DOWN SYNDROME AND CONGENITAL CARDIAC ANOMALIES: A QUALITY OF LIFE ASSESSMENT

By

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This thesis investigates the impact of congenital heart defects on the quality of life of individuals with Down syndrome through researching morbidity and mortality. The assessment includes information relating to the relative rates of morbidity and mortality, ethical considerations, and associated maternal outcomes. The purpose of this work is to create a consultation tool for parents expecting a neonate with both Down syndrome and a cardiac anomaly. Through my research I hope I can assist parents to make informed decisions regarding their child's medical care and future. Additionally, I would like to aid practicing physicians by generating readily available and accessible literature that discusses the modern implications of Down syndrome when it is compounded by a congenital heart defect.

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Introduction

Down syndrome is the most frequent chromosomal disorder for live birth surviving neonates. As Down syndrome is a well-observed chromosomal anomaly, much is known about its origins and its impacts on the health of a diagnosed individual. However, in recent years many advancements of medical science have enhanced the longevity and quality of life of affected individuals.

Down syndrome is most commonly caused by trisomy of chromosome 21 and is, in fact, the most common survivable human trisomy. In addition to the characteristic physical features and neural developmental delays of Down syndrome, many other health complications are associated with the disorder. Individuals with Down syndrome are at increased risk for many conditions including: immune deficiencies, certain types of leukemia, soft pallet deformations, and most notably congenital cardiac anomalies.

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Considering Down Syndrome in Conjunction with Cardiac Anomalies

Over the last hundred years the life expectancy of individuals with Down syndrome has dramatically increased. The current life expectancy, regardless severity of secondary conditions associated with Down syndrome, is over sixty-six years of age. Considering that the addition and severity of a congenital cardiac anomaly can greatly impact an individual's life, understanding exactly how various cardiac anomalies impact the outcome of an individual with Down syndrome is critical for providing thorough and comprehensive medical care.

The increased life expectancy for individuals with Down syndrome could be attributed to numerous factors. These include general increases in quality of medical care, more social awareness and reduced stigma of developmentally delayed individuals, greater emphasis on the social incorporation of these individuals, and better treatment and preventative care to address secondary health issues commonly associated with Down syndrome.

To eliminate these possible confounded variables, analysis is framed in terms of how individuals with Down syndrome and cardiac anomalies compare to individuals who have Down syndrome and no congenital heart defects. By allowing children, infants, and neonates with Down syndrome, but without cardiac anomalies, to act as the control it is possible to address explicitly how congenital heart defects impact the quality of life of individual with Down syndrome. Additionally, by utilizing a direct comparison group, which is equal considering all factors but cardiac anomalies, it is possible to generate more exact and specific data, while limiting the scope of the analysis.

Arguably, the greatest advancement in medical care for congenital heart defects is the modern surgical techniques used to correct them. Over the last thirty-five years the advancement and precision of techniques used in pediatric cardiac surgery have exponentially grown. Highlighting the advancements in pediatric cardiac surgery is necessary because the vast majority of operable cases of congenital heart disease are corrected before the child has undergone puberty. The extent of the correction can be so complete that an individual with a defect can lead an apparently normal life, even engaging in activities such as military service.

Historically, secondary health complications of Down syndrome, especially congenital heart defects, drastically shorten the life expectancy and quality of life of affected individuals. Even considering modern techniques and surgeries, individuals with Down syndrome and a fetal cardiac anomaly are currently more likely to experience both post neonatal and infant death than a neonate or infant with Down syndrome, but without a fetal cardiac anomaly (Fields, 2015). For specific statistics please see table 1.

This thesis further investigates the discrepancies in mortality and morbidity rates of neonates who have both a congenital cardiac anomaly and Down syndrome compared to similar groups who only have diagnosed Down syndrome. Maternal outcomes also factor into the analysis. In this comparison it is expected that cardiac anomalies in conjunction with Down syndrome will be associated with more negative outcomes for the neonate, than negative outcomes for individuals, who have Down syndrome without a diagnosed congenital cardiac anomaly

Ethical Considerations

Two of the most important principles of biomedical ethics are the idea that medicine should apply to the principles of nonmaleficence and beneficence (Beauchamp & Childress 2009). Nonmaleficence in its purest form means *Primum non nocere*, otherwise paraphrased as "first do no harm" (Beauchamp and Childress 2009 pp. 149). Beneficence is understood as actions meant to perpetuate the well being of others (Beauchamp & Childress 2009 pp. 197). The key distinction between the two is that nonmaleficence emphasizes the obligation of medical professionals to do no harm, while beneficence examines striving to create good and prevent future hardships.

While initially these principles may seem straightforward, in terms of maternal and fetal medicine they are not as clean cut. Typically when treating a patient, a doctor is treating one individual who is somewhat autonomous either mentally or physically. However, treating an individual who is pregnant introduces another complication; the provider is responsible for considering both maternal and fetal wellbeing. This is a truly unique case because what may be best for one may directly harm, in the traditional sense of the word, the other. Additionally, an embryo or fetus is neither autonomous nor able to give consent. This implies that in addition to their regular duties a caregiver is given much more power over the outcome of a fetus as they must assume a degree of responsibility, in conjunction with the mother, for anticipating what is in the fetus' best interest.

Considering fetuses with abnormalities, chromosomal or otherwise, this adds an additional ethical layer. In cases of extreme impairment, which would dramatically influence the quality and longevity of a child's life, is it ethical to terminate the

pregnancy on the grounds that it would prevent future suffering of both the mother and child?

At this point it becomes important to recognize several factors. First, that in the United States of America a woman, if she so chooses, is entitled to an abortion for any reason. This comes with the provision that states can restrict this right based on the estimated age of the fetus. Generally, abortions are available throughout the first and well into the second trimester. Second, while life undoubtedly begins at conception, life is not the same as personhood. While the embryonic heart may start to beat in the third week of pregnancy this is not the same as the embryo achieving autonomy or even being sentient. Considering this, because the fetus and mother are fundamentally dissimilar in their capacities and privileges, the concepts of nonmaleficence and beneficence cannot be applied equally without consideration of context.

When a mother is informed that her pregnancy is complicated by a fetal anomaly, many factors must be considered. After any potential threats to maternal immediate wellbeing have been addressed, the wellbeing of the fetus must be examined. Depending on the severity of the defect, the prognosis and expected outcomes of the fetus can vary dramatically. For example, a child with a clubfoot or clef lip may go on to have a relatively normal life after appropriate treatment. However, more severe anomalies such as achondroplasia present many more complications and can affect both the quality and longevity of the child's life (Wynn 2007).

Considering Down syndrome, the prognosis varies greatly amongst the cases. Many individuals with Down syndrome can live into adulthood and are able to participate and contribute in community and social life. However, in more extreme

cases individuals with Down syndrome can have a host of additional health complications and significantly diminished cognitive function. In such cases it is not uncommon that individuals are less able to integrate into society and require more care and supervision, often to an extent where their medical and physical needs must be met in a full time care facility.

In severe cases the family of these individuals are often put under extreme amounts of emotional and financial duress when determining the best treatment of their special needs child. For example, in 2007 the family of a nine-year old with static encephalopathy named Ashley underwent massive criticism (Liao 2007). The contentious issue at the time was the treatment that the parents had decided on to improve Ashley's quality of life. Her guardians and an ethics panel condoned a treatment that was intended to stunt her growth and prevent puberty. This was accomplished by supplying her with large quantities of estrogen to fuse her growth plates, removal of her breast buds, and a hysterectomy. This specific therapy would come to be known as the *Ashley treatment.*

As Ashley has the cognitive abilities of a three-month-old infant, she is completely reliant on her parents for care, feeding, and transportation. Her parents argued that these precautions would enable them to continue to provide at-home care and prevent the risk of pregnancy if she was sexually abused, and certain cancers to which Ashley was genetically predisposed. Critics of these methods cited that the treatments were only for the convenience of her caregivers and would undermine Ashley's basic right to human dignity. In their defense Ashley's parents cite the

conclusion of George Dvorsky, a doctor on the board of directors for the Institute of Ethics and Emerging Technologies:

> If the concern has something to do with the girl's dignity being violated, then I have to protest by arguing that the girl lacks the cognitive capacity to experience any sense of indignity. Nor do I believe this is somehow demeaning or undignified to humanity in general; the treatments will endow her with a body that more closely matches her cognitive state – both in terms of her physical size and bodily functioning. The estrogen treatment is not what is grotesque here. Rather, it is the prospect of having a full-grown and fertile woman endowed with the mind of a baby.

