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Prevalence of structural birth defects among infants with Down syndrome, 2013–2017: A US population-based study

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Abstract

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DATA AVAILABILITY STATEMENT

Research data are not shared due to privacy concerns.

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Background: Down syndrome is the most common chromosomal disorder at birth and is often accompanied by structural birth defects. Current data on major structural defects in this population are limited.

Methods: States and territorial population-based surveillance programs submitted data on identified cases of Down syndrome and identified structural birth defects during 2013–2017. We estimated prevalence by program type and maternal and infant characteristics. Among programs with active case ascertainment, we estimated the prevalence of birth defects by organ system and for specific defects by maternal age (<35, ≥35) and infant sex.

Results: We identified 13,376 cases of Down syndrome. Prevalence among all programs was 12.7 per 10,000 live births. Among these children, 75% had at least one reported co-occurring birth defect diagnosis code. Among 6,210 cases identified by active programs, 66% had a cardiovascular defect with septal defects being the most common: atrial (32.5%), ventricular (20.6%), and atrioventricular (17.4%). Defect prevalence differed by infant sex more frequently than by maternal age. For example, atrioventricular septal defects were more common in female children (20.1% vs. 15.1%) while limb deficiencies were more prevalent in male children (0.4% vs. 0.1%).

Conclusions: Our study provides updated prevalence estimates for structural defects, including rare defects, among children with Down syndrome using one of the largest and most recent cohorts to date. These data may aid clinical care and surveillance.

Keywords

birth defects; Down syndrome; infant sex; maternal age; trisomy 21

1 | INTRODUCTION

Down syndrome, also called trisomy 21, is the most common chromosomal disorder in the United States, affecting approximately 16 per 10,000 live births (Mai et al., 2019). This condition arises through several mechanisms: (1) a nondisjunction error during meiosis, which results in three copies of chromosome 21; (2) somatic mosaicism; or (3) an inherited balanced translocation of chromosome 21 (Bull, 2020). Nondisjunction errors account for approximately 95% of cases and increase in frequency with maternal age, resulting in a markedly higher risk of a pregnancy affected by Down syndrome for mothers above age 35 (Allen et al., 2009).

As the average maternal age has increased in the United States, so has the prevalence of Down syndrome (Mai et al., 2019; Martin, Hamilton, Osterman, & Driscoll, 2019). Despite regional variations, the prevalence of Down syndrome has also been increasing worldwide over the past few decades (Doidge, Morris, Harron, Stevens, & Gilbert, 2020; Loane et al., 2013; Mai et al., 2019). In the United States, prevalence increased from 13.7 to 15.7 per 10,000 live births between the year ranges 1999–2001 and 2010–2014 (Mai et al., 2019). Although no increase in the prevalence of Down syndrome at live birth was observed in England during 1998–2013 (Doidge et al., 2020) or within Europe during 1990–2009, after accounting for terminations the total prevalence of Down syndrome in Europe was also found to have increased (Loane et al., 2013).

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Structural birth defects occur at a higher rate among individuals with Down syndrome compared to the general population (Bull, 2020). Congenital heart defects (CHDs) are the most common—and most studied—structural defect, affecting approximately 44–58% of infants with Down syndrome (Brodwall et al., 2018; Bull, 2020; Stoll, Dott, Alembik, & Roth, 2015). Septal heart defects, particularly atrioventricular septal defects (AVSD), are highly overrepresented (Brodwall et al., 2018; Hartman et al., 2011; Mai et al., 2019). AVSD has been found to occur approximately 850 times more often among those with Down syndrome than among the general population (Brodwall et al., 2018).

Structural birth defects of other organ systems are also commonly found among infants and fetuses with Down syndrome. The gastrointestinal (GI) system is one of the most commonly affected organ systems—odds of a GI defect among infants with Down syndrome are 67 times higher than in chromosomally normal infants—with increased prevalence of esophageal and small intestinal atresias (Cleves et al., 2007). Other commonly affected organ systems are the musculoskeletal, orofacial, and nervous systems (Cleves et al., 2007; Morris et al., 2014; Stoll et al., 2015).

Survival for people with Down syndrome has increased over time (Kucik et al., 2013; Rankin, Tennant, Bythell, & Pearce, 2012). However, the presence of structural birth defects increases mortality for infants with Down syndrome five- to eight-fold compared to infants with Down syndrome alone (Brodwall et al., 2018;Kucik et al., 2013; Rankin et al., 2012). As the treatment of structural birth defects has improved over time, treatment of accompanying structural birth defects may be a driving force behind improved survival (Kucik et al., 2013; Rankin et al., 2012).

Evaluating the current prevalence of structural birth defects emphasizes the importance of understanding the care needs for infants with Down syndrome; however, there are limited recent data. We sought to generate up-to-date population-based estimates of the prevalence of structural birth defects among infants with Down syndrome in the United States. To accomplish this, we undertook a large, multi-state, population-based descriptive study of the occurrence of specific structural birth defects with Down syndrome between 2013 and 2017.

2 | METHODS

As a special call for data for the National Birth Defects Prevention Network (NBDPN), state and territorial birth defects surveillance programs were invited to report expanded data on children diagnosed with Down syndrome (trisomy 21). The call for data was open to programs using passive or active ascertainment methods. Active case ascertainment methods include the review of discharge diagnostic codes and hospital specific case lists from obstetrical, neonatal, surgical, and pathology services. Following initial identification of cases, medical records are abstracted from hospitals and other sources (e.g., genetics laboratories), which are then reviewed to confirm the report and ensure accurate defect classification. Passive case ascertainment relies on mandated reporting by physicians or hospitals, or on linkage of existing administrative health data sources, such as hospital discharge and claims data, to identify cases. Some programs also conduct follow-up medical records review.

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We requested information on children diagnosed with Down syndrome codes of 758.0 (International Classification of Diseases, ninth Revision, Clinical Modification [ICD-9-CM]), Q90.0–Q90.9 (International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM]), and 758.00–758.09 (Centers for Disease Control and Prevention [CDC]/British Paedatric Association [BPA]) for births from January 1, 2013 through December 31, 2017. Programs were asked to submit data on any co-occurring birth defects they collected for these infants and fetuses, including major and minor defects. We also requested case-level information by year of birth, maternal race/ethnicity, maternal age at delivery, infant sex, pregnancy outcome, birth weight, and gestational age at delivery. Data were submitted by state programs to CDC for cleaning and processing.

Because Down syndrome can be diagnosed in very early pregnancy and pregnancies may end prior to the ability to identify co-occurring structural birth defects, we limited analyses to infants and fetuses with a gestational age ≥20 weeks' at delivery or pregnancy end (Bull, 2020). All pregnancy outcomes (live birth, stillbirth, termination, unspecified non-live birth) were eligible for inclusion. For those missing data on gestational age we required a birth weight ≥350 g, whereas those missing both gestational age and birth weight were excluded from analysis.

