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The effect of Alaska Native status and other underlying risk factors for chromosomal anomalies in the Alaska population from 1996-2009

By

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Master of Public Health

Epidemiology

_____

Lyndsey Darrow, PhD

Committee Chair

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B.S., University of Illinois, Urbana-Champaign, 2010

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An abstract of

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

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Abstract

The effect of Alaska Native status and other underlying risk factors for chromosomal anomalies in the Alaska population from 1996-2009

By Cara Jane Bergo

This study examines reported chromosomal anomalies, Trisomy 13, 18 & 21, in the Alaska population from 1996-2009. Reports were used from the Alaska Birth Defects Registry and deterministically linked with birth and death certificate data from the Bureau of Vital Statistics. There were 143,781 births in Alaska during this time with 279 reported cases of chromosomal anomalies. Logistic regression was used to examine the effects of five predictors (prenatal care, alcohol/tobacco use, mother's age, region of birth) and the exposure of interest Alaska Native status on the outcome, reported chromosomal anomaly. Maternal age and region of birth were found to be significant predictors. The risk ratio for Alaska Native Status vs. Non-Native was 1.23 (95% CI=0.87, 1.74). The effect of maternal age was significant when comparing 30-34 vs. 20-29, RR=1.57 (95% CI=1.13, 2.19), 35-39 vs. 20-29 RR=2.73 (95% CI=1.94, 3.85), and 40-45 vs. 20-29 RR=10.55 (95% CI=7.45, 14.92). The effect on region of birth was significant when comparing Northern vs. Anchorage RR=1.69 (95% CI=1.02, 2.79). A sub analysis was performed to evaluate the effect among women who had late or no prenatal care, following this process there was no effect of Alaska Native Status, RR=1.07 (95% CI=0.63, 1.81).

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Table of Contents

Introduction

In the United States, major congenital anomalies are reported in about 3% to 4% of infants by their first birthday (Mili et al., 1991). Chromosomal anomalies are some of the most devastating anomalies contributing to a significant amount of fetal death (Stojilkovi et al., 2003). The three most prevalent and reported chromosomal anomalies in Alaska are Trisomy 13, 18 & 21 (Schoellhorn et al., 2005). Trisomy 13 & 18 are usually predicted to be fatal and terminated early but for reasons such as inadequate prenatal care or mother's personal beliefs there continue to be reported cases each year (Gessner, 2003).

According to the *Alaska Maternal and Child Health Data Book 2012: Birth Defects Surveillance Edition,* chromosomal anomalies affected an average of 20 Alaskan infants each year for birth years 1996-2011, with higher prevalence among Alaska Native births compared to non-Native births (22.4 per 10,000 live births versus 17.8 per 10,000 live births). The majority of cases reported are Trisomy 21 (approximately 17 cases per year) while approximately 2 cases of Trisomy 18 and 1 case of Trisomy 13 are reported annually.

During that same period 1996- 2011, prevalence of chromosomal anomalies was typically higher among Alaska Native children, with periods of marked increase (Schoellhorn et al., 2012). Reasons for the disparity between Alaska Native children and non-Native children have not been studied.

Prenatal care can screen for these anomalies and only 12% of parents who discover that their child has Trisomy 13 or 18 choose to continue the pregnancy (Parker et al., 2003). Maternal age is a known risk factor for all chromosomal anomalies and

sometimes the only indicator of need for specific prenatal screening (Forrester et al., 1999).

No research has been done regarding rates of chromosomal anomalies and their risk factors among the Alaska Native population. This research will help clarify risk factors for these birth defects and provide information for outreach programs. This evidence will help explain the differences between the populations and possibly show where intervention programs can be set in place.

Methods

Chromosomal anomalies are reported congenital anomalies to the Alaska Birth Defects Registry (ABDR). This study looked at the risk factors for three of the reported chromosomal anomalies, Trisomy 13, 18 & 21, and focused to see the risk for Alaska Natives versus the Non-Native population when taking into account other demographic and social indicators.

The research utilizes data from the Alaska Birth Defects Registry (ABDR), Bureau of Vital Statistics, and the Maternal-Infant Mortality Review and Child Death Review (MIMR-CDR). The research examines birth years 1996-2009 and deaths occurring from 1996-2010 for infants who died at less than one year of age. Chromosomal anomalies are reported by heath care providers in Alaska to ABDR and then selected cases are abstracted to verify the report. These reported cases were used in the evaluation and then linked to birth certificates & death certificates from the Bureau of Vital Statistics, and MIMR-CDR. Risk factor data, including mother's race, age and

prenatal care status, was obtained from the birth certificate. No personal identification material was used.

