Birth Defects

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What Are Birth Defects?

Birth defects, also known as congenital malformations, are abnormalities present at birth.(1–3) Depending on where you look or whom you speak with, the term birth defect may only include structural birth defects.

Structural defects affect the formation of parts of the body and are defined by physical abnormalities in one or more parts of the body. They present at birth and result in a physical disability such as an oral cleft, spina bifida, congenital heart defects, and upper and lower limb reduction. Historically, structural birth defects have been classified as either major or minor.(4,5)

Oral Clefts: Oral clefts, otherwise termed orofacial clefts, are a subcategory of facial birth defect made up of cleft lip and cleft palate.(6) The facial birth defects result from an incomplete joining of the tissue forming the facial structure. Oral clefts can occur alone, isolated, or along side other birth defects. Isolated oral clefts are one of the most common birth defects in the US. It is estimated that 2, 650 and 4,440 US infants with cleft palate and cleft lip with or without cleft palate are respectively born in the US annually.(7)

Spina Bifida: Spina Bifida is a category of neural tube defect that occurs when the neural tube fails to develop properly or does not close all the way causing the backbone to form in an abnormal way.(10) There are multiple types of spina bifida, which are defined by their physical presentation. The three most common forms are: myelomenigocele, menignocele, and spina bifida occulta. Listed in descending order by severity, myelomenigocele spina bifida is the most severe form and is defined by the occurrence of a sac of fluid containing part of the spinal cord protruding from an individual's back. Individuals with menignocele spina bifida also present with a protruding sac of fluid but the sac does not contain any part of the spinal cord. Spina bifida occulta, also known as hidden spina bifida, lacks an external sac but instead presents with only an internal gap within the spinal cord.(11) All together, spina bifida is estimated to affect 1,500 American newborns a year.(12)

Congenital Heart Defects: Congenital heart defects are conditions present at birth, which cause the blood to move through the heart in an abnormal fashion.(8) There are many forms of congenital heart defects and they involved abnormalities in the valves of the heart, interior walls, and arteries and veins moving the blood from or two the heart. The NIH reports that congenital heart defects affect 8 out of every 1,000 US infants born, making congenital heart defects the most common type of birth defect.(9)

Upper and lower limb reduction: When developing fetuses' arms (upper) or legs (lower) form abnormally or fail to present at all, the fetus is said to have an upper or lower limb reduction defect. It is estimated that upper limb reduction defects are about twice as common as lower limb reduction defects with an annual prevalence of 4 out of every 1000 live births within the US and 2 out of every 1000 live births, respectively.(13)

While not consistently used by the CDC, this limited definition is used in the birth defect prevalence estimates presented by the CDC's Birth Defects Facts about Birth Defects page.(14) A boarder definition of the term birth defects is used by many health organizations and includes other forms of abnormalities present at birth.

- Some organizations, such as the NIH, consider **functional defects** as birth defects if they result from one or more adverse events during fetal development. Functional defects, also known as developmental birth defects, can affect the nervous system, immune system, endocrine system, or other systems of the body, and may not become apparent for months or years.(15,16)
- The World Health Organization and NIH consider **metabolic defects**(17) to be subset of functional birth defects.(18,19) These defects involve abnormalities in an individual's body chemistry. Two prominent metabolic birth defects are Tay-Sachs(20) and phenylketonuria (PKU)(21).
- Considered by some to be birth defects, non**-disabling** defects are abnormalities that do not necessarily result in a disability, although they may be unwanted or cosmetically disfiguring, such as an extra finger. Small structural abnormalities should not be taken lightly, however, as they may be an external sign of functional issues in the future.

Tay-Sachs: Babies lacking an enzyme needed to break down certain fatty substances in brain cells. These substances build up and destroy brain cells, resulting in blindness, paralysis and death by age five. (22)
PKU: Babies with PKU cannot process an amino acid (a building block of proteins), which then builds up in the blood and causes brain damage. PKU is routinely detected with newborn screening tests, so affected babies can be placed on a special diet that prevents mental retardation. (23,24)

Table 1. Common Birth Defects (25)

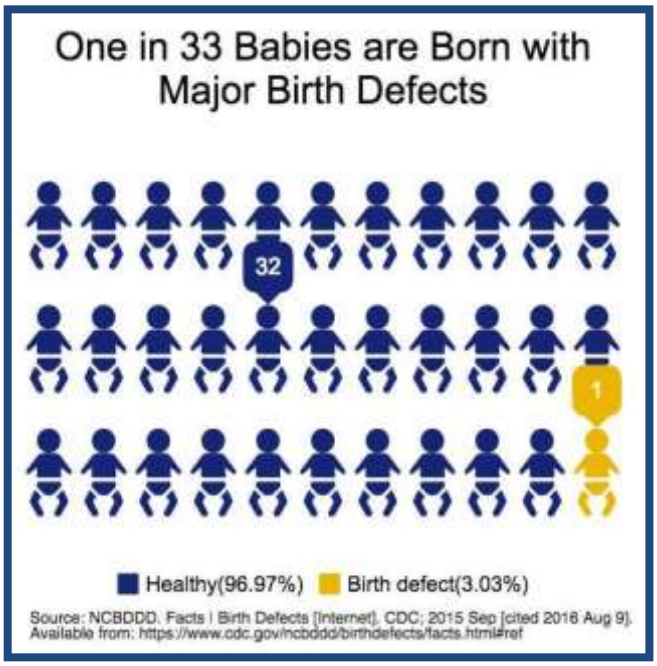
Functional(26,27)	Structural(28)	Metabolic(29)
Autism Spectrum Disorders	Anencephaly	Argininosuccinic acidemia
ADHD	Anotia/Microtia	Phenylketonuria (PKU)
Intellectual disabilities	Cleft Lip / Cleft Palate	Citrullinemia
Learning disabilities	Congenital Heart Defects	Homocystinuria
Down syndrome	Craniosynostosis	Maple syrup urine disease
Prader-Willi syndrome	Down Syndrome	
Fragile X syndrome	Encephalocele	
Cerebral palsy	Fetal Alcohol Syndrome	
Fetal Alcohol Syndrome	Gastroschisis	
Impaired vision	Hypospadias	
Loss of hearing	Microcephaly	
Degenerative disorders	Omphalocele	
Rett Syndrome	Sickle Cell Disease	
Muscular Dystrophy	Spina Bifida	
X-ALD	Upper Limb Reduction Defects	

