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Maternal Report of Family History of Birth Defects

from the Birth Defects Study To Evaluate Pregnancy exposureS

(BD-STEPS)

By

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B.S.
The University of Georgia
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Thesis Committee Chair: Dr. Michael Kramer, PhD

An abstract of
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Abstract

Maternal Report of Family History of Birth Defects

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(BD-STEPS)

By Jackie Bonilla

Background: Given that birth defects are complex in etiology, family history as a measure is valuable given that it captures both genetic and environmental risk factors. Our objectives were to determine if the frequency of maternal reporting of a family history of birth defects or other conditions was higher among cases compared to controls, to determine what maternal and paternal demographic characteristics were associated with reporting a family history of birth defects or other conditions, and to determine what specific birth defects or other conditions were reported, and whether the birth defects were the same as that reported in the index child.

Methods: The Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS) is a multisite, population-based, case-control study. All eligible birth defect cases and controls delivered during 2014-2019 were included. Mothers of 2,676 case and 1,577 control infants participated in the study. Of those participants, mothers of 583 case and 241 control infants answered affirmatively to family history questions and were included in the qualitative analysis. Free-text family history questions were categorized by type of birth defect or condition reported. A chi square test was used to assess which demographic or other characteristics were significantly associated with maternal reports of family history of birth defects or other conditions.

Results: Maternal reports of family history of a birth defect or other condition were common, reported by 583 (21.8%) case mothers and 241 (15.3%) control mothers. Demographic characteristics associated with maternal reports of family history of a birth defect or other condition included maternal and paternal race/ethnicity, maternal age, maternal and paternal education, interview language and language spoken at home, and maternal and paternal places of birth. Family history of a birth defect was reported by 261 (9.7%) case mothers and 70 (4.4%) control mothers.

Conclusion: Case mothers more frequently report a family history of birth defects or other conditions compared to control mothers. Demographics also influenced the level of reporting of birth defects and other conditions. More research could help inform the role of language, age, and race/ethnicity on reporting of family history.

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Chapter 1: Introduction

The concept of "familial history" of a condition encompasses shared genetic risks among family members, but it also incorporates other factors like social and cultural factors. Family history can include ethnic background that can affect nutrition as well as shared behaviors and other risk factors. Given that birth defects are often complex concerning their development and risk factors, measuring family history is valuable given that it captures a wide array of social and genetic components.

Birth defects are very prevalent among the general population given that about 8 million children are born with birth defects every year worldwide (Khokha et al., 2017), accounting for about 3-6% of newborns affected by birth defects in the world (Bermejo-Sánchez et al., 2018). In 1999, birth defects accounted for 20% of all infant deaths in the United States and were the largest contributor to infant deaths (Petrini et al., 2002). In 2017, 20.6% of infant deaths were caused by birth defects, making them the leading cause of infant mortality in the United States (Almli et al., 2020), and in 2020, the leading cause of infant mortality still remains as congenital malformations. They account for 111.9 infant deaths overall per 100,000 live births (Murphy et al., 2021). Birth defects are also important to study because there can be increased physical and cognitive challenges for individuals affected by birth defects.

Birth defects are critical to examine given that they have substantial impacts on the long-term health of children affected by birth defects and their families. One study found that adults with congenital heart defects were 5 to 8 times more likely to be living with a disability compared to the general population. Of the disabilities reported among those with congenital heart defects, cognitive disabilities were the most prevalent. Cognitive disabilities include problems concentrating and memory issues (Downing et al., 2021). Families of children impacted by birth defects can also be heavily affected. One study showed that parents of children with congenital heart defects experienced significant psychological stressors especially after heart surgery (Woolf-King et al., 2017). Some of the prominent findings from the analysis by Woolf-King et al. (2017) indicated that 80% of parents experienced clinically significant

levels of trauma similar to post traumatic stress disorder and 35-50% of parents experienced depression and/or anxiety (Woolf-King et al., 2017). Another study found that parents of babies affected by congenital anomalies had higher levels of psychological distress compared to parents of healthy babies. However, receiving a prenatal diagnosis was associated with better psychological quality of life (Fonseca et al., 2012). This indicates that receiving an earlier diagnosis can be better for adjustment and mental health of parents. The morbidity levels of children and families of children living with birth defects are expansive. Further research could help inform morbidity impact for families affected by birth defects.

Increased knowledge on birth defects and their causes allows for better understanding of preventative efforts and improved genetic counseling (Oliveira & Fett-Conte, 2013). Many of the risk factors for birth defects are unknown and can be multifactorial including having genetic and environmental influences. One benefit of studying and understanding family history is that it can be a proxy for genetic predisposition, and it can also describe shared environmental factors.

This descriptive analysis of qualitative responses about family history of birth defects that were collected during a maternal telephone interview as part of a case-control study on risk factors for birth defects can provide insight on commonly reported conditions and the clinical and demographic factors associated with maternal reports about family history. We will be exploring which birth defects were reported the most frequently during maternal interview in first degree relatives and whether they were the same as the defect in the affected case. Other areas of analysis will explore the demographic characteristics influencing reporting of a family history of a birth defect. Insights from this analysis will allow us to observe patterns in family history of birth defects and identify needed areas of research.

What is a birth defect?

There are two types of birth defects. The first type of birth defects are structural and are characterized as abnormalities in the skeleton and organs (Oliveira & Fett-Conte, 2013). The vast majority of structural birth defects occur within the first three months of pregnancy given that this is a

crucial period for embryologic development; however, there are some structural birth defects that develop later in pregnancy. The second type of birth defect are functional defects (Oliveira & Fett-Conte, 2013); however, in this project, only major structural birth defects will be explored.

