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Interpregnancy Interval and Autism Spectrum Disorders among California Siblings in the CHARGE Study

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Abstract

Interpregnancy Interval and Autism Spectrum Disorders among California Siblings in the CHARGE Study

Principal Investigator: Isabelle Hutchings

Background
Autism Spectrum Disorders (ASDs) have a significant health burden characterized by deficits in social skills and communication, repetitive behaviors, and stereotyped body movements usually beginning in early childhood. Short interpregnancy interval (≤ 12 months) has been associated with an increased risk of Autism Spectrum Disorders (ASDs) in previous birth-registry studies of sibling pairs. These studies, however, had limited ability to adjust for potential confounders.

Methods
ASDs were measured among California-born, singleton, full-sibling pairs in a case-control study. General population controls were selected from California birth files using stratified random sampling. Trained researchers collected information for index children for ASDs diagnoses using the Autism Diagnostic Interview-revised (ADI-R) and the Autism Diagnostic Observation Schedules (ADOS). They also used a variety of in-person and phone-based interviews to collect information on potential confounders from the index children's primary caregivers. Interpregnancy interval was defined as the time between the birth of a prior child and the conception of the index child in a full sibship. It was calculated based on information collected during interviews with the primary caregiver of the index child. Odds ratios were estimated by fitting logistic regression models.

Results
This study included 499 singleton, full sibling pairs born in California, 265 cases and 234 controls. The OR for ASDs in the index child comparing IPI ≤ 12 months adjusting for mother's age at conception of the index child, race, education, marital status, birthplace, desire to get pregnant, procedures used to conceive the index child, prenatal vitamin use in the first month of pregnancy of the index child, family home ownership, child's gender and preterm birth was 2.0 (95% CI 1.2-3.6).

Conclusions
This analysis found an increased odds of ASDs among births ≤ 12 months apart, consistent with previous studies. Due to the extensive data gathered by interviewing primary caregivers, this study was able to control for a variety of potential confounders that had not previously been examined.

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Table of Contents

Page

Chapter One

Introduction and Background

Autism Spectrum Disorders (ASDs) pose a significant public health burden with an estimated 1 in 88 children in the United States affected and reports of increasing prevalence. Despite concerted research efforts, many questions remain about contributing factors in the development of ASDs. The importance of environmental exposures in the periconceptional and prenatal periods is a growing area of interest for identifying ASDs risk factors. In particular, it has been suggested that interpregnancy interval (IPI) may play a role in ASDs risk.

One hypothesis is that the time between the birth of a previous child and the conception of the next, the IPI, may influence a mother's nutritional status at conception of her next child. With a shorter time between pregnancies, a woman's body may not have time to recover from the nutritional depletion of her previous pregnancy, resulting in lower levels of nutrients at the conception of her next child. It has been proposed that these lower levels of nutrients may contribute to a higher risk for ASDs. Understanding the role of IPI in ASDs risk can help to develop new guidelines regarding birth spacing with the ultimate goal of reducing ASDs risk. Decreasing risk for ASDs could help to mitigate the public health burden incurred from this complex, and in some cases debilitating, disease.

A. ASDs

ASDs are a pervasive and complicated range of neurological conditions with few known causes. These disorders are generally diagnosed during early childhood,

specifically in the first three years of life (1). Comprised of a range of disorders, ASDs include autism, Asperger syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS) (2). ASDs are characterized by deficits in social skills and communication, repetitive behaviors, and stereotyped body movements (1, 3). Intellectual disability is present in up to 75% of cases as well (4-6). The complexity and pervasive nature of ASDs make it a difficult disease to both diagnose and manage. In a public health context, the complexity of ASDs results in distress and difficulty for individuals and families.

While children can generally be identified with symptoms of ASDs at as young as 18 months, many are not diagnosed until social problems arise when they enter school (3). ASDs also present very differently among individuals, with each case falling upon a spectrum from mild to severe. The DSM-V criteria are based on the presentation of symptoms from early childhood, sensitivity to environmental changes, intense focus on inappropriate items or behaviors, and misreading nonverbal communication among other symptoms (7).

