HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2024 September 01.

Published in final edited form as:

J Pediatr. 2023 September ; 260: 113523. doi:10.1016/j.jpeds.2023.113523.

Narrowing the Survival Gap: Trends in Survival of Individuals with Down syndrome with and without Congenital Heart Defects Born 1979 – 2018

Lydia K. Wright, MD, MSc[1,2,3], **Erin B. Stallings, MPH**[3], **Janet D. Cragan, MD, MPH**[3], **Laura J. Pabst, MPH**[3], **CJ Alverson, MS**[3], **Matthew E. Oster, MD, MPH**[3,4,5]

[1]Department of Pediatrics, The Ohio State University College of Medicine, Columbus, OH

[2]Heart Center, Nationwide Children's Hospital, Columbus, OH

[3]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA

[4]Department of Pediatrics, Emory University School of Medicine, Atlanta, GA

[5]Children's Healthcare of Atlanta, Atlanta, GA

Abstract

Objective: To evaluate the hypothesis that childhood survival for individuals with Down syndrome (DS) and congenital heart defects (CHDs) has improved in recent years, approaching survival of those with DS without CHDs.

Study design: Individuals with DS born 1979–2018 were identified through the Metropolitan Atlanta Congenital Defects Program, a population-based birth defects surveillance system administered by the Centers for Disease Control and Prevention. Survival analysis was performed to evaluate predictors of mortality for those with DS.

Results: The cohort included 1,671 individuals with DS; 764 had associated CHDs. Five-year survival in those with DS with CHD improved steadily among individuals born in the 1980s through the 2010s (85% to 93%, p=0.01) but remained stable (96% to 95%, p=0.97) in those with DS without CHDs. The presence of a CHD was not associated with mortality through 5 years of age for those born 2010 or later (hazard ratio 2.63 [95% confidence interval 0.95 – 8.37]). In multivariable analyses, atrioventricular septal defects were associated with early (<1 year) and late (>5 year) mortality, while ventricular septal defects were associated with intermediate (1–5 years) mortality and atrial septal defects with late mortality, when adjusting for other risk factors.

Conclusions: The gap in five-year survival between children with DS with and without CHDs has improved over the last four decades. Survival after 5 years remains lower for those with CHDs,

---

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

although longer follow-up will be needed to determine if this difference lessens for those born in the more recent years.

Down syndrome (DS) is the most common chromosomal abnormality among live born infants, with an estimated prevalence of approximately 14 per 10,000 live births[1]. Congenital heart defects (CHDs) are present in 40–50% of individuals with DS, often in the form of left to right shunt lesions, with atrioventricular septal defect (AVSD) being the most common[2]. More complex CHDs, including single ventricle disease, are less common but reported in patients with DS[3].

While individuals with DS have historically had a shortened lifespan compared with those without DS, this has improved substantially in the last 50 years[4]. Presence of CHDs has been consistently associated with lower survival for individuals with DS[4–6], and the transition to offering corrective cardiac surgery to infants and children with DS has been thought to be a contributor to this improved survival[4, 7]. Timely cardiac surgery has been the standard of care for children with DS + CHD in the United States since at least the mid-1990s[8, 9]. Multiple studies have shown survival after cardiac surgery in infants and children with DS to be comparable or even better to that seen in children without DS[9–13]. Children with DS also likely have benefited from the overall improvement in morbidity and mortality after congenital heart surgery among affected children in general that has been seen in recent decades[14].

Through a population-based cohort study spanning the last 40 years, we aimed to evaluate the hypothesis that the survival gap between those with DS and CHDs and those with DS alone has narrowed significantly in recent decades.

Methods

Data were obtained from the Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance system administered by the Centers for Disease Control and Prevention (CDC). Through the use of active case-finding and multisource ascertainment, MACDP identifies birth defects in infants, fetuses, and children younger than six years of age born to residents of metropolitan Atlanta, including those with both DS and CHDs. From 1968–2011, the MACDP catchment area included the 5 central counties of metropolitan Atlanta; beginning in 2012, this area was reduced to 3 of the previously included counties. Detailed information on underlying CHDs, non-cardiac anomalies, and comorbidities such as prematurity are abstracted from medical records and reviewed by clinicians at the CDC.[15] Those infants born between 1979 and 2018 were eligible for inclusion. In this analysis, patent ductus arteriosus in infants less than 36 weeks corrected gestational age was not counted as a CHD but was counted if present at later corrected gestational ages. All liveborn individuals with a postnatal karyotype confirming Trisomy 21 were included in the final study cohort.

Clinical and demographic data were collected for each individual, including detailed description of the type of CHD, any non-cardiac anomalies, gestational age at birth, birthweight (BW), birth year, and maternal race/ethnicity. Our primary outcome of all-cause

mortality was assessed through medical record abstraction (up to 6 years of age), linkage with Georgia Vital Records, and linkage with the National Death Index (NDI).

Characteristics of patients with DS + CHDs and DS without CHDs were compared using chi-squared test for categorical variables and either two-sample T-tests (normally distributed variables) or Wilcoxon signed rank test (non-normally distributed variables). Survival analysis was used to evaluate the relationship between CHDs and mortality. Kaplan Meier curves were generated to evaluate overall survival stratified by type of CHD. In order to compare survival across decades, including the most recent decade with limited follow-up time, the primary survival analysis was limited to the first five years of life. Kaplan Meier curves were generated for each birth era (1979–1989, 1990–1999, 2000–2009, 2010–2018) to compare survival between children with DS+CHD and those with DS without CHDs, as well as stratified analysis by type of CHD. For multivariable analysis, Cox regression was used to evaluate the effect of types of CHD on mortality at three time periods, from birth to one year of age ("early"), from one to five years of age ("intermediate") and five years of age and older ("late"). All relevant available risk factors (presence of CHDs, sex, maternal race/ethnicity, maternal age, low BW [<2.5 kg], presence of extracardiac anomaly) were included in each multivariable model to mitigate potential confounding, except for birth era in the late model, given limited possibility for >5-year follow-up in the 2010–2018 birth cohort. Prematurity was not included in the models due to its high correlation with low birthweight. To evaluate decade-CHD interaction, additional models stratified by birth era were generated, modeling mortality through the first five years of life.