Structural birth defects can affect almost any part of the body and can range from being isolated to one organ system or they can involve multiple organ systems (Harris et al., 2017). About 20-30% of children have multiple congenital anomalies (Howley et al., 2022). The most common structural birth defects are congenital heart defects, musculoskeletal defects, genitourinary defects, orofacial defects, and neural tube defects (Simeone et al., 2015). Women with pregnancies affected by a birth defect are more likely to experience a pregnancy loss (Oliveira & Fett-Conte, 2013). Infants with birth defects are more likely than liveborn infants without birth defects to be of small gestational weight or to be born prematurely (Miquel-Verges et al., 2015). The relationship between these conditions and birth defects could be explored in more detail since there is limited knowledge and understanding in the area. In addition to prematurity and low birth weight, congenital cancer, and developmental disabilities can co-occur with birth defects.

Aside from the physical and mental burden that birth defects hold for children, there is a significant financial impact on families with children affected by birth defects. In a study investigating financial burden and mental health of families of children with congenital heart defects (CHD), there was a higher financial burden and more need for mental health services than among families of children without congenital heart defects (McClung et al., 2018). An analysis conducted using data from January 1 through December 31, 2013 among persons of all ages, found that birth defect related hospitalization accounted for 5.2% of hospital costs, and the estimated annual cost was $22.9 billion (Arth et al., 2017). These statistics illustrate the vast financial impact birth defects have on families with children affected by birth defects.

What causes birth defects?

The vast majority of birth defects are of unknown etiology. One study found that almost 80% of birth defects were of an unknown cause and 20% of birth defects had a known cause, the majority being chromosomal or genetic conditions (Marcia L. Feldkamp et al., 2017). Although there are some gaps in knowledge on the causes of birth defects, there are some known causes and risk factors. Birth defects are caused by a variety of factors like genetics, environmental conditions, certain medications (e.g., thalidomide), certain behaviors (e.g., smoking, drinking alcohol, and using illicit drugs), and certain chronic maternal conditions (e.g., diabetes) (Bermejo-Sánchez et al., 2018; Marcia L Feldkamp et al., 2017; Kim & Scialli, 2011; *What are Birth Defects?*, 2022). The underlying etiology of birth defects varies, so it is preferable to examine specific birth defect types when identifying risk factors. For example, genetic predisposition as well as reduced folate intake is a major risk factor for spina bifida (Copp et al., 2015).

Causes of birth defects can also be broken down into non-modifiable and modifiable causes. Some examples of truly non-modifiable risk factors are genetic predisposition and having a previous child who is affected by birth defects. These are factors that cannot be changed and are not within the control of a parent. On the other hand, modifiable risk factors are the use of certain medications, alcohol, and smoking (Harris et al., 2017). Factors like age at conception and family history may also be considered modifiable because they have social influences. There are still many gaps in knowledge in birth defects research and understanding how risk factors are measured is critical as a first step to increasing this area of research.

Examples of Risk Factors

Common risk factors and conditions reported by women whose pregnancies are affected by birth defects are exposure to teratogens and genetic disorders. An example of a teratogen associated with birth

defects is thalidomide. This association was discovered in 1961 by William McBride and Widukind Lenz (Lancaster, 2011). Birth defect predisposition can also be influenced by a variety of genetic mutations or genetic variations. However, these factors have not been thoroughly researched until recently. The increased availability of genome sequencing and genome-wide association studies could provide more insight on genetic risk factors (Wlodarczyk et al., 2011).

Demographics

Other variables that can be important to examine are parental age, education, and race/ethnicity. According to a previous systematic review and meta-analysis, it was determined that children of young (i.e., under the age of 20) fathers had an increased risk of urogenital abnormalities and chromosome disorders and children of older (i.e., over the age of 40) fathers had an increased risk of cardiovascular abnormalities, facial deformities, urogenital abnormalities, and chromosomal disorders (Fang et al., 2020). There is also literature supporting an association between maternal age and risk for birth defects. For example, one study found that infants with anomalous pulmonary venous return, amniotic band sequence, and gastroschisis were more likely to have mothers under 20 years of age. Conversely, infants with heart defects, hypospadias, and craniosynostosis were more likely to have mothers over the age of 30 (Gill et al., 2012).

Sociodemographic factors

Race and ethnicity are also critical to examine when studying birth defects. For example, one study found that Hispanic women have a higher risk of having babies with neural tube defects such as anencephaly and spina bifida (Canfield et al., 1996). Although there have been large advances towards reducing neural tube defects through the fortification of grains with folic acid, there have not been mandates to fortify corn-based products like tortillas that may be a large cultural dietary stable for many Hispanic households. Examining how culture can play a role in risk factors for birth defects is also important. In a previous analysis, it was found that women who completed a case control study interview

in Spanish were less likely to report a family history of birth defects (Green et al., 2008). However, in another study, having a Spanish interview and primarily speaking Spanish at home were both associated with a higher likelihood of delivering an infant with anotia/microtia (Hoyt et al., 2014). Disentangling the role of language as a proxy for acculturation and ethnicity in birth defect reporting and prevalence is important for prevention efforts and messaging.

Importance of family history research

Family history encompasses shared genetic risks among family members, but it also incorporates other factors like social and cultural factors. It can entail common health behaviors and habits among families (Dolan & Moore, 2007). However, few studies have measured the validity of measures of maternally reported family history of birth defects (Rasmussen et al., 1990; Romitti et al., 1997).

Methods to assess familial history of birth defects or other conditions are currently not consistent across the literature, and the validity of these measurements are study dependent. In some cases, self-reported family history is not considered validated data because it is not compared against medical records to see if the individuals actually have the condition. This occurs because linking this data can be impractical depending on how far back the individual reports their family history. Some of the conditions reported may also be unrelated to the birth defect of the index child or may be a different condition.

