HHS Public Access

Author manuscript

Birth Defects Res. Author manuscript; available in PMC 2022 March 11.

Published in final edited form as:

Birth Defects Res. 2022 January 15; 114(2): 57–61. doi:10.1002/bdr2.1975.

Co-occurrence of congenital anomalies by maternal race/ethnicity among infants and fetuses with Down syndrome, 2013–2017: A U.S. population-based analysis

Erin B. Stallings[1], **Jennifer L. Isenburg**[1], **Dominique Heinke**[2], **Stephanie L. Sherman**[3], **Russell S. Kirby**[4], **Philip J. Lupo**[5], **for the National Birth Defects Prevention Network**

[1]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[2]Massachusetts Department of Public Health, Center for Birth Defects Research and Prevention, Boston, Massachusetts, USA

[3]Department of Human Genetics, Emory School of Medicine, Atlanta, Georgia, USA

[4]College of Public Health, University of South Florida, Tampa, Florida, USA

[5]Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, Texas, USA

Abstract

Background: Individuals with Down syndrome (DS) have a higher prevalence of additional congenital anomalies, especially cardiovascular defects, compared to the general population. Several reports have indicated that the prevalence of DS among live births varies by race and ethnicity within the United States. We aim to examine variations in co-occurring congenital anomalies by maternal race/ethnicity among infants and fetuses diagnosed with DS born during 2013–2017.

Methods: State birth defect surveillance systems ($N = 12$) submitted data on infants and fetuses diagnosed with DS born during 2013–2017. We calculated the prevalence of co-occurring major and minor congenital anomalies, by organ system, and four selected cardiovascular birth defects, all stratified by maternal race/ethnicity.

Results: Among 5,836 cases of DS, 79.7% had one or more co-occurring congenital anomalies. There was a higher percentage of co-occurring congenital anomalies among infants and fetuses born to Hispanic mothers. The lowest percentage of co-occurring congenital anomalies, including three out of the four individual cardiovascular conditions examined, was among infants/fetuses born to non-Hispanic American Indian/Alaska Native mothers.

Correspondence Erin B. Stallings, Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities, 4770 Buford Highway, MS: S106-3, Atlanta, GA 30341-3717. icw6@cdc.gov.

AUTHOR CONTRIBUTIONS

Erin B. Stallings and Dominique Heinke wrote the manuscript. Jennifer L. Isenburg and Erin B. Stallings performed all analyses. Erin B. Stallings, Jennifer L. Isenburg, Dominique Heinke, and Philip J. Lupo conceptualized the project. All authors reviewed the manuscript and provided meaningful revisions.

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

Conclusions: We describe differences in DS co-occurrence with additional congenital anomalies among maternal racial/ethnic groups. These data may help focus future research on differences among racial/ethnic groups in the diagnosis and reporting of co-occurring congenital anomalies in infants/fetuses diagnosed with DS.

Keywords

birth defects; congenital anomalies; co-occurrence; down syndrome; maternal race/ethnicity; prevalence

1 | INTRODUCTION

Down syndrome (DS), also known as trisomy 21, is the most common chromosomal disorder, affecting one in every 635 births in the United States (Mai et al., 2019). Individuals with DS have a higher prevalence of additional congenital anomalies, especially cardiovascular defects, compared to the general population (Bull, 2020).

Several reports have indicated that the prevalence of DS varies by race and ethnicity within the United States. For example, the highest prevalence is among children born to Hispanic mothers (15.4–16.6 per 10,000 live births), while the prevalence among children born to non-Hispanic Black and non-Hispanic Asian or Pacific Islander mothers is lower (10.2–10.9 and 10.8–11.6 per 10,000 live births, respectively) (Heinke et al., 2021; Mai et al., 2019). However, patterns of co-occurring congenital anomalies by race and ethnicity are only beginning to be described (Freeman et al., 2008), which limits our understanding of disparities among individuals with DS.

Therefore, we sought to describe the prevalence of major and minor birth defects among infants/fetuses with DS by maternal race and ethnicity within a large, population-based sample of U.S. births.

