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Association between maternal *Chlamydia* during pregnancy and risk of cyanotic congenital heart defects in the offspring

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Association between maternal *Chlamydia* during pregnancy and risk of cyanotic congenital heart defects in the offspring

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MS
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An abstract of
A thesis submitted to the Faculty of the
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Abstract

Association between maternal *Chlamydia* during pregnancy and risk of cyanotic congenital heart defects in the offspring

By Yan Dong

BACKGROUND: Genital *Chlamydia* is a common bacterial sexually-transmitted infection among reproductive aged women, and particularly, younger populations. Cyanotic congenital heart defects (CCHDs) constitute about one quarter of all cardiac malformations at birth, and are associated with high rate of morbidity and mortality. Epidemiological research on the association between maternal *Chlamydia* during pregnancy and CCHDs in the offspring is lacking.
METHODS: Using data from the 2012 U.S. birth certificates, we examined the association between CCHDs and prenatal exposure to *Chlamydia* among live singleton births with CCHDs (n=2487) and unaffected singleton births (n= 3,334,424). We estimated adjusted odds ratios (aORs) and 95% confidence intervals (CIs) using unconditional logistic regression analysis for all CCHDs combined, and isolated CCHD (without other major congenital malformations).
RESULTS: Overall 1.7% of case and 1.7% of control mothers reported having *Chlamydia* during their index pregnancies**.** After controlling for several potential confounders, we found a weak positive association between maternal exposure to *Chlamydia* during pregnancy and all CCHDs combined (aOR=1.39; 95% CI, 1.02-1.90). A subgroup analysis for high-risk group of mothers aged 15-19 years and 20-24 years during the index pregnancy showed an increased risk for all CCHDs combined and isolated CCHDs; however, the associations were not statistically significant.
CONCLUSIONS: Maternal exposure to *Chlamydia* during pregnancy was weakly associated with higher risk of CCHDs in the offspring. Future studies should examine the association in other populations, and those at high-risk.

Association between maternal *Chlamydia* during pregnancy and risk of cyanotic congenital heart defects in the offspring

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INTRODUCTION

Congenital heart defects (CHDs) are the most common type of birth defects, with a prevalence of approximately 100 per 10,000 births in the United States (U.S.) (1). CHDs contribute to nearly 30% of all deaths caused by birth defects (2-3). Cyanotic congenital heart defects (CCHDs) are a sub-group of CHDs resulting from congenital abnormality in the heart's ability to pump blood effectively, thus significantly reducing the amount of oxygen in the blood flow, leading to cyanosis (4-7). Specifically, CCHDs include Epstein's anomaly, hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, total anomalous pulmonary venous return, transposition of great vessels, tricuspid atresia, and truncus arteriosus. Approximately, 25% of babies born with CHDs in the U.S. are affected with CCHDs (4, 8-9). Infants born with CCHDs suffer severe morbidity and mortality, and usually require repeated surgeries (5, 7). The one-year survival rate is 75% for infants with CCHDs compared to 97% for those with non-cyanotic CHDs (10). CCHD-related hospitalizations have disproportionately high costs compared with other pediatric hospitalizations (11). The embryo is most susceptible to cardiac malformation between 19 and 45 days of gestation, so the first trimester of pregnancy is a critical window of vulnerability for all heart defects (12-13). Advances in cardiovascular medicine and surgery have enabled a longer survival rates among infants born with CCHDs (10); however, reaching adulthood, they experience a disproportionately greater number of medical conditions such as pulmonary hypertension, heart failure, or stroke, leading to deterioration of their overall well-being, and imposing a substantial financial burden on their families and society (6,14).

The etiology of CCHDs is believed to be multifactorial in origin, with a variety of genetic and environmental factors (15-19). Despite the progress in understanding causal factors for CCHDs, a study by Wilson (1998) revealed that the overall attributable risk fractions range from 13.6% for hypoplastic left heart syndrome to 30.2% for transposition of the great arteries (20), leaving majority of etiology for CCHDs still unexplained. Maternal exposures to infections during pregnancy (e.g., infections of genital tract, upper respiratory tract, urinary tract, and gastroenteritis) have been shown to be associated with CHDs, including specific types of CCHDs (21-28). The three pathways proposed for malformation in the fetal heart include inhibition of cell growth, interference of blood supply, and/or cell death induced by inflammatory responses, with potential gene-environment interactions (12-13, 29-30). The basis for the teratogenicity due to an infectious agent was postulated to arise from a prolonged fetal exposure to toxic metabolites produced in the mother during an infection (31). While it is not clear how maternal genital tract infections would result in birth defects in the offspring, experimental models on mice show that the host cells infected with genital *Chlamydia* release intracellular factors that contribute to inflammatory responses, which may lead to cell death (29). Although the uterus and the fetal membrane provide protection to the developing fetus, ascending infections may pass through the cervical canal and harm the fetus (32-33).

Chlamydia is one of the most prevalent bacterial sexually transmitted infections (STIs) in the U.S. A recent study using the 2005-2008 National Health and Nutrition Examination Survey (NHANES) estimated genital *Chlamydia* is prevalent in about 3.1% of U.S. women aged 15-24 years old, and 0.87% of women aged 25-39 years old (34).

The Centers for Disease Control and Prevention (CDC) estimates the prevalence of *Chlamydia* among women receiving antenatal care in the U.S. to be 7.7% (35). The prevalence is much higher among pregnant adolescents (36). If left untreated, *Chlamydia* during pregnancy can result in pelvic inflammatory disease, ectopic pregnancy, infertility, stillbirth, preterm birth, perinatal death, neonatal eye infection or pneumonia (37-38). *Chlamydia* can be cured with early diagnosis and prompt treatment with antibiotics such as amoxicillin and azithromycin (39). Published studies have suggested gestational exposure to antibiotics used to treat *Chlamydia* is not associated with an increase in the rate of major malformations in the offspring (40-41).

Studies on the association between *Chlamydia* and CCHDs are lacking. Maternal exposures to different genital tract infections (e.g., genital herpes, acute pelvic inflammatory disease) during pregnancy have been shown to be associated with certain types of CHDs in the offspring (21-23). The National Birth Defects Prevention Study surveyed mothers about their periconceptional (one month before conception through the first trimester) exposure to various genital tract infections to examine the association with different types of CHDs, including CCHDs in live births, still births and elective terminations (24). However, in their analysis, mothers who reported exposures to *Chlamydia*, gonorrhea or pelvic inflammatory disease were pooled together; and no significant association was observed with any type of CHDs (24). The inconclusive associations observed in past studies may have been partly due to chance, or due to varied criteria employed in defining exposure to *Chlamydia*, or defining and classifying CCHDs.

With a concerning prevalence of genital *Chlamydia* among young women and women of reproductive age in the U.S; and the significant morbidity, mortality, and high financial burden associated with CCHDs, it is of increasing importance to examine the association between maternal *Chlamydia* and CCHDs. The purpose of our study was to examine whether maternal exposure to *Chlamydia* during pregnancy increases the risk of CCHDs in live-born singleton offspring, using data from the 2012 U.S. vital records. Compared to previous studies, the current study is novel in specifically addressing the association between *Chlamydia* and CCHDs, and should be viewed as exploratory and hypothesis-generating.

METHODS

Data Source

We used data from all singleton live births registered in the 2012 U.S. birth certificates. The 2012 U.S. standard birth certificate collected information on 12 major congenital anomalies or anomaly groups separately at the time of birth (including anencephaly, meningomyelocele/spina bifida, CCHD, 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) from the revised reporting area including 38 states, New York City, and the District of Columbia (42). Thus, information on congenital anomalies in the aforementioned reporting area represents 86.3% of all U.S. births in the year 2012. The birth certificate collects information on congenital anomalies in a checkbox format, allowing for the reporting of more than one anomaly. The certificate also allows a choice of "none of the above". When incomplete, an item is classified as "not stated." Overall, less than 1% of

records were classified as “not stated” for congenital anomalies in the year 2012. The National Center for Health Statistics (NCHS) at the CDC assembled and compiled the birth data (42).

Case and Control Selection

Cases were comprised of singleton live-born infants with CCHDs recorded on the birth certificates. We excluded from our analysis infants with Down syndrome or chromosomal disorders. The status of CCHDs in the birth certificates was collected directly from the medical records at birth using a facility worksheet with detailed instructions and definitions. We further stratified cases into two groups: 1) isolated CCHDs, defined as cases with CCHDs but without any of the other aforementioned birth defects reported in the birth certificate; and 2) all CCHDs, defined as CCHDs with or without additional birth defects recorded on the birth certificate. Control infants in this study were singleton live-born infants who did not have any birth defects checked on their birth certificates.