Understanding family history of birth defects in more detail can help expand the use of self-reported family history and use it more widely as a public health tool. Better understanding can include the degree of accuracy of reporting correct birth defects and conditions that can be done by comparing to clinical documents. Another important factor to investigate would be to understand the level of detail reported by the mother as well as certain demographics associated with higher or lower levels of reporting. Examining parental awareness of birth defects in family history and validating the content and frequency of reporting can be beneficial when looking at family history of birth defects. Improved quality of information on family history of birth defects can also be used to target preventative measures for

expecting mothers such as folic acid supplementation (Romitti, 2007). Use of family history information in addition to electronic health records also has the added benefit of being low cost and more accessible than genomic tools and can be used to assess risk and motivate preventative measures (Valdez et al., 2010).

Research aims

Our qualitative family history project will be an updated analysis of a previously published paper utilizing data from the National Birth Defects Prevention Study (NBDPS), a case control study examining risk factors for birth defects. Factors associated with the report of family history of birth defects were explored using data from 1997-2001. In the previous paper, Green et al. found that 21% of NBDPS study participants reported family history of birth defects, 7% reported genetic disorders, 11% reported developmental disabilities, and 4% reported low birth weight or prematurity (Green et al., 2008). Approximately 17% of mothers of birth defect cases reported family history in a first or second degree relative compared to 10% of mothers of liveborn controls. Other factors that were associated with higher reports of family history of birth defects included maternal race/ethnicity and maternal education. White non-Hispanic mothers and those who had an education of 12 years or more had higher frequency of reporting. Participants who were interviewed in Spanish were less likely to report family history of birth defects (Green et al., 2008).

In the previous analysis, there were differences in the level of detail reported when looking at the type of birth defect. Level of detail reported was also impacted by the frequency of reporting. The main purpose of Green et al.'s study was to determine the usefulness of maternally reported family history information. This motivated our study to update the previous findings using more current data. In this new analysis, we have included 2014-2019 data collected as part of the Birth Defects Study to Evaluate Pregnancy ExposureS (BD-STEPS), a more recent case-control study focusing on modifiable risk factors for birth defects.

There are three research aims for this analysis. First, we will be determining if the frequency of reporting family history of a birth defect or other condition is higher among mothers of cases compared to mothers of controls. The second aim of the study is to determine what demographic characteristics of the mother and father are associated with report of a family history of birth defect. The final aim is to determine what specific conditions are reported among individuals who report family history of a birth defect.

Chapter 2: Methods

Description of dataset

BD-STEPS is a population-based, multi-site case-control study examining modifiable risk factors for birth defects (Tinker et al., 2015). The sites for the study are located in Arkansas, California, Iowa, Massachusetts, New York, North Carolina, and Georgia. English and Spanish speaking women who lived in the designated area for birth defect surveillance and who had experienced at least one pregnancy affected by a birth defect were included. Live births, stillbirths, and terminated, to the extent possible, pregnancies were all ascertained. Controls were obtained through vital records and birth hospital logs (Tinker et al., 2015). Information was collected through a Computer Assisted Telephone Interview (CATI), which is administered to mothers of case and controls. The interview asked questions about demographic characteristics, health, medication use, and other variables like family history of birth defects.

Description of sample and measures

Our analytic sample consisted of all eligible birth defect cases and controls who participated in BD-STEPS from 2014-2019. A total of 4,253 mothers participated in the study. Of those participants, 824 answered affirmatively to at least one of the family history or heart section questions.

Outcomes

This project is a descriptive analysis of the family history of a birth defect or other conditions reported by the mother of cases or controls concerning such conditions in the index infant's mother, father, siblings, or twin/multiple gestation. Women could report any birth defect (or other condition) during the interview questions specific to family history. However, only a subset of birth defects is captured in BD-STEPS and thus categories were retained for these specific types of birth defects, in particular: spina bifida, any orofacial clefts, diaphragmatic hernia, anotia and microtia, esophageal atresia, anophthalmos and microphthalmos, gastroschisis, transverse limb deficiency, and critical congenital heart defects. (For this analysis in particular, these categories were also chosen to match those used in the analysis by Green et al., so that data from both the NBDPS and BD-STEPS could eventually be combined for analyses).

Spina bifida is considered a neural tube defect and is defined as malformation of the spinal cord (Iskandar & Finnell, 2022). It can also affect other organs in the body and lead to disability (Iskandar & Finnell, 2022). Orofacial clefts can affect the lip or the palate or both (Schutte & Murray, 1999). Diaphragmatic hernia is a hole in the diaphragm, and it can cause respiratory issues (Tovar, 2012). Anotia is the absence of the outer ear and microtia is characterized as the underdevelopment or malformation of the outer ear (Harris et al., 1996). Esophageal atresia occurs when the esophagus is not properly developed (Baldwin & Yadav, 2023). Anophthalmos and microphthalmos are both eye defects. Anophthalmia is the absence of the eye and microphthalmia is a small eye (A. S. Verma & D. R. Fitzpatrick, 2007). Gastroschisis is a birth defect where there is a hole in the abdominal wall and the organs are outside of the body at birth (Holland et al., 2010). Transverse limb deficiencies are birth defects that can affect the arm, leg, or toes and it is defined as an "amputation" of the specific limb. There are various congenital heart defects that affect the structure of the heart. Those included in BD-STEPS are pulmonary atresia, tetralogy of Fallot, and hypoplastic left heart syndrome, transposition of great arteries, truncus arteriosus, tricuspid atresia, coarctation of the aorta, and anomalous pulmonary venous return.

