HHS Public Access

Author manuscript

Am J Med Genet A. Author manuscript; available in PMC 2025 October 01.

Published in final edited form as:

Am J Med Genet A. 2024 October ; 194(10): e63714. doi:10.1002/ajmg.a.63714.

Classification of isolated versus multiple birth defects: An automated process for population-based registries

Renata H. Benjamin[1], **Joanne M. Nguyen**[2], **Margaret Drummond-Borg**[2], **Angela E. Scheuerle**[3], **Peter H. Langlois**[4], **Mark A. Canfield**[4], **Charles J. Shumate**[2], **Laura E. Mitchell**[1], **A.J. Agopian**[1]

[1]Department of Epidemiology, Human Genetics, and Environmental Sciences, The University of Texas Health Science Center at Houston (UTHealth) School of Public Health, Houston, Texas

[2]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas

[3]Department of Pediatrics, Division of Genetics and Metabolism, University of Texas Southwestern Medical Center, Dallas, Texas

[4]Department of Epidemiology, Human Genetics, and Environmental Sciences, UTHealth School of Public Health at Austin, Austin, Texas

Abstract

Epidemiologic studies of birth defects often conduct separate analyses for cases that have isolated defects (e.g. spina bifida only) and cases that have multiple defects (e.g. spina bifida and a congenital heart defect). However, in some instances, cases with additional defects (e.g. spina bifida and clubfoot) may be more appropriately considered as isolated because the co-occurring defect (clubfoot) is believed to be developmentally related to the defect of interest. Determining which combinations should be considered isolated can be challenging and potentially resource intensive for registries. Thus, we developed automated classification procedures for differentiating between isolated versus multiple defects, while accounting for developmentally-related defects, and applied the approach to data from the Texas Birth Defects Registry (1999–2018 deliveries). Among 235,544 non-syndromic cases in Texas, 89% of cases were classified as having isolated defects, with proportions ranging from 25% to 92% across 43 specific defects analyzed. A large proportion of isolated cases with spina bifida (44%), lower limb reduction defects (44%), and holoprosencephaly (32%) had developmentally-related defects. Overall, our findings strongly support the need to account for isolated versus multiple defects in risk factor association analyses

Correspondence A.J. Agopian, Department of Epidemiology, Human Genetics and, Environmental Sciences, UTHealth School of Public Health, 1200 Pressler St, Houston, TX, 77030, a.j.agopian@uth.tmc.edu.

Author Contributions

Renata H. Benjamin: Conceptualization, formal analysis, and writing – original draft, and writing - review and editing. Joanne M. Nguyen, Margaret Drummond-Borg, Angela E. Scheuerle, Laura E. Mitchell: Data interpretation, methodology, and writing - review and editing. Charles J. Shumate, Mark A. Canfield, Peter H. Langlois: Funding and data acquisition, project administration, data interpretation, and writing - review and editing. A.J. Agopian: Conceptualization, funding and data acquisition, project administration, data interpretation, and writing - review and editing.

Conflict of Interest

The authors have no conflicts of interest to disclose.

and to account for developmentally-related defects when doing so, which has implications for interpreting prior studies.

Keywords

algorithms; birth defects; case classification; congenital abnormalities; registries

1 INTRODUCTION

Non-syndromic structural birth defects (i.e., those not due to a genetic abnormality or teratogenic exposure) can occur in isolation or co-occur with other birth defects. Classifying cases as having an isolated defect or having multiple defects, generally defined as two or more structural defects in different organ systems that are not part of a recognized sequence (Calzolari et al., 2014; Garne et al., 2011; Rasmussen et al., 2003), can help advance etiologic investigations by creating more homogenous case groups (Khoury et al., 1992; Tinker et al., 2015). The most straightforward approach to case classification would assign all cases with only one defect as having an isolated defect (e.g., Langlois et al., 2023); however, classification is more nuanced when co-occurring defects involve (1) two or more defects in the same organ system due to potentially related developmental processes (e.g., intestinal atresia and intestinal malrotation; (Adams & Stanton, 2014)), or (2) a primary defect with one or more secondary defects occurring in a developmental sequence (e.g., spina bifida with clubfoot; Copp et al., 2015). Hereafter, we refer to these as “same system defects” and “sequences,” respectively, and refer to “birth defects” as “major” structural malformations (those with medical, surgical, or serious cosmetic consequences; Rasmussen et al., 2003), which are the focus of most birth defects surveillance systems. Typically, developmentally-related co-occurring defects (i.e., same system defects and sequences) are thought of as representing a single, “isolated” defect and cases would be classified as such, whereas cases presenting with co-occurrence of seemingly unrelated defects would optimally be classified as having multiple defects (Tinker et al., 2015). The inclusion of cases with developmentally-related defects in the group with isolated defects is expected to result in a larger analytic sample and improved power for association analyses within that group.

