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Survival, Mortality, and Life Expectancy

Steven M. Day and Robert J. Reynolds

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Abstract

Cerebral palsy (CP) is a heterogenous condition, with level of disability ranging from immaterial to profound. In concert with the continuum of level of severity of disability/independent functioning, health care needs, therapies, medications, surgical interventions, costs of care, daily demands on parents and other family members, and expectations for the future in terms of education, employment, and other milestones of life all vary widely. Similarly, life expectancy in CP follows a continuum, from far lower than to potentially as high as general population life expectancy, that parallels the continuum of levels of disability. Here we review the literature documenting this, and examine the specific factors that are known to be strongly associated with mortality and longevity in CP. We also examine the evidence regarding causes of death in CP, and present some new findings related to this. Finally, we outline important methodological considerations for future research in this area.

Keywords: cerebral palsy, life expectancy, survival, mortality, developmental disability

1. Introduction

Just as Americans headed home for the year-end holidays, the Centres for Disease Control and Prevention (CDC) issued its annual report on mortality—which had no news to celebrate. According to the report, published on December 21st, life expectancy in America fell in 2016, for the second year in a row. An American baby born in 2016 can expect to live on average 78.6 years, down from 78.9 in 2014. The last time life expectancy was lower than in the preceding year was in 1993. The last time it fell for two consecutive years was in 1962-1963. - The Economist, 4 January 2018 [1].

The concept of life expectancy is familiar to most people by virtue of reports in newspapers, online sources, or on television or radio. Comparisons of life expectancy at birth in various industrialized countries are common, and thus many people may know or will not be surprised to find that life expectancy is higher in Japan than it is in the US, or that in Russia it is lower than in most countries of Europe. Many may also have some general ideas as to why such differences may exist: diet, exercise, smoking prevalence, access to healthcare may all contribute. Mortality is the ultimate endpoint for studies of health and wellbeing, and life expectancy is one way to summarize the survival and mortality experiences of different groups of people.

Few give much thought as to how exactly we can know that life expectancy in America fell in 2016, as The Economist reports [1]. To fully understand how we can know that (or know that life expectancy in Japan is higher than it is in the US, or that life expectancy for the Hispanic population in the US is greater than it is for people in the US overall, or that women have a greater life expectancy than men almost universally), one needs to understand what life expectancy is, and how it is calculated. In this chapter we will begin with a brief review of the life table, the principle tool used by demographers, actuaries, biostatisticians and epidemiologists in examining questions of life expectancy. In these contexts, life expectancy has a very specific meaning, and must not be confused with the actual survival time of a given individual.

Just as it is known that life expectancy in Japan is greater than in the US, it is also known that life expectancy for groups of people with differing medical conditions, behavior patterns, or professions can differ. It is probably not surprising, for example, that children born with complex congenital heart defects have a lower life expectancy than that of any general population (GP) of age- and sex-matched children (including all comers, with or without heart defects). Similarly, persons with various types of cancer have life expectancies that are lower than those of age- and gender-matched populations (including all comers with or without cancer). Within the population of children born with congenital heart defects, or persons with cancer, variation in life expectancy exist as the group is sub-divided according to level of complexity of heart defects, or site/stage/grade/histology of tumor. Similar statements apply when considering the life expectancy in cerebral palsy (CP). That people with cerebral palsy compose a heterogeneous group will be well understood by most readers of this chapter; as we shall see, the life expectancy of the group as a whole and of meaningfully defined subgroups differ dramatically as a consequence.

The life expectancy of persons with cerebral palsy (CP) is of interest to many audiences for varying reasons. Parents would like to know how long they might have to fulfill the often-challenging physical, emotional, and monetary demands of caring for a child with special needs; they wonder how long they might get to enjoy the rewards of that relationship and wonder and worry whether their child might outlive them. Resource allocation for long-term care facilities depends in part on their residents' longevity, a fact of interest to governments or private insurance companies providing funding for such facilities. Life insurance and structured settlement underwriters must consider life expectancy and other information in a life table in pricing insurance or annuities. Finally, and perhaps most controversially, in cases of litigation related to medical care and treatment alleged to have contributed to an outcome of

CP, life expectancy can be a critical factor in developing and valuing a life-care plan, the expected present value of which may be a large part of potential damages in such litigation.[1] Our interest in this chapter is to provide information based on sound scientific principles and evidence.

2. The life table and survival curve

Life expectancy (LE) is the arithmetic average survival time remaining for a cohort, hypothetical or real. In more technical statistical terms, it is the expected value of a population of random survival times. Alternatively, one can think of it as the average survival time for an individual member of a given population or cohort if such an individual could (hypothetically) live life over and over again.

In order to understand the meaning of life expectancy, and to gain insight into the questions posed above, a basic understanding of the life table is extremely helpful. As we shall see, information presented in a life table can also be set out in, or gleaned from, a survival curve. An understanding of the relationship between the life table and its corresponding survival curve will be helpful in understanding life expectancy *per se*, and in understanding the connection between many studies of long-term survival of children and adults with cerebral palsy, many of which report survival curves or the equivalent, and life tables and life expectancy.

