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Maternal Chlamydia Infection During Pregnancy Among Younger Mothers and Risk of Gastroschisis in Singleton Births

By

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Maternal Chlamydia Infection During Pregnancy Among Younger Mothers and Risk of Gastroschisis in Singleton Births

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

Maternal Chlamydia Infection During Pregnancy Among Younger Mothers and Risk of Gastroschisis in Singleton Births

By Tessa Horslev

BACKGROUND: Gastroschisis is a congenital birth defect characterized by the protrusion of the intestines through an opening in the abdominal wall and without a membrane covering. Prevalence of gastroschisis has been increasing in the United States (US) since the 1980s and younger women are at increased risk for delivering offspring with gastroschisis. Genital infection with *Chlamydia*, a bacterial sexually-transmitted disease, has also been increasing in prevalence over the last several years worldwide, particularly among young women. The etiology of gastroschisis is unknown, ongoing research suggests multiple causal factors may be involved, including infectious agents such as *Chlamydia*.

METHODS: We conducted a case-control study to examine the association between prenatal *Chlamydia* exposure in women 16 to 25 years of age and gastroschisis in their offspring (restricting to singleton births) from the 2014 US vital statistics data. Cases consisted of live births with gastroschisis (n=806) and controls were singleton births with no major birth defects (n=1,260,293). We performed unconditional logistic regression analysis to estimate crude and adjusted odds ratios (cOR and aOR) and 95% confidence intervals (CI) for all gastroschisis combined and isolated gastroschisis (without other selected major congenital malformations).

RESULTS: Among all cases, 4.5% of women reported an infection with *Chlamydia* during pregnancy compared to 3.6% of control women (P=0.21). Women who delivered babies with gastroschisis were significantly more likely to be younger (16-20 years of age) at the time of delivery compared to control mothers (P<0.0001). Our unadjusted analysis did not yield a statistically significant association between maternal exposure to *Chlamydia* and gastroschisis, either among all gastroschisis cases (cOR=1.24; 95% CI=0.89, 1.73) or isolated gastroschisis cases (cOR=1.24; 95% CI=0.88, 1.74). The effect estimates were further attenuated after controlling for potential confounders (all gastroschisis: aOR=1.06; 95% CI=0.66, 1.70 and isolated gastroschisis aOR=1.08; 95% CI=0.67, 1.73).

CONCLUSION: Our study was based on recent data including births occurring in the US in 2014. We were unable to find support for our hypothesis that there is a significant positive association between prenatal exposure to *Chlamydia* and gastroschisis in the offspring born to younger mothers in the US. We recommend that future studies investigate the hypothesis using other population-based studies.

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Table of Contents

INTRODUCTION

Gastroschisis is a congenital birth defect in which the intestines, and occasionally other abdominal contents, protrude through an opening in the abdominal wall and are not covered by a membrane (1). The malformation occurs very early in pregnancy, between the fourth and eighth week after conception (2). It is the most common abdominal wall birth defect, with a United States (US) birth prevalence estimated at 4.49 (95% Confidence Interval (CI): 4.28 – 4.69) per 10,000 live births (2). In Europe, the European Registry of Congenital Anomalies and Twins (EUROCAT), estimates a European birth prevalence of 2.80 (95% CI: 2.64-2.96) for the period 2008 to 2012 (3). Gastroschisis prevalence has been increasing significantly since the 1980s both in the US and worldwide (4, 5), nearly doubling during the period 1995 to 2005 (6). Globally, according to one review of available literature, it is estimated that prior to the 1950s, prevalence may have been as low as 1 in 50,000 births, but that prevalence today may be as much as 10 to 20 times higher (7).

Gastroschisis has a relatively low co-occurrence rate with other major defects. One international study, using data from twenty-four registries, all members of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), comprised of 3,322 cases found that approximately 86% of cases were isolated cases, 2% were associated with recognizable syndromes and 12% were cases with multiple congenital anomalies (8). Another study, using data from all infants diagnosed with gastroschisis discharged from 348 neonatal intensive care units (4687 infants) in North America managed by the Pediatrix Medical Group from 1997 to 2012, found 8% of gastroschisis cases (365 infants) were diagnosed with at least one other anomaly (8, 9).

One hypothesis on the mechanism of gastroschisis formation theorizes that an early tear in the umbilical cord prior to closure of the umbilical ring results in the defect. Another theory posits that one or more folds of the abdominal wall fail to fuse correctly, leading to a defect and herniation into the amniotic fluid (10), while others hypothesize that the defect is a result of thromboembolism or other vascular disruption (11, 12). Surgical repair is always required and typically occurs shortly after birth, placing neonates at increased risk for medical complications and infant mortality associated with the defect itself as well as surgical repair of the defect (13).

With its increasing birth prevalence, gastroschisis is a concern and public health issue. It is one of the most expensive birth defects in the US according to a 2003 Centers for Disease Control (CDC) report (5). In the US, infants born with gastroschisis make up less than 5% of all major birth defects but have the highest hospital length of stay (14). This is due to gastroschisis related intestinal dysfunction (GRID) and feeding intolerance associated with infants born with this malformation (15). Patients with GRID experience intestinal malabsorption and dysmotility, which can lead to dependence on total parenteral nutrition, infectious complications and intestinal failure (16). Mortality due to gastroschisis has decreased over the last two decades due to improved specialized care for these infants; however, the decrease in mortality has been accompanied by an increase in morbidity and monetary costs associated with this birth defect (5, 17). One published study estimated that the average hospital cost in the US in 2014 for infants with gastroschisis was $197,848, compared to a cost of $2,344 for an uncomplicated birth (5). The total annual economic burden of GRID in the US was estimated at over $128 million in 2004 dollars (16).

While there have been very few genetic studies of gastroschisis and no known definitive genetic cause of gastroschisis, case reports of gastroschisis in twins and siblings as well as familial recurrences suggest a possible genetic contribution to the condition (18-23). Utah Birth Defect Network found a statistically significant increased risk of gastroschisis among 30 multigenerational families; whether this increased risk related to familial factors was due to genetic susceptibility, environmental risk factors or a combination of the two was unknown (24). One small study in Indonesia (46 patients with gastroschisis and 89 matched controls) investigated a possible link between genetic prothrombotic polymorphisms and gastroschisis based on the theory that the defect is caused by vascular or thrombotic disruption. The study found a two-fold increase (95% CI: 1.13-3.86, p=0.018) in gastroschisis risk for mothers carrying the methylenetetrahydrofolate reductase (MTHFR) allele, one of three common prothrombotic polymorphisms (25). Another study investigating the possibility of a pathogenetic mechanism for gastroschisis compared 57 infants born in California between 1987 and 1989 to 506 control infants using a multilocus genotyping assay. Polymorphisms of four genes were found to have an association (odds ratio of approximately two) with gastroschisis. One of the polymorphisms also showed a gene-environment interaction with maternal smoking in which smoking mothers carrying an infant who had at least one variant allele had a higher risk for gastroschisis than nonsmoker or smokers who carried infants who did not have that particular variant allele (26). These studies suggest gene-environment interactions likely play a role in development of the defect.

Environmental causal factors have also been proposed for gastroschisis. Maternal age has been consistently identified as a risk factor for gastroschisis in multiple population-based case control studies (1, 4, 27-34). Younger mothers, especially those less than 20 years of age, are at greatest risk of delivering babies with gastroschisis. Published studies have also demonstrated an association between gastroschisis and young paternal age, even after adjusting for maternal age (1, 35, 36). Maternal immunologic response to novel paternal antigens may also be involved, with studies demonstrating an association between change in paternity and gastroschisis as well as short length of sexual cohabitation and gastroschisis in the offspring (33, 37). The season in which conception occurred may also be associated with gastroschisis development (38-40). Analysis of socioeconomic factors and their relationship to gastroschisis have yielded conflicting results, with some studies suggesting that lower socioeconomic status (as determined by selected variables such as income, maternal education or marital status) may be a risk factor for gastroschisis while other studies have not demonstrated this link (1, 28, 29, 34, 41). Cigarette smoking, alcohol consumption and illicit drug use (particularly vasoconstrictive drugs such as cocaine, amphetamines and ecstasy) have all been shown in various studies to be associated with an increased risk of gastroschisis (1, 34, 41-45). A few studies have also shown an association between maternal body mass index (BMI) and gastroschisis, with a higher BMI associated with a lower risk (43, 46, 47) and a lower BMI associated with an increased risk (1, 45, 48, 49). Studies have also identified associations with first trimester exposure to a number of medications including aspirin, ibuprofen, acetaminophen, pseudoephedrine and phenylpropanolamine and gastroschisis (50-52). While these medications vary in their mechanisms of action, all

can be indicated for infection or inflammation in the mother (53). In particular, acetaminophen, ibuprofen and aspirin might be used to relieve pain and fever associated with pelvic inflammatory disease, a common sequela of *Chlamydia*. Maternal exposure to genitourinary infections and sexually transmitted diseases has also been shown to be associated with increased risk of gastroschisis (45, 54, 55).

The underlying cause or causes of the recent increase in gastroschisis occurrence have yet to be identified. In its January 22, 2016 Morbidity and Mortality Weekly Report (MMWR), the CDC analyzed data from 14 state surveillance programs to investigate the average annual percent change (AAPC) in gastroschisis prevalence and compare prevalence during the period 2006-2012 to the period 1995-2005. Gastroschisis increased from 3.6 per 10,000 births during the period 1995-2005 to 4.9 per 10,000 births during 2006-2012, a 30% increase (4). From 1995 to 2012, gastroschisis prevalence increased across every category of maternal age and race/ethnicity. In non-Hispanic white mothers less than 20 years of age the AAPC was 3.1% (an overall 68% increase) during this time period, and non-Hispanic black mothers saw an AAPC of 7.9% during the same period (an overall 263% increase) (4). While non-Hispanic black mothers experienced the largest increase in prevalence (compared to non-Hispanic white and Hispanic mothers), the prevalence of gastroschisis among mothers younger than 20 years of age was highest among white mothers (18.1 per 10,000 live births) and Hispanic mothers (16.1 per 10,000 live births), compared to black mothers (10.2 per 10,000 live births) during the period 2006-2012 (4).

While the etiology of gastroschisis is uncertain, the rate and global scope of the increase in occurrence of gastroschisis make this change unlikely to be caused by

alterations in gene frequency (55). The epidemiologic patterns of this defect suggest that risk factors disproportionately affecting young women, such as lifestyle behaviors, environmental exposures or infectious agents may play a role (4). One investigation that used data from the National Birth Defects Prevention Study (NBDPS) from 1997-2003 found that women who reported having genitourinary infections (kidney, bladder and/or urinary tract infection) immediately prior to or during early pregnancy had a moderately increased risk of gastroschisis in their offspring. This risk was highest in women that also reported having a sexually transmitted infection (such as chlamydia, human papillomavirus, genital herpes, trichmoniasis, gonorrhea, bacterial vaginosis and self-report of pelvic inflammatory disease) in addition to genitourinary infection (STI only: aOR for isolated cases: 1.3 95% CI: 0.7, 2.4, aOR for all cases: 1.3 95% CI: 0.7, 2.3) and (STI plus UTI: aOR for isolated cases: 2.9 95% CI: 0.9, 9.5, aOR for all cases: 4.0 95% CI: 1.4, 11.6) (55).

One small, hospital-based, case-control study of 99 women (33 cases and 66 controls) found that women who were seropositive for IgG3 antibody to *Chlamydia* (a short-lived antibody involved in early response to the disease) had a 3.9 fold increased risk for gastroschisis in their offspring (54). Experimental evidence also confirms a teratogenic impact of *Chlamydia*. Studies on mice have shown that host cells infected with genital *Chlamydia* release intracellular factors that contribute to the inflammatory response, possibly leading to cell death (56). While the uterus and the fetal membrane afford protection to the developing fetus, it is still possible for ascending infections to pass through the cervical canal and cause harm to the fetus (57, 58). An exact mechanism by which maternal *Chlamydia* infection could lead to gastroschisis is

unknown. One theory suggests that proinflammatory cytokines induced by *Chlamydia* impair the normal abdominal wall development (54). Squamous cells line the cervical epithelium of adult females but immature undifferentiated columnar epithelial cells line the genital tracts of adolescents and young women. The immature epithelium is believed to be more susceptible to pathogens and is the preferred site for *Chlamydia* (54).

Chlamydia is a notifiable sexually transmitted disease caused by infection with the bacteria *Chlamydia trachomatis*. Since 1994, *Chlamydia* has been the most common sexually transmitted disease (STD) reported to the CDC (59). Infection with Chlamydia is typically asymptomatic, causing many infections to go undiagnosed and, consequently, unreported and untreated. According to CDC surveillance data, the national rate of reported cases increased 2.8% from the period 2011-2013 to the period 2013-2014, from 443.5 cases per 100,000 to 456.1 cases per 100,000, respectively. Adolescents and young adults aged 15-24 have the highest reported rates of *Chlamydia*. In 2014, the rate among women aged 15-19 years was 2,941.0 cases per 100,000 females and 3,651.1 cases per 100,000 for women aged 20-24 years (59). According to data from the 2007-2012 National Health and Nutrition Examination Survey (NHANES), the overall prevalence of *Chlamydia* was 1.7% among individuals aged 14-39 years. These rates vary widely by age and race/ethnicity: among sexually active females aged 14-24 years of age the overall prevalence was 4.7% and among non-Hispanic black females was 13.5% (60).