The decrease in the ascertainment area of MACDP in 2012 from five to three counties had the potential to result in a change in sample characteristics. To ensure that this change did not affect results, a sensitivity analysis was conducted with only those individuals in the three counties that participated for the duration of the study. All above analyses were included in this sensitivity analysis.

Results

The final cohort included 1,671 individuals with DS, 764 (46%) of whom had a CHD. Those with DS + CHDs were more likely to be female (51% vs 42%, p<0.001), have birthweight <2.5 kg (27% vs 21%, p = 0.002) and premature (gestational age <37 weeks [31% vs 22%, p <0.001]), and have an intestinal atresia (7% vs 3%, p <0.001) than those with DS without CHDs (Table 1). Maternal race/ethnicity and age were not significantly different between the two groups. Atrioventricular septal defects (AVSD) were the most common type of CHD, present in 331 (43% of those with CHDs), followed by ventricular septal defects (VSD) (232 [30%]), and atrial septal defects (ASD) (104 [14%]). Details on type of CHDs and specific lesions can be found in Table 2 (available at www.jpeds.com).

Over a median follow-up time of 17.0 years, there were 150 deaths, 105 (70%) of which were in the DS + CHDs group. Median age at death was 0.4 years (IQR 0.1 – 4.5 years). Overall survival was significantly different based on presence of CHDs and underlying type of CHDs (Figure 1). Children with DS and an ASD had similar survival to those with no CHDs (pairwise log-rank p=0.868), while those with DS and VSD had slightly lower

survival (p=0.047). Survival was significantly lower for children with DS and underlying AVSD or other CHDs (p<0.001 compared with no CHDs for both).

In evaluation of risk factors for early (<1 year), intermediate (1–5 years) and late (>5 year) mortality, there were noticeable differences particularly depending on the type of CHD (Table 3), with all types of CHD conferring mortality risk at some, but not all, time periods. Presence of AVSD and other CHD lesions was associated with early mortality compared with having no CHDs, while VSDs and other lesions were associated with mortality from 1–5 years, and AVSDs and ASDs were associated with mortality after 5 years of age. Birthweight <2.5 kg was also associated with early mortality, as was birth between 1990–2009 compared with birth between 2010–2018. Maternal non-Hispanic Black race was associated with mortality between 1–5 years, while male sex was associated with late mortality. Extracardiac anomalies did not confer a mortality risk in any period when adjusting for other factors.

Stratified analysis by birth era revealed important changes in the impact of CHDs on survival over time, as seen in Figure 2. Survival through five years in those without CHDs remained stable over the birth eras (estimated five-year survival between 96–97% in each era), while those with CHDs saw a significant improvement in survival starting with those born in the year 2000 (five-year survival of 85% in the 1980s, 84% in the 1990s, 92% in the 2000s, and 93% in the 2010s, p=0.010). By the most recent birth era (2010–2018), there was no significant difference in five-year survival between those with any CHD and those without. Multivariable stratified analysis, adjusting for sex, maternal age and race, low birthweight, and presence of extracardiac anomalies confirmed this finding. The adjusted hazard ratio (HR) for CHDs for those born in the 1979–1989 was 3.38 (95% [confidence interval] CI 1.36– 8.39) compared with 2.59 (95% CI 0.81 – 8.28) for those born after 2010 (Table 4; available at www.jpeds.com). Birthweight less than 2.5 kg was significantly associated with mortality in all birth eras after 1990, with the strongest effects seen after 2000 (HR 3.34; 95% CI 1.73 – 6.44 for those born 2000–2009, HR 3.10; 95% CI 1.07–8.94 for those born 2010–2018). For those born in these later birth eras, low birthweight was a stronger predictor of mortality than presence of a CHD.

Sensitivity analysis restricting to those born in the three counties covered throughout the study period (n=1,253) is shown in Tables 5 and 6 (available at www.jpeds.com). Those with DS+CHDs were more likely to have cleft lip/palate than those with DS without CHDs in this cohort. Increasing maternal age was significantly associated with lower mortality in the intermediate risk period (p=0.028), whereas in the main model it neared significance (p=0.055). There were no other significant differences between the analyses.

Discussion

In this large, population-based study of children with DS born over the last 40 years, we found that all types of CHDs placed those with DS at higher risk of mortality compared with those with DS without CHDs, but the magnitude and timing of that risk varied depending on the type of CHD. We also saw a significant era effect, with improving five-year survival for those with DS + CHDs starting with those born 2000–2009; for those children born from

2010 – 2018, there was no longer a significant difference in survival up to age five for those with CHDs compared with those without.