The MIMR-CDR is a review panel that convenes to discuss maternal, infant and child deaths in the state of Alaska. Each month a group of health care providers and professionals reviews medical records, autopsy reports, and other relevant records for all infant, child and maternal deaths in the state of Alaska, excluding infant deaths that occurred before the child left the hospital, and make consensus decisions regarding causes and contributing factors to the deaths. The panel includes multiple health care providers, health department employees and other community members. This team reviews the death and all associated, available medical records to decide on the cause of death. These evaluations are then stored for future analysis.

The main dataset is from ABDR. It is a primarily passive surveillance system for the state of Alaska where health care providers report congenital anomalies but a portion of congenital anomalies are confirmed through abstraction. For the purpose of this study some of the chromosomal anomalies were actively abstracted and verified by a state health department employee following a case report from a health care provider but not all therefore making the information obtained primarily passive reporting. Vital statistics including birth and death certificates were used which provided information regarding other risk factors. Also, birth certificates were linked to the MIMR-CDR dataset for deaths within the cohort.

The ABDR dataset was deterministically linked to the Vital Statistics data and MIMR. ABDR was linked to a file containing birth certificate numbers and then this set

was linked to the Vital Statistics. This set was then linked to the MIMR on birth certificate number as well. 899 reported congenital anomalies were not linked to an Alaska Birth Certificate and therefore removed from analysis.

Study Population and Variables

The outcome of interest for this study is a birth linked to an Alaska birth certificate with a reported chromosomal anomaly, Trisomy 13, 18 or 21. There were 143,781 births from 1996-2009 in Alaska. From those births, 8,536 were reported with at least one major congenital anomaly defined by the National Birth Defects Prevention Network (NBDPN 2007). There were 279 cases of chromosomal anomalies reported and confirmed in the ABDR during 1996-2009 including 234 cases of Trisomy 21, 30 cases of Trisomy 18 and 15 cases of Trisomy 13.

The exposure variables were maintained from the Bureau of Vital Statistics through the birth certificate information. These variables were chosen based on past studies showing associations, background and demographic information, and other categories of interest.

The primary exposure of interest was mother's race defined as Alaska Native/ American Indian, Asian/ Pacific Islander, Black, White, and Missing. These groups were defined according to the US Census Bureau. As seen in Table 1 the largest groups are Alaska Native/ American Indian with 25% of the population and White with 62.8% of the population. For the purpose of all analyses race was defined as Alaska Native versus non-Native, combining all other race groups including White, Black, Asian and other.

Maternal age was calculated from the birth certificate information and coded into age groups according to ABDR protocol: 15-19 years, 20-29 years, 30-34 years, 35-39 years and 40-45 years. 20-29 years was used as the comparison group for all analyses. The 30-39 age group was divided into 30-34 and 35-39 due to higher risks of chromosomal anomaly in women in their late 30's.

Region of birth was defined from the birth certificate and then coded through ABDR protocol according to mother's residence community. Births to mothers residing outside the state of Alaska were excluded. Six major regions are identified with over half the population (51.2%) living in the Anchorage/ Mat-Su Region. This region was used as the comparison region for all analyses.

Alcohol and tobacco use were coded from the birth certificate information. This information was self-reported from the mother at time of birth and is likely to be underreported. Reported alcohol and tobacco use are likely underreported due to the social stigma of these behaviors. This misclassification is primarily in one direction, as women who reported consuming alcohol and smoking during pregnancy would not have a motivation to falsely report these behaviors. No reported alcohol/tobacco use was designated as the comparison group for all analyses.

Birth weight was not used as an exposure variable because it is, in part, a consequence of the outcome chromosomal anomalies, but it was looked at for descriptive purposes. It was divided in 3 categories Low, Very Low and Normal. Low was considered to be less than 2500 grams while very low was defined as below 1500 grams.

Prenatal care was defined from the birth certificate information according to when the woman began having visits as first trimester (months 1-3), second trimester (months 4-6) or later (months 7-9 or none reported). This exposure may be related to increase termination of pregnancy therefore fewer cases among women with earlier prenatal care. To further investigate the issue of prenatal care a subanalysis was performed among women who received late to no prenatal care. First trimester prenatal care was used as the comparison group for all analyses.

