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Birth defects that co-occur with non-syndromic gastroschisis and omphalocele

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AUTHOR CONTRIBUTIONS

Omobola O. Oluwafemi drafted the original manuscript and assisted with manuscript revision. Renata H. Benjamin and Maria Luisa Navarro Sanchez contributed to data analysis, data interpretation, and manuscript revision. Angela E. Scheuerle, Christian P. Schaaf, Laura E. Mitchell, Peter H. Langlois, Mark A. Canfield, Michael D. Swartz, Daryl A. Scott, Hope Northrup, Joseph W. Ray, Scott D. McLean, Katherine L. Ludorf, and Han Chen assisted with data interpretation and manuscript revision. Philip J. Lupo and A. J. Agopian supervised all research and assisted with manuscript revision.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Due to data confidentiality restrictions and existing data agreements, these data cannot be shared.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Abstract

Gastroschisis and omphalocele are the two most common abdominal wall birth defects, and epidemiologic characteristics and frequency of occurrence as part of a syndromic condition suggest distinct etiologies between the two defects. We assessed complex patterns of defect co-occurrence with these defects separately using the Texas Birth Defects Registry. We used co-occurring defect analysis (CODA) to compute adjusted observed-to-expected (O/E) ratios for all observed birth defect patterns. There were 2,998 non-syndromic (i.e., no documented syndrome diagnosis identified) cases with gastroschisis and 789 (26%) of these had additional co-occurring defects. There were 720 non-syndromic cases with omphalocele, and 404 (56%) had additional co-occurring defects. Among the top 30 adjusted O/E ratios for gastroschisis, most of the co-occurring defects were related to the gastrointestinal system, though cardiovascular and kidney anomalies were also present. Several of the top 30 combinations co-occurring with omphalocele appeared suggestive of OEIS (omphalocele, exstrophy of cloaca, imperforate anus, spinal defects) complex. After the exclusion of additional cases with features suggestive of OEIS in a post-hoc sensitivity analysis, the top combinations involving defects associated with OEIS (e.g., spina bifida) were no longer present. The remaining top combinations involving omphalocele included cardiovascular, gastrointestinal, and urogenital defects. In summary, we identified complex patterns of defects that co-occurred more frequently than expected with gastroschisis and omphalocele using a novel software platform. Better understanding differences in the patterns between gastroschisis and omphalocele could lead to additional etiologic insights.

Keywords

CODA; co-occurring birth defect; gastroschisis; non-syndromic; omphalocele

1 | INTRODUCTION

Gastroschisis and omphalocele are the two most common types of abdominal wall defects. Both of these defects involve a protrusion of the intestines outside of the body through an opening in the abdomen, but omphalocele originates within the umbilicus and involves the presence of a membrane that surrounds the exposed intestines, whereas the intestines are not membrane-enclosed in gastroschisis, and the abdominal wall opening is generally not thought to involve the umbilicus (Opitz, Feldkamp, & Botto, 2019; Stoll, Alembik, Dott, & Roth, 2008). There is some debate, however, that gastroschisis is instead a primary midline malformation of the umbilical ring rather than abdomen; with a protrusion through the umbilical ring, to the right of the cord with no involvement of the abdominal wall (Lubinsky, 2019; Opitz et al., 2019). Globally, the prevalence of gastroschisis and omphalocele are around 1–4 and 2–3 per 10,000 live births, respectively, and there is a great deal of evidence suggesting that the prevalence of gastroschisis has increased in recent years, particularly

among mothers <20 years old (Allman et al., 2016; Calzolari, Bianchi, Dolk, & Milan, 1995; Henrich, Huemmer, Reingruber, & Weber, 2008; Hwang & Kousseff, 2004; Ledbetter, 2006; Parker et al., 2010; Stallings et al., 2019; Stoll et al., 2008). Gastroschisis and omphalocele are both associated with increased infant mortality (3–10% for gastroschisis and 12–29% for omphalocele) and both require surgery soon after delivery (Bradnock et al., 2011; Henrich et al., 2008; Ledbetter, 2006). Although most affected individuals gain relatively normal intestinal function when the abdominal wall defect is repaired, the repair may involve several surgeries, and parenteral nutrition and prolonged hospitalizations are common (Ledbetter, 2006; U.S. National Institutes of Health National Library of Medicine, 2019). In fact, gastroschisis is the birth defect with the highest hospital length of stay in the United States and ranks among the top six most costly birth defects (Centers for Disease & Prevention, 2007).

Maternal characteristics associated with gastroschisis and omphalocele differ. Non-syndromic gastroschisis is associated with young maternal age, whereas omphalocele is associated with older maternal age (Haddow, Palomaki, & Holman, 1993; Hwang & Kousseff, 2004; Salihu, Boos, & Schmidt, 2002). Gastroschisis is associated with maternal exposure to smoking and alcohol use (Brindle, Flageole, Wales, & Canadian Pediatric Surgery, 2012; Ledbetter, 2006; U.S. National Institutes of Health National Library of Medicine, 2019), while high maternal body mass index has been linked to a decreased risk of gastroschisis (Lam, Torfs, & Brand, 1999; Waller et al., 2007). By contrast, these characteristics are not established risk factors for omphalocele (Agopian, Marengo, & Mitchell, 2009; Frolov, Alali, & Klein, 2010; Mac Bird et al., 2009; Shiono, Klebanoff, & Berendes, 1986).