Exposure Assessment

Maternal *Chlamydia* during pregnancy was ascertained based on a question on the birth certificate inquiring about presence or absence of *Chlamydia* during the index pregnancy. The 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 mothers who had other infections, including gonorrhea, syphilis, 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 (expected cell frequencies <5). We compared selected covariates, including infant's sex (male, female), gestational age at delivery (<37, ≥37 weeks), birth weight (<2500, ≥2500 grams); and maternal age at delivery (15-19, 20-24, 25-29, 30-34, ≥35 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), education (<12, 12, >12 years), prepregnancy body mass index (BMI) (<18.5, 18.5-24.9, 25.0-29.9, ≥30 Kg/m^2), parity (primipara, multipara), periconceptional smoking status (yes, no), initiation time of prenatal care (no prenatal care, 1^{st} trimester, 2^{nd} trimester, 3^{rd} trimester), prepregnancy diabetes (yes, no), prepregnancy hypertension (yes, no), and use of assisted reproductive technology (ART) (e.g., in vitro fertilization or intra-fallopian transfer in the index pregnancy) (yes, no). All covariates were selected *a priori*, based on the literature review of published studies (43-54). Information on mother's age, race/ethnicity, smoking status, education, height, and pre-pregnancy weight was reported directly by the mother. We categorized BMI to be consistent with previous studies which investigated the relation between maternal obesity and CHDs (24, 50). The birth certificates record information on prepregnancy diabetes, prepregnancy hypertension, parity, initiation time of prenatal care, and use of ART from the mother's medical records.

We used unconditional logistic regression to estimate the association between maternal *Chlamydia* during pregnancy and risk of CCHDs in the offspring. Separate analyses were performed for: 1) all CCHDs combined, and 2) isolated CCHDs. We estimated crude and adjusted odds ratios (cORs and aORs, respectively) and

corresponding 95% confidence intervals (CIs) for all CCHDs combined and isolated CCHDs separately. For adjusted analysis, we included all of the aforementioned maternal covariates in the regression models based on biologic plausibility. Additionally, we performed subgroup analyses restricted to mothers 15-19 years and 20-24 years of age. We conducted sensitivity analyses by including multiple births and applying penalized maximum likelihood in the multivariate regressions to address the potential problem of small number of cases exposed to *Chlamydia*. We also compared the groups with and without missing data to assess for any systemic differences in distributions of the outcome, Chlamydia exposure, and maternal 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 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Overall, we identified 2,498 live-born eligible singleton infants with CCHDs and 3,349,721 live born singleton infants without any congenital malformations. Of these, 2 cases and 6,687 controls were excluded from the analysis because of non-resident status of their mothers. Additionally, 9 case and 8,610 control infants were excluded due to missing or unknown status of exposure to *Chlamydial* infection in-utero. The analyzed study sample included 2,487 all CCHDs combined, of which 2,395 were isolated CCHDs; and 3,334,424 control infants.

CCHD case infants were statistically more likely than controls to be male, low birth weight, and preterm ($P < 0.0001$) (Table 1). Compared to mothers of control infants, mothers of CCHD cases were more likely to be 30 years or older at the time of delivery, non-Hispanic white, had a prepregnancy BMI >30 kg/m^2 (obese) before pregnancy, had

at least high school education, diabetic or hypertensive before the index pregnancy, used ART, smoked, and had initiated prenatal care in the third trimester. Similar findings were observed between isolated CCHD cases and control infants, as well as their mothers.

We did not find a significant difference between case and control mothers with regard to *Chlamydia* during pregnancy. Overall, 43 case mothers (1.7%) and 55,834 control mothers (1.7%) (P=0.83) reported *Chlamydia* during pregnancy (Table 1). Comparison of maternal characteristics among case and control mothers according to whether or not they had *Chlamydia* during pregnancy showed that mothers who had *Chlamydia* were more likely to be less than 25 years old at the time of delivery, non-Hispanic black, had less than high school education, and smoked during periconceptional period (Table 2a-b). In addition, control mothers who were exposed to *Chlamydia* during pregnancy also differed by parity, prepregnancy BMI, timing of prenatal care initiation, and use of ART compared to mothers who did not have *Chlamydia* ($P < 0.05$).

In our unadjusted analyses, we found a null association between maternal exposure to *Chlamydia* during pregnancy and all CCHDs combined (cOR: 1.03, 95% CI: 0.77-1.40), or isolated CCHDs (cOR: 1.00, 95% CI: 0.73-1.36). But adjusting for potential confounders in the multivariable model revealed a significant but weak positive association between maternal *Chlamydia* during pregnancy and all CCHDs combined (aOR: 1.39, 95% CI: 1.02-1.90) (Table 3). For isolated CCHDs, the association was also positive, but only marginally significant (aOR: 1.34, 95% CI: 0.96, 1.74) (Table 3). In addition, we performed a subgroup analysis for high-risk groups of mothers 15-19 years and 20-24 years of age at the time of delivery. In the analysis for mothers aged 15-19 years old, we found that having *Chlamydia* during pregnancy increased the risk of all

CCHDs as well as isolated CCHDs in the offspring by 55% (aOR: 1.55, 95% CI: 0.78-3.09) and 59% respectively (aOR: 1.59, 95% CI: 0.80-3.16), although the association did not reach statistical significance. For mothers aged 20-24 years old, the observed associations between maternal *Chlamydia* and all CCHDs (aOR: 1.36, 95% CI: 0.86-2.16) as well as isolated CCHDs (aOR: 1.26, 95% CI: 0.77-2.05) in the offspring were similar to the findings from the overall analysis (data not shown). Sensitivity analysis by including multiple births (twins or higher) attenuated the risk for all CCHDs combined (aOR: 1.31, 95% CI: 0.96-1.79) and for isolated CCHDs (aOR: 1.26, 95% CI: 0.91-1.74), and neither of these associations reached statistical significance (data not shown). Application of penalized maximum likelihood method did not change the results. The group without missing data did not differ systematically from the group with missing data.

DISCUSSION

To our knowledge, we report novel findings on the association between maternal *Chlamydia* during pregnancy and risk of CCHDs in the offspring. Using the 2012 U.S. birth certificate data, we show that maternal *Chlamydia* during pregnancy is associated with a weak positive risk for all CCHDs combined. Restriction of analysis to isolated CCHDs produced a marginally positive association with maternal *Chlamydia* during pregnancy. Subgroup analyses for two groups of mothers who have the highest prevalence for *Chlamydia* (15-19 years old, and 20-24 years old) magnified the potential association between maternal *Chlamydia* and risk for CCHDs in the offspring among mothers 15-19 years of age; however, that association did not reach statistical significance.

National Birth Defects Prevention Study (1997–2004) was used to examine the association between periconceptional exposure to maternal *Chlamydia*, gonorrhea, and/or pelvic inflammatory disease as a group and various birth defects; however, they found null association with congenital heart defects (24). While in our study, maternal *Chlamydia* was examined as an exclusive exposure, and was derived from birth certificates based on information abstracted from medical records. The adjusted odds ratio for all CCHDs combined in our study is similar to that for Tetralogy of Fallot (i.e. most common CCHDs subtype) in the National Birth Defects Prevention Study. Whereas, the specificity of CHDs in the previous study may be more robust compared to that reported in birth certificates. However, CCHDs, as well as other major birth defects reported in the birth certificate are abstracted directly from medical records and have been shown to be valid (55-58). Although it has been well documented that congenital anomalies have historically been under-reported in birth certificate data, there is support to show that the sensitivity is better for the most visible and most severe congenital defects such as CCHDs (55-58). Also, we were unable to include stillbirths and elective terminations in our analysis. Thus, differences in the study participant selection criteria, and exposure and outcome measurement, may have led to differences in the findings of the two studies. We are unable to compare findings from the current study with any other previous research due to paucity of studies that examined the relation between maternal *Chlamydia* during pregnancy and CCHDs in the offspring specifically.

In 2012 U.S. vital statistics data reported the rate of CCHDs per 10,000 births to be 8.76 among births to mothers of all ages from 38 reporting states and the District of Columbia (42). The prevalence rate of *Chlamydia* infections among mothers of control

infants in our study was 1.7%, while Carter et al. (2011) reported a much lower prevalence (0.58%) in their sample of control mothers (24). This difference can be attributed to the source of information, as the former was based on medical records, and latter was obtained through maternal report. The stigma of genital tract infection among mothers may potentially lead to under-reporting.

Our subgroup analyses, restricting to mothers aged 15-19 years old and 20-24 years old, shed light on an important concern. We found that women of these two age groups have the highest prevalence of *Chlamydia*, and although not statistically significant, there was a magnified positive association between maternal *Chlamydia* and CCHDs in mothers 15-19 years of age, in which maternal *Chlamydia* during pregnancy increased the risk of all CCHDs as well as isolated CCHDs in offspring by 55% and 59% respectively. It may be that the small number of exposed cases may have limited the power of our subgroup analyses. The observed magnification in our study drives an interesting hypothesis that younger women, who are at a higher risk for *Chlamydial* infection, may be at an increased risk for having offspring with CCHDs. Future studies should re-examine this specific age group of mothers for targeted prevention.