Estimated prevalence of ASDs in all populations has changed over time, with trends indicating increased prevalence of ASDs since the 1 in 115 estimate of the mid-1980s among children 8 years of age (8). A 2007 study conducted by Kogan indicated that there were approximately 673,000 U.S. children between the ages of 2 and 18 with ASDs based on parent-report (2). The 2012 CDC estimate of ASDs prevalence based on educational and medical records is 11.3 per 1,000 (range 4.8-21.2), or 1 in 88 children 8 years of age (9). This estimation marks a rise in previous ASDs prevalence. Among the highest prevalence estimates is The National Health Statistics Report published in March

2013, which used parent-reported diagnosis of ASDs among U.S. children aged 6-17 to estimate that 1 in 50 children in 2011-2012 had been diagnosed with ASDs (3). With increases in ASDs awareness, changes in diagnostic criteria, more complex ascertainment, younger ages of diagnosis, and increased funding for ASDs-related services, it is difficult to determine whether the observed rise in prevalence is the result of increased diagnosis or a true increase in prevalence of ASDs (10).

Genetic

In addition to efforts to understand the true nature of trends in ASDs prevalence, there has been considerable research focused on the genetic components of ASDs. Twin and family studies have reported that ASDs are highly heritable with genetic control from multiple loci (11-13). A 2013 study estimated a relative risk of 6.9 (95% Confidence Interval (CI) 6.1-7.8) for children whose older full-siblings had been diagnosed with ASDs compared with those whose older full-siblings were not diagnosed with ASDs (14). Additionally, concordance between monozygotic twins has been estimated at close to 60% for both males and females (15).

Recurrent protein-altering mutations in CHD8 and NTNG1 genes, among several others, have been reported to increase risk of ASDs (11). A single nucleotide polymorphism in chromosome 5p14, de novo mutations, and the expression of non-protein coding RNA are significantly associated with ASDs (12, 16, 17). Such findings have resulted in the scientific consensus that ASDs are highly heterogeneous.

In addition to genetic components, other risk factors have been recognized as important components in ASDs development, with the most consistently reported being demographic, environmental, and prenatal/periconceptional exposures.

Sex

One of the most striking and consistently reported differences in ASDs risk is seen based on sex, with males being approximately 4.5 times more likely to be diagnosed with ASDs than females (18). A 2002 California-based study of 3.5 million children reported that males were 4.3 times as likely to have autism as females when controlling for birth weight, plurality, birth order, maternal age, maternal race, maternal birthplace and maternal education (RR 4.3; 95% CI 4.0-4.6) (19). Other studies such as a 2010 British study (n=1963) have reported even higher estimates with ASDs gender ratio estimated at 6.8 based on the year of birth between 1986 and 2007 (20). Though little is understood about the underlying biological mechanism, one of the leading hypotheses is that ASDs is an extreme manifestation of the male brain which could be affected by fetal testosterone levels (21).

Maternal Age

Maternal age at conception is also a strong predictor of ASDs risk, with one study reporting that mothers older than 34 show a 54% increased odds of having children with ASDs compared with mothers aged 25-29 years (OR 1.54, 95% CI 1.04-2.30) controlling for maternal birthplace and education (22). A 2002 study reported risk ratios for 20-24 year old mothers at 1.5 (95%CI 1.3-1.7), 25-29 year old mothers at 2.1 (95% CI 1.8-2.4), 30-34 year old mothers at 3.1 (2.7-3.6) and mothers greater than 35 at 3.9 (95% CI 3.4-4.5) as compared to mothers younger than 20 years old (19). Similar results have been

reported by a variety of other large studies examining the role of maternal age in ASDs risk (4, 19, 23).

Socioeconomic Status (SES)

In addition to differential risk for males and females, ASDs prevalence has also been associated with increasing SES in a dose-response manner (24, 25). A 2010 U.S. cross-sectional study examined 3,680 8-year old children with ASD and computed ASDs prevalence by SES tertiles. They reported prevalence ratios of 0.70 (95% CI 0.64-0.76) for low SES and 1.25 (95% CI 1.16-1.35) for high SES as compared to the reference of medium SES(24).