Chlamydia is treatable and can be cured with early diagnosis and antibiotic treatment, typically amoxicillin and azithromycin (61). However, approximately 80-90% of chlamydial infections in women are asymptomatic, a factor which may contribute to a woman's delay in seeking medical care and treatment (62). Routine screening of

sexually-active young women under the age of 25 for *Chlamydia* is recommended by the US Preventive Services Task Force in order to identify these infections (60, 63). If not treated, women infected with *Chlamydia trachomatis* can develop pelvic inflammatory disease, which can lead to negative reproductive outcomes, including ectopic pregnancy, infertility, stillbirth, preterm birth, neonatal ophthalmia and pneumonia (64-66). Gestational exposure to the antibiotics used to treat *Chlamydia* has not been associated with an increased risk of malformations in the offspring (67, 68).

Gastroschisis is an unusual birth defect in that it more frequently affects younger mothers. The increasing prevalence of *Chlamydia* infection in young women and the concurrent rise in gastroschisis cases, combined with the large financial burden, morbidity and mortality of the defect merits further investigation into the possibility of an association between the two. The nature of *Chlamydia* infection makes this research difficult; it is often subclinical and can resolve spontaneously, making maternal self-reporting of the disease highly susceptible to under-reporting. Specifically, studies on the association between *Chlamydia* and gastroschisis are lacking. Published studies have shown an association between genitourinary infection and/or sexually transmitted disease exposure in the mother and gastroschisis in the offspring (53, 55). A few studies have suggested a possible link between gastroschisis and *Chlamydia* but further investigation is needed. The purpose of this study is to examine whether maternal exposure to *Chlamydia* during pregnancy increases the risk of gastroschisis in live-born singleton offspring using data from the 2014 US vital records.

METHODS

Data Source

We designed a population-based case-control study to examine our hypothesis. We used data from all singleton live births registered in the 2014 US birth certificates. The data represent all births registered in the 50 states, the District of Columbia and New York City. The 2014 US standard birth certificate collected information on 12 congenital anomalies or anomaly groups at the time of birth from the revised reporting area comprised of 47 states and the District of Columbia. These data represent 96.2% of all births to US residents in 2014. The congenital anomalies assessed include: anencephaly, meningomyelocele/spina bifida, cyanotic congenital heart disease, congenital diaphragmatic hernia, omphalocele, gastroschisis, limb reduction defect, cleft lip with or without cleft palate, cleft palate alone, Down Syndrome, suspected chromosomal disorder and hypospadias. Information on congenital anomalies is recommended to be collected directly from the medical record using detailed instructions and definitions in the Guide to Completing the Facility Worksheets for the Certificate of Live Birth and Report of Fetal Death. Information on congenital anomalies is collected in a checkbox format, allowing for the reporting of more than one anomaly as well as a choice of "none of the above." When information is incomplete, the item is classified as "not stated." Less than 0.5% of records were classified as "not stated" for congenital anomalies in 2014. The CDC's National Center for Health Statistics (NCHS) collects and compiles the data, which has been prepared from individual records processed by registration area. The study received a waiver from the Institutional Review Board at Emory University since all data were publicly available and void of personal identifiers.

Case and Control Selection

We limited this study to live births occurring in women 16 to 25 years of age and excluded from this analysis infants with birth certificates on which birth defects information was left blank or coded as "unknown." Cases consisted of singleton live-born infants of women between 16 and 25 years of age with gastroschisis recorded on the birth certificates. We excluded from our analysis infants with Down syndrome or other chromosomal disorders. The status of gastroschisis in the birth certificates was collected directly from the medical records at birth using a facility worksheet with detailed instructions and definitions. We stratified cases into two groups: (1) isolated gastroschisis, defined as cases with gastroschisis but none of the other birth defects assessed by the birth certificates (as listed previously); and (2) all gastroschisis, defined as isolated gastroschisis cases and gastroschisis with additional birth defects recorded on the birth certificate. Control infants in this study were singleton live-born infants born to mothers who were comparable in age to case mothers, and who were also born in 2014 and did not have any birth defects checked on their birth certificates.

Exposure Assessment

Maternal *Chlamydia* during pregnancy was determined based on a question on the birth certificate inquiring about the presence or absence of *Chlamydia* during the index pregnancy. Information concerning maternal infections during pregnancy was collected directly from the medical record and coded "yes", "no", "unknown", or "blank (not on the certificate)." We excluded from this analysis infants with birth certificates on which the maternal infection information was left blank or coded as "unknown." We also excluded women who had hepatitis B or hepatitis C during pregnancy.

Statistical Analysis

We conducted descriptive analysis and compared cases and controls using Chi square test or Fisher's exact test (for expected cell frequencies <5). Covariates were selected *a priori* based on a literature review of published studies. Selected covariates include infant's sex (male, female), gestational age at delivery (<37, ≥37 weeks), birth weight (<2500, ≥2500 grams), season (spring, summer, fall, winter) conception occurred; and maternal factors including age at delivery (16-17, 18-19, 20-22, 23-25 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), education (<12, 12, >12 years), pre-pregnancy BMI (<18.5, 18.5-24.9, 25.0-29.9, ≥30 kg/m^2), parity (primipara, multipara), periconceptional smoking status (none, 1-20 cigarettes/day, >20 cigarettes/day), initiation time of prenatal care (no prenatal care, 1st trimester, 2nd trimester, 3rd trimester), gonorrhea infection, syphilis infection, pre-pregnancy diabetes (yes, no), pre-pregnancy hypertension (yes, no), use of assisted fertility (e.g. infertility treatment, fertility enhancing drugs or assisted reproductive technology (yes, no)) and mother's marital status (married, not married). We also examined paternal age (<20, 20-24, ≥25 years). Birth certificates rely on self-reporting for maternal age, race/ethnicity, smoking status, education, height and pre-pregnancy weight. Birth certificate information on pre-pregnancy diabetes, hypertension, parity, initiation time of prenatal care, presence of infection and use of assisted fertility methods is obtained from medical records. Maternal age, paternal age and BMI were categorized to be consistent with previously published studies investigating the relationship between these variables and gastroschisis. Season in which conception occurred was estimated using the month in which the infant was born and the obstetric estimate of gestational age in weeks. All births were assumed to occur in the middle of the month and the obstetric estimate of

gestation age in weeks was then used to estimate the month in which conception occurred. December, January and February were classified as winter; March, April and May were classified as spring; June, July and August were classified as summer and September, October and November comprised the fall months.

Unconditional logistic regression was used to estimate the association between a woman's exposure to *Chlamydia* during pregnancy and the risk of gastroschisis in the offspring. Separate analyses were performed for: (1) all gastroschisis cases combined, and (2) isolated gastroschisis cases. Crude and adjusted odds ratios (cORs and aORs, respectively) and corresponding 95% confidence intervals (CIs) were estimated. For the adjusted analysis, all of the maternal covariates were included in the regression model based on *a priori* considerations from noted risk factors identified during our extensive literature review. We also conducted backward logistic regression to achieve a parsimonious model. A covariable was included in the parsimonious model if the exposure estimate changed by 20% when the covariable was deleted from the model. Additionally, we compared the groups with and without missing data to assess for any systematic differences in distributions of the outcome, *Chlamydia* exposure, and other characteristics. A two-sided P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were conducted using SAS® version (9.4) (SAS Institute Inc., Cary, NC).

RESULTS

Overall, for mothers 25 years of age and younger, we identified 821 live-born eligible singleton infants with gastroschisis and 1,266,622 live born singleton infants without any congenital malformations from births reported in 2014 in the US. Of these, 6

case and 2,412 controls were excluded from the analysis because the mother was not a US resident. Additionally, 6 case and 3,917 control infants were excluded due to missing or unknown status of exposure to *Chlamydia* infection in utero. All gastroschisis cases combined totaled 809 (98.5% of the total identified cases) infants, of which 785 (95.6% of all identified cases) were isolated gastroschisis cases. There were 1,260,293 control infants in our final analysis.

Gastroschisis case infants were statistically more likely than controls to be preterm and have low birth weight and a gestational age of less than 37 weeks ($P < 0.05$) (Table 1). Women who delivered babies with gastroschisis were significantly more likely to be younger (16-20 years of age) at the time of delivery, non-Hispanic white, have a pre-pregnancy BMI <25 kg/m^2 (underweight or normal weight), have just a high school education, be primiparous, smoked, initiate prenatal care after the 1st trimester, unmarried and report paternal age less than 25 years compared to women who delivered babies without gastroschisis ($P < 0.05$). Gastroschisis infants were more likely to be conceived in the spring than control infants. Similar findings were observed for isolated gastroschisis cases.

Our study did not find a significant difference in the frequency of *Chlamydia* infection between controls and cases; 36 women with case (4.5%) and 45,689 (3.6%) women with control infants ($P = 0.21$) reported *Chlamydia* during pregnancy (Table 1). Comparison of maternal characteristics among cases according to whether or not they had *Chlamydia* during pregnancy showed that women who had *Chlamydia* were more likely to have less than a high school education ($P < 0.05$) (Table 2). Among controls, women who had *Chlamydia* were more likely to be less than 23 years old at the time of delivery,

have less than a high-school education, smoked during the periconceptional period, pre-pregnancy hypertension, be unmarried and have paternal age less than 20 years. In addition, women who were exposed to *Chlamydia* during pregnancy also differed by parity, pre-pregnancy BMI, maternal race, timing of initiation of prenatal care and season of conception ($P < 0.05$) (Table 2).

In our unadjusted analyses, we found a null association between maternal exposure to *Chlamydia* during pregnancy and all gastroschisis cases combined (cOR: 1.24, 95% CI: 0.89, 1.73), as well as a null association for isolated gastroschisis cases (cOR: 1.24, 95% CI: 0.88, 1.74) (Table 3). In the multivariable model (*a priori* model), adjusting for gestational age, maternal exposure to *Chlamydia*, gonorrhea and syphilis during pregnancy, maternal age at delivery in years, maternal race and ethnicity, maternal education level, maternal pre-pregnancy BMI, parity, periconceptional smoking, timing of prenatal care initiation, pre-pregnancy diabetes, pre-pregnancy hypertension, assisted fertility, marital status, paternal age and season of conception showed a null association between *Chlamydia* exposure during pregnancy and gastroschisis, combined (aOR: 1.06, 95% CI: 0.66, 1.70) or isolated (aOR: 1.08, 95% CI: 0.67, 1.73) (Table 4). No significant interaction between *Chlamydia* exposure and the other variables under investigation was observed. Those with missing data did not differ systematically with respect to exposure (*Chlamydia*) and outcome (gastroschisis) compared to those without missing data, except for the following variables: marital status, paternal age, pre-pregnancy diabetes and pre-pregnancy hypertension varied by exposure to *Chlamydia* and gender varied by gastroschisis outcome (data not shown). Of these variables, only marital status was a

statistically significant predictor of gastroschisis (all gastroschisis combined aOR: 0.68, 95% CI: 0.55, 0.84 and isolated gastroschisis aOR: 0.69, 95% CI: 0.56, 0.85).

In our backward logistic regression analysis, the association between *Chlamydia* exposure during pregnancy and gastroschisis remained largely unchanged (all gastroschisis combined aOR: 1.06, 95% CI: 0.66, 1.70 and isolated gastroschisis aOR: 1.08, 95% CI: 0.67, 1.73). The excluded variables were maternal gonorrhea exposure during pregnancy, assisted fertility, pre-pregnancy diabetes and pre-pregnancy hypertension. The covariables included in our parsimonious model were gestation age, paternal age, season of conception and the following maternal characteristics: syphilis exposure during pregnancy, maternal age at delivery, race and ethnicity, education level, pre-pregnancy BMI, parity, periconceptional smoking, prenatal care initiation and marital status.

DISCUSSION

Our study did not find a significant association between maternal exposure to *Chlamydia* and risk of gastroschisis in the offspring. While the association appears to be a weakly positive one, it did not reach the level of statistical significance in either the unadjusted or adjusted analyses. Among all case mothers, 4.4% (36/809) reported infection with *Chlamydia* during pregnancy, compared to 3.8% (45,689/1,214,604) of control mothers ($P = 0.21$). Among women of all ages, isolated gastroschisis prevalence in 2014 was 2.93 per 10,000 births according to US birth certificate data.