2.1 | Analyses

We estimated the prevalence of Down syndrome by case ascertainment method, maternal race/ethnicity, maternal age, and infant sex stratified by program type and pregnancy outcome. We report prevalence estimates as the number of infants and fetuses with Down Syndrome per 10,000 live births. We limited analyses of co-occurring birth defects to programs with active case ascertainment methodology and that collected pregnancy outcomes beyond live births. Not all participating programs track all potential co-occurring birth defects. Thus, analyses of specific co-occurring defects were limited to only the subset of programs that report tracking the defect(s) of interest.

To examine co-occurring birth defects, we grouped all additionally identified birth defects, including any reported minor defects, by organ system, as specified by ICD-9-CM codes (740–759—congenital anomalies) and/or ICD-10-CM codes (Q00–Q99—congenital malformations, deformations, and chromosomal anomalies). We then analyzed selected specific major birth defects, as defined by the NBDPN (Table A1). Co-occurring birth defects were further stratified by maternal age (<35, ≥35 years) and infant sex (female, male). Prevalence of co-occurring defects is reported as the number of infants and fetuses with the defect per 100 infants with Down syndrome. We used 95% confidence intervals calculated by the exact Poisson methodology for prevalence estimates and exact binomial methodology for percentages (Daly, 1992). Data analysis was performed using SAS Version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

We obtained data on infants and fetuses with Down syndrome from 25 US state-based and territorial birth defects surveillance programs. These programs covered 10,573,314 total live births from 2013 to 2017. Table 1 presents counts, prevalence (per 10,000 live births), and

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percentages of cases by maternal and child covariates and case-finding methodology. To evaluate the representativeness of the sample of programs used for the analysis of structural defects, we further stratified these data to present prevalence estimates among live births from all programs (n = 13,376) and among all pregnancy outcomes from active case-finding programs who ascertain more than live births (n = 6,210).

The prevalence of Down syndrome was 12.7 per 10,000 among liveborn infants (Table 1). After we restricted our analysis to active case-finding programs, Down syndrome prevalence was 13.3 per 10,000 among all pregnancy outcomes. When we considered the occurrence of Down syndrome among both live births and all pregnancy outcomes, children born to Hispanic mothers had the highest prevalence (16.0 and 15.4, respectively). Prevalence estimates were higher for children of mothers 40+ years of age with maternal age 45+ having the highest estimates regardless of pregnancy outcome (maternal age 40–44:87.5 [live births] vs. 100.1 [all pregnancy outcomes]; maternal age 45+: 108.9 vs. 135.8). Male children showed a slightly higher prevalence than females among live births and among all pregnancy outcomes (13.3 vs. 12.0 [live births], 13.9 vs. 12.5 [all pregnancy outcomes]).

In Tables 2 and 3, we show the percentage of structural birth defects among infants and fetuses with Down syndrome by organ system for 12 surveillance programs who use active case-finding to monitor all pregnancy outcomes. Table 2 is stratified by maternal age at delivery (in years) and Table 3 is stratified by infant sex. We identified 4,662 children with Down syndrome (75.1%) who had at least one co-occurring code within the full birth defects range. The most common co-occurring codes were within the cardiovascular system (65.6% of all cases) followed by codes for ear/face/neck (36.1%), eye (29.0%), limbs (22.5%), and skin (22.0%) organ systems. When examining individual birth defects, cardiovascular defects also occurred most frequently: atrial septal defect (ASD; 32.5%), ventricular septal defect (VSD; 20.6%), and atrioventricular septal defect (AVSD; 17.4%). The least common co-occurring organ system codes were those in the orofacial clefts system (0.5%). Additionally, several individual birth defects, including gastroschisis, were not observed at all or were observed very infrequently within this population.

We found that the prevalence of defects by organ systems rarely varied by maternal age at delivery (younger mothers [<35 years] vs. older mothers [≥35 years]). We identified small differences among ear, face, and neck organ system codes (younger mothers: 37.4% vs. older mothers: 34.9%) and limb codes (24.3% vs. 20.7%). Among individual defects, omphalocele (0.1% vs. 0.3%), hypospadias (1.9% vs. 2.8%) and ASD (31.6% vs. 33.5%) were more common in children of older mothers, while coarctation of the aorta (2.0% vs. 1.4%) and AVSD (18.2% vs. 16.6%) were more common in children of younger mothers (Table 2).

However, when we examined defect prevalence by infant sex, we identified multiple differences (Table 3). Cardiovascular codes overall were more likely to occur among female than male children with Down syndrome (males: 64.7% vs. females: 67.2%), including VSD (19.3% vs. 22.2%), AVSD (15.1% vs. 20.1%), and pulmonary valve atresia and stenosis (0.7% vs. 1.2%). Codes in the ear, face, and neck (37.2% vs. 35.2%), genital (9.4% vs. 1.4%), renal (6.9% vs. 4.6%), musculoskeletal (15.1% vs. 12.3%), limbs (24.4% vs. 20.5%),

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and skin (23.5% vs. 20.6%) organ systems co-occurred more frequently in male compared to female infants. Among individual defects clubfoot (1.0% vs. 0.5%), limb deficiencies (0.4% vs. 0.1%), and esophageal atresia/tracheoesophageal fistula (0.6% vs. 0.2%) co-occurred more commonly in males as well.

4 | DISCUSSION

Among 6,210 cases from registries using active case-finding methods, we observed that 75% of children with Down syndrome had at least one reported major or minor birth defect code. This estimate is higher than previous reports of diagnoses of defects among 32–64% of children with Down syndrome (Cleves et al., 2007; Stoll, Dott, Alembik, & Roth, 2015). When limiting to the 46 NBDPN birth defects selected for our analysis, we observed that 63% of children had at least one major birth defect (data not shown); still higher than most previous reports. As discussed below, this may be due to substantial improvements in diagnosis of heart defects for the birth cohorts included in our study, differences in case ascertainment methods (i.e., our study used active case-finding with medical record follow-up), inclusion of non-live births, which may have a higher defect prevalence, as well as differences in the major birth defects examined. Thus, the included programs in our analysis may have more complete identification of structural defects than prior studies. This up-to-date population-based data on the prevalence of birth defects among children with Down syndrome can aid clinical evaluation and monitoring.