Several studies have suggested that the reason for lower prevalence in lower SES groups may to be due to reporting bias, however, rather than a reflection of the true discrepancies within the populations (26-28). It has been suggested that lower SES groups have lower recognition of ASDs symptoms and poorer access to healthcare for diagnosis (26). Children from lower SES families are also more likely to be diagnosed at a later age and have decreased access to healthcare services (2).

Folic Acid Intake

Another area of study has focused on nutritional risk factors, especially folic acid. A 2012 study looked at the role of folic acid intake and ASDs risks, reporting that mean daily folic acid intake of $\geq$ 600 micrograms during pregnancy may reduce the risk of ASDs in the children of women with inefficient folate metabolism (OR 0.62; 95% CI 0.42-0.92) (29). Additionally, a 2013 Norwegian study (n= 85, 176) reported a protective effect of OR 0.61 (95% CI, 0.41-0.90) for mothers who used folic acid supplementation during pregnancy controlling for year of birth, maternal education level, and parity (30).

No association was found with Asperger syndrome or PDD-NOS, but the authors noted that power was limited.

B. Interpregnancy Interval (IPI)

IPI is defined as the length of time between the birth of the first child and the conception of the index pregnancy (31). Shorter intervals (defined as < 9 months, ≤ 12 months, <18 months) between a singleton birth and a subsequent singleton conception have been associated with higher risk of preterm birth (32), low birth weight (32), schizophrenia (33), excessive maternal weight gain (34), and ASDs.

Short IPI has been hypothesized to cause adverse pregnancy outcomes through a biological mechanism of maternal nutritional depletion. Maternal nutritional depletion occurs during the course of pregnancy with the increasing nutritional needs of the fetus causing decreased maternal levels of folic acids and other essential nutrients (35). Nutritional status of the mother at conception of the second child affects the balance between the division of nutrients between the mother and the fetus, potentially leading to nutritionally suboptimal conditions that increase the risk of ASDs because the mother does not have sufficient nutrients to support typical development (29, 35).

Given the importance of maintaining nutrient levels, folic acid supplementation is widely recognized as a critical factor in early pregnancy (29, 35-37). It plays an important role in early development of nucleic acid synthesis, cell division, gene regulation, and neurotransmitter synthesis (37). Significant dose-response relationships have been reported between maternal folate levels and neural tube development (38). Pregnancy has also been shown to deplete maternal levels of folic acid from mid-pregnancy through 12 months postpartum (35, 39, 40). Furthermore, when women use folic acid supplements,

the risk of ASDs in their offspring decreases (29, 41). Though other important nutrients are also depleted during pregnancy, the post-pregnancy depletion period is only 1-3 months,shorter than that of folates (29, 42).

In addition to this mechanistic hypothesis and the role of folate, there are several characteristics associated with short IPI. An IPI of <18 months has been associated with older maternal age, being married, and initiating childbearing after age 30 (43). Using contraception during IPI increases its length and is associated with better health outcomes for the index child (44).

C. The Intersection of ASDs and IPI

The relationship between IPI and ASDs has been explored in several previous studies. Cheslack-Postava et al. used birth records of all California births from 1992-2002 to assess IPI and the odds of ASDs in second-born singleton siblings (n= 662 ,730) (45). The authors reported that IPIs of less than 12 months, 12-23 months, and 24-35 months were associated with elevated ASDs odds ratios (95% CI) of 3.39 (3.00–3.82), 1.86 (1.65–2.10), and 1.26 (1.10–1.45) relative to IPIs of ≥36 months.

The authors' hypothesized that ASDs diagnosis or symptoms in a first child might impact the decision to have a second child and that parents who got pregnant after a short IPI would have a shorter time between births in which to observe the development of the first child and potentially decide not to have a second child. This potential bias was controlled for by analyzing only subjects whose first sibling did not have an autism diagnosis. If the first child does not display symptoms or tendencies of ASDs, then ASDs cannot affect the decision to conceive a subsequent child. While this was a strength of

their analysis, it does limit the generalizability of the study to only those families whose first child does not have an ASDs diagnosis.