Lower Limb Reduction Defects

The table above demonstrates that defining defects of this nature is complex and that one defect may present with multiple forms of abnormalities. Further convoluting the definition of birth defect is the fact that comorbidities(30), or the presence of two or more conditions at the same time, are common within individuals with birth defects.(31–33)

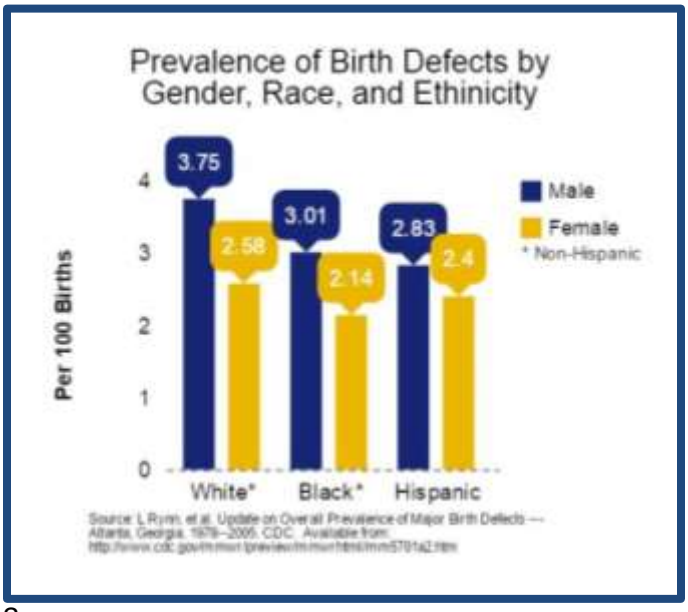
The Commonality of Birth Defects

The CDC reports that one in every 33 infants born in the US has a major structural or genetic birth defect according to medical records. This equates to one child born with a major birth defect every 4.5 minutes or 120,000 children born with birth defects annually.(34,35)

