Recent trends in cerebral palsy survival. Part I: period and cohort effects

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AIM To determine whether the trend of improved survival among individuals with cerebral palsy (CP) in California during the 1980s and 1990s has continued during the most recent decade.

METHOD In an observational cohort study we evaluated individuals with CP, aged 4 years and older, who were clients of the California Department of Developmental Services. Medical diagnoses, functional disabilities, and special health care requirements were assessed with Client Development Evaluation Reports made between 1983 and 2010. Trends in birth cohort survival were analyzed with Kaplan–Meier curves and Cox regression. Calendar year period effects were analyzed with Poisson regression.

RESULTS A total of 51 923 persons with CP (28 789 males [55%], 23 134 females [45%]; mean age 14y 11mo, SD 14y 1mo, range 4y 0mo to 96y 10mo) collectively contributed 662 268 years of follow-up. There were 7690 deaths for an overall mortality rate of 11.6 per 1000 persons per year. No significant birth cohort effects on survival were observed in 4-year-olds who had no severe disabilities. By contrast, children who did not lift their heads in prone position who were born in more recent years had significantly lower mortality rates (Cox hazard ratio 0.971, $p<0.001$) than those with comparable disabilities born earlier. With regard to calendar year period effects, we found that age-, sex-, and disability-specific mortality rates declined by 1.5% (95% CI 0.9–2.1) year-over-year from 1983 to 2010. The estimate increased to 2.5% (95% CI 1.9–3.1) per year when we additionally controlled for tube-feeding status. Mortality rates in tube fed adolescents and adults, ages 15 to 59 years, declined by 0.9% (95% CI, 0.4–1.4) per year. No improvement was observed for adolescents or adults who fed orally or for those over age 60. In fact, the ratio of age-specific mortality rates for these latter groups to those in the general population, increased by 1.7% (95% CI 1.3–2.0) per year during the study period.

INTERPRETATION The trend toward improved survival has continued throughout the most recent decade. Declines in CP childhood mortality are comparable to the improvements observed in the United States general population (i.e. the mortality ratio in childhood has remained roughly constant over the last three decades). In contrast, the mortality ratio for most adolescents and adults with CP, relative to the general population, has increased.

Trends in survival are perhaps the most essential evidence of the effectiveness of advances in medicine and public health. For example, it is generally accepted that increases in general population life expectancy over the last century are largely due to the reductions in infant and childhood mortality caused by improvements in prevention and treatment of infectious diseases. Although there are only limited data from the early part of the 20th century regarding mortality among children with cerebral palsy (CP), advances in public health and medicine, including the advent of antibiotic drugs, undoubtedly has had a major impact on their survival.

Since the 1980s several large follow-up studies have investigated survival in persons with CP.[1–15] As a result it is now widely recognized that severity of disability is the most important predictor of long-term survival. Controlled comparisons of the survival data from California with those from the UK, Australia, and Sweden have revealed remarkably similar survival probabilities across these countries.[2,14,15]

Whether advances in medicine and public health have led to improved survival during the past two or three decades is less clear. Several studies of large CP registers have failed to find any improvement.[3,5,9,12] The sole exception

is our California study,[1] which documented a substantial improvement in mortality among children and adults with severe disability. Given the similarity of survival probabilities across countries, the discrepant findings on trends over time are surprising and warrant further investigation.

To properly consider the differences between these studies, it is essential to clarify the precise research questions asked and the analytic methods used to answer them. As the data collected in the UK and Australian CP registers pertain to birth cohorts, it is not surprising that research in these countries has focused on cohort effects. *Cohort effect* analyses ask whether mortality rates across the life span are lower for persons born in more recent calendar years.[16]

Our California study contains information collected since 1983 on persons with CP who received state services for their developmental disability. It includes data on persons born in recent years, but it is not a birth register. There is also information on persons with CP born well before 1983. Evaluations of each participant are performed across their life span on an annual basis. Our analyses of time trends in mortality have focused on calendar year period effects. *Period effect* analyses ask whether mortality rates have declined in more recent calendar years, without a focus on year of birth.[16]

It is important to recognize that the choice between period effect or cohort effect analyses should be driven by the research question of interest. To answer the question 'what effect have advances in medicine or public health had on age- and disability-specific mortality rates in CP?', the period effect analysis is more appropriate because general improvements in care are unlikely to be limited to persons born in specific years. For example, more widespread acceptance of tube feeding in recent calendar years has undoubtedly affected the nutritional health of persons with severe disabilities across the age span, not just those from a particular birth year.