Another limitation of this study was that although the authors hypothesized that nutritional factors were involved in the mechanism underlying IPI, they did not have data to address background nutritional status or use of prenatal vitamins. Further, ASDs diagnoses were based on case files from the Department of Developmental Services (DDS). The DDS has been estimated to include 75%-80% of ASDs children within the state of California, but people who do not register for these services would not be identified for this study, introducing a potential selection bias if registration is differential by IPI.

Dodds et al. also reported short IPI to be associated with increased risk of ASDs in a retrospective longitudinal cohort study of children born between 1990 and 2002 in Nova Scotia, Canada (n=129,733). Women with IPIs of < 18 months had a relative risk of ASDs in their children of 1.46 (95% CI 1.12, 1.91) compared with women with IPIs ≥ 18 months (46).

As in the previous study, a limitation was a limited ability to control for potential confounders. The authors adjusted for having a sibling with autism or a mother with a history of diagnosed psychiatric disorders. Unlike Cheslack Postava, this study included third- and later-born children. Later-born children may be affected by compounded nutritional depletion, further increased maternal age, and behavioral surveillance leading to earlier diagnoses.

Concurring with the prior studies, a 2013 Norwegian registry-based study (n= 223,476) reported the adjusted OR for autism alone was 2.18 (95% CI 1.42-3.26) when

an IPI of < 9 months was compared to ≥ 9 month IPI (47). The odds of autism also increased for IPIs of 9-11 months compared with ≥ 12 months in the adjusted analysis, with an OR of 1.71 (95% CI 1.07-2.64) (47). When the other ASDs (Asperger's disorder and PDD-nOS) were included in the analysis, however, estimates were non-significant (effect estimates not reported).

As in prior studies, this study employed birth-registry data which minimizes the potential for selection biases and results in minimal missing data. Further, this study was strengthened by the confirmation of ASDs diagnoses during in-person interviews for all children in the Autism Birth Cohort Study. A weakness, however, was that they were only able to control for year of birth, sex, maternal age, paternal age, and maternal education.

Conclusion

The present study will further examine the association between IPI and ASDs. The greatest strengths of all previous studies are that, by using birth-records data, they were able to obtain very large sample sizes. The common drawback is that this type of data collection resulted in few available covariates. While the current study employs a much smaller sample size, it is able to control for many more potential confounders. Furthermore, the CHARGE study a provides more accurate diagnosis for ASDs than some previous studies.

Chapter Two

Introduction

Autism Spectrum Disorders (ASDs) are a pervasive and complicated range of neurological conditions with few known causes. These disorders, generally diagnosed during early childhood, include autism, Asperger syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS) (1, 2). They are characterized by deficits in social skills and communication, repetitive behaviors, stereotyped body movements, and intellectual disability (1, 3, 4). Prevalence of ASDs in the United States in 2012 was estimated by the CDC to be 11.3 per 1,000 (range 4.8-21.2), or 1 in 88 children 8 years of age (9).

One area of increasing research interest is the relationship between ASDs and interpregnancy interval (IPI). IPI is defined as the time between the birth of one child and the conception of the next. Short IPIs (ranging from 9-18 months), have been associated with increased risk of a variety of adverse birth outcomes including ASDs, preterm birth, low birth weight, schizophrenia and excessive maternal weight gain (32-34, 45-47).

Previous studies based on birth registry information have suggested that shorter IPI is associated with ASDs (45-47). However, these studies had limited ability to validate ASDs diagnoses and to control for potential confounders.

In light of these reports, the aim of this study was to examine the association between IPI and the odds of ASDs using data from CHARGE (Childhood Autism Risks from Genetics and the Environment), a California-based case-control study with detailed information on potential confounders. Additionally, the CHARGE study provides more accurate diagnosis for ASDs than some prior studies.

Methods

Study Population

The CHARGE study is a case-control study begun in 2002 to evaluate the role of environmental factors in the development of ASDs and developmental delay (DD). The study population is drawn from three groups: 1) children with autism, 2) children with DD, and 3) randomly selected children from the general population matched to children with autism or DD based on age, gender, and residential area. All index children had to meet the inclusion criteria of 1) aged 2-5 years at enrollment, 2) residence within designated catchment area, 3) born in California and 4) living with a biological parent who speaks English or Spanish.