Moreover, the majority of gastroschisis occurs among non-syndromic (i.e., no documented chromosomal or genomic syndrome present) individuals and in isolation (e.g., additional co-occurring birth defects are present in only 10–15% of cases) (Brantberg, Blaas, Salvesen, Haugen, & Eik-Nes, 2004; Henrich et al., 2008; Rankin, Dillon, & Wright, 1999). By contrast, 30–80% of non-syndromic omphalocele occurs among subjects with additional co-occurring birth defects (Benjamin & Wilson, 2014; Fisher, Attah, Partington, & Dykes, 1996; Henrich et al., 2008; Hwang & Kousseff, 2004; Ledbetter, 2006; Mayer, Black, Matlak, & Johnson, 1980; Murphy, Mazlan, Tarheen, Corbally, & Puri, 2007; Rankin et al., 1999; Stoll et al., 2008). These differences support the notion that these conditions are etiologically distinct.

Although the overall proportion of cases with non-syndromic gastroschisis or omphalocele and co-occurring birth defects has been calculated in several populations, descriptions, and comparisons of specific complex patterns of co-occurrence (e.g., involving two or more co-occurring defects) have been limited. Exploring differences in the patterns of complex co-occurrence of gastroschisis and omphalocele with other defects could lead to additional etiologic insights. Thus, we assessed patterns of defect co-occurrence with gastroschisis and omphalocele in a large, population-based birth defect registry.

2 | METHODS

2.1 | Editorial policies and ethical considerations

Our protocol was approved by the UTHealth Institutional Review Board. The Texas Birth Defects Registry has legislative authority to collect data without informed consent.

2.2 | Study subjects

The study population included live births, stillbirths, fetal deaths, and induced pregnancy terminations from the Texas Birth Defects Registry (TBDR), with delivery dates between 1999 and 2014. The TBDR is a population-based, active surveillance system that monitors all deliveries by women who reside in the state of Texas (Texas Department of State Health Services, 2013). To be included in the registry, potential cases must have at least one monitored structural birth defect or chromosomal anomaly documented in medical records that were diagnosed prenatally or no later than the age of 1 year.

Birth defects in the TBDR are coded based on a modified British Pediatric Association (BPA) Classification of Diseases, used by the Centers for Disease Control and Prevention (CDC). For the present analyses, the data set was restricted to major defects (based on criteria from the National Birth Defects Prevention Study and additional input from clinicians at the TBDR). Cases with gastroschisis or omphalocele were identified based on the presence of a corresponding BPA code in the registry (756.700 and 756.710, respectively). To allow for the analysis of distinct categories of co-occurring birth defects, all major defects were grouped by categories created from the first four digits of the six-digit BPA code, as previously described (Benjamin et al., 2019). Registry data were also linked to vital records and demographic data (e.g., maternal race/ethnicity) from birth and fetal death certificates from the Vital Statistics Section at the Texas Department of State Health Services. When data were missing from vital records, data from medical records that were abstracted by TBDR staff as part of the registry were used.

To limit heterogeneity and focus on cases with an unexplained etiology, we excluded cases that were identified as having a syndrome, chromosome abnormality, or malformation sequence or complex (e.g., Vertebral defects, Anorectal malformations, Cardiac defects, Tracheoesophageal fistula, Renal anomalies, and Limb abnormalities [VACTERL]). Such cases were identified based on both BPA codes and through a manual review of text abstracted from medical records by trained registry staff. Cases identified in the TBDR as having OEIS complex (Omphalocele, Exstrophy of the cloaca, Imperforate anus, and Spinal defects) were excluded. In addition, cases with omphalocele and imperforate anus as well as cloacal exstrophy (BPA codes 751.55 and 756.79) or bladder exstrophy plus imperforate anus (BPA codes 753.5 and 751.23–751.24), which are likely to have OEIS, were excluded. Non-syndromic cases that were twins or higher-order multiples were also excluded.

2.3 | Statistical analysis

All analyses were conducted separately for cases with gastroschisis and cases with omphalocele and were limited to birth defect combinations with at least three observed cases. Counts and proportions of subjects were tabulated across different categories of infant

and maternal characteristics (e.g., race/ethnicity) separately for isolated and non-isolated cases. We identified cases with all possible cooccurring defect combinations among 144 major defect categories, exclusive of gastroschisis and omphalocele. The total number and proportion of cases with each individual co-occurring defect were tabulated (e.g., the number and proportion of cases with spina bifida among cases with omphalocele).

To assess patterns of birth defect co-occurrence, we used cooccurring defect analysis (CODA) (Benjamin et al., 2019). CODA is an R-based program that computes adjusted observed-to-expected (O/E) ratios for birth defects combinations (Agopian, Evans, & Lupo, 2018; Benjamin et al., 2019; Khoury, James, & Erickson, 1990). Briefly, the observed prevalence of a particular combination of birth defects is compared to the expected prevalence of the combination of birth defects (based on the prevalence of each component defect in the combination). Thus, combinations that co-occur more often than would be expected by chance have an O/E ratio greater than one. CODA also implements a method proposed by Khoury et al. to adjust for the tendency of birth defects in the combination being assessed to co-occur with other birth defects (Khoury et al., 1990).