While it is possible to argue with Doctor Dvorsky's conclusion about what is considered grotesque in terms of humanity, this quote demonstrates that professionals in both the field of medical care and ethics recognize that ethical standards of beneficence and nonmaleficence depend greatly on the context and the specific situation of the patient. It also demonstrates that, to an extent, parents have the right and responsibility to act as an executor of what is in their child's best interest when the affected individual is otherwise unable.

While Ashley did not have Down syndrome, she does face some of the same challenges in her life that a severely neurodevelopmentally delayed individual with Down syndrome does: Primarily, she is unable to care for herself and relies on her parents and other providers for survival. As her parents are the responsible party for her care, a significant burden is placed on them. Generally, it would be fair to say that their quality of life has been directly impacted by Ashley's dependency on them. This is not to say that they do not love or wish to have Ashley in their life, but it is a partial truth to imply that their life and the life of their family has not been impacted by Ashley's severe disability.

While Ashley's parents are able to provide her with the care she needs, it is not unreasonable to expect that many individuals with severely impaired children would struggle to provide the appropriate care and accommodations needed for their children to thrive.

In terms of Down Syndrome, parents not only need to address the means needed to provide care for their children, but also the expected quality of life their children could hope to achieve. While individuals with Down syndrome can currently live into middle age with appropriate medical care, this was not always the case. In fact, until 1972 it was not uncommon for doctors and parents to withhold treatment and surgery necessary for the survival of a child with Down syndrome if their prognosis was considered intolerably substandard, even if they could potentially survive infancy (Robertson 2004). In fact, it was not until the 1984 Child Abuse Amendments where criteria was standardized for when intervention was not mandatory (Robertson 2004).

When Down syndrome is exacerbated by other underlying conditions, such as a congenital cardiac anomaly, the quality of life of the child is likely to be impacted. Unfortunately, in some cases this may cause an otherwise manageable condition to become unmanageable and otherwise all-consuming for the caretakers, in addition to severely impacting the health and well-being of the affected individual. Additionally, there is the possibility that risk of any procedures to correct such defects, such as surgical correction, could result in further impairment or mortality.

In considering the significant obligations involved in raising a child with Down syndrome, it is not unreasonable for a parent to question if they are physically, emotionally, and financially able to care for their baby. This question only grows in

importance when considering that issue of a fetal cardiac anomaly in conjunction with Down syndrome. If given a prenatal diagnosis, and parents consider their options and find themselves unable to raise the child for any reason, it is not an unreasonable option to consider termination of the pregnancy. In terms of biomedical ethics this is justifiable as the potential interventions required to save the child's life and ensure their survival may violate the concepts of both beneficence and nonmaleficence; the resulting treatments and interventions may cause undue physical pain and suffering for the child, and ongoing burden of increased care may negatively impact the quality of maternal and family life to an extent that is unmanageable for a given family unit.

This research is neither promoting carrying a pregnancy with fetal anomalies to term or advising its termination. It is only summarizing knowledge and drawing conclusions about the expected outcomes correlated with standards of medical care in the field. The intention is to create a resource that can summarize what might be expected in cases of Down syndrome that are complicated by a fetal cardiac anomaly in comparison to the expected outcomes of individuals with Down syndrome where such complications are not present. The decision to proceed with or terminate an atypical pregnancy is dependent on context and the explicit wishes of the fetus' parents.

The Inherent Variability of Down Syndrome

According to the Center for Disease Control, Down syndrome accounts for approximately 1 in every 700 live births. This estimation indicates that in a given year in America there are around 6000 new cases of Down syndrome. Summarizing and synthesizing concise data about individuals with Down syndrome is challenging, as the impact of the disorder is so variable. Not all individuals who are affected have the same symptoms or same degree of expression.

It is important to clarify that there are multiple forms of chromosomal expression across different cases of Down syndrome. The three most prevalent types, as stipulated by the National Association for Down Syndrome, are listed below:

1.Trisomy 21 (nondisjunction) is caused by a faulty cell division that results in the baby having three #21 chromosomes instead of two. Prior to or at conception, a pair of #21 chromosomes in either the egg or the sperm fails to separate properly. The extra chromosome is replicated in every cell of the body. Ninety-five percent of all people with Down syndrome have Trisomy 21.

2.Translocation accounts for only 3% to 4% of all cases. In translocation a part of chromosome #21 breaks off during cell division and attaches to another chromosome. The presence of an extra piece of the 21st chromosome causes the characteristics of Down syndrome. Unlike Trisomy 21, which is the result of random error in the early cell division, translocation may indicate that one of the parents is carrying chromosomal material that is arranged in an unusual manner. Genetic counseling can be sought to ascertain more information when these circumstances occur.

3. Mosaicism occurs when nondisjunction of chromosome #21 takes place in one of the initial cell divisions after fertilization. When this happens, there is a mixture of two types of cells, some containing 46 chromosomes and some 47. The cells with 47 chromosomes contain an extra 21st chromosome. Because of the “mosaic” pattern of the cells, the term mosaicism is used. This type of Down syndrome occurs in only one to two percent of all cases of Down syndrome.

Looking at the reported percentages, it is important to recognize that the vast majority of research regarding the outcomes and abilities of individuals with Down syndrome represent individuals with a nondisjunction trisomy of chromosome 21, as the majority of the population of patients with Down syndrome have this pattern of chromosomal expression. However, within these patterns of chromosomal expression differences appear between individuals who are diagnosed with a particular form of Down syndrome.

For example, individuals who have Mosaicism appear to have generally higher IQs than individuals with more typical trisomy of chromosome 21; the average recorded IQ of individuals with trisomy 21 is 52 and the average IQ of individuals with mosaic expression is 67 (Fishler 1976). Figure 1 compares the development of individuals with trisomy and mosaic Down syndrome. However, it is important to note that the ages of study participants range from 2 year to 18 years, and neurodevelopmental delays in individuals with Down syndrome become more pronounced as they advance in age. Additionally, not all individuals with mosaic Down syndrome have the same percentage of affected cells with atypical expression of chromosome 21. In addition to relatively higher IQs, individuals who have Mosaicism tend to have lower relative rates of mortality (Zhu 2012).

Generally, individuals with a translocation as opposed to a trisomy of chromosome 21 had less severe degrees of learning disabilities even though the two groups had comparable physical characteristics, thyroid status, and blood chemistry levels. However, individuals with a translocation have higher rates of diagnosed mental health disorders, including depression and dementia (Prasher 1995). Similarly, when

assessed using the Adaptive Behavior Scale, individuals with trisomy 21 had relatively higher scores when tested on independent functioning but lower scores for maladaptive behaviors when compared to patients who had chromosomal translocations (Prasher 1995). Tables 2 and 3 show results from the Prasher study and illustrate some of the population demographics of their sample.

Even inside of the most common form of Down syndrome, a trisomy of chromosome 21, there is a significant amount of variability in the characteristics and abilities of these affected individuals. Not every individual displays every physical characteristic associated with Down syndrome, has secondary health complications, or has the same degree of developmental impairment. For example, both the Fishler and Prasher studies demonstrate that individuals with a trisomy vary greatly in their individual abilities and health status when compared to others inside their cohort.

This inherent variation of the symptoms and characteristics of individuals with Down syndrome are some of the aspects that make preparing for a child with Down syndrome so challenging. This issue only becomes further exacerbated when Down syndrome is compounded with a cardiac anomaly. In many respects congenital cardiac anomalies also possess a wide range of variability: both in the specific variety of the anomaly and the general severity of the defect.

While investigating the impact of congenital cardiac defects on the outcomes of individuals with Down syndrome, it is important to remember that the control used is represented by an aggregation of the average individual with Down syndrome and without a cardiac anomaly. This is one of the limitations of this assessment.

Therefore, given the vast amount of variability and the tendency of most cases to be more similar to the average than deviant from it, it is a reasonable strategy to use the average case as the control baseline.

Down Syndrome in the Absence of Congenital Cardiac Anomalies:

Morbidity and Mortality

In this assessment it is assumed that apart from congenital cardiac anomalies, individuals serving as the baseline (patients with Down syndrome but without a congenital cardiac defect) have the same risk for conditions that affect the general population with Down syndrome. Below is a list, compiled by the Center for Disease Control and Prevention, of associated health problems that individuals with Down syndrome are at increased risks for. It is important to note that congenital cardiac defects have been omitted.