2 | METHODS

Data on infants/fetuses diagnosed with DS 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 Pediatric Association [BPA]) delivered between January 1, 2013 and December 31, 2017 were collected from 12 U.S. state- and territorial-based birth defects surveillance programs: Arkansas, California, Delaware, Georgia (Metropolitan Atlanta), Iowa, Massachusetts, North Carolina, Oklahoma, Puerto Rico, South Carolina, Texas, and Utah. 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.

We restricted our dataset to birth defects surveillance programs that use active case ascertainment and that captured information on all pregnancy outcomes. We limited cases

to ≥20 weeks gestation (or 350 g birthweight where gestational age was missing) to allow for diagnosis of co-occurring congenital anomalies. To examine co-occurring congenital anomalies, we followed the methods described in Heinke et al. (2021). However, due to the small cell sizes resulting from stratification by maternal race/ethnicity, we limited this analysis to major and minor congenital anomalies by organ systems and four selected cardiovascular birth defects commonly associated with DS: atrial septal defect (ASD), atrioventricular septal defect (AVSD), tetralogy of Fallot (TOF), and ventricular septal defect (VSD). Co-occurring congenital anomalies were stratified by maternal race/ethnicity (White, non-Hispanic [W-NH]; Black, non-Hispanic [B-NH]; Hispanic; Asian or Pacific Islander, non-Hispanic [API-NH]; American Indian or Alaska Native, non-Hispanic [AIAN-NH]). Additional information about each state program's data collection methodology is available in the most recent birth defects program directory (Stallings et al., 2019).

Co-occurrence for congenital anomalies is represented as prevalence per 100 DS cases. We calculated 95% confidence intervals for percentages using the exact binomial methodology (Daly, 1992). Because our objective is to describe prevalence by race/ethnicity, we elected to not perform any statistical modeling or adjusted analyses (Conroy & Murray, 2020). Data analysis was performed using SAS Version 9.4 (SAS Institute, Cary, NC). This activity was reviewed by CDC, deemed public health surveillance, and was conducted consistent with applicable federal law and CDC policy.[1]

3 | RESULTS

We obtained data on infants/fetuses diagnosed with DS from 12 U.S. state- and territorial-based birth defects surveillance programs. Table 1 shows percentage (i.e., prevalence per 100 DS cases) of co-occurring congenital anomalies among infants and fetuses with DS by organ system and four selected cardiovascular birth defects, further stratified by maternal race/ethnicity. Out of a total of 5,836 infants and fetuses with DS, we identified 4,654 (79.7%) with one or more co-occurring diagnosis codes within the congenital anomalies code range.

The percentage of infants/fetuses diagnosed with one or more co-occurring anomalies ranged from 75 to 80%, with the lowest percentage among infants/fetuses of AIAN-NH mothers (75.9%) and the highest percentage among infants/fetuses of W-NH and Hispanic mothers (80.3 and 80.0%, respectively). A range of 65–71% of infants/fetuses were reported to have at least one code within the cardiovascular system, with the highest percentage among infants/fetuses of Hispanic mothers (71.5%) and the lowest percentage among infants/fetuses of AIAN-NH mothers (65.5%). Among the individual cardiovascular birth defects we examined, the highest percentage co-occurring was seen for infants/fetuses of AIAN-NH for ASD (43.1%), infants/fetuses of B-NH mothers for AVSD (25.1%), infants/fetuses of API-NH mothers for TOF (4.0%), and infants/fetuses of Hispanic mothers for VSD (22.8%).

[1]See for example, C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S. C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3,501 et. seq.

Among the congenital anomaly codes we considered, infants/fetuses of Hispanic mothers had the highest percentage co-occurring for 10 out of 16 organ systems; those of AIAN-NH mothers had the lowest percentage co-occurring for at least 12 out of 16 organ systems. Adequate comparisons could not be made among the central nervous system, orofacial clefts, lower gastrointestinal, genital, and renal organ systems due to low case counts among infants/fetuses of AIAN-NH mothers. This pattern of lower reported percentage co-occurring conditions continued among the individual cardiovascular birth defects we examined, with infants/fetuses of AIAN-NH mothers having the lowest percentage co-occurring for three out of the four included conditions (AVSD, TOF, and VSD).