The prevalence and types of CHDs seen in our cohort were comparable to those reported in other DS populations[6, 16]. Importantly, the type of CHDs was a key predictor of both magnitude and timing of mortality. Early survival (< 1 year) amongst those with VSDs and isolated ASDs did not differ significantly from that of children without CHDs when adjusting for other risk factors, while those with AVSDs and other less common types of CHDs had lower survival up to age 1. This is consistent with previous reports on large populations of children with DS. In an evaluation of children with DS in Norway born between 1994–2009, Brodwell and colleagues noted excellent early survival in those with ASD, VSD, or PDA, similar to that seen in those without CHDs, but significantly worse survival for those with all other types of CHDs, including AVSD and other less common types of CHDs[6]. Evaluation of operative mortality in children with DS undergoing CHDs repair in the United States demonstrated similar findings[17]. Mortality outside of infancy was less common in our cohort, but the presence of CHDs was a major risk factor for these later deaths. In the one-to-five-year age group, VSDs and other cardiac lesions were associated with mortality, while after five years, AVSDs conferred the greatest risk. ASDs, interestingly, were only noted to be associated with late mortality in multivariable analysis. Multiple factors may explain these varying effects over the lifespan. There have been reports of higher rates of complications for repair of both AVSDs and VSDs in children with DS compared with those without, which may account for some late mortality[12, 18]. Children with DS and left-to-right shunts (including AVSDs, VSDs, and ASDs) are also at increased risk of developing pulmonary hypertension, both after surgical repair as well as if surgical repair is not pursued, which may contribute to mortality across the lifespan[2, 19]. These findings support the need for continued cardiac care of those with DS + CHDs to evaluate for late complications, though the rate and magnitude of these complications may be changing with shifts in early care.

Our data confirm previous reports that have attributed improved overall DS survival and life expectancy over the last 40 years to improved survival for those with cardiac defects[4]; we saw equivalent five-year survival in those with DS without CHDs across the study period, but a major improvement in survival over the same time period for those with DS + CHDs starting for those born in the year 2000. Two major changes might explain this finding: 1) more widespread diagnosis and repair of CHDs in infants with DS and 2) overall improvement in mortality and morbidity with improvements in congenital heart surgery and postsurgical care. In the 1970s, routine performance of surgery for CHDs in infants became more widely available, but fewer than 50% of infants with DS with correctible CHDs lesions underwent surgical repair.[2, 9] Legal and ethical attitudes regarding the rights of those with DS and other disabilities prompted a steady increase in surgery for CHDs and other correctible congenital anomalies, both in the U.S. and Europe. A recent population-based study of individuals with DS in Germany showed a steady increase in the likelihood of left-to-right shunt lesion CHDs being treated surgically before the age of one year based on calendar year of birth, with only 2.1% of the 1970s birth cohort undergoing repair, compared with 86% of those born after 2000.[2] By 1994, the American Academy of Pediatrics recommended universal screening for CHDs among infants with

DS, suggesting that corrective repair had become the standard of care in this country.[8] Previous work evaluating survival in infants with DS in metropolitan Atlanta from 1979–1998, however, demonstrated that the presence of CHDs remained a significant risk factor for early mortality even with increased correction of underlying lesions, without significant improvement based on year of birth.[20] The authors proposed that CHD correction before the start of their study period was responsible for the lack of change across birth years. We did not see improved survival in those with DS+CHDs until the 2000–2009 birth cohort. This suggests that general improvements in cardiac surgical care may be a larger driver than simply more access to surgical repair. Peterson and colleagues noted this era effect in their evaluation of children with DS undergoing congenital heart surgery from 1982–2003 using data from the U.S. multicenter Pediatric Cardiac Care Consortium.[10] Surgery before 1998 was an independent predictor of increased mortality in children with and without DS. Similar trends in improved overall post-cardiac surgery survival over this time period have been seen, for both children with and without DS.[14, 21, 22] And while early studies suggested that children with DS had worse outcomes following congenital heart surgery than those without DS [23], more recent studies have shown children with DS to have similar or better perioperative outcomes compared with children without DS with similar lesions.[11, 17, 24, 25] The timing of improved survival in those with CHDs in our cohort points to overall improvement in cardiac surgical mortality having a significant impact on early survival for those with DS + CHDs.

Low birthweight was also found to be a significant risk factor for early mortality. This was true in both the CHD and non-CHD cohorts; and, while low birthweight was more common in the CHD group, there did not appear to be a differential effect on survival depending on presence or absence of CHDs. Both prematurity and low birthweight for gestational age have been seen as risk factors for mortality in previous reports, both in those with CHDs and those without.[4, 17] We saw a changing effect of low birthweight over time; for those born before 1990, low birthweight was not associated with lower survival when adjusting for other factors, while it was for those born since 1990 and the effect was strongest for those born after 2000. By the most recent era (2010–2018), low birthweight had overtaken CHDs as the most important predictor of early mortality for individuals with DS. For those who survived infancy, however, low birthweight did not seem to have a lasting effect, which is consistent with previous reports.[4]

The present study had several strengths. The MACDP has been collecting data on children with both DS and CHDs for over 50 years, allowing for robust monitoring of trends over time. The linkage with state and national death records also allows for complete mortality assessment. Additionally, all CHD cases are reviewed by pediatric cardiologists and thus include detailed anatomic details that are often missing from other epidemiologic datasets; this allowed us to provide unique insight into trends in survival and the long-term effects of various types of CHDs.

However, there were also several limitations. While detailed anatomic details were available to characterize the CHDs, treatment pathways, including if the child underwent surgery and the details of the surgery, if performed, were not always available, preventing complete understanding of the role of type and timing of congenital heart surgery on outcomes.

Cause of death data were also incomplete, which made robust analysis of circumstances of both early and late death in the sample impossible. Additionally, we only included those children with karyotyping results, which may have led to exclusion of some children with DS who were not karyotyped, particularly in earlier eras. Finally, the birth cohorts were of unequal size with a small number of those in the most recent cohort having <5 years of follow-up. This leaves open the possibility of being underpowered to detect small differences in survival in the smaller cohorts.

