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A Machine Learning Approach to Investigate Epidemiologic Risk Factors of Gastroschisis and Omphalocele in Iowa, 1997-2011

By

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Degree to be awarded: Master of Public Health

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A Machine Learning Approach to Investigate Epidemiologic Risk Factors of Gastroschisis and Omphalocele in Iowa, 1997-2011

By

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Abstract

A Machine Learning Approach to Investigate Epidemiologic Risk Factors of Gastroschisis and Omphalocele in Iowa, 1997-2011

By Sitong Chen

BACKGROUND: Gastroschisis and omphalocele are common abdominal wall birth defects with prevalence (per 10,000 live births) in the United States of 4.3 and 2.6, respectively. Risk factors for these defects include gene variants and environmental (non-genetic) exposures. To date, there has been very limited use of machine learning to explore environmental risk factors associated with both gastroschisis and omphalocele. Using a retrospective population-based case-control study design, this study applied a contrast machine learning method to evaluate the relationships between several selected child and maternal risk factors and gastroschisis and omphalocele.
METHODS: Data for the current study were obtained from the Iowa Center of the National Birth Defects Prevention Study (NBDPS). Children diagnosed with gastroschisis or omphalocele (cases) and unaffected children (controls) were delivered from 1997-2011. Maternal NBDPS interview data for 133 children with gastroschisis and 31 children with omphalocele and 1,300 control children comprised the analytic sample. Gradient boosted regression was applied to evaluate selected child and maternal risk factors for predicting and classifying a delivery as being a case child (i.e., diagnosed with gastroschisis or omphalocele) or a control child. Variable importance and partial dependence plots were generated to examine effectiveness and classification probabilities of each risk factor.
RESULTS: For the 164 cases (gastroschisis and omphalocele) combined, important predictors with higher classification probabilities associated with being a case child were maternal age <20 years at delivery, high school or less education at delivery, multigravida, pre-pregnancy body mass index <18.5 kg/m^2, periconceptional (one month prior through the third pregnancy month) active smoking, infection, and folic acid-containing supplementation. Child sex, maternal race/ethnicity, fever, chronic hypertension, chronic diabetes, periconceptional alcohol consumption and cannabis use were not identified as important predictors.
CONCLUSIONS: The current study is only the second to use a machine learning approach to examine risk factors for gastroschisis and first to examine those factors for omphalocele. Findings associated with increased risk of these defects observed in the current study tended to support some but not all factors identified using more traditional epidemiologic analyses. Future studies should aim to increase sample sizes to improve the sensitivity and accuracy of this analysis.

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KEYWORDS AND ABBREVIATIONS

Keywords: public health; epidemiology; gastroschisis; omphalocele; machine learning; birth defects; abdominal wall defects; pregnancy; gradient boosting; partial dependency.

Abbreviations:

aOR	adjusted odds ratio
BMI	body mass index
CI	confidence interval
cOR	crude odds ratio
EDD	estimated date of delivery
EUROCAT	European congenital anomalies registry network
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
NBDPN	National Birth Defects Prevention Network
NBDPS	National Birth Defects Prevention Study
OR	odds ratio
PR	prevalence ratio
ROC AUC	Two-dimensional area underneath the entire receiver operating characteristic curve
RR	rate ratio
SB	spina bifida
US	United States

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CHAPTER I

LITERATURE REVIEW

Gastroschisis and omphalocele are the two most common musculoskeletal defects affecting the abdominal wall. Gastroschisis is characterized by a small opening usually to the right of the umbilicus which eviscerates abdominal organs [1] and is categorized as "simple" or "complex" based on the presence or absence of intestinal atresia, stenosis, perforation, necrosis, or volvulus [2]. Gastroschisis usually presents as an isolated defect with an estimated 7% of affected individuals diagnosed with other structural birth defects [3], including central nervous system, cardiovascular, gastrointestinal, urogenital, and musculoskeletal defects [4, 5]. By comparison, omphalocele is a midline abdominal wall defect in which all or part of the small intestine or other internal organs exist outside of the abdomen in a membranous sac [1, 6]. Omphalocele is categorized into three types: ruptured omphalocele with exposed liver, giant omphalocele in which the sac measures ≥5 cm at birth and contains at least 75% of the liver, and small omphalocele in which the liver is absent from in the sac [7-9]. Nearly 80% of omphalocele cases are estimated to present with other birth defects, including chromosomal, cardiovascular, gastrointestinal, and urogenital defects [5, 10-12].

Diagnosis and Management

Gastroschisis: Prenatal diagnosis of gastroschisis includes maternal serum alpha fetoprotein (AFP) screening and obstetric ultrasound [13]. Ultrasound has been reported to detect 82% of isolated cases, 100% of syndromic cases, and 87% of gastroschisis cases associated with other structural defects [14]. Except for some case reports of first trimester diagnosis, gastroschisis is most often diagnosed during the second trimester [15,

16]. Following diagnosis, expectant mothers are often referred to a multidisciplinary prenatal care team for confirmatory testing and joint planning to facilitate sustaining the pregnancy to term delivery [17]. Fetuses with gastroschisis have been recommended to be monitored with serial growth ultrasound for the risk of intrauterine growth restriction (fetal weight <10th percentile) and to be tested for antepartum fetal heart rate during 32-34 weeks of gestation, in the absence of other indications for earlier evaluation [18]. Prenatal diagnosis also contributes greatly to postnatal management, including identifying reliable predictors of postnatal outcomes, and the selection of infants for novel therapies [13]. Following delivery, the immediate treatment for infants with gastroschisis focuses on physiological support and bowel protection to prevent progression of the intestinal injury due to exposure and mechanical irritation, along with reducing heat and water loss in infants [19]. An infant with gastroschisis is typically transferred to a neonatal intensive care unit for surgery to close the defect. Surgical closure options include primary closure, silo placement with staged closure, and sutureless closure, which all aim to reduce viscera and avoid abdominal compartment syndrome [20].

***Omphalocele*:** Omphalocele is diagnosed based on the presence of an anterior abdominal wall defect with herniation of abdominal contents into the umbilical stalk; prenatally it is often diagnosed late first trimester to mid-second trimester using high resolution ultrasound [21-23]. Prenatal ultrasound after the first trimester can identify most fetuses with omphalocele and accurately distinguish omphalocele from gastroschisis [22]. Examples of other approaches to detect omphalocele include an elevated maternal serum AFP level that can lead to a comprehensive ultrasound evaluation and fetal magnetic

resonance imaging [24, 25]. Prenatal ultrasound diagnosis will lead to counseling of the family, appropriate obstetric follow-up, and a smooth introduction into postnatal care [22]. Fetuses with omphalocele diagnosed prenatally have been shown to experience lower mortality (21.7%), compared to those (63.3%) identified postnatally [10]. Initial management of a newborn with omphalocele requires assessment of cardiopulmonary conditions to identify if there is unsuspected pulmonary hypoplasia which requires immediate intubation and ventilation. Following this assessment, a comprehensive search for additional structural defects is conducted [21]. The goal in managing omphalocele in the newborn is the reduction of abdominal contents and closure of the abdominal wall defect after the infant has been medically stabilized, without causing excessive intra-abdominal pressure or abdominal wall tension [10, 21]

Cost of Care

Gastroschisis: Limited data are available on cost of care for gastroschisis. The most recent study in the United States (US) study identified estimated mean hospital charges associated with this defect were $153,993 (95%CI=153,776-154,275) for services rendered in 2003 [26].

Omphalocele: Similarly, data on cost of care for omphalocele are limited with the aforementioned study having estimated mean hospital charges associated with omphalocele in 2003 to be $141,724 (95%CI=128,514-154,934) [26]

Prevalence

Gastroschisis: In a recent population-based report, Stallings et al. (2019) analyzed data for 2012-2016 births from 42 population-based surveillance programs in the US National Birth Defects Prevention Network (NBDPN) and observed an estimated prevalence of

gastroschisis of 4.3 per 10,000 live births (95%CI=4.1-4.4) [27]. A comparison of NBDPN data from 1999-2001 with those from 2005-2007 showed that the prevalence of gastroschisis increased by 83% across 11 surveillance programs [28]. For mothers <20 years of age, the average annual percent increase was 10.1% overall; estimates examined for these women by maternal race/ethnicity showed average annual percent increases of 9.2%, 25.7%, and 7.7% among non-Hispanic white, non-Hispanic black, and Hispanic mothers, respectively [28]. A recent report from the population-based European congenital anomalies registry network (EUROCAT) estimated the prevalence of gastroschisis during 1990-2019 to be 2.52 per 10,000 live births with increasing prevalence during that time period [29].