- Hearing loss (up to 75% may be affected)
- Obstructive sleep apnea, a condition where a person's breathing temporarily stops while asleep (between 50 -75%)
- Ear infections (between 50 -70% may be affected)
- Eye diseases, like cataracts (up to 60%)
- Eye issues requiring glasses (50%)
- Heart defects present at birth (50%)
- Intestinal blockage at birth requiring surgery (12%)
- Hip dislocation (when the thigh bone slips out of the hip socket) (6%)
- Thyroid disease (a problem with metabolism) (4-18%)
- Anemia (red blood cells can't carry enough oxygen to the body) (3%)
- Iron deficiency anemia (red blood cells don't have enough iron to carry oxygen to the body) (10%)
- Leukemia (1%) in infancy or early childhood
- Hirschsprung disease (an illness of the gut that can cause constipation) (<1%)

While it is important to recognize that each of these conditions contribute to the overall health of an individual, not all of them contribute equally to the quality of life of the neonate or infant during their first year of life.

Generally speaking, the quality of life during the first year is impacted by factors that directly contribute to morbidity and mortality. A fairly easy method to investigate conditions associated with both mortality and morbidity is to look at conditions for which infants and neonates with Down syndrome are hospitalized and the associated outcomes of these hospital stays. Data from a 2013 study conducted by Fitzgerald et al. detailed the hospital admission records of 405 individuals with Down syndrome born between 1983 and 1999. Data was analyzed up through 2004. During the first year of life the most common reasons for admission included: endocrine and metabolism issues associated with neonatal jaundice, cardiac anomalies (often relating to septum defects) lower respiratory tract disorders and general respiratory tract disorders. The average age of admissions for these conditions were respectively 4 days, 4 months, 10 months, and 1.1 years (Fitzgerald et al. 2013). Please see Table 1 for a complete description of admitted conditions and their average associated ages.

While the researchers did not track all ongoing health issues affecting each admitted individual, one can assume that the above admissions are relatively representative of common issues that contribute to the morbidity of individuals with Down syndrome during their first year of life. It should also be recognized that over the course of the study, of 405 individuals a relatively small portion, 36 individuals, died. The rates of mortality dramatically decreased over the course of a calendar year from

birth; additionally this risk was compounded when a cardiac anomaly was present (Fitzgerald et al. 2013).

In further investigating the mortality of neonates with Down syndrome, an additional factor that contributed to higher rates of death was the birth weight of the neonate. Neonates categorized as having low (less than 2500 grams) or very low (less than 1500 grams) birth weights were less likely to survive their first year of life than infants of a normal birth weight; 89.9% and 56% survivability respectively (Kucik at al. 2013). While these numbers do not control for the rates of congenital cardiac anomalies within the sample, the authors do note that the presence of a cardiac anomaly increases the rate of postneonatal death nearly five-fold, with an adjusted hazard ratio of 4.6 (Kucik at al. 2013). Please see Figure 2 for an illustration of the likelihood of survivability for factors including birth weight and presence of a congenital heart defect. Figure 2 also illustrates racial disparities typical to mortality for individuals with Down syndrome.

An Introduction to Congenital Cardiac Anomalies

Embryo heart development begins very early in gestation. The tissue that will eventually form the heart begins in the embryonic disc as a paired tube inside the developing pericardial cavity. In week three the embryonic heart starts to beat, and by week four of gestation the heart is capable of circulating blood (Hill 2016). The heart continues to develop until approximately nine-week gestation when it mirrors an adult heart in structure, but will continue to grow in size throughout the pregnancy. Defects in the heart may be detected as early as eleven weeks and, if detected, should be monitored throughout the course of the pregnancy (Eleftheriades 2012).

Congenital cardiac anomalies affect approximately 6 in 1000 live births, and are present in an estimated 50% of cases of Down syndrome (CDC 2014 & Fields 2016). While many children with Down syndrome are diagnosed with congenital cardiac anomalies, they are not the only affected patients; in the United States congenital heart anomalies are among the most common birth defects. There are three primary types of known factors that contribute to fetal cardiac anomalies: environmental, maternal health, and genetic or chromosomal factors, such as Down syndrome.

These defects can range in severity from benign to requiring surgical intervention shortly after birth. Cardiac anomalies range in severity from small abnormalities that require little medical intervention to life threating conditions, which require imminent medical intervention. The American Heart association recognized at least eighteen classifications of defects, but there are many variations inside of these categories. Not all fetal cardiac anomalies occur at the same rate in the same populations. Additionally, some of the most common defects, such as ventricular septal

defects (VSD), where the wall separating the right and left ventricle does not completely fuse before birth, may resolve themselves when mild. The American heart association recognizes five complex common heart defects. Table 5 summarizes these common anomalies and includes treatment descriptions (American Heart Association 2013).

Down Syndrome with Congenital Cardiac Anomalies: Morbidity and Mortality

It is difficult to find research stipulating the specifics of how the presence of a congenital cardiac anomaly would moderate and influence additional health conditions. Due to the inherent variability of Down syndrome symptoms, it is likely that the various phenotypes are expressed independently or possibly regulated by specific gene expression (Prandini et al. 2007). Additionally, individuals with congenital cardiac anomalies seem to have similar rates of risk factors for additional morbidity and mortality (including premature birth and birth weight under 2500 grams) as individuals with Down syndrome but without congenital heart defects (Frid et al. 2004). The concept that congenital cardiac anomalies occur independently of other characteristics of Down syndrome is demonstrated in the 2009 study by Rihtman et al. where they concluded that when cognitive function was assessed (using measures such as the Stanford Binet Intelligence Scale, Vineland Adaptive Behavior Scales, and beery–Buktenica Developmental Test of Visual Moto Integration):

> No significant difference was noted on the scores of any measure on ANOVAs calculated to investigate between-group differences between children with out cardiac anomalies, those with minor cardiac anomalies, and those with major cardiac anomalies.

This further suggests that the presence of a congenital cardiac anomaly was unrelated to other phenotypic expressions of Down syndrome, such as neural developmental delays, later in development after sufficient recovery from treatment occurred (Alsaied 2016). Considering this information, it seems appropriate to treat the presence of a congenital

anomaly as an independent factor in affecting the mortality and morbidity of individuals with Down syndrome.

Given that congenital cardiac anomalies appear to be an independent factor modulating the quality of life, individuals with a congenital anomaly and Down syndrome should express the same rates of secondary health complications as the general population of patients with Down syndrome. This would imply that the presence of a congenital cardiac anomaly would have an additive effect in terms of both morbidity and mortality of individuals with Down syndrome. This conclusion supports the results of the Fitzgerald et al. 2013 study in which risk for mortality was increased by the presence of a congenital cardiac anomaly. The Kucik et al. 2013 study data also supports this conclusion as the presence of cardiac anomaly increased the rate of postneonatal death nearly five-fold.

Specific Congenital Cardiac Anomalies and Their Impact

From investigating Table 1 it is apparent that not all congenital cardiac anomalies have the same impact on mortality of neonates and infants with Down syndrome. In examining the table, it should be noted that the data only applies to individuals in their first year of life. It should also be noted that there is no significant difference in the neonatal mortality (defined as death before 28 days of life) rates of neonates with Down syndrome and cardiac anomalies and neonates with Down syndrome who are unaffected.

Three types of anomalies had higher mortality rates. Non-specified congenital cardiac anomalies had increased rates of both post neonatal death (3.5 vs. 1.3%) and infant death (4.8 vs. 2.0%). Endocardia cushion defects followed a similar trend: post neonatal (8.2 vs. 1.2%) and infant (9.8 vs. 2.0%). Finally, ventricular septal defects had higher rates of post neonatal mortality (3.4 vs. 1.4%).

As seen in Table 5, it it is not uncommon for endrocardial cushion defects, also known as atrioventricular septal defects, to require surgical correction. While it is not uncommon for neonates to be born with ventricular septal defects, which if small may spontaneously close, more serious cases require surgical intervention which often takes place during the first year of life (Layangool et al. 2014).