Our study has several strengths. First, the national vital statistics data, with a population size of 3.5 million births allowed estimation of the association between maternal *Chlamydia* during pregnancy and relatively rare outcome of CCHDs. CCHDs, as well as other major birth defects, reported in the birth certificate are abstracted directly from medical records and have been shown to be valid (55-58). Data on *Chlamydia* diagnosis and other genital-urinary tract infections are also collected directly from medical records, and thus suffer less bias due to maternal reporting. Our sub-group

analyses of maternal *Chlamydial* infections in maternal age groups of 15-19 years and 20-24 years show a higher proportion of *Chlamydia* as reported in the literature, and further strengthen the validity of our data. Because birth certificates collect information on a wide variety of maternal variables, we were able to examine several covariates, and adjust for many potential confounders. Use of ART can be a proxy for infertility, which is a potential confounder for the *Chlamydia*-CCHDs relation. Untreated *Chlamydia* may lead to infertility (38-39). Previous population-based studies have reported a positive association between use of ART and increased risk for CHDs in the offspring, including CCHDs (49). Validity of our findings may therefore be enhanced by accounting for use of ART.

The findings of this study, however, should be interpreted with caution as there are some limitations to birth certificate data. Responses on some exposures in birth certificates can be underreported, or missing, compared to other types of maternal and infant survey designs. There can be systematic differences between individual states in data collection. For example, it was suggested that the number of CCHD births in Massachusetts may have been inflated due to inaccurate reporting (42). The power of the analysis many have been adversely impacted by the small number of cases exposed to *Chlamydia*. To address this limitation, we conducted sensitivity analysis by applying penalized maximum likelihood method and observed minimal changes in both point estimates and confidence intervals. The birth certificates provided limited information about the month or trimester during the pregnancy when the infection occurred, or whether the infection is active or not. We also lacked information on whether the mother was undergoing treatment for the infection during pregnancy. Therefore, we were not

able to distinguish between the potential underlying differences in the risk of having a child with CCHDs and the timing of the infection during pregnancy, and the role of treatment for the same. As such, literatures on treatment rates for *Chlamydia* in general population are non-existent. It was also impossible to discern confounding by indication, with respect to medications used to treat the infection. Published studies, however, have suggested gestational exposure to antibiotics used to treat *Chlamydia* is not associated with an increase in the rate of major malformations in the offspring (40-41). Although we accounted for several established risk factors for CCHDs, we were not able to address other factors such as seizure medications, or family history of congenital heart defects because these data elements were not reported in the birth certificates. Furthermore, some pre-existing conditions recorded on birth certificates such as self-reported maternal smoking were likely underreported or misreported (59-60). In addition, we were not able to validate or evaluate individual CCHDs type because birth certificates collect only the information on aggregate CCHDs. We excluded women with other sexually transmitted diseases such as gonorrhea. The co-infection rate for *Chlamydia* and gonorrhea in our sample was 7.7%, well within the general reported rates in the population (2 – 13%) (61-62). Lastly, some subjects were eliminated from the logistic regression analysis due to missing data. However, the groups with and without missing data were not found to be systematically different in our sensitivity analysis.

In summary, findings from our study suggest a weak positive association between maternal *Chlamydia* during pregnancy and CCHDs in the offspring. Our study was exploratory and hypothesis-generating. Additional studies are needed to re-examine the association using more robust data sources, and in other populations. Meanwhile,

screening and timely treatment to prevent *Chlamydia* and other genital tract infections among women of reproductive age should be undertaken preemptively both to reduce the prevalence and incidence of these infections, and possibly treat and minimize the burden of associated adverse health outcomes.

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Table 1. Maternal and infant characteristics of CCHD cases and controls

Characteristics	**Controls** (N=3,334,424) n (%)	**All CCHD** (N=2,487) n (%)	**Isolated CCHD** (N=2,395) n (%)
Infant Characteristics			
Sex			
Female	1628803 (48.9)	1093 (44.0) *	1059 (44.2) *
Male	1705621 (51.1)	1394 (56.0)	1336 (55.8)
Gestation age (weeks)			
Preterm (<37)	322340 (9.7)	634 (25.5) *	605 (25.3) *
Term (≥ 37)	3009079 (90.2)	1850 (74.4)	1787 (74.6)
Birth weight (grams)			
Low (<2500)	203106 (6.1)	553 (22.2) *	515 (21.5) *
Normal (≥2500)	3128455 (93.8)	1927 (77.5)	1874 (78.3)
Maternal Characteristics			
Chlamydia during pregnancy			
No	3278590 (98.3)	2444 (98.3)	2355 (98.3)
Yes	55834 (1.7)	43 (1.7)	40 (1.7)
Age at delivery (years)			
15-19	260352 (7.8)	140 (5.6)*	137 (5.7)*
20-24	778666 (23.4)	513 (20.6)	492 (20.5)
25-29	954302 (28.6)	694 (27.9)	667 (27.9)
30-34	850975 (25.5)	653 (26.3)	628 (26.2)
≥35	487005 (14.6)	483 (19.4)	468 (19.5)
Race and ethnicity			
Non-Hispanic white	1790102 (53.7)	1631 (65.6)*	1569 (65.5)*
Non-Hispanic black	480573 (14.4)	304 (12.2)	296 (12.4)
Hispanic	794445 (23.8)	385 (15.5)	371 (15.5)
Other	242479 (7.3)	137 (5.5)	130 (5.4)
Education (years)			
<12	566253 (17.0)	328 (13.2)*	314 (13.1)*
12	824662 (24.7)	534 (21.5)	517 (21.6)
>12	1903182 (57.1)	1581 (63.6)	1521 (63.5)
Prepregnancy BMI (kg/m^2)			
Underweight (<18.5)	124996 (3.8)	79 (3.2)*	76 (3.2)
Normal weight (18.5-24.9)	1505734 (45.2)	1082 (43.5)	1039 (43.4)
Overweight (25.0-29.9)	811878 (24.4)	614 (24.7)	601 (25.1)
Obese (≥30)	752857 (22.6)	617 (24.8)	588 (24.6)
Parity			
Primipara	1342218 (40.3)	1032 (41.5)	997 (41.6)
Multipara	1977467 (59.3)	1450 (58.3)	1393 (58.2)
Periconceptional Smoking			
No	2805713 (84.1)	2107 (84.7)*	2037 (85.1)*
Yes	365680 (11.0)	331 (13.3)	312 (13.0)

Table 1. *Continued*

Characteristics	**Controls** (N=3,334,424) n (%)	**All CCHD** (N=2,487) n (%)	**Isolated CCHD** (N=2,395) n (%)
Maternal Characteristics			
Prenatal Care Initiation			
No prenatal care	45184 (1.4)	22 (0.9)*	21 (0.9)*
1st Trimester	2384607 (71.6)	1744 (70.1)	1680 (70.2)
2nd Trimester	641796 (19.3)	418 (16.8)	403 (16.8)
3rd Trimester	146593 (4.4)	148 (6.0)	140 (5.9)
Prepregnancy diabetes			
No	3306515 (99.2)	2395 (96.3)*	2307 (96.3) *
Yes	24888 (0.8)	89 (3.6)	85 (3.6)
Prepregnancy hypertension			
No	3284705 (98.5)	2403 (96.6)*	2316 (96.7) *
Yes	46698 (1.4)	81 (3.3)	76 (3.2)
ART			
No	3312968 (99.4)	2437 (98.0)	2346 (98.0)
Yes	12673 (0.4)	30 (1.2)*	29 (1.2) *

CCHD: cyanotic congenital heart defects; frequency; ART, assisted reproductive technology BMI, body mass index; kg, kilograms; m, meter; *$p < 0.05$ for cases vs. controls; Fisher's Exact test for cell frequency<5

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

Table 2a. Maternal characteristics of all CCHDs cases and controls stratified by *Chlamydia*

Characteristics	**Controls**		**All CCHDs**	
	No *Chlamydia* (N=3278590) n (%)	*Chlamydia* (N=55834) n (%)	No *Chlamydia* (N=2444) n (%)	*Chlamydia* (N=43) n (%)
Age at delivery (years)				
15-19	245951 (7.5)[#]	14401 (25.8)	130 (5.3) *	10 (23.3)
20-24	753453 (23.0)	25213 (45.2)	494 (20.2)	19 (44.2)
25-29	943993 (28.8)	10309 (18.5)	684 (28.0)	10 (23.3)
30-34	846828 (25.8)	4147 (7.4)	650 (26.6)	3 (7.0)
≥35	485415 (14.8)	1590 (2.9)	482 (19.7)	1 (2.3)
Race and ethnicity				
Non-Hispanic white	1770568 (54.0) [#]	19534 (35.0)	1610 (65.9)*	21 (48.8)
Non-Hispanic black	460084 (14.0)	20489 (36.7)	318 (12.0)	10 (23.3)
Hispanic	780975 (23.8)	13470 (24.1)	377 (15.4)	8 (18.6)
Other	240411 (7.3)	2068 (3.7)	133 (5.4)	4 (9.3)
Education (years)				
<12	548795 (16.7) [#]	17458 (31.3)	319 (13.1)*	9 (20.9)
12	803722 (24.5)	20940 (37.5)	516 (21.1)	18 (41.9)
>12	1886216 (57.5)	16966 (30.4)	1565 (64.0)	16 (37.2)
Prepregnancy BMI (kg/m^2)				
Underweight (<18.5)	122117 (3.7) [#]	2879 (5.2)	77 (3.2)	2 (4.7)
Normal weight (18.5-24.9)	1481219 (45.2)	24515 (43.9)	1063 (43.5)	19 (44.2)
Overweight (25.0-29.9)	798516 (24.4)	13362 (23.9)	608 (24.9)	6 (13.9)
Obese (≥30)	739863 (22.6)	12994 (23.3)	601 (24.6)	16 (37.2)
Parity				
Primipara	1314216 (40.1) [#]	28002 (50.2)	1010 (41.3)	22 (51.2)
Multipara	1950047 (59.5)	27420 (49.1)	1429 (58.5)	21 (48.8)
Periconceptional Smoking				
No	2764021 (84.3) [#]	41692 (74.7)	2075 (84.9)*	32 (74.4)
Yes	354324 (10.8)	11356 (20.3)	320 (13.1)	11 (25.6)
Prenatal Care Initiation				
No prenatal care	44374 (1.4) [#]	810 (1.5)	21 (0.9)	1 (2.3)
1st Trimester	2352713 (71.8)	31894 (57.1)	1718 (70.3)	26 (60.5)
2nd Trimester	625011 (19.1)	16785 (30.1)	408 (16.7)	10 (23.3)
3rd Trimester	142063 (4.3)	4530 (8.1)	143 (5.9)	5 (11.6)
Prepregnancy diabetes				
No	3251105 (99.2) [#]	55410 (99.2)	2352 (96.2)	43 (100)
Yes	24519 (0.8)	369 (0.7)	89 (3.6)	0 (0.0)
Prepregnancy hypertension				
No	3229673 (98.5)	55032 (98.6)	2360 (96.6)	43 (100.0)
Yes	45951 (1.4)	747 (1.3)	81 (3.3)	0 (0.0)
ART				
No	3257231(99.4) [#]	55737 (99.8)	2394 (98.0)	43 (100.0)
Yes	12652 (0.4)	21 (0.04)	30 (1.2)	0 (0.0)