In this article we analyze time trends in mortality among individuals with CP in California. For comparison with studies by other research groups we consider birth cohort effects, with and without adjustment for severity of disability. Our major focus, however, is on period effects in age- and disability-specific mortality rates. In an extended analysis, we test whether the improvement in CP mortality rates differs from that observed in the United States general population. How these findings apply to survival prognosis in individual patients with CP is discussed in the companion article.

METHOD
Participants
The study population included persons age 4 years and older with CP who were clients of the California Department of Developmental Services between January 1983 and December 2010.

Clients were assessed annually with the Client Development Evaluation Report (CDER).[17] The CDER contains

What this paper adds
- Analyzes trends in mortality among individuals with CP in California between 1983 and 2010.
- Clarifies differences between cohort and period effects.
- Compares trends in CP mortality with those in the US general population.

over 200 medical, functional, behavioral, and cognitive items. For each client, a physician makes medical diagnoses, including the assessment of CP, while functional skills are assessed by other professionals familiar with that aspect of the client's development. Persons with an International Classification of Disease (9th revision)[18] diagnosis of degenerative conditions or acquired conditions (e.g. traumatic brain injury or injury resulting from near drowning) as the etiology of disability were excluded from all analyses. The pattern of disability with regard to motor function was classified according to skills in head lifting in the prone position, rolling, sitting, crawling, and walking. Self-feeding skills and tube-feeding interventions were also recorded. Functional skills describe voluntary actions that are performed on a consistent basis in typical settings. They do not represent the best level that may be achieved in specialized settings. We worked with demographic and functional skill data recorded on the CDERs; less than 1% of these data had missing values. Missing data were imputed using the last observation carried forward. The CDER assessments of these skills have been independently validated[19] and have interrater reliabilities exceeding 0.85.[20] For consistency with our 2007 study, we studied persons age 4 years and older and classified their disabilities as 'severe' if they did not crawl, stand, or walk, and were fed completely by others. Persons who performed at least one of these skills were classified as 'not severe.'

Follow-up for survival was commenced at age 4 years or at the age of the first CDER evaluation, whichever came later. Vital status was determined using electronic death records from the California Department of Health Services. Individuals who were not matched to a death record within 3 years of their last CDER evaluation were considered lost to follow-up at the 3-year mark. Individual survival times were censored at the date of loss to follow-up or at the study end date 31 December 2010, whichever came first.

Statistical analysis
Each individual contributed information on survival only during the ages at which they were actually followed in the study. Because follow-up did not commence until age 4 years, survival statistics were not computed for ages 0 to 3 years. If a child entered the study at age 6, that child would not contribute any information to the survival statistics at ages 4 or 5 years. Further, the time-dependent functional skills were attributed to each child from the age they were actually assessed. The biases that may be incurred by retrospective survival ascertainment have been pointed out in earlier work.[3,21]

Birth cohort effects on survival were estimated with Kaplan–Meier survival curves and Cox proportional hazards regression.[21] Both of these methods are appropriate for the analysis of cohort effects and were selected in part to facilitate more direct comparisons with other published studies. In these analyses, age in years was taken to be the underlying time variable.

Period effects in mortality rates were analyzed in the same time-dependent data framework as in our prior study.[1] In this framework, the follow-up data for each person is divided into a discrete set of 'person-time' observations, where each observation is associated with a small interval of follow-up time. The maximum interval length was taken to be 1/10 of a year. For example, if a person had 10.43 years of total follow-up time then that individual would contribute 105 observations to the analysis. The first 104 observations would be associated with 0.1 years of follow-up time, while the last would be associated with 0.03 years. Each person-time observation contains information on time-dependent measures of that person's age, pattern of disability, the current calendar year, and an indicator of whether the person died at the end of that particular observation interval.

With this person-time data format, we modeled the age-, disability-, and calendar year-specific mortality rates using Poisson regression.[22] The model is a simple extension of standard Poisson regression (typically used to model death counts), which includes the natural logarithm of the amount of follow-up time for each observation as an offset on the right-hand side of the regression equation. The method is asymptotically equivalent to person-time logistic regression as the length of the time interval decreases to zero. It is preferable to the Cox model with time-dependent covariates because it relaxes the proportional hazards assumption and allows straightforward estimation of age-specific calendar year period effects.