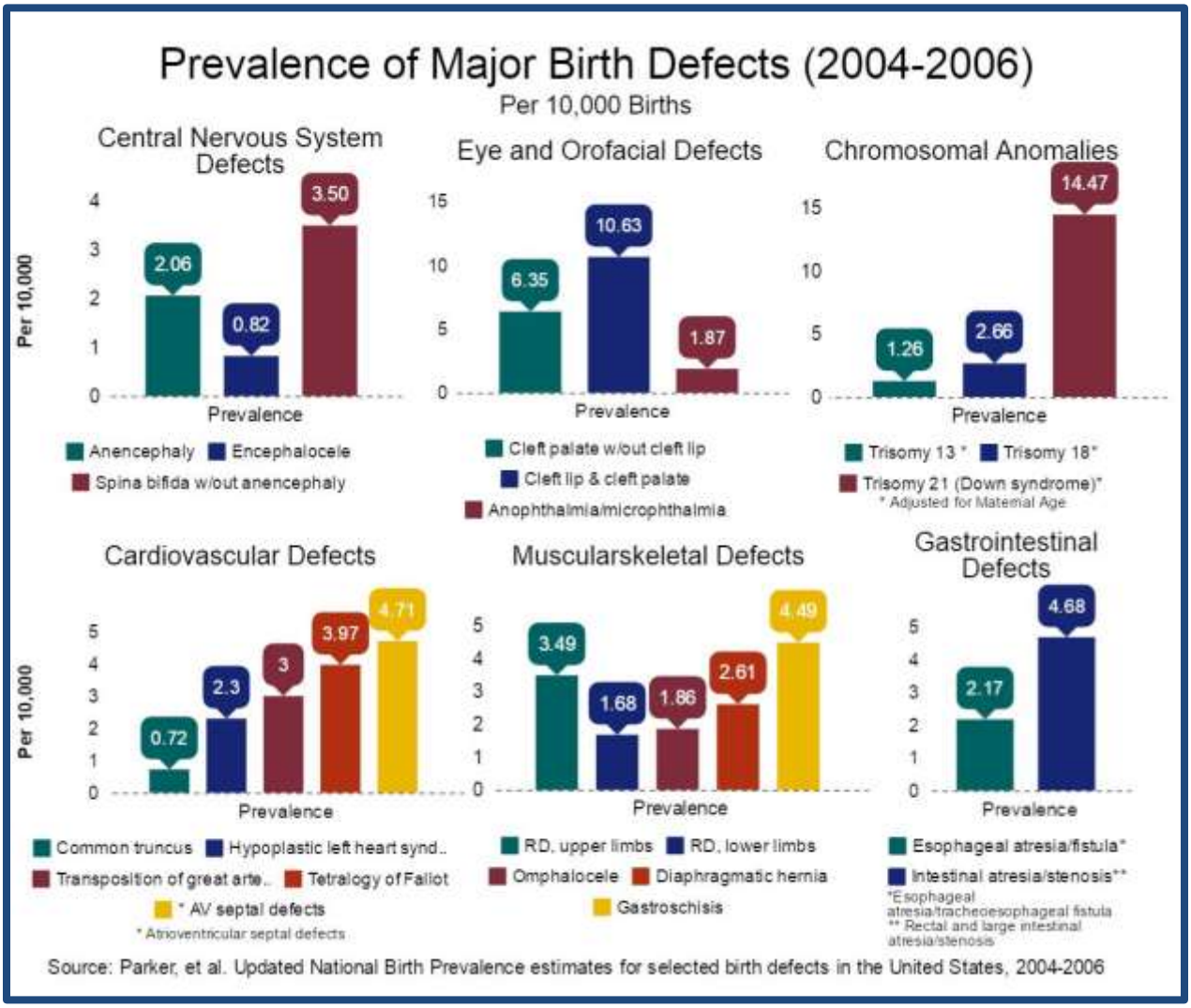


Globally, it is estimated that 6% of all newborns are born with a serious genetic or partially genetic birth defect.(36) The large discrepancy between the US and global estimates may be due to a combination of multiple factors, such as wealth, infection rate, nutrition, and other environmental factors. (37)

The 3% of children with birth defects is not evenly distributed within the population and the prevalence differs by both gender and race/ethnicity. This was demonstrated by Rynn et al.'s examination of major birth defects in Atlanta, Georgia between 1978 and 2005. Key results of their study are visually presented in the figure to the left.(38)



Different birth defects are more or less common within the United States. Table one presented common birth defects by abnormality type but how common are different birth defects? Parker et al. explored this question in their 2010 investigation of the occurrence of 21 common birth defect.(39) Key findings from their study are present in the following figure.



It has been suggested that 3% is an underestimate of the true prevalence of birth defects within the US. One of the largest studies of structural birth defects, the Collaborative Perinatal Project, observed that approximately 16 out of every 100 children born in the study had a structural abnormality. The project recorded birth outcomes for 50,000 pregnant women at 20 different medical centers and followed the children for up to seven years after birth. They found that about half of the structural birth defects (7-8 per 100 live births) were major birth defects and the remainder were less serious.(40)

The reason behind the uncertain and low estimate presented by the CDC may be due to the fact that data on birth defects are not collected in a uniform and complete way. Inconsistencies in birth defect record collection include:

- One fifth of the states in the US lack any system for tracking birth defects(41)
- Within states that do track, how babies are identified and diagnosed is not consistent(42)

- The CDC only funds population based tracking in 14 states and tracking is limited to major birth defects (structural)(43)
- Many states use passive tracking systems, or systems in which reporting is voluntary (44)
- States do not track functional defects in the same way they do structural disabilities. Existing reporting programs rely upon medical records collected in 14 or fewer communities and national surveys. For more information about functional defect track refer to the CDC programs:
    - Autism and Developmental Disabilities Monitoring (ADDM) Network(45)
    - National Health Interview Survey(46)
    - Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP)(47)
- Most birth defect research and monitoring efforts have focused on major structural abnormalities such as oral clefts(48) (facts about cleft lip), heart defects(49), spina bifida(50), and limb defects (51).(52)
- The differences in definitions exemplified above add to the challenges faced by those who study the causes of birth defects and how they have changed over time.

How are Birth Defects Detected?

Birth defects can occur at any stage of pregnancy but most occur within the first 3 months (first trimester) of pregnancy.(53) Modern medical technologies allow birth defects to be detected prenatally, at birth, or later in an individual's life.(54) Prenatal screenings can occur in the first or second trimester.

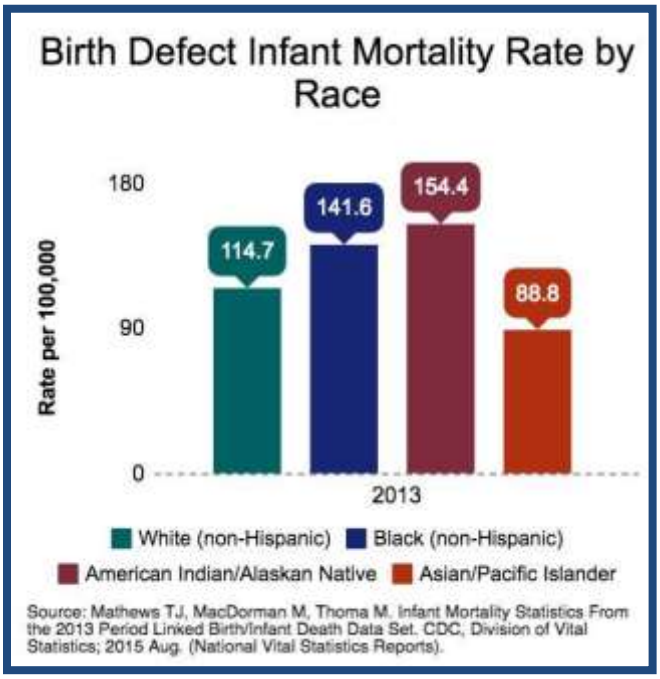
- First trimester screenings are used to identify heart and chromosomal defects using maternal blood screens and ultrasounds. (55)
- Second trimester screenings test for structural anomalies using maternal serum screens and anomaly ultrasounds. (56)

Primary newborn screenings are performed on all babies born within the US but each state has control over which tests are required.(57) The timing of these screenings is within 48 hours of delivery. Some states require a secondary screening two weeks after the primary screen. If a child is born outside of a hospital system it is important to bring them in for screenings within the proper screening windows. This applies to children with visible birth defects and visibly health children. (58,59)