International agreement regarding universal consensus and guidelines for distinguishing developmentally-related co-occurrence patterns from combinations of multiple unrelated defects is lacking. This hinders the ability of birth defects surveillance systems to implement classification of isolated versus multiple defects. Further, many birth defect registries have limited resources for clinicians to conduct a manual review of data from each individual case to determine isolated versus multiple classification on a case-by-case basis. Thus, at present, many registries do not routinely assign isolated versus multiple defect classification, which hampers use of registry data in risk factor association studies. Registries could benefit from automated approaches that would streamline the process. Our primary objective was therefore to develop and apply automated classification procedures for differentiating isolated versus multiple defects without clinical review, accounting for both same system defects and sequences in the isolated defect group.

2 MATERIALS AND METHODS

2.1 Study Population

To develop criteria and apply our automated classification procedures for isolated versus multiple defect classification, we used data from 1999-2018 deliveries in the Texas Birth Defects Registry (TBDR), managed by the Texas Birth Defects Epidemiology and Surveillance Branch at the Texas Department of State Health Services. The TBDR ascertains birth defects statewide among all pregnancy outcomes (live births, fetal deaths, and terminations) (Texas Department of State Health Services, 2023). Briefly, TBDR staff conduct active surveillance at delivery and tertiary facilities throughout the state to identify cases delivered by Texas residents. To be included in the TBDR, potential cases must have a monitored birth defect (including chromosomal abnormalities and syndromes) diagnosed within the first year of life. Demographic and diagnostic information is collected from the medical record and each identified birth defect is recorded using Centers for Disease Control and Prevention-modified British Pediatric Association (CDC/BPA) codes, which are generally more specific for birth defect phenotypes than analogous International Classification of Diseases (ICD) codes. TBDR records are routinely linked to vital records (birth certificates, death certificates, and fetal death certificates) to obtain additional information (e.g., demographic characteristics, vital status).

For the analyses in this manuscript, we excluded birth defects considered minor by the National Birth Defects Prevention Study (Rasmussen et al., 2003) or the TBDR (Langlois et al., 2023). Additionally, we identified and excluded cases with documented syndromes from isolated versus multiple defect classification, as previously described (Benjamin et al., 2023).

2.2 Criteria Development

EUROCAT, a European network of population-based registries for the epidemiological surveillance of congenital anomalies, conducts semi-automated classification of isolated versus multiple defect status among member European surveillance systems, based on ICD birth defect codes. The EUROCAT algorithm classified cases as potentially having multiple defects unless meeting one of the following criteria for having isolated defects: having only one defect code; all defects were in the same organ system (EUROCAT, 2022); or all defects were part of an identified sequence in EUROCAT's criteria (anencephaly, spina bifida, holoprosencephaly, ano-rectal atresia/stenosis, annular pancreas, bilateral renal agenesis/dysgenesis, diaphragmatic hernia, or gastroschisis/omphalocele; (EUROCAT, 2022)).

Because their approach represents a strong initial framework, we first adapted EUROCAT's ICD-based criteria, as detailed in Guide 1.5, Section 3.4 "Multiple Congenital Anomaly Algorithm" (EUROCAT, 2022), to a CDC/BPA-based framework to create our preliminary criteria. This was done using a crosswalk of ICD codes to CDC/BPA codes when available (National Birth Defects Prevention Network [NBDPN], 2004) and otherwise making manual decisions about definitions with clinician input. We applied this initial translation of EUROCAT's algorithm to the TBDR. To further refine the criteria, a clinical geneticist

familiar with the TBDR then conducted a targeted review of defect combinations among the cases initially classified as having multiple defects for three groups of defect combinations:

1. All of the top 100 most frequent pairwise defect combinations (e.g., vertebral defects and rib defects) among all of the cases initially classified as having multiple defects;
2. For each primary defect in one of the sequences included in the EUROCAT classification scheme (e.g., spina bifida), all defects that co-occurred in >5% of the cases;
3. All defect combinations among cases with only defects with the same first 4-digits of CDC/BPA codes (i.e., to identify same system defects that our initial definitions missed).

The results of this review were used to refine definitions of same system defects and sequences, with input from two additional clinical geneticists familiar with the TBDR.

2.3 Final Algorithm Application

To quantify the added case counts that the more nuanced approach would add, after finalizing the criteria and definitions, we developed an automated SAS program to implement the algorithm. Briefly, the program builds upon the data management framework from our prior classification algorithm (Langlois et al., 2023), which classified cases with one defect as having isolated defects and cases with more than one defect as having multiple defects. The new algorithm classifies each case as having isolated defects (hierarchically sub-classified as one isolated defect, isolated same system defects, or isolated sequences) or multiple defects, while accounting for related defects.