Omphalocele: NBDPN data (1995-2005) across 12 surveillance programs showed that the estimated prevalence of omphalocele was 1.92 per 10,000 live births, with no consistent temporal trend identified [30]. However, NBDPN data (1999-2007) from 11 surveillance programs, including data for some programs (Arizona, Colorado, Georgia, and New York) overlapping with those used by Marshall et al., 2015, reported an 11% increase in omphalocele prevalence during the study period [28]. Other studies using NBDPN data (2010-2016) reported prevalence estimates ranging from 2.1-2.5 per 10,000 live births [27, 31]. A multi-national study (2000-2012) from several member surveillance programs of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) estimated the prevalence of omphalocele to be 2.6 per 10,000 births (95%CI=2.5-2.7), with no temporal patterns identified [32]. Data from EUROCAT (1990-2019) estimated the prevalence of omphalocele to be 2.64 per 10,000 births with no temporal patterns identified [29].

Mortality

Gastroschisis: Data from the National Center for Health Statistics (Center for Disease Control and Prevention) for all US registered births (2009-2013) showed the rate of infant mortality from gastroschisis to be 5.9%, with about 40% of these deaths occurring on the day of delivery [33]. The study also reported that despite increasing prevalence of gastroschisis during this time period, the mortality rate attributed to this defect remained stable [33]. A multi-center study from eight US tertiary care centers (2005-2012) reported a mortality rate of 5% at hospital discharge among all gastroschisis cases [34], whereas data from the Vermont Oxford Network (2009-2014) showed that the overall one-year mortality of infants born with gastroschisis was 2.2% [35]. A large international research collaborative of consecutive patients with gastroschisis followed for a minimum of 1 month during October 2018 – April 2019 reported wide variation in mortality outcomes by country income status, with 90%, 32%, and 1.4% mortality in low-, middle-, and high-income countries, respectively [36]. Mortality rates for gastroschisis have also been shown to differ by simple and complex case status, with infants diagnosed with complex gastroschisis experiencing higher mortality due to bowel complications, including intestinal atresia, perforation, or necrotic segments of volvulus [33, 37].

Omphalocele: The multi-national study from ICBDSR mentioned above reported an overall mortality rate of 32% (95%CI=30-34%) for omphalocele; most deaths occurred in the neonatal period and among children with multiple birth defects or syndromic omphalocele [32]. A study from nine US pediatric centers (2005-2013) estimated an overall mortality of 19%/13% among those with small/median omphalocele and 24% among those with large/giant omphalocele [38]. Infants with isolated omphalocele

experienced approximately 10% mortality by age 1-year but those with co-occurring congenital heart defects and central nervous system defects experienced 2.4- and 2.9-times higher likelihood of death, respectively [30]. Developments in surgical and neonatal care have improved survival of infants with omphalocele, but they still face a significant risk of respiratory failure, prolonged intensive care stay, poor feeding and growth, and neurodevelopmental delay [39, 40].

Embryology and Development of Gastroschisis and Omphalocele

Gastroschisis: To date, four main embryologic hypotheses have been proposed for gastroschisis. Duhamel [41] hypothesized that gastroschisis occurs when the mesoderm fails to form in the body wall, whereas Shaw [42] hypothesized that gastroschisis occurs due to rupture of the amniotic membrane around the umbilical ring with subsequent herniation of the bowel. DeVries [43] hypothesized that gastroschisis results from the weakened body wall and gut herniation due to abnormal involution of the right umbilical vein. Hoyme and colleagues [44] hypothesized that gastroschisis occurs due to the disruption of omphalomesenteric artery, which leads to subsequent body wall damage and gut herniation. More recently, Feldkamp et al. [45] proposed that gastroschisis results from an abnormal folding of the body wall, leading to a ventral body wall defect through which the gut herniates and presents clinically as gastroschisis.

Omphalocele: The term "gastroschisis" was assigned by Johns in 1946 to all manners of abdominal defects until 1953 at which time omphalocele was separated from gastroschisis by Moore and Strokes [46]. Omphalocele is thought to arise from a primary malformation of the ventral wall of the embryo, but the mechanisms involved remain unclear. Also, the lack of an appropriate animal model for omphalocele has limited the

understanding of precise embryological steps [47]. Gross and Blodgett [48] hypothesized that omphalocele results from arrested development of the body cavity between the 8th and 12th weeks of gestation, preventing the herniated midgut from recovery. A similar theory advanced by Gary and Skandalakis [49] describes omphalocele as arising from developmental arrest when there is a physiologic herniation of the gut in the umbilical coelom. Margulies [50] hypothesized that the development of omphalocele before the 3rd week of gestation occurs during the process of formation of the supra-umbilical part of the abdominal wall, either due to mesodermal transverse septum failure to unite with its amniotic covering or due to failure in proliferation of embryonic connective tissue in the transverse septum. A recent review of proposed mechanisms of embryology and development of omphalocele showed that many were based on clinical observations and little experimental evidence [51]. The review also concluded that the most widely accepted theory for development of omphalocele was a combination of embryonic dysplasia theory and malfunction of the ectodermal placodes [51].

Risk Factors

Gastroschisis and omphalocele have been associated with both genetic and environmental risk factors including genetic variants, chromosomal syndromes, child sex, child plurality, maternal race/ethnicity, maternal age at delivery, maternal education attainment, maternal pre-pregnancy body mass index (BMI), maternal folic acid fortification, parity, selected maternal medical conditions including fever, hypertension, diabetes, maternal smoking, alcohol and illicit drug use.

Genetic Risk Factors

Gastroschisis: Limited evidence summarized in a recent review [60] suggests genetic risk factors for gastroschisis, but findings are inconclusive. The recurrence risk for gastroschisis has been reported to range from 2.4-6.9% [61-71]. Several studies have also identified familial cases of gastroschisis suggesting an underlying genetic susceptibility for this defect, and associations with genetic variants [60, 65, 72-74]. As examples, a study by Makhmudi et al. [74] identified three common prothrombotic polymorphisms (MTHFR c.677C>T, F2 c.20210G>A, and F5 Leiden) elevated in frequency in 46 gastroschisis patients and reported a significant association between MTHFR c.677C>T and gastroschisis. Salinas-Torres et al. (2018) conducted a pooled analysis of studies of genetic variants associated with gastroschisis and reported significant associations with four single-nucleotide variants from three genes: rs4961(ADD1), rs5443(GNB3), rs1042713, and rs1042714 (ADRB2) [60]; each of these genes is related to blood pressure regulation and may play an important role of vascular disruption in the pathogenesis of gastroschisis.

Omphalocele: Omphalocele often presents with chromosomal defects, including Trisomy 13, 18, and 21 [53, 55, 63, 75-85]. A review of literature published between 1952 and 2008 identified 10 studies that reported trisomy 13, 18, and 21 as frequently diagnosed concurrently with omphalocele, with trisomy 18 being the most common [1]. In other chromosome abnormalities syndromes, Beckwith-Wiedemann syndrome was commonly diagnosed [1, 55, 86].

Child Sex

Gastroschisis: Child sex was not observed to be a risk factor for gastroschisis in several studies [87-91], although some studies reported an excess of male cases [92-94]. Pooled

analysis of available data from three studies identified in a systematic review of studies published from 1970-2017 reported an increased susceptibility to gastroschisis among males (percent of affected, adjusted for proband = 2.5%) compared to females (percent of affected, adjusted for proband = 1.3%) [60]. A recent international meta-analysis of the five largest studies for gastroschisis published through 2018 reported a higher prevalence among males compared to females (prevalence ratio (PR)=1.10, 95% CI=1.07-1.13) [95].

Omphalocele: A male excess among omphalocele cases has been well established [56, 77, 96-99] and supported by a recent meta-analysis of the five largest studies published through 2018 for this defect (PR=1.16, 95%CI=1.12-1.2) [95].