4 | DISCUSSION

We observed that infants and fetuses born to W-NH and Hispanic mothers had the highest reported percentage co-occurring congenital anomalies (80.3 and 80%, respectively). Infants/fetuses of Hispanic mothers had the highest reported percentage co-occurring among most organ systems (10/16 systems) while infants/fetuses of AIAN-NH mothers had the lowest reported percentage co-occurring among organ systems (at least 12/16). Variation in occurrence of specific defects by race/ethnicity has been reported previously, but most studies only compared birth defect prevalences among the three most common race/ethnicity groups in the United States—W-NH, B-NH, and Hispanic. This limits of our awareness and understanding of prevalence differences among children born to API-NH and AIAN-NH mothers. Importantly, we observed a higher prevalence of ASD among infants/fetuses of AIAN-NH mothers in this report, which is consistent with a previous report among the general population in California by Aggarwal, Warmerdam, Wyatt, Ahmad, and Shaw (2015). Canfield et al. (2014) found a higher prevalence of TOF, orofacial clefts, and musculoskeletal defects among AIAN-NH mothers, which we did not see in this co-occurrence analysis.

Infants/fetuses of Hispanic mothers have both the highest rates of DS in general (Mai et al., 2019) and the highest percentage co-occurrence of congenital anomalies in 11 of the 16 organ systems examined in this analysis. Some of these differences may result from lower reported rates of elective termination after DS diagnosis among the Hispanic population (de Graaf, Buckley, & Skotko, 2015); however, included surveillance systems reported all birth outcomes (terminations, stillbirths, and live births). Hispanic and W-NH mothers have also been reported to have lower rates of termination among all pregnancies than B-NH mothers (Dehlendorf, Harris, & Weitz, 2013). In addition, several birth defects are reported more frequently in infants/fetuses of Hispanic mothers in the U.S. population than other racial/ethnic groups (Mai et al., 2019).

The reasons for these differences among ethnic groups require more study. In particular, further evaluation of the ability of surveillance systems to fully capture anomalies in all racial/ethnicity groups should be evaluated. For example, the lower prevalence of co-occurring conditions among the AIAN-NH population could be due to a true difference in incidence or a result of underdiagnosis of co-occurring congenital anomalies among the AIAN-NH population, possibly due to inadequate access to healthcare (Tolbert, Orgera, Singer, & Damico, 2019); this difference could also be a result of poor ascertainment

or inability to confirm defects among Native populations by state surveillance systems. Such investigations may identify areas for improvement of health equity and birth defects surveillance systems.

Our study utilized data from 12 active population-based birth defect registries including data on all birth outcomes between 2013 and 2017. There are some limitations to consider. For example, as we limited our analysis to pregnancies of ≥20 weeks gestation when most birth defects can be diagnosed, we likely missed early terminations that may have affected our results, especially given different rates of elective terminations among racial/ethnic groups (de Graaf et al., 2015). In addition, the programs included in our analysis are not necessarily demographically representative of the U.S. population. Furthermore, due to small cell size, we examined co-occurring congenital anomalies by organ system rather than specific birth defects—including both major and minor anomalies—which limits our conclusions. We performed a sensitivity analysis examining a subset of major birth defects by maternal race/ethnicity, which showed similar results to our organ system analysis. This sub-analysis of major birth defects could not be shown due to small cell sizes but reinforced our results. Nonetheless, this remains one of the most complete and comprehensive assessments of co-occurring congenital anomalies by race and ethnicity among infants/fetuses with DS.

5 | CONCLUSION

There are limited data available comparing co-occurring congenital anomalies among infants/fetuses with DS by maternal race/ethnicity, and even fewer that include infants/fetuses of API-NH and AIAN-NH mothers. These data may help focus future research on the differences among racial/ethnic groups in the diagnosis and reporting of co-occurring congenital anomalies in infants/fetuses diagnosed with DS and help improve surveillance strategies among all racial/ethnic groups. These data also help fill gaps in available data for smaller racial/ethnic groups in the United States and may help identify opportunities for improving perinatal health equity.