To compare mortality in CP with that in the general population we modeled the ratio of the observed death count to the number of deaths expected under standard age-, sex-, and year-specific rates for the general population. This is equivalent to modeling the ratio of mortality rates. The model is a further extension of Poisson regression similar to the mortality rate model described above, except that the offset term is replaced by the natural logarithm of the expected number of deaths under general population mortality rates.[22] Standard rates for the general population were obtained from the Human Mortality Database.[23]

Data were managed and analyzed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA) and R version 3.0 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS
Participant characteristics
The study population included 51 923 persons (28 789 males [55%], 23 134 females [45%]; mean age 14y 11mo years, SD 14y 1mo, range 4y 0mo to 96y 10mo) with CP aged 4 years or older. The median follow-up time was 12.8 years, and the total follow-up for the entire study group was 662 268 person-years. During the study 7690 persons died, for an overall death rate of 11.6 per 1000 persons per year. Data on these individuals were abstracted from 539 842 CDER evaluations.

Participant characteristics assessed at the beginning of follow-up are summarized in Table I. Overall, 19% of the study participants had severe functional disabilities at their first CDER evaluation; 6% of participants did not lift their head when lying in the prone position. Fifty-nine per cent of participants walked either with or without a supportive aid, and 31% walked unaided for at least 20 feet and balanced well. Tube feeding, most often by gastrostomy, was more common in children than in adults. In all age groups, the use of feeding tubes has become more prevalent in recent years. About 13% of children born in the 2000s already had a feeding tube at their first follow-up evaluation as compared with 9% of those born in the 1990s and only 6% of those born in the 1980s. By the end of the follow-up period, roughly 15% of children born in the 1980s or later had feeding tubes in place.

Birth cohort effects
For 4-year-olds born in the 1970s, 1980s, 1990s, and 2000s, the probabilities of survival to age 10 were 92%, 94%, 95%, and 95%, respectively. The survival curves by birth decade were not significantly different from one another (log rank test: χ^2=4.96 df=3, p=0.175). The univariate Cox regression, however, yielded a hazard ratio of 0.990 (95% CI 0.982–0.997) for each more recent year of birth.

We found no significant birth cohort effects in the survival of children who could crawl, walk, or feed themselves independently (log rank test for birth decade: χ^2=0.92 df=3, p=0.821; hazard ratio for birth cohort year=0.992, 95% CI 0.978–1.007). We did, however, find statistically

Table I: Participant characteristics (*n*=51 923) on first CDER

Male (%)			55
Age in years (%)	4–7		48
	8–14		13
	15–30		24
	30–60		14
	60–100		1
Functional skills (%)	Not severe[a]	Walks well alone at least 20 feet	31
		Walks with support or unsteadily alone	28
		Does not walk	22
	Severe[a]	Rolls or sits	7
		Lifts head or chest in prone	6
		Does not lift head in prone	6
Tube fed (%)			6
Mean calendar year of follow-up (SD)			1991 (8.0)

[a]Severe: does not crawl, stand, or walk, and is fed completely by others; not severe: crawls independently or walks (with or without aids), or feeds self. CDER, Client Development Evaluation Report.

significant cohort effects in children who were unable to lift their heads when lying in the prone position (log rank test: $\chi^2=12.29$ df=3, $p=0.006$; Cox hazard ratio=0.971, 95% CI 0.957–0.985). The Kaplan–Meier survival curves for these more severely disabled cohorts are shown in Figure 1.

Calendar year period effects

Period effect estimates are presented in Table II. Without adjustment for disability, age-specific mortality rates for children under age 15 years improved (i.e. declined) at a rate of 1.6% per year. The improvement was 1.5% per year with adjustment for motor and feeding skills, and increased to 2.5% per year with further adjustment for gastrostomy dependence. The mortality rates of tube fed adolescents and adults aged 15 to 59 years declined by 0.9% per year. There was no trend of improvement in orally fed adolescents or adults or in adults over age 60 years.

Comparison with the general population

The rate of improvement in CP mortality as compared with that in the United States general population is summarized in Table III. Among children under age 15, and also in tube fed adolescents and adults aged 15 to 59 years, the rate of decline in mortality among children with CP was not significantly different from that in the United States general population. For orally fed adolescents and adults aged 15 to 59 years and all adults over 60, the analysis indicated that the mortality ratio (i.e. the ratio of age-specific mortality rates in CP to those in the general

Figure 1: Survival of 4-year-old children with CP who do not lift their heads when lying in the prone position ($n=1147$) by birth cohort.

population) actually increased by 1.7% year-over-year during the study period.