NBDPS (1997-2003) data has also been used to examine the association between periconceptional exposure to genitourinary infections, including urinary tract infections (UTI) and sexually transmitted diseases (STI) and/or pelvic inflammatory disease as a

group and gastroschisis. Using NBDPS data, investigators found a mildly positive association between genitourinary infections and gastroschisis, with the highest risk among women reporting both urinary tract infection and a sexually transmitted disease (STI only: cOR: 1.7, 95% CI: 1.0, 3.0, aOR for isolated cases: 1.3 95% CI: 0.7, 2.4, aOR for all cases: 1.3 95% CI: 0.7, 2.3) and (STI plus UTI: cOR: 6.8, 95% CI: 2.6, 17.5, aOR for isolated cases: 2.9 95% CI: 0.9, 9.5, aOR for all cases: 4.0 95% CI: 1.4, 11.6) (55). Investigators adjusted for maternal age, BMI before conception, smoking status and Hispanic ethnicity. While the pathogen was not documented for most exposures in the NBDPS study, among women who did report a urinary tract infection plus a sexually transmitted infection (STI), *Chlamydia* was the most common (18% of control mothers and 43% of case mothers) (55). Another study utilized a large, live birth cohort database derived from linked hospital discharge, birth certificate and death records maintained by the California Office of Statewide Health Planning and Development to investigate maternal factors associated with gastroschisis (69). Using singleton live births over the period 2005 through 2010, the study found a small but statistically significant association between maternal sexually transmitted infection during pregnancy and risk of gastroschisis in younger mothers (cOR: 2.7, 95% CI: 1.7, 4.4; aOR for women less than 20 years of age: 2.0, 95% CI: 1.1, 3.6) (69). These findings showed a stronger association between maternal *Chlamydia* exposure and gastroschisis risk than our study (isolated gastroschisis cOR: 1.24, 95% CI: 0.88, 1.74 and aOR: 1.08, 95% CI: 0.67, 1.73; all gastroschisis cOR: 1.24, 95% CI: 0.89, 1.73 and aOR: 1.06 95% CI: 0.66, 1.70).

In a more recent small pilot study, Chlamydia seropositivity was also shown to be associated with an increased risk of gastroschisis (age-adjusted OR: 3.9, 95% CI: 1.1, 13.2) (54).

The prevalence rate of *Chlamydia* infections among women of all ages delivering control infants using 2014 US vital statistics data was 1.7%. The same prevalence rate was found in a previous study utilizing 2012 US vital statistics data (2, 70). These rates are higher than an NBDPS study investigating the relationship between maternal genital tract infections during pregnancy and the risk of birth defects, which found a prevalence rate of 0.58% (71). In our study, infection status was based on information obtained in the medical record. In the latter study, genital tract infection was based on maternal self-report. It is very possible that the social stigma associated with genital tract infection as well as the subclinical nature of *Chlamydia* infection led to under-reporting in the NBDPS study.

One strength of our study in investigating a relatively rare outcome, like gastroschisis, is the large population size of nearly 4 million births among women of all ages, and just over 1.25 million births among our control population of women 16 to 25 years of age. In addition, data on *Chlamydia* diagnosis is also obtained directly from the medical record and is therefore subject to less bias due to maternal self-reporting. Also, birth certificates collect and contain information on a large number of different maternal variables, allowing us to examine multiple covariates and adjust for potential confounders. Beginning with the 2014 data year, NCHS transitioned to the use of the obstetric estimate of gestational age based on increasing evidence that its validity was greater than the previously used clinical estimate based on last normal menses (72-75).

We used the obstetric estimate of gestational age and birth month to estimate a season of conception.

This study has several limitations due to the use of birth certificate data. Several studies have noted that congenital anomalies tend to be under-reported in birth certificate data, though sensitivity is somewhat better for more visible and severe congenital defects (76-78) like gastroschisis. Underreporting of congenital anomalies in birth certificate data may account for the lower gastroschisis prevalence rate in our study data (in 2014, US vital statistics data reported a gastroschisis rate of 2.93 per 10,000 births) compared to the NBDPS prevalence rate (4.49 cases per 10,000 births) (2). Also, because birth certificate data does not include stillbirths or elective terminations, we were unable to include these in our analysis. In addition, signs and symptoms of some birth defects may not be present at birth or before discharge, therefore our study may include undiagnosed birth defects among control infants. In addition, some exposures may be underreported or missing compared with other survey designs. Also, data collection is carried out by individual states and there may be systematic differences by state in terms of data collection. It is also possible that the power of the analysis may have been impacted by the relatively small number of cases exposed to *Chlamydia* (n=36).

Birth certificate data also do not supply information as to the timing of *Chlamydia* infection relative to the pregnancy. Gastroschisis is thought to occur early in pregnancy; using US vital statistics data does not allow us to differentiate the timing of *Chlamydia* infection. Thus, women infected with *Chlamydia* during their 2nd and 3rd trimesters would also be included in our exposure group, even though exposure during this time frame would not lead to gastroschisis development. This could have artificially lowered

our crude and adjusted odds ratios. In addition, birth certificate data do not contain information on whether the infection was treated or with what medications; it is therefore impossible to discern if treatment for infection with *Chlamydia* might be associated with gastroschisis development. Previous studies, however, have not demonstrated an association between gestational exposure to antibiotics used to treat *Chlamydia* and the risk of major malformations in the offspring (67, 68). Finally, other potential risk factors for gastroschisis are not accounted for in US birth certificate data and thus we were unable to account for them in our study. These include specific genetic risk factors (such as the MTHFR allele), illicit drug use, exposure to specific medications, short cohabitation time and change in paternity.

In conclusion, we were unable to confirm our hypothesis that there was a significant positive association between prenatal exposure to *Chlamydia* and gastroschisis in the offspring. Due to the limitations of birth certificate data, including lack of information regarding timing of *Chlamydia* infection and treatment status as well as possible underreporting or misreporting of data (including major malformations), our study should be interpreted with care. The concurrent increase in both *Chlamydia* infection rates and gastroschisis prevalence over the last several decades merits further investigation into a possible association between the two. The majority of *Chlamydia* infections are subclinical, without the use of more accurate methods of diagnosing periconceptional *Chlamydia* infection, it is possible that a statistically significant association could be missed. Future research utilizing different study designs including the use of *Chlamydia* specific biomarkers are recommended, particularly in light of a recent study showing a strong association between *Chlamydia* IgG seropositivity and

gastroschisis (54). Future research should also investigate the role of the body's inflammatory and immune response to *Chlamydia* on gastroschisis risk. In the interim, routine screening for *Chlamydia* as recommended by the US Preventive Services Task Force and appropriate treatment are the best available measures to help reduce the rate of infection and mitigate the corresponding negative health consequences associated with *Chlamydia*.

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Table 1. Maternal and infant characteristics of gastroschisis (GS) cases and controls

Characteristics	Controls (N=1,260,293) n(%)	All GS (N=809) n (%)	Isolated GS (N=785) n (%)
Infant Characteristics			
Sex			
Female	615353 (48.8)	402 (49.7)	388 (49.4)
Male	644921 (51.2)	406 (50.2)	397 (50.6)
Gestation age (weeks)			
Preterm (<37)	123744 (9.8)	427 (52.8)	410 (52.2)
Term (≥37)	1102302 (87.5)	362 (44.8)*	356 (45.4)*
Birth weight (grams)			
Low (<2500)	87231 (6.9)	465 (57.5)	446 (56.8)
Normal (≥2500)	1172275 (93.0)	342 (42.3)*	337 (42.9)*
Maternal Characteristics			
Chlamydia during pregnancy			
No	1214604 (96.4)	773 (95.6)	750 (95.5)
Yes	45689 (3.6)	36 (4.5)	35 (4.5)
Gonorrhea during pregnancy			
No	1257396 (99.8)	808 (99.9)	784 (99.9)
Yes	2897 (0.2)	1 (0.1)	1 (0.1)
Syphilis during pregnancy			
No	1259360 (99.9)	808 (99.9)	784 (99.9)
Yes	933 (0.1)	1 (0.1)	1 (0.1)
Age at delivery (years)			
16-20	365397 (29.0)	366 (45.2)	358 (45.6)
21-25	894703 (71.0)	443 (54.8)*	427 (54.4)*
Age at delivery (years)			
16-17	56052 (4.5)	42 (5.2)	40 (5.1)
18-19	173431 (13.8)	182 (22.5)	178 (22.7)
20-22	458578 (36.4)	346 (42.8)	339 (43.2)
23-25	572039 (45.4)	239 (29.5)*	228 (29.0)*
Race and ethnicity			
Non-Hispanic white	582220 (46.2)	447 (55.3)	433 (55.2)
Non-Hispanic black	238768 (19.0)	77 (9.5)	75 (9.6)
Hispanic	272707 (21.6)	151 (18.7)	148 (18.9)
Other	79602 (6.3)	80 (9.9)*	78 (9.9)*
Education (years)			
<12	285657 (22.7)	171 (21.1)	167 (21.3)
12	491676 (39.0)	377 (46.6)	362 (46.1)
>12	471583 (37.4)	253 (31.3)*	248 (31.6)*
Pre-pregnancy BMI (kg/m^2)			
Underweight (<18.5)	66427 (5.3)	57 (7.1)	53 (6.8)
Normal weight (18.5-24.9)	560619 (44.5)	464 (57.4)	454 (57.8)
Overweight/obese (≥25)	589027 (46.7)	256 (31.6)*	250 (31.9)*
Pre-pregnancy BMI (kg/m^2)			

Underweight (<18.5)	66427 (5.3)	57 (7.1)	53 (6.8)
Normal weight (18.5-24.9)	560619 (44.5)	464 (57.4)	454 (57.8)
Overweight (25-29.9)	299052 (23.7)	180 (22.3)	179 (22.8)
Obese (≥30)	289975 (23.0)	76 (9.4)*	71 (9.0)*
Parity			
Primipara	691760 (54.9)	534 (66.0)	521 (66.4)
Multipara	563320 (44.7)	272 (33.6)*	261 (33.3) *
Periconceptional Smoking			
No	1038570 (82.4)	580 (71.7)	564 (71.9)
Yes	197924 (15.7)	220 (27.2)*	212 (27.0)*
Periconceptional Smoking			
No	1038570 (82.4)	580 (71.7)	564 (71.9)
≤ 20 cigarettes/day	192683 (15.3)	212 (26.2)	205 (26.1)
>20 cigarettes/day	29040 (2.3)	17 (2.1)*	16 (2.0)*
Prenatal care initiation			
No prenatal care	25000 (2.0)	17 (2.1)	16 (2.0)
1st Trimester	836280 (66.4)	462 (57.1)	452 (57.6)
2nd Trimester	277637 (22.0)	223 (27.6)	216 (27.5)
3rd Trimester	71939 (5.7)	52 (6.4)*	51 (6.5)*
Pre-pregnancy diabetes			
No	1253658 (99.5)	803 (99.3)	779 (99.2)
Yes	5957 (0.5)	3 (0.4)	3 (0.4)
Pre-pregnancy hypertension			
No	1248630 (99.1)	802 (99.1)	778 (99.1)
Yes	10985 (0.9)	4 (0.5)	4 (0.5)
Assisted Fertility			
No	1258948 (99.9)	806 (99.6)	782 (99.6)
Yes	331 (0.0)	0 (0.0)	0 (0.0)
Marital Status			
Not married	840608 (66.7)	622 (76.9)	600 (76.4)
Married	418742 (33.2)	185 (22.9)*	183 (23.3)*
Other characteristics			
Paternal age (years)**			
<20	76223 (6.1)	89 (11.0)	88 (11.2)
20-24	422919 (33.6)	314 (38.8)	306 (39.0)
≥25	497284 (39.5)	216 (26.7)*	212 (27.0)*
Season of conception			
Spring	321490 (25.5)	245 (30.3)	238 (30.3)
Summer	302816 (24.0)	175 (21.6)	166 (21.2)
Fall	314439 (25.0)	191 (23.6)	184 (23.4)
Winter	320518 (25.4)	197 (24.4)*	196 (25.0)*

Frequency of cases and controls may vary because of missing data, percentages may not equal 100 because of missing data.