CCHD: cyanotic congenital heart defects; ART, assisted reproductive technology; BMI, body mass index; kg, kilograms; m, meter; *$p < 0.05$ for cases vs. controls; [#]$p<0.05$ among controls; Fisher's Exact test for cell frequency<5
Frequency of cases and controls may vary because of missing data. Percentages may not equal 100 because of missing data.

Table 2b. Maternal characteristics of isolated CCHDs cases and controls stratified by *Chlamydia*

Characteristics	**Controls**		**Isolated CCHD**	
	No *Chlamydia* (N=3278590) n (%)	*Chlamydia* (N=55834) n (%)	No *Chlamydia* (N=2355) n (%)	*Chlamydia* (N=40) n (%)
Age at delivery (years)				
15-19	245951 (7.5)[#]	14401 (25.8)	127 (5.4)*	10 (25.0)
20-24	753453 (23.0)	25213 (45.2)	475 (20.2)	17 (42.5)
25-29	943993 (28.8)	10309 (18.5)	658 (27.9)	9 (22.5)
30-34	846828 (25.8)	4147 (7.4)	625 (26.5)	3 (7.5)
≥35	485415 (14.8)	1590 (2.9)	467 (19.8)	1 (2.5)
Race and ethnicity				
Non-Hispanic white	1770568 (54.0)[#]	19534 (35.0)	1550 (65.8)*	19 (47.5)
Non-Hispanic black	460084 (14.0)	20489 (36.7)	287 (12.2)	9 (22.5)
Hispanic	780975 (23.8)	13470 (24.1)	363 (15.4)	8 (20.0)
Other	240411 (7.3)	2068 (3.7)	126 (5.4)	4 (10.0)
Education (years)				
<12	548795 (16.7)[#]	17458 (31.3)	305 (13.0)*	9 (22.5)
12	803722 (24.5)	20940 (37.5)	500 (21.2)	17 (42.5)
>12	1886216 (57.5)	16966 (30.4)	1507 (64.0)	14 (35.0)
Prepregnancy BMI (kg/m^2)				
Underweight (<18.5)	122117 (3.7)[#]	2879 (5.2)	74 (3.1)	2 (5.0)
Normal weight (18.5-24.9)	1481219 (45.2)	24515 (43.9)	1020 (43.3)	19 (47.5)
Overweight (25.0-29.9)	798516 (24.4)	13362 (23.9)	595 (25.3)	6 (15.0)
Obese (≥30)	739863 (22.6)	12994 (23.3)	575 (24.4)	13 (32.5)
Parity				
Primipara	1314216 (40.1)[#]	28002 (50.2)	976 (41.4)	21 (52.5)
Multipara	1950047 (59.5)	27420 (49.1)	1374 (58.3)	19 (47.5)
Periconceptional Smoking				
No	2764021 (84.3)[#]	41692 (74.7)	2006 (85.2)	31(77.5)
Yes	354324 (10.8)	11356 (20.3)	303 (12.9)	9 (22.5)
Prenatal Care Initiation				
No prenatal care	44374 (1.4)[#]	810 (1.5)	20 (0.9)*	1 (2.5)
1st Trimester	2352713 (71.8)	31894 (57.1)	1657 (70.4)	23 (57.5)
2nd Trimester	625011 (19.1)	16785 (30.1)	393 (16.7)	10 (25.0)
3rd Trimester	142063 (4.3)	4530 (8.1)	135 (5.7)	5 (12.5)
Prepregnancy diabetes				
No	3251105 (99.2)[#]	55410 (99.2)	2267 (96.3)	40 (100.0)
Yes	24519 (0.8)	369 (0.7)	85 (3.6)	0 (0.0)
Prepregnancy hypertension				
No	3229673 (98.5)	55032 (98.6)	2276 (96.7)	40 (100.0)
Yes	45951 (1.4)	747 (1.3)	76 (3.2)	0 (0.0)
ART				
No	3257231(99.4)[#]	55737 (99.8)	2306 (97.9)	40 (100.0)
Yes	12652 (0.4)	21 (0.04)	29 (1.2)	0 (0.0)

CCHD: cyanotic congenital heart defects; ART, assisted reproductive technology; BMI, body mass index; kg, kilograms; m, meter; *$p < 0.05$ for cases vs. controls; [#]$p<0.05$ among controls; Fisher's Exact test for cell frequency<5
Frequency of cases and controls may vary because of missing data. Percentages may not equal 100 because of missing data.

Table 3. Multivariate analysis for maternal *Chlamydia* and CCHDs

Exposure	**Controls** (N=3,334,424) n (%)	**All CCHD** (N=2,487) aOR (95%CI)	**Isolated CCHD** (N=2,395) aOR(95% CI)
Maternal Chlamydia			
No	3278590 (98.3)	referent	referent
Yes	55834 (1.7)	1.39 (1.02,1.90)	1.34 (0.97,1.84)
Age at delivery (years)			
15-19	260352 (7.8)	referent	referent
20-24	778666 (23.4)	1.23 (0.99,1.52)	1.22 (0.98,1.52)
25-29	954302 (28.6)	1.28 (1.03,1.59)	1.27 (1.03,1.59)
30-34	850975 (25.5)	1.32 (1.05,1.65)	1.33 (1.04,1.64)
≥35	487005 (14.6)	1.68 (1.33,2.12)	1.69 (1.34,2.14)
Race and ethnicity			
Non-Hispanic white	1790102 (53.7)	1.38 (1.21,1.59)	1.37 (1.19,1.57)
Non-Hispanic black	480573 (14.4)	referent	referent
Hispanic	794445 (23.8)	0.79 (0.67,0.93)	0.77 (0.65,0.91)
Other	242479 (7.3)	0.84 (0.67,1.05)	0.81 (0.65,1.02)
Education (years)			
<12	566253 (17.0)	referent	referent
12	824662 (24.7)	0.99 (0.85,1.15)	0.98 (0.84,1.15)
>12	1903182 (57.1)	1.12 (0.97,1.30)	1.11 (0.96,1.29)
Prepregnancy BMI (kg/m^2)			
Underweight (<18.5)	124996 (3.8)	0.90 (0.70,1.15)	0.90 (0.70,1.15)
Normal weight (18.5-24.9)	1505734 (45.2)	referent	referent
Overweight (25.0-29.9)	811878 (24.4)	1.06 (0.95,1.18)	1.09 (0.98,1.21)
Obese (≥30)	752857 (22.6)	1.07 (0.96,1.19)	1.08 (0.97,1.20)
Parity			
Primipara	1342218 (40.3)	referent	referent
Multipara	1977467 (59.3)	0.94 (0.86,1.03)	0.93 (0.85,1.02)
Periconceptional Smoking			
No	2805713 (84.1)	referent	referent
Yes	365680 (11.0)	1.11 (0.98,1.27)	1.09 (0.95,1.24)
Prenatal Care Initiation			
No prenatal care	45184 (1.4)	0.75 (0.47,1.22)	0.74 (0.45,1.21)
1^{st} Trimester	2384607 (71.6)	referent	referent
2^{nd} Trimester	641796 (19.3)	0.97 (0.86,1.08)	0.97 (0.86,1.09)
3^{rd} Trimester	146593 (4.4)	1.50 (1.25,1.80)	1.49 (1.23,1.79)
Prepregnancy diabetes			
No	3306515 (99.2)	referent	referent
Yes	24888 (0.8)	3.98 (3.11,5.10)	3.92 (3.04,5.05)
Prepregnancy hypertension			
No	3284705 (98.5)	referent	referent
Yes	46698 (1.4)	1.63 (1.26, 2.11)	1.59 (1.22, 2.08)
ART			
No	3312968 (99.4)	Ref	Ref
Yes	12673 (0.4)	2.39 (1.61, 3.53)	2.37 (1.59, 3.53)

aOR, Adjusted Odds Ratio; ART, assisted reproductive technology; CI, Confidence Interval; BMI: body mass index;
Frequency of cases and controls may vary because of missing data. Percentages may not equal 100 because of missing data.