Exposures

The family history section of the BD-STEPS CATI asks questions about birth defects and other health conditions among first degree relatives of the case/control infant including the mother, father, and full siblings. Ten questions were used from the family history and heart condition section of the CATI to create the family history variables. Family history of a birth defect was defined as an affirmative response to at least one of following questions for the mother, father, or sibling of the index child: "Did you/they have a health problem at birth or a birth defect that was diagnosed in childhood?" and "What was it?" From the heart section of the CATI, the questions used were "Do you/they have a heart problem that has been present since birth? Please do not include problems that went away on their own." and "What is it?". Some conditions reported by participants were not birth defects, so any birth defect or condition reported was considered 'any' family history.

Definition of categories

Mothers could report a family history of any conditions, and these free responses were categorized as birth defects, genetic conditions, developmental disabilities, prematurity or low birth weight, or 'other.' These categories were chosen to mirror the previously published NBDPS analysis (Green et al., 2008) so that the data from NBDPS and BD-STEPS could be combined in the future. There is also current literature on potential associations with conditions that were the basis for these categories (Green et al., 2008). The first aim of this study was to determine what type of conditions were reported to have occurred among family members (mother, father, siblings) of birth defect cases and live born controls. There were set conditions for each category to maintain consistency. The birth defect category consisted of eligible BD-STEPS birth defects (e.g., anotia/microtia, gastroschisis, and orofacial clefts). Genetic conditions could include Down syndrome, Cornelia de Lang syndrome, and neurofibromatosis although this is not a comprehensive list. Examples of developmental disability include autism, Tourette's, and

dyslexia. ‘Other’ conditions included asthma, eczema, and diabetes. Birth defects were also characterized by anatomical group. Level of detail was also examined.

The covariates of interest were chosen based on literature describing risk factors for birth defects. We wanted to determine if maternal report of family history varied by the report of ‘any’ family history (i.e., birth defects or other conditions) compared to no report of ‘any’ family history. We also wanted to determine if there were any differences within those that reported family history of the same birth defect as the case infant versus those who did not report family history of the same defect. The covariates included whether the baby is still living, parity, whether the mother and father were born in the United States, language spoken at home, maternal/paternal race ethnicity, maternal/paternal education level, and maternal/paternal age.

Analyses

The first step was to classify free-text maternal responses to family history questions on birth defects. This included identifying and categorizing the birth defects or conditions listed in the free responses given during maternal interview. If there were multiple conditions or birth defects reported, an individual variable was created for each. Each response was blinded to case/control status. Categories were defined using the guidelines from the previous NBDPS analysis by Green et al. before the free text information was coded (Green et al., 2008).

The next step was to further classify any birth defects by anatomical group. The categories used for this variable, which were based on the previous analysis by Green et al. of NBDPS data, were amnion ruptures, neural tube defects (NTDs), eye, ear, heart, choanal atresia, orofacial clefts, gastrointestinal defects, hypospadias, renal agenesis, transverse limb deficiencies, craniosynostosis, sacral agenesis, diaphragmatic hernia, and abdominal wall defects. Categories were also created to record if the response was unclear. Finally, the level of detail (high, medium, or low) that the mother reported was specified if the mother reported a family history of birth defects or genetic conditions. An example of a high level of

detail reported would be if the participant gave the correct medical terminology or correct descriptive layman's terms. A medium level of detail would be assigned if the report was descriptive but did not include precise name. Finally, the responses were coded as having low detail if the defect or condition was non-specific. The coding of these variables was based off the coding found in the previous NBDPS article (Green et al., 2008). If the coder was unsure, a variable was created to specify certainty (yes/no). This was done to ensure quality of data and to flag for any concerns.

Analysis of research aims

The research questions of interest were determining what maternal and paternal demographic characteristics were associated with reporting of any family history compared to those not reporting any family history. The second question was to determine the frequency of reporting family history of birth defects or other conditions by mothers of cases vs controls. The last question was to analyze what specific birth defects are reported among mothers who report a family history of birth defects.

The first step of the analysis was to assess factors associated with any report of a family history of a condition, among cases and controls combined. 'Any' family history indicates that the participants responded affirmatively to any of the selected family history questions while 'no family history' means that they did not respond to any family history questions. A chi square test was used to assess which demographic or other characteristics were significantly ($p<0.05$) associated with maternal reports of a family history of any condition or birth defects. The second part of the analysis consisted of conducting descriptive frequencies of the reporting of birth defects and other conditions by case/control status. The third part of the analysis was reporting the frequencies of the types of birth defects that were reported by case/control status of the index pregnancy. We also compared the reported family history of birth defects against the actual birth defect present in the index case.

Chapter 3: Results

A total of 4,253 birth defect cases and controls delivered from 2014-2019, and their mothers, participated in BD-STEPS. Of these, 2,676 were cases and 1,577 were controls. For our analysis, we identified mothers who responded affirmatively to family history questions for the mother, father, and siblings (including twins) of the index pregnancy. In total, 824 (19.4%) mothers of eligible cases and controls responded affirmatively to at least one of the family history questions; 583 (70.8%) were mothers of cases and 241 (29.3%) were mothers of controls. Overall, 331 participants (n=261 cases, n=70 controls) reported having a family history of a birth defect (Figure 1).