DISCUSSION

There have been substantial improvements in childhood mortality of persons with CP in California over the past three decades. Age- and disability-specific mortality rates declined by 1.5% per year from 1983 to 2010. Further adjustment for tube-feeding status resulted in an increased estimate of 2.5% per year. Similar improvements have co-occurred in childhood mortality rates in the United States general population. For example, using national mortality tables, Singh et al.[24] found that mortality rates for 5- to 14-year-old children in the United States general population improved at roughly 2.7% per year during the same period. Indeed, we found that after adjustment for age, severity of disability, and tube-feeding status, the mortality ratio for children with CP compared to children in the general population has not changed significantly over the last 30 years.

The difference in the estimates, 2.5% versus 1.5%, raises the question of whether it is appropriate to make the statistical adjustment for tube-feeding status. While many CP registers have not collected information on this factor,[3–7,9,12,13] all others have found tube feeding to be associated with substantially elevated mortality rates.[1,2,7,8,10,11] The reason is that tube feeding is a treatment reserved primarily for persons with high risk of aspiration, malnutrition, or both. Thus the need for tube feeding serves as a marker for severity of CP.

Tube feeding has become much more widespread in children with CP. We found that 6% of children born in the 1980s had a gastrostomy at their first evaluation and an additional 9% had a tube inserted during the study period. Supplementary analyses revealed that, as expected, the 6% had more severe functional disabilities than the 9% who had the tubes placed later in the study period. On the other hand, the 9% who had tubes placed after the initial evaluation had disabilities that were still worse than those of the remaining 85% who fed orally throughout the study period. This demonstrates that while tube feeding is still a marker for more severe disabilities, there has been some shift toward placement of tubes into children with less severe disabilities. Further, an increasing number of clinicians have embraced mixed tube and oral feeding, such that gastrostomy is no longer an 'all-or-nothing' intervention. In the present study, we were unable to make distinctions between children who were completely tube fed and those with feeding tubes who took a significant proportion of their nutrition orally.

Perhaps related to the shift in medical practice, there has been decline in the average severity of disability in *both* the tube fed and the orally fed groups. This could explain why the disability-specific mortality rate reductions in both the tube fed and orally fed groups, 2.5% per year, is greater than the trend for the combined group, 1.5% per
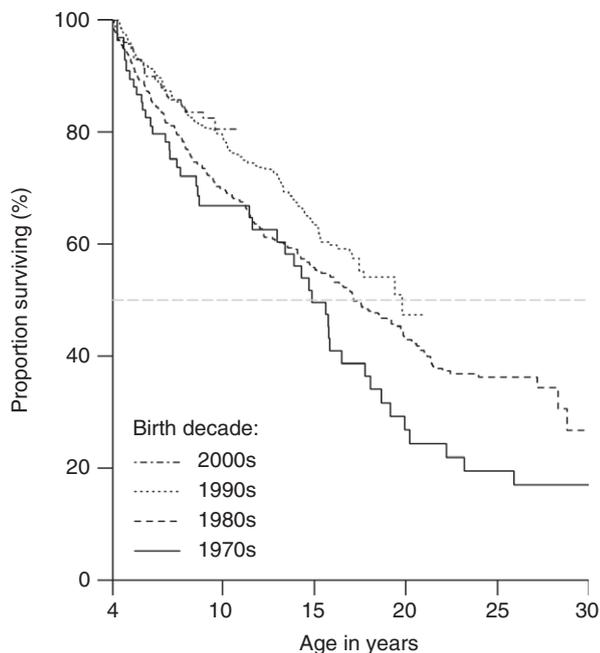
Table II: Period effects in age-, sex-, and disability-specific mortality rates (Poisson regression)

Group	Annual % change in mortality rate with 95% CI		
	Adjusted for age and sex	Adjusted for age, sex, motor and feeding skills[a]	Adjusted for age, sex, motor and feeding skills,[a] and tube feeding
Children <15y	−1.6 (−2.2, −1.0)	−1.5 (−2.1, −0.9)	−2.5 (−3.1, −1.9)
Adults 15–59y	0.0 (−0.3, 0.4)	0.6 (0.2, 0.9)	TF −0.9 (−1.4, −0.4)
			NT 0.4 (0.0, 0.8)
Adults ≥60y	2.4 (1.9, 3.0)	2.2 (1.7, 2.8)	0.4 (0.0, 0.8)

[a]Motor and feeding skills include the pattern of disability in head lifting, rolling and sitting, crawling, standing, walking, and self-feeding. NT, not tube fed; TF, tube fed.