Appendix

```
libname DD 'H:\THESIS'; RUN;
 RUN;

 PROC CONTENTS DATA=DD.BIRTHS_2012;
 RUN;


/*RECODE BIRTH DEFECTS AND INFECTION VARIABLES AND COVARIATE*/
DATA DD.BIRTHS_2012_RECODE;
SET DD.BIRTHS_2012(KEEP=MAGER MAGER9 RESTATUS  MRACEREC UMHISP
MRACEHISP MAR MEDUC  FAGEREC11 TBO_REC LBO_REC ILPCV_DOB PRECARE_REC
UPREVIS
WTGAIN_REC WTGAIN WIC CIG_0 CIG_1 CIG_2 CIG_3 CIG_REC
RF_DIAB RF_GEST RF_PHYP RF_GHYP RF_ECLAM RF_PPTERM RF_PPOUTC RF_INFTR
URF_DIAB URF_CHYPER URF_PHYPER URF_ECLAM IP_GONN IP_SYPH IP_CHLAM
IP_HEPB IP_HEPC DMETH_REC PAY_REC DPLURAL SEX GESTREC10 GESTREC3  BWTR4
CA_CCHD ILIVE BMI ILLB_R11 ILP_R11 CA_DOWN
IP_HEPB IP_HEPC 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 PAY_REC RF_CESAR);
ID=_N_;
IF 1<=MRACEHISP<=5 THEN MOMRACE=3;
ELSE IF MRACEHISP=6 THEN MOMRACE=1;
ELSE IF MRACEHISP=7 THEN MOMRACE=2;
ELSE IF MRACEHISP=8 THEN MOMRACE=4;
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=1 THEN MOMMAR=1;
ELSE MOMMAR=0;
DROP MAR;
IF PRECARE_REC=1 THEN PRENAT_CARE=1;
ELSE IF PRECARE_REC=2 THEN PRENAT_CARE=2;
 ELSE IF PRECARE_REC=3 THEN PRENAT_CARE=3;
 ELSE IF PRECARE_REC=4 THEN PRENAT_CARE=0;
 ELSE PRENAT_CARE=.;
 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 RF_CESAR='Y' THEN PRE_CESAR=1;
 ELSE IF RF_CESAR='N' THEN PRE_CESAR=0;
 ELSE PRE_CESAR=.;
 IF PAY_REC=1 THEN MOMPAY=1;
 ELSE IF 2<=PAY_REC<=4 THEN MOMPAY=2;
 ELSE MOMPAY=.;
IF CA_CCHD='Y' THEN CCHD=1;
ELSE IF CA_CCHD='N' THEN CCHD=0;
ELSE  CCHD=.;
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 IF MNSB=.;
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_HYPO='Y' THEN HYPO=1;
ELSE IF CA_HYPO='N' THEN HYPO=0;
ELSE HYPO=.;
IF CA_DOWN='C' THEN DOWNS=1;
ELSE IF CA_DOWN='N' THEN DOWNS=0;
ELSE DOWNS=.;
IF CA_DISOR='C' THEN CHROMS=1;
ELSE IF CA_DISOR='N' THEN CHROMS=0;
ELSE CHROMS=.;
IF IP_CHLAM='Y' THEN CHLAM=1;
ELSE IF IP_CHLAM='N' THEN CHLAM=0;
ELSE CHLAM=.;
IF IP_GONN='Y' THEN GONN=1;
ELSE IF IP_GONN='N' THEN GONN=0;
ELSE GONN=.;
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_CCHD CA_ANEN CA_MNSB CA_CDH CA_OMPH CA_GAST CA_LIMB CA_CLEFT
CA_CLPAL CA_DOWN
CA_DISOR CA_HYPO IP_CHLAM IP_GONN IP_SYPH IP_HEPB IP_HEPC;
IF MAGER<20 THEN MOMAGE=1;
ELSE IF 20<=MAGER<35 THEN MOMAGE=2;
ELSE IF MAGER>=35 THEN MOMAGE=3;
IF WTGAIN=99 THEN WTGAIN=.;
IF WTGAIN_REC=9 THEN WTGAIN_REC=.;
IF BMI>69.9 THEN DO; BMI=.; BMI_GP=.; END;
ELSE IF BMI^=. AND BMI<=24.9 THEN BMI_GP=1;
```

```
ELSE IF 24.9<=BMI<=69.9 THEN BMI_GP=2;
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_REC='Y' THEN MOMCIG=1;
ELSE IF CIG_REC='N' THEN MOMCIG=0;
ELSE  MOMCIG=.;
DROP CIG_REC;
IF RF_DIAB='Y' THEN PRE_DIAB=1;
ELSE IF RF_DIAB='N' THEN PRE_DIAB=0;
ELSE PRE_DIAB=.;
DROP RF_DIAB;
IF RF_GEST='Y' THEN GEST_DIAB=1;
ELSE IF RF_GEST='N' THEN GEST_DIAB=0;
ELSE GEST_DIAB=.;
DROP RF_GEST;
IF RF_PHYP='Y' THEN PRE_HTN=1;
ELSE IF RF_PHYP='N' THEN PRE_HTN=0;
ELSE PRE_HTN=.;
DROP RF_PHYP;
IF RF_GHYP='Y' THEN GEST_HTN=1;
ELSE IF RF_GHYP='N' THEN GEST_HTN=0;
ELSE GEST_HTN=.;
DROP RF_GHYP;
IF RF_ECLAM='Y' THEN GEST_ECLAM=1;
ELSE IF RF_ECLAM='N' THEN GEST_ECLAM=0;
ELSE  GEST_ECLAM=.;
DROP RF_ECLAM;
IF RF_PPTERM='Y' THEN PRE_PTERM=1;
ELSE IF RF_PPTERM='N' THEN PRE_PTERM=0;
ELSE PREV_PTERM=.;
DROP RF_PPTERM;

IF SEX='F' THEN BABY_SEX=1;
ELSE IF SEX='M' THEN BABY_SEX=2;
DROP SEX;
IF GESTREC3=1 THEN GESTAGE=1;
ELSE IF GESTREC3=2 THEN GESTAGE=2;
ELSE GESTAGE=.;
DROP GESTREC3;
IF 1<=BWTR4<=2 THEN BIRTHWT=1;
ELSE IF BWTR4=3 THEN BIRTHWT=2;
ELSE BIRTHWT=.;
DROP BWTR4;
IF DPLURAL=1 THEN PLURAL=1;
ELSE PLURAL=2;

LABEL MOMAGE='1=<20 2=20-34 3=35+'
      BMI_GP='1=NORMAL WT<25, 2=OVERWEIGHT>=25'
      MOMCIG_01='0=NOSMOKING 3 MONTHS PRIOR TO AND DURING 1ST TRIMESTER,
1=SMOKING PRIOR TO AND DURING 1ST TRIMESTER'
      MOMCIG='0=NO SMOKING DURING PREGNANCY 1=SMOKING DURING EGNANCY'
      PREV_PTERM='PREVIOUS PRETERM 1=YES 0=NO'
      BABY_SEX='1=FEMALE, 2=MALE'
      GESTAGE='1=<37 WKS, 2=37WKS+'
      BIRTHWT='1=<2500, 2=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 TRIMIESTER 2=2ND
TRIMESTER 3=3RD TRIMESTER'
      PRE_CESAR='1=PREVIOUS CESAREAN 0=NO PREVIOUS CESAREAN'
      ASSIS_FET='1=HAD ASSISTED FERTILIGY, 0=NO ASSISTED FERTILITY'
      MOMPAY='1=MEDICAID, 2=NON-MEDICAID'
      PLURAL='1=SINGLETON 2=MULTIPLE';
      PROC FREQ;
      TABLES CHLAM GONN SYPH CCHD MOMAGE MOMRACE MOMEDU MOMCIG_01
PRENAT_CARE ASSIS_FET MOMMAR MOMPAY BMI_GP BABY_SEX GESTAGE BIRTHWT
PRE_CESAR PLURAL; RUN

/*delete those with missing or unknown birth defects info*/

data BIRTHS_BD;
set DD.BIRTHS_2012_RECODE;
if cchd=. or ANEN=. OR MNSB=. OR CDH=. OR OMPH=. OR GAST=. OR LIMB=. OR
CLEFT=. OR CLPAL=. OR HYPO=.
or DOWNS=. AND CHROMS=. then delete;
proc freq;
tables plural cchd;
run;

/*IDENTIFY CASES, ONLY WANT SINGLTON BIRTHS*/
DATA SINGLETON;
SET BIRTHS_BD; WHERE PLURAL=1;
PROC FREQ;
TABLES CCHD;
RUN;

DATA CCHD;
SET SINGLETON;
IF CCHD=1;
IF DOWNS=0 AND CHROMS=0;
PROC SORT; BY ID;
RUN;

DATA OTHER_DEFECT_NODOWNS;
SET BIRTHS_BD(KEEP=ID ANEN MNSB CDH OMPH GAST LIMB CLEFT CLPAL DOWNS
CHROMS HYPO CCHD PLURAL);WHERE PLURAL=1;
IF ANEN=1 OR MNSB=1 OR CDH=1 OR OMPH=1 OR GAST=1 OR LIMB=1 OR CLEFT=1
OR CLPAL=1 OR HYPO=1;
IF DOWNS=0 AND CHROMS=0;
PROC SORT NODUPKEY; BY ID;
RUN;

DATA CCHD_ONLY;
MERGE CCHD(IN=A)OTHER_DEFECT_NODOWNS(IN=B KEEP=ID);
BY ID;
IF ^B;
CCHD_ONLY=1;
PROC SORT; BY ID;
RUN;
```

```
DATA CCHD_MULT;
MERGE CCHD(IN=A) OTHER_DEFECT_NODOWNS(IN=B KEEP=ID);
BY ID;
IF A; IF B;
CCHD_MULT=1;
PROC SORT; BY ID;
RUN;

DATA ALL_CCHD;
SET CCHD_ONLY CCHD_MULT;
CASE=1;
PROC SORT; BY ID;
PROC FREQ;
TABLES CCHD_ONLY CCHD_MULT CASE;
RUN;

/*IDENTIFY CONTROLS*/
DATA CONTROLS;