Over the last 40 years, we saw significant improvement in survival through five years of age for individuals with DS+CHDs, leading to a statistically nonsignificant survival gap between those with DS + CHDs and those with DS without CHDs in the most recent decade. It remains to be seen whether these improvements will translate into improved longer-term survival into adolescence and adulthood, as certain CHDs continue to be a risk factor for late mortality for those who survive past five years. Longitudinal follow-up will be needed to determine if this pattern persists for those born in more recent years.

Funding:

This study was supported in part by the National Heart, Lung, and Blood Institute through the Pediatric Heart Network INCLUDE Scholars Program.

References

[1]. Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, et al. Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004–2006. Birth Defects Res A Clin Mol Teratol. 2010;88:1008–16. [PubMed: 20878909]

[2]. Körten MA, Helm PC, Abdul-Khaliq H, Baumgartner H, Kececioglu D, Schlensak C, et al. Eisenmenger syndrome and long-term survival in patients with Down syndrome and congenital heart disease. Heart. 2016;102:1552–7. [PubMed: 27325590]

[3]. Pfitzer C, Helm PC, Rosenthal LM, Berger F, Bauer UMM, Schmitt KR. Dynamics in prevalence of Down syndrome in children with congenital heart disease. Eur J Pediatr. 2018;177:107–15. [PubMed: 29127498]

[4]. Glasson EJ, Jacques A, Wong K, Bourke J, Leonard H. Improved Survival in Down Syndrome over the Last 60 Years and the Impact of Perinatal Factors in Recent Decades. J Pediatr. 2016;169:214–20 e1.

[5]. Zhu JL, Hasle H, Correa A, Schendel D, Friedman JM, Olsen J, et al. Survival among people with Down syndrome: a nationwide population-based study in Denmark. Genet Med. 2013;15:64–9. [PubMed: 22878506]

[6]. Brodwall K, Greve G, Leirgul E, Klungsøyr K, Holmstrøm H, Vollset SE, et al. The five-year survival of children with Down syndrome in Norway 1994–2009 differed by associated congenital heart defects and extracardiac malformations. Acta Paediatr. 2018;107:845–53. [PubMed: 29341296]

[7]. Yang Q, Rasmussen SA, Friedman JM. Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. Lancet. 2002;359:1019–25. [PubMed: 11937181]

[8]. Health supervision for children with Down syndrome. American Academy of Pediatrics Committee on Genetics. Pediatrics. 1994;93:855–9. [PubMed: 8165098]

[9]. Champagne CR, Lewis M, Gilchrist DM. Should we mend their broken hearts? The history of cardiac repairs in children with Down syndrome. Pediatrics. 2014;134:1048–50. [PubMed: 25367533]

[10]. Peterson JK, Kochilas LK, Knight J, McCracken C, Thomas AS, Moller JH, et al. Long-Term Survival and Causes of Death in Children with Trisomy 21 After Congenital Heart Surgery. J Pediatr. 2021;231:246–53 e3.

[11]. Atz AM, Hawkins JA, Lu M, Cohen MS, Colan SD, Jaggers J, et al. . Surgical management of complete atrioventricular septal defect: associations with surgical technique, age, and trisomy 21. J Thorac Cardiovasc Surg. 2011;141:1371–9. [PubMed: 21163497]

[12]. Fudge JC Jr., Li S, Jaggers J, O'Brien SM, Peterson ED, Jacobs JP, et al. Congenital heart surgery outcomes in Down syndrome: analysis of a national clinical database. Pediatrics. 2010;126:315–22. [PubMed: 20624800]

[13]. Formigari R, Di Donato RM, Gargiulo G, Di Carlo D, Feltri C, Picchio FM, et al. Better surgical prognosis for patients with complete atrioventricular septal defect and Down's syndrome. Ann Thorac Surg. 2004;78:666–72; discussion 72. [PubMed: 15276542]

[14]. Spector LG, Menk JS, Knight JH, McCracken C, Thomas AS, Vinocur JM, et al. Trends in Long-Term Mortality After Congenital Heart Surgery. J Am Coll Cardiol. 2018;71:2434–46. [PubMed: 29793633]

[15]. Riehle-Colarusso T, Strickland MJ, Reller MD, Mahle WT, Botto LD, Siffel C, et al. Improving the quality of surveillance data on congenital heart defects in the metropolitan Atlanta congenital defects program. Birth Defects Res A Clin Mol Teratol. 2007;79:743–53. [PubMed: 17990334]

[16]. Baban A, Olivini N, Cantarutti N, Cali F, Vitello C, Valentini D, et al. Differences in morbidity and mortality in Down syndrome are related to the type of congenital heart defect. Am J Med Genet A. 2020;182:1342–50. [PubMed: 32319738]

[17]. Evans JM, Dharmar M, Meierhenry E, Marcin JP, Raff GW. Association between Down syndrome and in-hospital death among children undergoing surgery for congenital heart disease: a US population-based study. Circ Cardiovasc Qual Outcomes. 2014;7:445–52. [PubMed: 24755908]

[18]. Tucker EM, Pyles LA, Bass JL, Moller JH. Permanent pacemaker for atrioventricular conduction block after operative repair of perimembranous ventricular septal defect. J Am Coll Cardiol. 2007;50:1196–200. [PubMed: 17868813]

[19]. Bush D, Galambos C, Ivy DD, Abman SH, Wolter-Warmerdam K, Hickey F. Clinical Characteristics and Risk Factors for Developing Pulmonary Hypertension in Children with Down Syndrome. J Pediatr. 2018;202:212–9 e2.