Following classification, we calculated the proportion of cases classified as having isolated defects (by subgroups) or multiple defects. This was separately performed for each defect type among 43 defect groups reported annually by the TBDR (Texas Department of State Health Services, 2022), for cases with one or more congenital heart defect (CHD) overall (CDC/BPA codes 745.000-747.430), and among all cases with any monitored major birth defect overall (NBDPN, 2004); Appendix 5.1, Texas Disease Index). Due to small numbers in some isolated subgroups, we combined the same system defects and sequences groups into a single group for presentation in figures. We then had a clinical geneticist review 100 randomly selected cases with congenital diaphragmatic hernia (CDH) to assess agreement between classification via the algorithm and clinician review. We calculated the kappa statistic comparing classification via the two methods and the 95% confidence interval around that statistic. Finally, in *post-hoc* analyses we tabulated the number and proportion of cases classified as having isolated, multiple, or syndromic (chromosomal abnormalities, genetic syndromes, or association) defects. Analyses were conducted in SAS (Version 9.4, SAS Institute Inc, Cary, NC, USA) and R (Version 4.1.2, R Core Team, Vienna, Austria).

2.4 Bias Assessment

To quantify the potential impact of combining isolated and multiple cases in etiologic analyses rather analyzing them separately, we used the Bias Analysis in Syndromic

IncLusion (BASIL) tool (Benjamin et al., 2023). Briefly, BASIL allows users to vary parameters for hypothetical scenarios where analyses were conducted using all cases, without separating etiologically heterogeneous groups (initially developed to assess syndromic and non-syndromic cases). Working under the assumption that an exposure of interest would be associated with birth defect occurrence in only one subgroup of cases (i.e., those with isolated defects), BASIL calculates the prevalence ratio (PR) for that subgroup and calculates the percent bias between that PR and the full group PR (i.e., calculated in cases with both isolated and multiple defects). Adapting the tool for this isolated/multiple defect framework, we analyzed hypothetical scenarios with varying proportions of isolated cases (75%, 50%, or 25%), while holding the full group prevalence ratio (1.5), number of cases (2,000), number of live births (6,000,000), and proportion exposed (20%) constant.

2.5 Editorial Policies and Ethical Considerations

This project was approved by the Institutional Review Board of the Texas Department of State Health Services and the UTHealth Committee for the Protection of Human Subjects.

3 RESULTS

3.1 Criteria Development

After translating EUROCAT's ICD-based multiple congenital anomaly algorithm to CDC/BPA-based coding, there were 11 groups of defects in the same organ system (400 CDC/BPA codes) and eight sequences (113 CDC/BPA codes). We then conducted a review to evaluate and add appropriate additional defects to the criteria. For example, when conducting a review of the most frequently co-occurring defects in the TBDR, a large number of cases with intestinal atresia/stenosis also had anomalies of intestinal fixation (751.400-751.495) and/or other intestinal anomalies (751.500-751.590). Neither of these groups were part of the EUROCAT group of same system defects, which restricted this group to small intestinal atresia codes. We expanded this group to include these additional intestinal anomalies so that cases with combinations of multiple intestinal anomalies were classified as isolated in our final algorithm. Decisions about how to group defects considered the developmental processes involved, e.g., tracheoesophageal fistula/esophageal atresia and intestinal atresia were not grouped together because they likely result from different etiologic processes.

Similarly, when reviewing sequences, we observed that >5% of cases with holoprosencephaly sequence also had co-occurring agenesis or underdevelopment of the nose (748.100), which was not included in the EUROCAT holoprosencephaly sequence criteria, initially resulting in a case-level classification of "multiple defects" among cases with holoprosencephaly and nose agenesis/underdevelopment, but ultimately resulting in an "isolated defect" classification in our final algorithm. Our final criteria included 14 groups of defects in the same system, encompassing 476 CDC/BPA codes (Table 1), and eight sequences, encompassing 152 CDC/BPA codes (Table 2). The algorithm used to classify cases via the criteria in Tables 1 and 2 is available in the Supplementary Appendix.

3.2 Final Algorithm Application

There were 273,752 cases in the TBDR with at least one major structural birth defect, chromosomal abnormality, or identified syndrome. Cases with a possible, probable, or definite diagnosis of a chromosomal abnormality (8%) or syndrome (6%) were dropped from analyses prior to applying the automated isolated/multiple algorithm. After this exclusion, there were 235,544 (86%) non-syndromic cases remaining.

After running our final automated algorithm, approximately 89% of cases (N=208,618) were classified as having an isolated defect and 11% were classified as having multiple defects (Figure 1 and Table S3). Cases with one isolated defect (one CDC/BPA code) recorded in the TBDR represented 82% (N=171,934) of those classified as having an isolated defect (Figure 1 and Table S3), while 17% of cases classified as isolated had two or more defects in the same system (N=35,115) and cases with defects in one of the included sequences accounted for a smaller proportion (1% of cases classified as isolated, N= 1,569; Table S3).