GS gastroschisis, n frequency, BMI body mass index, *kg* kilograms, *m* meter

**Paternal age as reported by mother

*p<0.05 for cases versus controls; Chi-square test excludes missing data; Fisher's Exact test for cell frequency<5

Table 2a. Maternal and infant characteristics of controls and all gastroschisis cases stratified by status of *Chlamydia*

Characteristics	Controls		All gastroschisis	
	No *Chlamydia* (N=1,214,604) n(%)	*Chlamydia* (N=45,689) n(%)	No *Chlamydia* (N=773) n(%)	*Chlamydia* (N=36) n(%)
Infant Characteristics				
Sex				
Female	592946 (48.8)	22407 (49.0)	383 (49.6)	19 (52.8)
Male	621639 (51.2)	23282 (51.0)	389 (50.3)	17 (47.2)
Gestation age (weeks)				
Preterm (<37)	118588 (9.8)	5156 (11.3)	407 (52.7)	20 (55.6)
Term (≥37)	1062901 (87.5)	39401 (86.2)*	346 (44.8)	16 (44.4)
Birth weight (grams)				
Low (<2500)	83507 (6.9)	3724 (8.2)	439 (56.8)	26 (72.2)
Normal (≥2500)	1130336 (93.1)	41939 (91.8)*	332 (43.0)	10 (27.8)
Maternal Characteristics				
Gonorrhea during pregnancy				
No	1211707 (99.8)	45689 (100.0)	772 (99.9)	36 (100.0)
Yes	2897 (0.2)	0 (0.0)*	1 (0.1)	0 (0.0)
Syphilis during pregnancy				
No	1213671 (99.9)	45689 (100.0)	772 (99.9)	36 (100.0)
Yes	933 (0.1)	0 (0.0)*	1 (0.1)	0 (0.0)
Age at delivery (years)				
16-20	345418 (28.4)	19979 (43.7)	344 (44.5)	22 (61.1)
21-25	868995 (71.6)	25708 (56.3)*	429 (55.5)	14 (38.9)
Age at delivery (years)				
16-17	52554 (4.3)	3498 (7.7)	38 (4.9)	4 (11.1)
18-19	163676 (13.5)	9755 (21.4)	170 (22.0)	12 (33.3)
20-22	439340 (36.2)	19238 (42.1)	333 (43.1)	13 (36.1)
23-25	55843 (46.0)	13196 (28.9)*	232 (30.0)	7 (19.4)
Race and ethnicity				
Non-Hispanic white	566485 (46.6)	15735 (34.4)	428 (55.4)	19 (52.8)
Non-Hispanic black	223217 (18.4)	15551 (34.0)	73 (9.4)	4 (11.1)
Hispanic	264624 (21.8)	8083 (17.7)	146 (18.9)	5 (13.9)
Other	76520 (6.3)	3082 (6.8)*	75 (9.7)	5 (13.9)
Education (years)				
<12	271661 (22.4)	13996 (30.6)	157 (20.3)	14 (38.9)
12	472218 (38.9)	19458 (42.6)	367 (47.5)	10 (27.8)
>12	459665 (37.8)	11918 (26.1)*	242 (31.3)	11 (30.6)[¥]
Pre-pregnancy BMI (kg/m^2)				
Underweight (<18.5)	63770 (5.3)	2657 (5.8)	52 (6.7)	5 (13.9)
Normal weight (18.5-24.9)	539985 (44.5)	20634 (45.2)	446 (57.7)	18 (50.0)
Overweight/obese (≥25)	568040 (46.8)	20987 (45.9)*	246 (31.8)	10 (27.8)
Pre-pregnancy BMI (kg/m^2)				
Underweight (<18.5)	63770 (5.3)	2657 (5.8)	52 (6.7)	5 (13.9)
Normal weight (18.5-24.9)	539985 (44.5)	20634 (45.2)	446 (57.7)	18 (50.0)
Overweight (25-29.9)	288388 (23.7)	10664 (23.3)	171 (22.1)	9 (25.0)
Obese (≥30)	279652 (23.0)	10323 (22.6)*	75 (9.7)	1 (2.8)

Parity				
Primipara	665526 (54.8)	26234 (57.4)	505 (65.3)	29 (80.6)
Multipara	544007 (44.8)	19313 (42.3)*	265 (34.3)	7 (19.4)
Periconceptional Smoking				
No	1003071 (82.6)	35499 (77.7)	555 (71.8)	25 (69.4)
Yes	188425 (15.5)	9499 (20.8)*	210 (27.2)	10 (27.8)
Periconceptional Smoking				
No	1003071 (82.6)	35499 (77.7)	555 (71.8)	25 (69.4)
≤ 20 cigarettes/day	183455 (15.1)	9228 (20.2)	202 (26.1)	10 (27.8)
>20 cigarettes/day	28078 (2.3)	962 (2.1)*	16 (2.1)	1 (2.8)
Prenatal care initiation				
No prenatal care	24338 (2.0)	662 (1.5)	16 (2.1)	1 (2.8)
1st Trimester	809562 (66.7)	26718 (58.5)	440 (56.9)	22 (61.1)
2nd Trimester	264491 (21.8)	13146 (28.8)	217 (28.1)	6 (16.7)
3rd Trimester	68275 (5.6)	3664 (8.0)*	49 (6.3)	3 (8.3)
Pre-pregnancy diabetes				
No	1208244 (99.5)	45414 (99.4)	767 (99.2)	36 (100.0)
Yes	5744 (0.5)	213 (0.5)	3 (0.4)	0 (0.0)
Pre-pregnancy hypertension				
No	1203489 (99.1)	45141 (98.8)	766 (99.1)	36 (100.0)
Yes	10499 (0.9)	486 (1.1)*	4 (0.5)	0 (0.0)
Assisted Fertility				
No	121331 (99.9)	45617 (99.8)	770 (99.6)	36 (100.0)
Yes	327 (0.0)	4 (0.0)*	0 (0.0)	0 (0.0)
Marital Status				
Not married	800524 (65.9)	40084 (87.7)	592 (76.6)	30 (83.3)
Married	413188 (34.0)	5554 (12.2)*	179 (23.2)	6 (16.7)
Other characteristics				
Paternal age (years)**				
<20	72761 (6.0)	3462 (7.6)	84 (10.9)	5 (13.9)
20-24	408500 (33.6)	14419 (31.6)	301 (38.9)	13 (36.1)
≥25	487265 (40.1)	10019 (21.9)*	211 (27.3)	5 (13.9)
Season of conception				
Spring	309485 (25.5)	12005 (26.3)	235 (30.4)	10 (27.8)
Summer	292057 (24.1)	10759 (23.6)	168 (21.7)	7 (19.4)
Fall	303300 (25.0)	11139 (24.4)	184 (23.8)	7 (19.4)
Winter	308742 (25.4)	11776 (25.8)*	185 (23.9)	12 (33.3)

Frequency of cases and controls may vary because of missing data, percentages may not equal 100 because of missing data.

GS gastroschisis, n frequency, BMI body mass index, *kg* kilograms, *m* meter

**Paternal age as reported by mother

* p<0.05 among controls; Chi-square test excludes missing data; Fisher's Exact test for cell frequency<5

¥p<0.05 among cases; Chi-square test excludes missing data; Fisher's Exact test for cell frequency<5

Table 2b. Maternal and infant characteristics of controls and isolated gastroschisis cases stratified by status of *Chlamydia*

Characteristics	Controls		Isolated gastroschisis	
	No *Chlamydia* (N=1,214,604) n(%)	*Chlamydia* (N=45,689) n(%)	No *Chlamydia* (N=750) n(%)	*Chlamydia* (N=35) n(%)
Infant Characteristics				
Sex				
Female	592946 (48.8)	22407 (49.0)	370 (49.3)	18 (51.4)
Male	621639 (51.2)	23282 (51.0)	380 (50.7)	17 (48.6)
Gestation age (weeks)				
Preterm (<37)	118588 (9.8)	5156 (11.3)	391 (52.1)	19 (54.3)
Term (≥37)	1062901 (87.5)	39401 (86.2)*	340 (45.3)	16 (45.7)
Birth weight (grams)				
Low (<2500)	83507 (6.9)	3724 (8.2)	421 (56.1)	25 (71.4)
Normal (≥2500)	1130336 (93.1)	41939 (91.8)*	327 (43.6)	10 (28.6)
Maternal Characteristics				
Gonorrhea during pregnancy				
No	1211707 (99.8)	45689 (100.0)	749 (99.9)	35 (100.0)
Yes	2897 (0.2)	0 (0.0)*	1 (0.1)	0 (0.0)
Syphilis during pregnancy				
No	1213671 (99.9)	45689 (100.0)	749 (99.9)	35 (100.0)
Yes	933 (0.1)	0 (0.0)*	1 (0.1)	0 (0.0)
Age at delivery (years)				
16-20	345418 (28.4)	19979 (43.7)	337 (44.9)	21 (60.0)
21-25	868995 (71.6)	25708 (56.3)*	413 (55.1)	14 (40.0)
Age at delivery (years)				
16-17	52554 (4.3)	3498 (7.7)	37 (4.9)	3 (8.6)
18-19	163676 (13.5)	9755 (21.4)	166 (22.1)	12 (34.3)
20-22	439340 (36.2)	19238 (42.1)	326 (43.5)	13 (37.1)
23-25	55843 (46.0)	13196 (28.9)*	221 (29.5)	7 (20.0)
Race and ethnicity				
Non-Hispanic white	566485 (46.6)	15735 (34.4)	415 (55.3)	18 (51.4)
Non-Hispanic black	223217 (18.4)	15551 (34.0)	71 (9.5)	4 (11.4)
Hispanic	264624 (21.8)	8083 (17.7)	143 (19.1)	5 (14.3)
Other	76520 (6.3)	3082 (6.8)*	73 (9.7)	5 (14.3)
Education (years)				
<12	271661 (22.4)	13996 (30.6)	154 (20.5)	13 (37.1)
12	472218 (38.9)	19458 (42.6)	352 (46.9)	10 (28.6)
>12	459665 (37.8)	11918 (26.1)*	237 (31.6)	11 (31.4)[¥]
Pre-pregnancy BMI (kg/m^2)				
Underweight (<18.5)	63770 (5.3)	2657 (5.8)	48 (6.4)	5 (14.3)
Normal weight (18.5-24.9)	539985 (44.5)	20634 (45.2)	437 (58.3)	17 (48.6)
Overweight/obese (≥25)	568040 (46.8)	20987 (45.9)*	240 (32.0)	10 (28.6)
Pre-pregnancy BMI (kg/m^2)				
Underweight (<18.5)	63770 (5.3)	2657 (5.8)	48 (6.4)	5 (14.3)
Normal weight (18.5-24.9)	539985 (44.5)	20634 (45.2)	437 (58.3)	17 (48.6)
Overweight (25-29.9)	288388 (23.7)	10664 (23.3)	170 (22.7)	9 (25.7)
Obese (≥30)	279652 (23.0)	10323 (22.6)*	70 (9.3)	1 (2.9)

Parity				
Primipara	665526 (54.8)	26234 (57.4)	493 (65.7)	28 (80.0)
Multipara	544007 (44.8)	19313 (42.3)*	254 (33.9)	7 (20.0)
Periconceptional Smoking				
No	1003071 (82.6)	35499 (77.7)	539 (71.9)	25 (71.4)
Yes	188425 (15.5)	9499 (20.8)*	203 (27.1)	9 (25.7)
Periconceptional Smoking				
No	1003071 (82.6)	35499 (77.7)	539 (71.9)	25 (71.4)
≤ 20 cigarettes/day	183455 (15.1)	9228 (20.2)	196 (26.1)	9 (25.7)
>20 cigarettes/day	28078 (2.3)	962 (2.1)*	15 (2.0)	1 (2.9)
Prenatal care initiation				
No prenatal care	24338 (2.0)	662 (1.5)	15 (2.0)	1 (2.9)
1st Trimester	809562 (66.7)	26718 (58.5)	431 (57.5)	21 (60.0)
2nd Trimester	264491 (21.8)	13146 (28.8)	210 (28.0)	6 (17.1)
3rd Trimester	68275 (5.6)	3664 (8.0)*	48 (6.4)	3 (8.6)
Pre-pregnancy diabetes				
No	1208244 (99.5)	45414 (99.4)	744 (99.2)	35 (100.0)
Yes	5744 (0.5)	213 (0.5)	3 (0.4)	0 (0.0)
Pre-pregnancy hypertension				
No	1203489 (99.1)	45141 (98.8)	743 (99.1)	35 (100.0)
Yes	10499 (0.9)	486 (1.1)*	4 (0.5)	0 (0.0)
Assisted Fertility				
No	121331 (99.9)	45617 (99.8)	747 (99.6)	35 (100.0)
Yes	327 (0.0)	4 (0.0)*	0 (0.0)	0 (0.0)
Marital Status				
Not married	800524 (65.9)	40084 (87.7)	571 (76.1)	29 (82.9)
Married	413188 (34.0)	5554 (12.2)*	177 (23.6)	6 (17.1)
Other characteristics				
Paternal age (years)**				
<20	72761 (6.0)	3462 (7.6)	83 (11.1)	5 (14.3)
20-24	408500 (33.6)	14419 (31.6)	293 (39.1)	13 (37.1)
≥25	487265 (40.1)	10019 (21.9)*	207 (27.6)	5 (14.3)
Season of conception				
Spring	309485 (25.5)	12005 (26.3)	229 (30.5)	9 (25.7)
Summer	292057 (24.1)	10759 (23.6)	159 (21.2)	7 (20.0)
Fall	303300 (25.0)	11139 (24.4)	177 (23.6)	7 (20.0)
Winter	308742 (25.4)	11776 (25.8)*	184 (24.5)	12 (34.3)

Frequency of cases and controls may vary because of missing data, percentages may not equal 100 because of missing data.
GS gastroschisis, n frequency, BMI body mass index, *kg* kilograms, *m* meter
**Paternal age as reported by mother
* p<0.05 among controls; Chi-square test excludes missing data; Fisher's Exact test for cell frequency<5
¥p<0.05 among cases; Chi-square test excludes missing data; Fisher's Exact test for cell frequency<5

Table 3. Unadjusted odds ratios of various characteristics with singleton live births with gastroschisis

