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SHORT COMMUNICATION

Why Has Gastroschisis Increased Over Time and Why Is It More Common in Infants of Young Mothers?

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Keywords: birth defects | congenital abnormalities | gastroschisis | maternal age | time trends

ABSTRACT

Background: Although many factors are associated with gastroschisis risk, studies have not systematically explored whether they account for its increasing frequency over the past decades or its inverse association with maternal age. We examined whether previously reported risk factors for gastroschisis from the National Birth Defects Prevention Study (NBDPS) explain the association with increasing temporal prevalence or young maternal age.

Methods: Using data from the NBDPS (1997–2011), crude odds ratios (ORs) were calculated for birth years 2005–2011 versus 1997–2004 and maternal age < 25 versus 25+ years. We then adjusted for 16 factors separately with logistic regression (paternal age, interpregnancy interval, parity, alcohol, cigarettes, illicit drugs, oral contraceptives, cold/flu with fever, genitourinary infection, polycyclic aromatic hydrocarbons, diet quality, prepregnancy body mass index, parental race and ethnicity, language spoken at home, years lived in the United States, and household income).

Results: The birth year OR (1.28; 95% CI: 1.14, 1.44) was attenuated by 16% after adjustment for polycyclic aromatic hydrocarbon exposure (OR 1.08; 95 CI: 0.92, 1.26). The young maternal age OR (7.76; 95% CI: 6.71, 8.97) was attenuated by 30% after adjustment for paternal age (OR 5.43; 95% CI: 4.55, 6.48) and separately for interpregnancy interval (OR 5.45; 95% CI: 4.43, 6.69).

Conclusion: Some evidence suggests that risk factors for gastroschisis account for small amounts of the time trend and maternal age associations. However, it remains unclear what factors underlie the complete calendar time or maternal age associations.

1 | Introduction

Gastroschisis is a severe congenital malformation that results in the herniation of the bowel and occasionally other organs through a hole usually to the right of the umbilicus in newborns. Although rare, gastroschisis occurs more frequently in the offspring of mothers < 25 years old relative to mothers ≥ 25 years old (Jones et al. 2016), and the prevalence of gastroschisis has increased over time in the United States (Jones et al. 2016; Kirby et al. 2013) and internationally (Loane et al. 2007).

While many studies have sought to identify environmental and maternal factors that increase the risk for gastroschisis after controlling for potential confounding by maternal age, it is not clear whether previously identified risk factors explain the strong inverse association with maternal age or the increasing trend over time. We examined whether previously reported risk factors for gastroschisis identified in the National Birth Defects Prevention Study (NBDPS) explain the associations with time or maternal age.

2 | Methods

The NBDPS was a multisite, population-based, case–control study designed to investigate risk factors associated with pregnancies affected by major congenital anomalies with deliveries during or after October 1997 and estimated dates of delivery (EDD) during or before December 2011. Cases were identified from birth defects surveillance systems in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah, and included live births, stillbirths, and terminations. Controls were live-born infants without major structural malformations, randomly selected from birth certificates or hospitals in the same catchment areas as cases. After informed consent, mothers of cases and controls were interviewed by telephone within 2 years after EDD about demographics, reproductive history, occupation, medication use, illnesses, lifestyle, and other exposures. The study was approved by the institutional review board at each participating site and the Centers for Disease Control and Prevention (CDC).

A clinical geneticist reviewed gastroschisis case records, and those with known chromosomal anomalies, genetic defects, and phenotypes consistent with amniotic band sequence or limb–body wall complex were excluded. Data for this study were from previous NBDPS investigations (Feldkamp et al. 2014; Lupo et al. 2012; Werler et al. 2018) and included gastroschisis cases with or without other structural malformations. Other details of the study design have been described previously (Reefhuis et al. 2015).