SET DD.BIRTHS_2012_RECODE; WHERE PLURAL=1;
IF CCHD=0 AND ANEN=0 AND MNSB=0 AND CDH=0 AND OMPH=0 AND GAST=0 AND
LIMB=0 AND CLEFT=0 AND CLPAL=0 AND HYPO=0
AND DOWNS=0 AND CHROMS=0;
CASE=0;
RUN;

DATA CASECONTROL_US; /*EXCLUDE NON-US RESIDENTS*/
SET ALL_CCHD CONTROLS;
IF CCHD_ONLY=. THEN CCHD_ONLY=0;
IF CCHD_MULT=. THEN CCHD_MULT=0;
IF RESTATUS=4 THEN DELETE;
PROC FREQ;
TABLES CASE CCHD_ONLY CCHD_MULT;
RUN;

DATA DD.CASE_CONTROL_SINGLE_2012;/*EXCLUDE MISSING EXPOSURE*/
SET CASECONTROL_US;
IF CHLAM=. OR GONN=. OR SYPH=. THEN DELETE;
DROP ANEN MNSB CDH OMPH GAST LIMB CLEFT CLPAL DOWNS CHROMS HYPO;
PROC FREQ;
TABLES CASE CCHD_ONLY CCHD_MULT;
RUN;

DATA STI;
SET DD.CASE_CONTROL_SINGLE_2012;
WHERE CHLAM=1 OR GONN=1 OR SYPH=1;
IF HEPB=0 AND HEPC=0;
STI=1;
PROC FREQ;
TABLES CHLAM GONN SYPH;
PROC SORT; BY ID;
RUN;

DATA CHLAM GONN SYPH;
SET STI (KEEP=ID CHLAM GONN SYPH);
IF CHLAM=1 THEN OUTPUT CHLAM;
IF GONN=1 THEN OUTPUT GONN;
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```
IF SYPH=1 THEN OUTPUT SYPH;
PROC SORT DATA=CHLAM; BY ID;
PROC SORT DATA=GONN; BY ID;
PROC SORT DATA=SYPH; BY ID;
RUN;
DATA CHLAM_ONLY;
MERGE CHLAM(KEEP=ID IN=A) GONN(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 GONN_ONLY;
MERGE CHLAM(KEEP=ID IN=A) GONN(KEEP=ID IN=B) SYPH(KEEP=ID IN=C);
BY ID;
IF ^A; IF ^C;
GONN_ONLY=1;
PROC SORT NODUPKEY; BY ID;
RUN;

DATA SYPH_ONLY;
MERGE CHLAM(KEEP=ID IN=A) GONN(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 GONN_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 GONN_ONLY SYPH_ONLY;
PROC SORT DATA=ALL_STI; BY ID;
RUN;

PROC SORT DATA=DD.CASE_CONTROL_SINLE_2012;
BY ID;
RUN;

DATA DD.FINAL_CASECONTROL_SINGLE_2012;
MERGE ALL_STI(IN=A) DD.CASE_CONTROL_SINGLE_2012(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 GONN_ONLY=. THEN GONN_ONLY=0;
IF SYPH_ONLY=. THEN SYPH_ONLY=0;
IF BMI>69.9 THEN DO; BMI=.; BMIGP4=.; END;
ELSE IF BMI^=. AND BMI<18.5 THEN BMIGP4=1;
ELSE IF 18.5<= BMI<=24.9 THEN BMIGP4=2;
ELSE IF 24.9<BMI<30 THEN BMIGP4=3;
ELSE IF BMI>=30 THEN BMIGP4=4;
LABEL BMIGP4='1=UNDERWT 2=NORMAL 3=OVERWT 4=OBESE';
IF LBO_REC=1 THEN PARITY=1;
ELSE IF 2<=LBO_REC<=8 THEN PARITY=2;
ELSE PARIY=.;
IF TBO_REC=1 THEN GRAVIDITY=1;
ELSE IF 2<=TBO_REC<=8 THEN GRAVIDITY=2;
ELSE GRAVIDITY=.;
IF 15<=MAGER<=19 THEN MOMAGE5=1;
ELSE IF 20<=MAGER<=24 THEN MOMAGE5=2;
ELSE IF 25<=MAGER<=29 THEN MOMAGE5=3;
ELSE IF 30<=MAGER<=34 THEN MOMAGE5=4;
ELSE IF MAGER>=35 THEN MOMAGE5=5;
IF RF_INFTR='Y' THEN INFTR=1;
ELSE IF RF_INFTR IN ('N','X') THEN INFTR=0;
ELSE INFTR=.;
IF RF_FEDRG='Y' THEN FEDRG=1;
ELSE IF RF_FEDRG IN ('N','X') THEN FEDRG=0;
ELSE FEDRG=.;
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_INFTR ='Y' THEN FERT_TX=1;
 ELSE IF RF_FEDRG IN ('N', 'X') AND RF_INFTR IN('N','X') THEN
FERT_TX=0;
 ELSE FERT_TX=.;
 LABEL FERT_TX='INTERTILITY TREATMENT OR USE OF FERTILITY DRUGS'
       INFTR='INFERTILITY TREATMENT'
       FEDRG='USE OF FERTILITY ENHANCING DRUGS'
       ARTEC='USE OF ASSISTED REPRODUCTIVE TECHNOLOGY';

LABEL PARIY='# OF LIVE BIRTHS 1=PRIMIPAROUS 2=MULTIPAROUS'
      GRAVIDITY='# OF TOTAL PREGNANCIES 1=PRIMIGRAVIDA 2=MULTIGRAVIDA'
      MOMAGE5 ='1=15-19 2-20-24 3=25-29 4=30-34 5=35+';
PROC FREQ;
TABLES CASE CCHD_ONLY STI STI_ONLY CHLAM_ONLY GONN_ONLY SYPH_ONLY
MOMAGE5 BMIGP4 FERT_TX FEDRG ARTEC INFTR PARITY PLURAL;RUN;


/*TABLE 1 MATERNAL AND INFANT CHARACTERISTICS FOR CASES AND CONTROL*/

PROC FREQ DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
TABLES CASE*(CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY MOMCIG_01
PRENAT_CARE PRE_DIAB PRE_HTN BABY_SEX GESTAGE BIRTHWT ARTEC)/MISSING;
RUN;

PROC FREQ DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
TABLES CASE*(CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY MOMCIG_01
PRENAT_CARE PRE_DIAB PRE_HTN BABY_SEX GESTAGE BIRTHWT ARTEC)/CHISQ;
RUN;
```

```
PROC FREQ DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
TABLES CCHD_ONLY*(CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY
MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN BABY_SEX GESTAGE BIRTHWT
ARTEC)/MISSING;
RUN;

PROC FREQ DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
TABLES CCHD_ONLY*(CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY
MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN BABY_SEX GESTAGE BIRTHWT
ARTEC)/CHISQ;
RUN;

/*TABLE 2 MATERNAL CHARACTERISTICS FOR CASES AND CONTROLS STRTIFIED BY
CHLAMYDIA STATUS*/
PROC FREQ DATA=DD.FINAL_CASECONTROL_SINGLE_2012; WHERE
CASE=0;/*CONTROL*/
TABLES CHLAM_ONLY*(MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY MOMCIG_01
PRENAT_CARE PRE_DIAB PRE_HTN BABY_SEX GESTAGE BIRTHWT ARTEC)/MISSING;
RUN;
PROC FREQ DATA=DD.FINAL_CASECONTROL_SINGLE_2012; WHERE
CASE=0;/*CONTROL*/
TABLES CHLAM_ONLY*(MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY MOMCIG_01
PRENAT_CARE PRE_DIAB PRE_HTN BABY_SEX GESTAGE BIRTHWT ARTEC)/CHISQ
FISHER;
RUN;

PROC FREQ DATA=DD.FINAL_CASECONTROL_SINGLE_2012; WHERE CASE=1;
TABLES CHLAM_ONLY*(MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY MOMCIG_01
PRENAT_CARE PRE_DIAB PRE_HTN BABY_SEX GESTAGE BIRTHWT ARTEC)/MISSING;
RUN;
PROC FREQ DATA=DD.FINAL_CASECONTROL_SINGLE_2012; WHERE CASE=1;
TABLES CHLAM_ONLY*(MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY MOMCIG_01
PRENAT_CARE PRE_DIAB PRE_HTN BABY_SEX GESTAGE BIRTHWT ARTEC)/CHISQ
FISHER;
RUN;

PROC FREQ DATA=DD.FINAL_CASECONTROL_SINGLE_2012; WHERE
CCHD_ONLY=1;/*ISOLATED CASES*/
TABLES CHLAM_ONLY*(MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY MOMCIG_01
PRENAT_CARE PRE_DIAB PRE_HTN BABY_SEX GESTAGE BIRTHWT ARTEC)/MISSING;
RUN;

PROC FREQ DATA=DD.FINAL_CASECONTROL_SINGLE_2012; WHERE