Exposure	Controls (N=1,260,293) n(%)	All GS (N=809) cOR (95% CI)	Isolated GS (N=785) cOR (95% CI)
Infant Characteristics			
Gestation age (weeks)			
Preterm (<37)	123744 (9.8)	Referent	Referent
Term (≥37)	1102302 (87.5)	0.10 (0.08, 0.11)	0.10 (0.09, 0.11)
Maternal Characteristics			
Chlamydia during pregnancy			
No	1214604 (96.4)	Referent	Referent
Yes	45689 (3.6)	1.24 (0.89, 1.73)	1.24 (0.88, 1.74)
Gonorrhea during pregnancy			
No	1257396 (99.8)	Referent	Referent
Yes	2897 (0.2)	0.54 (0.08, 3.82)	0.55 (0.08, 3.94)
Syphilis during pregnancy			
No	1259360 (99.9)	Referent	Referent
Yes	933 (0.1)	1.67 (0.24, 11.89)	1.72 (0.24, 12.25)
Age at delivery (years)			
16-20	365397 (29.0)	2.02 (1.76, 2.32)	2.05 (1.78, 2.36)
21-25	894703 (71.0)	Referent	Referent
Age at delivery (years)			
16-17	56052 (4.5)	1.79 (1.29, 2.49)	1.79 (1.28, 2.51)
18-19	173431 (13.8)	2.51 (2.07, 3.05)	2.58 (2.12, 3.13)
20-22	458578 (36.4)	1.81 (1.53, 2.13)	1.86 (1.57, 2.19)
23-25	572039 (45.4)	Referent	Referent
Race and ethnicity			
Non-Hispanic white	582220 (46.2)	2.38 (1.87, 3.03)	2.37 (1.85, 3.03)
Non-Hispanic black	238768 (19.0)	Referent	Referent
Hispanic	272707 (21.6)	1.72 (1.31, 2.26)	1.73 (1.31, 2.28)
Other	79602 (6.3)	3.12 (2.28, 4.26)	3.12 (2.27, 4.28)
Education (years)			
<12	285657 (22.7)	Referent	Referent
12	491676 (39.0)	1.28 (1.07, 1.54)	1.26 (1.05, 1.51)
>12	471583 (37.4)	0.90 (0.74, 1.09)	0.90 (0.74, 1.10)
Pre-pregnancy BMI (kg/m^2)			
Underweight (<18.5)	66427 (5.3)	1.04 (0.79, 1.37)	0.99 (0.74, 1.31)
Normal weight (18.5-24.9)	560619 (44.5)	Referent	Referent
Overweight/obese (≥25)	589027 (46.7)	0.53 (0.45, 0.61)	0.52 (0.45, 0.61)
Pre-pregnancy BMI (kg/m^2)			
Underweight (<18.5)	66427 (5.3)	1.04 (0.79, 1.37)	0.99 (0.74, 1.31)
Normal weight (18.5-24.9)	560619 (44.5)	Referent	Referent
Overweight (25-29.9)	299052 (23.7)	0.73 (0.61, 0.86)	0.74 (0.62, 0.88)
Obese (≥30)	289975 (23.0)	0.32 (0.25, 0.40)	0.30 (0.24, 0.39)
Parity			
Primipara	691760 (54.9)	Referent	Referent
Multipara	563320 (44.7)	0.63 (0.54, 0.72)	0.62 (0.53, 0.71)

Periconceptional Smoking			
No	1038570 (82.4)	Referent	Referent
Yes	197924 (15.7)	1.99 (1.70, 2.33)	1.97 (1.68, 2.31)
Periconceptional Smoking			
No	1038570 (82.4)	Referent	Referent
≤ 20 cigarettes/day	192683 (15.3)	1.97 (1.68, 2.31)	1.96 (1.67, 2.30)
>20 cigarettes/day	29040 (2.3)	1.05 (0.65, 1.70)	1.02 (0.62, 1.67)
Prenatal care initiation			
No prenatal care	25000 (2.0)	Referent	Referent
1st Trimester	836280 (66.4)	1.23 (0.76, 2.00)	1.18 (0.72, 1.95)
2nd Trimester	277637 (22.0)	1.45 (1.24, 1.71)	1.44 (1.22, 1.69)
3rd Trimester	71939 (5.7)	1.31 (0.98, 1.74)	1.31 (0.98, 1.75)
Pre-pregnancy diabetes			
No	1253658 (99.5)	Referent	Referent
Yes	5957 (0.5)	0.79 (0.25, 2.44)	0.81 (0.26, 2.52)
Pre-pregnancy hypertension			
No	1248630 (99.1)	Referent	Referent
Yes	10985 (0.9)	0.57 (0.21, 1.51)	0.58 (0.22, 1.56)
Assisted Fertility			
No	1258948 (99.9)	Referent	Referent
Yes	331 (0.0)	0.00 (0.00, >1000)	0.00 (0.00, >1000)
Marital Status			
Not married	840608 (66.7)	Referent	Referent
Married	418742 (33.2)	0.60 (0.51, 0.70)	0.61 (0.52, 0.72)
Other characteristics			
Paternal age (years)**			
<20	76223 (6.1)	Referent	Referent
20-24	422919 (33.6)	0.64 (0.50, 0.80)	0.63 (0.49, 0.79)
≥25	497284 (39.5)	0.37 (0.29, 0.48)	0.37 (0.29, 0.47)
Season of conception			
Spring	321490 (25.5)	Referent	Referent
Summer	302816 (24.0)	0.76 (0.63, 0.92)	0.74 (0.61, 0.90)
Fall	314439 (25.0)	0.80 (0.66, 0.96)	0.79 (0.65, 0.96)
Winter	320518 (25.4)	0.81 (0.67, 0.97)	0.83 (0.68, 1.00)

Frequency of controls may vary because of missing data; percentages may not equal 100 because of missing data.

GS gastroschisis, n frequency, BMI body mass index, *kg* kilograms, *m* meter, cOR crude odds ratio

**Paternal age as reported by mother

Table 4. Multivariate analysis for maternal *Chlamydia* and gastroschisis

Exposure	Controls (N=1,260,293) n(%)	All GS (N=809) aOR (95% CI)	Isolated GS (N=785) aOR (95% CI)
Infant Characteristics			
Gestation age (weeks)			
Preterm (<37)	123744 (9.8)	Referent	Referent
Term (≥37)	1102302 (87.5)	0.08 (0.07, 0.10)	0.09 (0.07, 0.10)
Maternal Characteristics			
Chlamydia during pregnancy			
No	1214604 (96.4)	Referent	Referent
Yes	45689 (3.6)	1.06 (0.66, 1.70)	1.08 (0.67, 1.73)
Gonorrhea during pregnancy			
No	1257396 (99.8)	Referent	Referent
Yes	2897 (0.2)	1.17 (0.16, 8.36)	1.19 (0.17, 8.54)
Syphilis during pregnancy			
No	1259360 (99.9)	Referent	Referent
Yes	933 (0.1)	4.97 (0.69, 35.81)	5.08 (0.71, 36.65)
Age at delivery (years)			
16-17	56052 (4.5)	0.91 (0.51, 1.61)	0.92 (0.52, 1.63)
18-19	173431 (13.8)	1.49 (1.10, 2.03)	1.54 (1.13, 2.09)
20-22	458578 (36.4)	1.41 (1.13, 1.77)	1.42 (1.13, 1.79)
23-25	572039 (45.4)	Referent	Referent
Race and ethnicity			
Non-Hispanic white	582220 (46.2)	2.82 (1.99, 4.02)	2.85 (1.99, 4.07)
Non-Hispanic black	238768 (19.0)	Referent	Referent
Hispanic	272707 (21.6)	2.50 (1.72, 3.64)	2.54 (1.74, 3.70)
Other	79602 (6.3)	4.07 (2.67, 6.20)	4.10 (2.68, 6.27)
Education (years)			
<12	285657 (22.7)	Referent	Referent
12	491676 (39.0)	1.65 (1.26, 2.14)	1.60 (1.23, 2.09)
>12	471583 (37.4)	1.56 (1.16, 2.08)	1.53 (1.15, 2.05)
Pre-pregnancy BMI (kg/m^2)			
Underweight (<18.5)	66427 (5.3)	0.98 (0.71, 1.36)	0.96 (0.69, 1.33)
Normal weight (18.5-24.9)	560619 (44.5)	Referent	Referent
Overweight (25-29.9)	299052 (23.7)	0.76 (0.61, 0.95)	0.78 (0.63, 0.97)
Obese (≥30)	289975 (23.0)	0.35 (0.25, 0.47)	0.35 (0.25, 0.47)
Parity			
Primipara	691760 (54.9)	Referent	Referent
Multipara	563320 (44.7)	0.72 (0.59, 0.88)	0.71 (0.58, 0.87)
Periconceptional Smoking			
No	1038570 (82.4)	Referent	Referent
≤ 20 cigarettes/day	192683 (15.3)	1.51 (1.21, 1.88)	1.48 (1.19, 1.85)
>20 cigarettes/day	29040 (2.3)	2.79 (1.23, 6.30)	2.83 (1.25, 6.40)
Prenatal care initiation			
No prenatal care	25000 (2.0)	0.53 (0.22, 1.28)	0.43 (0.16, 1.16)
1st Trimester	836280 (66.4)	Referent	Referent
2nd Trimester	277637 (22.0)	1.35 (1.11, 1.64)	1.36 (1.11, 1.65)

3rd Trimester	71939 (5.7)	1.44 (1.00, 2.06)	1.47 (1.02, 2.10)
Pre-pregnancy diabetes			
No	1253658 (99.5)	Referent	Referent
Yes	5957 (0.5)	0.56 (0.14, 2.24)	0.57 (0.14, 2.28)
Pre-pregnancy hypertension			
No	1248630 (99.1)	Referent	Referent
Yes	10985 (0.9)	0.71 (0.23, 2.20)	0.72 (0.23, 2.25)
Assisted Fertility			
No	1258948 (99.9)	Referent	Referent
Yes	331 (0.0)	0.00 (0.00, >1000)	0.00 (0.00, >1000)
Marital Status			
Not married	840608 (66.7)	Referent	Referent
Married	418742 (33.2)	0.68 (0.55, 0.84)	0.69 (0.56, 0.85)
Other characteristics			
Paternal age (years)**			
<20	76223 (6.1)	Referent	Referent
20-24	422919 (33.6)	0.76 (0.56, 1.01)	0.75 (0.56, 1.00)
≥25	497284 (39.5)	0.61 (0.44, 0.85)	0.61 (0.44, 0.86)
Season of conception			
Spring	321490 (25.5)	Referent	Referent
Summer	302816 (24.0)	0.78 (0.61, 1.00)	0.77 (0.60, 0.99)
Fall	314439 (25.0)	0.79 (0.62, 1.01)	0.78 (0.61, 0.99)
Winter	320518 (25.4)	0.84 (0.66, 1.06)	0.85 (0.67, 1.07)

Frequency of controls may vary because of missing data, percentages may not equal 100 because of missing data.

GS gastroschisis, n frequency, BMI body mass index, *kg* kilograms, *m* meter, cOR crude odds ratio

**Paternal age as reported by mother

Table 5. Parsimonious model for maternal Chlamydia and gastroschisis

Exposure	**Controls** (N=1,260,293) n(%)	**All GS** (N=809) aOR (95% CI)	**Isolated GS** (N=785) aOR (95% CI)
Infant Characteristics			
Gestation age (weeks)			
Preterm (<37)	123744 (9.8)	Referent	Referent
Term (≥37)	1102302 (87.5)	0.08 (0.07, 0.10)	0.09 (0.07, 0.10)
Maternal Characteristics			
Chlamydia during pregnancy			
No	1214604 (96.4)	Referent	Referent
Yes	45689 (3.6)	1.06 (0.66, 1.70)	1.08 (0.67, 1.73)
Syphilis during pregnancy			
No	1259360 (99.9)	Referent	Referent
Yes	933 (0.1)	4.97 (0.69, 35.73)	5.08 (0.71, 36.57)
Age at delivery (years)			
16-17	56052 (4.5)	0.92 (0.52, 1.62)	0.93 (0.52, 1.64)
18-19	173431 (13.8)	1.50 (1.11, 2.03)	1.54 (1.13, 2.10)
20-22	458578 (36.4)	1.41 (1.13, 1.77)	1.43 (1.14, 1.79)
23-25	572039 (45.4)	Referent	Referent
Race and ethnicity			
Non-Hispanic white	582220 (46.2)	2.82 (1.98, 4.01)	2.85 (1.99, 4.07)
Non-Hispanic black	238768 (19.0)	Referent	Referent
Hispanic	272707 (21.6)	2.51 (1.73, 3.64)	2.54 (1.74, 3.71)
Other	79602 (6.3)	4.07 (2.68, 6.20)	4.10 (2.68, 6.27)
Education (years)			
<12	285657 (22.7)	Referent	Referent
12	491676 (39.0)	1.65 (1.26, 2.14)	1.61 (1.23, 2.09)
>12	471583 (37.4)	1.56 (1.17, 2.08)	1.53 (1.15, 2.05)
Pre-pregnancy BMI (kg/m^2)			
Underweight (<18.5)	66427 (5.3)	0.99 (0.72, 1.36)	0.96 (0.69, 1.33)
Normal weight (18.5-24.9)	560619 (44.5)	Referent	Referent
Overweight (25-29.9)	299052 (23.7)	0.76 (0.61, 0.95)	0.78 (0.63, 0.97)
Obese (≥30)	289975 (23.0)	0.34 (0.25, 0.47)	0.34 (0.25, 0.47)
Parity			
Primipara	691760 (54.9)	Referent	Referent
Multipara	563320 (44.7)	0.72 (0.59, 0.88)	0.71 (0.58, 0.87)
Periconceptional Smoking			
No	1038570 (82.4)	Referent	Referent
≤ 20 cigarettes/day	192683 (15.3)	1.51 (1.21, 1.88)	1.48 (1.19, 1.86)
20 cigarettes/day	29040 (2.3)	2.79 (1.24, 6.31)	2.84 (1.26, 6.41)
Prenatal care initiation			
No prenatal care	25000 (2.0)	0.53 (0.22, 1.28)	0.43 (0.16, 1.16)
1st Trimester	836280 (66.4)	Referent	Referent
2nd Trimester	277637 (22.0)	1.35 (1.11, 1.64)	1.36 (1.12, 1.66)
3rd Trimester	71939 (5.7)	1.44 (1.00, 2.06)	1.47 (1.02, 2.11)
Marital Status			