Factors selected for inclusion in this study included those previously reported to be associated with an increased risk for gastroschisis in NBDPS publications, including genitourinary infection (Feldkamp et al. 2019), estimated cumulative exposure to PAHs across all jobs (Lupo et al. 2012), years lived in the United States at the time of delivery (Khodr et al. 2013), language spoken at home (Khodr et al. 2013), cold or flu with fever (Waller et al. 2018), diet quality index (Feldkamp et al. 2014), maternal alcohol use (Richardson et al. 2011; Werler et al. 2018), cigarette smoking (Werler et al. 2018), maternal illicit drug use (Werler et al. 2018), parental race and ethnicity (Khodr et al. 2013), household income (Neo et al. 2023; Petersen et al. 2021), parity (Khodr et al. 2013), interpregnancy interval (Petersen et al. 2021), paternal age (Green et al. 2010), oral contraceptive use (Waller et al. 2010), and prepregnancy body mass index (BMI) (Siega-Riz et al. 2009). For alcohol use, cigarette smoking, illicit drug use, oral contraceptive use, genitourinary infection, cold or flu with fever, and estimated cumulative exposure to PAHs (including restriction to assignment with greatest confidence by industrial hygienist) (Lupo et al. 2012), we considered mothers exposed if they reported exposure for the interval beginning 1 month before through the first 3 months of pregnancy. Additional details on exposure definitions have been published previously (Feldkamp et al. 2019; Feldkamp et al. 2014; Green et al. 2010; Khodr et al. 2013; Lupo et al. 2012; Neo et al. 2023; Petersen et al. 2021; Richardson et al. 2011; Siega-Riz et al. 2009; Waller et al. 2010; Waller et al. 2018; Werler et al. 2018).

2.1 | Data Analysis

To represent the increasing trend of gastroschisis occurrence across the 1997–2011 time period, we dichotomized birth year at the halfway point of the study period (2005–2011 vs. 1997–2004). Maternal age at conception was also dichotomized (< 25 years old vs. ≥ 25 years old). We used separate logistic regression models to estimate odds ratio (OR) for the time trend and maternal age categories. Risk factors were each separately added to the crude logistic regression model and percent change was calculated: [(e.g., crude $OR_{time\ trend}$ − adjusted $OR_{time\ trend}$)/crude $OR_{time\ trend}$] (Greenland and Pearce 2015; Weng et al. 2009). All statistical analyses were conducted using SAS Enterprise Guide 8.3 (SAS Institute Inc., Cary, NC, USA).

3 | Results

There were 1278 cases and 10,611 controls. The crude OR for the time trend (2005–2011 vs. 1997–2004) in gastroschisis was 1.28 (95% CI: 1.14, 1.44). Adjustment for estimated cumulative exposure to PAHs across all jobs (OR = 1.08; 95% CI: 0.92, 1.26), parental race and ethnicity (OR = 1.24; 95% CI: 1.11, 1.40), years lived in the United States (OR = 1.26; 95% CI: 1.12, 1.42), and illicit drug use (OR = 1.27; 95% CI: 1.13, 1.43) resulted in the OR for the gastroschisis year parameter moving closer to the null (Table 1). The OR for the time trend was most attenuated with adjustment for estimated cumulative exposure to PAHs across all jobs (15.6%).

The crude OR for maternal age (< 25 years vs. ≥ 25 years) and gastroschisis was 7.76 (95% CI: 6.71, 8.97), which decreased with adjustment for paternal age, interpregnancy interval, parity, cigarette smoking, maternal illicit drug use, estimated cumulative exposure to PAHs across all jobs, parental race and ethnicity, household income, genitourinary infection, oral contraceptive use, prepregnancy BMI, and cold or flu with fever (Table 2). We observed the largest attenuation of the OR with adjustment for factors known to be strongly correlated with maternal age, particularly paternal age (OR = 5.43; 95% CI: 4.55, 6.48; 30.0% change), interpregnancy interval, (OR = 5.45; 95% CI: 4.43, 6.69; 29.8% change), and parity (OR = 6.61; 95% CI: 5.70, 7.67; 14.8% change). The adjusted OR accounting for these three factors in a multivariable model was 4.19 (95% CI: 3.26, 5.37; 46.0% change).