2.1. The life table

Table 1 is an abbreviated version of the latest life table (2017 table based on 2013 data) for all US persons (males and females combined) from the US National Center for Health Statistics (NCHS) [2]. Life expectancy at each whole integer age is given in the column labeled *e(x)*. We can see from **Table 1**, for example, that the LE in the US is 78.8 years at birth; 50.1 remaining years at age 30 years; 23.2 remaining years at age 60; and 2.3 remaining years at age 100. Generally, the meaning of LE is the average remaining lifespan from a given age. This is not to be confused with the age to which a cohort of a given age is expected to live. Thus LE is 78.8 remaining years, to age 78.8, for newborns of age 0; it is 2.3 remaining years, to age 102.3, for those fortunate enough to survived to age 100.

In addition to LE, a life table provides other information, including (for example) (1) the likelihood that a person born today will be alive at age 50, 80, or 100; (2) the 5-year survival probability from any age; (3) the probability of surviving beyond age 70; (4) the median survival time, that is, the time at which half of the hypothetical cohort will have died and beyond which half will continue to live; and (5) the conditional probability of living to age 65 given one has already lived to age 40. Depending on the context, any of these figures may be of greater interest or importance than the LE at a given age; however, LE is the most often cited

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[1]For full disclosure, we acknowledge that we, the authors of this chapter, have provided expert opinions on behalf of both plaintiffs and defendants in such legal cases, and will undoubtedly do so in the future.

summary measure of survival. For further details about the columns of the life table and their inter-relationships, the reader is directed to the many references included below [2–6].

2.2. Survival curves

We now focus on age and the column *l(x)* of **Table 1**. If we divide the figures in the *l(x)* column by the radix of the table (*l(0)* = 100,000), we obtain the probability of survival to each age. **Figure 1** plots the resulting survival probabilities against age, the survival curve corresponding to the full US life table (males and females combined).

The unabbreviated version of the life table [2] and the corresponding survival curve (**Figure 1**) provide essentially the same information. The area under the survival curve equals the LE calculated in the life table; if a line vertical line is drawn at any given age in the survival curve figure, the area under the curve (and bounded by the x- and y-axes) from that point to the right will be the life expectancy at that age. In **Figure 1**, the area under the curve from age 70 to age

Age	l(x)	d(x)	q(x)	m(x)	L(x)	T(x)	e(x)
0	100,000	596	0.006	0.0060	99,702	7,882,920	78.8
1	99,404	42	0.000	0.0004	99,383	7,783,218	78.3
2	99,362	25	0.000	0.0003	99,350	7,683,835	77.3
3	99,337	18	0.000	0.0002	99,328	7,584,486	76.4
4	99,318	16	0.000	0.0002	99,311	7,485,158	75.4
5	99,303	14	0.000	0.0001	99,295	7,385,847	74.4
6	99,288	13	0.000	0.0001	99,282	7,286,552	73.4
7	99,275	12	0.000	0.0001	99,270	7,187,270	72.4
8	99,264	10	0.000	0.0001	99,259	7,088,000	71.4
9	99,254	9	0.000	0.0001	99,249	6,988,742	70.4
10	99,244	9	0.000	0.0001	99,240	6,889,493	69.4
20	98,953	70	0.001	0.0007	98,918	5,898,013	59.6
30	98,062	105	0.001	0.0011	98,009	4,912,689	50.1
40	96,811	165	0.002	0.0017	96,729	3,937,892	40.7
50	94,352	390	0.004	0.0041	94,157	2,980,312	31.6
60	88,788	785	0.009	0.0089	88,395	2,061,381	23.2
70	78,308	1475	0.019	0.0190	77,570	1,220,609	15.6
80	57,879	2854	0.049	0.0506	56,453	528,563	9.1
90	24,208	3443	0.142	0.1534	22,486	110,867	4.6
100	1971	703	0.357	0.4411	1620	4540	2.3

**Table 1.** Life table of the US general population, 2017 [2].
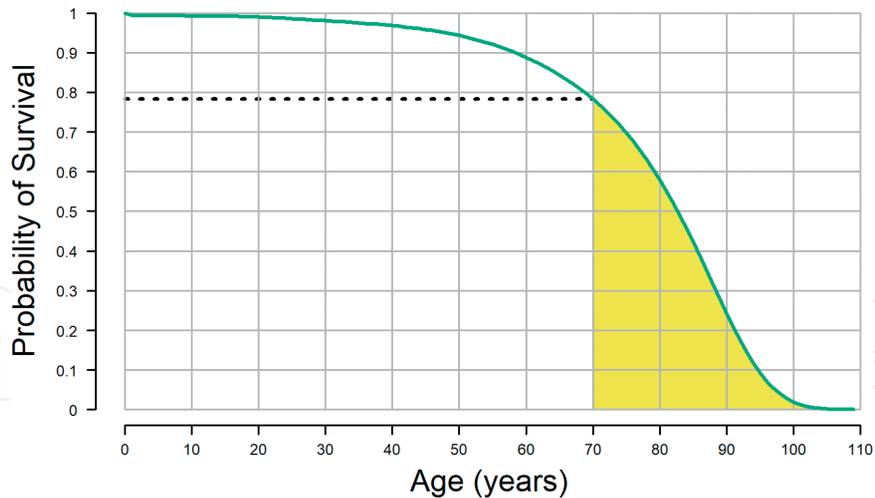
Figure 1. Survival curve for the US GP, 2013. Total area under the survival curve is equal to the life expectancy at birth. Area under the curve from age 70 (shaded in yellow) is estimated by *T(70)* ÷ 100,000 in the life table, 1,220,609 person-years ÷ 100,000 persons = 12.2 years. This can be estimated in the figure by counting rectangles in the shaded area. This area, normalized by dividing by the probability of survival to age 70, 0.78308, is equal to the life expectancy at age 70: 12.2 years ÷ 0.78308 = 15.6 remaining years.