4.1 | Prevalence of structural defects

Cardiovascular defects are the most commonly reported birth defects in children with Down syndrome; the odds of a cardiovascular defect are 74 times higher than in children without Down syndrome (Cleves et al., 2007). In our assessment, 65.6% of children had a co-occurring cardiovascular defect, which is higher than previous population-based studies (Stoll et al., 2015). Although most studies report AVSD as the most common defect in this population, we found ASD to be the most frequent, followed by VSD, then AVSD. However, results of studies with birth cohorts after 1990 are consistent with our results (Cleves et al., 2007; Morris et al., 2014), whereas studies showing AVSD to be the most frequent defect all include births from before 1990 (Bergström et al., 2016; Freeman et al., 1998; Stoll et al., 2015). Of note, the proportion of children with Down syndrome diagnosed with these defects was higher in our study than the next most recent (Morris et al., 2014): ASD 32.5% vs. 17.8%, VSD 20.6% vs. 14.6%, and AVSD 17.4% vs. 14.1%. Similarly, Bergström et al. (2016), found an increase in simple septal defects and a decrease in AVSD between the early 1990s to the early 2010s for infants with Down syndrome. This shift in the predominant defect over time is likely the result of substantial improvements in prenatal and postnatal cardiovascular imaging, resulting in the detection of more minor or subtle septal defects in later years, rather than true changes in incidence (International Society of Ultrasound in Obstetrics and Gynecology et al., 2013; Ravi et al., 2018).

The association between gastrointestinal defects and Down syndrome has also been reported extensively (Cleves et al., 2007; Morris et al., 2014; Stoll et al., 2015). Our estimates of small intestinal atresia/stenosis (3.7%) and esophageal atresia/tracheoesophageal fistula

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(0.4%) are similar to those of Cleves et al. (3.7 and 0.6%, respectively) and Morris et al. (2.9% and 0.4%, respectively), but our estimate of rectal and large intestinal atresia/stenosis (1.2%) is higher than the estimate found by Cleves et al. (0.9%). This difference could be due to temporal trends or differences in the ascertainment of birth defects between these studies (i.e., hospital reports vs. active surveillance; Cleves et al., 2007).

Other organ systems where >10% of children were affected included eye; ear, face, and neck; respiratory; musculoskeletal; other musculoskeletal; limbs; and skin. Although our estimates are higher than previously reported, elevated prevalence of defects in these organ systems is consistent with prior studies. Again, these differences likely represent differences in the included birth defects. For example, Cleves et al. reported 1.7% of children with Down syndrome (202 out of 11,372) had a co-occurring eye defect compared to our estimate of 29%. But when comparing specific defects, our estimates of congenital cataracts (0.7%) and anophthalmia/microphthalmia (0.6%) were generally consistent with Cleves et al. (1.3 and 0.3% respectively).

Several low-frequency birth defects occurred more commonly in children with Down syndrome in our analysis than in the general population while some more common defects occurred relatively infrequently; this is consistent with prior studies (Cleves et al., 2007; Morris et al., 2014; Stoll et al., 2015). For example, we found that 0.2% ($n = 10$) of children had choanal atresia, which has a birth prevalence in the general population of 1 in 10,000 (Case & Mitchell, 2011). There were also some birth defects that were relatively infrequent in our population. For example, there were no cases of gastroschisis, which has a birth prevalence of 1 in 2,000, and only one case of spina bifida (1 in 2,700), similar to prior studies (Mai et al., 2019).

4.2 | Prevalence of structural defects by maternal age and infant sex

Overall, differences in the prevalence of structural birth defects by maternal age were primarily among individual cardiovascular defects. Interestingly, despite older maternal age being a known risk factor for congenital heart defects (Miller, Riehle-Colarusso, Siffel, Frías, & Correa, 2011), the prevalence of several cardiovascular defects was lower or no different among children with older mothers, including AVSD, VSD, and coarctation of the aorta. However, prevalence of ASD was higher for maternal age ≥35 years, which is the pattern found among mothers of children with isolated non-syndromic heart defects (Miller et al., 2011). The consistency of this pattern for ASD and tetralogy of Fallot among Down syndrome and non-syndromic children could indicate that age-related risk dominates while the inversion for AVSD may be unique to Down syndrome (Miller et al., 2011). However, other studies have suggested decreased prevalence of all septal heart defects in children with Down syndrome and older mothers (Allen et al., 2009). In addition to the cardiovascular defects, hypospadias and omphalocele were more common among children of older mothers. Both non-syndromic hypospadias and omphalocele have been previously associated with infants of older mothers (Agopian, Marengo, & Mitchell, 2009; Reefhuis & Honein, 2004).

In contrast, there were notable differences in the prevalence of birth defects across multiple organ systems by infant sex. Our findings are consistent with previous studies among the general population and among children with Down syndrome (Morris et al., 2014; Tennant,

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Samarasekera, Pless-Mulloli, & Rankin, 2011). Conversely, the prevalence of tetralogy of Fallot, which shows a male preponderance in non-syndromic cases (Michalski et al., 2015), showed no difference by infant sex in our study or that of Morris et al. (2014).

Differences in the prevalence of birth defects by maternal age or infant sex may arise from two main pathways: (1) differences in the underlying incidence or (2) differences in survival with the defect until observation. These factors may also exist in the general population or could point to sex or maternal age-specific risks that are unique to children with Down syndrome. Future studies of these differences may aid our understanding of sex and maternal age-related differences in the development of and survival with Down syndrome and birth defects.

4.3 | Potential origins of the elevated prevalence of structural defects in Down syndrome

While beyond the scope of this assessment, the mechanisms underlying the associations between various structural birth defects and Down syndrome are unclear. A long-standing hypothesis in trisomy 21 research is that structural birth defect phenotypes may be due to gene dosage effects. In children with Down syndrome, gene dosage effects would lead to a 50% increase in expression of genes on chromosome 21. Given that chromosome 21 includes >300 genes, some of these could explain defect phenotypes in these children—specifically those genes involved in organ development (Gardiner, Fortna, Bechtel, & Davisson, 2003). For example, recent studies have suggested that within chromosome 21 there is a “congenital heart defect critical region”. Other potential mechanisms could include genomic instability (George, Venkatesan, Ashok, Saraswathy, & Hande, 2018) or interaction with other genes not localized on chromosome 21 and altered DNA methylation (Gensous, Franceschi, Salvioli, Garagnani, & Bacalini, 2019) that could lead to birth defects in children with trisomy 21.

4.4 | Strengths and limitations

Our study included over 13,300 liveborn infants with Down syndrome and over 6,000 identified cases among all pregnancy outcomes from programs with active case ascertainment. To our knowledge, only two other studies have included comparable sample sizes: (1) Cleves et al. (2007) that included 11,372 cases of Down syndrome from US hospital discharge data during 1993–2002; and (2) Morris et al. (2014) included 14,109 cases from EUROCAT (a European network of population-based birth defects registries) during 2000–2010. Other studies often included <1,000 cases or were based on cohorts from before the 1990s (Stoll et al., 2015). Our estimates of overall prevalence, specific defects, and our observed relationships between defect prevalence by maternal age and infant sex are consistent with prior studies, which supports the representativeness of our study.