4 | Discussion

Gastroschisis has two distinct epidemiologic features that set it apart from other congenital anomalies: increased birth prevalence during past decades and higher prevalence among younger

TABLE 1 | Gastroschisis odds ratios and 95% confidence intervals for time trend after adjustment, National Birth Defects Prevention Study, 1997–2011.

Adjustment factors	Dichotomization (if applicable) 2005–2011 vs. 1997–2004	Number of Obs 11,889	OR for time trend (95% CI) 1.28 (1.14, 1.44)	Percent change (OR)
Gastroschisis year parameter moved closer to the null				
Estimated cumulative exposure to PAHs across all jobs (μg/m^3 hours) (B1-P3)[a]	1 unit increase	8551	1.17 (1.01, 1.34)	8.6
PAH confidence ≥ 3[b]		*7616*	*1.08 (0.92, 1.26)*	*15.6*
Parental race and ethnicity	All other combinations vs. both parents non-Hispanic White	11,709	1.24 (1.11, 1.40)	3.1
Years lived in the US for mothers	< 6 years in the US vs. ≥ 6 years in the US or US born	11,620	1.26 (1.12, 1.42)	1.6
Maternal illicit drug use (B1-P3)	Yes vs. no	11,889	1.27 (1.13, 1.43)	0.8
Gastroschisis year parameter unchanged or moved away from the null				
Household income/number of people supported	≥ median vs. < median	10,783	1.28 (1.13, 1.45)	0.0
Language spoken at home	Other vs. English	11,855	1.28 (1.14, 1.44)	0.0
Cold or flu with fever (B1-P3)	Yes vs. no	11,889	1.28 (1.14, 1.44)	0.0
Maternal alcohol use (B1-P3)	Yes vs. no	11,889	1.28 (1.14, 1.44)	0.0
Genitourinary infection (B1-P3)[a]	Yes vs. no	11,889	1.29 (1.15, 1.45)	0.8
Parity	1+ vs. 0	11,887	1.29 (1.14, 1.45)	0.8
Prepregnancy body mass index (kg/m^2) (4 groups)	Healthy weight (18.5–24.9)/ overweight (25.0–29.9)/ obese (≥ 30.0) vs. underweight (< 18.5)	11,889	1.29 (1.15, 1.45)	0.8
Diet quality index	2 highest vs. 2 lowest quartiles	11,438	1.30 (1.15, 1.46)	1.6
Used oral contraceptives (B1-P3)	Yes vs. no	11,889	1.30 (1.15, 1.46)	1.6
Maternal age	< 25 years old vs. ≥ 25 years old	11,889	1.35 (1.19, 1.52)	5.5
Paternal age	< 25 years old vs. ≥ 25 years old	11,532	1.37 (1.21, 1.55)	7.0
Cigarette smoking (B1-P3)	Yes vs. no	11,885	1.39 (1.24, 1.57)	8.6
Interpregnancy interval[c]	< 12 months vs. ≥ 12 months	6826	1.40 (1.16, 1.71)	9.4

Note: Given that the confidence interval is more informative than a *p*-value, the confidence interval is reported. https://www.amstat.org/asa/files/pdfs/P-ValueStatement.pdf.
Abbreviations: CI, confidence interval; obs, observations; OR, odds ratio; PAH, polycyclic aromatic hydrocarbons.
[a]Exposure during the interval beginning 1 month before through the first 3 months of pregnancy.
[b]Because PAH variables were based on industrial hygienists assigning likelihood of exposure for a reported job, we conducted a sensitivity analysis by restricting to those whose exposure was assigned with greatest confidence (score ≥ 3, scale of 1–4).
[c]Excludes individuals with no previous pregnancies resulting in live birth or stillbirth.

mothers. Although biological mechanisms that result in this condition have been proposed (Bargy and Beaudoin 2014; Opitz, Feldkamp, and Botto 2019; Rittler, Vauthay, and Mazzitelli 2013) and numerous risk factors have been identified, it remains unclear why gastroschisis risk is higher in young mothers and why it increased over time. It is widely hypothesized that exposures thought to be more common among younger mothers explain these unique trends. Using data from the NBDPS, we show that previously reported risk factors for gastroschisis generally do not explain the increasing time trend or inverse maternal age association.