Not married	840608 (66.7)	Referent	Referent
Married	418742 (33.2)	0.68 (0.55, 0.84)	0.69 (0.56, 0.85)
Other characteristics			
Paternal age (years)**			
<20	76223 (6.1)	Referent	Referent
20-24	422919 (33.6)	0.76 (0.56, 1.01)	0.75 (0.56, 1.00)
≥25	497284 (39.5)	0.61 (0.44, 0.85)	0.61 (0.44, 0.86)
Season of conception			
Spring	321490 (25.5)	Referent	Referent
Summer	302816 (24.0)	0.78 (0.61, 1.00)	0.77 (0.60, 0.99)
Fall	314439 (25.0)	0.79 (0.62, 1.01)	0.78 (0.61, 0.99)
Winter	320518 (25.4)	0.84 (0.66, 1.06)	0.85 (0.67, 1.07)

Backwards logistic regression was used, covariable was retained for inclusion if the exposure estimate changed by 20% when the covariable was deleted from the model.
Frequency of controls may vary because of missing data, percentages may not equal 100 because of missing data.
GS gastroschisis, n frequency, BMI body mass index, *kg* kilograms, *m* meter, cOR crude odds ratio
**Paternal age as reported by mother

APPENDIX SAS CODES

```
libname project "T:\epiprojs\KANCHERLA_V\TESSA
H_THESIS\sascode\dataset_current";

data births2;
set project.births;
run;

*recode plurality and dob_mm and keep selected variables and
covariates;
Data births_recode;
Set births2 (keep=mager mracehisp dmar meduc fagerec11 lbo_rec precare5
wtgain_rec wtgain cig_0 cig_1 cig_rec bmi_r rf_pdiab rf_phype ip_gon
ip_syph ip_chlam ip_hepb ip_hepc dplural sex gestrec3 oegest_comb
dob_mm bwtr4 ca_cchd bmi ca_down ca_anen ca_cdh ca_cleft ca_clpal
ca_disor ca_gast ca_hypo ca_limb ca_mnsb ca_omph rf_fedrg rf_artec
rf_inftr rf_cesar imp_plur mar_imp mage_impflg mage_repflg mraceimp
imp_sex compgst_imp restatus dob_mm);
Id=_n_;
IF DOB_MM='1' THEN DOB_WK=54;
ELSE IF DOB_MM='2' THEN DOB_WK=58;
ELSE IF DOB_MM='3' THEN DOB_WK=63;
ELSE IF DOB_MM='4' THEN DOB_WK=67;
ELSE IF DOB_MM='5' THEN DOB_WK=71;
ELSE IF DOB_MM='6' THEN DOB_WK=76;
ELSE IF DOB_MM='7' THEN DOB_WK=80;
ELSE IF DOB_MM='8' THEN DOB_WK=85;
ELSE IF DOB_MM='9' THEN DOB_WK=89;
ELSE IF DOB_MM='10' THEN DOB_WK=93;
ELSE IF DOB_MM='11' THEN DOB_WK=98;
ELSE IF DOB_MM='12' THEN DOB_WK=102;
ELSE DOB_WK=.;
If imp_plur=1 then dplural=.;
If dplural=. then singleton=.;
If dplural=1 then singleton=1;
Else if dplural>1 then singleton=0;
*recode birth defects;
If ca_anen='Y' then anen=1;
Else if ca_anen='N' then anen=0;
else anen=.;
If ca_mnsb='Y' then mnsb=1;
Else if ca_mnsb='N' then mnsb=0;
else mnsb=.;
If ca_cchd='Y' then cchd=1;
Else if ca_cchd='N' then cchd=0;
else cchd=.;
If ca_cdh='Y' then cdh=1;
Else if ca_cdh='N' then cdh=0;
else cdh=.;
If ca_omph='Y' then omph=1;
Else if ca_omph='N' then omph=0;
else omph=.;
```

```
If ca_gast='Y' then gast=1;
Else if ca_gast='N' then gast=0;
else gast=.;
If ca_limb='Y' then limb=1;
Else if ca_limb='N' then limb=0;
else limb=.;
If ca_cleft='Y' then cleft=1;
Else if ca_cleft='N' then cleft=0;
else cleft=.;
If ca_clpal='Y' then clpal=1;
Else if ca_clpal='N' then clpal=0;
else clpal=.;
If ca_down='C' then down=1;
Else if ca_down='N' then down=0;
else down=.;
If ca_disor='C' then chdisor=1;
Else if ca_disor='N' then chdisor=0;
else chdisor=.;
If ca_hypo='Y' then hypo=1;
Else if ca_hypo='N' then hypo=0;
else hypo=.;
*recode infections;
If ip_chlam='Y' then chlam=1;
Else if ip_chlam='N' then chlam=0;
else chlam=.;
If ip_gon='Y' then gon=1;
Else if ip_gon='N' then gon=0;
else gon=.;
If ip_syph='Y' then syph=1;
Else if ip_syph='N' then syph=0;
else syph=.;
If ip_hepb='Y' then hepb=1;
Else if ip_hepb='N' then hepb=0;
else hepb=.;
If ip_hepc='Y' then hepc=1;
Else if ip_hepc='N' then hepc=0;
else hepc=.;

drop ca_anen ca_mnsb ca_cchd ca_cdh ca_omph ca_gast ca_limb ca_cleft
ca_clpal ca_down ca_disor ca_hypo ip_chlam ip_gon ip_syph ip_hepb
ip_hepc;
run;
*run some diagnostics (proc contents / proc print / proc freq);
proc print data=births_recode (obs=200); run;

proc contents data=births_recode; run;

*RECATEGORIZING AND LABELING VARIABLES;
data births_recode2;
set births_recode;
concept_week = dob_wk - oegest_comb;
if 8.6<=concept_week<=21.6 then conc_season=1;
if 60.7<=concept_week <=73.7 then conc_season=1;
if 21.7<=concept_week <=34.7 then conc_season=2;
if 73.9<=concept_week<=86.9 then conc_season=2;
if 34.9<=concept_week<=47.7 then conc_season=3;
if 87<=concept_week<=99.9 then conc_season=3;
```

```
if 47.9<=concept_week<=60.4 then conc_season=4;
if 100<=concept_week<=112.6 then conc_season=4;
IF MRACEIMP=1 THEN MRACEHISP=.;
IF MRACEIMP=2 THEN MRACEHISP=.;
IF MRACEHISP=. THEN MOMRACE=.;
IF 3<=MRACEHISP<=6 THEN MOMRACE=4;
ELSE IF MRACEHISP=1 THEN MOMRACE=1;
ELSE IF MRACEHISP=2 THEN MOMRACE=2;
ELSE IF MRACEHISP=7 THEN MOMRACE=3;
ELSE MOMRACE=.;
IF 1<=MEDUC<=2 THEN MOMEDU=1;
ELSE IF MEDUC=3 THEN MOMEDU=2;
ELSE IF 4<=MEDUC<=8 THEN MOMEDU=3;
ELSE MOMEDU=.;
IF MAR_IMP=1 THEN DMAR=.;
IF DMAR=. THEN MOMMAR=.;
IF DMAR=1 THEN MOMMAR=1;
IF DMAR=2 THEN MOMMAR=0;
IF DMAR=3 THEN MOMMAR=0;
IF DMAR=9 THEN MOMMAR=.;
IF PRECARE5=1 THEN PRENAT_CARE=1;
ELSE IF PRECARE5=2 THEN PRENAT_CARE=2;
ELSE IF PRECARE5=3 THEN PRENAT_CARE=3;
ELSE IF PRECARE5=4 THEN PRENAT_CARE=0;
ELSE PRENAT_CARE=.;
IF RF_ARTEC='Y' THEN ARTEC=1;
ELSE IF RF_ARTEC IN('N', 'X') THEN ARTEC=0;
ELSE ARTEC=.;
IF RF_FEDRG='Y' OR RF_ARTEC='Y' OR RF_INFTR='Y' THEN ASSIS_FET=1; ELSE
IF RF_FEDRG IN ('N', 'X') AND RF_ARTEC IN('N', 'X') AND RF_INFTR IN
('N', 'X') THEN ASSIS_FET=0;
ELSE ASSIS_FET=.;
IF MAGE_IMPFLG=1 THEN MAGER=.;
IF MAGER=. THEN MOMAGE=.;
IF 16<=MAGER<21 THEN MOMAGE=0;
IF 21<=MAGER<=25 THEN MOMAGE=1;
IF 12<=MAGER<16 THEN MOMAGE=2;
IF MAGER>25 THEN MOMAGE=3;
IF 16<=MAGER<18 THEN MOMAGE2=0;
IF 18<=MAGER<20 THEN MOMAGE2=1;
IF 20<=MAGER<23 THEN MOMAGE2=2;
IF 23<=MAGER<=25 THEN MOMAGE2=3;
IF 12<=MAGER<16 THEN MOMAGE2=4;
IF MAGER>25 THEN MOMAGE2=5;
IF 1<=FAGEREC11<=2 THEN DADAGE=1;
ELSE IF FAGEREC11=3 THEN DADAGE=2;
ELSE IF 3<FAGEREC11<=10 THEN DADAGE=3;
ELSE DADAGE=.;
IF BMI_R=1 THEN BMI_GP=1;
ELSE IF BMI_R=2 THEN BMI_GP=2;
ELSE IF 3<=BMI_R<=6 THEN BMI_GP=3;
ELSE BMI_GP=.;
IF BMI_R=1 THEN BMI_GP4=1;
ELSE IF BMI_R=2 THEN BMI_GP4=2;
ELSE IF BMI_R=3 THEN BMI_GP4=3;
ELSE IF 4<=BMI_R<=6 THEN BMI_GP4=4;
ELSE BMI_GP4=.;
```

```
IF CIG_1=0 AND CIG_0=0 THEN MOMCIG_01=0;
ELSE IF 1<=CIG_1<=98 OR 1<=CIG_0<=98 THEN MOMCIG_01=1;
ELSE MOMCIG_01=.;
IF CIG_1=0 AND CIG_0=0 THEN MOMCIG_02=0;
ELSE IF 1<=CIG_1<=20 OR 1<=CIG_0<=20 THEN MOMCIG_02=1;
ELSE IF 20<CIG_1 OR 20<=CIG_0 THEN MOMCIG_02=2;
ELSE MOMCIG_02=.;
IF CIG_REC='Y' THEN MOMCIG=1;
ELSE IF CIG_REC='N' THEN MOMCIG=0;
ELSE MOMCIG=.;
IF RF_PDIAB='Y' THEN PRE_DIAB=1;
ELSE IF RF_PDIAB='N' THEN PRE_DIAB=0;
ELSE PRE_DIAB=.;
IF RF_PHYPE='Y' THEN PRE_HTN=1;
ELSE IF RF_PHYPE='N' THEN PRE_HTN=0;
ELSE PRE_HTN=.;
IF IMP_SEX=1 THEN SEX=.;
IF SEX=. THEN MALE=.;
IF SEX='M' THEN MALE=1;
ELSE IF SEX='F' THEN MALE=0;
IF COMPGST_IMP=1 THEN GESTREC3=.;
IF GESTREC3=3 THEN UNDER37=.;
IF GESTREC3=1 THEN UNDER37=1;
ELSE IF GESTREC3=2 THEN UNDER37=0;
ELSE UNDER37=.;
IF 1<=BWTR4<=2 THEN LOWBIRTHWT=1;
ELSE IF BWTR4=3 THEN LOWBIRTHWT=0;
ELSE LOWBIRTHWT=.;
IF LBO_REC=1 THEN PRIMIPAROUS=1;
ELSE IF 2<=LBO_REC<=8 THEN PRIMIPAROUS=0;
ELSE PRIMIPAROUS=.;

LABEL MOMAGE='0= 16-20, 1= 21-25, 2=<16 3=26+'
      MOMAGE2='0= 16-17, 1= 18-19, 2=20-22 3=23-25 4=12-15 5=26+'
      BMI_GP='1=UNDER WT<18.5, 2=NORMAL WT 18.5-24.9, 3=OVERWT>=25'
      BMI_GP4='1=UNDER WT<18.5, 2=NORMAL WT 18.5-24.9, 3=OVERWT 25-
29.9, 4=OBESE>=30'
      MOMCIG_01='0=NO SMOKING 3 MONTHS PRIOR TO AND DURING 1ST
TRIMESTER, 1=SMOKING PRIOR TO AND DURING 1ST TRIMESTER'
      MOMCIG_02='0=NO SMOKING 3 MONTHS PRIOR TO AND DURING 1ST
TRIMESTER, 1=SMOKING <=20CIGS/DAY PRIOR TO AND DURING 1ST TRIMESTER,
2=SMOKING >20CIGS/DAY PRIOR TO AND DURING 1ST TRIMESTER'
      MOMCIG='0=NO SMOKING DURING PREGNANCY 1=SMOKING DURING PREGNANCY'
      MALE='1=MALE, 0=FEMALE'
      UNDER37='1=<37 WKS, 0=37WKS+'
      LOWBIRTHWT='1=<2500, 0=2500+'
      MOMRACE='1-NONHIS_WHITE, 2=NONHISP_BLACK, 3=HISPANICS, 4=OTHER'
      MOMMAR='1=MARRIED, 0=NOT MARRIED'
      MOMEDU='1=<12, 2=12, 3=>12 YEARS'
      PRENAT_CARE='0=NO PRENATAL CARE, 1=CARE IN 1ST TRIMESTER, 2=2ND
TRIMESTER, 3=3RD TRIMESTER'
      ASSIS_FET='1=HAD ASSISTED FERTILITY, 0=NO ASSISTED FERTILITY'
      SINGLETON='1=SINGLETON 0=MULTIPLE'
      PRIMIPAROUS='# OF LIVEBIRTHS, 1=PRIMIPAROUS, 0=MULTIPAROUS'
      CONC_SEASON='1=SPRING 2=SUMMER 3=FALL 4=WINTER';

      *run some diagnostics on recoded variables;
```

```
      proc freq;
      tables mraceimp mracehisp momrace mar_imp dmar mommar mage_impflg
mager momage imp_sex sex male compgst_imp gestrec3 under37 imp_plur
dplural singleton momedu prenat_care artec dadage bmi_gp bmi_gp4
momcig_01 momcig_02 pre_diab pre_htn lowbirthwt primiparous momage2
conc_season;
      tables gast*momage;
      run;

      *creates permanent merged file in t drive;
libname project 't:\epiprojs\kancherla_v\TESSA
H_THESIS\sascode\dataset_current';
data project.births_recode2; set births_recode2;
run;

libname project "T:\epiprojs\KANCHERLA_V\TESSA
H_THESIS\sascode\dataset_current";

data births2;
set project.births_recode2;
run;

*limit analysis to women age 16-20 and 21-25, eliminate all others;
data young_mothers;
set births2;
if momage=2 then delete;
if momage=3 then delete;
proc freq;
tables gast*momage;
run;

*delete datapoints with missing or unknown birth defects;
Data births_knowndefects;
Set young_mothers;
If anen=. Or mnsb=. Or cchd=. Or cdh=. Or omph=. Or gast=. Or limb=. Or
cleft=. Or clpal=. Or hypo=. Or down=. And Chdisor=. Then delete;
Proc freq;
Tables singleton gast;