Child Phenotype

Gastroschisis: Gastroschisis most often presents without other birth defects or chromosomal defects [100-103]. Data from ICBDSR (1974-2004) showed that 2854 (85.9%) of 3322 gastroschisis cases presented as isolated [102]; a similar proportion (284/387; 84.5%) of isolated cases was reported by the Utah Birth Defect Network (1997-2011) [101], but a lower proportion (1,237/1,831; 68%) was reported by the Texas Birth Defects Registry (1999-2008) [100]. The study from ICBDSR also showed that 1.2% of infants with gastroschisis had chromosomal defects [102]. A study from the Northeastern French birth defects monitoring system (1979-2003) showed 83.3% (50/60) of gastroschisis cases were isolated [103]. Other clinical and epidemiologic studies reported infrequent presentation of chromosomal defects or single-gene disorders with gastroschisis [63, 75, 98].

Omphalocele: Omphalocele cases are less likely than gastroschisis cases to present as isolated [53, 100, 104]. NBDPN data for 2,308 cases (1995-2005) showed only 22%

(502/2308) presented as isolated [53]. A similar proportion (160/814; 20%) of isolated cases were reported from the Texas Birth Defects Registry (1999-2008) [100], but a somewhat higher proportion (79/207; 38%) was observed in nationwide Swedish population-based cohort (1997-2016) [104].

Child Plurality

Gastroschisis: NBDPN data (1995-2005) from 15 surveillance programs showed that multiple gestation pregnancies were less likely to be affected by gastroschisis compared with singleton pregnancies (adjusted PR=0.76, 95%CI=0.60-0.98) [105]. Similar findings were reported by the Texas Birth Defect Registry (1996-2002; PR=0.74; 95%CI=0.43-1.17) [89]. In contrast, analysis of NBDPS data (1997-2003) suggested that gastroschisis cases were more likely to be multiple gestation births (adjusted odds ratio (OR)=1.32; 95%CI=0.52-3.28) [56].

Omphalocele: Previous studies have reported that the prevalence of omphalocele was higher among multiple gestations compared to singletons [53, 55, 56, 63]. These studies included analysis of NBDPS data (1997-2003; adjusted OR=2.93, 95%CI=1.43-6.00) [56]; NBDPN data (1995-2005; adjusted PR=2.22, 95%CI=1.85-2.66) [53]; Florida birth defect surveillance program data (1992-1999; 9/127, 7.1%) [63] and Texas Birth Defect Registry data (1999-2004; PR=2.03; 95%CI=1.22-3.37) [55].

Maternal Race/Ethnicity

Gastroschisis: Several studies reported that black mothers have a lower risk of delivering a child with gastroschisis [106-111], but results are mixed for the association between gastroschisis and mothers of Hispanic ethnicity [53, 56, 75, 89, 111-114]. A recent meta-analysis that assessed 58 epidemiological studies from January 1990 – July 2018

concluded that there was a decreased risk of gastroschisis for infants born to black mothers compared with non-Hispanic white mothers (pooled relative risk (RR)=0.49; 95%CI=0.38-0.63), whereas no association was observed among Hispanic white mothers compared to non-Hispanic white mothers (pooled RR=1.00 ; 95% CI=0.85-1.18) [115].

Omphalocele: Findings are mixed for associations between maternal race/ethnicity and omphalocele [27, 75]. Analyses using New York State Congenital Malformations Registry data (1992-1999) showed that black infants had a 70% higher risk of omphalocele compared to white infants [75], but NBDPN data (2012-2016) showed a higher prevalence of omphalocele among infants born to Hispanic mothers and lower prevalence among those born to non-Hispanic black mothers [27].

Maternal Age

Gastroschisis: Younger maternal age is a well-established risk factor of gastroschisis [3, 4, 27, 53, 56, 75-77, 89, 106, 114, 116-130]. Detailed analyses of NBDPN data (1995-2005) showed that women younger than age 20 years were 7.2-times more likely to deliver offspring with gastroschisis compared with women 25-29 years of age (PR=7.18, 95%CI=6.51-7.92), and women 20-24 years of age were three times more likely to deliver offspring with gastroschisis (PR=3.25, 95%CI=2.95-3.58); additional analyses showed that as maternal age increased, risk of gastroschisis gradually reduced [105].

Omphalocele: Young [53, 75, 123] and advanced [53, 75] maternal age have been reported to be associated with omphalocele. Data from the Metropolitan Atlanta Congenital Defects Program (1968-2000) showed that young maternal age (14-17 year old) increased risks of omphalocele (OR=2.08, 95%CI=1.39-3.12) [123]. Data from the New York State Congenital Malformations Registry (1992-1999), showed the maternal

age distribution among omphalocele mother was U-shaped [75]. NBDPN data (1995-2005) showed a higher prevalence of omphalocele among infants born to older mothers (≥35 years) (PR=1.77, 95% CI= 1.54-2.04) as well as young mothers (<20 years) (PR=1.34, 95% CI=1.14-1.56) [53].

Maternal Education

Gastroschisis: Lower maternal education has been associated with an increased risk of gastroschisis [89, 94, 117, 131].

Omphalocele: The lone study identified for the relationship between maternal education and omphalocele reported no association [125].

Maternal Pre-Pregnancy BMI

***Gastroschisis*:** Women with a low BMI (<22kg/m^2) or being underweight have been reported to have an increased risk of delivering an offspring with gastroschisis [117, 130, 132], whereas those with BMI indicative of obesity had a lower risk of having their pregnancies affected by gastroschisis [91, 113, 133-135]. An analysis from the California Birth Defects Monitoring Program (1988-1990) showed that underweight mothers were at higher risk of gastroschisis (OR=3.2, 95%CI=1.4-7.3), but overweight mothers were at lower risk (OR=0.2, 95%CI=0.05-0.9) [132]. Maternal obesity was reported to be associated with a 60% to 83% reduction in the risk of gastroschisis [91, 133, 134], and a systematic review and meta-analysis of studies published from 1966 to 2008 concluded the risk of gastroschisis among obese mothers was significantly reduced (pooled OR=0.17; 95% CI=0.10-0.30) [134]. A recent Finnish study, examining births during 2004-2014, reported that maternal obesity significantly mitigated the risk of gastroschisis, regardless of maternal age or gestational diabetes [91]. In addition to obesity, Baer et al.

[133] observed overweight mothers had a 40% reduced risk of delivering a baby with gastroschisis compared to normal weight mothers.

Omphalocele: Being overweight and obese were reported to be associated with an increased risk of delivering a child with omphalocele [27, 135, 136]. Data from NBDPS (1997-2002) showed that increased maternal BMI (>30 kg/m^2) was associated with 63% higher risk of having a baby with omphalocele (adjusted OR=1.63; 95%CI=1.07-2.47) compared to normal weight mothers [135]. The Atlanta Birth Defects Risk Factors Surveillance Study reported that obese women (BMI≥30 kg/m^2) were 3.3-times more likely to have a baby with omphalocele compared with average-weight women [136]. Findings from an analysis of NBDPN data (2012-2016) also showed that mothers of infants with omphalocele were more likely to be overweight or obese [27].

Maternal Folic Acid Fortification

Gastroschisis: Early pregnancy maternal folic acid supplementation was associated with a 10% reduced risk of gastroschisis in offspring [137, 138]. In contrast, prevalence of gastroschisis in Canada showed a significant increase during the post-fortification compared to pre-fortification period; however, this increase paralleled that observed in several countries, as documented earlier [139].

Omphalocele: Canfield et al reported a 21% statistically significant reduction in birth prevalence of omphalocele post-food fortification in the US [140]. A small case-control study using data from New York State and examining single nucleotide polymorphisms in folate-related enzyme genes observed a thermolabile variant of MTHFR, 677→T to be positively associated with omphalocele, suggesting a protective mechanism through multivitamins with folic acid [141].

Parity

Gastroschisis: Several [91, 108, 142] but not all [113, 133] studies suggest nulliparity as a risk factor for gastroschisis. Analyses of Texas Birth Defect Registry data (1999-2003) showed nulliparous women were more likely to have a child with gastroschisis than women with two or more previous live births (adjusted PR=1.64, 95%CI=1.17-2.36) [108]. Similar findings were reported from NBDPS (1997-2007) (adjusted OR=1.77, 95%CI=1.46-2.14) [142] and an analysis from the Finnish Register of Congenital Malformations (2004-2014) (adjusted OR=2.00, 95%CI=1.29-3.11) [91]. In a study of all live births in California (2005-2010), Baer et al. [133] showed that the risk for gastroschisis in nulliparous women was confined to women over 20 years of age at term. A California NBDPS study (1997-2011) reported lower odds (adjusted OR=0.80, 95%CI=0.67-0.96) for gastroschisis among women aged 20 or older with higher parity [113].