Analysis

All statistical analyses were done using SAS 9.3(SAS Institute Cary, NC). This study used logistic regression to assess the relationship of the five covariates (prenatal care, alcohol/tobacco use, mother's age, region of birth) and the main exposure of interest (Alaska Native status) with the outcome of a reported chromosomal anomaly. Backward elimination was used to assess the statistical significance of each covariate. A chunk test was used to assess the significance of all interaction variables in the model, first with interaction variables independent of the exposure of interest and next with interaction variables and the exposure of interest. Each of the five covariates were then assessed individually for statistical significance and removed if no confounding of the Alaska Native association was observed.

Results

Backward elimination was used with a logistic regression model to assess significant predictors and the odds ratio of the main exposure of interest, Alaska Native status. The odds ratios from these models are interpreted as risk ratios given that the disease is extremely rare. With all predictors and interaction terms (those with the exposure variable and those without) in the model, the risk ratio was 1.225. The risk ratio was assessed for confounding after each set of variables or individual variables were removed from the model to be within 10% of the gold standard model (1.225). No group of interaction terms were found to be significant and were taken out following a chunk test.

The first individual variable which was the least significant and not significant at a 0.05 level in the model was alcohol use (p=0.86). Alcohol use was removed from the model and the following risk ratio was within 10% of the gold standard (1.217) so found not to be confounding. The new model without alcohol use showed that tobacco use was the least significant predictor in the model (p=0.85). Again, the following risk ratio was within 10% of the gold standard (1.223) so found not to be confounding. The model then had prenatal care, maternal age, mother's residence, and Alaska Native status. Prenatal care was not significant (p=0.65) and therefore removed from the model. The risk ratio after removing prenatal care was within 10% of the gold standard (1.219) so found not to be confounding. With only three variables remaining in the model, mother's residence was not significant (p=0.11) but when removed from the model, the

risk ratio for the exposure of interest increased to outside of 10% of the gold standard (1.46). Mother's residence was then added back into the model.

The final model included mother's residence, maternal age and Alaska Native status with the outcome of a Trisomy 13, 18 or 21 reported. The final risk ratio for Alaska Native Status vs. Non-Native is 1.23 (95% CI=0.87, 1.74). This effect is not significant. The effect in age was significant when comparing 30-34 vs. 20-29, RR=1.57 (1.13, 2.19), 35-39 vs. 20-29 RR=2.73 (1.94, 3.85), and 40-45 vs. 20-29 RR=10.55 (7.45, 14.92). The effect in region of birth was significant when comparing Northern vs. Anchorage RR=1.69 (1.02, 2.79). These effects were found to be significant in the final model and gold standard model. Maternal age was always found to be a significant predictor but was removed to assess for confounding. Maternal age was found to be a confounder if removed from the model with a RR=1.03 (0.73, 1.46) outside 10% of the gold standard model.

Final Model:

$$\text{Logit P(X)} = a + b_1 E_1 + \sum_{j=1}^{4} b_j V_j + \sum_{i=1}^{5} b_i Z_i$$

D = Chromosomal Anomaly (1=yes, 0=no)

E_1 = Alaska Native Status (1=yes, 0=no)

V_j= Maternal Age Variables

Z_i= Region of Birth Variables

Following the main analysis I performed a subanalysis on women who did not have prenatal care until the third semester or none at all. By restricting to women

receiving late or no prenatal care, any differences observed between racial groups are less likely to be driven by early detection and termination. This subanalysis included 41,433 births with 81 cases. The same process was performed beginning with the gold standard model and continuing to a final model through backwards elimination but only among women with late or no prenatal care. Following this process there was no effect of Alaska Native Status, RR=1.07 (0.63, 1.81). Also, region of birth was dropped from the model while alcohol use was kept in the model RR=2.13 (1.01, 5.35). The final model for this subanalysis included maternal age, Alaska Native status, and maternal alcohol use.

Discussion

This analysis examined the effect of Alaska Native status on chromosomal anomalies among births in Alaska from 1996-2009. The data showed that Alaska Native status is not a strong risk factor when controlling for region of birth and maternal age. Due to the limited number of cases a small effect cannot be ruled out. This examination showed confounding of Alaska Native status by region and showed the expected association between chromosomal anomalies and maternal age. Maternal age was found to be a confounder which parallels the understanding that on average Alaska Native maternal age is younger than Non-Natives. When the model controlled for maternal age it showed the populations as different but when not controlled for, the populations look more similar and decreased the risk ratio towards the null.