For specific defects, the proportions of cases classified as having isolated defects after applying the algorithm ranged from 25% (agenesis or aplasia of the lung) to 92% (pyloric stenosis) (Figure 1). Among cases with non-cardiac defects, cases with spina bifida or reduction defects of the lower limbs had the largest proportions of cases with same system defects or sequences that were classified as isolated after applying the algorithm (both 44%), followed by holoprosencephaly (32%; Figure 1). For cases with spina bifida, those with a sequence accounted for 61% of isolated cases (Table S3). For holoprosencephaly, there were many cases that were ultimately classified as having isolated defects who had holoprosencephaly with only other central nervous system [CNS] defects (17% of cases with isolated holoprosencephaly) or suspected holoprosencephaly sequence (holoprosencephaly with CNS and/or eye and/or nose and/or oral cleft defects) (15%) (Table S3).

Other defects with large proportions of cases with defects all in the same system included upper limb reduction defects (26%), renal agenesis/dysgenesis (22%), and microphthalmia (21%) (Table S3). For most of the specific CHDs evaluated (10 out of 13 CHDs), over 50% of cases had additional heart defects and no additional non-cardiac defects. The proportion of cases with CHDs classified as having isolated defects after applying the algorithm ranged from 62% to 87% among the specific CHDs analyzed (Table S3 and Figure S2).

Among 100 randomly selected CDH cases, there were 51 cases classified via the algorithm as having isolated CDH and 49 classified as having multiple defects. Classification via clinical review differed for one case, which the clinician classified as isolated rather than multiple. The kappa statistic showed strong agreement between the two methods (kappa 0.98, 95% CI: 0.94-1.00).

Finally, *post-hoc* analyses assessing the distribution of cases overall classified as having isolated, multiple, or syndromic defects by defect type revealed cases with pyloric stenosis, gastroschisis, and hypospadias had the smallest proportion of syndromic cases and also had high proportions of isolated cases (Table S4). Microphthalmia and anophthalmia were among the defects with the largest proportion of syndromic cases (56.8% and 48.0%,

respectively); both also had relatively high proportions of cases classified as having multiple defects.

3.3 Bias Assessment

We conducted analyses to understanding the impact of combining etiologically heterogeneous cases with isolated and multiple defects into a single analytic group. In hypothetical scenarios with 75%, 50%, or 25% of cases classified as having an isolated defect and a full group PR of 1.5, the resulting estimated "true" isolated PR (i.e., that which would be observed after excluding cases with multiple defects) ranged from 1.7 to 3.9 (Table 5). The resulting estimated bias percentages ranged from 11% to 61% (Table 5).

4 DISCUSSION

Our report provides initial hypothetical and applied examples that help to understand the expected impact of both 1) not accounting for isolated versus multiple defects in risk factor association studies and 2) not accounting for developmentally-related defects when classifying isolated versus multiple defects. Considering that reported associations from much of the prior birth defects epidemiology literature have not accounted for both of these factors, our findings indicate that associations from studies that do not differentiate may be biased to at least some degree. Automated or semi-automated classification processes may aid association studies using registry data to reduce the potential for bias by creating more homogenous analytic groups.

Results from our bias assessment highlight the potential importance of analyzing isolated cases separately from cases with multiple defects. For example, the etiology of isolated spina bifida (with or without other developmentally-related defects, such as clubfoot) may differ from the etiology of spina bifida with developmentally unrelated co-occurring defects (spina bifida with CHDs and hypospadias) (e.g., valproic acid associated with isolated spina bifida; Ornoy, 2009). Under this scenario, failing to conduct stratified or restricted analyses is expected to bias the association estimate toward the null, substantially so in certain scenarios (e.g., >50% bias). Most defects we evaluated had less than 75% of cases classified as isolated, which was expected to result in ~10% bias for full group PRs of 1.5 or higher in our hypothetical scenarios. This potential change-in-estimate underscores the need to account for isolated versus multiple birth defects in association studies, typically via stratification, and may impact the interpretation of prior effect estimates reported from association studies that have not done so. Particular concern is warranted for analyses of defects with the lowest proportion of cases with isolated defects, such as microphthalmia, tracheoesophageal fistula/esophageal atresia, bladder exstrophy, and anophthalmia. Criteria to automate case classification therefore may allow population-based registries to more easily implement these procedures and facilitate separate analyses of cases with isolated and multiple defects in association studies.