Further strengths of this study include use of population-based registries covering 52% of US births during 2013–2017 and for our analysis of structural defect prevalence: inclusion of all pregnancy outcomes, use of data from active case-finding programs, and the limitation of analyses to pregnancies of ≥20 weeks’ gestation. These features improve the completeness of our identification of both children with Down syndrome and of individual birth defects among children while remaining representative of the general population covered by the

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included registries. Limiting our analysis to pregnancies of ≥20 weeks' gestation helps to ensure more complete diagnosis of co-occurring birth defects, as many are not commonly diagnosed prior to 20 weeks gestation. Additionally, we analyzed specific defects that have been previously found to be well-captured and well-defined with common definitions across our study sites based on NBDPN guidelines (Birth Defects Surveillance Guidelines - National Birth Defects Prevention Network, n.d.). Nonetheless, there are some limitations to consider. Despite the large population, evaluation of relatively infrequent birth defects is challenging, especially in stratified analyses. Although the included registries cover a large proportion of US births, they are not demographically representative of US births. Finally, because some birth defects–such as biliary atresia and craniosynostosis–are difficult to identify among terminations, stillbirths, and early infant deaths, prevalence of these defects and others in children with Down syndrome may be underestimated (Heinke et al., 2020).

5 | CONCLUSIONS

In one of the largest and most recent assessments of co-occurring birth defects in children with Down syndrome, we confirmed several previous associations and provided further evidence of differences in structural defect prevalence by maternal age and infant sex. As Down syndrome remains the most common chromosomal abnormality, our findings could inform clinical assessments in children with these conditions, which could ultimately improve diagnosis and surveillance strategies, as well as outcomes in children with Down syndrome.

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APPENDIX

See Table A1.

TABLE A1

Birth defects and organ systems as defined by the National Birth Defects Prevention Network (NBDPN) by disease classification codes

Birth defects by organ system[a]	ICD-9-CM Codes[a]	ICD-10-CM Codes[a]	CDC/BPA Codes[a]
Congenital anomalies (740–759)/congenital malformations, deformations and chromosomal abnormalities (Q00–Q99)	740–759	Q00–Q99	740–759
Central nervous system (740–742, Q00–07)	740–742	Q00–07	740–742
Anencephaly	740.0–740.1	Q00.0–Q00.1	740.00–740.10
Encephalocele	742.0	Q01.0–Q01.9	742.00–742.09

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Birth defects by organ system[a]	ICD-9-CM Codes[a]	ICD-10-CM Codes[a]	CDC/BPA Codes[a]
Holoprosencephaly	742.2	Q04.2	742.26
Spina bifida without anencephaly	741.0, 741.9 w/o 740.0–740.1	Q05.0–Q05.9, Q07.01, Q07.03 w/o Q00.0–Q00.1	741.00–741.99 w/o 740.00–740.10
Eye (743, Q10–15)	743	Q10–Q15	743
Anophthalmia/microphthalmia	743.0, 743.1	Q11.0–Q11.2	743.00–743.10
Congenital cataract	743.30–743.34	Q12.0	743.32
Ear, face, neck (744, Q16–18)	744	Q16–Q18	744
Anotia/microtia	744.01, 744.23	Q16.0, Q17.2	744.01, 744.21
Cardiovascular (745–747, Q20–28)	745–747	Q20–Q28	745–747
Aortic valve stenosis	746.3	Q23.0	746.3
Atrial septal defect	745.5	Q21.1	745.51–745.59
Atrioventricular septal defect	745.60, .61, .69	Q21.2	745.60–745.69, 745.487
Coarctation of aorta	747.10	Q25.1	747.10–747.19
Common truncus (truncus arteriosus or TA)	745.0	Q20.0	745.00 only (excluding 745.01)
Double outlet right ventricle (DORV)	745.11	Q20.1	745.13–745.15
Ebstein anomaly	746.2	Q22.5	746.20
Hypoplastic left heart syndrome	746.7	Q23.4	746.7
Interrupted aortic arch (IAA)	747.11	Q25.2, Q25.4	747.215–747.217, 747.285
Pulmonary valve atresia and stenosis	746.01, 746.02	Q22.0, Q22.1	746.00, 746.01
Single ventricle	745.3	Q20.4	745.3
Tetralogy of Fallot (TOF)	745.2	Q21.3	745.20–745.21, 747.31
Total anomalous pulmonary venous connection (TAPVC)	747.41	Q26.2	747.42
Transposition of the great arteries (TGA)	745.10, .12, .19	Q20.3, Q20.5	745.10–745.12, 745.18–745.19
Tricuspid valve atresia and stenosis	746.1	Q22.4	746.100, 746.106 (excluding 746.105)
Ventricular septal defect	745.4	Q21.0	745.40–745.49 (excluding 745.487, 745.498)
Respiratory (748, Q30–34)	748	Q30–Q34	748
Choanal atresia	748.0	Q30.0	748.0
Orofacial clefts (749, Q35–37)	749	Q35–Q37	749
Cleft lip alone (without cleft palate)	749.1	Q36.0–Q36.9	749.10–749.19
Cleft lip with cleft palate	749.20–749.25	Q37.0–Q37.9	749.20–749.29
Cleft palate alone (without cleft lip)	749.0	Q35.1–Q35.9	749.00–749.09
Upper gastrointestinal (750, Q38–40)	750	Q38–Q40	750
Esophageal atresia/tracheoesophageal fistula	750.3	Q39.0–Q39.4	750.30–750.35
Lower gastrointestinal (751, Q41–45)	751	Q41–Q45	751
Biliary atresia	751.61	Q44.2–Q44.3	751.65
Rectal and large intestinal atresia/stenosis	751.2	Q42.0–Q42.9	751.20–751.24
Small intestinal atresia/stenosis	751.1	Q41.0–Q41.9	751.10–751.19

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Birth defects by organ system[a]	ICD-9-CM Codes[a]	ICD-10-CM Codes[a]	CDC/BPA Codes[a]
Genital (752, Q50–56)	752	Q50–Q56	752
Hypospadias	752.61	Q54.0–Q54.9 (excluding Q54.4)	752.60–752.62 (excluding 752.61 and 752.621)
Renal (753, Q60–64)	753	Q60–Q64	753
Bladder exstrophy	753.5	Q64.10, Q64.19	753.5
Cloacal exstrophy	751.5	Q64.12	751.555
Congenital posterior urethral valves	753.6	Q64.2	753.60
Renal agenesis/hypoplasia	753.0	Q60.0–Q60.6	753.00–753.01
Musculoskeletal (754, Q65–68)	754	Q65–Q68	754
Clubfoot	754.51, 754.70	Q66.0, Q66.89	754.50, 754.73 (excluding 754.735)
Limbs (755, Q69–74)	755	Q69–Q74	755
Limb deficiencies (reduction defects)	755.2–755.4	Q71.0–Q71.9, Q72.0–Q72.9, Q73.0–Q73.8	755.20–755.49
Other musculoskeletal (756, Q75–79)	756	Q75–Q79	756
Craniosynostosis	No specific code	Q75.0	756.00–756.03
Diaphragmatic hernia	756.6	Q79.0, Q79.1	756.610–756.617
Gastroschisis	756.73	Q79.3	756.71
Omphalocele	756.72	Q79.2	756.70
Skin (757, Q80–84)	757	Q80–Q84	757
Chromosomal (758, Q90–99)	758	Q90 –Q99	758
Deletion 22 q11.2	758.32	Q93.81	758.37
Trisomy 13	758.1	Q91.4–Q91.7	758.10–758.19
Trisomy 18	758.2	Q91.0–Q91.3	758.20–758.29
Trisomy 21 (down syndrome)[b]	758.0	Q90.0–Q90.9	758.00–758.09
Turner syndrome	758.6	Q96.0–Q96.9	758.60–758.69
Other (759, Q85–89)	759	Q85–Q89	759