[20]. Rasmussen SA, Wong LY, Correa A, Gambrell D, Friedman JM. Survival in infants with Down syndrome, Metropolitan Atlanta, 1979–1998. J Pediatr. 2006;148:806–12. [PubMed: 16769392]

[21]. Erikssen G, Liestøl K, Seem E, Birkeland S, Saatvedt KJ, Hoel TN, et al. Achievements in congenital heart defect surgery: a prospective, 40-year study of 7038 patients. Circulation. 2015;131:337–46; discussion 46. [PubMed: 25538230]

[22]. Larsen SH, Olsen M, Emmertsen K, Hjortdal VE. Interventional Treatment of Patients With Congenital Heart Disease: Nationwide Danish Experience Over 39 Years. J Am Coll Cardiol. 2017;69:2725–32. [PubMed: 28571637]

[23]. Reller MD, Morris CD. Is Down syndrome a risk factor for poor outcome after repair of congenital heart defects? J Pediatr. 1998;132:738–41. [PubMed: 9580782]

[24]. Ginde S, Lam J, Hill GD, Cohen S, Woods RK, Mitchell ME, et al. Long-term outcomes after surgical repair of complete atrioventricular septal defect. J Thorac Cardiovasc Surg. 2015;150:369–74. [PubMed: 26048271]

[25]. St Louis JD, Jodhka U, Jacobs JP, He X, Hill KD, Pasquali SK, et al. Contemporary outcomes of complete atrioventricular septal defect repair: analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. J Thorac Cardiovasc Surg. 2014;148:2526–31. [PubMed: 25125206]

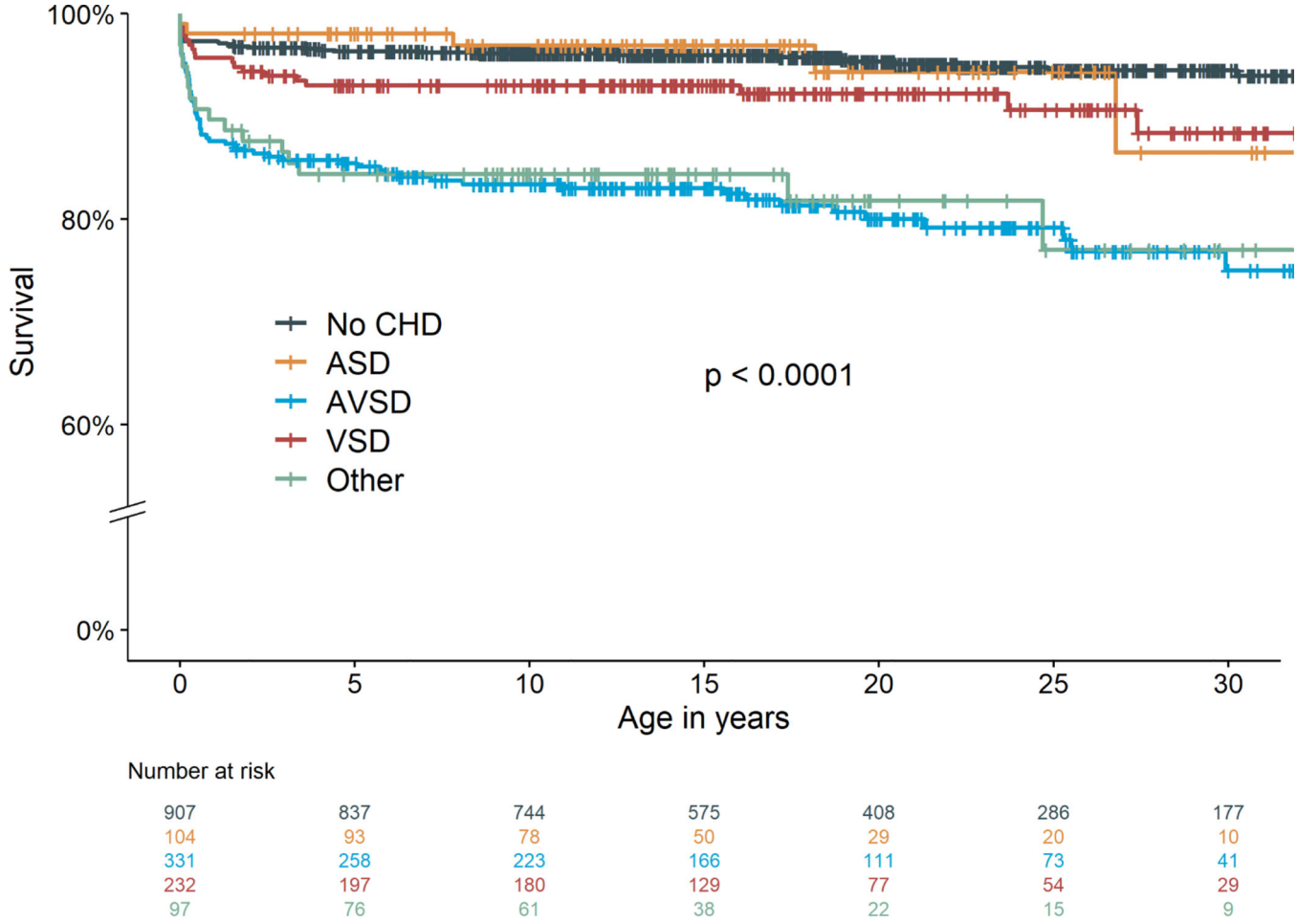

Figure 1 –.