Further, accounting for developmentally-related co-occurring defects in isolated classification, rather than only considering infants with one defect code substantially impacts the overall proportion of cases classified as having an isolated defect (89% versus 73% classified as isolated in our data, respectively). This 16% difference emphasizes the need for

a nuanced approach for defining isolated versus multiple defects that moves beyond a focus on only the presence of one versus more than one defect code.

For many defects, accounting for developmentally-related defects substantially increased the number of cases in the isolated analytic group. This would result in increased power to detect risk factor associations and potentially provide a more complete sample of non-syndromic cases. The expected benefit would vary widely by defect type. Specifically, only 28% of cases with spina bifida were initially classified as having an isolated defect based simply on whether or not an additional major defect was present, whereas another 44% of cases were ultimately classified as having isolated spina bifida when using an algorithm that accounted for secondary defects. Accounting for developmentally-related defects also more than tripled the proportion of cases classified as having isolated holoprosencephaly (45%) versus the proportion that would have been deemed isolated when only considering cases with no other birth defect code (13%).

Several defects studied had a high proportion of cases with only co-occurring defects in the same system (e.g., limb reduction defects, kidney/urinary tract defects, eye defects). This was particularly impactful for CHDs, for which 25% of cases had only additional cardiac defects. While our current classification approach distinguished between cases with CHDs with versus without additional extra-cardiac defects, more nuanced classification may be needed for certain heart defects, depending on the research question. For example, it may be important to further distinguish between cases with particular CHD combinations in outcome studies (e.g., more versus less severe phenotypes).

The observed proportion of isolated defects in Texas was fairly similar to comparable estimates from other registries. The proportion of non-syndromic cases classified as having isolated defects in this study (89%) was comparable to population-based registry estimates from EUROCAT (91% in Garne et al., 2011 and 92% in Calzolari et al., 2014) and Australia (88% in Schneuer et al., 2019) that used EUROCAT's classification algorithm. Of note, these two EUROCAT studies included supplemental manual clinical review of birth defect data for individual cases potentially classified as having multiple defects, whereas our fully automated approach did not involve manual review. As another example, the proportion of cases with isolated spina bifida in this study was similar to the proportion reported in a recent EUROCAT report (64% of live births) (Glinianaia et al., 2022); syndromic cases were included in the EUROCAT denominator and the comparable TBDR estimate was 62% (Table S4). By contrast, the proportion of cases with isolated spina bifida was substantially higher in an NBDPS study (88%) (Marchincin et al., 2023), where participant consent was required and individual case review was conducted to identify and exclude syndromic cases and classify cases as isolated, multiple, or complex (Rasmussen et al., 2003; Reefhuis et al., 2015).

This may support the notion that manual clinical classification should remain the gold standard for at least some defects, though automated classification of isolated defect status may be useful when resources are not available for manual classification of all ascertained cases, which is the case for many surveillance systems. We found strong agreement between our automated algorithm and clinical review in a small subset of cases with CDH. It is

worth noting that a potential benefit of our automated approach is that it is less subjective than manual review and may result in fewer differences across reviewers, surveillance systems, and/or time. Thus, when resources for manual review are available, there may still be supplemental uses for an automated approach, such as identifying potential errors with manual classification to improve data quality or reducing administrative burden by allowing for prioritization of a more focused manual review on a smaller number of cases after implementing the automated approach in the wider group.

The automated approach we implemented has limitations. First, all defects within the groups of same system defects and sequences are assumed to be developmentally-related, based on current understanding of developmental overlap, and it may be more appropriate to make different decisions based on future understanding of birth defect sequences or for certain research questions, e.g., a study of infants with clubfoot may want to exclude cases secondary to spina bifida. Additionally, our case classification findings (i.e., proportion of cases with isolated versus multiple defects after implementing the algorithm) may not be directly comparable and applicable to all other registries due to differences in procedures (e.g., criteria for case inclusion, defect ascertainment procedures), population demographics, facility practices, and data collection methods. For example, the TBDR does not code certain defects present in combination with a primary defect (e.g., dextrocardia, mesocardia, liver displacement, or pulmonary hypoplasia are not coded with CDH; hypotelorism is not coded with holoprosencephaly). Registries without these specific coding procedures would likely want to revise the criteria presented here in order to include these defects in their sequence definitions. Classification of non-syndromic cases as having an isolated defect or multiple defects will also depend in part on the criteria used to identify syndromic cases (e.g., some birth defects registries have little to no information on syndrome diagnoses) and which birth defects are considered minor or prematurity-related defects as opposed to major structural defects (Benjamin et al., 2023; Rasmussen et al., 2003). Nevertheless, the criteria and process described here should be generalizable and adaptable to other population-based birth defects registries. This automated approach may be particularly helpful when classifying cases in an entire registry, evaluating a spectrum of defects, or conducting a combined analysis across pooled data from multiple population-based registries. Thus, automated consideration of isolated versus multiple defects is expected to prove itself a useful tool in working toward improved understanding in the determinants of birth defects and working toward their prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding information