110 (the end of the figure) has been shaded. If one counts the shaded rectangles (and fractions thereof) and divides by the probability of survival to age 70 (0.78308), one will find a number close to the $e(x)$ number for age 70 in the life table, namely 15.6 remaining years (which would be to age 85.6).

This connection between the life table and the area under the survival curve gives a way to visualize the implications for life expectancy of evidence provided in many studies of CP survival. **Figure 2** provides a hypothetical, but typical, survival curve for children with relatively severe CP
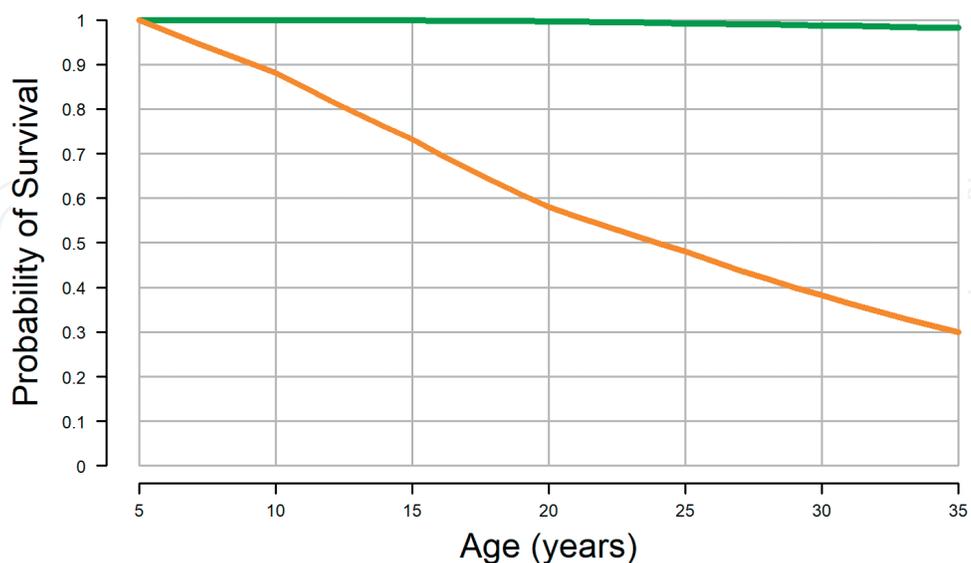

Figure 2. Survival curve for US GP (green) and a cohort with relatively severe CP (orange), from age 5 to age 35. The area under the CP survival curve must clearly be less than that under the GP curve, even if we extend the curves to ages above 100. Methods for extrapolating the CP curve to old ages have been discussed and tested in the literature [3, 5–7].

from age 5 to 35 years. On the same figure, we include the corresponding GP survival curve over the same ages. One can immediately see that the area under the CP curve has to be less than that below the GP curve, and this would be true even if both curves extended to ages over 100 years. Published studies of survival of CP (or almost any medical condition) provide estimates of survival across a limited age span - but survival to all ages is needed to estimate life expectancy. Thus some method of extrapolating information to ages 100 or beyond is necessary to use such empirical evidence to estimate life expectancy.

An in-depth explanation of the issues involved in such extrapolations is beyond the scope of this chapter. Descriptions and comparisons of various methods may be found in the references cited below [3, 5–7]. In the next section, we review the factors that have been shown to be strongly associated with long-term survival in CP.

3. Factors associated with long-term survival, mortality risk, and thus with life expectancy in CP

In the preceding section, we provided a general introduction to the concept of life expectancy and touched upon the idea that persons with various medical conditions may have life expectancies lower than those of age- and gender-matched general populations. In this section we identify the main factors associated with longevity and life expectancy in CP. We will delineate these factors roughly in order of importance, beginning with those having the greatest potential impact on life expectancy. The reader should keep in mind, however, that everything is relative in this regard. Thus, while gross motor functioning may rightly be identified as a major factor, and often the most significant factor effecting life expectancy in CP, for those with only minor deficits in gross motor functioning, another factor may in fact be more relevant. Thus, for any given individual or group, the factors identified in this section may need to be re-ordered for importance.

3.1. Gross motor functioning

"The contraction of the muscle…causes dilation of the arterioles, capillaries, and lymph spaces, allowing more oxygenized blood to flow to the muscular fibers, which abstract from it what they require for their nutrition and let the remainder, together with used-up material, pass partly into the veins, partly into the lymph spaces and the lymphatic vessels. By this process the muscle is nourished, the products of decomposition are removed, metabolism is promoted, and heat is produced. …

The most natural of all muscular exercises, as pointed out by Hippocrates, is walking exercise. A great part of all the muscles in the body is activated by it; the action of the heart and respiratory organs is increased; the blood is passed with greater force from the heart into the blood vessels of the body, which are obliged to contract more vigorously, carry more blood to the different organs of the body, nourish the latter, and are themselves nourished through their work." Sir Herman Weber, *On the Influence of muscular exercise on longevity.* 1918 [13].