Using CODA, we computed adjusted O/E ratios for all observed birth defect combinations involving 1–4 additional defects among the 144 defect categories. In other words, including gastroschisis/omphalocele, these represented two- to five-way birth defect combinations. Two post hoc sensitivity analysis were also conducted: (a) among the subgroup of cases with gastroschisis and mothers <20 years old and (b) among cases with omphalocele that did not have text descriptions highly suggestive of OEIS (i.e., we excluded cases with text indicative of OEIS for this sensitivity analysis) (as described below).

3 | RESULTS

After excluding syndromic cases and non-syndromic twins and higher-order multiples, there were 2,998 cases with gastroschisis, and 789 of these (26%) were non-isolated cases that is with co-occurring defects (Table 1). There were 720 cases with omphalocele. Of these, 404 (56%) were non-isolated cases. The majority of mothers of cases with non-isolated gastroschisis were White non-Hispanic (32.7%) and Hispanic (57.9%). A similar distribution was seen among mothers of cases with non-isolated omphalocele, with 29.6% White non-Hispanic and 46.8% Hispanic. Mothers of cases with gastroschisis were more likely to be younger with around 40% of isolated and non-isolated gastroschisis cases having a maternal age of less than 20. Compared to gastroschisis, mothers of cases with omphalocele were more likely to have a greater than high school education and more likely to be obese.

We tabulated the counts of each observed defect co-occurring with gastroschisis and omphalocele and ordered them by frequency of co-occurrence (Tables 2 and 3, Supplemental Table 2). The defects cooccurring most frequently with gastroschisis were atresia and stenosis of the small intestine (18.5%), ostium secundum type atrial septal defect (17.5%), anomalies of intestinal fixation (16.5%), atresia and stenosis of the large intestine, rectum, and anal canal (9.8%), and obstructive defects of renal pelvis and ureter (9.6%). Ostium secundum type atrial septal defects co-occurred most frequently with omphalocele (29.7%).

Other defects that frequently co-occurred with omphalocele included ventricular septal defect (18.1%), obstructive defects of renal pelvis and ureter (9.9%), atresia and stenosis of the large intestine, rectum, and anal canal (7.4%), and other deformities of feet (6.4%).

We calculated the adjusted O/E ratio for all possible two-, three-, four-, and five- way combinations of defects involving gastroschisis and omphalocele (Tables 4 and 5). There were a total of 489 observed combinations assessed for gastroschisis and 2,257 observed combinations for omphalocele. Only combinations with at least three cases were assessed. Because of differences in the distributions of adjusted O/E ratios, we focused on ratios >10 for gastroschisis patterns and omphalocele patterns. Among the top results, several combinations were subsets or permutations of other patterns (e.g., the three-way combination of atresia and stenosis of the small intestine, other anomalies of intestine and gastroschisis was a subset of the four-way combination of atresia and stenosis of the small intestine, anomalies of intestinal fixation, other anomalies of intestine and gastroschisis.)

Among cases with gastroschisis, the highest adjusted O/E ratio was for co-occurring anomalies of the pulmonary artery and congenital hiatus hernia (three cases, adjusted O/E ratio = 134.3) (Table 4). The combination of gastroschisis, atresia, and stenosis of the small intestine, anomalies of intestinal fixation, and other anomalies of intestine was also observed to occur more frequently than expected, with nine cases and adjusted O/E ratio = 124.3. Congenital hiatus hernia and anomalies of intestinal fixation also co-occurred with gastroschisis more often than expected (six cases, adjusted O/E ratio = 107.4). The adjusted O/E ratio range for the remaining top combinations was 5.0–50.2. Of all 54 defects found to co-occur with gastroschisis among the top 30 combinations, 40 (79.7%) were related to the gastrointestinal system.

Given the known association between young maternal age and gastroschisis (Allman et al., 2016; Henrich et al., 2008; Stallings et al., 2019), we also conducted a post-hoc sensitivity analysis among the subgroup of cases with gastroschisis and mothers <20 years old; results were similar to those from the main analysis (data not shown), though fewer combinations could be assessed among this subgroup due to small numbers.

Among the highest adjusted O/E ratios for omphalocele, many defect combinations included spina bifida, atresia and stenosis of the large intestine rectum and anal canal, and disorder of sexual development. For example, the top combination involving omphalocele included atresia and stenosis of the large intestine, rectum, and anal canal, disorder of sexual development, and other deformities of feet (three cases, adjusted O/E ratio = 199.3) (Table 5). The combination of omphalocele, spina bifida, atresia and stenosis of the large intestine, rectum, and anal canal, and disorder of sexual development also occurred much more frequently than expected (three cases, adjusted O/E ratio = 198.2), as did the combination of omphalocele, spina bifida, and disorder of sexual development (five cases, adjusted O/E ratio = 162.3).

A post-hoc review of these combinations was conducted by two medical geneticists to consider if any combinations represented hallmark features of common syndromes. For example, we were particularly interested in identifying any combinations suggestive of the

OEIS complex. Our clinical review also included consideration of defect combinations that seemed unexpected, such as defects in organ systems with different embryologic/developmental origins.