[a]Birth defect surveillance programs may have modified the requested code ranges used to define a select defect as necessary. Programs provided the code ranges where they differed from those requested by the National Birth Defects Prevention Network (NBDPN). If a program defined a defect using a different code range then the created estimates use the program-specific code range, where no alternate code range was specified the NBDPN code range was used. ICD-9-CM: International Classification of Diseases, ninth Revision, Clinical Modification; ICD-10-CM: International Classification of Diseases, 10th Revision, Clinical Modification; CDC/BPA: Centers for Disease Control and Prevention / British Pediatric Association Classification of Diseases.

[b]Trisomy 21 (Down syndrome) is the focus of this manuscript and therefore is not evaluated in Tables 2 & 3.

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Birth Defects Res. Author manuscript; available in PMC 2021 March 19.

TABLE 1

Down syndrome (Trisomy 21) counts and prevalence (prevalence per 10,000 live births) for 25 US population-based surveillance programs,[a] 2013–2017

	Live births from all programs[a]			All pregnancy outcomes from active programs[b]		
Variable values	**Count**	**Prevalence**	**95% CI[c]**	**Count**	**Prevalence**	**95% CI[c]**
Total[d]	13,376	12.7	12.4–12.9	6,210	13.3	13.0–13.6
Case ascertainment methodology[a]						
Active case finding	6,798	12.8	12.5–13.1	6,210	13.3	13.0–13.6
Passive case finding	6,578	12.5	12.2–12.8	-	-	-
Maternal race/ethnicity						
White, non-Hispanic	6,686	11.6	11.3–11.9	2,574	12.3	11.8–12.7
Black, non-Hispanic	1,754	11.9	11.3–12.4	673	10.9	10.1–11.8
Hispanic	3,961	16.0	15.5–16.5	2,441	15.4	14.8–16.0
Asian or Pacific islander, non-Hispanic	540	9.1	8.4–9.9	246	10.8	9.5–12.2
American Indian or Alaska native, non-Hispanic	126	12.7	10.5–15.1	90	12.9	10.4–15.9
Maternal age (years)						
<20	446	6.9	6.2–7.5	225	6.7	5.8–7.6
20–24	1,428	6.3	6.0–6.6	680	6.2	5.8–6.7
25–29	2,040	6.5	6.2–6.8	930	6.9	6.4–7.3
30–34	2,952	10.4	10.0–10.7	1,280	10.7	10.1–11.3
35–39	3,719	27.3	26.4–28.2	1,800	32.2	30.7–33.7
40–44	2,519	87.5	84.2–91.0	1,173	100.1	94.4–106.0
45+	264	108.9	96.2–122.9	116	135.8	112.2–162.8
Child sex						
Male	7,244	13.3	13.0–13.6	3,328	13.9	13.5–14.4
Female	6,123	12.0	11.7–12.3	2,855	12.5	12.1–13.0

[a] Contributing programs (total live births = 10,573,314) by case-finding methodology: Active case-finding: Arizona, California, Delaware, Georgia (Metropolitan Atlanta), Iowa, Louisiana, Massachusetts, Minnesota, North Carolina, Oklahoma, Puerto Rico, South Carolina, Texas, Utah; Passive case-finding: Alaska, Colorado, Illinois, Indiana, Kentucky, Michigan, New Jersey, New York, Ohio, Oregon, West Virginia.

[b] Active case finding programs that ascertained more than live births: Arizona, California, Delaware, Georgia (Metropolitan Atlanta), Iowa, Massachusetts, North Carolina, Oklahoma, Puerto Rico, South Carolina, Texas, Utah.

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[c] CI: Confidence interval. For prevalence confidence interval is calculated using exact Poisson methodology.

[d] Cases were included when gestational age was greater than or equal to 20 completed weeks gestation. If gestational age was missing birth weight was used as a proxy. Counts across subgroups may not add to the total due to other/unknown categories (not shown).

Birth Defects Res. Author manuscript; available in PMC 2021 March 19.

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TABLE 2

Co-occurring birth defects by maternal age for Down syndrome (Trisomy 21) from 12 US active case-finding population-based surveillance programs, 2013–2017

	Maternal age (years)						Total (n = 6,210)[b]		
	<35 (n = 3,115)			35+ (n = 3,089)					
Birth defects by organ system[a]	**Count**	**Percent**	**95% CI**[c]	**Count**	**Percent**	**95% CI**[c]	**Count**	**Percent**	**95% CI**[c]
Congenital anomalies (740–759)/congenital malformations, deformations and chromosomal abnormalities (Q00–Q99)	2,353	75.5	74.0–77.0	2,305	74.6	73.0–76.1	4,662	75.1	74.0–76.1
Central nervous system (740–742, Q00–07)	143	4.6	3.9–5.4	144	4.7	3.9–5.5	287	4.6	4.1–5.2
Anencephaly	0	-	-	0	-	-	0	-	-
Encephalocele	1	0.0	0.0–0.2	0	-	-	1	0.0	0.0–0.1
Holoprosencephaly	0	-	-	2	0.1	0.0–0.2	2	0.0	0.0–0.1
Spina bifida without anencephaly	0	-	-	1	0.0	0.0–0.2	1	0.0	0.0–0.1
Eye (743, Q10–15)	915	29.4	27.8–31.0	882	28.6	27.0–30.2	1,799	29.0	27.8–30.1
Anophthalmia/microphthalmia	21	0.7	0.4–1.0	18	0.6	0.3–0.9	39	0.6	0.4–0.9
Congenital cataract[d]	22	0.7	0.5–1.1	22	0.7	0.5–1.1	44	0.7	0.5–1.0
Ear, face, neck (744, Q16–18)	1,164	37.4	35.7–39.1	1,077	34.9	33.2–36.6	2,244	36.1	34.9–37.3
Anotia/microtia	4	0.1	0.0–0.3	6	0.2	0.1–0.4	10	0.2	0.1–0.3
Cardiovascular (745–747, Q20–28)	2,036	65.4	63.7–67.0	2,036	65.9	64.2–67.6	4,074	65.6	64.4–66.8
Aortic valve stenosis	7	0.2	0.1–0.5	5	0.2	0.1–0.4	12	0.2	0.1–0.3
Atrial septal defect[e]	892	31.6	29.9–33.3	937	33.5	31.7–35.2	1,829	32.5	31.3–33.7
Atrioventricular septal defect	566	18.2	16.8–19.6	514	16.6	15.3–18.0	1,080	17.4	16.5–18.4
Coarctation of aorta	61	2.0	1.5–2.5	43	1.4	1.0–1.9	104	1.7	1.4–2.0
Common truncus (truncus arteriosus or TA)	3	0.1	0.0–0.3	1	0.0	0.0–0.2	4	0.1	0.0–0.2
Double outlet right ventricle (DORV)	13	0.4	0.2–0.7	6	0.2	0.1–0.4	19	0.3	0.2–0.5
Ebstein anomaly	7	0.2	0.1–0.5	5	0.2	0.1–0.4	12	0.2	0.1–0.3
Hypoplastic left heart syndrome	4	0.1	0.0–0.3	1	0.0	0.0–0.2	5	0.1	0.0–0.2
Interrupted aortic arch (IAA)	5	0.2	0.1–0.4	5	0.2	0.1–0.4	10	0.2	0.1–0.3
Pulmonary valve atresia and stenosis[f]	28	1.0	0.6–1.4	26	0.9	0.6–1.3	54	0.9	0.7–1.2
Single ventricle	2	0.1	0.0–0.2	2	0.1	0.0–0.2	4	0.1	0.0–0.2