The one region of birth that was significantly different than Anchorage was the Northern region with a RR=1.69 (1.02, 2.79). This region is 91% Alaska Native and has

the longest geographical distance from a city in Alaska. These effects should be further studied and examined for possible interventions. This can be a factor in showing a possible cultural distinction within the Alaska Native population compared to genetic differences.

The subanalysis showed that Alaska Native status becomes even less significant among women who received late or no prenatal care. Within this subanalysis, region of birth becomes insignificant while alcohol use stays in the model and is a significant risk factor for chromosomal anomalies. This new risk factor implies that among women with little to no prenatal care, alcohol use is a significant risk factor and confounder for a birth outcome of a chromosomal anomaly. This subanalysis showed the same direction of association as the main analysis but it was also not significant.

Strengths and Weaknesses

The ABDR is primarily a passive surveillance system. Abstractions are done on selected subset of congenital anomalies. The passive surveillance leads to misreporting since most reports are not substantiated. Any health care provider can report an anomaly without proof of true diagnosis. This can be a form of misclassification if a child is diagnosed with a nonexistent anomaly or incorrect anomaly. Also, since the ABDR is a passive surveillance system, many cases will be underreported and misclassified as non-cases.

With these data there are sample size and power limitations especially when divided into subgroups. The population of Alaska is small compared to other states and Trisomy

13, 18 and 21 are rare outcomes, so more in-depth analysis may be a challenge. As seen with Trisomy 21, when cases are stratified by race groups, statistical power is extremely limited, but risk factors can still be examined descriptively and may generate hypotheses to be examined in larger datasets.

The vital statistics dataset contains demographic information, but some of it is missing or incomplete. However, missing and incomplete data is minimal and does not affect the study and the overall analysis, results or conclusions. Maternal race was used as an identifier for child's race due to missing data regarding paternal race.

Rates of terminated pregnancy are a limitation in this study. The actual incidence of chromosomal anomalies is unknown in Alaska because of early termination following screening and detection of this congenital defect. Therefore, we can only assess live births in this cohort and their associated risk factors. These risk factors could possibly differ between groups of women who choose to terminate their pregnancy and those who choose to continue with the pregnancy. I conducted one subanalysis restricted to women who did not receive early prenatal care and thus did not have the opportunity for early detection and termination. In this analysis the association between Native Alaskan Status and chromosomal abnormality was RR=1.07 (0.63, 1.81) suggesting similar rates of chromosomal abnormality between racial groups.

Future Directions

This study opens up new possibilities for targeted programs regarding the appropriate health care for women at risk of chromosomal anomalies. Women of high

maternal age should continue to be rigorously screened for chromosomal anomalies during their prenatal visits. A new finding brought light to the risk of living in the Northern region of Alaska. This region has the smallest population of births (7,774) of the six regions in Alaska and should be targeted in the future for programs assessing the risks of chromosomal anomalies.

References

"Chromosome Abnormalities Fact Sheet." *Chromosome Abnormalities Fact Sheet*. N.p., 13 Oct. 2011. Web.

Forrester, Mathias B., and Ruth D. Merz. "Trisomies 13 and 18: Prenatal Diagnosis and Epidemiologic Studies in Hawaii, 1986-1997." *Genetic Testing* 3.4 (1999): 335-40. Print.

Gessner, Bradford D. "Reasons for Trisomy 13 or 18 Births despite the Availability of Prenatal Diagnosis and Pregnancy Termination." *Early Human Development* 73 (2003): 53-60. Print.

Mili, Fatima, Larry D. Edmonds, Muin J. Khoury, and Anne B. McClearn. "Prevalence of Birth Defects Among Low-Birth-Weight Infants, A Population Study." *AJDC* 145 (1991): 1313-318. Print.

NBDPN. Guidelines for Conducting Birth Defects Surveillance. http://www.nbdpn.org/current/resources/bdsurveillance.html

Parker, M. J., J. L. Budd, E. S. Draper, and I. D. Young. "Trisomy 13 and Trisomy 18 in a Defined Population: Epidemiological, Genetic and Prenatal Observations." *Prenatal*

Diagnosis, Department of Clinical Genetics, Leicester Royal Infirmary, Leicester, UK. 23.10 (2003): 856-60. Print.

Schoellhorn, Janine and Beery, Amanda. *Alaska Maternal and Child Health Data Book 2005*. Birth Defects Surveillance Edition. Anchorage: Alaska Maternal and Child Health Epidemiology Unit-Section of Woman's Children's and Family Health, Alaska Division of Public Health, 2005. Print.