Omphalocele: Findings are inconsistent for the association between parity and omphalocele [55, 56, 142, 143]. Texas Birth Defects Registry data (1999-2004) showed nonsyndromic omphalocele cases were significantly more common among nulliparous than multiparous women (adjusted PR=1.80, 95%CI=1.41-2.30) [55]. Decreased odds of omphalocele for multiparous women were reported from NBDPS (1997-2003) (adjusted OR=0.44, 95%CI = 0.30-9.65), controlling for maternal age [56]. Conversely, a different analysis of NBDPS data (1997-2007) showed an increased risk among both multiparous (adjusted OR=1.47, 95%CI=1.01-2.13) and nulliparous women (adjusted OR=2.33, 95%CI=1.68-3.22) [142]. A recent study from Finland (2004-2013) reported that nulliparity was not associated with omphalocele [143].

Selected Maternal Medical Conditions

Gastroschisis: Selected maternal medical conditions – such as episodes of fever; infections including kidney infection, bladder infection and urinary tract infections; and conditions, including gestational hypertension and gestational diabetes – have been examined for associations with gastroschisis [91, 133, 144-147]. Reported maternal fever during any time in pregnancy was not associated with the risk of gastroschisis among all live births in Spain (1976-1996) and a sample of live births in 15 cities across US and Canada (1995-2005)[144, 147]. NBDPS data (1997-2003) showed an increased risk of gastroschisis (adjusted OR=4.0; 95% CI=1.4-11.6) in infants born to mothers who self-reported a urinary tract infection during pregnancy, which included bladder or kidney infections, plus sexually transmitted infections [148]. Using data for all live births in California (2005-2010), Baer et al. [133] reported a positive association between urinary tract infections and gastroschisis among mothers <20 years of age (adjusted OR=1.4, 95%CI=1.1-1.9). A recent study conducted in Brazil (2013-2015) reported a 3-fold increase in risk of gastroschisis among infants born to mothers with urinary tract infections during pregnancy compared to those without infections [146]. Baer et al. [133] also identified that maternal gestational hypertension was associated with a reduced risk of gastroschisis (adjusted OR=0.6, 95% CI=0.4-0.9), and this reduced risk was observed across all maternal age groups. Gestational diabetes was reported to have an inverse effect on gastroschisis with a 50% reduction in risk in a study using data from the Finnish nationwide register [91].

Omphalocele: Previously published reports on maternal medical conditions and omphalocele are lacking.

Maternal Smoking, Alcohol, and Illicit Drug Use

Gastroschisis: Maternal smoking, alcohol, and illicit drug use during pregnancy have been reported to increase the risk of gastroschisis in offspring [54, 87, 113, 137, 149]. A recent meta-analysis of 29 studies published from 1990 to 2018 indicated maternal smoking, alcohol consumption, and illicit drug use during pregnancy were associated with an increased risk of gastroschisis with pooled risk ratios of 1.56 for maternal smoking; 1.39 for maternal alcohol consumption, and 2.14 for illicit drug use anytime during pregnancy [115]. An increased risk of gastroschisis associated with maternal smoking was also reported from a study in the United Kingdom (adjusted odds ratio = 2.7; 95%CI=1.1-6.8) [137]. However, a recent study of genomic deoxyribonucleic acid (DNA) methylation profiles in fetuses with gastroschisis reported no association between maternal smoking and alcohol consumption from one month before conception through the first trimester of pregnancy [150]. Multiple independent studies reported that the use of illicit drugs including cocaine, methamphetamines, and marijuana any time during pregnancy increased risk for gastroschisis [87, 94, 113, 151-154].

Omphalocele: Maternal smoking and alcohol consumption before and any time during pregnancy have been shown to be risk factors for omphalocele [56, 57, 155]. NBDPS data (1997-2003) showed no association between maternal exposure to light smoking (<1 pack/day) or moderate smoking (1 pack/day) and omphalocele; however, a strong positive association was noted for heavy smoking (>1 pack/day) (adjusted OR=4.26; 95% CI=1.58, 11.52) [56]. NBDPS data (1997-2003) also showed any maternal alcohol consumption 3 months before conception through each month until the end of pregnancy to have a positive association with omphalocele (adjusted OR=1.53; 95% CI=1.04, 2.25)

[56]. Another study with additional NBDPS data (1997-2005) reported a positive association between periconceptional alcohol consumption and omphalocele (OR=1.50, 95%CI=1.15-1.96) [54]. Research on illicit drug use and omphalocele is lacking.

Goal and Significance of the Study

With the numerous epidemiologic risk factors reported for gastroschisis and omphalocele, together with only one previous study that used a machine learning approach to examine risk factors for gastroschisis [113], the goal of this study is to use a machine learning approach to investigate epidemiologic risk factors associated with gastroschisis and omphalocele using Iowa NBDPS data. This study will use a retrospective population-based case-control study design, and the analysis will evaluate the degree to which risk factors can predict probability of cases based on environmental data; partial dependence plots and summary statistics will help to describe the nature of this unknown relationship. The analysis will also include a contrast machine learning approach to investigate the shared and unshared risk factors between gastroschisis and omphalocele.

CHAPTER II

MANUSCRIPT

Introduction

Gastroschisis and omphalocele are common musculoskeletal defects affecting the abdominal wall. Gastroschisis is characterized by a small opening, usually to the right of the umbilicus, which eviscerates abdominal organs [1]. It most often presents as an isolated defect; co-occurring defects with gastroschisis may include central nervous system, cardiovascular, gastrointestinal, urogenital, and musculoskeletal defects [3-5]. Omphalocele is a large (>4cm) midline abdominal wall defect in which all or part of the small intestine or other internal organs exist outside of the abdomen in a membranous sac [1, 6]. Unlike gastroschisis, omphalocele most often presents with other structural birth defects, including cardiovascular, gastrointestinal, and urogenital defects [5, 10-12].

United States (US), population-based prevalence estimates differ, but those for survival tend to be similar between gastroschisis and omphalocele. Data on deliveries (2012-2016) from the National Birth Defects Prevention Network (NBDPN) showed the prevalence (per 10,000 live births) to be 4.3 for gastroschisis and 2.1 for omphalocele [27]. A comparison of NBDPN data (1999-2001 vs. 2005-2007) showed that prevalence of gastroschisis increased by 83%, whereas prevalence of omphalocele increased by 11% [28]. With regard to survival, data from eight US tertiary care centers (2005-2013) reported a survival estimate of 95% at hospital discharge among gastroschisis cases [34], but infants diagnosed with complex gastroschisis may experience lower survival due to bowel complications, including intestinal atresia, perforation, or necrotic segments of volvulus [33]. Survival of infants with omphalocele also varies among cases with and

without additional structural defects. Infants with isolated omphalocele experience approximately 90% survival by age 1-year but those with congenital heart defects and central nervous system defects were 2.4 and 2.9 times more likely to die [53].

Both gastroschisis and omphalocele are thought to be multifactorial disorders, with both genetic and environmental (broadly define as non-genetic) risk factors. Evidence for genetic factors includes familial cases of gastroschisis and omphalocele [60, 65, 72-74, 80, 99, 156-160], single-nucleotide variants from three genes with gastroschisis: rs4961(ADD1), rs5443(GNB3), rs1042713, and rs1042714 (ADRB2) [60], and chromosomal defects including Trisomy 13, 18 and 21 with omphalocele [53, 55, 63, 75-85].

Associations between gastroschisis and omphalocele and child characteristics have been observed for male infant sex [95, 161] and multiple gestation [53, 55, 56, 63, 105]. Associations between each defect and maternal characteristics or exposures include maternal race and ethnicity [27, 75, 115], young age at delivery with gastroschisis and omphalocele [3, 4, 27, 53, 56, 75-77, 89, 106, 114, 116-130], advanced age at delivery with omphalocele [53, 75], maternal educational attainment at delivery [89, 94, 117, 131], low BMI (<22 kg/m^2) or underweight [117, 130, 132], obesity and being overweight [27, 91, 133-136], folic acid supplementation [137, 138, 140, 141], gravidity [55, 56, 108, 142, 143, 162, 163], maternal medical conditions including infection, bladder infection and urinary tract infections; and conditions, including gestational hypertension and gestational diabetes [133, 144-147, 162], maternal smoking, alcohol consumption and illicit drug use during pregnancy [56, 57, 115, 155].