The 1.28-fold greater risk of gastroschisis for births in the second half of the NBDPS study period was altered after controlling for estimated cumulative exposure to PAHs across all jobs, reducing the time trend OR to 1.08. To our knowledge, this is the first study to evaluate the role of PAHs in time trend analyses of gastroschisis. All other exposures we examined did not account for the increasing time trend. A study that used birth certificate data also found that maternal and infant characteristics did not independently account for the increasing time trend (Vo and Langlois 2015). Additionally, an ecologic study that compared trends in gastroschisis with

TABLE 2 | Gastroschisis odds ratios and 95% confidence intervals for maternal age after adjustment, National Birth Defects Prevention Study, 1997–2011.

Adjustment factors	Dichotomization (if applicable)	Number of Obs	OR for maternal age (95% CI)	Percent change (OR)
	< 25 years vs. 25+ years	**11,889**	**7.76 (6.71, 8.97)**	
Maternal age parameter moved closer to the null				
Paternal age	< 25 years old vs. ≥ 25 years old	11,532	5.43 (4.55, 6.48)	30.0
Interpregnancy interval[a]	< 12 months vs. ≥ 12 months	6826	5.45 (4.43, 6.69)	29.8
Parity	1+ vs. 0	11,887	6.61 (5.70, 7.67)	14.8
Cigarette smoking (B1-P3)[b]	Yes vs. no	11,885	7.06 (6.09, 8.18)	9.0
Maternal illicit drug use (B1-P3)	Yes vs. no	11,889	7.25 (6.27, 8.39)	6.6
Estimated cumulative exposure to PAHs across all jobs (μg/m^3-hours) (B1-P3)	1 unit increase	8551	7.30 (6.17, 8.64)	5.9
PAH confidence ≥ 3[c]		*7616*	*7.28 (6.06, 8.73)*	*6.2*
Parental race and ethnicity	All other combinations vs. both parents non-Hispanic White	11,709	7.45 (6.43, 8.64)	4.0
Household income/number of people supported	≥ median vs. < median	10,783	7.45 (6.42, 8.76)	4.0
Genitourinary infection (B1-P3)	Yes vs. no	11,889	7.54 (6.52, 8.72)	2.8
Used oral contraceptives (B1-P3)	Yes vs. no	11,889	7.63 (6.60, 8.83)	1.7
Prepregnancy body mass index (4 groups)	Healthy weight (18.5–24.9)/overweight (25.0–29.9)/obese (≥ 30.0) vs. underweight (< 18.5)	11,889	7.67 (6.64, 8.87)	1.2
Cold or flu with fever (B1-P3)[b]	Yes vs. no	11,889	7.74 (6.69, 8.94)	0.3
Multivariable[d]		6669	4.19 (3.26, 5.37)	46.0
Maternal age parameter unchanged or moved away from the null				
Language spoken at home	Other vs. English	11,855	7.77 (6.72, 8.99)	0.1
Years lived in the US for mothers	< 6 years in the US vs. ≥ 6 years in the US or US-born	11,620	7.80 (6.74, 9.03)	0.5
Diet quality index	2 highest vs. 2 lowest quartiles	11,438	7.82 (6.74, 9.07)	0.8
Maternal alcohol use (B1-P3)	Yes vs. no	11,889	8.04 (6.95, 9.30)	3.6

Note: Given that the confidence interval is more informative than a *p*-value, the confidence interval is reported. https://www.amstat.org/asa/files/pdfs/P-ValueStatement.pdf.
Abbreviations: CI, confidence interval; obs, observations; OR, odds ratio; PAH, polycyclic aromatic hydrocarbons.
[a]Excludes individuals with no previous pregnancies resulting in live birth or stillbirth.
[b]Exposure during the interval beginning 1 month before through the first 3 months of pregnancy.
[c]Because PAH variables were based on industrial hygienists assigning likelihood of exposure for a reported job, we conducted a sensitivity analysis by restricting to those whose exposure was assigned with greatest confidence (score ≥ 3, scale of 1–4).
[d]Adjusted for paternal age, interpregnancy interval, and parity.

concurrent trends in prenatal use of illicit drugs reported no association (Forrester and Merz 2006).