Unfortunately, screenings are not able to detect all birth defects. Modern medical advances have helped reduce the number of missed diagnosis but remain imperfect. A 2015 study run by the CDC estimated that 1755 infants with critical congenital heart defects were diagnosed late, or more than three days after birth. Of these infants, it was estimated that 875 would have been diagnosed on time if screening included pulse oximetry, however an almost equal amount (880) would remain undiagnosed.(60) Pulse oximetry, is a painless test that measures the amount of oxygen in an individual's blood. The Secretary of Health and Human Services recommended the addition of pulse oximetry to newborn screening in 2011, but as of 2015 only 43 states have taken action to implement this recommendation and even few require this form of screening.(61) This CDC study

highlights the importance of the inclusion of modern medical procedures while shining a light of their continued limitations.(62)

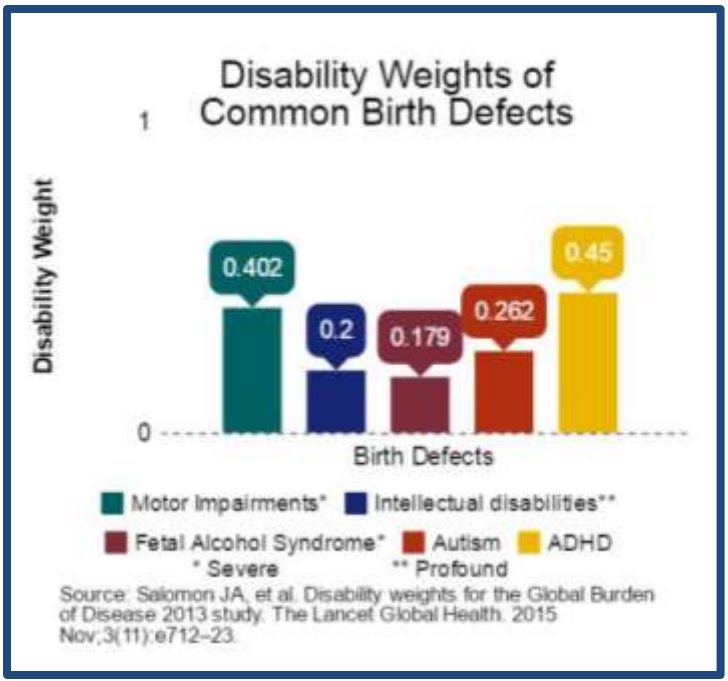
How Serious are Birth Defects?



Many birth defects pose profound physical, mental, social, and economic hardships on the affected individuals and their families. As of 2013, birth defects were the leading cause of infant mortality in the US and the second leading cause of under-five mortality making up 22.66% of deaths in this age group.(63,64) As of 1994, the leading birth defects associated with infant death were heart defects (31%), respiratory defects (15%), nervous system defects (13%), multiple abnormalities (13%), and musculoskeletal abnormalities (7%).(65)

Birth defects affect prenatal as well as postnatal survival. Annually, a million fetal deaths occur within the United States.(66) Of the fetal deaths with known causes, birth defects are a major cause.(67) According to a report by the March of Dimes organization, approximately 14% of stillborn babies (a type of fetal death) have one or more birth defects.(68)

The severity of a birth defect is dependent on the organ or part of the body affected as well as the by the extent of the abnormality.(69) Differences in the severity of birth defect is depicted by Salomon et al.'s 2015 Global Burden of Disease Disability Weights study. A disability weight is a metric (or measure) of the health impact a disease has on a human. They were estimated using survey data on perceived disease and defect severity collected from people residing in multiple countries. The survey asked respondents to rank the health impact of different diseases against each other. This allowed for the creation of a health impact number (disability weight) for each disease The disability weights range from zero to one, where larger numbers indicate a greater negative health impact (for example blindness has a larger disability weight than mild vision loss). In their study, Salomon et al. found that severe motor impairments outranked severe and profound intellectual disabilities but the opposite was true

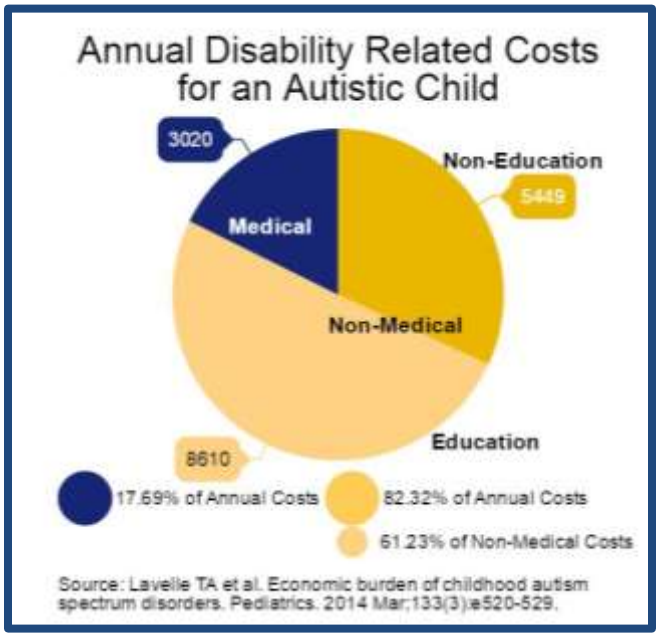


for the mild and moderate forms of these impairments/disabilities.(70) To the right is a figure showing the estimated disability weights for common birth defects and aggregated birth defect groupings.