It has long been understood that voluntary physical activity helps promote health and longevity, and that, conversely, a sedentary lifestyle leads to elevated risk of morbidity and mortality [8–13]. The negative consequences of involuntary inactivity, after injury, illness, or surgery, have also been documented [14]. That the limitations in volitional gross motor functioning that often manifest in persons with CP might negatively impact survival and life expectancy should therefore come as no surprise. Nevertheless, clear evidence of this association for CP and other encephalopathies affecting gross and fine motor functioning was not published before 1990.

In 1990, a *Special Article* published in the New England Journal of Medicine reported on the life expectancy of severely neurologically disabled people [15]. Drawing on the recent work that had identified severe intellectual disability (or mental retardation, as it was called at the time) as a marker for mortality rates far exceeding those of age- and gender-matched GPs [16], the study provided life tables stratified by level of disability. For the first time in a major medical journal, level of gross motor functioning emerged as a profound indicator of elevated mortality risk: Life expectancy for immobile children were reported to be less than 10% of age-matched GP life expectancy, and less than 20% that of ambulatory children with comparable levels of intellectual disability. Unfortunately, the article had a serious flaw that rendered all actual life expectancy figures too low, and all mortality rates too high by something on the order of a factor of 3.

Subsequent evaluations of life expectancy of CP specifically based on the same source of data (but without errors of arithmetic) have subsequently been reported and have confirmed what was perhaps the primary finding in the NEJM Special Article: life expectancy varies on a seeming continuum with level of independent gross motor functioning. Evidence in support of this hypothesis is abundant now, coming from numerous countries around the globe. Examples are easily found in the references at the end of this chapter. A summary of life expectancy estimates per se will be found in a recent review of literature from 1990 to 2014 [7]. Life expectancy for young children range from as low as 15 remaining years for those with little or no purposeful gross motor functional ability, to nearly as high as that of their peers in the GP for those who are able to walk without difficulty (and who have no other significant comorbidities related to their CP).

3.2. Fine motor functioning and feeding ability

In published studies, the ability to dress independently and to feed oneself have served as surrogates for overall fine motor functioning, and the connection to longevity is again straightforward: The greater the independent abilities in these areas, the longer the life expectancy. Numerous studies from California have focused on feeding ability [17–21]. Studies from England have focused on combinations of self-feeding and dressing abilities [22–27], and one study from Israel accounted for independent/non-independent feeding ability [28]. The association of mortality risk with fine motor functioning is not nearly as strong as with gross motor functioning, and a number of studies have not addressed this factor at all. Thus, if one is able to account for a specific category of gross motor functioning, a further adjustment for precise levels of fine motor functioning would be expected to have a smaller impact, all else being equal.

As we have alluded to above, the issue of enteral nutrition (via gastrostomy or otherwise) deserves special attention, and a number of studies have addressed this to one degree or another [17–20, 28–32]. Taken as a whole, these studies provide evidence of a strong association between placement of (and need for) a feeding tube with elevated mortality risk, all else being equal. Of course, association is not causation, and a number of reviews have pointed out the difficulties in interpretation of this association [33–37]. As one noted, "Mortality rates range from 7 to 29% but there is no way to ascertain the degree to which mortality can be attributed to the intervention" [33].

3.3. Intellectual disability

Historically, level of intellectual disability has been considered a strong driver of mortality rates and survival of people with a wide variety of neurological disabilities. Within the category of CP, level of intellectual disability may be of great importance for those whose gross and fine motor functional abilities are high; for those who are immobile and unable to feed themselves, the further impact of level of intellectual disability is small.

3.4. Epilepsy/seizures

Many studies have addressed the association of epilepsy, including remote symptomatic epilepsy, with elevated risk of mortality as a general medical condition, irrespective of any underlying disability [38, 39]. For remote symptomatic epilepsy, comparisons of mortality with the GP may be misleading, as some of the excess may be associated with an underlying brain injury or other neurological condition precipitating the seizures. A California study attempted to measure excess mortality risk associated with seizures by focusing on people with mild developmental disabilities and comparing mortality among those with and without a history of seizures [40, 41]. In studies of CP seizures have also been shown to be markers for excess mortality, above and beyond the excess mortality risk associated with limitations in mobility or feeding ability and other CP-associated disabilities [17, 18, 42, 43]. The relative impact of epilepsy on life expectancy is greater for those with greater levels of independent gross motor functioning.

The reason for the elevated risk of mortality in CP associated with seizures is likely multifactorial. First, as we will see in a subsequent section, seizures and convulsions do manifest as a cause of death in CP, and thus a direct link with mortality is evident. The presence of seizures may also be a marker for overall more involved brain injuries, which in turn may be associated with greater risk of long-term morbidity and mortality. And finally, some anti-epileptic drugs are associated side-effects that can be life threatening, including toxicities, liver failure, anemia, metabolic acidosis, and thrombocytopenia, among others [44, 45].