CCHD_ONLY=1;/*ISOLATED CASES*/
TABLES CHLAM_ONLY*(MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY MOMCIG_01
PRENAT_CARE PRE_DIAB PRE_HTN BABY_SEX GESTAGE BIRTHWT)/CHISQ FISHER;
RUN;

/*CHECKING MULTICOLLINEARITY*/
PROC REG DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
MODEL CASE=CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY MOMCIG_01
PRENAT_CARE
PRE_DIAB PRE_HTN BABY_SEX GESTAGE BIRTHWT ART/TOL VIF;
RUN;
```

```
/*CRUDE OR*/
PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
MODEL CASE(EVENT='1')=CHLAM_ONLY;
RUN;

PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
MODEL CCHD_ONLY(EVENT='1')=CHLAM_ONLY;RUN;

/*FULL MODEL, CHECKING FOR INTERACTION*/

PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
CLASS MOMAGE5 (PARAM=REF REF='1');/*1=15-19*/
CLASS MOMRACE (PARAM=REF REF='2');/*2=BLACK*/
CLASS BMIGP4 (PARAM=REF REF='2');/*2=NORMAL WT*/
CLASS MOMEDU (PARAM=REF REF='1');/*1=<12*/
CLASS BABY_SEX (PARAM=REF REF='1');/*1=FEMALE*/
CLASS GESTAGE (PARAM=REF REF='2');/*2=>=37*/
CLASS BIRTHWT (PARAM=REF REF='2');/*2=>=2500*/
CLASS PRENAT_CARE (PARAM=REF REF='1');/*1=PRENAT 1ST TRIMESTER*/
MODEL CASE(EVENT='1')=CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY
MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN ARTEC
CHLAM_ONLY*ARTEC/SELECTION=BACKWARD SLSTAY=0.01 DETAILS LACKFIT;
RUN;

/*TABLE 3 FULL MODEL*/
PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
CLASS MOMAGE5 (PARAM=REF REF='1');/*1=15-19*/
CLASS MOMRACE (PARAM=REF REF='2');/*2=BLACK*/
CLASS BMIGP4 (PARAM=REF REF='2');/*2=NORMAL WT*/
CLASS MOMEDU (PARAM=REF REF='1');/*1=<12*/
CLASS PARITY (PARAM=REF REF='1'); /*1=PRIMPAROUS*/
CLASS PRENAT_CARE (PARAM=REF REF='1');/*1=PRENAT 1ST TRIMESTER*/
MODEL CASE(EVENT='1')=CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY
MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN ARTEC/LACKFIT;
RUN;

/*FIRTH OPTION--PENALIZED LOGISTIC REGRESSION*/
PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
CLASS MOMAGE5 (PARAM=REF REF='1');/*1=15-19*/
CLASS MOMRACE (PARAM=REF REF='2');/*2=BLACK*/
CLASS BMIGP4 (PARAM=REF REF='2');/*2=NORMAL WT*/
CLASS MOMEDU (PARAM=REF REF='1');/*1=<12*/
CLASS PARITY (PARAM=REF REF='1'); /*1=PRIMPAROUS*/
CLASS PRENAT_CARE (PARAM=REF REF='1');/*1=PRENAT 1ST TRIMESTER*/
MODEL CASE(EVENT='1')=CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY
MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN ARTEC/FIRTH LACKFIT;
RUN;

/*TREND TEST FULL MODEL*/
PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
MODEL CCHD(EVENT='1')=CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY
MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN ARTEC;
RUN;
```

```
/*TABLE 3: ISOLATED CCHD, FULL MODEL*/

PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
CLASS MOMAGE5 (PARAM=REF REF='1');/*1=15-19*/
CLASS MOMRACE (PARAM=REF REF='2');/*2=BLACK*/
CLASS BMIGP4 (PARAM=REF REF='2');/*2=NORMAL WT*/
CLASS MOMEDU (PARAM=REF REF='1');/*1=<12*/
CLASS PARITY (PARAM=REF REF='1'); /*1=PRIMPAROUS*/
CLASS PRENAT_CARE (PARAM=REF REF='1');/*1=PRENAT 1ST TRIMESTER*/
MODEL CCHD_ONLY(EVENT='1')=CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4
PARITY  MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN ARTEC/LACKFIT;RUN;

/*FIRTH OPTION--PENALIZED LOGISTIC REGRESSION*/
PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
CLASS MOMAGE5 (PARAM=REF REF='1');/*1=15-19*/
CLASS MOMRACE (PARAM=REF REF='2');/*2=BLACK*/
CLASS BMIGP4 (PARAM=REF REF='2');/*2=NORMAL WT*/
CLASS MOMEDU (PARAM=REF REF='1');/*1=<12*/
CLASS PARITY (PARAM=REF REF='1'); /*1=PRIMPAROUS*/
CLASS PRENAT_CARE (PARAM=REF REF='1');/*1=PRENAT 1ST TRIMESTER*/
MODEL CCHD_ONLY(EVENT='1')=CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4
PARITY  MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN ARTEC/FIRTH LACKFIT;
RUN;

/*TREND TEST FULL MODEL*/
PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
MODEL CCHD_ONLY(EVENT='1')=CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4
PARITY MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN ARTEC;
RUN;

/*SENSITIVITY ANALYSIS INCLUDING MULTIPLE BIRTHS*/
PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_STI_2012;
CLASS MOMAGE5 (PARAM=REF REF='1');/*1=15-19*/
CLASS MOMRACE (PARAM=REF REF='2');/*2=BLACK*/
CLASS BMIGP4 (PARAM=REF REF='2');/*2=NORMAL WT*/
CLASS MOMEDU (PARAM=REF REF='1');/*1=<12*/
CLASS PARITY (PARAM=REF REF='1'); /*1=PRIMPAROUS*/
CLASS PRENAT_CARE (PARAM=REF REF='1');/*1=PRENAT 1ST TRIMESTER*/
MODEL CASE(EVENT='1')=CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY
MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN ARTEC/LACKFIT;
RUN;

PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_STI_2012;
CLASS MOMAGE5 (PARAM=REF REF='1');/*1=15-19*/
CLASS MOMRACE (PARAM=REF REF='2');/*2=BLACK*/
CLASS BMIGP4 (PARAM=REF REF='2');/*2=NORMAL WT*/
CLASS MOMEDU (PARAM=REF REF='1');/*1=<12*/
CLASS PARITY (PARAM=REF REF='1'); /*1=PRIMPAROUS*/
CLASS PRENAT_CARE (PARAM=REF REF='1');/*1=PRENAT 1ST TRIMESTER*/
MODEL CCHD_ONLY(EVENT='1')=CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4
PARITY MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN ARTEC/LACKFIT;
RUN;
```

```
/*SUBGROUP FOR AGE=15-19*/

PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012; WHERE MOMAGE5=1;
CLASS MOMRACE (PARAM=REF REF='2');/*2=BLACK*/
CLASS BMIGP4 (PARAM=REF REF='2');/*2=NORMAL WT*/
CLASS MOMEDU (PARAM=REF REF='1');/*1=<12*/
CLASS PARITY (PARAM=REF REF='1'); /*1=PRIMPAROUS*/
CLASS PRENAT_CARE (PARAM=REF REF='1');/*1=PRENAT 1ST TRIMESTER*/
MODEL CASE(EVENT='1')=CHLAM_ONLY MOMRACE MOMEDU BMIGP4 PARITY MOMCIG_01