Upon review of the individual clinical text descriptions for each co-occurring birth defect, three of 115 unique cases (2.6%) among the top combinations in the main analyses of omphalocele had text descriptions highly suggestive of OEIS (i.e., all four hallmark features). An additional six cases (5.2%) among the top combinations in the main analyses of omphalocele had OIS (i.e., three features). To better understand how the inclusion of these cases affected our main analyses, we repeated our analyses after excluding these nine cases for which text fields in the TBDR (e.g., procedure notes) were highly suggestive of OEIS. Specifically, the sensitivity analysis excluded cases with text mentioning cloacal exstrophy (e.g., without BPA codes 751.55 and 756.79), as well as cases with a combination of defects that included omphalocele, imperforate anus, and spinal defects (OIS).

Upon exclusion of these cases, nearly all combinations that involved spina bifida or atresia and stenosis of the large intestine rectum and anal canal were no longer present in the top combinations (as indicated in Table 5 footnote). Otherwise, the top combinations and ranks were similar to those among the main analysis. For example, the top patterns included omphalocele and (a) disorder of sexual development, other anomalies of the lower limb including pelvic girdle (e.g., rotational abnormality of the pelvis); (b) microcephalus, a disorder of sexual development; (c) craniorachischisis; (d) persistent omphalomesenteric duct; and (e) other anomalies of the aorta, anomalies of gallbladder bile ducts and liver.

4 | DISCUSSION

We report on the patterns of birth defects that co-occurred with gastroschisis and omphalocele more often than expected in a large, population-based registry. While previous studies have described simple co-occurrence patterns (i.e., two-way combinations), there have been few studies on complex (three-way or greater) patterns of defects co-occurring with gastroschisis or omphalocele utilizing population-based methods (summarized in Table S1). We used a method based on comparing the observed-to-expected proportion of infants with co-occurring birth defects (Benjamin et al., 2019), which allowed for a framework to compute up to five-way combinations of a large number of birth defect categories. We observed patterns of non-syndromic birth defect co-occurrence that were very different for gastroschisis and omphalocele. While co-occurring defects were found in 26% of cases with gastroschisis, 56% of cases with omphalocele had co-occurring defects. This difference in defect co-occurrence was consistent with previous estimates (range: 11–32% for gastroschisis and 54–80% for omphalocele, Table S1) (Benjamin & Wilson, 2014; Calzolari et al., 1995; Forrester & Merz, 2008; Hwang & Kousseff, 2004; Mayer et al., 1980; Murphy et al., 2007).

In our study, most of the gastroschisis combinations that occurred much more frequently than expected included gastrointestinal defects. This was consistent with previous literature that has reported that gastrointestinal-related defects are the most common birth defects associated with gastroschisis (Fisher et al., 1996; Henrich et al., 2008; Ledbetter, 2006;

Mayer et al., 1980; Stoll et al., 2008). Such conditions (e.g., intestinal atresia and malrotation) are often seen with gastroschisis but are widely regarded as being secondary to or a component of gastroschisis rather than being unrelated “primary” defects. For example, atresia of the ileum is a birth defect affecting the small intestine that completely obstructs the lower part of the intestines. Since gastroschisis involves the development of the bowel outside of the body and in direct contact with amniotic fluid, it is not uncommon for the intestines and related organs to become irritated or damaged (U.S. National Institutes of Health National Library of Medicine, 2019). Thus, it would be expected that atresia of the ileum and other gastrointestinal-related defects would frequently co-occur with gastroschisis. In fact, the decision to include these defects as potential separate co-occurring defects in both our study and past studies may be debatable and would result in higher estimates of the proportion of non-isolated versus isolated gastroschisis.

Outside of gastrointestinal-related defects co-occurring with gastroschisis, cardiovascular, and kidney anomalies were present among many of the combinations with large adjusted O/E ratios, though few of these combinations had adjusted O/E ratios higher than 40. These findings support those from previous studies, which also found cardiovascular and kidney anomalies to be among the most frequent defects associated with gastroschisis (Benjamin & Wilson, 2014; Hwang & Kousseff, 2004; Mastroiacovo et al., 2007; Stoll et al., 2008). A review of all the corresponding individual-level data did not reveal further explanation (e.g., obvious known patterns or undiagnosed syndromes). It is unclear why these defects seem to co-occur with gastroschisis more often than expected, and this could suggest that gastroschisis may have some degree of etiologic overlap with these defects among some individuals.

There were few brain-related anomalies (e.g., microcephalus; congenital hydrocephalus; reduction deformities of the brain) that frequently co-occurred with gastroschisis. Although there are limited data in this area, some studies have proposed that gastroschisis may be the result of vascular events that cause thrombosis of fetal vessels (Folkerth et al., 2013; Lubinsky, 2019). This mechanism might explain the concurrent disruption of the fetal abdominal wall as well as hypoxic-ischemic brain injury and related defects (Burge & Ade-Ajayi, 1997; Folkerth et al., 2013; Lubinsky, 2014, 2019; Raveenthiran, 2012).