3.5. Visual and auditory disability

There is little evidence to suggest that auditory or visual disabilities impact directly on mortality risk in cerebral palsy. One Australian study did include deafness and blindness among five "additional impairments" that they found to have a significant impact on mortality rates after

Factor	Comment
Hydrocephalus	Level of risk diminishes with age but risk of infection and malfunction of ventriculoperitoneal shunt may persist across the lifespan.
Scoliosis, kyphosis	Severe cases may impact heart and lung function; surgical intervention is relatively safe and effective in such cases.
Frequent aspiration	Related to swallowing dysfunction, dysphagia, paletopharyngeal incoordination, or gastroestophageal reflux; leading to aspiration pneumonia or other respiratory infections.
Contractures	May impact negatively on survival given that they can further limit volitional movement.
Decubitus ulcers	Pose infection risk. More common among less mobile, and are part of the reason for excess mortality risk associated with immobility.
Tracheostomy	Poses infection risk. At least one study of people with developmental disabilities reported an excess mortality risk of about 1% across all ages.
Ventilator	Poses risk independent of tracheostomy.

Table 2. Other issues that may be associated with excess mortality risk beyond the major factors discussed in preceding sections.

accounting for level of gross motor impairment [43]. A number of studies from the UK identified severe visual disability as marker for elevated mortality [23, 25–27]. It may be that these disabilities are more common among more severely disabled people, and thus they may serve as a marker for overall level of brain injury.

3.6. Other issues

There are any number of additional factors relative to survival and mortality of persons with CP that have, to date, not been studied extensively. Factors that may well have some further impact on life expectancy, beyond the major known factors discussed above, are listed in **Table 2**.

4. Causes of death in CP

Life expectancy in CP is lower than expected in age- and gender-matched GPs. The question naturally arises as to what causes of death are driving the higher mortality rates and lower life expectancies, in this population? A number of studies have addressed this question, most focusing on either *underlying* cause of death or *immediate* (*principal, primary*) cause of death [24, 27, 42, 46–51]. At least two studies were vague as to whether an immediate cause or underlying cause was identified [52, 53]. Most of these studies relied on information reported in death certificates, [24, 27, 42, 46–51, 54] with at least one basing cause of death on a review of medical records from the time of death [53]. An *underlying* cause of death is meant to be the medical condition or other event that started a chain of events ending in death due to an *immediate* cause. In this section we will highlight some of the main underlying and immediate causes of death that have been found to be more common in CP than in the GP, and a few that are in fact less common.
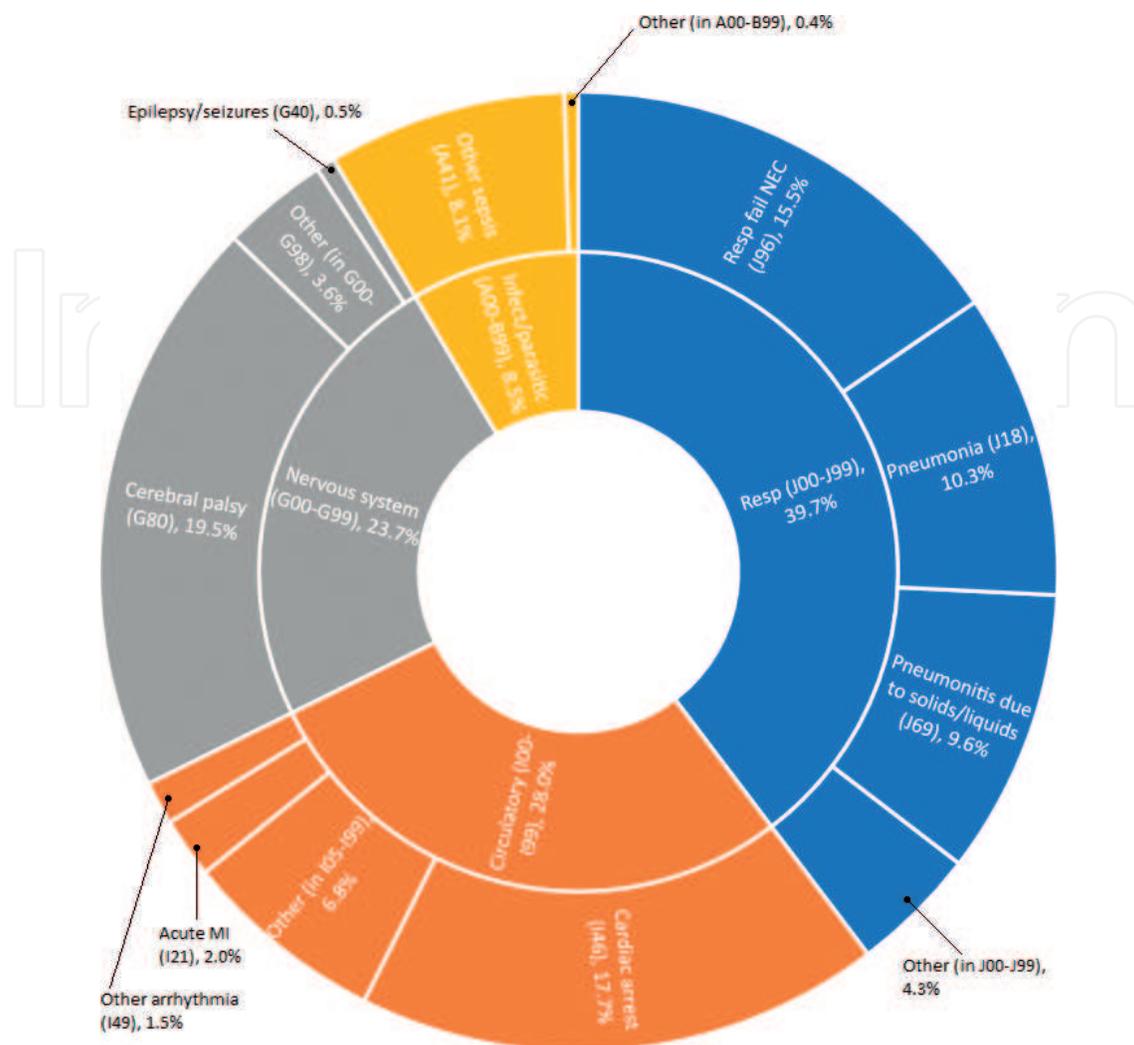
Figure 3. Top four broad categories and corresponding subcategories of immediate cause of death among deaths with a mention of CP on the death certificate.