Most environmental risk factor studies to date for gastroschisis and omphalocele have tended to focus on a single risk factor or a small number of risk factors. Given that each defect has been reported to be associated with several factors, the goal of this study is to use a machine learning approach to investigate environmental risk factors associated with gastroschisis and omphalocele in Iowa. Using a retrospective population-based case-control study design, the analysis will evaluate the degree to which these risk factors can predict probability of an individual diagnosed with gastroschisis or omphalocele based on simultaneous examination of several previously identified risk factors for gastroschisis and omphalocele; partial dependence plots and summary statistics will help to describe the nature of this unknown relationship. In addition, this analysis will include a contrast machine learning approach to investigate the shared and unshared risk factors between gastroschisis and omphalocele.

Methods

Study Subjects

The study sample was obtained from the National Birth Defects Prevention Study (NBDPS); details for NBDPS have been described previously [123]. Briefly, NBDPS is the largest US population-based case-control study and included over 30 different major structural birth defects. NBDPS data collection was conducted during 1998-2013 for deliveries occurring during October 1997 – December 2011. Participating centers from 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah) followed a common protocol for enrollment, classification, and maternal interviews. Case children were diagnosed with one or more NBDPS-eligible birth defects [164].

Control children were randomly selected from live born infants in the same study region as the case children using birth certificates or birth hospital records. A computer-assisted telephone interview was conducted in English or Spanish between 6 weeks and 24 months after the estimated date of delivery (EDD). After completion of interviews, families received buccal cell collection kits for the child (if living), mother, and father (if available). Overall, 47,832 eligible case and 18,272 eligible control children were identified; of these, mothers of 32,187 (67%) case and 11,814 (65%) children provided interview information about their pregnancies. Among those interviewed were mothers of 2,305 children with gastroschisis and 747 with omphalocele. The current analysis was restricted to interview data for 133 children with gastroschisis and 31 with omphalocele (cases) and 1,300 children without a birth defect (controls) from the Iowa Center.

Outcomes

Clinical geneticists at the Iowa Center reviewed clinical data abstracted from medical records for each child with a diagnosis of gastroschisis or omphalocele to identify those with a nonsyndromic phenotype; a case child with a known chromosomal or single gene disorder was excluded from NBDPS. Each nonsyndromic case child was classified as isolated (one major birth defect diagnosed with or without minor defects, two or more major defects developmentally related to each another as a sequence, or two or more major defects diagnosed in the same organ system); multiple (two or more major defects diagnosed in different organ systems and the defects did not represent a sequence or a complex case); or complex (pattern of major defects that are embryologically related and likely represented an early problem in morphogenesis, often akin to a developmental

field defect) [164]. The current analysis excluded complex cases with gastroschisis (n=4); none of the omphalocele cases were classified as complex.

Exposures

Based on the current literature, data for 15 characteristics or exposures (child=2; mother=13) were selected for the 133 Iowa children diagnosed with gastroschisis and 31 with omphalocele available for study. Child characteristics analyzed were sex (male, female) and plurality (1, ≥1). Maternal characteristics and exposures analyzed were race/ethnicity (non-Hispanic White, Other), age at delivery (<20, 20-34, ≥34 years), educational attainment at delivery (high school degree or less, more than a high school degree), pregnancy body mass index (BMI: underweight: <18.5, normal weight: 18.5-24.9, overweight: 25-29.9, obese: ≥30 kg/m^2), gravidity (0, ≥1), chronic hypertension (yes, no), chronic diabetes (yes, no), and periconceptional (one month before through three months following conception) fever (yes, no), infections (yes, no), folic acid supplementation (i.e. use of a folic acid-containing supplement; yes, no), smoking (active only, passive only, active and passive, and none), alcohol consumption (binge drinking [≥4 drinks on one occasion], drinking but no binge drinking, and none), and cannabis use (yes, no).

Statistical Analysis

The objective of the analysis was to evaluate exposures for effectively predicting and classifying a delivery as being a case (diagnosed with gastroschisis or omphalocele) or a control child. Chi-Square tests were used to compare characteristics and exposures between the 164 case children (gastroschisis and omphalocele) and 1300 control children with a p-value cutoff of 0.05. Case and control children were compared for the selected

child and maternal characteristics and exposures using gradient boosted regression. Gradient boosting is a combination of forward stagewise additive modeling and gradient descent numerical optimization used to fit boosted models by minimizing a loss function [165]. The gradient boosted regression analysis was performed in R software using the 'Machine Shop' package [166]. Decision trees were fit by minimizing the Bernoulli loss function over the training data; this function is used to estimate model coefficients for categorical outcomes in gradient boosting [165]. The final model performance was evaluated with test data by measuring Brier score, accuracy, specificity, and sensitivity. Variable importance plots and partial dependence plots were generated.

Results

The distribution of infant characteristics and maternal characteristics and exposures are shown in Table 1. Data were missing for one or more variables for 4.9% (63/1300) of control children and mothers and 6.1% (10/164) for case children and mothers. Among the 133 children with gastroschisis, 61 (45.9%) were male infants, 121 (91.0%) were classified as isolated, and 124 (93.2%) were singletons. Among the 31 children with omphalocele, 18 (58.1%) were male infants, 22 (71.0%) were classified as isolated, and 28 (90.3%) were singletons. Among control children, 656 (50.5%) were males and 1254 (96.5%) were singletons. Most mothers in the sample were non-Hispanic white: 108 (81.2%) and 29 (93.5%) among those with offspring with gastroschisis and omphalocele, respectively, and 1156 (89.1%) among those with unaffected children.

Comparison of characteristics and exposures between case and control children and mothers showed statistical differences ($p<0.05$) for several variables. Case children were more likely to be multiple births. Case mothers were more likely to be <20 years of

age, achieve a high school degree or less, be underweight (BMI < 18.5 kg/m^2) or normal weight (BMI 18.5-24.9 kg/m^2), nulliparous, normo-tensive, and have a periconceptional exposure to an infection, or report active smoking or exposure to both active and passive smoking. Statistical differences were not observed for the remainder of characteristics and exposures examined.

To conduct the machine learning analysis, a training set with 976 observations and a testing set with 488 observations were built. The candidate models were fit with training data, decision trees were constructed using a tuning grid developed through cross-validation, and decision trees were applied to classify unseen examples in the testing set. Based on the tuning grid, a number of different models were fit using different combinations of interaction depths and number of tree parameters. Performance metrics for each combination of tuning parameters were grouped sequentially (group1: model1-3; group2: model 4-6; group3: model 7-9) and plotted in Figure 1. The final model performance with testing data is shown in Table 2. A Brier score of 0.10 was achieved from the model, indicating the minimized mean square error applied to predicted probabilities for a dichotomous outcome. The model achieved an accuracy value of 0.87, Kappa of 0.05, and an area under the receiver operating characteristics curve of 0.65. Due to the rare occurrence of gastroschisis and omphalocele, the sample size for case children (n=164) was limited and much smaller than the sample size for control children (n=1300). This rather large difference in counts between the case and control children produced a model with a very low sensitivity (0.054) and very high specificity (0.980), indicating a 5.4% probability for the model to correctly identify case children and a 98% probability for the model to correctly identify control children.

A variable importance plot (Figure 2) was generated using gradient boosted regression analyses. Eight important predictors were identified with positive Brier scores for gastroschisis and omphalocele including maternal age at delivery, periconceptional smoking, pre-pregnancy BMI, plurality, maternal periconceptional infections, gravidity, folic acid supplementation, and educational attainment at delivery. Maternal age at delivery was the most important factor achieving a 100.00 permute mean Brier score. The mean Brier scores for other variables were 19.65 for maternal smoking status, 6.25 for maternal BMI, 3.68 for plurality, 3.33 for maternal periconceptional infection, 3.18 for gravidity 1.33 for maternal periconceptional folic acid-containing supplement use, and 0.1 for maternal educational attainment at delivery.

