Improved Survival in Down Syndrome over the Last 60 Years and the Impact of Perinatal Factors in Recent Decades

Emma J. Glasson, PhD, Angela Jacques, MBiostat, Kingsley Wong, MPH, Jenny Bourke, MPH, and Helen Leonard, MBChB

Objective To calculate the survival of people with Down syndrome over the past 60 years and the influence of major perinatal factors by using linked population-based data.

Study design A data linkage between 2 Western Australian (WA) data sets (the Register for Developmental Anomalies and the Intellectual Disability Exploring Answers database) was used to identify 772 children born with Down syndrome in WA from 1980-2010. Perinatal and mortality data were extracted from the WA Midwives Information System and WA death registrations and compared with the remaining WA population born during that same era. An additional 606 children with Down syndrome living in WA prior to 1980 were available from a disability services database and were used for predicting survival into adulthood.

Results Overall, for cases born 1953-2010, 88% (95% CI 86%, 90%) survived to 5 years of age, 87% (95% CI 85%, 89%) to 10 years, and 83% (95% CI 80%, 85%) to 30 years. Children live-born with Down syndrome were significantly more likely (all $P > .001$) to have mothers older than 35 years (32.7% vs 13.4%), a gestational age less than 37 weeks (23.8% vs 7.9%), a cesarean delivery (28.9% vs 23.0%), and a birth weight less than 2500 g (20.4% vs 6.1%). Down syndrome survival was reduced in the presence of a cardiovascular defect, younger gestational age, low birth weight, or earlier birth years.

Conclusions Improved survival for children born with Down syndrome over the last 60 years has occurred incrementally, but disparities still exist for children who are preterm or have low birth weight. *(J Pediatr 2016;169:214-20)*.

Over the past 30 years, the live-birth prevalence of Down syndrome has remained relatively stable in many developed countries.[1] Although prenatal detection of Down syndrome and subsequent pregnancy terminations have risen, such has been offset by a greater number of pregnancies occurring at advanced maternal ages when the risk of a Down syndrome conception is increased.

The survival of children born with Down syndrome has continued to improve over recent decades,[2-6] with rates at 1, 5, and 10 years of age all exceeding 90% in developed countries.[7,8] This improved survival has been influenced particularly by earlier treatment of heart defects[7,9] that affect around 50% of children with Down syndrome and are a leading cause of mortality in early life.[9] The earlier detection of Down syndrome in utero and in the neonate after delivery has allowed more rapid response times for monitoring and treating newborns with cardiac anomalies and other comorbidities. Earlier interventions have improved short-term survival and presumably have longer-term benefits in the prevention or reduction of the impact of comorbidities later in life.

Survival estimates for people with birth defects, including Down syndrome, have also been linked to demographics at birth, such as maternal age and ethnicity, and to perinatal outcomes, such as gestational age and plurality.[7,10-12] However, these relationships are often reported differently and observed in varying birth cohorts, highlighting a need for clarity by using longitudinal population-based data. The influence of time period is also particularly important for people with Down syndrome, given the significant changes that have occurred in early childhood care and the impact of birth year on life expectancy with each new decade. The aim of this research is to describe survival for people with Down syndrome by birth cohort in a single population over a period of 60 years and to estimate the influence of major perinatal factors over the past 30 years.

CVD	Cardiovascular defect
DSC	Disability Services Commission
HR	Hazard ratio
IDEA	Intellectual Disability Exploring Answers
SEIFA	Socioeconomic Indexes for Areas
t_0	Time of observation
WA	Western Australian
WARDA	WA Register for Developmental Anomalies

From the Telethon Kids Institute, The University of Western Australia, West Perth, Western Australia, Australia

Supported by the Australian National Health and Medical Research Council (572742). The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.10.083

Methods

Children born with Down syndrome in Western Australian (WA) from 1953-2010 were identified through 2 sources: (1) the WA Intellectual Disability Exploring Answers (IDEA) database (1953-2010),[13] which contains data on individuals with intellectual disability from both the WA Disability Services Commission (DSC, 1953-2010) and the WA Department of Education (1983-2010); and (2) the WA Register for Developmental Anomalies (WARDA, 1980-2010). Cases were merged from both data sources using data-linkage techniques.[14]

Data on the perinatal period and maternal obstetric factors were available only for cases born 1980-2010 from the WA Midwives Notification System, which is a statutory database of maternal, obstetric, and perinatal information on all WA births since 1980.[14,15] Information on birth defects (ie, the presence of cardiac defects and Down syndrome) was extracted for cases born since 1980 from the WARDA database, which collects data on birth defects for children born in WA since 1980 and diagnosed up to the age of 6 years.[15]

Information on dates of deaths was extracted from the state death registrations available from 1969 and supplemented from DSC records since 1953. Data describing the cause of death were available from the deaths registry for cases born 1980-2010.