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Birth defects by organ system[a]	Maternal age (years) <35 (*n* = 3,115) Count	Percent	95% CI[c]	35+ (*n* = 3,089) Count	Percent	95% CI[c]	Total (*n* = 6,210)[b] Count	Percent	95% CI[c]
Tetralogy of Fallot (TOF)	78	2.5	2.0–3.1	88	2.8	2.3–3.5	166	2.7	2.3–3.1
Total anomalous pulmonary venous connection (TAPVC)	2	0.1	0.0–0.2	1	0.0	0.0–0.2	3	0.0	0.0–0.1
Transposition of the great arteries (TGA)[f]	0	-	-	2	0.1	0.0–0.3	2	0.0	0.0–0.1
Tricuspid valve atresia and stenosis[f]	17	0.6	0.3–0.9	9	0.3	0.1–0.6	26	0.5	0.3–0.7
Ventricular septal defect[e]	576	20.4	18.9–21.9	580	20.7	19.2–22.3	1,157	20.6	19.5–21.6
Respiratory (748, Q30–34)	538	17.3	16.0–18.6	492	15.9	14.7–17.3	1,031	16.6	15.7–17.6
Choanal atresia[d]	3	0.1	0.0–0.3	7	0.2	0.1–0.5	10	0.2	0.1–0.3
Orofacial clefts (749, Q35–37)	14	0.4	0.2–0.8	20	0.6	0.4–1.0	34	0.5	0.4–0.8
Cleft lip alone (without cleft palate)	1	0.0	0.0–0.2	1	0.0	0.0–0.2	2	0.0	0.0–0.1
Cleft lip with cleft palate	6	0.2	0.1–0.4	10	0.3	0.2–0.6	16	0.3	0.1–0.4
Cleft palate alone (without cleft lip)	7	0.2	0.1–0.5	9	0.3	0.1–0.6	16	0.3	0.1–0.4
Upper gastrointestinal (750, Q38–40)	308	9.9	8.9–11.0	273	8.8	7.9–9.9	582	9.4	8.7–10.1
Esophageal atresia/tracheoesophageal fistula[d]	17	0.6	0.3–0.9	7	0.2	0.1–0.5	24	0.4	0.3–0.6
Lower gastrointestinal (751, Q41–45)	240	7.7	6.8–8.7	255	8.3	7.3–9.3	495	8.0	7.3–8.7
Biliary atresia[d]	2	0.1	0.0–0.2	6	0.2	0.1–0.4	8	0.1	0.1–0.3
Rectal and large intestinal atresia/stenosis[g]	32	1.2	0.8–1.6	33	1.2	0.8–1.7	65	1.2	0.9–1.5
Small intestinal atresia/stenosis[d]	105	3.5	2.8–4.2	119	4.0	3.3–4.7	224	3.7	3.2–4.2
Genital (752, Q50–56)	166	5.3	4.6–6.2	187	6.1	5.2–7.0	353	5.7	5.1–6.3
Hypospadias[h]	30	1.9	1.3–2.7	42	2.8	2.0–3.8	72	2.4	1.9–3.0
Renal (753, Q60–64)	180	5.8	5.0–6.7	178	5.8	5.0–6.6	359	5.8	5.2–6.4
Bladder exstrophy	0	-	-	1	0.0	0.0–0.2	1	0.0	0.0–0.1
Cloacal exstrophy[i]	0	-	-	0	-	-	0	-	-
Congenital posterior urethral valves[j]	0	-	-	0	-	-	0	-	-
Renal agenesis/hypoplasia[g]	9	0.3	0.2–0.6	12	0.4	0.2–0.8	21	0.4	0.2–0.6
Musculoskeletal (754, Q65–68)	446	14.3	13.1–15.6	406	13.1	12.0–14.4	853	13.7	12.9–14.6

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Birth defects by organ system[a]	Maternal age (years) <35 (*n* = 3,115) Count	Percent	95% CI[c]	35+ (*n* = 3,089) Count	Percent	95% CI[c]	Total (*n* = 6,210)[b] Count	Percent	95% CI[c]
Clubfoot[k]	18	0.7	0.4–1.2	21	0.9	0.5–1.3	39	0.8	0.6–1.1
Limbs (755, Q69–74)	757	24.3	22.8–25.8	640	20.7	19.3–22.2	1,398	22.5	21.5–23.6
Limb deficiencies (reduction defects)	8	0.3	0.1–0.5	7	0.2	0.1–0.5	15	0.2	0.1–0.4
Other musculoskeletal (756, Q75–79)	458	14.7	13.5–16.0	430	13.9	12.7–15.2	889	14.3	13.5–15.2
Craniosynostosis[e]	4	0.1	0.0–0.4	2	0.1	0.0–0.3	6	0.1	0.0–0.2
Diaphragmatic hernia	11	0.4	0.2–0.6	15	0.5	0.3–0.8	27	0.4	0.3–0.6
Gastroschisis	0	-	-	0	-	-	0	-	-
Omphalocele	2	0.1	0.0–0.2	10	0.3	0.2–0.6	12	0.2	0.1–0.3
Skin (757, Q80–84)	711	22.8	21.4–24.3	657	21.3	19.8–22.8	1,369	22.0	21.0–23.1
Chromosomal (758, Q90–99)	29	0.9	0.6–1.3	28	0.9	0.6–1.3	57	0.9	0.7–1.2
Deletion 22 q 11.2[l]	0	-	-	0	-	-	0	-	-
Trisomy 13	0	-	-	0	-	-	0	-	-
Trisomy 18	1	0.0	0.0–0.2	2	0.1	0.0–0.2	3	0.0	0.0–0.1
Turner syndrome[m]	1	0.1	0.0–0.4	0	-	-	1	0.0	0.0–0.2
Other (759, Q85–89)	30	1.0	0.7–1.4	23	0.7	0.5–1.1	53	0.9	0.6–1.1

Note: Active case-finding programs that ascertained more than live births: Arizona, California, Delaware, Georgia (Metropolitan Atlanta), Iowa, Massachusetts, North Carolina, Oklahoma, Puerto Rico, South Carolina, Texas, Utah.