For omphalocele, many defect combinations among the highest adjusted O/E ratios included spina bifida, atresia and stenosis of the large intestine rectum and anal canal (e.g., imperforate anus), and disorder of sexual development (e.g., genital defects). A number of combinations also involved permutations of these defects along with lower limb defects (e.g., clubbed foot, likely secondary to spina bifida). Although we had excluded subjects with documented diagnoses of known syndromes and complexes (including OEIS complex) in the registry, these patterns seemed suggestive of the OEIS complex, and we suspect that some of these cases had undiagnosed OEIS. For example, it is possible that OEIS was either diagnosed after the first year of life (and therefore not documented in the registry) or that OEIS diagnosis records were missing from the registry for these cases. In fact, from our review of individual-level clinical data, we also observed nine cases with omphalocele, spina bifida, and atresia and stenosis of the large intestine rectum without a specific diagnosis of OEIS complex listed, and two of these cases also had text descriptions of cloacal exstrophy.

Subsets of these defects among our top results, in combination with other gastrointestinal defects, spinal defects, renal defects, and/or bladder exstrophy, were likely at least partially explained by undocumented OEIS, though we cannot rule out the possibility that some cases may have had a subset of OEIS features but did not meet the full, traditional OEIS definition (e.g., non-malformed cloaca). A less severe continuum of birth defects known as exstrophy-epispadias complex has been described (a spectrum ranging in severity from epispadias and exstrophy of the bladder and/or cloacal exstrophy to subsets of OEIS complex features) (Ebert, Reutter, Ludwig, & Rosch, 2009; Keppler-Noreuil, 2001; Smith, Chambers, Furness, & Haan, 1992). In the absence of cloacal exstrophy or full OEIS, some observed combinations may have been suggestive of this clinical spectrum.

In analyses primarily related to specific known defect co-occurrence patterns (e.g., OEIS, Coloboma, Heart anomaly, choanal Atresia, Retardation of growth and development, and Genital and Ear anomalies [CHARGE]), Kallen et al. reported on a small number of pairwise and three-way associations involving omphalocele among data from a four international birth defect surveillance systems (Kallen et al., 1999; Kallen, Castilla, Robert, Mastroiacovo, & Kallen, 2000). Specifically, there was a strong association between omphalocele and the pairwise combination of spina bifida and anal atresia (odds ratio = 12.7, 95% confidence interval [CI] = 6.2–26.0) (Kallen et al., 2000). They also reported an odds ratio of 86.4 (95% CI = 18.4–96.5) for the association between omphalocele and the two-way combination of spina bifida and bladder exstrophy. Similar to our results, these combinations seemed suggestive of the OEIS complex. Another study assessed data on infants registered in the Metropolitan Atlanta Congenital Defects Program and used log-linear models to test for two-way and three-way associations among seven specific birth defects (Beaty, Yang, Khoury, Harris, & Liang, 1991), including omphalocele. A strong association was reported between omphalocele and anal-rectal atresia, which may also be suggestive of the OEIS complex. There was also a significant association between the combination of omphalocele, neural tube defects, and cleft lip with or without cleft palate. (Beaty et al., 1991; Oyen, Boyd, Poulsen, Wohlfahrt, & Melbye, 2009). These defects were also among the top combinations in our data.

Among our results, certain defects among the top combinations may have been secondary to omphalocele. Omphalocele is associated with intestinal malrotation and other intestinal problems (e.g., intestinal atresia) (Ford, Senac Jr., Srikanth, & Weitzman, 1992; Hsu et al., 2002). Depending on the size of the omphalocele, it can also cause the displacement of other organs (Dunn & Fonkalsrud, 1997; Towne, Peters, & Chang, 1980). Thus, anomalies of the diaphragm, anomalies of gallbladder bile ducts and liver, and other anomalies of ribs and sternum may have been secondary to omphalocele. In line with previous literature, heart defects were also found to commonly co-occur with omphalocele among our top combinations (Benjamin & Wilson, 2014; Hwang & Kousseff, 2004; Mastroiacovo et al., 2007; Mayer et al., 1980; Murphy et al., 2007). Since the development of both the heart and midgut occurs concurrently (at about 8 weeks into pregnancy), it is possible that shared etiologic mechanisms may be involved (Ayub & Taylor, 2019), though it is unclear what those specific mechanisms might be. There were also unexpected defects involving the head and brain present among the top combinations. Since syndromic cases (e.g., trisomies 13 and 18) were excluded from analysis, it is unclear why these combinations were present among

the top combinations and future work to confirm and better understand these combinations may be helpful.

One major strength of our study was our comprehensive and agnostic analytic approach involving a large number of complex combinations. We utilized a very large population-based, state-wide registry, which spanned a 16-year time period. Another strength was the use of BPA codes, which allowed for differentiation between gastroschisis and omphalocele, which is not possible in some versions of the International Classification of Diseases (ICD) codes.

There were some limitations to our study. The TBDR probably under-ascertains terminated pregnancies. For example, some cases resulting in a non-live birth are not seen in hospitals, where the TBDR focuses its surveillance, and TBDR staff do not routinely collect data in small clinics and physician's offices that perform terminations (Parks, Canfield, & Ramadhani, 2011). Because surveillance for deliveries of less than 20 weeks in Texas is limited, our results may not be generalizable to earlier deliveries less than 20 weeks (Ethen & Canfield, 2002; Parks et al., 2011). However, results from our sensitivity analyses among liveborn cases are consistent with the notion that potentially missed terminated cases would not have had a major impact on our results.