Overall survival of all individuals with Down syndrome stratified by type of congenital heart defect, Metropolitan Atlanta 1979–2018;

CHD= congenital heart defect, ASD = atrial septal defect, AVSD = atrioventricular septal defect, VSD=ventricular septal defect

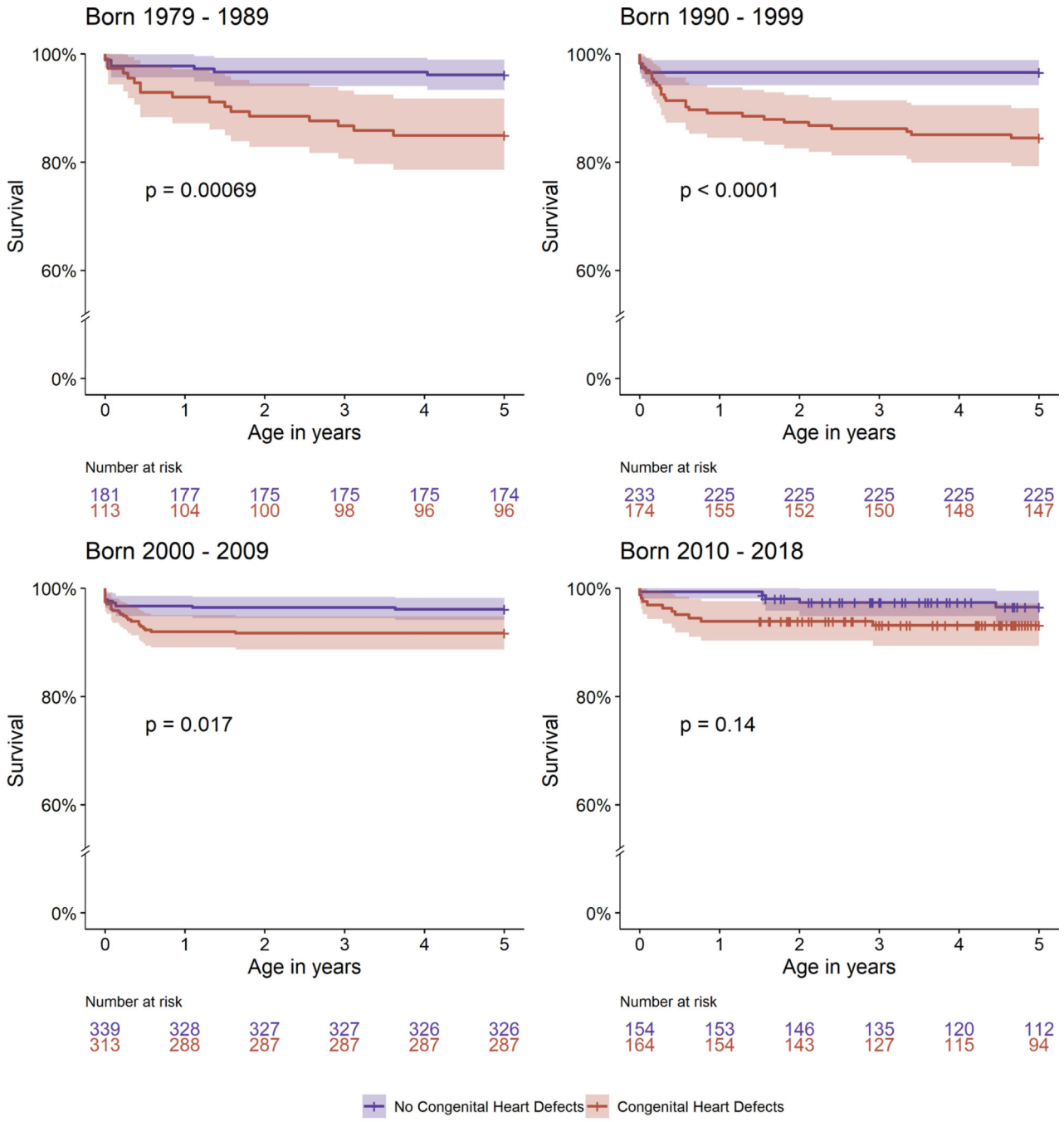

Figure 2 –.

Survival through 5 years of age for individuals with Down syndrome with and without congenital heart defects stratified by birth era, Metropolitan Atlanta 1979–2018; p-value represents results of log-rank test comparing survival across all strata; the difference in survival between those with congenital heart defects is no longer significantly lower than those without congenital heart defects for those born 2010 – 2018.

Table 1:

Baseline characteristics and outcome of children with Down Syndrome (DS) with and without congenital heart defects (CHDs), Metropolitan Atlanta, 1979–2018

	All individuals with DS (n=1,671) Median (IQR) or N (%)	DS without CHDs (n=907) Median (IQR) or N (%)	DS with CHDs (n=764) Median (IQR) or N (%)	p-value*
Sex				<0.001
Male	893 (54%)	521 (58%)	372 (49%)	
Female	771 (46%)	384 (42%)	387 (51%)	
Unknown/missing	7	< 5	5	
Birthweight (kg)	2.9 (2.5 – 3.3)	3.0 (2.6 – 3.3)	2.9 (2.5 – 3.3)	0.005
Low birthweight <2.5 kg	385 (23%)	182 (21%)	203 (27%)	0.002
Preterm birth (<37 weeks)	410 (26%)	188 (22%)	222 (31%)	<0.001
Maternal age (years)	33 (27 – 38)	33 (27 – 38)	33 (27 – 37)	0.762
Maternal race/ethnicity				0.783
Non-Hispanic white	710 (43%)	394 (44%)	316 (42%)	
Non-Hispanic Black	597 (36%)	316 (35%)	281 (38%)	
Hispanic	266 (16%)	148 (16%)	118 (16%)	
Other	75 (5%)	42 (5%)	33 (4%)	
Unknown /missing	23	7	16	
Extracardiac anomalies				
CNS abnormalities	46 (3%)	19 (2%)	27 (4%)	0.073
Cleft lip/palate	10 (1%)	<5 (<1%)	7 (1%)	0.122
Intestinal atresias	84 (5%)	30 (3%)	54 (7%)	<0.001
Birth era				0.004
1979–1989	294 (18%)	181 (20%)	113 (15%)	
1990–1999	407 (24%)	233 (26%)	174 (23%)	
2000–2009	652 (39%)	339 (37%)	313 (41%)	
2010–2018	318 (19%)	154 (17%)	164 (22%)	
Age at death	150 (9%)	45 (5%)	105 (14%)	<.0001
<1 year of age#	87 (58%)	24 (53%)	63 (60%)	
1–5 years #	27 (18%)	9 (20%)	18 (17%)	
>5 years#	36 (24%)	12 (27%)	24 (23%)	