[a] Birth defects that fall outside the 740–759 range for ICD-9-CM and/or CDC/BPA or outside the Q00–Q99 range for ICD-10-CM were not examined. Cases are counted separately for each organ system and birth defect (categories are not mutually exclusive). Birth defect surveillance programs may have modified the requested code ranges used to define a select defect as necessary. Programs provided the code ranges where they differed from those requested by the National Birth Defects Prevention Network (NBDPN) (Appendix). If a program defined a defect using a different code range then the created estimates use the program-specific code range, where no alternate code range was specified the NBDPN code range was used.

[b] Cases were included when gestational age was greater than or equal to 20 completed weeks gestation. If gestational age was missing birth weight was used as a proxy. Counts across subgroups may not add to the total due to other/unknown categories (not shown).

[c] CI: Confidence interval calculated using exact binomial methodology.

[d] Excludes Puerto Rico.

[e] Excludes Arizona.

[f] Excludes California.

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[g] Excludes Arizona and Puerto Rico.

[h] Excludes Arizona. Percent co-occurring is calculated as male and unknown cases of hypospadias divided by male trisomy 21 cases.

[i] Excludes Arizona, Oklahoma, and Puerto Rico.

[j] Excludes Arizona, Puerto Rico, and Texas. Percent co-occurring is calculated as male and unknown cases of congenital posterior urethral valves divided by male trisomy 21 cases.

[k] Excludes Arizona, California, and South Carolina.

[l] Excludes Arizona, and North Carolina.

[m] Excludes Arizona. Percent co-occurring is calculated as female and unknown cases of turner syndrome divided by female trisomy 21 cases.

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TABLE 3

Co-occurring birth defects by child sex for Trisomy 21 (Down syndrome) from 12 US active case-finding population-based surveillance programs, 2013–2017

	Child sex						Total (n = 6,210)[b]		
	Male (n = 3,328)			Female (n = 2,855)					
Birth defects by organ system[a]	**Count**	**Percent**	**95% CI**[c]	**Count**	**Percent**	**95% CI**[c]	**Count**	**Percent**	**95% CI**[c]
Congenital anomalies (740–759)/congenital malformations, deformations and chromosomal abnormalities (Q00–Q99)	2,495	75.0	73.5–76.4	2,160	75.7	74.0–77.2	4,662	75.1	74.0–76.1
Central nervous system (740–742, Q00–07)	153	4.6	3.9–5.4	132	4.6	3.9–5.5	287	4.6	4.1–5.2
Anencephaly	0	-	-	0	-	-	0	-	-
Encephalocele	0	-	-	1	0.0	0.0–0.2	1	0.0	0.0–0.1
Holoprosencephaly	1	0.0	0.0–0.2	1	0.0	0.0–0.2	2	0.0	0.0–0.1
Spina bifida without anencephaly	1	0.0	0.0–0.2	0	-	-	1	0.0	0.0–0.1
Eye (743, Q10–15)	979	29.4	27.9–31.0	819	28.7	27.0–30.4	1,799	29.0	27.8–30.1
Anophthalmia/microphthalmia	21	0.6	0.4–1.0	18	0.6	0.4–1.0	39	0.6	0.4–0.9
Congenital cataract[d]	27	0.8	0.5–1.2	17	0.6	0.4–1.0	44	0.7	0.5–1.0
Ear, face, neck (744, Q16–18)	1,238	37.2	35.6–38.9	1,005	35.2	33.4–37.0	2,244	36.1	34.9–37.3
Anotia/microtia	4	0.1	0.0–0.3	6	0.2	0.1–0.5	10	0.2	0.1–0.3
Cardiovascular (745–747, Q20–28)	2,152	64.7	63.0–66.3	1,919	67.2	65.5–68.9	4,074	65.6	64.4–66.8
Aortic valve stenosis	6	0.2	0.1–0.4	6	0.2	0.1–0.5	12	0.2	0.1–0.3
Atrial septal defect[e]	961	31.9	30.2–33.6	868	33.5	31.7–35.4	1,829	32.5	31.3–33.7
Atrioventricular septal defect	503	15.1	13.9–16.4	575	20.1	18.7–21.7	1,080	17.4	16.5–18.4
Coarctation of aorta	55	1.7	1.2–2.1	49	1.7	1.3–2.3	104	1.7	1.4–2.0
Common truncus (truncus arteriosus or TA)	2	0.1	0.0–0.2	2	0.1	0.0–0.3	4	0.1	0.0–0.2
Double outlet right ventricle (DORV)	9	0.3	0.1–0.5	10	0.4	0.2–0.6	19	0.3	0.2–0.5
Ebstein anomaly	6	0.2	0.1–0.4	6	0.2	0.1–0.5	12	0.2	0.1–0.3
Hypoplastic left heart syndrome	1	0.0	0.0–0.2	4	0.1	0.0–0.4	5	0.1	0.0–0.2
Interrupted aortic arch (IAA)	5	0.2	0.0–0.4	5	0.2	0.1–0.4	10	0.2	0.1–0.3
Pulmonary valve atresia and stenosis[f]	23	0.7	0.5–1.1	31	1.2	0.8–1.7	54	0.9	0.7–1.2
Single ventricle	1	0.0	0.0–0.2	3	0.1	0.0–0.3	4	0.1	0.0–0.2

