

# Improved survival in Down syndrome over the last 60 years and the impact of perinatal factors in recent decades

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*Keywords:*

Intellectual disability; life expectancy; trends; obstetric factors; patient care.

*Short title:*

Down syndrome survival and perinatal trends.

*Financial assistance and conflicts of interest statement:*

This study was supported by Australian National Health and Medical Research Council (NHMRC) Program Grant #572742.

## **ABSTRACT**

### Objective:

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

### Study design:

Data linkage between two Western Australian (WA) data sets; the Register for Developmental Anomalies and the Intellectual Disability Exploring Answers database was used to identify 772 live born children with Down syndrome born in WA 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 1980-2010. An additional 606 Down syndrome cases living in WA prior to 1980 was available from a disability services database and were used for predicting survival into adulthood.

### Results:

Children live-born with Down syndrome were more likely to have mothers older than 35 years (32.7% vs 13.4%), a gestational age less than 37 weeks (23.8% vs 7.9%), experience a caesarean section delivery (28.9% vs 23.0%) and have a birth weight of less than 2500g (20.4% vs 6.1%).

Down syndrome survival was reduced if a cardiovascular defect was present, for younger gestational age, low birth weight, or earlier birth years.

### Conclusion:

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.

## INTRODUCTION

In many developed countries over the past 30 years, the live-birth prevalence of Down syndrome has remained relatively stable<sup>(1)</sup>. Although prenatal detection of Down syndrome and subsequent terminations have risen, this 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<sup>(2-6)</sup>, with rates at 1, 5 and 10 years of age all exceeding 90% in developed countries<sup>(7, 8)</sup>. This has been particularly influenced by earlier treatment of heart defects<sup>(7, 9)</sup> that affect around 50% of children with Down syndrome and are a leading cause of mortality in early life<sup>(9)</sup>. 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, also have been linked to demographics at birth, such as maternal age and ethnicity, and to perinatal outcomes, such as gestational age and plurality<sup>(7, 10-12)</sup>. 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 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 sixty years and to estimate the influence of major perinatal factors over the past thirty years.

## **METHODS**

### **Study population and datasets**

People with Down syndrome born in WA 1953-2010 were identified through two sources; 1) the WA Intellectual Disability Exploring Answers (IDEA) database (1953-2010)<sup>(13)</sup> 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<sup>(14)</sup>.

Data on the perinatal period and maternal obstetric factors were only available 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<sup>(14, 15)</sup>. Information on birth defects (the presence of cardiac defects and Down syndrome) was extracted for cases born since 1980 from the WA Register for Developmental Anomalies database, which collects data on birth defects for children born in WA since 1980 and diagnosed up to the age of six years<sup>(15)</sup>. 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 methods**

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 gender. Estimated probabilities of survival and corresponding 95% confidence intervals were calculated for survival ages 1, 5, 10, 25, 30, 50 and 60 years, where 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 Down syndrome cases 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 minimise survival bias. Time of origin was defined as year of birth, time of observation ( $t_0$ ) 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  $t_0$  and therefore was not included (i.e. they died prior to the opportunity for DSC registration). Therefore, inclusion in the analysis was conditional on survival until at least time  $t_0$  (DSC registration).

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

Frequency distributions for cases with Down syndrome only were described for place of birth (metropolitan or rural, based on residential postcode), presence of a cardiovascular defect (CVD) and the SEIFA Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) tertile (low advantage, medium advantage, and high advantage)<sup>(16)</sup>. 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% confidence intervals were calculated for survival at 1 and 5 years of age. Time of origin ( $t_0$ ) 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 utilised to produce hazard ratios of mortality for gender, 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, two multivariable models (one with and without the SEIFA index) adjusting for gender, 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,  $p < 0.05$  was considered statistically significant. Data were analysed using Stata SE (version 12.0 for Windows: StataCorp LP, Texas) and SPSS statistical software (version 19.0: Chicago, Illinois).