Costs of Birth Defects

According to an analysis by the California Birth Defects Monitoring Program(71), the estimated lifetime costs for children born each year in the US with one or more of the most significant major birth defects, including cerebral palsy, were approximately $8 billion (in 1992 dollars).(72) Below is the list of birth defects included within this number:

- Cerebral palsy
- Spina bifida
- Truncus arteriosus
- Single ventricle
- Transposition/Double outlet right ventricle
- Tetralogy of fallot
- Tracheo-esophageal fistula
- Colorectal atresia
- Cleft lip or palate
- Atresia/stenosis of small intestine
- Renal agenesis
- Urinary obstruction
- Lower-limb reduction
- Upper-limb reduction
- Omphalocele
- Gastroschisis
- Down syndrome
- Diaphragmatic hernia



More recent data further highlights the costly nature of birth defects within the US. For example, the annual cost of non-medical care and medical care for a child with an autism spectrum disorder (a functional birth defect if present at birth) are approximately $14,000 and $3000 respectively, with over $8000 of the non-medical care cost going to specialized education.(73,74) Children with ADHD incur medical and loss of work costs three times those of children without ADHD and are more likely to have major injuries, asthma, and hospital inpatient and outpatient care.(75,76) A study by Allison Russo and Anne Elixhauser found that the 139,000 hospital stays caused by birth defects in 2004 cost $2.6 billion in hospital cost alone. Of that, $1.4 billion was spent on heart defect hospital care.(77)

What Causes Birth Defects?

There are many causal factors of birth defects. Genetic, nutritional, infectious, and other environmental factors, such as radiation, pharmaceuticals, and toxic chemicals, contribute to the total incidence of birth defects, but the percentage attributable to each is not known.(78, 79) Additionally, the cause of approximately 50% of birth defects is altogether unknown. (80)

Genetics

A birth defect caused by an abnormality in genetic material is said to be caused by genetic factors.(81) Genetic abnormalities which cause birth defects include gene sequence changes (mutations) and changes in the number of chromosomes.(82) These abnormalities may be passed along from the ancestral line (inherited) or result from random mutation within one or both parent's gametes (egg and sperm), an abnormal reproductive cell formation, or from chromosomal damage in the developing embryo.(83–85)

There are two forms of inherited genetic birth defects, recessive and dominant. The terms recessive and dominant refer to the effect a copy of a gene, allele, has on the phenotype, or appearance, of that person. Humans have two copies of each gene (making us diploid organisms). A defect is considered to be dominant if only one of the two gene copies within a person is required to be nonfunctional for the defect to occur. On the other hand, recessive defects are defects in which both gene copies are required to be nonfunctional for the defect to occur.(86)

Both dominant and recessive defects can be X-link or not X-linked (autosomal). X-linked defects occur when the nonfunctional gene is located on the X chromosome while autosomal defects occur when the nonfunctional gene is located on one of the 22 non-sex chromosomes. The inheritance pattern of X-linked and autosomal defects is dependent on their dominance.(87) For more information about genetic dominance refer to Natures Genetic Dominance: Genotype – Phenotype Relationships.(88)

Demographics

Race, ethnicity, and parental age are all risk factors for birth defects.(89,90) In a 2014 study on race and major birth defects, Canfield et al. found that race and ethnicity were associated with numerous birth defects including: anotia/microtia, spina bifida, and down syndrome. Additionally, they found that in comparison to non-Hispanic whites, Cubans and Asians had a lower occurrence of many of the studied birth defects.(91) However, a large limitation of the study was not adjusting for risk factors such as socioeconomic status, medical care access, or nutrition level. Without such factors, it is not possible to tease apart the underlying cause of the prevalence difference see between the races and ethnicities. For more information regarding race, ethnicity, and birth defects please refer to the CDC's Birth Defect Key Findings: Racial and Ethnic Differences in the Occurrence of Major Birth Defects page.(92)

Both younger and older mothers have an increased risk of certain, but different, birth defects.(93) Older (over 34 years old) women are at an increased risk of having a child with chromosomal abnormalities, such as Down syndrome, and non-chromosomal abnormalities, such as non-

chromosomal heart defects.(94–96) On the other hand, younger (teenage) women are more likely to have a child with gastroschisis, premature birth, and impaired fetal growth.(97–99) Premature birth and impaired fetal growth are associated with numerous structural and functional birth defects.(100) For more information on this refer to the Reproductive Health page and the Learning and Developmental Disability page.

While less understood and rarely discussed, paternal age is also a risk factor for birth defects. Most likely due to age-related genetic mutation, older men are more likely to have children with functional and structural birth defects.(101) Diseases that commonly present as birth defects and have been shown to be associated with older paternal age include: Down syndrome(102), Crouzon Syndrome(103), and Pfeiffer syndrome(104).(105)

Environmental Factors

Infections, nutritional deficiencies, and other health factors during pregnancy have been linked to some birth defects. Examples are:

- A deficiency of the B vitamin **folic acid** during pregnancy can lead to neural tube defects, such as anencephaly, spina bifida and encephalocele. Folic acid is a vitamin that helps make red blood cells, the oxygen carrying work horses of the human body and is a requirement for epigenetic replication and programming. It is recommended that women take 400 micrograms of folic acid prior to pregnancy and 600 micrograms during pregnancy. The easiest way to get the proper amount of folic acid is through a daily vitamin but folic acid is also found in many types of food. According to NIH's Office of Dietary Supplements foods with the highest natural concentration of folic acid are beef liver, spinach, and black-eyed peas (in descending order).(106) Additionally, in the mid 1990s the FDA began requiring manufacturers to fortify grain products such as breads, flours, and rice. And as of 2016, the FDA approved folic acid fortification of corn masa flour.(107)
- Multiple viruses may cause birth defects if infection occurs during pregnancy.
- The **parasitic disease** toxoplasmosis, transmitted through raw meat and cat feces, can cause malformations of the brain, liver and spleen if infection occurs during the first

Rubella: Infection with rubella (German measles) in the first trimester of pregnancy can result in multiple birth defects (congenital rubella syndrome). Rubella is a contagious, viral disease that causes mild-flu like symptoms and a skin rash in about half of all infected individuals but has significant impact on developing babies. Due to US childhood vaccination requirements, rubella has been eliminated within the US but remains common in other countries. For more information on Rubella please see the CDC's(108) and March of Dimes'(109) pages on Rubella.