ACKNOWLEDGEMENTS

We would like to thank the states and analysts/epidemiologists that collected and provided the data for this report. We would also like to thank the NBDPN Data Committee for their input and feedback. This was funded in part by National Institutes of Health, Grant/Award Number: R01CA24986701 (Philip J. Lupo).

Funding information

National Institutes of Health, Grant/Award Number: R01CA24986701

DATA AVAILABILITY STATEMENT

Research data are not shared.

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TABLE 1

Co-occurring birth defects by organ system for Down syndrome[h] from 12 active case-finding population-based surveillance programs,[a] 2013–2017

Organ systems and birth defects[b]	Maternal race/ethnicity																	
	White, non-Hispanic (*n* = 2,473)			Black, non-Hispanic *n* = 670)			Hispanic (*n* = 2,225)			Asian or Pacific islander, non-Hispanic (*n* = 224)			American Indian or Alaska native, non-Hispanic (*n* = 58)			Total (*n* = 5,836)		
	Count	Percent	95% CI[i]	Count	Percent	95% CI[i]	Count	Percent	95% CI[i]	Count	Percent	95% CI[i]	Count	Percent	95% CI[i]	Count	Percent	95% CI[i]
Congenital anomalies (740–759)/congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	1,986	80.3	78.7–81.9	516	77.0	73.6–80.2	1,780	80.0	78.3–81.6	177	79.0	73.1–84.2	44	75.9	62.8–86.1	4,654	79.7	78.7–80.8
Central nervous system (740–742, Q00–07)	119	4.8	4.0–5.7	34	5.1	3.5–7.0	115	5.2	4.3–6.2	9	4.0	1.9–7.5	<5	—	—	287	4.9	4.4–5.5
Eye (743, Q10–15)	624	25.2	23.5–27.0	159	23.7	20.6–27.1	856	38.5	36.4–40.5	64	28.6	22.8–35.0	<5	—	—	1,793	30.7	29.5–31.9
Ear, face, neck (744, Q16–18)	790	31.9	30.1–33.8	197	29.4	26.0–33.0	1,057	47.5	45.4–49.6	84	37.5	31.1–44.2	7	12.1	5.0–23.3	2,246	38.5	37.2–39.7
Cardiovascular (745–747, Q20–28)	1,718	69.5	67.6–71.3	458	68.4	64.7–71.9	1,591	71.5	69.6–73.4	151	67.4	60.8–73.5	38	65.5	51.9–77.5	4,089	70.1	68.9–71.2
Atrial septal defect[c]	741	30.0	28.2–31.8	187	27.9	24.5–31.5	788	35.4	33.4–37.4	69	30.8	24.8–37.3	25	43.1	30.2–56.8	1,876	32.1	30.9–33.4
Atrioventricular septal defect[d]	508	20.5	19.0–22.2	168	25.1	21.8–28.5	282	12.7	11.3–14.1	37	16.5	11.9–22.0	6	10.3	3.9–21.2	1,038	17.8	16.8–18.8
Tetralogy of Fallot (TOF)[e]	74	3.0	2.4–3.7	26	3.9	2.6–5.6	52	2.3	1.8–3.1	9	4.0	1.9–7.5	0	—	—	164	2.8	2.4–3.3
Ventricular septal defect[f]	498	20.1	18.6–21.8	115	17.2	14.4–20.2	508	22.8	21.1–24.6	37	16.5	11.9–22.0	7	12.1	5.0–23.3	1,199	20.5	19.5–21.6
Respiratory (748, Q30–34)	343	13.9	12.5–15.3	106	15.8	13.1–18.8	485	21.8	20.1–23.6	38	17.0	12.3–22.5	<5	—	—	1,030	17.6	16.7–18.7
Orofacial clefts (749, Q35–37)	12	0.5	0.3–0.8	<5	—	—	15	0.7	0.4–1.1	<5	—	—	0	—	—	29	0.5	0.3–0.7