## RESULTS

Two groups totalling 1,389 cases were identified: (1) children born alive with Down syndrome in WA 1980-2010 (n=783) either from 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 which 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; online). Congenital heart disease was the most common primary cause (n=39, 50%), followed by pneumonia (n=10, 13%) and leukaemia (n=7, 9%). Cause of death was not known/reported in 13 cases (13/78, 17%), of which the cause of death was blank for five cases and recorded as 'Down syndrome' for eight cases (10% of deaths).

At the time of data extraction there were 167 deceased cases in the older group born 1953-1979. The birth prevalence of children born with Down syndrome over the period 1980-2010 was 1 in 1,003 live births.

### *Overall survival of people with Down syndrome born in WA 1953-2010:*

Overall, for cases born 1953-2010, 88% (95% confidence interval [CI] 86%,90%) survived to five years of age, 87% (95% CI 85%,89%) to 10 years, 83% (95% CI 80%,85%) to 30 years, 72% (95% CI 68%,76%) to 50 years and 57% (95% CI 49%,64%) to 60 years. Survival estimates were dependent on decade of birth, with each new birth decade showing positive improvements in survival (Figure 2). For those born 1953-1959, survival was 75% (95% CI 26%,94%) to five years of age and 74% (95% CI 26%,93%) to 10 years of age. For the 1990-1999 birth cohort, survival estimates were 97%

(95% CI 93%,98%) to 1 year of age and 95% (95% CI 92%,98%) at both 5 and 10 years of age. There was no significant difference in overall survival by gender over the period 1953-2010 ( $p=0.280$ ).

*Influence of the perinatal profile on survival, for live born children with and without Down syndrome 1980-2010:*

We compared the perinatal profile of children live born with Down syndrome ( $n=783$ ) 1980-2010 with the remainder of the population ( $n= 785,732$ ) (Table 1; online), and investigated the effect of perinatal factors on survival. Differences in survival were observed for some perinatal factors, but none were increasingly significant beyond the 5-year survival statistic (Table 2; Figure 3).

*Maternal age:* Live-born children with Down syndrome were more likely to have mothers aged 35 years or older than the population comparison group (32.7% vs 13.4%;  $p<0.001$ ) (Table 1; online). However survival of children with Down syndrome to five years of age did not differ when mothers aged under 35 years were compared with those over 35 years (0.91 CI 0.88, 0.93 vs 0.93 CI 0.89, 0.96 ;  $p=0.287$ ) (Table 2) and this pattern was consistent over the 30-year time period.

*Gestational age:* Children with Down syndrome were more likely to be born preterm (< 37 weeks gestation) compared with the rest of the population (23.8% vs 7.9%;  $p<0.001$ ). The proportion of children with Down syndrome born preterm increased from 20% between 1980-1985 to 29% between 2006-2010. However the proportion of preterm births for non-Down syndrome births also increased from 7.0% to 8.6% over the same period. Survival to five years of age improved with advancing gestational age for all children with Down syndrome born 1980-2010, with only a 60% (95% CI 13%,88%) survival rate to five years of age for children born less than 28 weeks gestation compared with a 93% (95% CI 89%,96%) survival rate for children born after 39 weeks (Table 2).

*Birth weight:* Children with Down syndrome were more likely to have a birth weight of less than 2500g compared with the non-Down syndrome population (20.4% vs 6.1%,  $p<0.001$ ). Far fewer Down syndrome births were over 3500g (17.1%) compared with the non-Down syndrome population (41.1%). Survival at one year of age was lower for children with Down syndrome who weighed less than 2500g (0.90, 95% CI 0.84,0.94) compared to those who weighed at least 2500g at birth (0.97, 95% CI 0.95,0.98), ( $p=<0.001$ ).

*Caesarean section:* Children born with Down syndrome 1980-2010 were more likely to be delivered by caesarean section compared to children without Down syndrome (28.9% vs 23.0%;  $p<0.001$ ). Children with Down syndrome delivered by caesarean section had poorer survival at one year of age (92% vs 97%,) than those delivered vaginally, as well as at 5 years (89% vs 93%) ( $p=0.153$ ).