Zika: Prenatal exposure to the Zika virus is best known for causing microcephaly, a structural birth defect in which an infant's head is smaller than other infants of its same age, weight, and gestation.(NCBDDD microcephaly) However, prenatally exposed fetuses and infants have been seen to have eye defects, hearing deficits, and impaired growths as well as in increased prevalence of Guillain-Barre(110) syndrome. Zika causes mild symptoms, if any, in adults and is primarily transmitted by infected *Aedes* species mosquitoes. For more information regarding Zika refer to the CDC Zika(111) pages.

trimester. A mother's immunity developed through prior Toxoplasma infection will generally protect a fetus during development. However, some experts advise delaying pregnancy for six months following a Toxoplasma infection.(113)

- Syphilis is a common sexually transmitted **bacterial disease** that causes genital sores and if left untreated may lead to serious organ damage.(114,115) If infection occurs during pregnancy, syphilis can be transmitted to a developing fetus and can cause severe adverse outcomes including: fetal death, premature birth, brain damage, blindness, hearing loss, and problems with bones and teeth.(116)
- Birth defects are more frequent in children of mothers who have preexisting **chronic diseases**, such as diabetes or thyroid disorders.(117,118)

Herpes: The herpes virus called cytomegalovirus (CMV) can cause birth defects in the infants if infected prior to birth. CMV is very common, it is estimated that half of all 40 year olds have been infected with CMV, and once an individual is infected they are always infected. (112)

Exposure to toxicants during and prior to pregnancy

Environmental agents known to cause birth defects are termed **teratogens**.(119) Teratogens include the exposures in Table 2 categorized as strong while exposures with a categorization of good have known associations but lack a proven causal link. Table two comes from the Collaborative on Health and the Environments Toxicant Database(120) and is supplemented with additional toxicant research. However, it should not be considered exhaustive.

Table 2: Chemical Toxicants Associated with Birth Defects(121)

Disease/Disorder	Toxicant	Source
Cardiac congenital malformations	**Strong Evidence**	
	Ethyl Alcohol (Ethanol)	Drinking alcohol
	Good Evidence	
	Anesthetic Gases	Workplace exposure for medical staff in hospital and stand-alone operating rooms, recovery rooms, dental offices, and veterinary facilities(122)
	Solvents	Workplace exposure - used to dissolve or thin grease, oil, paint, pigment, glue, pesticides, and epoxy resins(123)
	Tobacco Smoke	First-hand and Second-hand
	Trichloroethylene (Tce)	
Congenital malformations - general	**Strong Evidence**	
	Anesthetic Gases	Workplace exposure for medical staff in hospital and stand-alone operating rooms, recovery rooms, dental offices, and veterinary facilities(124)
	Ethyl Alcohol (Ethanol)	Drinking alcohol
	Ionizing Radiation	Energy waves and particles including sun, gamma rays, x rays, visible light, infrared light, microwaves, and radiowaves (125)
	Thalidomide(126)	Medication taking during pregnancy to reduce nausea and vomiting used from 1950 to 1960s(127)
	Good Evidence	
	Ecstasy – MDMA (128)	Commonly used stimulant primary administered orally(129)
	Agent Orange	Former chemical weapon used heavily during the Vietnam War(130)
	Arsenic	Consumed through drinking contaminated water using

		contaminated water to process or wash foods, and smoking tobacco (131)
	Carbon Monoxide	Vapor produced while burning fuel in cars, trucks, grills, fireplaces, or other fuel burning items(132)
	Cocaine (133)	A common stimulate, cocaine can be snorted through the nose, rubbed on the gums, dissolved in water and injected, or smoked (134)
	Diethylstilbestrol (DES)(135)	Synthetic estrogen used from 1940-1971(136)
	Dilantin(137)	Antiepileptic drug(138)
	Ethylene Glycol Ethers	Solvent in resins, lacquers, paints, varnishes, gum, perfume, dyes, inks and component of paints, pastes, cleaning compounds, liquid soaps, cosmetics, and hydraulic fluids(139)
	Mercury	Contaminated fish and shellfish and to a lesser extent inhaled in a workplaces such as a dental office or smelting operations(140)
	Methamphetamine(141)	Commonly use stimulant primary taken orally, smoked, snorted, or dissolved in water and injected(142)
	Nitrates(143)	Contaminated water supplies(144)
	Solvents	Workplace exposure - used to dissolve or thin grease, oil, paint, pigment, glue, pesticides, and epoxy resins(145)
	Tobacco Smoke	First-hand and Second-hand
Cranio-facial malformations	**Strong Evidence**	
	Ethyl Alcohol (Ethanol)	Drinking alcohol
	Toluene	Solvent used to make aviation gasoline, spray and wall paints, paint thinner, medicine, dyes, explosives, detergents, fingernail polish, spot, removers, lacquers, adhesives, rubber, and antifreeze(146)
	Good Evidence	
	Ethylene Glycol Ethers	Solvent in resins, lacquers, paints, varnishes, gum, perfume, dyes, inks and component of paints, pastes, cleaning compounds, liquid soaps, cosmetics, and hydraulic fluids(147)
	Ionizing Radiation	Energy waves and particles including sun, gamma rays, x rays, visible light, infrared light, microwaves, and radiowaves (148)
	Mercury	Contaminated fish and shellfish and to a lesser extent inhaled in a workplaces such as a dental office or smelting operations(149)
	PCBs (Polychlorinated biphenyls), Not Otherwise Specified	A good insulating material previously used widely as coolants and lubricants in electrical equipment (150)
	Solvents	Workplace exposure - used to dissolve or thin grease, oil, paint, pigment, glue, pesticides, and epoxy resins(151)
Oral clefts	**Good Evidence**	
	Ethyl Alcohol (Ethanol)	Drinking alcohol
	Tobacco Smoke	First-hand and Second-hand