*Denotes differences between DS with CHDs and DS without CHDs, by chi-square test for categorical variables and Wilcoxon signed rank test for continuous variables

DS = Down Syndrome, CHD=congenital heart defect, IQR = interquartile range; CNS = central nervous system

#Percent among total deaths

Table 2 –

Frequency of primary CHD in DS + CHD cohort, Metropolitan Atlanta, 1979–2018

Type of CHD	Primary lesion	Total N = 764 N (%)
Atrioventricular septal defect (AVSD)	Isolated AVSD	290 (38%)
	AVSD + TOF	19 (2%)
	Complex AVSD	15 (2%)
	Unbalanced/Single ventricle	7 (1%)
Ventricular septal defect (VSD)	Isolated VSD	182 (24%)
	Complex VSD	50 (7%)
Atrial septal defect (ASD)	Isolated ASDs	104 (14%)
Other	Tetralogy of Fallot	24 (3%)
	Isolated patent ductus arteriosus	21 (3%)
	Vascular rings/slings	19 (2%)
	Mitral valve disease	6 (1%)
	Pulmonary stenosis/atresia	5 (1%)
	Bicuspid aortic valve	<5 (<1%)
	Double outlet right ventricle	<5 (<1%)
	Tricuspid valve disease	<5 (<1%)
	Transposition of the great arteries	<5 (<1%)
	PAPVR	<5 (<1%)
	Coarctation of the aorta	<5 (<1%)
	Other not specified	10 (1%)

Complex VSD = VSD plus any of the following: coarctation, ASD, RVOTO, sub AS, Complex AVSD = AVSD plus any of the following: coarctation, LVOT obstruction, PAPVR, RVOTO (but not TOF)

Table 3:

Multivariable analysis of risk factors for early (<1 year), intermediate (1–5 years) and late (>5 year) mortality in individuals with DS, Metropolitan Atlanta, 1979–2018

	Birth to 1 year of age			1 – 5 years of age			> 5 years of age		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p - value**	**HR**	**95% CI**	**p-value**
Type of CHD									
AVSD	5.05	2.99 – 8.51	<0.001	2.34	0.83 – 6.57	0.107	5.35	2.51 – 11.40	<0.001
VSD	1.49	0.70 – 3.14	0.301	4.09	1.39 – 12.00	0.010	1.36	0.38 – 4.85	0.638
ASD	0.72	0.17 – 3.07	0.659	*	-		4.05	1.12 – 14.63	0.033
Other	3.83	1.81 – 8.12	0.005	8.17	2.60 – 25.73	0.003	2.53	0.56 – 11.34	0.226
None	Ref	-	-	Ref	-	-	Ref	-	-
Male sex	1.42	0.92 – 2.20	0.117	0.82	0.38 – 1.80	0.624	3.59	1.62 – 7.96	0.002
Maternal age	0.98	0.95 – 1.01	0.168	0.94	0.89 – 1.00	0.055	1.02	0.97 – 1.07	0.478
Maternal race/ethnicity									
NH White	Ref	-	-	Ref	-	-	Ref	-	-
NH Black	1.24	0.76 – 2.03	0.383	2.97	1.18 – 7.47	0.021	1.64	0.82 – 3.26	0.162
Hispanic	1.10	0.53 – 2.28	0.800	0.72	0.08 – 6.27	0.765	0.94	0.21 – 4.27	0.939
Other	1.99	0.82 – 4.85	0.128	3.50	0.69 – 17.61	0.129	*	-	-
Low birthweight (<2.5 kg)	3.47	2.25 – 5.37	<0.001	1.21	0.51 – 2.89	0.672	1.63	0.79 – 3.38	0.188
Extracardiac anomaly	0.97	0.49 – 1.93	0.940	0.92	0.26 – 3.25	0.896	0.80	0.23 – 2.75	0.718
Birth era[#]									
1979 – 1989	1.36	0.59 – 3.14	0.476	2.65	0.77 – 9.07	0.121			
1990 – 1999	2.12	1.03 – 4.35	0.041	1.35	0.39 – 4.71	0.636			
2000 – 2009	2.01	1.01 – 3.99	0.047	3.73	0.08 – 1.70	0.202			
2010 – 2018	Ref	-	-	Ref	-	-			

[*] Unable to calculate HR secondary to no deaths occurring in this group in period at risk

[#] Variable not included in multivariable model for late period given lack of meaningful follow-up >5 years in reference group

HR = Hazard ratio, CI = confidence interval, NH = Non-Hispanic, CHD = congenital heart defect; AVSD=atrioventricular septal defect, VSD=ventricular septal defect, ASD = atrial septal defect

Table 4 –

Multivariable model evaluating risk factors for survival through 5 years of age, stratified by birth decade