Gestational Age and its Relation to Surgical Mortality and Morbidity

Considering that the congenital cardiac anomalies, which are associated with high rates of mortality within the first year of life, both require surgical correction as a treatment, it is reasonable to assume that additional neonatal factors may modulate the success of these operations. Many variables contribute to the outcomes of neonates with congenital heart disease who undergo surgical correction for their defect. Some of these factors include the type and severity of the defect, length and difficulty of surgical procedure, and birth weight. Unfortunately, these are factors that are difficult to model in a laboratory and track in a retrospective study. However, gestational age, which is often tracked in conjunction with infant and neonatal outcomes, is correlated with many indicators of health. As a result, it is an available, easily defined, and specific variable to consider when investigating surgical outcomes.

Gestational age has amazing predictive value when considering neonatal outcomes. Generally speaking, as gestational age increases, neonate and infant mortality decreases and the risk of long-term neural developmental delays (NDD) also decreases. Typically, fetuses with cardiac defects are induced between the gestational ages of 37 and 42 weeks in order to coordinate and plan for the additional medical attention the neonates will require (Cosetllo 2014). Additionally, as gestational age increases, birth weight increases; low birth weight is correlated with more adverse surgical outcomes (Cosetllo 2014). Birth weight and gestational age are not only correlated in terms in of predicting neonatal outcomes, but also hold individual predictive value when optimizing outcomes (Salas 2016). In neonates with cardiac anomalies, birth weight of less than 2.5 kg is associated with higher mortality rates and

longer hospital and intensive care unit stays after a corrective or palliative surgery (Alsoufi 2014).

In investigating the surgical outcomes of these fetuses, both morbidity and mortality are considered adverse outcomes. The Costello study retrospectively investigated the outcomes on 4,784 neonates with prenatal and postnatal diagnosis of a congenital heart defect who underwent a primary cardiovascular operation in the first 4 weeks of life. The analysis did not include deaths that occurred outside of surgery or from related complications. In their analysis it was determined that the optimal gestational age when considering surgical correction was between 39-40 weeks as they were correlated with the lowest rates of morbidity, mortality, and surgical complications. Table 6 summarizes their findings on mortality unadjusted for patient's risk level or exact type of surgery.

Both birth weight and gestational age have protective effects for a neonate undergoing corrective surgery. During the last month of pregnancy the fetus undergoes a period of rapid growth; this growth includes weight gain, an estimated 0.23 kg a week, and further development of the brain, lungs, and other vital organs. The exact mechanisms of the protective nature of birth weight and GA are unknown; however, it is hypothesized that factors such as diminished fat stores, less functional organs, underdeveloped lungs, differences in pharmacology, higher risk of infection, and overall smaller size of lower GA neonates contributes to their higher rates of morbidity and mortality when undergoing surgery compared to neonates of higher GAs and birth weights (Williams 2011).

However, an accurate picture of the optimal gestational age for fetuses with cardiac anomalies would not be complete without considering other factors, specifically outcomes before birth and the risks of increased GA. While the risk of neural developmental delays and infant and neonatal mortality decrease as gestational age increase, the risk of inner uterine fetal death (IUFD), or stillbirth, increases. Considering this risk, identifying a gestational age where IUFD, mortality, and neural developmental delays are minimized would be useful.

A 2016 study conducted by Fields investigated factors that influenced outcomes of infants with cardiac anomalies in an attempt to identify the optimal gestational age. In the study Fields uses a decision-analytic model to compare outcomes IUFD, infant death, and neural developmental delays) at gestational ages of 36-39 weeks of a theoretical cohort of 40,000 pregnancies. When considering factors such as IUFD, it was determined that 38 weeks gestation resulted in the lowest relative proportion of stillbirths in relation to incidences of infant death. Table 7 summarizes the rates of infant death and IUFD for the study; each cell assumes 40,000 births occurred. Figure 3 contains a sample of the probability model used to derive the study results.

Hypothesized support for the increased IUFD in CHD pregnancies includes the inability to circulate sufficient oxygen rich blood to the developing fetus. Pregnancies complicated by a cardiac anomaly are at higher risk for some maternal and fetal conditions, which can become exacerbated at greater GA. Pregnancies with congenital cardiac anomalies are at higher risk for intrauterine growth restriction (IUGR) a condition where the fetus suffers from restricted growth. Additionally, pregnancies with

fetal CHD are at higher risk for maternal pre-eclampsia, a specific type of gestational high blood pressure with protein markers in the urine (Ruiz 2016). While IUGR implicates fetal deficiencies in nutrients and oxygen rich blood, pre-eclampsia, through vasoconstriction, can result in diminished oxygen rich blood flow through the placenta to the developing fetus. As later in gestation oxygen demands increase, retarded growth and blood flow associated with these conditions, compounded by impaired circulation as a result of a CHD, could factor into the increased rate of IUFD in fetuses with congenital anomalies.

It is important to remark that while many of the studies referenced above do not specifically use patients with Down syndrome as the population, there is sufficient evidence for assuming that their results would still apply to individuals with Down syndrome and a congenital cardiac anomaly. Specifically, the optimal gestational age for both demographics, individuals with Down syndrome and individuals with congenital cardiac defects coincide at around 38 weeks (Sparks 2016).

Maternal Outcomes

Maternal life post-partum is affected by several outcomes associated with having a child with Down syndrome. While the impact of having a child with Down syndrome lasts more than a year, some of the effects of caring for a neonate with additional health concerns is immediate. It is often suggested that after delivering a child with an intellectual disability women will display greater degrees of stress and anxiety in addition to decreased emotional well-being.

The long-term effects of having a child with Down syndrome seem more ambiguous; over time, mothers with a child with Down syndrome appear to be more resilient to psychiatric disorders compared to mothers whose children had other developmental delays (Fairthorne 2015). The short-term effects were less ambiguous. In a population of Norwegian mothers, the birth of a child with Down syndrome has been associated with increased psychological distress (as measured using a 25-item Hopkins symptom checklist) as well as a decrease in life satisfaction (as measured using Satisfaction With Life Scale). For mothers with children with Down Syndrome, life satisfaction reached an all-time low at six months postpartum. Correspondingly, during the same period psychological distress sharply spiked at six months postpartum and continued to rise through the end of the study (Nes 2014). Please see their results in Figures 5 and 6 respectively.

This information is helpful in establishing a baseline for the emotional well-being of mothers of children with Down syndrome, but it does not establish how their emotional state is affected by the additional presence of a congenital cardiac anomaly.

A useful item for thinking about this is a measure of disease burden, such as quality-adjusted life-year (QALY). QALYs factor in both the perceived quality of a life and the associated life span of a particular condition. In these measures the values range from 1 to 0, where 1 is a year of perfect health and 0 is a placeholder for death. Generally speaking, when a child has a life-long condition, such as Down syndrome or a serious congenital heart defect, both their and their mother's QALYs are impacted as QALYs account for emotional well-being as well as physical. Since, in theory, QALYs of multiple conditions are additive, the presence of congenital cardiac anomalies in addition to the presence of Down syndrome would result in lower maternal QALYs the remainder of the mother's life. This indicates that there are grounds to suspect the presence of a congenital heart defect would further decrease the emotional well-being of a mother whose child also had Down syndrome.

While a specific study using QALYs to verify this relationship has not been conducted, studies examining the parental stress of infants with Down syndrome and congenital cardiac anomalies compared to infants with Down syndrome but without congenital cardiac anomalies found that the parents whose infant had both a congenital cardiac anomaly and Down syndrome also had lower responsivity scores, which measure emotional and verbal responses of the mother, 8.9 compared to 10.7 (Visootsak 2016).

Responsivity is a measure of the HOME assessment described below:

The HOME assessment has the following six subscales: emotional and verbal responsiveness, avoidance and restriction, organization and physical environment, learning materials, parental involvement with child, and opportunities for variety in daily life. The HOME assessment is conducted at the home with the parent and child present, and it consists of a combination of interview and observation by a qualified psychometrician. The questionnaire is the standard research instrument for the assessment of environ- mental factors associated with development in children with disabilities. Of note, the psychometricians who conducted the Bayley-III and HOME assessments were not aware of the child's cardiac status.

Conclusion

Advancements in medical science and care over the last fifty years have directly contributed to the improvements in both the quality and longevity of life for individuals with Down syndrome. However, individuals with Down syndrome are not a homogenous population and secondary health complications frequently moderate experiences of both morbidity and mortality. Congenital cardiac anomalies are one example of these moderating factors.