A number of these and other environmental factors are linked to functional alterations in the developing brain. For more information on this please see the Learning and Developmental Disability, Autism, and ADHD pages. Many unidentified chemicals may additionally be associated with birth defects but the evidence is limited. For example, almost 1000 chemicals have been identified as potential **endocrine disrupting chemicals**(152), which research shows can cause birth defects in laboratory animals and are likely to contribute to birth defects in people. See The Endocrine Disruption Exchange for up-to-date information.(153)

Major Sources of Exposure

There are major sources of chemical toxicants that are positively associated (exposure causes an increased risk) with birth defects. A few of these sources are listed below.

- **Hazardous waste sites:** Women who live within a quarter of a mile of a Superfund site during the first 3 months of pregnancy (first trimester) may have a greater risk of having a baby with serious heart and neural tube defects, according to a California Birth Defects Monitoring Program study.(154) Additionally, the CDC reports that living near hazardous waste sites may be linked with birth defects including: spina bifida, cleft lip or palate, gastroschisis, hypospadias, chromosomal congenital anomalies such as Down syndrome, and some heart and blood vessel defects.(155) However, Kuehn et al. found that the risk imposed by hazardous waste sites is modified by the urbanicity of the mother's environment.(156)
- **Household and commercial pesticides:** A number of studies link pesticides with certain types of birth defects, including birth defects that result in fetal death. The Collaborative on Health and the Environment identified six pesticides that are associated with cognitive impairment or developmental delays, a disease category including functional birth defects. It additionally identifies ten pesticides with known associations with impaired fetal growth.(157)

Pesticide Example – Atrazine:
Atrazine is an herbicide that is associated with the intestinal birth defect gastroschisis(158), a life-threatening condition where the intestines protrude through a hole in the abdomen.(159)

- **Chemicals found in household plastics:** According to animal studies, Bisphenol A (a chemical found in plastic food and drink packaging, baby bottles, CDs, and medical devices) is linked to chromosomal birth defects including Down syndrome and miscarriages.(160,161) Despite the limited nature of this research, the NIH recommends that parents and caregivers limit their children's exposure to this compound.

How to Limit PBA Exposure (162):
* Use glass or stainless steel containers if possible
* Don't microwave polycarbonate plastic food containers
* Avoid plastic containers with BPA (commonly 3 or 7)
* Use fewer canned foods

Complex Mixture of Causes

There are a subset of birth defects with known necessary causes, this includes environmental exposures such as alcohol (fetal alcohol syndrome)(163) and single-gene mutations such as one in the FMR1 gene (fragile x syndrome) (164). However, a growing number of experts believe that most birth defects result from a combination of multiple factors such as an interaction between one or more genes, behavioral factors, and the prenatal or preconception environments.(165,166)

Environmental factors and genetic material interact in numerous ways to form birth defects.

- **Environmental factors can alter the DNA sequence**
  Radiation exposure is a type of teratogen called a genotoxicant or an agent that injures the DNA of a cell. While radiation may lead to DNA changes in humans of all ages, the rapid

nature of cell division during embryonic development makes this period of human develop highly vulnerable to radiation caused DNA damage. Depending on the dosage and timing of exposure, radiation may lead to miscarriage/fetal death or congenital malformations. (167) [Toxipedia]

- **Environmental factors can impact gene expression during pregnancy (epigenetic programming)**
  Recent research demonstrates that altered DNA methylation during pregnancy is associated with birth defects.(168) For more information please see the box to the right.

- **Environmental factors experienced by the father can impact gene expression (epigenetic programming)**
  As with parental age, paternal influences should not be ignored when addressing and examining epigenetic programming. Paternal exposures are associated with the occurrence of birth defects; a type of defect termed paternal mediated birth defect. Unfortunately, the research on this topic is more limited than on maternal mediated birth defects.(170) In 2013, a large case-control study was conducted on the National Birth Defects Prevention Study data looking at association between paternal occupation and birth defects. The study looked for links between specific birth defects and over 50 professions and found statistically significant associations.(171) A more recent study examined the role of a father's lifestyle on the risk of birth defects of his offspring. In their 2016 review, Days et al. found that preconception exposures to factors such as alcohol, limited diet, and cigarette smoking were associated with birth defects. They conclude that the as with the mother, the environment of the father impacts the gene expression of their offspring for generations to come.(172)

Genetics and Epigenetic Programming: As with most chronic diseases, genetic variants play a role in fetal development, causing some birth defects. However, having a specific gene variant, or set of variants, does not always mean that an individual will have a defect. Often with genetic components of diseases and disorders, an individual's environment—nutrition, activity, chemical exposures, sleep quality and so on—can either promote or inhibit the physical expression of genes. See the Gene-Environment Interactions webpage. The term "epigenetic programming" refers to mechanisms that can turn on or off genes or sections of chromosomes, changing their functioning. These changes are maintained as the cell replicates, and some research has shown that these changes can pass down to offspring. Changes in a fetus's genes by the mother's nutritional status during pregnancy are an example of epigenetic programming. See our section on Epigenetics on the Gene-Environment webpage.