PRENAT_CARE PRE_DIAB PRE_HTN ARTEC/ LACKFIT;
RUN;

PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012; WHERE MOMAGE5=1;
CLASS MOMRACE (PARAM=REF REF='2');/*2=BLACK*/
CLASS BMIGP4 (PARAM=REF REF='2');/*2=NORMAL WT*/
CLASS MOMEDU (PARAM=REF REF='1');/*1=<12*/
CLASS PARITY (PARAM=REF REF='1'); /*1=PRIMPAROUS*/
CLASS PRENAT_CARE (PARAM=REF REF='1');/*1=PRENAT 1ST TRIMESTER*/
MODEL CCHD_ONLY(EVENT='1')=CHLAM_ONLY MOMRACE MOMEDU BMIGP4 PARITY
MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN ARTEC/ LACKFIT;
RUN;

/*SUBGROUP FOR AGE=20-24*/
PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012; WHERE MOMAGE5=2;
CLASS MOMRACE (PARAM=REF REF='2');/*2=BLACK*/
CLASS BMIGP4 (PARAM=REF REF='2');/*2=NORMAL WT*/
CLASS MOMEDU (PARAM=REF REF='1');/*1=<12*/
CLASS PARITY (PARAM=REF REF='1'); /*1=PRIMPAROUS*/
CLASS PRENAT_CARE (PARAM=REF REF='1');/*1=PRENAT 1ST TRIMESTER*/
MODEL CASE(EVENT='1')=CHLAM_ONLY MOMRACE MOMEDU BMIGP4 PARITY MOMCIG_01
PRENAT_CARE PRE_DIAB PRE_HTN ARTEC/LACKFIT;
RUN;

PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012; WHERE MOMAGE5=2;
CLASS MOMRACE (PARAM=REF REF='2');/*2=BLACK*/
CLASS BMIGP4 (PARAM=REF REF='2');/*2=NORMAL WT*/
CLASS MOMEDU (PARAM=REF REF='1');/*1=<12*/
CLASS PARITY (PARAM=REF REF='1'); /*1=PRIMPAROUS*/
CLASS PRENAT_CARE (PARAM=REF REF='1');/*1=PRENAT 1ST TRIMESTER*/
MODEL CCHD_ONLY(EVENT='1')=CHLAM_ONLY MOMRACE MOMEDU BMIGP4 PARITY
MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN ARTEC/LACKFIT;
RUN;

/*EXERCISE ON MODEL BUILDING*/
/*BACKWARD SELECTION*/
PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
CLASS MOMAGE5 (PARAM=REF REF='1');/*1=15-19*/
CLASS MOMRACE (PARAM=REF REF='2');/*2=BLACK*/
CLASS BMIGP4 (PARAM=REF REF='2');/*2=NORMAL WT*/
CLASS MOMEDU (PARAM=REF REF='1');/*1=<12*/
CLASS PARITY (PARAM=REF REF='1'); /*1=PRIMPAROUS*/
CLASS PRENAT_CARE (PARAM=REF REF='1');/*1=PRENAT 1ST TRIMESTER*/
MODEL CASE(EVENT='1')=CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY
MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN ARTEC/
SELECTION=BACKWARD SLSTAY=0.2 INCLUDE=1 DETAILS LACKFIT;
RUN;
```

```
/*CHECK FOR CONFOUNDING OF BMI AND PARITY COMPARING AOR WITHOUT THE
VARIABLE TO THE ONE FROM FULL MODEL*/

PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
CLASS MOMAGE5 (PARAM=REF REF='1');/*1=15-19*/
CLASS MOMRACE (PARAM=REF REF='2');/*2=BLACK*/
CLASS BMIGP4 (PARAM=REF REF='2');/*2=NORMAL WT*/
CLASS PARITY (PARAM=REF REF='1'); /*1=PRIMPAROUS*/
CLASS PRENAT_CARE (PARAM=REF REF='1');/*1=PRENAT 1ST TRIMESTER*/
MODEL CASE(EVENT='1')=CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU PARITY
MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN ARTEC;RUN;

PROC LOGISTIC DATA=DD.FINAL_CASECONTROL_SINGLE_2012;
CLASS MOMAGE5 (PARAM=REF REF='1');/*1=15-19*/
CLASS MOMRACE (PARAM=REF REF='2');/*2=BLACK*/
CLASS BMIGP4 (PARAM=REF REF='2');/*2=NORMAL WT*/
CLASS MOMEDU (PARAM=REF REF='1');/*1=<12*/
CLASS PRENAT_CARE (PARAM=REF REF='1');/*1=PRENAT 1ST TRIMESTER*/
MODEL CASE(EVENT='1')=CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4
MOMCIG_01 PRENAT_CARE PRE_DIAB PRE_HTN ARTEC;
RUN;


/*CHECK FOR IMPACT OF MISSING DATA IN COVARIATES*/
/*PROPORTION AND PATTERN OF MISSINGNISS*/
PROC MEANS DATA=DD.FINAL_CASECONTROL_SINGLE_2012 NMISS;
VAR MOMAGE5 MOMRACE MOMEDU BMIGP4 MOMCIG_01 PRENAT_CARE PRE_DIAB
PRE_HTN ARTEC;
OUTPUT OUT=MEAN(DROP=_TYPE_ _FREQ_) NMISS=/AUTONAME;
RUN;
PROC TRANSPOSE DATA=MEAN PREFIX=NMISS OUT=MISS1;
VAR _NUMERIC_;
RUN;

DATA MISS2;
SET MISS1;
PMISS=NMISS1/3336911*100;
PROC PRINT DATA=MISS2;
RUN;

ODS SELECT MISSPATTERN
PROC MI DATA =DD.FINAL_CASECONTROL_SINGLE_2012  nimpute=0;
 var MOMAGE5 MOMRACE MOMEDU BMIGP4 MOMCIG_01 PRENAT_CARE PRE_DIAB
PRE_HTN ARTEC;
run;/*NON-MONOTONE MISSINGNESS--SHOULD USE MICE MI*/


/*COMPARE GROUPS WITH AND WITHOUT MISSING DATA*/

DATA CASE_NOMISSING;
SET DD.FINAL_CASECONTROL_SINGLE_2012 (KEEP=CASE CHLAM_ONLY MOMAGE5
MOMRACE MOMEDU BMIGP4 PARITY  MOMCIG_01 PRENAT_CARE
PRE_DIAB PRE_HTN ARTEC); WHERE CASE=1;
MISS=0;
```

```
IF MOMAGE5^=. AND  MOMRACE^=. AND  MOMEDU^=. AND  BMIGP4^=. AND
PARITY^=. AND   MOMCIG_01^=. AND  PRENAT_CARE^=.
AND PRE_DIAB^=. AND  PRE_HTN^=. AND  ARTEC^=.;
RUN;

DATA CASE_MISSING;
SET DD.FINAL_CASECONTROL_SINGLE_2012 (KEEP=CASE CHLAM_ONLY MOMAGE5
MOMRACE MOMEDU BMIGP4 PARITY  MOMCIG_01 PRENAT_CARE
PRE_DIAB PRE_HTN ARTEC); WHERE CASE=1;
MISS=1;
IF MOMAGE5=. OR  MOMRACE=. OR  MOMEDU=. OR  BMIGP4=. OR  PARITY=. OR
MOMCIG_01=. OR  PRENAT_CARE=.
OR PRE_DIAB=. OR  PRE_HTN=. OR  ARTEC=.;
RUN;

DATA CONTROL_NOMISSING;
SET DD.FINAL_CASECONTROL_SINGLE_2012 (KEEP=CASE CHLAM_ONLY MOMAGE5
MOMRACE MOMEDU BMIGP4 PARITY  MOMCIG_01 PRENAT_CARE
PRE_DIAB PRE_HTN ARTEC); WHERE CASE=0;
MISS=0;
IF MOMAGE5^=. AND  MOMRACE^=. AND  MOMEDU^=. AND  BMIGP4^=. AND
PARITY^=. AND   MOMCIG_01^=. AND  PRENAT_CARE^=.
AND PRE_DIAB^=. AND  PRE_HTN^=. AND  ARTEC^=.;
RUN;

DATA CONTROL_MISSING;
SET DD.FINAL_CASECONTROL_SINGLE_2012 (KEEP=CASE CHLAM_ONLY MOMAGE5
MOMRACE MOMEDU BMIGP4 PARITY  MOMCIG_01 PRENAT_CARE
PRE_DIAB PRE_HTN ARTEC); WHERE CASE=0;
MISS=1;
IF MOMAGE5=. OR  MOMRACE=. OR  MOMEDU=. OR  BMIGP4=. OR  PARITY=. OR
MOMCIG_01=. OR  PRENAT_CARE=.
OR PRE_DIAB=. OR  PRE_HTN=. OR  ARTEC=.;
RUN;

DATA NOMISS;
SET CASE_NOMISSING CONTROL_NOMISSING;
RUN;

DATA MISS;
SET CASE_MISSING CONTROL_MISSING;
RUN;

DATA COMPARE;
SET MISS NOMISS;
PROC FREQ;
TABLES MISS*(CASE CHLAM_ONLY MOMAGE5 MOMRACE MOMEDU BMIGP4 PARITY
MOMCIG_01 PRENAT_CARE
PRE_DIAB PRE_HTN ARTEC)/CHISQ;
RUN;/*P-VALUE FUNCTION OF SAMPLE SIZE, NOT APPROPRIATE IN THIS CASE;
WILL USE STANDARDIZED DIFFERENCES TO COMPARE*/
```