This project was supported in part by a grant from the Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD) (5R01HD093660), funding from the Centers for Disease Control and Prevention (CDC), as part of a birth defects surveillance cooperative agreement with the Texas Department of State Health Services (TX DSHS) (NU50DD000102), and funding from TX DSHS (HHS001177900001). The TX DSHS Birth Defects Epidemiology and Surveillance Branch is supported in part by Maternal and Child Health Services Title V Block Grant funds from the Health Resources and Services Administration (HRSA). The contents are those of the

author(s) and do not necessarily represent the official views of, nor an endorsement, by NICHD, CDC, TX DSHS, or HRSA.

Data Availability Statement

Due to data confidentiality governed by existing data use agreements, these data cannot be shared. Data from the Texas Birth Defects Registry may be requested by submitting a data use application to the Texas Department of State Health Services.

REFERENCES

Adams SD, & Stanton MP (2014). Malrotation and intestinal atresias. Early Hum Dev, 90(12), 921–925. 10.1016/j.earlhumdev.2014.09.017 [PubMed: 25448782]

Benjamin RH, Mitchell LE, Scheuerle AE, Langlois PH, Canfield MA, Drummond-Borg M, … Agopian AJ (2023). Identifying syndromes in studies of structural birth defects: Guidance on classification and evaluation of potential impact. Am J Med Genet A, 191(1), 190–204. 10.1002/ajmg.a.63014 [PubMed: 36286533]

Calzolari E, Barisic I, Loane M, Morris J, Wellesley D, Dolk H, … Garne E (2014). Epidemiology of multiple congenital anomalies in Europe: a EUROCAT population-based registry study. Birth Defects Res A Clin Mol Teratol, 100(4), 270–276. 10.1002/bdra.23240 [PubMed: 24723551]

Copp AJ, Adzick NS, Chitty LS, Fletcher JM, Holmbeck GN, & Shaw GM (2015). Spina bifida. Nat Rev Dis Primers, 1, 15007. 10.1038/nrdp.2015.7 [PubMed: 27189655]

EUROCAT. (2022). EUROCAT Guide 1.5. Retrieved from https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/guidelines-for-data-registration_en

Garne E, Dolk H, Loane M, Wellesley D, Barisic I, Calzolari E, … Group, E. W. (2011). Paper 5: Surveillance of multiple congenital anomalies: implementation of a computer algorithm in European registers for classification of cases. Birth Defects Res A Clin Mol Teratol, 91 Suppl 1, S44–50. 10.1002/bdra.20777 [PubMed: 21384529]

Glinianaia SV, Rankin J, Pierini A, Coi A, Santoro M, Tan J, … Morris JK (2022). Ten-Year Survival of Children With Congenital Anomalies: A European Cohort Study. Pediatrics, 149(3). 10.1542/peds.2021-053793

Khoury MJ, Moore CA, James LM, & Cordero JF (1992). The interaction between dysmorphology and epidemiology: methodologic issues of lumping and splitting. Teratology, 45(2), 133–138. 10.1002/tera.1420450206 [PubMed: 1615423]

Langlois PH, Marengo L, Lupo PJ, Drummond-Borg M, Agopian AJ, Nembhard WN, & Canfield MA (2023). Evaluating the proportion of isolated cases among a spectrum of birth defects in a population-based registry. Birth Defects Res, 115(1), 21–25. 10.1002/bdr2.1990 [PubMed: 35218607]

Marchincin SL, Howley MM, Van Zutphen AR, Fisher SC, Nestoridi E, Tinker SC, … National Birth Defects Prevention, S. (2023). Risk of birth defects by pregestational type 1 or type 2 diabetes: National Birth Defects Prevention Study, 1997–2011. Birth Defects Res, 115(1), 56–66. 10.1002/bdr2.2050 [PubMed: 35665489]

National Birth Defects Prevention Network (NBDPN) (2004). Guidelines for Conducting Birth Defects Surveillance. National Birth Defects Prevention Network. Retrieved from https://www.nbdpn.org/guidelines.php.