The 7.76-fold increased risk of gastroschisis for mothers < 25 years old (vs. ≥ 25) was attenuated to some extent by paternal age, parity, interpregnancy interval, income, and parental race and ethnicity. Maternal illicit drug use, cigarette smoking, oral contraceptive use, and genitourinary infections have each been suspected to underlie the inverse maternal age association; although some evidence of attenuation by these exposures was observed, they accounted for only a small amount of the 7.76-fold OR. Estimated cumulative exposure to PAHs is the only exogenous exposure that was observed to partially attenuate both the maternal age and time trend associations but left both associations largely unexplained. Reports of effect modification by maternal age for some gastroschisis risk factors, often with higher ORs for older mothers (Lupo et al. 2012; Weber et al. 2019; Werler et al. 2018), do not have bearing on our exploration of adjustments of the association between maternal age and gastroschisis.

Typically, multivariable models to estimate associations of exposures and risk of gastroschisis adjust for maternal age as a potential confounder (Feldkamp et al. 2019; Feldkamp et al. 2014; Khodr et al. 2013; Lupo et al. 2012; Neo et al. 2023; Petersen et al. 2021; Richardson et al. 2011; Waller et al. 2018). Calendar time is less often considered a potential confounder, but it has been examined as such in at least one study (Neo et al. 2023). In the present study, we considered maternal age and calendar time as separate, primary factors in association with gastroschisis, not as causal factors for gastroschisis. Therefore, our analysis of risk factors to explain either the birth year or maternal age associations is not within a causal framework. ORs were estimated as measures of association, but not causation. We do not believe that birth year or maternal age cause gastroschisis in and of themselves; therefore, the 16 risk factors examined are not considered confounders or intermediates. We are, however, particularly interested in learning whether the previously identified risk factors might explain the unique descriptive epidemiology of gastroschisis.

The present findings should be interpreted within the context of several limitations. The NBDPS collected exposure information retrospectively and is susceptible to recall inaccuracies, which can also lead to misclassification and residual confounding. Second, average participation rates were 65% for cases and 65% for controls (Reefhuis et al. 2015), and did decline across all NBDPS years. If risk factors were associated with participation differentially for cases and controls, selection bias is possible. Third, unknown, and unmeasured factors may account for both time and maternal age associations with gastroschisis. However, a previous study examining over 200 parental exposures and activities during the periconceptional period did not find many previously unreported associations with gastroschisis (Weber et al. 2019). Indeed, studies of self-reported exposures are limited, and measures of biomarkers would likely advance knowledge. Lastly, the data for these analyses are from an earlier period, which may not reflect current trends. In more recent years, the prevalence of gastroschisis in the United States has appeared to decrease; however, the higher risk among young maternal age remains (Clark et al. 2020; Stallings et al. 2024). Strengths of the study include the use of a population-based study spanning over a decade with data on a wide range of exposures, which allowed for in-depth analyses. Additionally, as part of this study, all cases were reviewed for eligibility based on standard case definitions and classified by clinical geneticists at each study site.

5 | Conclusion

While there is some evidence that gastroschisis risk factors account for small amounts of the calendar time trend and maternal age associations, it remains unclear what factors underlie the complete associations. To advance our understanding of the causes of gastroschisis, studies of early pregnancy biomarkers are necessary.

Acknowledgments

Coding of drug and supplement information in the NBDPS and/or the BD-STEPS used the Slone Drug Dictionary under license from the Slone Epidemiology Center of Boston University. Portions of the data analysis were replicated prior to submission per the replication policy of the NBDPS and the BD-STEPS.

Ethics Statement

The study was approved by the institutional review board at each participating site and the CDC.

Consent

Study participants provided informed consent.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The study questionnaires and process for accessing the data used in this study is described at https://www.cdc.gov/birth-defects/php/bd-steps-nbdps-data/index.html. The code book and analytic code may be made available upon request.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

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