Children with ASDs and DD were recruited through other studies at U.C. Davis, the California Department of Developmental Services Regional Center System, and general publicity. General population controls were selected from California birth files using stratified random sampling. Parents completed informed consent at the M.I.N.D. institute. All data were collected only after informed consent was obtained, and all protocols were approved by the UC Davis School of Medicine and the State of California Institutional Review Boards. Primary caretakers completed a comprehensive phone interview which assessed potential environmental and sociodemographic confounders. During the telephone interview, interviewers were blinded to the case status of the family. Further information about recruitment and data collection in the CHARGE Study has been previously published (48).

Outcome

Trained CHARGE personnel performed a complete psychometric and medical evaluation of all index children. Participants and their caretakers were evaluated with the Autism Diagnostic Interview-revised (ADI-R) and Autism Diagnostic Observation Schedules (ADOS) in order to confirm their diagnoses.

Exposure

The primary caretaker then completed an interview including questions about medical and reproductive history. IPI was calculated based on these interviews. The birth interval was defined as the period of time between the birth of the prior child and the conception of the index child. The birth interval was calculated by subtracting the birthdate of the prior sibling from the birthdate of the index child. The IPI was then calculated by subtracting the gestational age of the index child from the birth interval, leaving the length of time between the end of the prior pregnancy and the start of the next.

This study began with 1281 index children. DD children were excluded (n=254). A further 63 observations were excluded because they involved multiple infant births for either the prior (n=30) or the index child (n=33). Finally, 429 index children were excluded because they were the first-born child and an additional 36 children were excluded due to missing IPI data, leaving 499 sibling pairs for analysis.

Covariates

Using Directed Acyclic Graphs (DAGs) and the previous literature, potential confounders were identified as mother's age at conception of the index child, father's age at conception of the index child, mother's race, mother's smoking status during pregnancy, mother's education, mother's marital status, mother's birthplace, mother's

desire to get pregnant, procedures used to conceive the index child, prenatal vitamin use in the first month of pregnancy of the index child, family home ownership, child's sex, and preterm birth. Information on these potential confounders was collected during the primary caretaker's interview.

Statistical Analysis

Logistic regression models were used to predict the odds of giving birth to a child diagnosed with ASDs relative to giving birth to a child with typical development as a function of IPI adjusted for confounders. Sensitivity analyses were conducted considering different cutpoints for IPI and stratifying on prenatal vitamin use.

Results

Table 1 presents the descriptive characteristics of the index children in the study population (n =499). Index children with ASDs were less likely to have parents who owned their own home, have a mother born in the United States, or have mothers who used prenatal vitamins three months before conception or in the first month of gestation. Those with ASDs were more likely to have been breastfed for less than 6 months, smoke, be obese, be Hispanic, and have less education.

Males were more likely than females to have ASDs, with 86.4% of cases being male. Both case and control groups had very high breastfeeding at 92.1% and 92.7% respectively.

In the unadjusted model, a short IPI ($\leq$ 12 months) increased the odds of having a child with ASDs with an OR of 1.8 (95% CI 1.1, 2.8) as compared with an IPI > 12 months (Table 2).

After adjusting for mother's age at conception of the index child, race, education, marital status, birthplace, desire to get pregnant, procedures used to conceive the index child, prenatal vitamin use in the first month of pregnancy of the index child, family home ownership, child's gender, and preterm birth, women with an IPI of ≤ 12 months continued to have increased odds of having a child with ASDs (OR 2.0; 95% CI 1.2-3.6) (Table 2). Father's age at conception of the index child, mother's education level, and mode of delivery payment were dropped from the final model because such exclusion did not change the effect estimate by more than 10%.

Women who had an IPI of ≤ 12 months had an OR of 2.1 (95% CI 1.2-3.9) while women with an IPI of 12-24 months had an OR of 1.1 (0.7-1.8) compared with women who had an IPI of > 24 months after adjusting for confounders (Table 2).