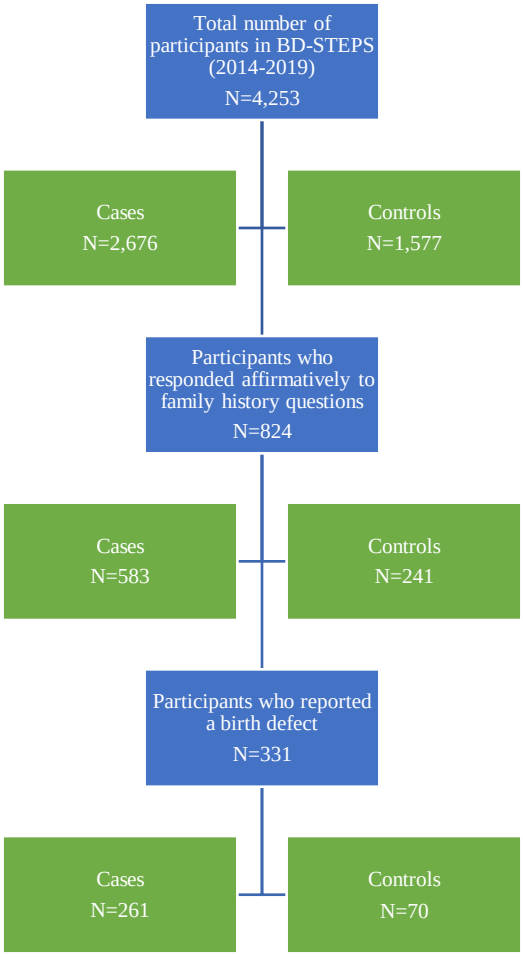

Figure 1 Participants in Family History study BD-STEPS 2014-2019

Demographic characteristics associated with any report of family history

Table 1 describes maternal and infant characteristics associated with maternal reports of 'any' first-degree family history of a birth defect or other condition, among cases and controls combined. A significantly higher proportion of mothers of cases (21.8%, n=584) reported 'any' family history compared to mothers of controls (15.3%, n=241). Maternal reporting of 'any' family history varied significantly by both maternal and paternal race ethnicity. The highest frequency of reporting occurred among mothers who identified as 'other' with 35.0% reporting 'any' family history. The lowest reporting occurred among mothers who identified as Asian, where 11.0% reported 'any' family history. For paternal race and ethnicity, infants of Native Hawaiian or other Pacific Islander paternal race/ethnicity

had the highest frequency of family history of a birth defect or other condition (31.3%) by maternal report. Fathers who, by maternal report, identified as Asian had the lowest frequency of any family history of birth defects or conditions with 12.7% having any family history. Associations between both maternal and paternal race ethnicity and maternal report of family history of a birth defect or other condition were statistically significant with a p-value of <0.0001.

Across categories of maternal age, the highest frequency of any family history of a birth defect or other condition was reported among women 26-29 of age (21.6%) and lowest among women less than 20 years of age (14.2%). Associations between maternal age and maternal report of family history of a birth defect or other condition were statistically significant with a p-value of 0.03. Maternal reports of a family history of a birth defect or other condition also varied significantly (p-value=0.01) by levels of maternal education, ranging from 10.0% (0-6 years of education) to 19.2% ($\geq$ 12 years of education). Two other demographic variables that influenced level of reporting were language of interview and language spoken at home. Participants who took the CATI in English and primarily spoke English at home reported family history of any condition more frequently (20.9% and 21.7%, respectively) compared to those who took the survey in Spanish and spoke another language at home (10.7% and 14.2%, respectively).

Maternal and paternal birthplace affected level of reporting as well; 22.1% of mothers who had a birthplace in the United States (US) reported a family history of a birth defect or other conditions, as did 21.8% whose infant's father was born in the US. This is higher than mothers and fathers born outside of the US, who had reporting rates of 11.4% and 13.1%, respectively. Both demographic characteristics were significant with p-values less than 0.0001. Finally, it was found that when fathers contributed to mother's answers, there was a higher reporting of birth defects or other conditions (32.7%) compared to when fathers did not contribute to answers (18.8%).

Table 1: Maternal and infant characteristics associated with maternal reports of any first-degree family history, Birth Defects Study to Evaluate Pregnancy Exposures, 2014-2019 (N=4,253)

	Any family history* N (%**)	No family history* N (%**)	P-value***
Total	824	3,429	
Infant case status			<0.0001
Case	584 (21.8)	2093 (78.2)	
Control	241 (15.3)	1,336 (84.7)	
Maternal race and ethnicity			<0.0001
Non-Hispanic White	490 (22.2)	1715 (77.8)	
Non-Hispanic Black	90 (18.7)	392 (81.3)	
Hispanic	179 (15.1)	1009 (84.9)	
Asian	22 (11.1)	176 (88.9)	
Native Hawaiian or Other Pacific Islander	2 (16.7)	10 (83.3)	
Other	7 (35.0)	13 (65.0)	
Missing	35 (23.5)	114 (76.5)	
Paternal race and ethnicity			<0.0001
Non-Hispanic White	431 (21.8)	1544 (78.2)	
Non-Hispanic Black	91 (19.0)	388 (81.0)	
Hispanic	162 (15.1)	912 (84.9)	
Asian	21 (12.7)	145 (87.4)	
Native Hawaiian or Other Pacific Islander	5 (31.3)	11 (68.8)	
Other	3 (20.0)	12 (80.0)	
Missing	112 (21.2)	417 (78.8)	
Maternal age (yr)			0.0344
<20	28 (14.2)	169 (85.8)	
20-25	196 (20.6)	758 (79.5)	
26-29	208 (21.6)	754 (78.4)	
30-34	224 (17.1)	1083 (82.9)	
35-39	138 (20.5)	535 (79.5)	
40 and older	31 (19.3)	130 (80.8)	
Missing	0 (0.0)	0 (0.0)	
Maternal education (years)			0.0125
0-6	15 (10.0)	135 (90.0)	
7-12 completed High School or equivalent	218 (19.2)	919 (80.8)	
>12 more than High School	523 (19.8)	2120 (80.2)	
Missing	69 (21.3)	255 (78.7)	
Paternal education (years)			0.0023
0-6	23 (11.0)	187 (89.1)	
7-12, completed High School or equivalent	298 (21.1)	1116 (78.9)	
>12 more than High School	412 (19.2)	1732 (80.8)	
Missing	92 (18.9)	394 (81.1)	
Language of interview			<0.0001
English	685 (20.9)	2601 (79.2)	
Spanish	63 (10.7)	528 (89.3)	
Missing	77 (20.4)	300 (79.6)	
Language spoken at home			<0.0001
English	640 (21.7)	2307 (78.3)	