Ornoy A. (2009). Valproic acid in pregnancy: how much are we endangering the embryo and fetus? Reprod Toxicol, 28(1), 1–10. 10.1016/j.reprotox.2009.02.014 [PubMed: 19490988]

Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA, & The National Birth Defects Prevention Study (2003). Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol, 67(3), 193–201. 10.1002/bdra.10012 [PubMed: 12797461]

Reefhuis J, Gilboa SM, Anderka M, Browne ML, Feldkamp ML, Hobbs CA, … The National Birth Defects Prevention Study (2015). The National Birth Defects Prevention Study: A review of the

methods. Birth Defects Res A Clin Mol Teratol, 103(8), 656–669. 10.1002/bdra.23384 [PubMed: 26033852]

Schneuer FJ, Bell JC, Shand AW, Walker K, Badawi N, & Nassar N (2019). Five-year survival of infants with major congenital anomalies: a registry based study. Acta Paediatr, 108(11), 2008–2018. 10.1111/apa.14833 [PubMed: 31046172]

Texas Department of State Health Services, Birth Defects Epidemiology and Surveillance Branch (2023). Birth Defects Data and Publications. Retrieved from https://www.dshs.texas.gov/texas-birth-defects-epidemiology-surveillance/birth-defects-data-publications

Tinker SC, Gilboa S, Reefhuis J, Jenkins MM, Schaeffer M, & Moore CA (2015). Challenges in Studying Modifiable Risk Factors for Birth Defects. Curr Epidemiol Rep, 2(1), 23–30. 10.1007/s40471-014-0028-y [PubMed: 26236577]

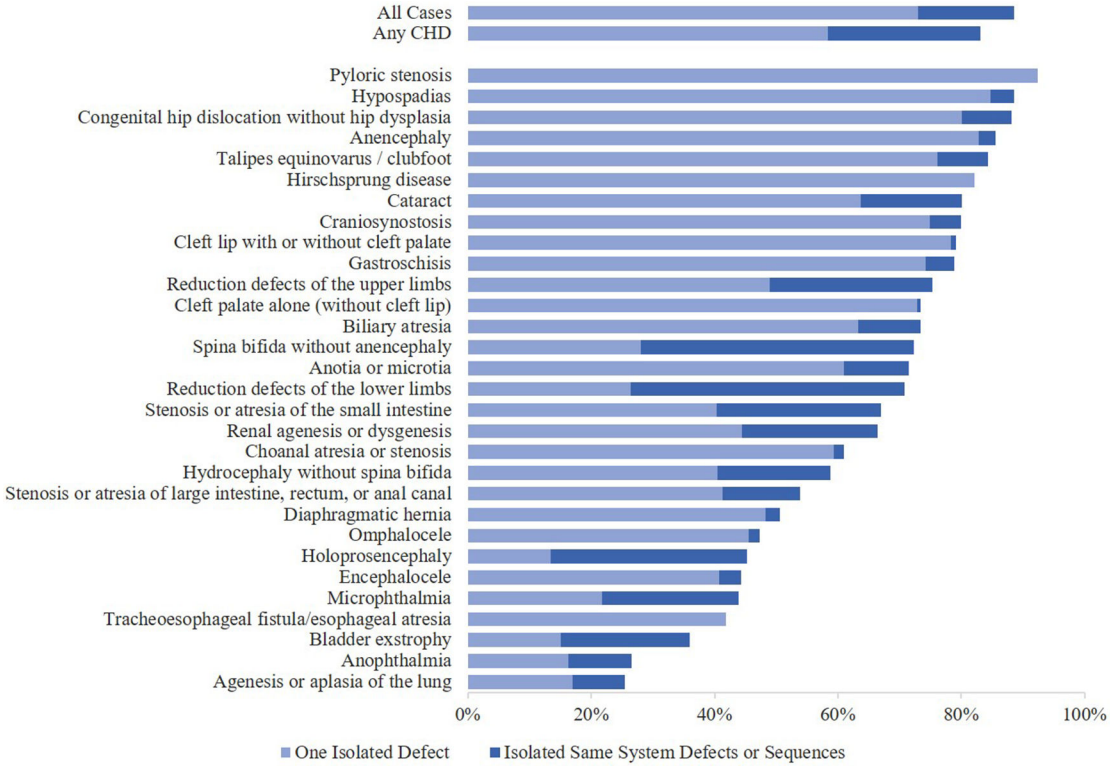

Figure 1.

Isolated type among non-syndromic cases, including all cases, cases with any congenital heart defect (CHD), and by specific defect (sorted by descending percentage of isolated cases), Texas Birth Defects Registry, 1999-2018

Table 1.