Although all syndromic cases with records of diagnoses by age one documented in the TBDR were excluded from the analysis, there were likely some cases with undocumented syndromes and complexes in the analysis that should have also been excluded, as noted above. This is a common limitation in birth defect registry analyses, and our results highlight this analytic challenge. We could not rule out the possibility of some degree of incomplete data (e.g., missing birth defects). Further, we did not have systematic information about the size or severity of the diagnosed defects. As there is no standard birth defect categorization system for this type of large-scale analysis, we used a four-digit BPA-based categorization system, but alternative categorization systems could have been considered, which might have resulted in certain categories being lumped together or split up. In addition, omphalocele is a component of Beckwith-Wiedemann syndrome, which is known to be positively associated with some types of artificial reproductive technology (Mussa et al., 2017). While every effort was made to exclude identified cases of Beckwith-Wiedemann, we were unable to control for assisted reproduction using TBDR data. The presence of combinations involving defects that may have been part of a developmental sequence (i.e., concurrent gastrointestinal defects) involving gastroschisis and omphalocele highlight this challenge.

In conclusion, we used CODA to characterize and describe two to five-way defect combinations occurring with gastroschisis and omphalocele more frequently than expected in a large population-based registry. Examining the clustering of birth defects can help identify specific patterns that may point to shared etiologies. Further research in this area could confirm our findings and reveal new patterns of co-occurring birth defects, which could be helpful in terms of further understanding both the determinants of and natural history for gastroschisis and omphalocele.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Characteristics of mothers of infants with gastroschisis and omphalocele in the Texas Birth Defects Registry, 1999–2014

TABLE 1

Characteristic	Non-isolated gastroschisis ^a (N = 789)	Isolated gastroschisis (N = 2,209)	Non-isolated omphalocele ^a (N = 404)	Isolated omphalocele (N = 316)
Maternal race/ethnicity				
White non-Hispanic	257 (32.7)	764 (34.6)	159 (39.6)	118 (37.5)
Black non-Hispanic	60 (7.6)	155 (7.0)	40 (10.0)	57 (18.1)
Hispanic	455 (57.9)	1,240 (56.2)	188 (46.8)	120 (38.1)
Other	14 (1.8)	49 (2.2)	15 (3.8)	20 (6.4)
Number of co-occurring Defects				
0	N/A	2,209 (100)	N/A	316 (100)
1	550 (69.7)	N/A	194 (48.0)	N/A
2	163 (20.7)	N/A	97 (24.0)	N/A
3	46 (5.8)	N/A	48 (11.9)	N/A
> 3	30 (3.8)	N/A	65 (16.1)	N/A
Maternal age (years)				
< 20	318 (40.3)	882 (39.9)	51 (12.6)	38 (12.0)
20–24	333 (42.2)	908 (41.1)	110 (27.2)	76 (24.1)
25–29	92 (11.7)	300 (13.6)	93 (23.0)	92 (29.1)
30–34	32 (4.1)	89 (4.0)	79 (19.6)	63 (19.9)
> 34	14 (1.8)	30 (1.4)	71 (17.6)	47 (14.9)
Maternal education				
< high school	279 (37.1)	815 (38.7)	94 (26.3)	59 (21.8)
High school	288 (38.3)	760 (36.1)	114 (31.8)	77 (28.4)
> high school	186 (24.7)	530 (25.2)	150 (41.9)	135 (49.8)
Maternal prepregnancy body mass index (kg/m²)^b				
Underweight (<18.5)	48 (8.7)	117 (7.9)	13 (6.0)	6 (3.5)
Normal weight (18.5–<25)	386 (69.8)	985 (66.4)	104 (47.7)	79 (46.2)
Overweight (25–<30)	87 (15.7)	288 (19.4)	45 (20.6)	43 (25.2)
Obese (≥ 30)	32 (5.8)	94 (6.3)	56 (25.7)	43 (25.2)
Infant sex				

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Characteristic	Non-isolated gastroschisis ^a (N = 789)	Isolated gastroschisis (N = 2,209)	Non-isolated omphalocele ^a (N = 404)	Isolated omphalocele (N = 316)
Male	402 (51.3)	1,170 (53.1)	219 (54.8)	160 (52.1)
Female	380 (48.5)	1,030 (46.8)	173 (43.2)	146 (47.6)
Pregnancy outcome				
Live Birth	746 (94.6)	2,065 (93.5)	323 (80.0)	242 (76.6)
Fetal death	30 (3.8)	124 (5.6)	53 (13.1)	57 (18.0)
Induced termination of pregnancy	13 (1.7)	16 (0.7)	28 (6.9)	17 (5.4)
Birth year				
1999–2004	210 (26.6)	639 (28.9)	157 (38.9)	109 (34.5)
2005–2009	301 (38.1)	778 (35.2)	125 (30.9)	104 (32.9)
2010–2014	278 (35.2)	792 (35.9)	122 (30.2)	103 (32.6)

^aMore than one major birth defect present as grouped by the first four digits of the BPA code.

^bMaternal prepregnancy weight and height available beginning in 2005.