Partial dependence plots were generated for the eight important predictors from model fit to estimate each category's effect on prediction of a case or control child (Figure 3). The partial dependence plot provides a graphical depiction of the marginal effect of a variable on the outcome probability (classification) [167]. Higher classification probabilities were observed for mothers who delivered at < 20 years of age (0.39), reported periconceptional active smoking (0.21), were underweight (BMI < 18.5 kg/m^2) (0.18), had plurality ≥ 2 (0.17), reported a periconceptional infection (0.16), were nulliparous (0.12), did not report periconceptional folic acid-containing supplement use (0.13), and had a high school degree or less education at delivery (0.11) (Figure 3).

Discussion

Using Iowa NBDPS data and applying gradient boosted regression, environmental risk factors for gastroschisis and omphalocele were explored. Findings suggest that important predictors associated with a gastroschisis or omphalocele case child were

maternal age < 20 years at delivery, periconceptional active smoking, maternal underweight, plurality, and maternal periconceptional infection, gravidity, periconceptional folic acid-containing supplement use, and educational attainment at delivery.

Only one previous study was identified that used machine learning analysis to study risk factors for gastroschisis. Among the important predictors identified from this study that used California NBDPS data, a logistic regression model was included to further estimate odds ratios. In comparison, this study generated partial dependence plots and estimated outcome classification probabilities for important predictors identified from model fit. The California study observed higher consumption of chocolate, low intake of iron, acetaminophen use, and urinary tract infection during the beginning of pregnancy were associated with higher odds among mothers aged < 20 years; for mothers ≥ 20 years, higher odds were observed for US-born Hispanic mothers and for parental substance abuse, and lower odds were observed for obese mothers, those who consumed cereal before pregnancy, and those with higher gravidity [113]. Consistent results were observed in this study for maternal age at delivery, periconceptional infection, pre-pregnancy BMI, and parity, but the current study also observed young maternal age at delivery, maternal periconceptional active smoking, plurality ≥2, maternal periconceptional folic acid supplementation to have higher probabilities to be gastroschisis or omphalocele cases.

Comparing findings in the current study with those that used more traditional epidemiologic analyses (e.g. multivariate logistic regression) showed agreement with several studies that reported associations of young maternal age at delivery with

gastroschisis [3, 4, 27, 53, 56, 75-77, 89, 106, 114, 116-130] and omphalocele [53, 75, 123]. Findings did not support associations previously reported for advanced maternal age and omphalocele [53, 75], which showed a much lower classification probability in the current data.

Maternal periconceptional active smoking was observed to be the second most important predictor in the model fit with active smoking achieving the highest outcome classification probability. This finding agrees with a meta-analysis that reported a pooled risk ratio of 1.56 for maternal smoking during pregnancy and gastroschisis [115] and with previous studies showing maternal smoking during pregnancy to be associated with an increased risk of omphalocele [56, 57, 137]. The finding differed from a recent study showing no association between maternal smoking preconception through the first trimester of pregnancy and gastroschisis [150].

Maternal pre-pregnancy BMI was also identified as an important predictor. Maternal BMI <18 kg/m^2 achieved the highest outcome classification probability with BMI ≥30 kg/m^2 showing the lowest probability, consistent with previous reports of increased risk of gastroschisis among women with a relatively lower BMI or being underweight [117, 130, 132] and lower risk among those who were obese [91, 133-135]. For omphalocele, this finding differed from reports that mothers with BMI ≥30 kg/m^2 were more likely to deliver a child with omphalocele compared to average weight women [27, 135, 136].

Additional important predictors identified were plurality (multiple gestation) and maternal periconceptional infection which have been shown in most previous studies to be associated with increased risk of gastroschisis [56, 133, 146, 148] and omphalocele

[53, 55, 56, 63], except those that reported a positive association for singleton birth and gastroschisis [89, 105]. Increased but less important predictors identified were lack of maternal periconceptional folic acid-containing supplement use, educational attainment at delivery (high school degree or less) and gravidity (nulliparity) which are consistent with several studies of gastroschisis [89, 94, 108, 117, 131, 137, 138, 142, 162, 163], and omphalocele [55, 56, 140, 141], except for a null association between maternal education and omphalocele [125], multiparity and omphalocele [142], and a null association between nulliparity and omphalocele [143].

Child sex, along with maternal race/ethnicity, fever, chronic hypertension, chronic diabetes, and periconceptional alcohol consumption and cannabis use were not identified as important predictors in the current study. For gastroschisis, these findings are consistent with some previous studies for child sex [87-90, 162], maternal race/ethnicity [115], fever [144, 147], and alcohol consumption [150], but not all studies of these factors [95, 115, 161]. Findings also were not consistent with previous studies of illicit drug use and gastroschisis [87, 94, 151-154]. Findings for maternal chronic hypertension and chronic diabetes and gastroschisis were not directly comparable to previous studies that reported a positive association between gestational hypertension and gastroschisis [133] and an inverse association between gestational diabetes and gastroschisis [162]. For omphalocele, no consistencies were observed between these findings with previous studies. These findings differ with previous studies for child sex [95], maternal race/ethnicity [27, 75], and alcohol consumption [56, 57, 137]. Previous research on fever, chronic hypertension, chronic diabetes, and illicit drug use with omphalocele were lacking.

Strength and Limitations

The primary strength of this analysis was a representative sample of Iowa deliveries [168]. Another strength was the systematic case review by clinical geneticists to identify and classify nonsyndromic case children with gastroschisis or omphalocele, reducing the potential for case misclassification. Exposure data were obtained from detailed maternal interview reports using the NBDPS questionnaire, providing reports for several child and maternal risk factors for applying gradient boosted regression to simultaneously explore these factors and examine a large number of variables while accounting for others simultaneously.

Limitations of the study include the small sample size for each defect group, particularly for omphalocele cases and the large difference in case and control counts resulted in a model with a very low sensitivity and a very high specificity. Associations identified tended to largely agree with those previous reported for gastroschisis, but somewhat less so for those reported for omphalocele. The difference in numbers of children with gastroschisis (n=133) compared to omphalocele (n=31) may have masked associations between for omphalocele, leading to findings that differed from previous reports for advanced maternal age [53, 75], being overweight or obese [27, 135, 136], and multiparity [142]. Associations observed may also have been impacted by recall bias given most were self-reported in the NBDPS interview. In addition, due to the nature of data mining such as gradient boosting, there are concerns regarding multiple testing and spurious associations, which may lead to observed associations being due to chance alone.

The current study is only the second to use a machine learning approach to examine several risk factors for gastroschisis and the first to examine those factors for omphalocele. Eight important predictors were observed from the model fit: maternal age <20 years at delivery, educational attainment at delivery, gravidity, multiple gestation, pre-pregnancy underweight, and periconceptional active smoking, infection, folic acid-containing supplement use. Future studies should aim to increase sample sizes to examine gastroschisis and omphalocele independently to improve the sensitivity and accuracy of this analysis.

CHAPTER III

DISCUSSION

Using Iowa NBDPS data and applying a well-established, gradient boosted regression approach, several risk factors for gastroschisis and omphalocele were explored. Findings suggest that important predictors associated with a gastroschisis or omphalocele case child were maternal age <20 years at delivery, periconceptional active smoking, pre-pregnancy underweight, plurality, and maternal periconceptional infection, gravidity, periconceptional folic acid supplementation, and educational attainment at delivery. However, child sex, maternal race/ethnicity, chronic hypertension, chronic diabetes, and periconceptional fever, alcohol consumption, and cannabis use were not observed to be important predictors in the current study, as has been identified in some previous studies.

This study identified several important infant and maternal characteristics that predict the risk of child being delivered with gastroschisis or omphalocele. Findings can guide pre-conception counseling in women planning their pregnancy. The counseling can be aimed at modifiable risk factors identified in our study, promoting smoking cessation programs, recommended folic acid supplement intake, and healthy pre-pregnancy BMI. Risk reduction can also be managed through health education messages targeting all women of reproductive age through various channels.

In the current study, identification of explanatory environmental factors has been modestly productive for the unique epidemiologic profiles that characterize gastroschisis and omphalocele. Using a more novel and comprehensive approach to generate new hypotheses and examine suggested risk factors reported in previous studies, the current

study adds evidence to associations observed with many suggested risk factors, particularly given such factors were modeled simultaneously. In future studies, sample size of each defect can be increased to examine gastroschisis and omphalocele independently and improve the sensitivity and accuracy. In addition, as the prevalence of gastroschisis has been increased, future studies should expand risk factors by including parental demographic and lifestyle information, and interaction effects of genetic and environmental risks.