Isolated defect classification based on same system groups

System	Included Defects	Modified CDC/BPA Codes[a]
Neural tube defects	Anencephalus and similar anomalies; Spina bifida; Encephalocele	740; 741; 742.0
Central nervous system (not NTD)	Microcephalus; Reduction deformities of brain; Congenital hydrocephalus; Other specified anomalies of brain; Other specified anomalies of spinal cord; Other specified anomalies of nervous system; Unspecified anomaly of brain, spinal cord, and nervous system	742.1-742.9
Eye	Congenital anomalies of eye	743
Ear	Anomalies of ear causing impairment of hearing; Other specified anomalies of ear; Unspecified anomalies of ear	744.0-744.3
Cardiac	Congenital Wolff-Parkinson-White syndrome; Bulbus cordis anomalies and anomalies of cardiac septal closure; Other congenital anomalies of heart; Coarctation of aorta; Other anomalies of aorta; Anomalies of pulmonary artery; Anomalies of great veins	426.705; 745; 746; 747.1-747.4
Respiratory	Congenital anomalies of respiratory system	748
Orofacial clefts	Cleft palate alone; Cleft lip alone; Cleft lip with cleft palate	749.0-749.2
Intestinal	Atresia and stenosis of small intestine; Atresia and stenosis of large intestine, rectum, and anal canal; Anomalies of intestinal fixation; Other anomalies of intestine	751.1-751.2; 751.4-751.5
Biliary	Anomalies of gallbladder, bile ducts, and liver	751.6
Genital	Congenital anomalies of genital organs	752
Kidney/urinary tract	Hypospadias and epispadias; Congenital anomalies of urinary system	752.6; 753
Limb	Congenital dislocation of hip; Congenital genu recurvatum and bowing of long bones of leg; Varus (inward) deformities of feet; Valgus (outward) deformities of feet; Other deformities of feet; Other specified congenital musculoskeletal deformities; Other congenital anomalies of limbs	754.3-754.8; 755
Craniosynostosis	Craniosynostosis, NOS; Sagittal craniosynostosis; Metopic craniosynostosis; Coronal craniosynostosis; Lambdoidal craniosynostosis; Other craniosynostosis	756.000-756.030
Vertebral/rib	Anomalies of spine; Other anomalies of ribs and sternum	756.1; 756.3

[a] 3- and 4-digit codes listed also include the codes with additional digits

Table 2.

Isolated defect classification based on sequences

Primary Defect	Included Defects (CDC/BPA Codes)	Modified CDC/BPA Codes[a]
Anencephaly	Anencephalus and similar anomalies[b] with Anomalies of adrenal gland (absence, hypoplasia, other specified, or unspecified)	740[b] with 759.100; 759.110; 759.180; 759.190
Spina bifida	Spina bifida[b] with Anomalies of cerebrum; Anomalies of corpus callosum; Anomalies of cerebellum; Other specified anomalies of spinal cord; Obstructive defects of renal pelvis and ureter; Other specified anomalies of ureter; Congenital dislocation of hip; Varus (inward) deformities of feet; Valgus (outward) deformities of feet; Other deformities of feet; Other anomalies of lower limb, including pelvic girdle	741[b] with 742.200; 742.210; 742.230; 742.5; 753.2; 753.4; 754.3; 754.5- 754.7; 755.6
Holoprosencephaly	Holoprosencephaly[b] with Microcephalus; Reduction deformities of brain; Congenital hydrocephalus; Other specified anomalies of brain; Microphthalmos; Agenesis or underdevelopment of nose; Tubular nose, single nostril, proboscis, Cleft palate alone; Cleft lip alone; Cleft lip with cleft palate	742.260[b] with 742.1-742.4; 743.100; 748.100; 748.185; 749.0-749.2
Ano-rectal atresia/ stenosis	Atresia and stenosis of large intestine, rectum, and anal canal[b] with Ectopic anus; Congenital rectovaginal fistula; Congenital digestive-urinary tract fistulae	751.2[b] with 751.530; 752.420; 753.860
Annual pancreas	Annular pancreas[b] with Stenosis, atresia or absence of duodenum	751.720[b] with 751.100
Renal agenesis/ dysgenesis	Bilateral/NOS renal agenesis and dysgenesis[b] with Varus (inward) deformities of feet; Valgus (outward) deformities of feet; Other deformities of feet	753.000/753.009[b] with 754.5-754.7
Diaphragmatic hernia	(Absence of diaphragm; Congenital diaphragmatic hernia; Diaphragmatic hernia (Bochdalek); Diaphragmatic hernia (Morgagni); Hemidiaphragm)[b] with Anomalies of intestinal fixation	756.600-756.617[b] with 751.4
Abdominal wall	(Omphalocele; Gastroschisis)[b] with Atresia and stenosis of small intestine; Anomalies of intestinal fixation	756.700/756.710[b] with 751.1; 751.4

[a] 3- and 4-digit codes listed also include the codes with additional digits

[b] Indicates primary defect that must be present in the sequence of related defects

Table 5.

Assessment of potential bias in combined analyses of cases classified as having isolated versus multiple defects, conducted using the Bias Assessment in Syndromic IncLusion (BASIL) tool (Benjamin et al., 2023)

Prevalence ratio in all cases	Isolated Proportion	Prevalence ratio in isolated cases	Percent bias
1.5	75%	1.7	11%
	50%	2.1	29%
	25%	3.9	61%