TABLE 2

Co-occurring defects among cases with non-syndromic gastroschisis ($N = 789$) ordered by frequency, Texas Birth Defects Registry, 1999–2014

Defect ^a	No. of cases	Percent co-occurrence with non-syndromic gastroschisis
Atresia and stenosis of small intestine	146	18.5
Ostium secundum type atrial septal defect	138	17.5
Anomalies of intestinal fixation	130	16.5
Atresia and stenosis of large intestine rectum and anal canal	77	9.8
Obstructive defects of renal pelvis and ureter	76	9.6
Other anomalies of intestine (e.g., microcolon)	68	8.6
Ventricular septal defect	51	6.5
Microcephalus	26	3.3
Other deformities of feet (e.g., clubfoot, NOS ^b)	26	3.3
Congenital hiatus hernia	24	3.0
Other anomalies of aorta (e.g., narrowing of aorta)	21	2.7
Other specified anomalies of ureter (e.g., duplex right renal collecting system)	20	2.5
Anomalies of gallbladder bile ducts and liver	16	2.0
Other specified anomalies of brain (e.g., subependymal cyst)	16	2.0
Congenital hydrocephalus	13	1.6
Reduction deformities of brain	12	1.5
Anomalies of pulmonary artery	12	1.5
Other specified anomalies of unspecified limb (e.g., contractures of individual joints)	11	1.4
Other specified anomalies of the heart (e.g., ventricular septal thickening)	11	1.4
Other specified anomalies of kidney (e.g., enlarged kidney)	10	1.3
Other anomalies of the lower limb including pelvic girdle (e.g., bilateral large foot)	10	1.3
Cleft lip with or without cleft palate	9	1.1
Cystic kidney disease (e.g., cystic dysplasia kidney)	8	1.0
Congenital hypertrophic pyloric stenosis (e.g., pylorospasm)	8	1.0
Multiple congenital anomalies (e.g., NOS ^b)	7	0.9

^aFull range of BPA codes is listed in Table S2.

^bNOS, not otherwise specified.

TABLE 3

Co-occurring defects among cases with non-syndromic omphalocele ($N = 404$) ordered by frequency, Texas Birth Defects Registry, 1999–2014

Defect ^a	No. of cases	Percent co-occurrence with non-syndromic omphalocele
Ostium secundum type atrial septal defect	120	29.7
Ventricular septal defect	73	18.1
Obstructive defects of renal pelvis and ureter	40	9.9
Atresia and stenosis of large intestine rectum and anal canal	30	7.4
Other deformities of feet (e.g., clubfoot, NOS ^b)	26	6.4
Other specified anomalies of the heart (e.g., ventricular septal thickening)	24	5.9
Anomalies of spine	23	5.7
Anomalies of diaphragm	22	5.4
Other anomalies of aorta (e.g., narrowing of aorta)	22	5.4
Spina bifida	20	5.0
Other anomalies of ribs and sternum (e.g., less than 12 rib pairs)	17	4.2
Atresia and stenosis of small intestine	17	4.2
Other anomalies of intestine (e.g., short colon)	17	4.2
Renal agenesis and dysgenesis	16	4.0
Disorder of sexual development	15	3.7
Anomalies of intestinal fixation	15	3.7
Tetralogy of Fallot	15	3.7
Anomalies of great veins	15	3.7
Other unspecified anomalies of face and neck (e.g., microstomia)	14	3.5
Microcephalus	14	3.5
Anomalies of pulmonary artery	13	3.2
Persistent omphalomesenteric duct	12	3.0
Anomalies of gallbladder bile ducts and liver	12	3.0
Cleft lip with or without cleft palate	12	3.0
Anencephalus	11	2.7

^aFull range of BPA codes is listed in Table S2.

^bNOS, not otherwise specified.

Co-occurring defect combinations among cases with non-syndromic gastroschisis (N = 789) with adjusted O/E^a ratio > 10, Texas Birth Defects Registry, 1999–2014^b

TABLE 4

Defects	Adjusted O/E ^a ratio	No. of co-occurring cases
Anomalies of pulmonary artery; congenital hiatus hernia	134.3	3
Atresia and stenosis of the small intestine; anomalies of intestinal fixation; other anomalies of the intestine (e.g., short colon)	124.3	9
Congenital hiatus hernia; anomalies of intestinal fixation	107.4	6
Atresia and stenosis of small intestine; other anomalies of intestine	50.2 ^c	31
Atresia and stenosis of the small intestine; atresia and stenosis of the large intestine rectum and anal canal; other anomalies of the intestine	49.1	4
Atresia and stenosis of the small intestine; atresia and stenosis of the large intestine rectum and anal canal; anomalies of intestinal fixation	43.9	3
Atresia and stenosis of the small intestine; atresia and stenosis of large intestine rectum and anal canal	43.2 ^c	22
Atresia and stenosis of small intestine; other anomalies of intestine; obstructive defects of renal pelvis and ureter	36.4	3
Atresia and stenosis of small intestine; anomalies of intestinal fixation	30.0 ^c	19
Anomalies of intestinal fixation; other anomalies of intestine	28.1 ^c	13
Congenital hiatus hernia	27.0 ^c	24
Atresia and stenosis of small intestine	17.8 ^c	146
Anomalies of intestinal fixation; anomalies of gallbladder bile ducts and liver	17.8	3
Anomalies of intestinal fixation	17.4 ^c	130
Atresia and stenosis of large intestine rectum and anal canal; anomalies of intestinal fixation	16.5 ^c	7
Exstrophy of urinary bladder	15.8	6
Atresia and stenosis of large intestine rectum and anal canal; other anomalies of intestine	15.3 ^c	12
Other specified anomalies of esophagus	14.9	3
Anomalies of intestinal fixation; other specified anomalies of the kidney	12.9	3
Atresia and stenosis of small intestine; obstructive defects of renal pelvis and ureter	11.1 ^c	8

^aO/E, observed-to-expected.