Figures 3 and **4** shows the distribution of the leading immediate and underlying causes of death among 26,677 deaths in the US from 2005 to 2014 that mentioned CP anywhere on the death certificate (immediate cause of death, underlying cause, contributing cause, or other significant condition).[2] **Figure 3** shows the top 4 broad categories of immediate cause of death (accounting for 73% of all 26,677 deaths) as originally reported on death certificates [55], and as coded in the National Center for Health Statistics (NCHS) Multiple Cause of Death Records [56]. **Figure 4** similarly reports the distribution of the leading underlying causes of death (top 5 broad categories, accounting for 74% of all 26,677 deaths), but recoding some underlying causes originally attributed to CP on death certificates and in the NCHS death records (see next section for details on the recoding). **Figures 3** and **4** both report primarily broad categories

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[2]Such analyses of death certificate information do not capture all deaths of people with CP, of course, as in some cases (cases of very mild CP, or when a death clearly had no connection to CP) CP is not mentioned on the death certificate. Other studies have estimated that approximately 40-50% of deaths of people with CP include no mention of CP on the death certificate [24, 43, 47].
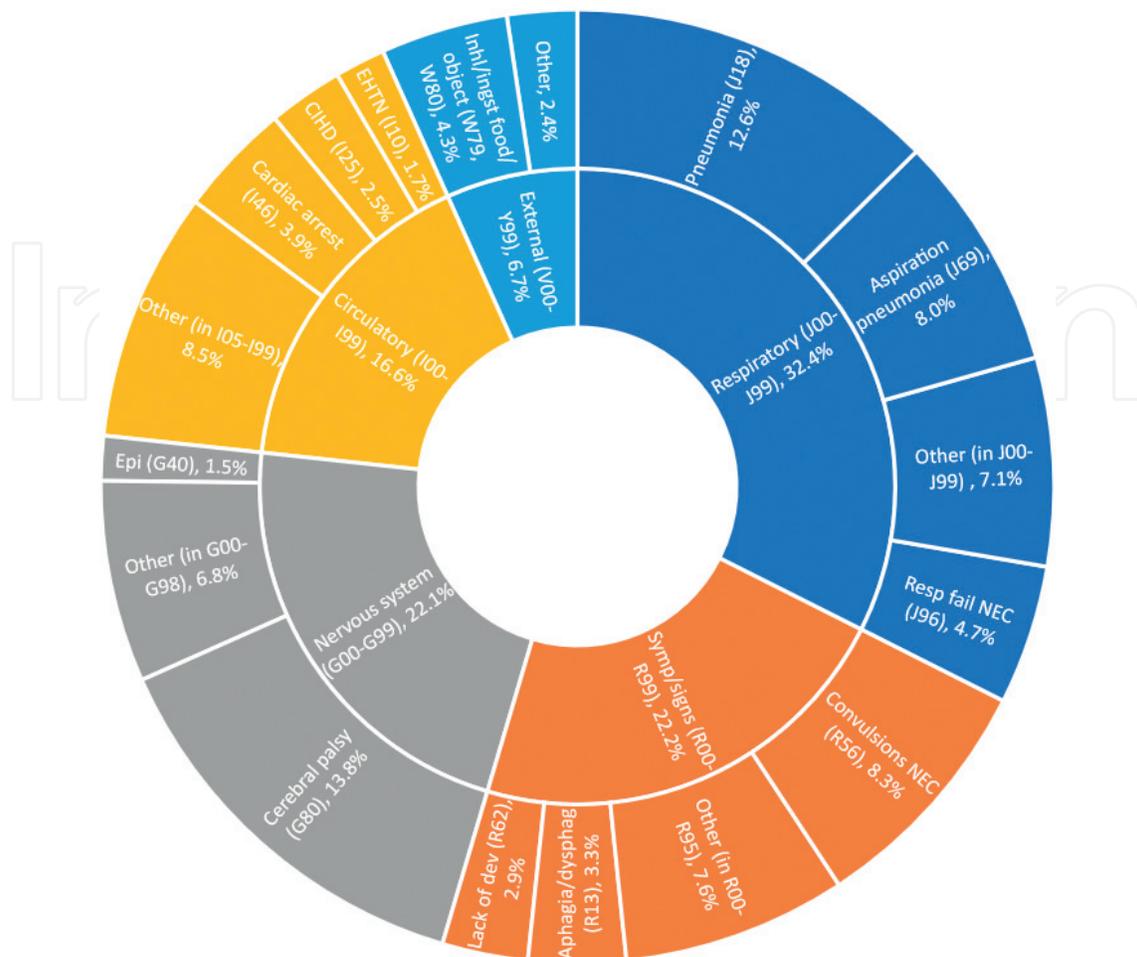
Figure 4. Top five broad categories and corresponding subcategories of underlying cause of death among deaths with a mention of CP on the death certificate.

of causes of death as classified by the World Health Organization's International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD 10) [57], though in some of the studies to be referenced, an earlier revision of the ICD was employed.