Among women who took prenatal vitamins, the OR for ASDs comparing women who had an IPI of ≤ 12 months vitamins with those who had an IPI of >12 months and took prenatal vitamins was 2.0 (95% CI 1.2-3.6). Women who had an IPI of ≤ 12 months and did not take prenatal vitamins had an OR of 2.0 (95% CI 1.4-3.8).

Discussion

This study explored the relationship between IPI and ASDs. We estimated that a short IPI (≤ 12 months) is associated with an adjusted OR of 2.0 (95% CI 1.2-3.6). This is consistent with previous studies which have also shown an increased odds ratio for short IPIs (45, 46).

Several biological mechanisms may play a role in the observed increased odds of ASDs with short IPIs. One of the most common hypotheses is that ASDs are a result of

maternal micronutrient depletion. Essential nutrients such as folic acids may be at suboptimal levels after the nutritional drain of pregnancy. Therefore, children conceived close to a prior pregnancy may experience a prenatal environment low in those nutrients. Such deficits have been shown to have adverse effects across a variety of developmental outcomes. However, in this study, prenatal vitamin use did not modify the estimated effect of IPI on ASDs. Prenatal vitamin use is not equivalent to folic acid use, and mothers may receive folic acid through mandatory fortification as well. Other explanations could include suboptimal hormone levels after a recent previous birth, incomplete uterine tissue repair, or residual confounding.

As in prior studies, IPI was also examined using multiple cutpoints. For this study an IPI of $\leq$ 12 months, 12-24 and > 24 months, provided observed odds ratios of 2.1 (95% CI 1.2-3.9), 1.1 (0.7-1.8) and 1.0 (ref), respectively. The Cheslack-Postava study which created cutpoints at similar intervals reported that that an IPI 12 months, 12-23 months, and 24-35 months were associated with ASDs odds ratios (95% CI) of 3.4 (3.00–3.82), 1.9 (1.65–2.10), and 1.26 (1.10–1.45) relative to IPIs of $\geq$36 months. This study, therefore, did not see a gradation of effect to the same degree observed in the Cheslack-Postava report. Due to the smaller sample size of this study, we were not able to directly comparison effect estimates. However, the magnitude of the effect was smaller in this study.

Breastfeeding data for the index children indicates that 45.1% of cases and 59.3% of controls were breastfed for more than 6 months. If rates are similar for the prior sibling, then IPI may be confounded by longer breastfeeding among the controls in this study, which would delay return to fertility and increase IPI.

This study adds to the growing body of knowledge concerning IPI and ASDs risk. A strength of this analysis was that the ASDs diagnosis for all participants was confirmed by trained research clinicians, decreasing the probability of ASDs misclassification. The previous California-based study relied solely on case files registered with the Department of Developmental Services (DDS). Prior studies considering IPI have been conducted through birth records, which inherently limited the ability to control for a range of confounders. Prior research was at most able to control for maternal age, education, birthplace and birth year of the index child. The study design employed here included a detailed interview which allowed for control for factors such as prenatal vitamin use and SES factors.

A limitation of this study, however, is the small sample size compared to previous birth record studies which had sample sizes ranging from 129,733 to 662,730. Another limitation is that in this study, prior siblings with ASDs did not qualify for exclusion of the sibling pair. Other studies have excluded sibling pairs in which the prior sibling was diagnosed with ASDs to control for potential genetic factors or birth spacing decisions. In this study they were retained to maintain sample size.

Future studies should consider employing more refined measurements of folic acid intake such as biomarkers or more detailed interviews, which could help assess whether IPI effects are modified based on folic acid levels.

In conclusion, using a case-control study, of 499 full-sibling pairs, IPI $\leq$ 12 months was associated with higher odds of ASDs. Understanding the role of IPI in ASDs risk is important because it may aid in the development of new guidelines regarding birth spacing.