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Birth defects by organ system[a]	Child sex						Total (n = 6,210)[b]		
	Male (n = 3,328)			Female (n = 2,855)					
	Count	Percent	95% CI[c]	Count	Percent	95% CI[c]	Count	Percent	95% CI[c]
Tetralogy of Fallot (TOF)	91	2.7	2.2–3.3	75	2.6	2.1–3.3	166	2.7	2.3–3.1
Total anomalous pulmonary venous connection (TAPVC)	1	0.0	0.0–0.2	2	0.1	0.0–0.3	3	0.0	0.0–0.1
Transposition of the great arteries (TGA)[f]	2	0.1	0.0–0.2	0	-	-	2	0.0	0.0–0.1
Tricuspid valve atresia and stenosis[f]	14	0.5	0.2–0.8	12	0.5	0.2–0.8	26	0.5	0.3–0.7
Ventricular septal defect[e]	581	19.3	17.9–20.7	575	22.2	20.6–23.9	1,157	20.6	19.5–21.6
Respiratory (748, Q30–34)	555	16.7	15.4–18.0	476	16.7	15.3–18.1	1,031	16.6	15.7–17.6
Choanal atresia[d]	3	0.1	0.0–0.3	7	0.3	0.1–0.5	10	0.2	0.1–0.3
Orofacial clefts (749, Q35–37)	22	0.7	0.4–1.0	12	0.4	0.2–0.7	34	0.5	0.4–0.8
Cleft lip alone (without cleft palate)	2	0.1	0.0–0.2	0	-	-	2	0.0	0.0–0.1
Cleft lip with cleft palate	11	0.3	0.2–0.6	5	0.2	0.1–0.4	16	0.3	0.1–0.4
Cleft palate alone (without cleft lip)	9	0.3	0.1–0.5	7	0.2	0.1–0.5	16	0.3	0.1–0.4
Upper gastrointestinal (750, Q38–40)	320	9.6	8.6–10.7	261	9.1	8.1–10.3	582	9.4	8.7–10.1
Esophageal atresia/tracheoesophageal fistula[d]	18	0.6	0.3–0.9	6	0.2	0.1–0.5	24	0.4	0.3–0.6
Lower gastrointestinal (751, Q41–45)	281	8.4	7.5–9.4	214	7.5	6.6–8.5	495	8.0	7.3–8.7
Biliary atresia[d]	5	0.2	0.1–0.4	3	0.1	0.0–0.3	8	0.1	0.1–0.3
Rectal and large intestinal atresia/stenosis[g]	39	1.3	0.9–1.8	26	1.0	0.7–1.5	65	1.2	0.9–1.5
Small intestinal atresia/stenosis[d]	111	3.4	2.8–4.1	113	4.1	3.4–4.9	224	3.7	3.2–4.2
Genital (752, Q50–56)	312	9.4	8.4–10.4	40	1.4	1.0–1.9	353	5.7	5.1–6.3
Hypospadias[h]	72	2.4	1.9–3.0	0	-	-	72	2.4	1.9–3.0
Renal (753, Q60–64)	229	6.9	6.0–7.8	130	4.6	3.8–5.4	359	5.8	5.2–6.4
Bladder exstrophy	0	-	-	1	0.0	0.0–0.2	1	0.0	0.0–0.1
Cloacal exstrophy[i]	0	-	-	0	-	-	0	-	-
Congenital posterior urethral valves[j]	0	-	-	0	-	-	0	-	-
Renal agenesis/hypoplasia[g]	15	0.5	0.3–0.8	6	0.2	0.1–0.5	21	0.4	0.2–0.6
Musculoskeletal (754, Q65–68)	501	15.1	13.9–16.3	352	12.3	11.1–13.6	853	13.7	12.9–14.6

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	Child sex								
	Male (*n* = 3,328)			Female (*n* = 2,855)			Total (*n* = 6,210)[b]		
Birth defects by organ system[a]	**Count**	**Percent**	**95% CI**[c]	**Count**	**Percent**	**95% CI**[c]	**Count**	**Percent**	**95% CI**[c]
Clubfoot[k]	27	1.0	0.7–1.5	12	0.5	0.3–0.9	39	0.8	0.6–1.1
Limbs (755, Q69–74)	812	24.4	22.9–25.9	586	20.5	19.1–22.1	1,398	22.5	21.5–23.6
Limb deficiencies (reduction defects)	12	0.4	0.2–0.6	3	0.1	0.0–0.3	15	0.2	0.1–0.4
Other musculoskeletal (756, Q75–79)	497	14.9	13.7–16.2	392	13.7	12.5–15.0	889	14.3	13.5–15.2
Craniosynostosis[e]	4	0.1	0.0–0.3	2	0.1	0.0–0.3	6	0.1	0.0–0.2
Diaphragmatic hernia	18	0.5	0.3–0.9	9	0.3	0.1–0.6	27	0.4	0.3–0.6
Gastroschisis	0	-	-	0	-	-	0	-	-
Omphalocele	10	0.3	0.1–0.6	2	0.1	0.0–0.3	12	0.2	0.1–0.3
Skin (757, Q80–84)	781	23.5	22.0–24.9	587	20.6	19.1–22.1	1,369	22.0	21.0–23.1
Chromosomal (758, Q90–99)	27	0.8	0.5–1.2	30	1.1	0.7–1.5	57	0.9	0.7–1.2
Deletion 22 q 11.2[l]	0	-	-	0	-	-	0	-	-
Trisomy 13	0	-	-	0	-	-	0	-	-
Trisomy 18	0	-	-	3	0.1	0.0–0.3	3	0.0	0.0–0.1
Turner syndrome[m]	0	-	-	1	0.0	0.0–0.2	1	0.0	0.0–0.2
Other (759, Q85–89)	31	0.9	0.6–1.3	22	0.8	0.5–1.2	53	0.9	0.6–1.1

Note: Active case-finding programs that ascertained more than live births: Arizona, California, Delaware, Georgia (Metropolitan Atlanta), Iowa, Massachusetts, North Carolina, Oklahoma, Puerto Rico, South Carolina, Texas, Utah.

[a] Birth defects that fall outside the 740–759 range for ICD-9-CM and/or CDC/BPA or outside the Q00–Q99 range for ICD-10-CM were not examined. Cases are counted separately for each organ system and birth defect (categories are not mutually exclusive). Birth defect surveillance programs may have modified the requested code ranges used to define a select defect as necessary. Programs provided the code ranges where they differed from those requested by the National Birth Defects Prevention Network (NBDPN) (Appendix). If a program defined a defect using a different code range then the created estimates use the program-specific code range, where no alternate code range was specified the NBDPN code range was used.

[b] Cases were included when gestational age was greater than or equal to 20 completed weeks gestation. If gestational age was missing birth weight was used as a proxy. Counts across subgroups may not add to the total due to other/unknown categories (not shown).

[c] CI: Confidence interval calculated using exact binomial methodology.

[d] Excludes Puerto Rico.

[e] Excludes Arizona.

[f] Excludes California.

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[g] Excludes Arizona and Puerto Rico.

[h] Excludes Arizona. Percent co-occurring is calculated as male and unknown cases of hypospadias divided by male trisomy 21 cases.

[i] Excludes Arizona, Oklahoma, and Puerto Rico.

[j] Excludes Arizona, Puerto Rico, and Texas. Percent co-occurring is calculated as male and unknown cases of congenital posterior urethral valves divided by male trisomy 21 cases.

[k] Excludes Arizona, California, and South Carolina.

[l] Excludes Arizona, and North Carolina.

[m] Excludes Arizona. Percent co-occurring is calculated as female and unknown cases of turner syndrome divided by female trisomy 21 cases.

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