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Table 1: Selected child and maternal characteristics and maternal exposures, Iowa NBDPS, 1997-2011.

	Controls	***Total Cases***	***Gastroschisis***	***Omphalocele***
	(N=1300)	(N = 164)	(N=133)	(N=31)
Child Characteristics				
Sex				
Female	644 (49.5%)	85 (51.8%)	72 (54.1%)	13 (41.9%)
Male	656 (50.5%)	79 (48.2%)	61 (45.9%)	18 (58.1%)
Phenotype				
Isolated	NA	143 (87.2%)	121 (91.0%)	22 (71.0%)
Multiple	NA	21 (12.8%)	12 (9.0%)	9 (29.0%)
Plurality[a]				
1	1254 (96.5%)	152 (92.7%)	124 (93.2%)	28 (90.3%)
≥2	46 (3.5%)	12 (7.3%)	9 (6.8%)	3 (9.7%)
Maternal Characteristics				
Race/Ethnicity				
Non-Hispanic White	1156 (89.1%)	137 (83.5%)	108 (81.2%)	29 (93.5%)
Other	142 (10.9%)	27 (16.5%)	25 (18.8%)	2 (6.5%)
Missing	2	0	0	0
Age at Delivery (years)[a]				
<20	77 (5.9%)	54 (32.9%)	54 (40.6%)	0 (0%)
20–34	1066 (82.0%)	105 (64.0%)	78 (58.6%)	27 (87.1%)
≥35	157 (12.1%)	5 (3.0%)	1 (0.8%)	4 (12.9%)
Education Level at Delivery[a]				
High School Degree or Less	384 (29.9%)	83 (52.9%)	76 (60.3%)	7 (22.6%)
More than a High School Degree	900 (70.1%)	74 (47.1%)	50 (39.7%)	24 (77.4%)
Missing	16	7	7	0
Pre-pregnancy BMI[a]				
Underweight (< 18.5)	60 (4.7%)	16 (9.8%)	14 (10.6%)	2 (6.5%)
Normal weight (18.5–24.9)	643 (50.3%)	92 (56.4%)	82 (62.1%)	10 (32.3%)
Overweight (25–29.9)	307 (24.0%)	39 (23.9%)	31 (23.5%)	8 (25.8%)
Obese (≥30)	269 (21.0%)	16 (9.8%)	5 (3.8%)	11 (35.5%)
Missing	21	1	1	0
All previous pregnancies (Gravidity)[a]				
0	375 (28.8%)	78 (47.9%)	62 (47.0%)	16 (51.6%)
≥1	925 (71.2%)	85 (52.1%)	70 (53.0%)	15 (48.4%)
Missing	0	1	1	0

Maternal Periconceptional Exposures				
Chronic Hypertension[a]				
Yes	148 (11.4%)	6 (3.7%)	4 (3.0%)	2 (6.5%)
No	1145 (88.6%)	157 (96.3%)	128 (97.0%)	29 (93.5%)
Missing	7	1	1	0
Chronic Diabetes				
Type 1 or type 2 diabetes diagnosed before or during index pregnancy	6 (0.5%)	0 (0%)	0 (0%)	0 (0%)
No type 1 or type 2 diabetes diagnosed before or during index pregnancy	1293 (99.5%)	164 (100%)	133 (100%)	31 (100%)
Missing	1	0	0	0
Fever				
Yes	140 (11.9%)	21 (14.2%)	15 (12.3%)	6 (23.1%)
No	1039 (81.1%)	127 (85.8%)	107 (87.7%)	20 (76.9%)
Missing	19	2	2	0
Infections[a,b]				
Yes	76 (6.0%)	17 (10.5%)	13 (9.9%)	4 (12.9%)
No	1193 (94.0%)	145 (89.5%)	118 (90.1%)	27 (87.1%)
Missing	31	0	2	0
Folic Acid-Containing Supplement Use				
Yes	1176 (91.8%)	145 (89.5%)	119 (90.8%)	26 (83.9%)
No	105 (8.2%)	17 (10.5%)	12 (9.2%)	5 (16.1%)
Missing	14	2	2	0
Cigarette Smoking[a]				
Active only	135 (10.9%)	29 (18.9%)	25 (20.0%)	4 (13.8%)
Passive only	89 (7.2%)	14 (9.1%)	13 (10.4%)	1 (3.4%)
Active and passive	195 (15.8%)	44 (28.6%)	37 (29.6%)	7 (24.1%)
None	818 (66.1%)	67 (43.5%)	50 (40.0%)	17 (58.6%)
Missing	63	10	8	2
Alcohol Consumption				
Drinking with binge episode (≥ 4 drinks on one occasion)	275 (21.8%)	42 (27.1%)	35 (28.2%)	7 (22.6%)
Drinking without binge episode	318 (25.2%)	31 (20.0%)	20 (16.1%)	11 (35.5%)
No drinking	669 (53.0%)	82 (52.9%)	69 (55.6%)	13 (41.9%)
Missing	38	9	9	0
Cannabis Use				

Yes	41 (3.2%)	9 (5.5%)	8 (6.0%)	1 (3.2%)
No	1259 (96.8%)	155 (94.5%)	125 (94.0%)	30 (96.8%)

BMI, body mass index; NBDPS, National Birth Defects Prevention Study.

[a]$p < 0.05$ for all gastroschisis and omphalocele cases combined compared to controls.

[b]Periconceptional infections include kidney infection, bladder infection, UTI, or pelvic inflammatory disease.

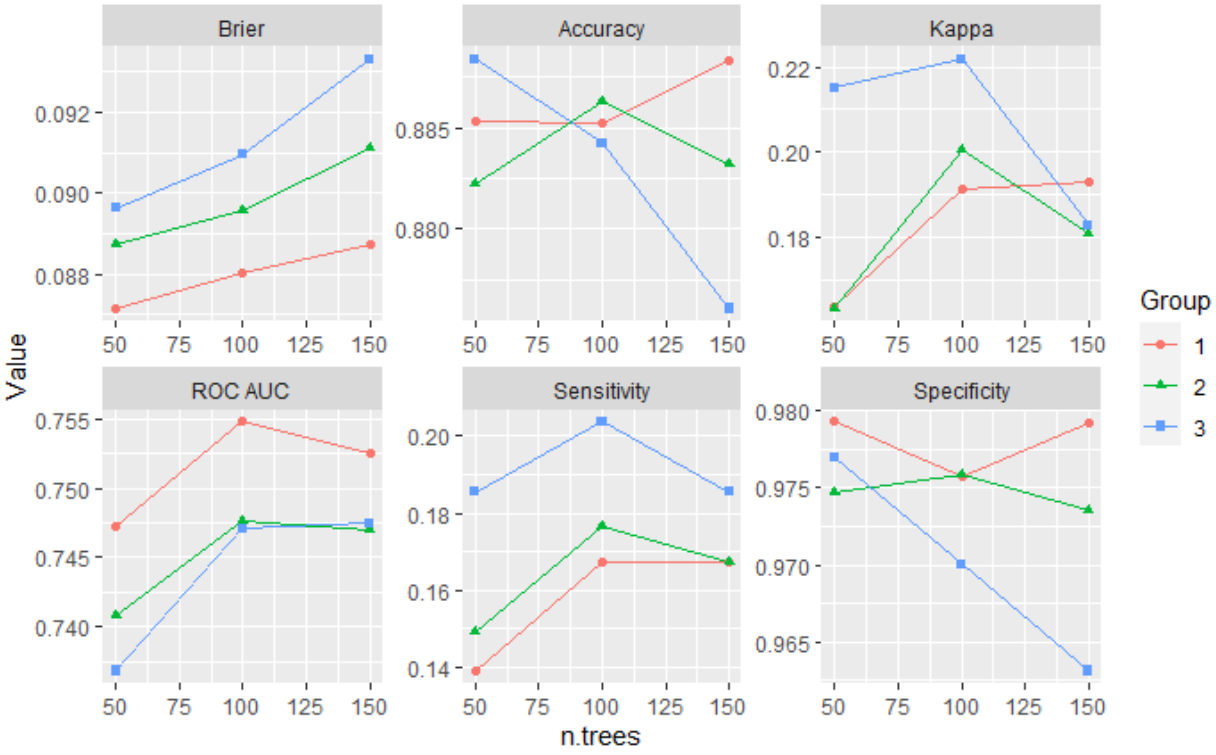

Figure 1: Generalization performance over a grid of tuning parameters, Iowa NBDPS, 1997-2011; NBDPS, National Birth Defects Prevention Study; ROC AUC, Two-dimensional area underneath the entire receiver operating characteristic curve.