As early as the first year of life for individuals with Down syndrome, congenital cardiac anomalies increase both rates of morbidity and mortality when compared to patients with Down syndrome but no congenital cardiac defects. In the first year of life of neonates and infants with both Down syndrome and a congenital cardiac defect, mortality rates and hospital admissions are higher than an unaffected patient with Down syndrome. Additionally, mothers and families of these neonates experience comparatively higher degrees of emotional stress during the post neonatal time period.

While not all congenital cardiac anomalies are as significant, two in particular are associated with increased mortality in children with Down syndrome. Both ventricular septal defects and endocardial cushion defects significantly increase rates of mortality when present in these individuals compared to the general Down syndrome population. It is expected that a large contribution to these relatively higher mortality rates are the surgical interventions preformed to enhance the quality of life of these neonates. Corrections for both of these aforementioned anomalies are typically preformed during the first year of life. Factors such as gestational age at birth and birth weight are recognized as having protective qualities against mortality for these neonates

and infants undergoing corrective surgery. While the exact prognosis of any particular child relies on the specific type of congenital anomaly present, birth weight, gestational age, and additional heath factors, it is possible using these factors to predict what their comparative morbidity and mortality risk are.

Ethically speaking, this paper recognizes a medical professional's commitment to preventing suffering and harm while promoting positive health benefits. It also recognizes that parents serve as an advocate for the overall wellbeing of their fetus. Through careful consideration of many factors, including but not limited to personal health status, obstetric history, and the fetus' diagnosis, a parent is capable of making the difficult decision of either terminating or carrying their pregnancy to term.

Limitations and Future Research

Most of the major limitations of the research lay in the availability of well-sorted data and assumptions made about the distribution of the phenotypic traits associated with Down syndrome. Additional factors for specifically predicting any given outcome of a particular neonate with both Down syndrome and a specific congenital cardiac anomaly would require more comprehensive health information from both neonates and mothers. Most data for this subject matter is either gathered from analysis of hospital admissions in conjunction with billing records. Given current patient privacy laws, such as HIPPA, it would likely be both illegal and unethical to aggregate and link specific personal health information of neonates and mothers as it could easily lead to patient identification.

This study also neglects to account for the racial disparities in the morbidity and mortality of patients with Down syndrome and congenital cardiac defects. Generally minority communities, especially African Americans, have higher rates of both mortality and morbidity of individuals with Down syndrome. The proposed explication for this is the underlying discrepancies in socioeconomic statuses between white and non-white Americans. As this assessment does not evaluate race, it is assumed that the complications associated with congenital cardiac anomalies in Down syndrome are not moderated by ethnic background, only socioeconomic status and access to affordable and unbiased medical care.

Appendix: Figures

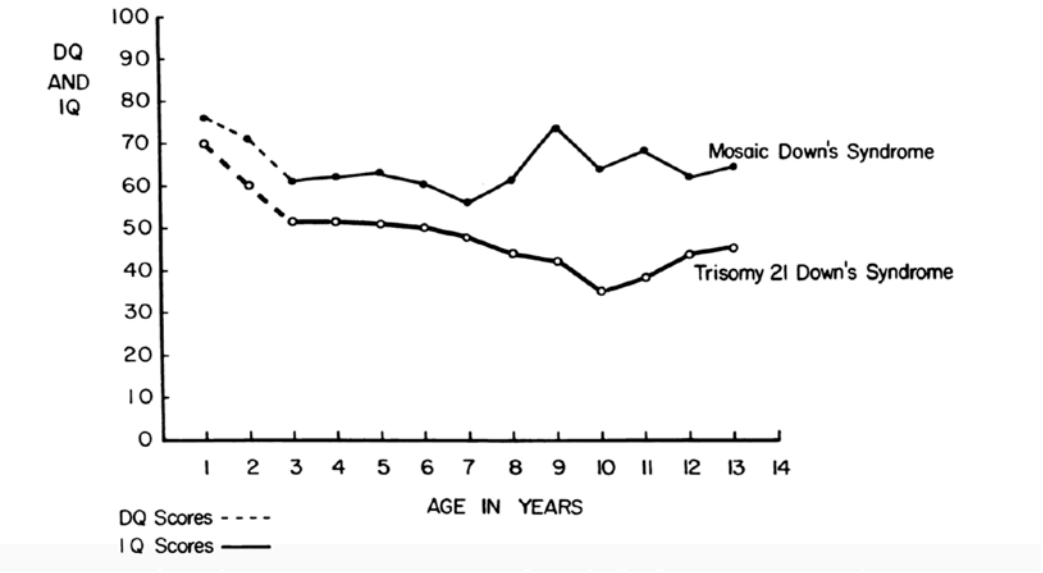

Figure 1: Comparison of development and intellectual progress in mosaic and trisomy 21 Down syndrome

This figure illustrates results from the Fishler study. The abbreviation IQ denotes intellectual quotients. The abbreviation DQ denotes developmental quotients, which are assessed using the Gesell Developmental Scale. Generally speaking DQ is a more accurate measurement of a young child's ability as the Gesell Developmental Scale measures sensory and neuromuscular function. This is a more developmentally appropriate marker of progress for very young children as IQ tests are not designed or accurate for these age groups.

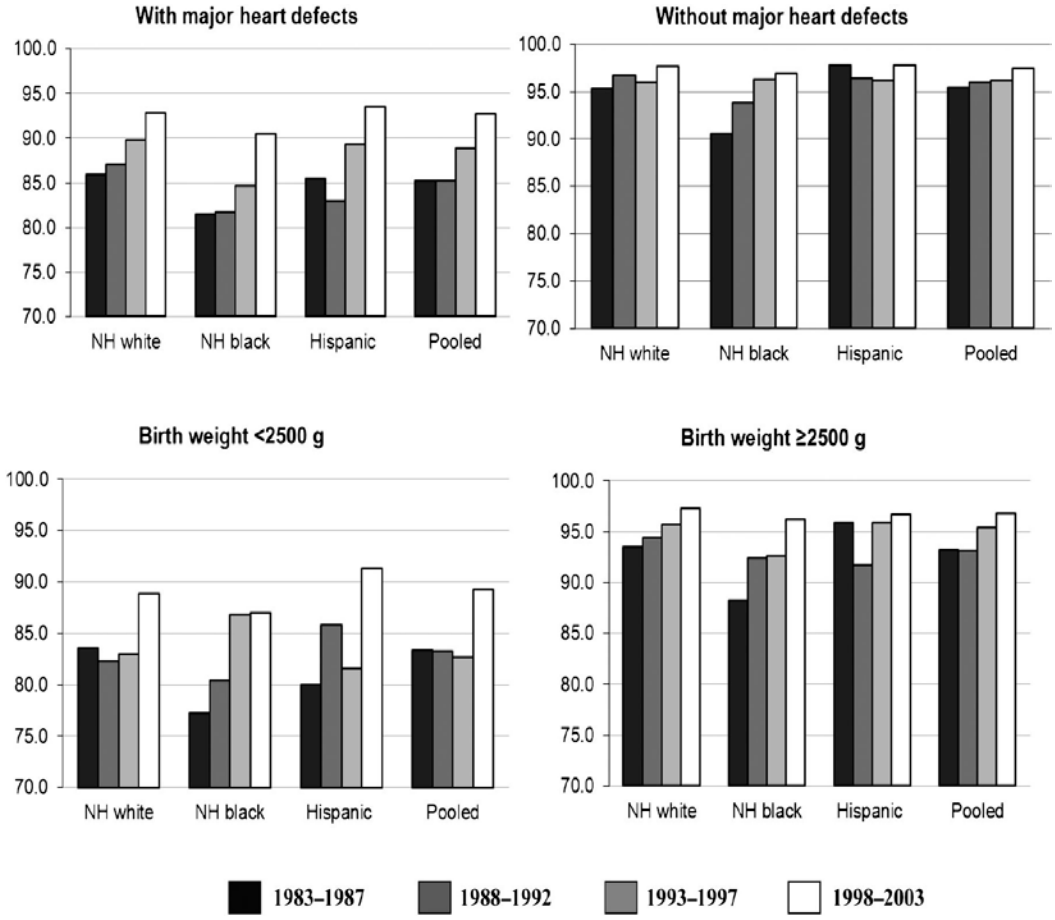

Figure 2: Racial and ethnic variation in one-year survival of children with Down syndrome in four states (CA, GA, IA, NY) by select clinical characteristics, 1983–2003.