Stojilkovic-Mikic, T., and C. H. Rodeck. "Screening for CHromosomal Anomalies: First or Second Trimest, Biochemical or Ultrasound?" *Annals Academy of Medicine* 32.5 (2003): 583-89. Print.

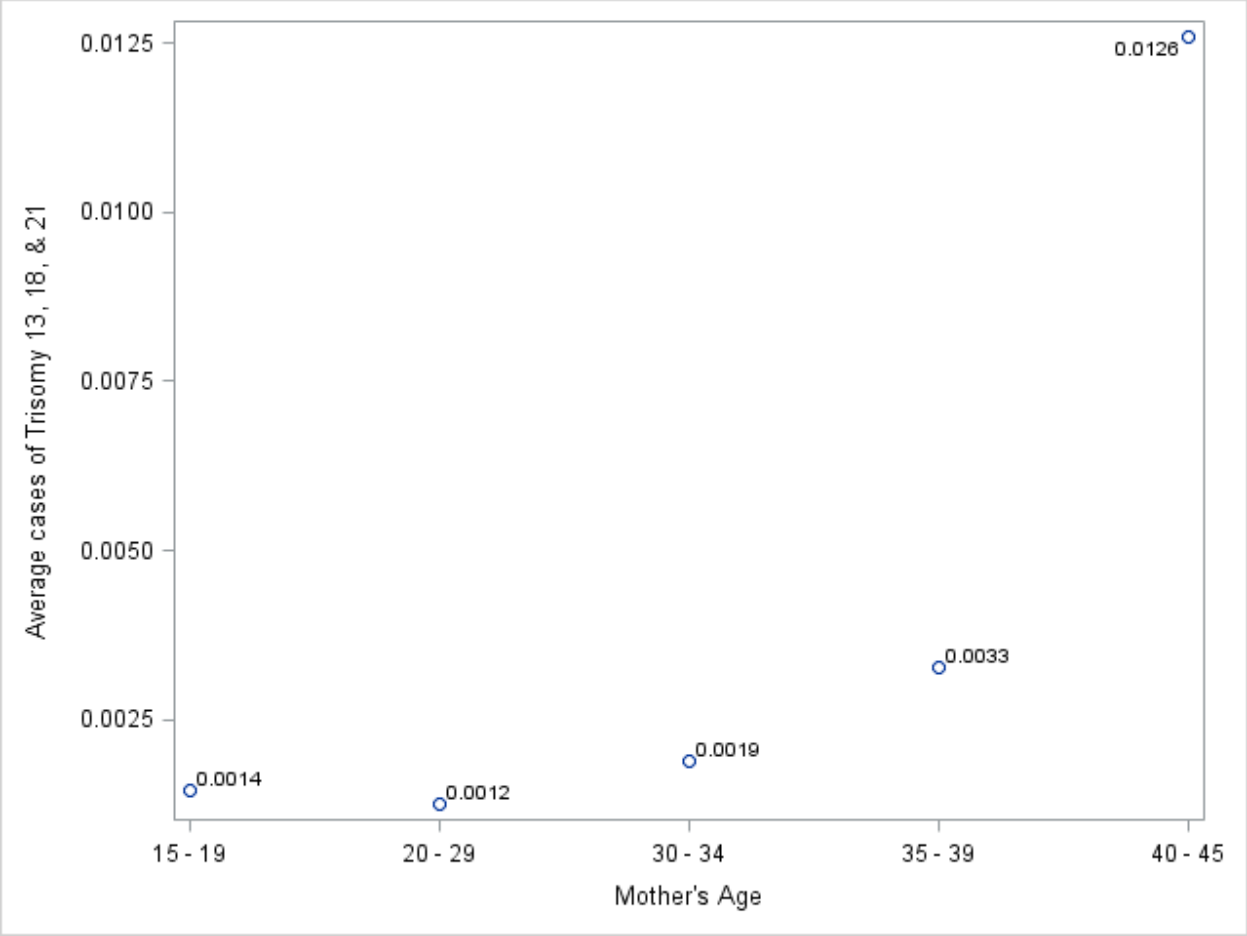
Tables

Table 1: Demographics for Alaska births 1996- 2009			
	All Alaska Births	Cases of Chromosomal Anomaly	Alaska Natives
	Frequency (%)	Frequency (%)	Frequency (%)
Race			
AK Native/American Indian	35915 (25.0)	83 (29.7)	N/A
Asian/Pacific Islander	9633 (6.7)	16 (5.7)	N/A
Black	5946 (4.1)	11 (3.9)	N/A
White	90223 (62.8)	165 (59.1)	N/A
Missing	2064 (1.4)	4 (1.4)	N/A
Maternal Age			
15-19	15217 (10.6)	22 (7.9)	6079 (16.9)
20-29	80427 (55.9)	100 (35.8)	20657 (57.5)
30-34	29021 (20.2)	55 (20.1)	5515 (15.4)
35-39	14928 (10.41)	49 (17.9)	2832 (7.9)
40-45	3811 (2.7)	48 (17.2)	704 (2.0)
Missing	377 (0.3)	5 (1.8)	128 (0.4)
Region of Birth			
Anchorage/ Mat-Su	73587 (51.2)	136 (48.7)	9705 (27.0)
Gulf Coast	13941 (9.7)	28 (10.0)	1799 (5.0)
Interior	24575 (17.1)	45 (16.1)	3559 (9.9)
Northern	7774 (5.4)	25 (9.0)	7057 (19.6)
Southeast	12367 (8.6)	15 (5.4)	3338 (9.3)
Southwest	11537 (8.0)	30 (10.8)	10457 (2.9)
Alcohol Use			
Yes	4089 (2.8)	10 (3.5)	2115 (5.9)
No	138675 (96.4)	262 (93.9)	33563 (93.5)
Missing	1017 (0.7)	7 (2.5)	237 (6.6)
Tobacco Use			
Yes	24635 (17.1)	47 (16.8)	11851 (33.0)
No	118259 (82.2)	227 (81.4)	23885 (66.5)
Missing	887 (0.6)	5 (1.8)	179 (0.5)
Birth Weight			
Low	6761 (4.7)	59 (21.1)	1671 (4.7)
Very Low	1573 (1.1)	24 (8.6)	407 (1.1)
Missing	217 (0.2)	3 (1.1)	81 (0.2)
Prenatal Care			
First Trimester	86789 (60.4)	161 (57.7)	19584 (54.5)