Other	185 (14.2)	1122 (85.9)	
Missing			
Maternal birthplace			<0.0001
U.S.	633 (22.1)	2231 (77.9)	
Outside of U.S.	123 (11.4)	953 (88.6)	
Missing	69 (22.0)	245 (78.0)	
Paternal birthplace			<0.0001
U.S.	605 (21.8)	2171 (78.2)	
Outside U.S.	141 (13.1)	935 (86.9)	
Missing	79 (19.7)	323 (80.4)	
Father contributed to mother's answers			<0.0001
Yes	51 (32.7)	105 (67.3)	
No	687 (18.8)	2966 (81.2)	
Missing	87 (19.6)	358 (80.5)	
Other person contributed to mother's answers			
Yes	8 (28.6)	20 (71.4)	0.2267
No	738 (19.2)	3113 (80.8)	
Missing			

* Family history of a birth defect was defined as an affirmative response to at least one of following questions for the mother, father, or sibling of the index child: "Did you/they have a health problem at birth or a birth defect that was diagnosed in childhood?" and "What was it?" or from the heart section of the CATI: "Do you/they have a heart problem that has been present since birth? Please do not include problems that went away on their own." and "What is it?". Some participants reported conditions that are not birth defects, so any birth defect or condition reported was considered 'any' family history
** row percent
*** Excludes missing

Maternal reports of family history of a birth defect or other condition by case/control status

Table 2 describes maternal reports of first-degree family history of a birth defect or other condition, by type of condition and case/control status of the index pregnancy. Among the 2,676 cases in BD-STEPS, mothers of 261 cases (9.8%) reported a family history of a birth defect compared to mothers of 70/1577 (4.4%) controls. The second most frequent condition reported was 'prematurity or low birth weight', reported by 2.2% of case mothers and 1.6% of control mothers. Only 29 case mothers (1.1%) and 19 (1.2%) control mothers reported a genetic condition. 'Other' conditions included, for instance, asthma, eczema, diabetes, endometriosis, and heart murmurs (with no accompanying details); 258 (9.6%) case mothers reported a family history of other conditions as did 124 (7.8%) control mothers.

Table 2. Maternal reports of first-degree family history by case/control status of the index pregnancy, Birth Defects Study to Evaluate Pregnancy Exposures, 2014-2019 (N=4,253).

	Cases N=2676 N (%)	Controls N=1577 N (%)	Total N
Any condition (At least one reported)	583 (21.8)	241 (15.3)	824
Birth defect	261 (9.8)	70 (4.4)	331
Prematurity or low birth weight	60 (2.2)	26 (1.6)	86
Developmental disorder	49 (1.8)	22 (1.4)	71
Genetic disorder	29 (1.1)	19 (1.2)	53
'Other' conditions*	258 (9.6)	124 (7.8)	382
Unsure/refused to provide specific condition**	35 (1.3)	22 (1.4)	57

* Includes conditions such as asthma, a heart murmur (with no accompanying details), eczema, diabetes, stillborn baby, and endometriosis

** Some women responded affirmatively to the initial questions about family history but could not recall or refused to provide the specific condition

Maternal reports of family history of defects by type of birth defect

Table 3 shows the frequency of maternal reports of first-degree family history of a birth defect, by type of birth defect and case/control status of the index pregnancy. Heart defects were the most frequently reported birth defect type, among mothers of both cases and controls. Out of the 261 cases that reported a family history of birth defects, 74 (28.4%) reported at least one instance of family history of heart defects. Mothers of cases also frequently reported a family history of orofacial clefts (n=71;27.2%) and limb deficiencies (n=31;11.9%). Mothers of controls most frequently reported a family history of heart defects (n=25;35.7%), limb deficiencies (n=12;17.1%), and gastrointestinal defects (n=10;(14.3%). Reports of choanal atresia and musculoskeletal defects were rare.

Table 3: Maternal reports of first-degree family history of a birth defect, by type of birth defect and case/control status of the index pregnancy, among cases and controls with a family history of a birth defect, Birth Defects Study to Evaluate Pregnancy Exposures, 2014-2019 (N=331).

	Cases N (%)	Controls N (%)	Total N
Maternally-reported birth defect	261	70	331
Heart	74 (28.4)	25 (35.7)	99
Orofacial Clefts	71 (27.2)	5 (7.1)	76
Limb Deficiency	31 (11.9)	12 (17.1)	43
Gastrointestinal Defects	18 (6.9)	10 (14.3)	28

Genitourinary Defects	14 (5.4)	6 (8.6)	20
Central Nervous System (excluding NTDs)	15 (5.7)	1 (1.4)	16
Eye	11 (4.2)	4 (5.7)	15
Neural Tube Defects (NTD)	11 (4.2)	3 (4.3)	14
Non-System Specific Defects*	10 (3.8)	2 (2.9)	12
Abdominal Wall Defects	6 (2.3)	4 (5.7)	10
Ear	6 (2.3)	1 (1.4)	7
Craniosynostosis	3 (1.1)	3 (4.3)	6
Diaphragmatic Hernia	5 (1.9)	0 (0.0)	5
Hypospadias	4 (1.5)	1 (1.4)	5
Renal Agenesis	2 (0.8)	1 (1.4)	3
Choanal Atresia	1 (0.4)	0 (0.0)	1
Musculoskeletal Defect	1 (0.4)	0 (0.0)	1