This figure from the 2013 Kucik at al. study illustrates the one-year survivability rates of children with Down syndrome under various conditions including birth weight and presence of congenital cardiac defects. NH is the abbreviation for non-Hispanic.

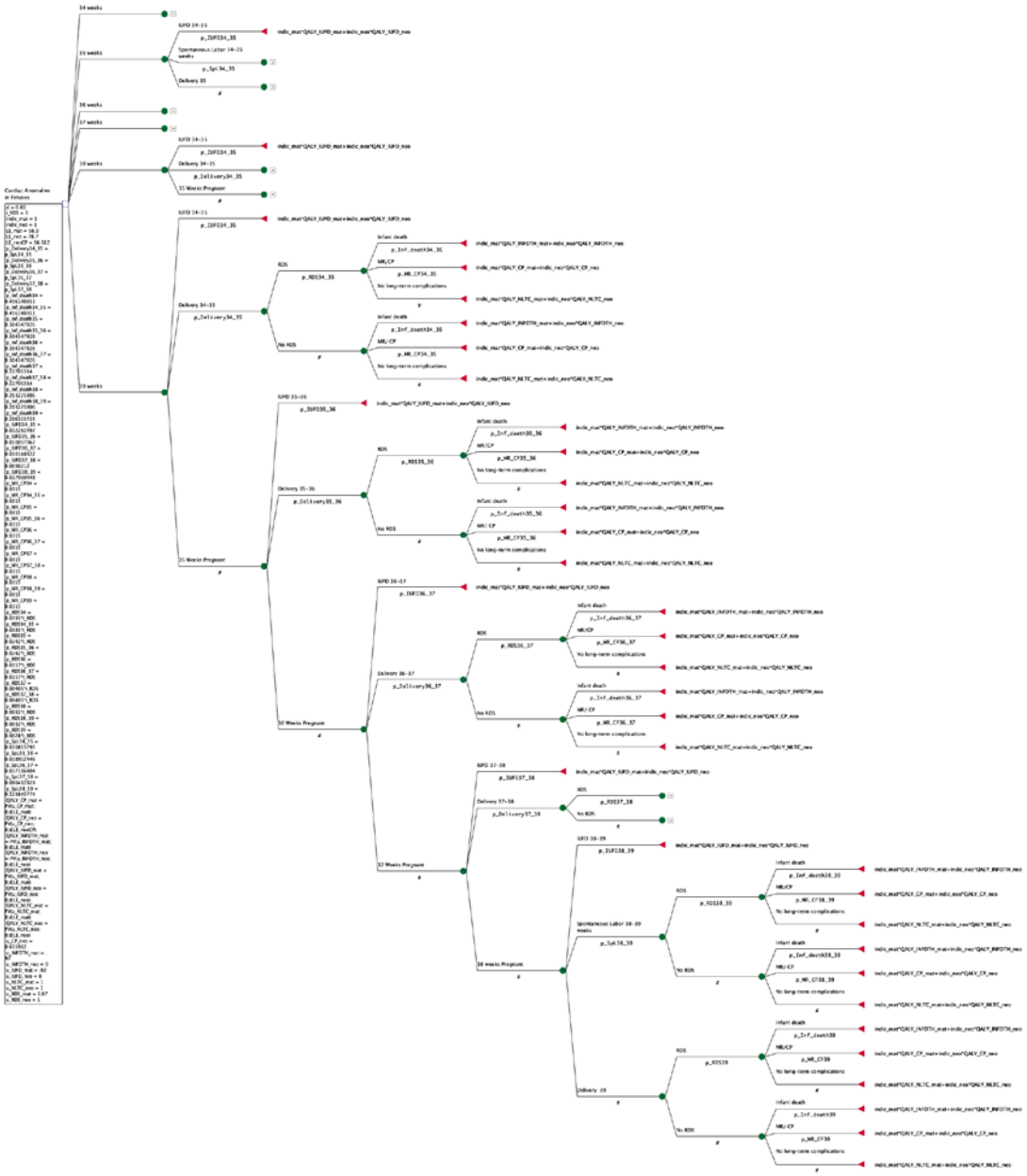

Figure 3: Condensed resolution tree for optimal gestational age of cardiac anomaly fetus

Sample of larger probability model use to derive the study's data.

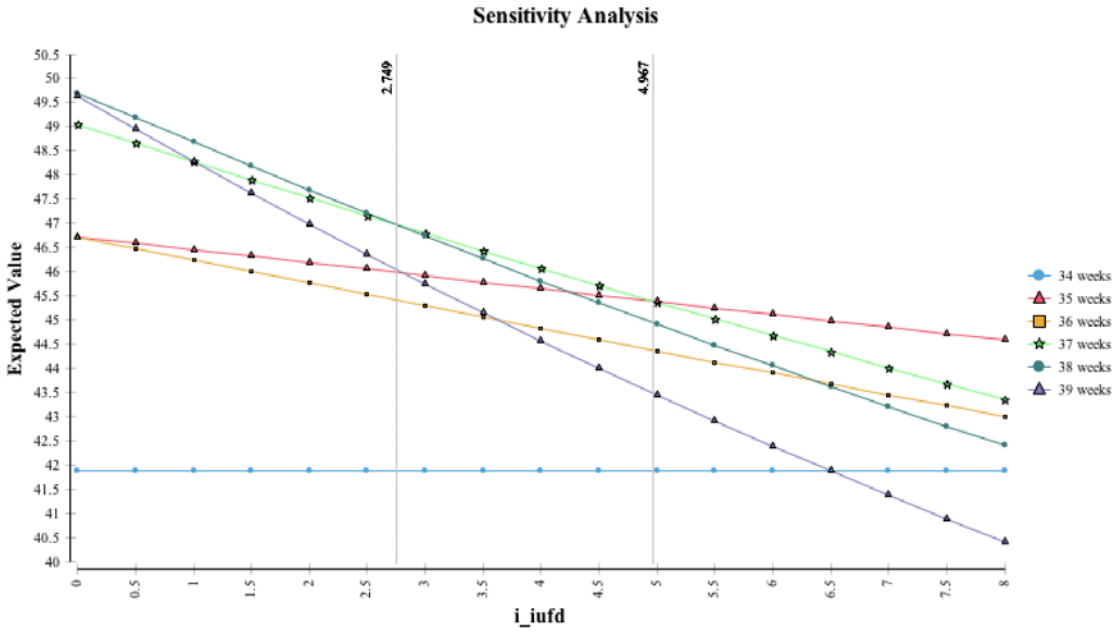

Figure 4: Sensitivity analysis to accompany Table 7

Sensitivity analysis shows when the overall risk of IUFD per week varied 38 weeks remained the optimal strategy until 2.5 times the baseline assumption.

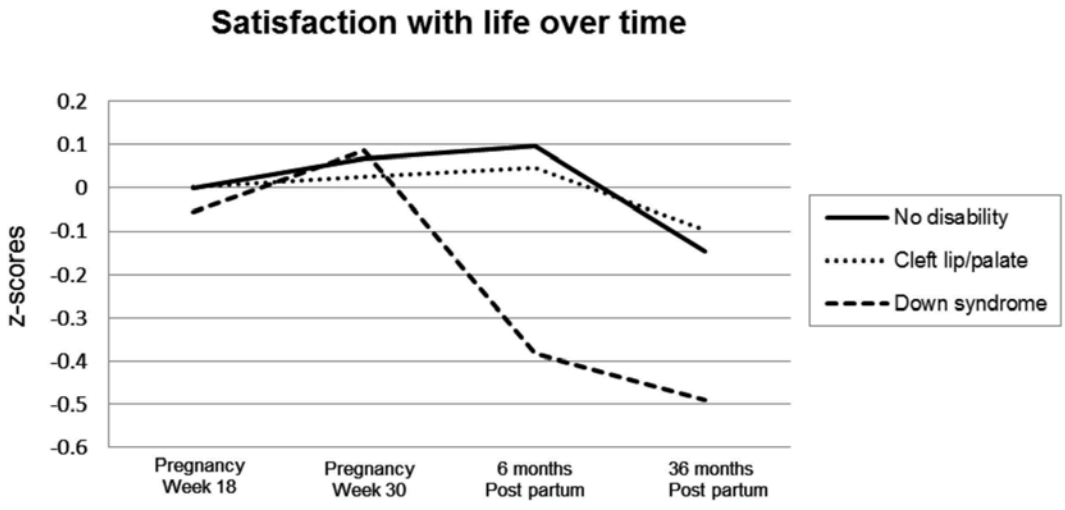

Figure 5: Satisfaction with Life Over Time

Figure shows maternal satisfaction with life from pregnancy week 17 to 3 years after birth. Scores represent standardized measures after the first assessment using SWLS.