Second Trimester	15412 (10.7)	37 (13.3)	5476 (15.2)
Later	41443 (28.8)	81 (29.0)	10829 (30.2)
Missing	137(0.1)	0 (0)	26 (0.1)

Gold Standard Model			
	Odds Ratio	95% CI	P-Value
Race			0.509
AK/ Native/ American Indian vs. Non-Native	1.228	(0.859, 1.755)	
Maternal Age			<0.0001
15-29 vs. 20-29	1.108	(0.695, 1.766)	
30-34 vs. 20-29	1.547	(1.106, 2.164)	
35-39 vs. 20-29	2.736	(1.933, 3.873)	
40-45 vs. 20-29	10.588	7.449, 15.051)	
Region of Birth			0.085
Gulf Coast vs. Anchorage	1.083	(0.718, 1.633)	
Interior vs. Anchorage	1.065	(0.743, 1.526)	
Northern vs. Anchorage	1.700	(1.021, 2.828)	
Southeast vs. Anchorage	0.561	(0.317, 0.994)	
Southwest vs. Anchorage	1.095	(0.663, 1.807)	
Alcohol Use			0.890
Yes vs. No	1.047	(0.549, 1.995)	
Tobacco Use			0.785
Yes Vs. No	0.954	(0.678, 1.342)	
Prenatal Care			0.678
Second Trimester vs. First	1.162	(0.798, 1.692)	
Later vs. First	0.970	(0.723, 1.300)	

Final Model			
	Odds Ratio	95% CI	P-Value
Race			
AK/ Native/ American Indian vs. Non-Native	1.231	(0.871, 1.741)	0.501
Maternal Age			<0.0001
15-29 vs. 20-229	1.087	(0.684, 1.729)	
30-34 vs. 20-29	1.572	(1.130, 2.187)	
35-39 vs. 20-29	2.730	(1.936, 3.848)	
40-45 vs. 20-29	10.546	(7.453, 14.921)	
Region of Birth			0.111
Gulf Coast vs. Anchorage	1.088	(0.723, 1.637)	
Interior vs. Anchorage	1.045	(0.743, 1.471)	
Northern vs. Anchorage	1.687	(1.020, 2.790)	
Southeast vs. Anchorage	0.599	(0.344, 1.041)	
Southwest vs. Anchorage	1.255	(0.780, 2.019)	

Figures


0.0125
0.0100
0.0075
0.0050
0.0025
Average cases of Trisomy 13, 18, & 21
0.0126
0.0033
0.0019
0.0014
0.0012
15 - 19
20 - 29
30 - 34
35 - 39
40 - 45
Mother's Age