influencing mortality that are modifiable, the previous factors are non-modifiable but require special management in order to prolong survival. For example CP children diagnosed with severe motor and intellectual impairment require extra care, monitoring and surveillance for survival prolongation. Without care and monitoring for these patients, we expect survival to be poor, given that severe motor impairment results in immobilization, loss of muscle mass, bedridden state and subsequent decubitus ulcers, which have a mortality rate of 3.8/100,000 according to studies [29]. Intellectual impairment in CP patients is characterized by severe mental retardation. Severe mental retardation is associated with neuro-motor dysfunction involving rectal and bladder dysfunction as well as pulmonary compromise due to immobility. Specifically, intellectual impairment predisposes one to pulmonary as well as gastrointestinal infections requiring special management in order to prolong survival.

Low birth weight and gestational age were shown to adversely impact survival. This observation is comparable to failure to thrive, which is related to low birth weight, poor nutritional status and gestational age. Low socioeconomic status, paradoxically, tended to improve survival, given the interaction between birth weight and SES. Our review found that children with normal birth weight born to affluent families had poorer survival than those born to non-affluent families. The observed differences in survival may be due to their immunologic status in terms of humoral immune response provided by antibodies, given the exposure to environmental antigens, such as pathogenic microbes in the less affluent environments.

Respiratory disorders, in most literature across the world, have been implicated in the causal pathway in CP mortality. Our systematic review confirms previous findings in this vein [21,24,26]. The management of respiratory disorders is essential in prolonging survival in children with CP, given that this is the most significant single causal factor in CP mortality. This systematic review suggests aggressive treatment and management of pulmonary infections, pneumonia, chronic obstructive pulmonary disease, asthma and bronchitis.

We have shown in this systematic review that children with CP tended to have lower survival compared with the general population. The relative lower survival observed in our systematic review is supported by previous findings [9]. It is however, expected that children with CP, given the co-morbidities, should have lower survival. However, one is not expected to find such differences in the adult population given survivorship (hawthorn effect).

Our review has not fully and clearly answered our proposed question as to whether or not survival has improved over time. This question could have been clearly addressed if we were able to perform a quantitative systematic review such as quantitative evidence synthesis (QES) as proposed by Holmes et al. [30]. While there have been changes and improvements in the management and treatment of CP patients with respect to respiratory conditions or issues, feeding and nutrition and overall functioning, survival does not seem to decrease significantly as we would expect. Our synthesis of literature supports the recently published paper by Reid et al. [18].

Despite the strength of this systematic review, there are limitations.

First, we were unable to perform a quantitative systematic review (meta-analysis) as stated earlier, due to several methodological flaws of the original articles that constitute this systematic review. Such an opportunity could have allowed us to quantify, using Cox proportional hazard models and relative survival of CP patients, and compare studies before and after 2000. Secondly, we were not able to perform a pooled analysis given the differences in the design of the studies as well as the variability in the point estimates or effect size. In spite of these limitations, we do not think that our systematic review is driven solely by these limitations.

In summary, this systematic review has indicated motor and intellectual impairment as two major contributing factors to CP survival among children. Additionally, respiratory disorders remain a most significant factor in the causal pathway of CP mortality. Furthermore, the survival of children with CP has not significantly improved over time, despite advancements in respiratory and feeding and nutrition management in these children. The finding in this systematic review is suggestive of aggressive management and treatment of respiratory problems in order to prolong survival of these children.

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