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Table 1. Characteristics of California, Singleton, Live Birth with Interpregnancy Interval by Case-Control Status (n=499)

	Case (n=265)	(%)	Control n=234)	(%)
Interpregnancy Interval				
Long (> 12 months)	207	(78.1)	202	(86.3)
Short (<= 12 months)	58	(21.9)	32	(13.7)
Maternal Age, years				
<25	23	(8.7)	22	(9.4)
25-35	165	(62.3)	156	(66.7)
>35	77	(29.1)	56	(23.9)
Paternal Age, years				
<25	14	(5.3)	14	(6.0)
25-35	141	(53.2)	130	(55.6)
>35	108	(40.8)	89	(38.0)
Sex of Child				
Female	36	(13.6)	45	(19.2)
Male	229	(86.4)	189	(80.8)
Ever Breastfed				
Yes	244	(92.1)	217	(92.7)
No	21	(7.9)	17	(7.3)
Maternal Race				
White	147	(55.5)	150	(64.1)
Black	13	(4.9)	7	(3.0)
American Indian/AK Native	1	(0.4)	1	(0.4)
Asian	21	(7.9)	14	(6.0)
Pacific Islander/HI Native	1	(0.4)	2	(0.9)
White Hispanic	74	(27.9)	46	(19.7)
non-White Hispanic	0	(0.0)	3	(1.3)
Multiracial	8	(3.0)	11	(4.7)
Child Race				
White	121	(45.7)	124	(53.0)
Black	11	(4.2)	6	(2.6)
American Indian/AK Native	0	(0.0)	0	(0.0)
Asian	17	(6.4)	7	(3.0)
Pacific Islander/HI Native	0	(0.0)	2	(0.9)
White Hispanic	86	(32.5)	56	(24.0)
non-White Hispanic	8	(3.0)	10	(4.3)
Multiracial	22	(8.3)	28	(12.0)
Missing			1	
Mom Smoked During Pregnancy				
Yes	18	(6.8)	7	(3.1)
No	238	(89.8)	218	(96.9)
Missing	9		9	
Prenatal Care				
Yes	254	(99.2)	225	(98.7)
No	2	(0.8)	3	(1.3)
Missing	9		6	
Prenatal Vitamin Use (1st month)				
Yes	120	(47.8)	132	(60.6)
No	131	(52.2)	86	(39.4)
Missing	14		16	

	Case (n=265)	(%)	Control (n=234)	(%)
Own Home				
Yes	164	(62.8)	174	(75.7)
No	97	(37.2)	56	(24.3)
Missing	4		4	
Mother's Education				
Less than high school	13	(4.9)	13	(5.6)
High school/GED	32	(12.1)	20	(8.5)
Some college	118	(44.5)	84	(35.9)
Bachelor	70	(26.4)	87	(37.2)
Graduate or Professional Degree	32	(12.1)	30	(12.8)
Mother's Birthplace				
US	184	(69.4)	193	(82.5)
Mexico	28	(10.6)	16	(6.8)
Other	53	(20.0)	25	(10.7)
Marital Status				
Married	225	(86.2)	205	(88.4)
Other	36	(13.8)	27	(11.6)
Missing	4		2	
Mother's Prepregnancy BMI				
Underweight <18.5	7	(2.8)	4	(1.8)
Healthy weight 18.5-24.9	131	(52.0)	120	(54.3)
Overweight 25.0-29.9	57	(22.6)	60	(27.1)
Obese >30	57	(22.6)	37	(16.7)
Missing	13		13	
Procedures to conceive				
Yes	9	(3.5)	7	(3.1)
No	246	(96.5)	222	(96.9)
Missing	10		5	
Wanted to get pregnant				
Yes	143	(56.1)	143	(62.7)
Intended to wait	43	(16.9)	20	(8.8)
No	26	(10.2)	18	(7.9)
No preference	43	(16.9)	46	(20.2)
Other	0		1	(0.4)
Missing	10		6	
Preterm (<= 36 weeks)				
Yes	17	(6.4)	11	(4.7)
No	247	(93.6)	223	(95.3)
Missing	1		0	
Length of Breastfeeding (months)				
< 6	134	(54.9)	87	(40.7)
> 6	110	(45.1)	127	(59.3)
Missing	21		20	