^bCombinations with <3 cases were not represented.

^cDenotes defect combinations accounted for in higher-order combinations (e.g., the combination of defects A and B accounted for in the higher-order combination of defects A, B, and C).

Co-occurring defect combinations among cases with non-syndromic omphalocele ($N = 404$) with adjusted O/E^a ratio > 10, Texas Birth Defects Registry, 1999–2014^b

TABLE 5

Defects	Adjusted O/E ^a ratio	No. of co-occurring cases
Atresia and stenosis of the large intestine rectum and anal canal; disorder of sexual development; other deformities of feet (e.g., clubfoot, not otherwise specified)	199.3 ^c	3
Spina bifida; atresia and stenosis of the large intestine rectum and anal canal; disorder of sexual development	198.2 ^c	3
Spina bifida; disorder of sexual development	162.3 ^{c,d}	5
Disorder of sexual development; other anomalies of the lower limb including pelvic girdle	136.7	4
Spina bifida; atresia and stenosis of the large intestine rectum and anal canal; obstructive defects of renal pelvis and ureter	102.6 ^c	4
Spina bifida; atresia and stenosis of the large intestine rectum and anal canal; other deformities of feet	98.2 ^c	4
Microcephalus; disorder of sexual development	92.1	3
Atresia and stenosis of large intestine rectum and anal canal; disorder of sexual development	75.1 ^c	5
Spina bifida; atresia, and stenosis of large intestine rectum and anal canal	62.3 ^{c,d}	9
Craniorachischisis	61.5	3
Disorder of sexual development; other deformities of feet	58.7 ^{c,d}	3
Persistent omphalomesenteric duct	58.0	12
Obstructive defects of renal pelvis and ureter; anomalies of adrenal gland	56.5 ^c	3
Spina bifida; other specified anomalies of ureter; Varus (inward) deformities of feet	46.3 ^c	3
Other anomalies of the aorta; anomalies of gallbladder bile ducts and liver	41.6	3
Anomalies of intestinal fixation; renal agenesis and dysgenesis	40.9 ^c	4
Spina bifida; other anomalies of intestine	29.6 ^c	3
Microcephalus; atresia and stenosis of the large intestine rectum and anal canal	29.5 ^c	5
Atresia and stenosis of the large intestine rectum and anal canal; other deformities of feet	28.8 ^d	7
Other deformities of feet; anomalies of spine	23.8	7
Renal agenesis and dysgenesis; anomalies of diaphragm	23.7	3
Anomalies of gallbladder bile ducts and liver; obstructive defects of renal pelvis and ureter	23.0 ^c	3

Defects	Adjusted O/E ^a ratio	No. of co-occurring cases
Exstrophy of urinary bladder	20.7	4
Other unspecified anomalies of face and neck; other deformities of feet	20.3 ^{c,d}	3
Disorder of sexual development	19.8 ^d	15
Other specified anomalies of the heart; anomalies of the diaphragm	19.6	4
Other anomalies of the lower limb including pelvic girdle; anomalies of the spine	18.3	4
Spina bifida; renal agenesis and dysgenesis	17.9 ^c	3
Anomalies of urachus	17.4	8
Other specified anomalies of the brain; ventricular septal defect; ostium secundum type atrial septal defect	16.7	3
Anomalies of great veins; anomalies of intestinal fixation	16.1	3
Ventricular septal defect; anomalies of diaphragm	14.5	6
Other specified anomalies of ureter; Varus (inward) deformities of feet	14.4 ^{c,d}	3
Other anomalies of the intestine; obstructive defects of renal pelvis and ureter	14.1	5
Other anomalies of the aorta; anomalies of intestinal fixation	13.1	3
Multiple congenital anomalies	12.7	5
Spina bifida; anomalies of spine	12.2 ^c	3
Anomalies of intestinal fixation; obstructive defects of renal pelvis and ureter	12.0	3
Transposition of great vessels; ventricular septal defect; anomalies of pulmonary valve; other specified anomalies of the heart	11.2	3
Other unspecified anomalies of face and neck; ventricular septal defect	11.1	4
Atresia and stenosis of the large intestine rectum and anal canal; other anomalies of the intestine	10.6	4
Ventricular septal defect; atresia and stenosis of small intestine	10.4	3
Transposition of great vessels; ostium secundum type atrial septal defect; anomalies of pulmonary valve; other specified anomalies of the heart	10.1	4

^aO/E, observed-to-expected.

^bCombinations with <3 cases were excluded.

^cAfter conducting a sensitivity analysis with exclusion of cases highly suggestive of OEIS or OIS, this combination was no longer among the top results.

^dDenotes defect combinations accounted for in higher-order combinations (e.g., the combination of defects A and B accounted for in the higher-order combination of defects A, B, and C).