	1979 – 1989		1990 – 1999		2000 – 2009		2010 – 2018	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
CHD	3.38	1.36 – 8.39	4.79	2.16 – 10.59	2.10	1.05 – 4.22	2.59	0.81 – 8.28
Male sex	1.26	0.55 – 2.88	0.91	0.47 – 1.78	1.82	0.92 – 3.60	0.80	0.29 – 2.23
Maternal age	0.92	0.86 – 0.99	0.99	0.95 – 1.04	0.99	0.94 – 1.03	0.95	0.89 – 1.02
Maternal race								
NH White	Ref	-		-		-		-
NH Black	1.98	0.79 – 4.95	1.46	0.72 – 2.97	1.74	0.79 – 3.85	1.59	0.40 – 6.33
Hispanic	-	-	-	-	1.14	0.44 – 2.99	1.92	0.42 – 8.73
Other	5.68	1.16 – 27.85	2.02	0.58 – 7.03	2.43	0.66 – 9.02	-	-
Low birthweight	2.07	0.90 – 4.77	2.29	1.15 – 4.55	3.34	1.73 – 6.44	3.10	1.07 – 8.94
Extracardiac anomaly	0.92	0.26 – 3.27	0.52	0.16 – 1.74	1.37	0.55 – 3.44	0.94	0.12 – 7.62

*All variables were included in the adjusted model to account for potential confounding

Table 5–

Baseline characteristics of children with DS + CHD and DS without CHD in three county cohort, Metropolitan Atlanta, 1979–2018

	All individuals with DS (n=1,253)	DS alone (n= 663) Median (IQR) or N (%)	DS + CHD (n=590) Median (IQR) or N (%)	p-value
Sex				0.019
Male	685 (55%)	384 (58%)	301 (51%)	
Female	561 (45%)	277 (42%)	284 (49%)	
Unknown	7	<5	5	
Birthweight (kg)	2.9 (2.5 – 3.3)	3.0 (2.6 – 3.3)	2.9 (2.4 – 3.2)	0.009
Birthweight <2.5 kg	325 (26%)	155 (23%)	170 (29%)	0.029
Premature (<37 weeks)	313 (27%)	137 (22%)	176 (32%)	0.001
Maternal age (years)	33 (27 – 38)	33 (27 – 38)	33 (27 – 38)	0.430
Maternal race/ethnicity				0.334
Non-Hispanic white	487 (39%)	266 (40%)	221 (38%)	
Non-Hispanic Black	481 (39%)	242 (37%)	239 (42%)	
Hispanic	209 (17%)	116 (18%)	93 (16%)	
Other	57 (5%)	34 (5%)	23 (4%)	
Unknown	19	5	14	
Extracardiac anomalies				
CNS abnormalities	41 (3%)	18 (3%)	23 (4%)	0.240
Cleft lip/palate	7 (1%)	<5 (<1%)	6 (1%)	0.040
Intestinal atresias	66 (5%)	24 (4%)	42 (7%)	0.008
Birth era				0.048
1979–1989	218 (17%)	129 (20%)	89 (15%)	
1990–1999	294 (23%)	160 (24%)	134 (23%)	
2000–2010	465 (37%)	245 (37%)	220 (37%)	
2010–2018	276 (22%	129 (20%)	147 (25%)	
Died	113 (%)	33 (5%)	80 (14%)	<0.001
<1 year of age *	63 (56%)	18 (55%)	45 (56%)	
1–5 years *	21 (19%)	7 (21%)	14 (18%)	
>5 years *	29 (26%)	8 (24%)	21 (26%)	

* Percent among total deaths

Table 6–

Multivariable cox regression for three-county cohort, Metropolitan Atlanta, 1979–2018

	Birth to 1 year of age			1 – 5 years of age			≥ 5 years of age		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p - value**	**HR**	**95% CI**	**p-value**
Type of CHD									
AVSD	4.42	2.41 – 8.13	<0.001	1.49	0.41 – 5.43	0.544	6.09	2.52 – 14.69	<0.001
VSD	1.24	0.52 – 3.00	0.631	4.44	1.32 – 15.00	0.016	1.72	0.45 – 6.51	0.432
ASD	0.53	0.07 – 3.98	0.534	-	-	-	4.56	0.94 – 22.10	0.060
Other	4.69	2.08 – 10.57	<0.001	9.59	2.81 – 32.71	<0.001	3.25	0.69 – 15.36	0.138
None	Ref	-	-	Ref	-	-	Ref	-	-
Male sex	1.34	0.80 – 2.24	0.263	0.93	0.38 – 2.31	0.873	3.23	1.35 – 7.73	0.009
Maternal age	1.00	0.96 – 1.04	0.893	0.93	0.87 – 0.99	0.028	1.04	0.98 – 1.09	0.207
Maternal race/ethnicity									
NH White	Ref	-	-	Ref	-	-	-	-	-
NH Black	1.05	0.59 – 1.84	0.877	3.70	1.17 – 11.68	0.026	1.88	0.85 – 4.19	0.121
Hispanic	1.02	0.43 – 2.40	0.967	0.95	0.10 – 9.15	0.963	1.27	0.26 – 6.06	0.768
Other	2.28	0.77 – 6.79	0.138	2.89	0.30 – 27.44	0.356	-	-	-
Low birthweight	3.79	2.28 – 6.31	<0.001	0.92	0.33 – 2.54	0.868	1.59	0.71 – 3.60	0.263
Extracardiac anomaly	0.65	0.27 – 1.55	0.331	1.30	0.35 – 4.81	0.699	0.91	0.26 – 3.18	0.877
Birth era									
1979 – 1989	2.97	0.95 – 9.26	0.061	1.86	0.51 – 6.83	0.350			
1990 – 1999	4.59	1.70 – 12.44	0.003	0.93	0.25 – 3.49	0.909			
2000 – 2009	4.27	1.61 – 11.31	0.004	0.27	0.05 – 1.55	0.143			
2010 – 2018	Ref	-	-	Ref	-	-			