*Plurality:* Among the Down syndrome births, 3.3% were from a multiple birth compared with 2.7% of non-Down syndrome births. Of the 26 children with DS from a multiple birth, all were from twin births and two of these males were a twin pair that was concordant for Down syndrome. Singletons with Down syndrome had a non-significant ( $p=0.355$ ) improved survival than multiples.

*Aboriginality:* Fewer children with Down syndrome were of Aboriginal heritage (5.1%) than the non-Down syndrome children (5.8%) ( $p=0.428$ ). Aboriginal children with Down syndrome had slightly poorer survival at one (92%; 95% CI 78%,97%) and five years of age (87%; 95% CI 72%,94%) compared with non-Aboriginal children at one (96%; 95% CI 94%,97%) and five years of age (92%; 95% CI 90%,94%) ( $p=0.244$ ).

*Place of birth:* Mothers of around one-fifth (20.7%) of children born with Down syndrome resided in rural settings, compared with 21.7% of mothers in the rest of the population. The children with Down syndrome whose mothers lived in rural settings 1980-2010 had a slightly better survival at one year of age than those in non-rural settings (98% (95% CI 93%,99%) vs 97% (95% CI 95%,98%))

but a slightly lower survival at 5 years (93% (95% CI 87%,96%) vs 94% (95% CI 92%,96%)) (p=0.395).

*SEIFA*: There was also a non-significant gradient effect of survival advantage with children with Down syndrome born in homes of higher economic index areas (the SEIFA index) having improved survival at one year of age (97%, 95% CI 94%,99%) compared to those in medium advantage (95%, 95% CI 91%,97%) and low advantage (96%, 95% CI 92%,98%) (p=0.852). Similarly, 5 year survival was 93% (95% CI 89%,96%) for those in higher economic index areas and 92% for those in both medium (95% CI 88%,95%) and lower advantage areas (95% CI 87%,95%).

*Cardiovascular defects (CVD)*: Among the 783 cases live-born with Down syndrome 1980-2010, 409 (52.2%) were recorded as having a CVD. The gender ratio for those with CVDs was similar, with 210 cases (51.3%) being female. Overall those without a CVD had better survival at one year (99% (95% CI 97%,100%) vs 92% (95% CI 89%,94%)) and five years of age (97% (95% CI 94%,98%) vs 87% (95% CI 83%,90%)) than those with a defect (p<0.001). However, this difference was much more pronounced in the earlier than the later birth cohorts. For those born 1980-1985 survival at 5 years was 74% (95% CI 62%,82%) with a cardiovascular defect and 93% (95% CI 83%,97%) in those without a defect. In contrast for those born 2006-2010 the figures were 92% (95% CI 81%,97%) and 95% (95% CI 88%,98%) respectively.

*Cox proportional hazards regression analyses*: Relative mortality risk increased by more than two-folds among Down syndrome births who were born 1) between 1980 and 1990 (HR 2.95; 95% CI 1.67,5.21), 2) with a cardiovascular defect (HR 2.92; 95% CI 1.74,4.91), 3) preterm (HR 2.37; 95% CI 1.50,3.73), or 4) with a birth weight of less than 2,500 grams (HR 2.31; 95% CI 1.45,3.69) (Table 3). In the final Cox proportional hazards regression model, after adjusting for pertinent covariates including gender and aboriginality, the effects of preterm and low birth weight on mortality were

less pronounced. However, poor survival was still strongly associated with the earliest birth cohort (1980-1990) (HR 2.92; 95% CI 1.64,5.19), and even more so with the presence of a cardiovascular defect (HR 3.12; 95% CI 1.82,5.28).

## DISCUSSION

Consistent with previous findings<sup>(7, 17-19)</sup>, this population-based sample showed incremental improvements in survival according to birth cohort. Ten-year survival increased from 74% in the 1953-1959 cohort to 95% in the 1990-1999 cohort. The dramatic improvements undoubtedly reflect a positive shift in care, knowledge and opportunity that has developed for people born with Down syndrome. Early intervention for cardiac anomalies remains a major contributing factor, and our finding of a 3% survival disadvantage after five years of age for children with a cardiac defect born 2006-2010 compared to a 19% survival disadvantage for children born 1980-1985, supports this association.