Table 2: Test model performance, Iowa NBDPS, 1997-2011.

Brier	Accuracy	Kappa	ROC AUC	Sensitivity	Specificity
0.10	0.87	0.05	0.65	0.05	0.98

NBDPS, National Birth Defects Prevention Study; ROC AUC, Two-dimensional area underneath the entire receiver operating characteristic curve.

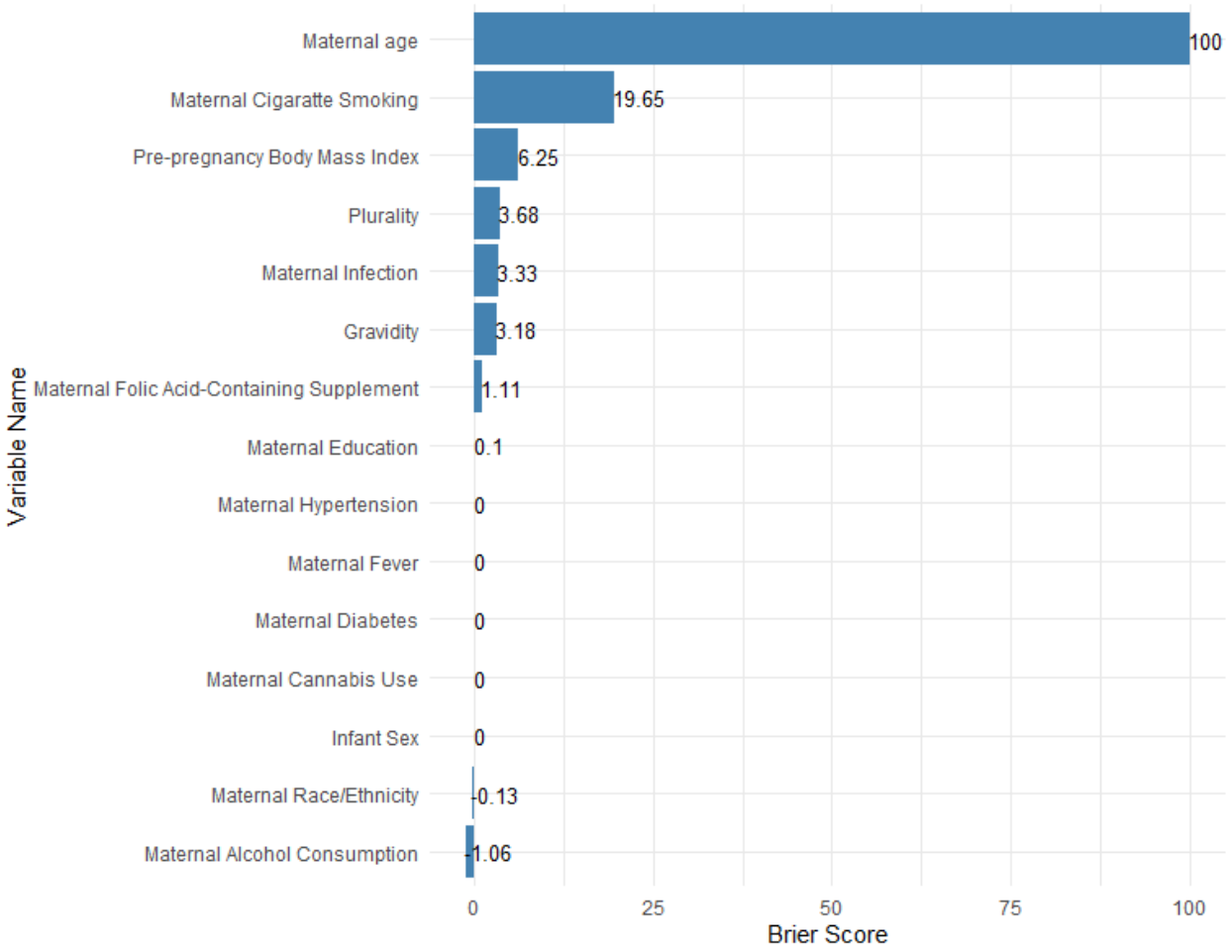

Figure 2: Ranking plot of variable importance in predicting risk of gastroschisis and omphalocele for 164 cases and 1300 controls, Iowa NBDPS 1997-2011.

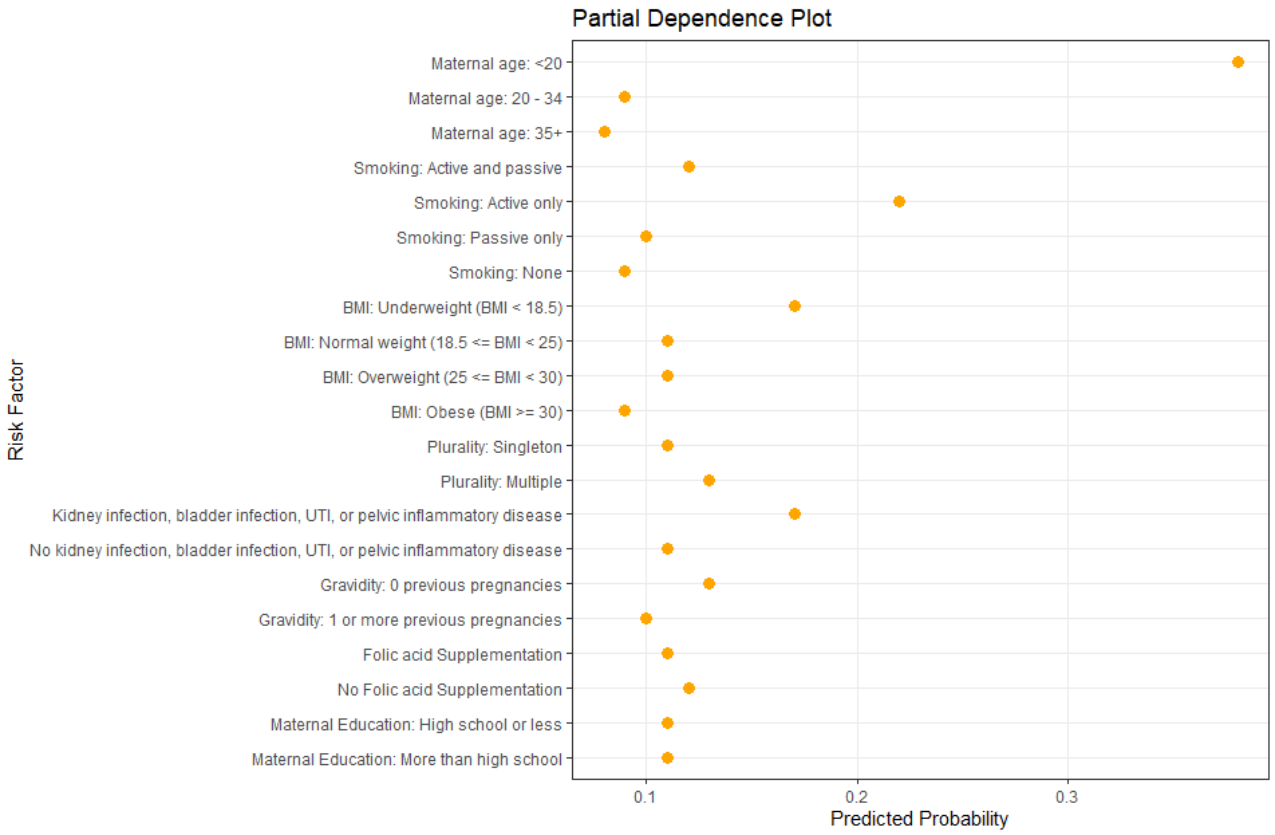

Figure 3: Partial dependence plot for six most outstanding important predictors from gradient boosted regression model.