4.1. Cerebral palsy as immediate or underlying cause of death in CP

As **Figure 3** (immediate causes of death) illustrates, CP (ICD 10 G80) was identified in US national death records as being the immediate cause of death in a substantial number of cases (19.5% of the leading causes, or 14.5% of all deaths). CP was far more common as an underlying cause of death among deaths including CP as any cause or contributing factor: initially, 59% of underlying causes of death were attributed to CP. We recoded these, when possible, to be (a) the last cause listed in Part 1 of a death certificate if that cause was not CP; or (b) the penultimate cause in Part 1 if one existed. After recoding, CP accounted for 10% of all underlying causes, or 13.8% of the top 5 leading causes (**Figure 4**). Many studies of causes of death in CP that have relied on death certificate information have reported CP itself to be among the most common underlying causes [24, 27, 46, 47, 49, 50]. Some authors have considered CP to

be "uninformative", or "not valid", as an underlying or principal cause of death [46, 58], and various methods of recoding such deaths have been undertaken [47, 51, 58]. That CP is often recorded as the underlying cause of death on death certificates may be unfortunate, as it is indeed somewhat uninformative.

4.2. Respiratory diseases (ICD 10 J00–J99)

Respiratory diseases have consistently been reported to be among the leading causes of death among children and adults with CP [24, 27, 43, 46–53]. **Figures 3** and **4** shows that, among deaths with any mention of CP on a death certificate, respiratory diseases were the most common immediate cause of death (39.7% of the top 4 causes of death, 29.5% of all deaths) and also the most common underlying cause after recoding many deaths originally attributed to CP (32.4% of the top 5 causes, 23.7% of all deaths).

Those with more severe levels of disability are at greater risk of mortality due to respiratory diseases. Standardized mortality ratios (SMRs) have been reported from as low as 10 or below in older ages for those with less severe disability, to as high as 600 or more at younger ages for those with more severe levels of disability [46]. Among respiratory diseases, pneumonias, and in particular pneumonia related to aspiration of solids or liquids, are common [24, 42, 43, 46–49, 52, 53] and the excess in observed deaths due to this cause is again more pronounced in those with greater levels of disability [46].

4.3. Circulatory diseases (I00–I99)

Circulatory diseases are also elevated in frequency as a cause of death in CP, and is a common cause of death in this population, though this is primarily evidenced in deaths that occur at older ages (as is the case in the GP as well) [27, 46, 47, 51]. **Figures 3** and **4** show circulatory diseases to be the second leading immediate cause of death, and the fourth leading underlying cause (the latter after recoding of underlying causes of death with underlying cause originally attributed to CP).

4.4. Diseases of the nervous system (G00–G99)

The broad category of diseases of the nervous system includes CP itself (G80), as we have discussed above. Even after recoding deaths that are attributed to CP, it remains as a significantly common underlying cause of death (**Figure 4**), but other nervous system diseases become more prominent. Among the most common underlying causes of death within this broad category other than CP itself are seizures and hydrocephalus [51, 52].

4.5. Sepsis

Sepsis is an often life threatening condition caused by the body's system-wide inflammatory response to infection. Sepsis is a common cause of death in CP and in the GP, particularly in the elderly, the very young, or in those with severe disabilities or compromised immune systems. Because the ICD 10 classifies disease according to body system or, in the case of

infection, according to specific organism, sepsis is spread throughout its hierarchy, and across many of the broad categories of causes of death illustrated in **Figures 3** and **4**. Among the 26,677 deaths in the US from 2005 to 2014 that included CP anywhere on the death certificate, sepsis was noted to be the immediate cause in 1628 deaths (6.1%). Among these deaths, 98% were coded as ICD 10 A41 (other sepsis), of which most (97%) were coded as A41.9 (sepsis, unspecified organism).

4.6. Neoplasms, cancer (C00–D46)

Cancers, including both malignant and benign tumors, were an underlying cause of death in only 924 records out of the 26,677 deaths contributing to the analyses of **Figures 3** and **4**, thus not a leading immediate or underlying cause of death, and not included in those figures. Nevertheless, some interesting results have been reported regarding cancer mortality in CP. A large California study reported that those with CP were at greater risk of death due to cancer of the esophagus (SMR = 5.4, 95% CI 3.1–8.8), colon (2.2, 1.4–3.3), liver (2.2, 1.1–4.1), breast (1.8, 1.2–2.6), and bladder (4.6, 2.1–8.7); but at a five-fold decreased risk of death due to cancer of the trachea, bronchus and lung (SMR = 0.2, 0.1–0.4) [59]. The number of cancer deaths is likely small due primarily to its typical manifestation in older ages, ages to which many with more severe levels of CP do not live owing to competing risks.