*Non-system specific defects include amnion rupture and skin defects like hemangiomas as well as endocrine defects

Type of birth defect reported among cases by birth defect of case infant

Table 4 shows the number of maternal reports of birth defects in first-degree relatives, by type of birth defect of the index case, among cases with a family history of a birth defect. The most frequently reported birth defect among mothers of the 106 cases with oral cleft were orofacial clefts (n=55). Other commonly reported birth defects were hypospadias (n=32), limb deficiencies (n=12), and heart defects (n=12). A family history of heart defects was also the most common birth defect reported among the 79 cases of heart defects (n=43); other commonly reported birth defects were orofacial clefts (n=8) and limb deficiencies (n=7). Among the 21 cases of spina bifida, only 5 had a family history of an NTD; other commonly reported defects were heart defects (n=6) and orofacial clefts (n=5). Among the 14 cases of diaphragmatic hernia, 3 cases had a reported a family history of a diaphragmatic hernia and 4 of heart defects. Of the 16 cases of esophageal atresia, 4 reported a family history of gastrointestinal defects. Among the 13 cases of anotia/microtia, 4 mothers reporting a family history of ear defects and four reported limb deficiencies. Among the 16 cases of gastroschisis, 2 had a family history of an abdominal wall defect. Out of the 3 cases of anophthalmos/microphthalmos, 2 reported a family history of an eye defect. Of the 5 mothers of cases with transverse limb deficiency, 1 reported a family history of a limb defect.

Table 4: Maternal reports of birth defects in first-degree relatives, by type of birth defect of index case, among cases with a familiar history of a birth defect, Birth Defects Study to Evaluate Pregnancy Exposures, 2014-2019 (N=261).

Type of birth defect reported in first-degree relative	Birth Defect of BD-STEPS Case Infant* , N								
	Any Cleft N=106	Any Heart Defect N=79	Spina Bifida N=21	Diaphragmatic Hernia N=14	Esophageal Atresia N=16	Anotia/Microtia N=13	Gastroschisis N=16	Anopthalmos/Microphthalmos N=3	Transverse Limb Deficiency N=5
Orofacial Clefts	**55**	8	5	0	2	1	1	0	0
Heart	12	**43**	6	4	2	2	5	1	0
Hypospadias	32	0	0	0	2	0	0	0	0
All Limb Deficiencies	12	7	1	1	0	4	4	1	**1**
Gastrointestinal Defects	7	5	0	1	**4**	1	0	0	0
Neural Tube Defects (NTD's)	1	3	**5**	2	0	1	0	0	0
Central Nervous System (excluding NTD's)	4	3	4	0	1	0	1	1	1
Eye	6	2	0	0	1	0	0	**2**	0
Ear	1	1	0	0	0	**4**	0	0	0
Choanal Atresia	1	0	0	0	0	0	0	0	0
Renal Agenesis	1	0	0	0	0	0	0	0	1
Craniosynostosis	2	1	0	0	0	0	0	0	0
Diaphragmatic Hernia	2	0	0	**3**	0	0	0	0	0
Abdominal Wall Defects	1	1	0	2	0	0	**2**	0	0
Genitourinary Defects	3	6	2	2	1	0	1	0	0
Non-System Specific Defects	2	0	3	1	2	1	0	0	1
Musculoskeletal Defect	0	1	0	0	0	0	0	0	0
Total	142	81	26	16	15	14	14	5	4

Bold=family history of the same defect

* Columns could sum to more than the total because cases could have family history of more than one birth defect

Chapter 4: Discussion

In this analysis, our first question of interest was to determine whether the frequency of maternally reported family history of a birth defect or other condition varied between birth defect cases and controls. We also wanted to determine what maternal and paternal characteristics were associated with a report of a family history of birth defects. The third goal of this analysis was to determine what conditions were reported to have occurred among first-degree family members of birth defect cases and live born controls.

In this analysis of birth defect cases and controls delivered during 2014-2019, we found that maternal reports of family history of a birth defect or other condition were quite common, being reported by 583 (21.8%) case mothers and 241 (15.3%) control mothers. Birth defects were commonly reported (9.7% of case mothers and 4.4% of control mothers). 'Other' conditions were also highly reported (9.6% of case mothers and 7.8% of control mothers) (e.g., asthma, heart murmur with no accompanying details, eczema, diabetes, stillbirth, endometriosis). Demographic characteristics associated with maternal report of any family history of a birth defect or other condition among first-degree relatives included maternal and paternal race/ethnicity, maternal age, maternal and paternal education, as well as interview language and language spoken at home, and maternal and paternal place of birth. Mothers identifying as 'other' race category reported the most family history and among paternal race/ethnicity, 'Native Hawaiian or other Pacific Islander' reported the most. Another demographic of interest is maternal age, the lowest level of reporting was among the less than 20-year-old category. This could be due to less awareness of birth defects within their family and the father's family. The most commonly reported birth defects in first degree family members of cases were heart defects (28.4%), orofacial clefts (27.2%), and limb deficiencies (11.9%). In first degree family members of controls, the most commonly reported birth defects were heart defects (35.7%), limb deficiencies (17.1%), and gastrointestinal defects (14.3%).