Statistical Analyses

For cases born between 1953 and 2010, Kaplan-Meier survival functions were calculated for the total live-born cohort and stratified by period of birth and sex. Estimated probabilities of survival and corresponding 95% CI were calculated for survival ages 1, 5, 10, 25, 30, 50, and 60 years, when available. As the most recent year of death was 2013, the data were censored at year-end 2013. Tests of homogeneity of survivor functions across strata were based on the log-rank test. As data identifying Down syndrome at the time of birth was not available prior to 1980, information on cases of Down syndrome who died prior to having the opportunity to be registered with DSC was missing. Therefore, only for cases born prior to 1980, left truncation was used to adjust for the missing cases and minimize survival bias. Time of origin was defined as year of birth time of observation commenced from year of DSC registration, and time of failure was defined as either year of death or censoring at year end 2013 if alive. Left truncation occurred if the subject died before time of observation and, therefore, was not included (ie, they died prior to the opportunity for DSC registration). Therefore, inclusion in the analysis was conditional on survival until at least time of observation (DSC registration).

Perinatal, maternal, and birth defect data were available only for cases born from 1980. The categorical data were summarized using frequency distributions, including births and deaths by sex and 10-year birth cohorts (1980-1989; 1990-1999; and 2000-2010), maternal age (<35 years and ≥35 years), gestational age (<28, 28-31, 32-36, 37-38, and ≥39 weeks), plurality, aboriginality, birth weight (<2500 g and ≥2500 g), and delivery mode (vaginal vs cesarean).

Frequency distributions for cases with Down syndrome were described only for place of birth (metropolitan or rural, based on residential postcode), presence of a cardiovascular defect (CVD), and the Socioeconomic Indexes for Areas (SEIFA) Index of Relative Socioeconomic Advantage and Disadvantage tertile (low advantage, medium advantage, and high advantage).[16] For cases born 1980-2010, Kaplan-Meier survival functions were also calculated for maternal age, gestational age, plurality, aboriginality, birth weight, delivery mode, place of birth, and presence of a CVD. Estimated probabilities of survival and corresponding 95% CI were calculated for survival at 1 and 5 years of age. Time of origin was defined as year of birth, and time of failure was defined as either year of death or censoring at 25 years if alive. Tests of homogeneity of survivor functions across strata were based on the log-rank test.

Cox proportional hazard models were used to produce hazard ratios (HRs) of mortality for sex, birth cohort, maternal age, plurality, aboriginality, birth weight, delivery mode, place of birth, presence of a CVD, and SEIFA index. Interactions were tested for pertinent covariates.

Because of the large amount (20%) of missing data for the SEIFA index, 2 multivariable models (one with and without the SEIFA index) adjusting for sex, birth cohort, aboriginality, presence of a CVD, and including univariably significant covariates, were implemented in order to retain the maximum number of cases in the second model. Proportional hazard assumptions were assessed graphically using log-log survival curves and observed vs predicted survival curves.

For all analyses, P values of <.05 was considered statistically significant. Data were analyzed using Stata SE (v 12.0 for Windows; StataCorp LP, College Station, Texas) and SPSS statistical software (v 19.0; SPSS Inc, Chicago, Illinois).

Results

Two groups totaling 1389 cases were identified: (1) children born alive with Down syndrome in WA 1980-2010 (n = 783) from either WARDA or IDEA; and (2) all people with Down syndrome born in WA 1953-1979 (n = 606) from IDEA (through their registration with DSC).

For cases born 1980-2010, 11 cases died within 24 hours of birth. We excluded these 11 early deaths from the survival analysis of the live-born cases, leaving 772 cases in this group, of whom 78 became deceased after the first day of life. For these deceased cases, the median age at death was 1 year 1 month (range 1 day-31 years), and cause of death was available in 65 cases (**Figure 1**; available at www.jpeds.com). Congenital heart disease was the most common primary cause (n = 39, 50%), followed by pneumonia (n = 10, 13%), and leukemia (n = 7, 9%). Cause of death was not known/reported in 13 cases (13/78, 17%), of which the