Run;

*identify cases, only want singleton births;
Data singletononly;
Set births_knowndefects; where singleton=1;
Proc freq;
Tables gast;
Run;

Data gast;
Set singletononly;
If gast=1;
If down=0 and chdisor=0;
Proc sort;
By id;
Run;
proc freq;
tables gast;
run;
```

```
Data other_defects;
Set births_knowndefects; where singleton=1;
If anen=1 or mnsb=1 or cdh=1 or omph=1 or cchd=1 or limb=1 or cleft=1
or clpal=1 or hypo=1;
If down=0 and chdisor=0;
Proc sort nodupkey; by id;
Run;

Data gast_only;
Merge gast (in=a) other_defects (in=b keep=id);
By id;
If ^b;
Gast_only=1;
Proc sort; by id;
Run;
Data gast_mult;
Merge gast(in=a) other_defects(in=b keep=id);
By id;
If a; if b;
Gast_mult=1;
Proc sort; by id;
Run;
Data all_gast;
Set gast_only gast_mult;
Case=1;
Proc sort; by id;
Proc freq;
Tables gast_only gast_mult case;
Run;
*identify controls;
Data controls;
Set births_knowndefects; where singleton=1;
If gast=0 and anen=0 and mnsb=0 and cdh=0 and omph=0 and cchd=0 and
limb=0 and cleft=0 and clpal=0 and hypo=0 and down=0 and chdisor=0;
Case=0;
Run;
proc freq;
tables case*momage;
run;
*exclude non-us residents;
Data casecontrol_us;
Set all_gast controls;
If gast_only=. Then gast_only=0;
If gast_mult=. Then gast_mult=0;
If restatus=4 then delete;
Proc freq;
Tables case gast_only gast_mult;
Run;
*exclude missing exposure;
Data case_control_single;
Set casecontrol_us;
If chlam=. Or gon=. Or syph=. Then delete;
Drop anen mnsb cdh cchd omph limb cleft clpal down chdisor hypo;
Proc freq;
Tables case gast_only gast_mult;
Run;
Data sti;
```

```
Set case_control_single;
Where chlam=1 or gon=1 or syph=1;
If hepb=0 and hepc=0;
Sti=1;
Proc freq;
Tables chlam gon syph;
Proc sort; by id;
Run;
Data chlam gon syph;
Set sti (keep=id chlam gon syph);
If chlam=1 then output chlam;
If gon=1 then output gon;
If syph=1 then output syph;
Proc sort data=chlam; by id;
Proc sort data=gon; by id;
Proc sort data=syph; by id;
Run;

Data chlam_only;
Merge chlam (keep=id in=a) gon (keep=id in=b) syph (keep=id in=c);
By id;
If ^b; if ^c;
Chlam_only=1;
Proc sort nodupkey; by id;
Run;

Data gon_only;
Merge chlam (keep=id in=a) gon (keep=id in=b) syph (keep=id in=c);
By id;
If ^a; if ^c;
gon_only=1;
Proc sort nodupkey; by id;
Run;

Data syph_only;
Merge chlam (keep=id in=a) gon (keep=id in=b) syph (keep=id in=c);
By id;
If ^a; if ^b;
syph_only=1;
Proc sort nodupkey; by id;
Run;

Data sti_only;
Set chlam_only gon_only syph_only;
Sti_only=1;
Proc sort; by id;
Run;

Data all_sti;
Merge sti (keep=id sti in=a) sti_only (in=b);
By id;
If a;
If sti_only=. Then sti_only=0;
Proc freq;
Tables sti sti_only chlam_only gon_only syph_only;
Proc sort data=all_sti; by id;
Run;
```

```
Proc sort data=case_control_single;
By id;
Run;

Data final_casecontrol_single;
Merge all_sti (in=a) case_control_single(in=b);
By id;
If b;
If sti=. Then sti=0;
If sti_only=. Then sti_only=0;
If chlam_only=. Then chlam_only=0;
If gon_only=. Then gon_only=0;
If syph_only=. Then syph_only=0;
Proc freq;
Tables case gast_only sti sti_only chlam_only gon_only syph_only
singleton bmi_gp4 momage2 momcig_02 conc_season; run;

*creates permanent merged file in t drive;
libname project 't:\epiprojs\kancherla_v\TESSA
H_THESIS\sascode\dataset_current';
data project.final_casecontrol_single; set final_casecontrol_single;
run;


libname project "T:\epiprojs\KANCHERLA_V\TESSA
H_THESIS\sascode\dataset_current";

data test;
set project.final_casecontrol_single;
run;

*this creates tables for the different exposure variables (Table 1);
proc freq data= test;
      tables (momage momage2 momrace momedu bmi_gp bmi_gp4 prenat_care
male under37 lowbirthwt chlam_only gon_only syph_only primiparous
momcig_01 momcig_02 pre_diab pre_htn artec dadage mommar conc_season) *
case / missing;
run;

proc freq data= test;
      tables (momage momage2 momrace momedu bmi_gp bmi_gp4 prenat_care
male under37 lowbirthwt chlam_only gon_only syph_only primiparous
momcig_01 momcig_02 pre_diab pre_htn artec dadage mommar conc_season) *
case / chisq;
run;

proc freq data= test;
      tables (momage momage2 momrace momedu bmi_gp bmi_gp4 prenat_care
male under37 lowbirthwt chlam_only gon_only syph_only primiparous
momcig_01 momcig_02 pre_diab pre_htn artec dadage mommar conc_season) *
gast_only / missing;
run;

proc freq data= test;
      tables (momage momage2 momrace momedu bmi_gp bmi_gp4 prenat_care
male under37 lowbirthwt chlam_only gon_only syph_only primiparous
```

```
momcig_01 momcig_02 pre_diab pre_htn artec dadage mommar conc_season) *
gast_only / chisq;
run;

libname project "T:\epiprojs\KANCHERLA_V\TESSA
H_THESIS\sascode\dataset_current";

data test;
set project.final_casecontrol_single;
run;

*this creates tables for the different exposure variables (Table 2);
Proc freq data=test;
Tables case*chlam_only;
Run;

proc freq data= test; where case=0;/*control*/
tables (momage momage2 momrace momedu bmi_gp bmi_gp4 prenat_care male
under37 lowbirthwt chlam_only gon_only syph_only primiparous momcig_01
momcig_02 pre_diab pre_htn artec dadage mommar conc_season) *
chlam_only / missing;
run;

proc freq data= test; where case=0;/*control*/
tables (momage momage2 momrace momedu bmi_gp bmi_gp4 prenat_care male
under37 lowbirthwt chlam_only gon_only syph_only primiparous momcig_01
momcig_02 pre_diab pre_htn artec dadage mommar conc_season) *
chlam_only / chisq fisher;
run;

proc freq data= test; where case=1;/*case*/
tables (momage momage2 momrace momedu bmi_gp bmi_gp4 prenat_care male
under37 lowbirthwt chlam_only gon_only syph_only primiparous momcig_01
momcig_02 pre_diab pre_htn artec dadage mommar conc_season) *
chlam_only / missing;
run;

proc freq data= test; where case=1;/*case*/
tables (momage momage2 momrace momedu bmi_gp bmi_gp4 prenat_care male
under37 lowbirthwt chlam_only gon_only syph_only primiparous momcig_01
momcig_02 pre_diab pre_htn artec dadage mommar conc_season) *
chlam_only / chisq fisher;
run;

proc freq data= test; where gast_only=1;/*isolated cases*/
tables (momage momage2 momrace momedu bmi_gp bmi_gp4 prenat_care male
under37 lowbirthwt chlam_only gon_only syph_only primiparous momcig_01
momcig_02 pre_diab pre_htn artec dadage mommar conc_season) *
chlam_only / missing;
run;

proc freq data= test; where gast_only=1;/*case*/
tables (momage momage2 momrace momedu bmi_gp bmi_gp4 prenat_care male
under37 lowbirthwt chlam_only gon_only syph_only primiparous momcig_01
momcig_02 pre_diab pre_htn artec dadage mommar conc_season) *
chlam_only / chisq fisher;
run;
```

```
libname project "T:\epiprojs\KANCHERLA_V\TESSA
H_THESIS\sascode\dataset_current";

data test;
set project.final_casecontrol_single;
run;

*check multicollinearity;
proc reg data=test;
model case=chlam_only momage momrace momedu bmi_gp primiparous
momcig_01 prenat_care pre_diab pre_htn artec dadage male under37 mommar
lowbirthwt conc_season/ tol vif;
run;

*crude odds ratio;
Proc logistic data=test;
class chlam_only (param=ref ref='0');*0=no chlamydia;
Model case(event='1')=chlam_only;
Run;

Proc logistic data=test;
class chlam_only (param=ref ref='0');*0=no chlamydia;
Model gast_only(event='1')=chlam_only;
Run;

Proc logistic data=test;
class gon_only (param=ref ref='0');*0=no gonorrhea;
Model case(event='1')=gon_only;
Run;

Proc logistic data=test;
class gon_only (param=ref ref='0');*0=no gonorrhea;
Model gast_only(event='1')=gon_only;
Run;
Proc logistic data=test;
class syph_only (param=ref ref='0');*0=no syphilis;
Model case(event='1')=syph_only;
Run;

Proc logistic data=test;
class syph_only (param=ref ref='0');*0=no syphilis;
Model gast_only(event='1')=syph_only;
Run;

Proc logistic data=test;
class under37 (param=ref ref='1');*1=<37 weeks;
Model case(event='1')=under37;
Run;

Proc logistic data=test;
class under37 (param=ref ref='1');*1=<37 weeks;
Model gast_only(event='1')=under37;
Run;

Proc logistic data=test;
```

```
class momage (param=ref ref='1');*1=21-25;
Model case(event='1')=momage;
Run;

Proc logistic data=test;
class momage (param=ref ref='1');*1=21-25;
Model gast_only(event='1')=momage;
Run;

Proc logistic data=test;
class momage2 (param=ref ref='3');*1=23-25;
Model case(event='1')=momage2;
Run;

Proc logistic data=test;
class momage2 (param=ref ref='3');*1=23-25;
Model gast_only(event='1')=momage2;
Run;


Proc logistic data=test;
class momrace (param=ref ref='2');*2=black;
Model case(event='1')=momrace;
Run;

Proc logistic data=test;
class momrace (param=ref ref='2');*2=black;
Model gast_only(event='1')=momrace;
Run;

Proc logistic data=test;
class momedu (param=ref ref='1');*1=<12;

Model case(event='1')=momedu;
Run;

Proc logistic data=test;
class momedu (param=ref ref='1');*1=<12;
Model gast_only(event='1')=momedu;
Run;

Proc logistic data=test;
class bmi_gp (param=ref ref='2');*normal wt;
Model case(event='1')=bmi_gp;
Run;

Proc logistic data=test;
class bmi_gp (param=ref ref='2');*normal wt;
Model gast_only(event='1')=bmi_gp;
Run;

Proc logistic data=test;
class bmi_gp4 (param=ref ref='2');*normal wt;
Model case(event='1')=bmi_gp4;
Run;

Proc logistic data=test;
```

```
class bmi_gp4 (param=ref ref='2');*normal wt;
Model gast_only(event='1')=bmi_gp4;
Run;

Proc logistic data=test;
class primiparous (param=ref ref='1');*1=primiparous;
Model case(event='1')=primiparous;
Run;

Proc logistic data=test;
class primiparous (param=ref ref='1');*1=primiparous;
Model gast_only(event='1')=primiparous;
Run;

Proc logistic data=test;