- **Genetic makeup influences how environmental factors impact development**
  Prenatal alcohol exposure is a necessary factor for the occurrence of fetal alcohol syndrome, however, the risk is also dependent on a mother's alcohol metabolic process.(173) Similarly, BPA is associated with birth defects in animal studies but the strength of association is dependent on the mother's ability to metabolize BPA.(174) The ability to metabolize the exposures in these cases is dependent on the gene variant, allele, the mother carries.

Challenges in associating environmental factors with birth defects

Researchers face many challenges when assessing the connections between environmental factors and birth defects. Below are a few of these challenges.

- Most commonly encountered chemicals (other than pesticides and drugs) are not tested for their ability to cause birth defects. This is demonstrated by the fact that over 200 industrial chemicals have been found to be neurotoxins in adults and 1,000 chemicals have been reported as neurotoxins during laboratory animal studies.(175,176) However, fewer than 15 compounds were identified as causing any type of developmental disabilities according to the CHE database and only five industrial compounds are recognized to cause neurodevelopmental disorders.(177,178)
- Tests required for new pesticides and medical drugs are often not sensitive enough to identify less obvious birth defects, including many functional defects. Additionally, pregnant women are not commonly included in drug safety testing causing there to be limited data on the effects of medical drugs taken during pregnancy.(179)
- Laboratory animals used in birth defect etiology research are genetically very similar to each other and have carefully controlled diets and exposures. These tests can provide evidence of association within these controlled environments but cannot always predict what will happen in the real world, which is far more complex and diverse. Many factors confound or mediate the associations between environmental toxicants and birth defects including: genetic backgrounds, parental age, lifestyles, health conditions, and additional exposures.(180)
- Interactions between multiple factors (chemicals, genes, nutrition, infections, health) make it hard to pinpoint the contribution of one factor. Not all people are equally susceptible to birth defects; genetic and nutritional factors may combine with other environmental factors to increase the risk. This combination of factors makes it difficult to accurately identify associations between birth defects and toxicants, especially when the risk factors are not well understood or hard to measure.(181,182)
- Study participants are commonly unable to accurately recollect their exposures. This may lead to biased association estimates.(183)
- Identifying, quantifying, and estimating the timing of chemical exposures during fetal development are major challenges for researchers investigating the role of environmental factors on birth defect development. A large body of scientific research shows that not only the magnitude of exposure but also its timing is an extremely important determinant of risk because of the specific sequencing of developmental events.(184,185) The ability of an agent to cause birth defects is affected by the stage of fetal development; a concept termed critical windows of development.(186) If the timing of potentially harmful exposures is not known, a link between birth defects and environmental factors may be missed. Currently, there are two major, nationwide studies examining

<u>The Effects of Timing:</u>
Children exposed to the drug thalidomide between the 24th and 33rd day of gestation often suffered severe limb deformities, while children exposed at differing times had either no or different health effects. Early exposures to thalidomide, approximately 20-23 days after conception, increased the risk of an infant missing an ear. (190)

gestational time of drug exposure as a risk factor for birth defects. The two studies are: Vaccines and Medications in Pregnancy Surveillance System(187) and Birth Defects Study to Evaluate Pregnancy Exposures(188).(189)

- Certain birth defects are rare, making it hard to design studies powerful enough to reliably detect associations. One way to increase study power (or the statistical ability to correctly accept the testing hypothesis) is to increase the sample size. In order to increase sample sizes, researcher may "lump together" defects and in doing so are decreasing their study sensitivity or their ability to detect an existing association.(191) For example, "Heart defects" are often considered to be a single category, but within this group are individual kinds of defects that may have distinct environmental associations.
- Some birth defects are not apparent until years or decades after birth.
- There is no comprehensive national system for monitoring or reporting birth defects. (192)

Social and Inclusion Issues

The term birth defects carries a certain connotation within our society that many individuals feel is harmful. In their 2012 publication "Public perception of birth defects terminology," Mai et al. found that 36.4% of study participants without birth defects preferred the term "birth defect" over alternatives while 28.5% of participants with birth defects preferred this term. They also found 21.2% of all participants found the term offensive.(193)

Specific birth defects carry their own negative connotations and stigmas. The stigmas are focused both on the affected individual and the parental role in the defect acquisition. For example, the National Organization on Fetal Alcohol Syndrome has a "Stomp out Stigma" campaign. The campaign focuses on removing the stigmas facing all individuals affected by fetal alcohol syndrome, from the child to birth and adopted parents. They state that the stigma is so negative and pervasive that some doctors will purposefully misdiagnosis children with FAS as having ADHD or bipolar thus reducing the social impact of the disease. For more information regarding the campaign, FASD stigmas, or to find a supportive community please refer the National Organization on Fetal Alcohol Syndrome's Stigma Campaign(194), Statement on Stigma of FASD(195), and Circle of Hope(196) pages.(197,198)

Despite continued stigmas and negative connotations surrounding birth defects, there has been a lot of progress over the last 60 years to include and provide proper support to individuals with birth defects. Current law prohibits discrimination in regards to employment and ensures access to specialized educational and early development services. For more information on the history of disability laws please refer to the Legal History section of the Learning and Developmental Disability Page.

Conclusion

We know that the developing embryo and fetus is extraordinarily and uniquely vulnerable to environmental exposures. Prenatal exposures can result not only in structural birth defects, but can also impact the function of the nervous, immune, reproductive, and other systems of the body.

The environmental exposures experienced by men and women throughout their lifetime can lead to chromosomal abnormalities impacting the health of their offspring. Additionally, the toxicants accumulated by a woman throughout her life and during pregnancy can transfer in large quantities to the developing fetus, a time when exposures have the greatest impact.

A "better safe than sorry" approach based on the precautionary principle should be taken when dealing with chemicals that may cause birth defects. Both individual action and societal judgment free prevention from government and industry are needed to safeguard individuals and families.

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