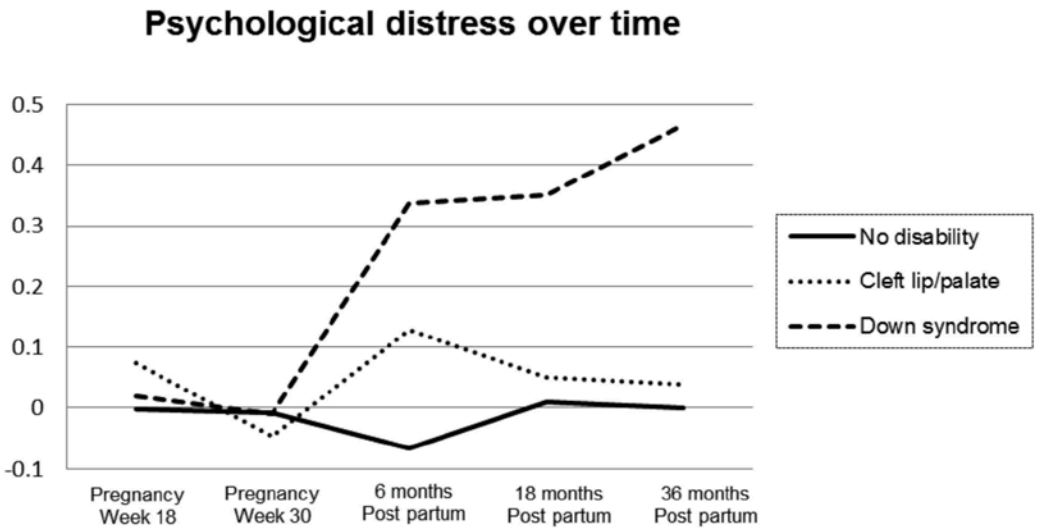

Figure 6: Psychological Distress Over Time

Figure shows maternal psychological distress from pregnancy week 17 to 3 years after birth. Scores represent standardized measures after the first assessment using SCL-25.

Appendix: Tables

	Neonatal Death	Post Neonatal Death	Infant Death
Fetal Cardiac Anomaly **N= 312**	1.3% vs. 0.8% P=0.254	3.5% vs. 1.3% *P=0.007	4.8% vs. 2.0% *P=0.006
Double Outlet Right Ventricle **N=6**	0.0% vs. 0.8% P=0.951	17% vs. 1.6% P=0.093	17% vs. 2.4% P=0.138
Tetralogy Fallot **N=32**	0.0% vs. 0.8% P=0.764	3.1% vs. 1.6% P=0.408	3.1% vs. 2.4% P=0.550
Ventricular Septal Defect **N=267**	0.4% vs. 0.9% P=0.328	3.4% vs. 1.4% *P=0.021	3.8% vs. 2.3% P=0.107
Ostium Secundum Type Atrial Septal Defect **N=409**	1.0% vs. 0.8% P=0.451	1.5% vs. 1.7% P=0.500	2.4% vs. 2.4% P=0.557
Endocardial Cushion Defects **N=122**	1.6% vs. 0.8% P=0.269	8.2% vs. 1.2% *P<0.001	9.8% vs. 2.0% *P<0.001

Table 1: Mortality rates of Down syndrome patients with cardiac anomalies compared to Down syndrome patients without fetal cardiac anomalies at specific life stages

This table examines the rates of mortality at various times for children with congenital cardiac anomalies and Down syndrome compared to children with only Down syndrome at the same date. Neonatal death is defined as death in the first 28 days of life, while post neonatal death is after 28 days of life. The anomalies featured have the highest mortality rates according the NCHS database.

Findings		Translocated DS	Trisomy 21 DS
Age	**Mean**	37.0 years	36.9 years
	S.D.	13.7	13.5
	Range	18-53 years	18-55 years

Sex	**Males**	5	5
	Females	4	4
Residence	**Hospital**	2	2
	Group home	2	2
	Family home	5	5
Severity of LD	**Mild**	4	2
	Moderate	5	2
	Severe	-	5
Cytogenetic findings	**14/21 translocation**	5	-
	21/21 translocation	4	-

Table 2: Information for translocated and trisomy 21 groups.

This table shows information recorded from the Prasher study. Portrayed above are important demographics detailing the characteristics of the study population. The titles of the columns have been edited for ease of reading in this format. DS is an abbreviation for Down syndrome.

Domain		**Translocated Group Mean (S)**	**Trisomy 21 Group Mean (S)**	**Significance**
Part I	**Independent functioning**	53.56 (16.40)	70.44 (14.32)	$p<0.05$
	Physical development	16.00 (5.89)	20.11 (2.85)	NS
	Economic activity	0.89 (1.27)	5.33 (4.02)	$p<0.05$
	Language development	12.22 (6.96)	21.11 (5.95)	$p<0.05$
	Numbers and time	2.11 (2.71)	3.89 (2.52)	NS
	Domestic activity	4.22 (3.80)	7.33 (3.39)	NS

	Vocational activity	1.11 (3.33)	2.33 (4.64)	NS
	Self-direction	8.00 (3.67)	12.58 (4.03)	$p<0.05$
	Responsibility	1.22 (1.09)	3.33 (1.73)	$p<0.05$
	Socialization	12.11 (5.21)	17.11 (4.37)	$p<0.05$
Part I overall score		111.44 (35.97)	163.56 (42.48)	$p<0.05$
Part II overall score		21.11 (16.47)	8.44 (11.67)	NS

Table 3: Adaptive behaviour scale scores for translocated and trisomy 21 groups

This table depicts the scores form the Adaptive Behavior Scale assessment in the Pasher study. Domain one assesses independent functioning where domain two assesses maladaptive behaviors. The abbreviation NS communicates that the results of the analysis were not statistically significant.