Organ systems and birth defects[b]	Maternal race/ethnicity																	
	White, non-Hispanic (*n* = 2,473)			Black, non-Hispanic *n* = 670)			Hispanic (*n* = 2,225)			Asian or Pacific islander, non-Hispanic (*n* = 224)			American Indian or Alaska native, non-Hispanic (*n* = 58)			Total (*n* = 5,836)		
	Count	Percent	95% CI[i]	Count	Percent	95% CI[i]	Count	Percent	95% CI[i]	Count	Percent	95% CI[i]	Count	Percent	95% CI[i]	Count	Percent	95% CI[i]
Upper gastrointestinal (750, Q38–40)	211	8.5	7.5–9.7	52	7.8	5.9–10.1	263	11.8	10.5–13.2	17	7.6	4.5–11.9	6	10.3	3.9–21.2	576	9.9	9.1–10.7
Lower gastrointestinal (751, Q41–45)	221	8.9	7.8–10.1	40	6.0	4.3–8.0	196	8.8	7.7–10.1	25	11.2	7.4–16.0	<5	—	—	501	8.6	7.9–9.3
Genital (752, Q50–56)	133	5.4	4.5–6.3	27	4.0	2.7–5.8	159	7.1	6.1–8.3	17	7.6	4.5–11.9	<5	—	—	355	6.1	5.5–6.7
Renal (753, Q60–64)	131	5.3	4.4–6.3	39	5.8	4.2–7.9	166	7.5	6.4–8.6	19	8.5	5.2–12.9	<5	—	—	372	6.4	5.8–7.0
Musculoskeletal (754, Q65–68)	295	11.9	10.7–13.3	66	9.9	7.7–12.4	415	18.7	17.1–20.3	36	16.1	11.5–21.5	<5	—	—	855	14.7	13.8–15.6
Limbs (755, Q69–74)	534	21.6	20.0–23.3	120	17.9	15.1–21.0	627	28.2	26.3–30.1	49	21.9	16.6–27.9	5	8.6	2.9–19.0	1,398	24.0	22.9–25.1
Other musculoskeletal (756, Q75–79)	316	12.8	11.5–14.2	68	10.1	8.0–12.7	432	19.4	17.8–21.1	34	15.2	10.7–20.6	<5	—	—	883	15.1	14.2–16.1
Skin (757, Q80–84)	467	18.9	17.4–20.5	108	16.1	13.4–19.1	685	30.8	28.9–32.8	51	22.8	17.4–28.8	<5	—	—	1,369	23.5	22.4–24.6
Chromosomal (758, Q90–99)[g]	30	1.2	0.8–1.7	5	0.7	0.2–1.7	18	0.8	0.5–1.3	<5	—	—	0	—	—	60	1.0	0.8–1.3
Other (759, Q85–89)	15	0.6	0.3–1.0	5	0.7	0.2–1.7	26	1.2	0.8–1.7	5	2.2	0.7–5.1	0	—	—	53	0.9	0.7–1.2

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

[b] 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 (National Birth Defect Prevention Network, 2017). 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.

[c] ICD-9-CM: 745.5; ICD-10-CM: Q21.1; CDC/BPA: 745.51–745.59.

[d] ICD-9-CM: 745.60, 745.61, 745.69; ICD-10-CM: Q21.2; CDC/BPA: 745.60–745.69, 745.487.

[e] ICD-9-CM: 745.2; ICD-10-CM: Q21.3; CDC/BPA: 745.20–745.21, 747.31.

[f] ICD-9-CM: 745.4; ICD-10-CM: Q21.0; CDC/BPA: 745.40–745.49 (excluding 745.487, 745.498).

[g] Co-occurring codes for the condition of primary interest, Down syndrome (ICD-9-CM: 758.0, ICD-10-CM: Q90.0-Q90.9, CDC/BPA: 758.00–758.09), were excluded from the counts of co-occurring codes in the chromosomal organ system.

[h] Down syndrome case definition ICD-9-CM: 758.0, ICD-10-CM: Q90.0-Q90.9, CDC/BPA: 758.00–758.09. 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). Counts less than five were suppressed to maintain confidentiality.

[i] CI, Confidence interval calculated using exact binomial methodology.