class momcig_01 (param=ref ref='0');*0=no maternal smoking;
Model case(event='1')=momcig_01;
Run;

Proc logistic data=test;
class momcig_01 (param=ref ref='0');*0=no maternal smoking;
Model gast_only(event='1')=momcig_01;
Run;

Proc logistic data=test;
class momcig_02 (param=ref ref='0');*0=no maternal smoking;
Model case(event='1')=momcig_02;
Run;

Proc logistic data=test;
class momcig_02 (param=ref ref='0');*0=no maternal smoking;
Model gast_only(event='1')=momcig_02;
Run;

Proc logistic data=test;
class prenat_care (param=ref ref='1');*1=prenat 1st trimester;
Model case(event='1')=prenat_care;
Run;

Proc logistic data=test;
class prenat_care (param=ref ref='1');*1=prenat 1st trimester;
Model gast_only(event='1')=prenat_care;
Run;

Proc logistic data=test;
class pre_diab (param=ref ref='0');*0=no pre-pregnancy diabetes;
Model case(event='1')=pre_diab;
Run;

Proc logistic data=test;
class pre_diab (param=ref ref='0');*0=no pre-pregnancy diabetes;

Model gast_only(event='1')=pre_diab;
Run;

Proc logistic data=test;
class pre_htn (param=ref ref='0');*0=no pre-pregnancy hypertension;
```

```
Model case(event='1')=pre_htn;
Run;

Proc logistic data=test;
class pre_htn (param=ref ref='0');*0=no pre-pregnancy hypertension;
Model gast_only(event='1')=pre_htn;
Run;

Proc logistic data=test;
class artec (param=ref ref='0');*0=no assisted repro tech;
Model case(event='1')=artec;
Run;

Proc logistic data=test;
class artec (param=ref ref='0');*0=no assisted repro tech;
Model gast_only(event='1')=artec;
Run;

Proc logistic data=test;
class mommar (param=ref ref='0');*0=not married;
Model case(event='1')=mommar;
Run;

Proc logistic data=test;
class mommar (param=ref ref='0');*0=not married;
Model gast_only(event='1')=mommar;
Run;

Proc logistic data=test;
class dadage(param=ref ref='1');*1=21-25;
Model case(event='1')=dadage;
Run;

Proc logistic data=test;
class dadage(param=ref ref='1');*1=21-25;
Model gast_only(event='1')=dadage;
Run;

Proc logistic data=test;
class conc_season(param=ref ref='1');*1=Spring;
Model case(event='1')=conc_season;
Run;

Proc logistic data=test;
class conc_season(param=ref ref='1');*1=Spring;
Model gast_only(event='1')=conc_season;
Run;

libname project "T:\epiprojs\KANCHERLA_V\TESSA
H_THESIS\sascode\dataset_current";

data test;
set project.final_casecontrol_single;
run;

*full model, checking for interaction;
proc logistic data=test;
```

```
class chlam_only (param=ref ref='0');*0=no chlamydia;
class gon_only (param=ref ref='0');*0=no gonorrhea;
class syph_only (param=ref ref='0');*0=no syphilis;
class under37 (param=ref ref='1');*1=<37 weeks;
class momage (param=ref ref='1');*1=21-25;
class momage2 (param=ref ref='3');*3=23-25;
class momrace (param=ref ref='2');*2=black;
class bmi_gp (param=ref ref='2');*normal wt;
class bmi_gp4 (param=ref ref='2');*normal wt;
class momedu (param=ref ref='1');*1=<12;
class primiparous (param=ref ref='1');*1=primiparous;
class momcig_01 (param=ref ref='0');*0=no maternal smoking;
class momcig_02 (param=ref ref='0');*0=no maternal smoking;
class prenat_care (param=ref ref='1');*1=prenat 1st trimester;
class pre_diab (param=ref ref='0');*0=no pre-pregnancy diabetes;
class pre_htn (param=ref ref='0');*0=no pre-pregnancy hypertension;
class artec (param=ref ref='0');*0=no assisted repro tech;
class mommar (param=ref ref='0');*0=not married;
class dadage(param=ref ref='1');*1=21-25;
class conc_season(param=ref ref='1');*1=Spring;
model case (event='1') = chlam_only gon_only syph_only momage2 momrace
momedu bmi_gp4 prenat_care male under37 mommar primiparous momcig_02
pre_diab pre_htn artec dadage conc_season chlam_only*gon_only
chlam_only*syph_only chlam_only*momage2 chlam_only*momrace
chlam_only*momedu chlam_only*bmi_gp4 chlam_only*prenat_care
chlam_only*male chlam_only*under37 chlam_only*mommar
chlam_only*primiparous chlam_only*momcig_02 chlam_only*pre_diab
chlam_only*pre_htn chlam_only*artec chlam_only*dadage
chlam_only*conc_season/ hierarchy=single selection=backward slstay=0.01
include=18 details lackfit;
run;

*no significant interaction found based on above query;
*full model for adjusted odds ratios - Table 4, all gastroschisis;
proc logistic data=test;
class chlam_only (param=ref ref='0');*0=no chlamydia;
class gon_only (param=ref ref='0');*0=no gonorrhea;
class syph_only (param=ref ref='0');*0=no syphilis;
class under37 (param=ref ref='1');*1=<37 weeks;
class momage (param=ref ref='1');*1=21-25;
class momage2 (param=ref ref='3');*3=23-25;
class momrace (param=ref ref='2');*2=black;
class bmi_gp (param=ref ref='2');*normal wt;
class bmi_gp4 (param=ref ref='2');*normal wt;
class momedu (param=ref ref='1');*1=<12;
class primiparous (param=ref ref='1');*1=primiparous;
class momcig_01 (param=ref ref='0');*0=no maternal smoking;
class momcig_02 (param=ref ref='0');*0=no maternal smoking;
class prenat_care (param=ref ref='1');*1=prenat 1st trimester;
class pre_diab (param=ref ref='0');*0=no pre-pregnancy diabetes;
class pre_htn (param=ref ref='0');*0=no pre-pregnancy hypertension;
class artec (param=ref ref='0');*0=no assisted repro tech;
class mommar (param=ref ref='0');*0=not married;
class dadage(param=ref ref='1');*1=21-25;
class conc_season(param=ref ref='1');*1=Spring;
```

```
model case (event='1') = chlam_only gon_only syph_only momage2 momrace
momedu bmi_gp4 prenat_care under37 mommar primiparous momcig_02
pre_diab pre_htn artec dadage conc_season/  lackfit;
run;

*full model for adjusted odds ratios - Table 4, gastroschisis only;
proc logistic data=test;
class chlam_only (param=ref ref='0');*0=no chlamydia;
class gon_only (param=ref ref='0');*0=no gonorrhea;
class syph_only (param=ref ref='0');*0=no syphilis;
class under37 (param=ref ref='1');*1=<37 weeks;
class momage (param=ref ref='1');*1=21-25;
class momage2 (param=ref ref='3');*3=23-25;
class momrace (param=ref ref='2');*2=black;
class bmi_gp (param=ref ref='2');*normal wt;
class bmi_gp4 (param=ref ref='2');*normal wt;
class momedu (param=ref ref='1');*1=<12;
class primiparous (param=ref ref='1');*1=primiparous;
class momcig_01 (param=ref ref='0');*0=no maternal smoking;
class momcig_02 (param=ref ref='0');*0=no maternal smoking;
class prenat_care (param=ref ref='1');*1=prenat 1st trimester;
class pre_diab (param=ref ref='0');*0=no pre-pregnancy diabetes;
class pre_htn (param=ref ref='0');*0=no pre-pregnancy hypertension;
class artec (param=ref ref='0');*0=no assisted repro tech;
class mommar (param=ref ref='0');*0=not married;
class dadage(param=ref ref='1');*1=21-25;
class conc_season(param=ref ref='1');*1=Spring;
model gast_only (event='1') = chlam_only gon_only syph_only momage2
momrace momedu bmi_gp4 prenat_care under37 mommar primiparous momcig_02
pre_diab pre_htn artec dadage conc_season /  lackfit;
run;

*backward selection;
proc logistic data=test;
class chlam_only (param=ref ref='0');*0=no chlamydia;
class gon_only (param=ref ref='0');*0=no gonorrhea;
class syph_only (param=ref ref='0');*0=no syphilis;
class under37 (param=ref ref='1');*1=<37 weeks;
class momage (param=ref ref='1');*1=21-25;
class momage2 (param=ref ref='3');*3=23-25;
class momrace (param=ref ref='2');*2=black;
class bmi_gp (param=ref ref='2');*normal wt;
class bmi_gp4 (param=ref ref='2');*normal wt;
class momedu (param=ref ref='1');*1=<12;
class primiparous (param=ref ref='1');*1=primiparous;
class momcig_01 (param=ref ref='0');*0=no maternal smoking;
class momcig_02 (param=ref ref='0');*0=no maternal smoking;
class prenat_care (param=ref ref='1');*1=prenat 1st trimester;
class pre_diab (param=ref ref='0');*0=no pre-pregnancy diabetes;
class pre_htn (param=ref ref='0');*0=no pre-pregnancy hypertension;
class artec (param=ref ref='0');*0=no assisted repro tech;
class mommar (param=ref ref='0');*0=not married;
class dadage(param=ref ref='1');*1=21-25;
class conc_season(param=ref ref='1');*1=Spring;
model case (event='1') = chlam_only gon_only syph_only momage2 momrace
momedu bmi_gp4 prenat_care under37 mommar primiparous momcig_02
```

```
pre_diab pre_htn artec dadage conc_season/  selection=backward
slstay=0.2 include=1 details lackfit;
run;

*backward selection;
proc logistic data=test;
class chlam_only (param=ref ref='0');*0=no chlamydia;
class gon_only (param=ref ref='0');*0=no gonorrhea;
class syph_only (param=ref ref='0');*0=no syphilis;
class under37 (param=ref ref='1');*1=<37 weeks;
class momage (param=ref ref='1');*1=21-25;
class momage2 (param=ref ref='3');*3=23-25;
class momrace (param=ref ref='2');*2=black;
class bmi_gp (param=ref ref='2');*normal wt;
class bmi_gp4 (param=ref ref='2');*normal wt;
class momedu (param=ref ref='1');*1=<12;
class primiparous (param=ref ref='1');*1=primiparous;
class momcig_01 (param=ref ref='0');*0=no maternal smoking;
class momcig_02 (param=ref ref='0');*0=no maternal smoking;
class prenat_care (param=ref ref='1');*1=prenat 1st trimester;
class pre_diab (param=ref ref='0');*0=no pre-pregnancy diabetes;
class pre_htn (param=ref ref='0');*0=no pre-pregnancy hypertension;
class artec (param=ref ref='0');*0=no assisted repro tech;
class mommar (param=ref ref='0');*0=not married;
class dadage(param=ref ref='1');*1=21-25;
class conc_season(param=ref ref='1');*1=Spring;
model gast_only (event='1') = chlam_only gon_only syph_only momage2
momrace momedu bmi_gp4 prenat_care under37 mommar primiparous momcig_02
pre_diab pre_htn artec dadage conc_season/  selection=backward
slstay=0.2 include=1 details lackfit;
run;
```