4.7. Other "uninformative" causes of death

Another category of causes that appears frequently on deaths certificates of persons with CP is "symptoms, signs, and abnormal results of clinical and laboratory tests, not classified elsewhere," (ICD 10 R00–R99). These causes have been considered to be uninformative (or perhaps uninteresting) [46]. Referring again to **Figure 4**, we see that this category was the second leading underlying cause in US deaths from 2005 to 2014 (after recoding as described above), accounting for 22.2% of the top five leading cause categories, or 16.3% of all 26,677 deaths. However, given that this category includes "convulsions, not elsewhere classified," (ICD 10 R56) which in some cases account for up to half of deaths in this category, and also includes deaths related to unspecified respiratory and circulatory system problems, which in one study accounted for more than half of all deaths in this category (ICD 10 R56) [51, 58], more careful scrutiny of this broad category may be warranted. When comparing results from various studies as to the most common underlying or immediate cause of death in CP, it should be borne in mind that some studies omit this, and other, categories from consideration.

5. Methodological considerations for future research

The studies cited and discussed in the foregoing sections of this chapter provide a wealth of information about long-term survival, mortality, and life expectancy of people with cerebral palsy. Many questions remain to be answered, however, and more studies will undoubtedly be carried out in the future in an attempt to answer them. The questions such researchers will face in planning and executing their studies will be many and complex, and a full discussion of all

factors that ought to be considered is beyond the scope of this chapter. In this section, we mention a few of the most important methodological considerations for future studies in the broad context of questions about CP survival and life expectancy. We will also point to a few areas of research that remain poorly explored but important.

5.1. External validity

In previous sections of this chapter, we have identified a number of risk factors that are known to be strongly associated with survival and life expectancy in CP. One of the most important factors is gross motor functioning, and any study of survival in CP must account for this. However, as the literature to date has demonstrated, there are many ways to form cohorts based on combinations of this and other functional abilities. Therefore, for the sake of comparing results across time and place, we advise forming cohorts according to Gross Motor Function Classification System (GMFCS) [60] level or other commonly employed measures of gross motor functioning. For similar reasons, when possible, scales such as the Manual Ability Classification System (MACS) [61], the Communication Function Classification System (CFCS) [62], and the Eating and Drinking Ability Classification System (EDACS) [63] should be utilized. Other factors to account for can be gleaned from Section 4, perhaps chief among them gastrostomy status. Some studies will be limited by data that has been collected historically, but prospective studies should seize the opportunity to measure and report results in a more standardized fashion.

5.2. Time-based biases

Consider the 2000 UK study by Hutton et al. [24] **Figure 1D** in this study illustrates survival for children with severe ambulatory disability (i.e., no independent walking ability) and for children without severe ambulatory disability. The survival curves begin at age 0. This is problematic. Was walking ability really measured at age 0? Surely all children would be considered to have severe ambulatory disability at age 0, by the definition employed in this study. Furthermore, CP is rarely diagnosed in any child before a year or two of age. These issues are important: be as precise as possible with regard to when any time varying covariates are measured, and also as to precisely when (at what age) CP was diagnosed. Failure to do so can lead to a phenomenon known as immortal time bias, a surprisingly common error in reports of survival in a variety of populations, [64] including at least one study of survival of children with neurological disabilities [65].

5.3. Methods for causal inference

Researchers in the fields of Epidemiology, Biostatistics, and Computer Science have collaborated in recent years to develop a framework for robust causal inference [66]. This framework provides the analytic techniques and needed assumptions for interpreting results obtained from observational (i.e. non-experimental) studies in a causal way. The framework also provides tools for thinking more clearly about hypotheses and identifying potential sources of bias and confounding in conventional analyses. Applying these methods to studies of mortality in CP may help to unravel complex questions which have thus far been impossible to address [67]. For example, on the subject of gastrostomy feeding, we might wonder several

things: (a) how much of the increase in mortality for people with a gastrostomy tube is caused by the need for a tube versus the placement and presence of the tube itself; (b) what if all children with CP of a given functional profile were given a gastrostomy tube; or (c) what if no children with CP of a given profile were given gastrostomy tubes? Given the right data and careful analysis, even in the absence of an ethically impractical randomized clinical trial [35], the causal inference framework could help answer these and other important questions.

6. Conclusions

In this chapter we have reviewed the general concepts of life expectancy, life tables, and survival curves. We reviewed the important predictors of mortality and life expectancy in CP, as well as the major causes of death common in CP.

Mobility is a strong predictor of mortality in CP, and as a consequence, a strong predictor of cause of death; in young and old with CP, respiratory diseases figure prominently as a cause of death, and circulatory diseases become more relevant in older ages. Neurologic disorders are also a major category of cause of death, even after reclassifying underlying causes initially attributed to CP to more informative causal categories. Seizures and hydrocephalus are important causes in this category as well.

Future research in the mortality and life expectancy of CP should focus on analyzing data using as many of the previously-identified risk factors as possible and should stratify patients using widely replicable scales of those factors, such as GMFCS. New tools of causal inference should be employed to help control bias and confounding in observational studies.

Though much has been learned about life expectancy and causes of death in CP, there is undoubtedly much to be learned. It is our hope that this review and our recommendations will help guide future research in its quest to answer the many open questions related to long-term mortality and survival, and life expectancy in cerebral palsy.

Author details

Steven M. Day* and Robert J. Reynolds

*Address all correspondence to: sday@mortalityresearch.com

Mortality Research and Consulting, Inc., City of Industry, California, USA

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