Diagnostic Group	*Subdiagnoses*	Children (%)	Admissions (%)	Rate/1000 PYAR[1] (95%CI)	Median age first admission
Upper Respiratory Tract		**237 (58.5)**	**457 (12.1)**	**91.4 (79.7, 104.8)**	**2.8 Years**
	Tonsils/Adenoids	139 (34.3)	158 (4.2)	31.6 (27.0,36.8)	5.1 Years
	Croup	67 (16.5)	116 (3.1)	23.2 (19.3, 27.7)	1.7 Years
	Sleep Apnoea	21 (5.2)	26 (0.7)	5.2 (3.5, 7.5)	8.6 Years
Lower Respiratory Tract		**152 (37.5)**	**405 (10.7)**	**81.0 (65.0, 100.9)**	**1.1 Years**
	Pneumonia	100 (24.7)	198 (5.2)	20.0 (16.3, 24.2)	2.4 Years
	Acute Bronchiolitis	57 (14.1)	89 (2.4)	17.8 (14.4, 21.8)	5 Months
	Asthma	28 (6.9)	64 (1.7)	12.8 (9.9, 16.2)	2 Years
Respiratory Tract General		**82 (20.2)**	**146 (3.9)**	**29.2 (21.5, 39.7)**	**10 Months**
	Congenital Anomalies	6 (1.5)	10 (2.5)	2.0 (1.0, 3.6)	1 Year
Ear and Hearing		**205 (50.6)**	**550 (14.5)**	**110.0 (96.0, 126.1)**	**2.5 Years**
	Otitis Media	194 (47.9)	457 (12.1)	91.4 (83.3, 100.1)	2.5 Years
Oral cavity/Teeth		**154 (38.0)**	**215 (5.7)**	**43.2 (37.4, 49.9)**	**7.8 Years**
	Congenital Oral Cavity Conditions	28 (17.6)	33 (0.9)	6.6 (4.6, 9.2)	6.7 Years
	Caries	101 (24.9)	123 (3.2)	24.6 (20.5, 29.3)	6.7 Years
Cardiac Conditions		**108 (26.7)**	**243 (6.4)**	**48.6 (42.8, 55.0)**	**4 Months**
	Cardiac Septum Defects (CSD)	92 (22.7)	189 (5.0)	37.8 (32.7, 43.4)	3 Months
	Patent Ductus Arteriosus (PDA)	14 (3.5)	15(4.0)	3.0 (1.7, 4.8)	1.2 Years
	Heart Failure	12 (3.0)	18 (4.8)	3.6 (2.2, 5.6)	7 Months
	Pulmonary Hypertension	7 (0.2)	4 (1.0)	0.8 (0.3, 1.9)	1.1 Years
Infections		**321 (79.3)**	**1243 (32.8)**	**24.9 (23.5, 26.3)**	**1.2 Years**
	Respiratory Infections	213 (52.6)	570 (15.1)	11.4 (10.5, 12.4)	1 Year
	Otitis Media	194 (47.9)	457 (12.1)	91.4 (83.3, 100.1)	2.5 Years
	Enteric or Diarrhoea-causing Infections	63 (15.6)	82 (2.2)	16.4 (13.1, 20.3)	2 Years
Digestive System		**153 (37.8)**	**380 (10.0)**	**76.0 (68.6, 83.9)**	**1.5 Years**
	Congenital digestive system abnormalities	28 (6.9)	62 (1.6)	1.2 (9.6, 15.8)	4 Days
	Upper Digestive Tract	22 (5.4)	31 (0.8)	6.2 (4.3, 8.7)	5.3 Years
	Lower Digestive Tract	37 (9.1)	110 (2.9)	22.0 (18.2, 26.4)	4.1 Years
	Enteric or Diarrhoea-causing Infections	63 (15.6)	82 (2.2)	16.4 (13.1, 20.3)	2 Years
Eye/vision Systems		**86 (21.2)**	**161 (4.3)**	**32.2 (27.5, 37.4)**	**2.7 Years**
	Disorders to eye movement & support	74 (18.3)	118 (3.1)	23.6 (19.6, 28.3)	3.1 Years
	Congenital eye anomalies	19 (0.5)	16 (4.0)	3.8 (2.4, 5.8)	2.9 Years
Renal/genitourinary System		**64 (15.8)**	**129 (3.4)**	**24.8 (16.5, 37.3)**	**4.7 Years**
	Congenital Anomalies	23 (5.7)	42 (1.1)	8.4 (6.1, 11.2)	4.5 Years
	Bladder	13 (3.2)	39 (1.0)	7.8 (5.6, 10.6)	3.1 Years
	Male Reproductive	31 (7.7)	37 (1.0)	7.4 (5.3, 10.1)	6.4 Years
External Causes		**65 (16.0)**	**76 (2.0)**	**15.2 (12.1, 18.9)**	**3.8 Years**
	Poisoning	11 (2.7)	11 (2.7)	2.2 (1.2, 3.8)	4.5 Years
	Foreign Bodies Needing Removal	11 (2.7)	12 (0.3)	2.4 (1.3, 4.1)	4.2 Years
	Burns	6 (1.5)	6 (0.2)	1.2 (0.5, 2.5)	3.1 Years
Musculoskeletal		**67 (16.5)**	**103 (2.7)**	**20.6 (16.9, 24.8)**	**5.3 Years**
	Congenital musculoskeletal conditions	10 (2.5)	11 (0.3)	2.2 (1.2, 3.8)	4.8 Years
	Fractures of an extremity	9 (2.2)	12 (0.3)	2.4 (1.3, 4.1)	7.8 Years
	Bone and rheumatic disorders	5 (1.2)	11 (0.3)	2.2 (1.2, 3.8)	6.6 Years
	Wounds, Abrasions, or lacerations	16 (4.0)	19 (0.5)	3.8 (2.4, 5.8)	5.2 Years
Skin/augmentary System		**47 (11.6)**	**63 (1.7)**	**12.8 (9.2, 17.9)**	**4.8 Years**
	Cyanosis	5 (1.2)	6 (0.2)	1.2 (0.5, 2.5)	9 Months
	Cellulitis	10 (2.5)	12 (0.3)	2.4 (1.3, 4.1)	3.9 Years
Endocrine/metabolic/immune		**34 (8.4)**	**60 (1.6)**	**14.0 (7.6, 25.8)**	**4 Days**
	Fetal Neonatal Jaundice	17 (4.2)	18 (0.5)	3.6 (2.2, 5.6)	1 Day
	Immunoglobulin Deficiencies	2 (0.5)	25 (0.7)	5.0 (3.3, 7.3)	4.8 Years
CNS Disorders		**20 (4.9)**	**32 (0.8)**	**6.4 (4.5, 8.9)**	**1.5 Years**
	Epilepsy	5 (1.2)	8 (0.2)	1.6 (0.7, 3.0)	1.6 Years
	Non-febrile Convulsions	5 (1.2)	7 (0.2)	1.4 (0.6, 2.8)	1.1 Years
Blood Disorders		**16 (4.0)**	**33 (0.9)**	**6.6 (4.6, 9.2)**	**3.1 Years**
	Anemia	7 (1.7)	9 (0.2)	1.8 (0.9, 3.3)	2.1 Years
	Agranulocytosis	4 (1.0)	10 (0.3)	2.0 (1.0, 3.6)	4.7 Years
Leukaemia		**16 (4.0)**	**281 (7.4)**	**56.2 (28.5, 110.9)**	**4.1 Years**
Generalised Infections		**63 (15.6)**	**88 (2.3)**	**17.6 (14.2, 21.5)**	**2.4 Years**
Other Non-clinical		**30 (7.4)**	**36 (1.0)**	**7.2 (5.0, 10.4)**	**0.6 Years**
Other Diagnoses		**175 (43.2)**	**245 (6.5)**	**49.0 (42.7, 56.2)**	**1 day**
Total[2]		**405**	**3,786**	**757.2 (680.2, 843.0)**	**2 Years**

[1]PYAR: person-years-at-risk of admission;
[2]includes 10 children with no record of admission on the HMDS.
doi:10.1371/journal.pone.0070401.t001

Table 4: Primary diagnosis by group, ordered by median age at first admission.

Illustrates diagnostics and their corresponding median age of admission. Data was collected using ICD9 codes in conjunction with hospital records.

Cardiac Defect	Description	Treatment
Tetralogy of Fallot	• Narrowing of pulmonary valve • VSD • Aorta placement over VSD, resulting in connection to • Thickening of right ventricle muscle	• Surgical intervention, and possible need for medication
Transposition of the great arteries (I and D)	• I transposition: lower section of heart fully reversed • D transposition: connections of aorta and pulmonary arteries are reversed, resulting in impaired blood flow	• I transposition: may go undetected, medications to improve heart function may be need • D transposition: early surgical intervention and possible medication
Atrioventricular septal defects	• Hole in heart effecting separation of four chambers	• Surgical intervention, medications may be needed

Table 5: Common Cardiac Defects and Treatments

Describes common congenital defects and summarizes common treatments associated with their occurrence.

GA (weeks)	Number of Patients	Observed mortality %	Mortality confidence interval %	P-value
34	132	15.2	9.5-22.4	<0.001
35	177	15.3	10.3-21.4	<0.001
36	357	16.2	12.6-20.5	<0.001
37	524	13.2	10.4-16.4	<0.001
38	949	9.0	7.2-11	<0.001
39.5	2321	7.3	6.3-8.4	Reference

Table 6: Costello Study Results

Describes the mortality rates for individuals at different GAs with congenital cardiac anomalies observed in the Costello study.

Outcomes Associated with Gestational Age at Delivery. Theoretical Cohort of 40,000 Fetuses with Previously Diagnosed Cardiac Anomalies.				
Outcome	36 Weeks	37 Weeks	38 Weeks	39 Weeks
IUFD	885.8	1270.9	1637.7	2180.03
Infant Death	11970.2	90589	8201	8166.8
QALYs	1849479.5	1931185.7	1947252.6	1931206.1

Table 7: 2016 Fields Study Results

The uses Tree-Age Pro, decision-analytic model software, to compare outcomes IUFD, infant death, and neural developmental delays) at gestational ages of 36-39 weeks of a theoretical cohort of 40,000 pregnancies. QALYs refer to quality of adjusted life years. These were calculated for both the neonates and their mothers. The totals were aggregated.

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