Infants born to mothers identifying as ‘other’ race/ethnicity had the highest frequency of a family history of a birth defect or other condition, as did those born to fathers of ‘Native Hawaiian or other Pacific Islander’ race/ethnicity. The lowest frequency of reporting of a family history of a birth defect or other condition by maternal age group was among mothers less than 20-years of age. This could be due to less awareness of birth defects within their family and the father’s family. These findings are consistent with the previous analysis by Green et al., in which women under the age of 25 years had less reporting of a family history of a birth defect compared to mothers above the age of 25 years (Green et al., 2008).

Infants born to mothers and fathers with < 6 years of education had the lowest frequency of maternal reporting of a family history of a birth defect or other condition. Language is another factor that influenced level of reporting. Language can be considered a proxy for factors like acculturations, health literacy, and knowledge of family history. Out of the mothers who took the interview in Spanish, only 10.7% reported any family history compared to 20.9% of mothers who took the interview in English. This finding is consistent with the previously published paper examining reporting of family history using NBDPS data from deliveries during 1997-2001 (Green et al., 2008). These findings suggest that further analyses could explore reasons for the relationship between language and reduced reporting. Birthplace outside of the US for both mothers and fathers also showed lower reporting. Of note, reports of a first-degree family member with a birth defect or other condition increased when fathers contributed to answers, indicating that it could be useful to obtain family history from both parents.

Birth defects and ‘other’ conditions were the most reported conditions among cases and controls. The CATI question asked specifically about any family history of birth defects so this could be a reason that mothers reported birth defects more frequently. However, participants reported a variety of conditions aside from birth defects. Of the birth defects reported, heart defects, orofacial clefts, and limb deficiencies were the most highly reported defects. This could indicate that there is a stronger genetic component for these defects. Family history of the same defect may support this hypothesis as well.

Maternal family history reports of the same birth defects found in the index case were most often reported for index cases with orofacial clefts and heart defects.

There could be potential genetic and environmental risk factors for these defects and more research is needed to better understand the relationship between family history as a proxy for these components. These findings are congruent with other recent studies showing a positive association between family history of orofacial clefts and prevalence of orofacial clefts (Silva et al., 2022). Another study found that prevalence of congenital heart defects in first-degree relatives was significantly higher compared to second-degree relatives for cases (Wang et al., 2014). Similarly for heart defects, one study conducted in Denmark found that there was strong clustering within family history of first-degree relatives, from 3- to 80-fold, depending on the type of heart defect, compared to the prevalence in the general population (Øyen et al., 2009). A recent study also found that NTDs may have a genetic link given that 16.9% of cases had a family history of NTDs (Dupépé et al., 2017). However, more research could be conducted in this area to determine the relationship between familial recurrence of birth defects and selected birth defects like heart defects, orofacial clefts, and neural tube defects. Among the 3 cases of anophthalmia and microphthalmia, 2 reported family history of an eye defect. Given the complex cause and development of these birth defects, including genetic mutations and environmental risk factors, more research should be conducted to determine the role family history plays as a risk factor (Amit S. Verma & David R. FitzPatrick, 2007).

One interesting finding that could warrant more research is the high level of reporting of a family history of hypospadias among mothers of infants with orofacial clefts who reported a family history of any birth defect. A retrospective review study conducted in South America from 1982-2011 found that orofacial anomalies were seen in 13.2% of cases of hypospadias, and the most common type was cleft lip/palate (Fernandez et al., 2016). Further research could examine if there is a relationship between hypospadias and orofacial clefts. Finally, gastroschisis had a low level of reporting for the corresponding birth defect group. This may indicate that there is not a strong genetic component. A literature and data

extraction study covering population based studies from 1970–2017 found that although there is usually low familial recurrence of gastroschisis, there may be environmental factors such as common family exposure that can be related to incidence of gastroschisis (Salinas-Torres et al., 2018).

These results highlight the heterogeneous nature of family history of birth defects. Some birth defects were more commonly reported among first degree relatives while others were less so. This preliminary analysis can serve as a starting point for further research in this area. Maternal reporting of a family history of a birth defect or other condition varies by characteristics such as race and ethnicity, education, language spoken at home, and age.

This analysis demonstrates the value of measuring the family history of birth defects in studies assessing risk factors for birth defects. Variation in maternal reports of family history of a birth defect or other condition by language of interview and nativity was observed. Understanding how nativity and language impacts survey responses could be a useful avenue for further research. This could include cognitive testing that assesses interpretation of questions in the source language to determine the quality of the translation (Schoua-Glusberg & Villar, 2014).

Limitations

Some limitations of this study are that the coding used to create the family history variables was subjective and only based on the review of one person. Given that another reviewer may code responses differently, there is the possibility for information bias. However, there were several ways that the coding was flagged for any uncertainty. First, there was a certainty variable created where the coder stated ‘yes’ or ‘no’ for certainty. If the coder reported ‘no’ for certainty, these responses were marked for further deliberation. In future analyses, these questions will be reviewed again with another coder and discussed to come to a consensus on how to report the family history. If an appropriate decision for the response is not reached, then the defect will be coded as “unsure.” Replication will also be conducted on the analysis, so there will be multiple qualitative coders for this analysis.

Recommendations for future research

This analysis serves as an initial descriptive study to examine factors associated with maternal reports of birth defects or other conditions and which birth defects may be more related to family history. These findings can motivate future projects that may be focused on specific birth defects like orofacial clefts, ear defects, and heart defects. Additionally, the demographic results were consistent with the previous analysis indicating that demographic characteristics such as language and place of birth might be worth exploring in greater detail. Finally, we can see that family history is more prevalent among cases suggesting that this is a valuable variable to take into consideration when looking at risk factors for birth defects.

Disclaimers:

The results presented are preliminary and might change in the final publication. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the North Carolina Department of Health and Human Services, Division of Public Health.

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