Children with Down syndrome were found to be at risk of being born preterm and of low birth weight (<2500g), for which survival was significantly compromised. We found low birth weight to occur in approximately 1 in 5 Down syndrome births and be a major risk factor of early mortality, which replicates findings from other large studies using similar birth cohorts<sup>(7, 12)</sup>. It is unknown how many of the cases were diagnosed prior to birth, either for Down syndrome, or conditions such as intra-uterine growth retardation, for which decisions may have been made to induce early. Further details regarding diagnostics and decisions are important for informing and influencing the care of mothers and their unborn children with Down syndrome.

A relationship between the type of congenital cardiovascular defect and birth weight has been reported elsewhere<sup>(20)</sup>, for example children with Down syndrome who have a low birth weight commonly have endocardial cushion defects, even when accounting for prematurity. Therefore children with Down syndrome who have low birth weight may be at a higher risk of poorer survival than other children born with low birth weight if they have particular cardiac defects. Both factors should be considered in the estimation of survival risk.

Although children with Down syndrome were more likely to be born to mothers aged 35 years or older, maternal age had no effect on survival over the time period. This has been also

found in other populations<sup>(10, 12)</sup>. It is an important finding because of the continuing trend of increasing maternal age among WA births and elsewhere<sup>(21, 22)</sup> and the well-documented heightened risk of Down syndrome for children born to mothers aged 35 years and over<sup>(23)</sup>.

For the Aboriginal children, fewer deaths were recorded for those born in more recent years with a 92% survival rate to one year of age across the 1980-2010 time period. A previous study using WA data 1980-1996 reported a 78% survival to one year of age for Aboriginal children with Down syndrome, which is much lower than our 92% survival statistic<sup>(24)</sup>. The difference may be accounted for by the extended years of data collection, the inclusion of cases who may have missed notification in early life to WARDA as being either Aboriginal or having Down syndrome at the time of the previous study, removal of early deaths from our analysis, variations in coding over time or better survival statistics in the additional Aboriginal cases who have been born in the most recent years.

## **CONCLUSION**

During the last 30 years, maternal ages have increased, thereby maintaining a relatively consistent birth incidence of Down syndrome population-wide, balanced by an increased number of terminations. The overall survival of children born with Down syndrome has increased greatly over the past 60 years, contributing to an increase in population prevalence and an ongoing need for appropriate services in this population as they age. The presence of cardiac anomalies is still identified as the largest factor impacting on survival, but the impact is significantly reduced if surgical intervention is undertaken. For children born preterm or with a low birth weight a survival disadvantage exists by 5 years of age and remains until at least 25 years of age.

## **ACKNOWLEDGEMENTS**

The authors are grateful to the Disability Services Commission, the Telethon Kids Institute, the Western Australia Department of Education, the Catholic Education Office and the Association of Independent Schools of Western Australia for assistance with data collection for the IDEA database.

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**Figure 1; online:** Primary cause of death per age group for children born with Down syndrome 1980-2010 surviving longer than the first 24 hours after birth (n=78).

**Figure 2:** Kaplan-Maier survival estimates by birth cohort, births 1953-2010, Western Australia (adjusted).

**Figure 3:** Kaplan-Meier estimate of the survival function for the live-born Down syndrome births, 1980-2010 in Western Australia, by selected perinatal characteristics (n=772).

**Table 1; online:** Survival comparison between live-born Down syndrome and non-Down syndrome births, 1980-2010 in Western Australia by perinatal characteristics.

**Table 2:** Comparative 1, 5, 10, 20 and 25-year survival of live-born Down syndrome births, 1980-2010 in Western Australia, by perinatal characteristics (n=772).

**Table 3:** Univariable and multivariable Cox proportional hazards regression analysis of risk of death in live-born Down syndrome births between 1980 and 2010 in Western Australia (n=772).