Table III: Comparison of age-, sex-, and disability-specific cerebral palsy mortality to that of the US general population

Group	Annual % change in mortality ratio[a] (95% CI)
Children <15y	0.3 (−0.3, 0.9)
Adults 15–59y TF	0.4 (−0.1, 1.0)
Adults 15–59y NT and Adults ≥60y	1.7 (1.3, 2.0)

[a]Mortality ratio is the age-, sex-, year-, and disability-specific mortality rate for CP divided by the age-, sex-, and year-specific mortality rate for the US general population. Poisson regression estimates adjusted for disability in head lifting, rolling and sitting, crawling and standing, and walking, and for dependence on a feeding tube. NT, not tube fed; TF, tube fed.

year. Because tube feeding remains one of the most powerful predictors of long-term survival, it should always be considered in the survival prognosis for an individual child. In our companion article we illustrate prognoses that take into account gastrostomy dependence and reflect the time trends discussed here.

The results of this study supersede those presented in our 2007 paper, which investigated trends through to 2002.[1] The 2.5% per year improvement here is consistent with the earlier results, though there are several points to consider. First and perhaps most importantly, the improvements in the 1980s and 1990s have persisted through to 2010. Second, while the earlier study suggested that improvements were limited to children who were unable to crawl, stand, walk, or feed themselves, our updated results indicate that the same relative mortality improvement (2.5% per year) applies equally to children with CP who have less severe disability. The improvements for mildly affected children are also consistent with the 2.7% per year improvement for children in the general population. Third, the improvement factor for tube fed adults (0.9% per year) is significantly lower than previously reported. It appears that the prior analysis lacked the power to detect the difference between the trends in children and adults with severe disabilities. Our expanded data, which includes over 200 000 additional person-years of follow-up and over 3000 more deaths, allowed more precise estimates.

Our results also shed light on apparent discrepancies between trends in California and other countries. In countries that do not collect information on head lifting or tube feeding, it would be unlikely to find period effect improvements in excess of 2% per year. Furthermore, the use of methods designed to estimate *cohort* effects may have masked any true *period* effects in mortality rates. Even with our sample of over 16 000 4-year-old children, the log rank test failed to detect significant differences in overall survival by birth decade, and the Cox model suggested only a modest 1% improvement in mortality rates by birth year. It seems unlikely that the various registers, which include far fewer individuals, would be sufficiently statistically powered to detect such trends. Indeed, most have reported none.[3,5,12] One possible exception, a study from the Victoria register,[13] focused on non-ambulatory children who also had at least three other disabilities. The published survival curves therein suggested that survival of the 1970s birth cohort was actually better than that of the 1980s and 1990s birth cohorts. This result, however, must be viewed cautiously as the data underlying that study was collected prospectively only from the mid 1980s.

Whether there have been period effects in CP childhood mortality in other countries remains to be seen. As in the United States, other countries have experienced significant trends toward improvement in general population childhood mortality. Thus it would be surprising, and perhaps cause for concern, if the medical or public health advances underlying the general population improvements did not have a positive effect on children with CP in these countries.

In contrast to children, it appears that there have been no major trends in the mortality rates of adolescents and adults with CP who feed orally. This negative finding implies that survival and life expectancy for these groups has not improved over the last 30 years. This compares unfavorably relative to the improvements that have been demonstrated in the general population. In fact, we found that the mortality ratio actually increased significantly by 1.7% year-over-year, which corresponds to a 60% increase over the 1983 to 2010 study period. As a practical consequence, life expectancy estimates based on the assumption that CP mortality improvements have and will continue to mirror those in the general population may be overly optimistic. We discuss this and other practical implications in the companion paper.

Perhaps the most important limitation of this study is that we did not formally identify specific causal factors that explain the observed trends. Like the trends themselves, the specific causal factors may differ according to age. They may also vary according to severity of disability. For example, the reasons for the improvements in children with mild disabilities are likely to mirror those for children without disabilities in the general population; an example may be improvement in road traffic safety measures. By contrast, improvements for those with severe disabilities may reflect advances in medical treatment of infections, epilepsy, or nutritional management. Cause of death data may provide some insight, though as noted in previous publications, cause of death in CP is often simply coded as 'cerebral palsy' and is therefore often uninformative.[4,12,25] Finally, we note that because our study was limited to persons who received services for CP, the extent to which the results apply to individuals with more mild CP who do not require state services is not clear.

CONCLUSION

There have been substantial improvements in mortality rates for children with CP in California. Childhood mortality rates in CP declined by 2.5% per year from 1983 to 2010, which is very similar to improvements found for children in the general population. Mortality rates in tube fed adolescents and adults have declined by 0.9% per year. The mortality ratio for orally fed adolescents and adults and adults over age 60, as compared with the United States general population, has actually increased. These trends should be taken into account for individual survival prognosis.

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