Spatio-Temporal Risk for Infantile Hypertrophic Pyloric Stenosis Among a Cohort of Iowa Births

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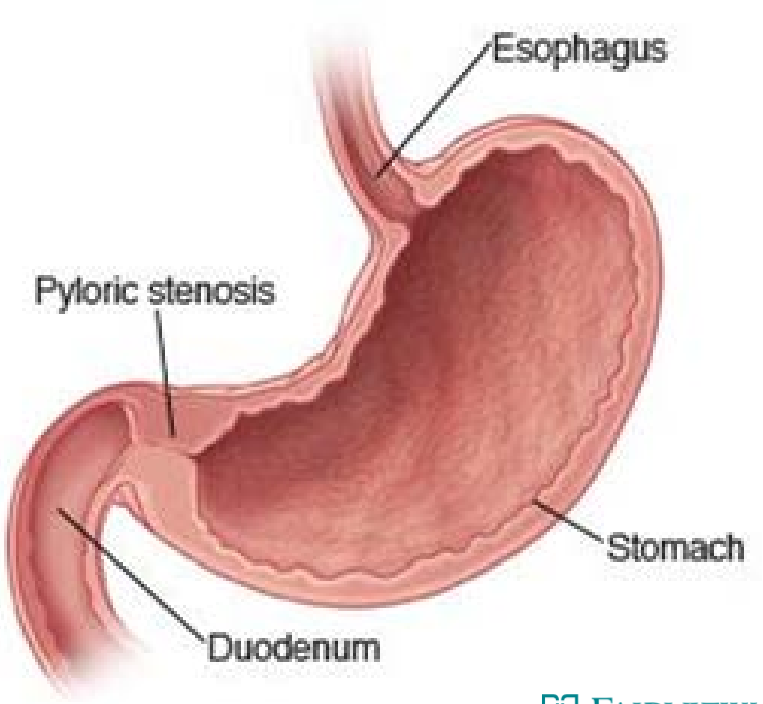
Grant HL147231

The University of Iowa

What is Infantile Hypertrophic Pyloric Stenosis (IHPS)?



FAIRVIEW

- Characterized by muscular hypertrophy of pyloric sphincter
  - Causes obstruction of gastric outlet
- Typically diagnosed from 2 to 8 weeks after birth
  - Surgery is most standard method of treatment
- Most common cause for surgery among infants

Descriptive Epidemiology and Risk Factors

- Affects 1 to 8 deliveries per 1,000 live births
- Higher among males compared to females (4:1)
- Highest among non-Hispanic whites and Native Americans, intermediate among Hispanics and non-Hispanic blacks, and lowest among Asians
- Higher among younger mothers compared to older mothers

- IHPS suspected to have a multifactorial etiology
- Previous studies have identified several gene variants associated with IHPS
- Several environmental exposures including maternal cigarette smoking and maternal and infant antibiotic use have also been identified

Goal and Objectives

- Beyond genetic risk factors for IHPS, our overall goal was to identify clues to other environmental risk factors

- To reach this goal, we conducted the following objectives
  - Estimated odds ratios for selected child and maternal covariates, including birth year
  - Analyzed geocoded coordinates of maternal residential address at birth to detect geographic clusters of IHPS
  - Generated spatial models, while controlling for covariates and time, to identify “hot spots” of IHPS occurrence for further investigation of environmental factors

Methods

Data

- 15-year sample of Iowa births (2001-2015)
- Cases: IHPS surgeries confirmed in Iowa residents ascertained by Iowa Registry for Congenital and Inherited Disorders (IRCID)
- Controls: 10% random sample of unaffected live births proportional by birth month and year, selected from Iowa birth certificates
- 60,071 total births (1,458 cases, 58,613 controls)
- Covariate data obtained from Iowa birth certificates
  - Child birth year, sex, plurality
  - Maternal education level at the time of delivery, age, race/ ethnicity, gravidity, and coordinates for maternal residential address at time of delivery

Descriptive Statistics

- Calculated frequencies of child and maternal covariates
- Estimated univariate and multivariate odds ratios and 95% confidence intervals for each covariate
- Generated density plots for cases and controls stratified by selected covariates
- Used Generalized Additive Models (GAM) with a spline to estimate probability of IHPS by location

Generalized Additive Model (GAM)

- Linear Regression Equation: $y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \epsilon, \epsilon \sim N(0, \sigma^2)$

$$\pi = P(Y = case)$$

$$\log(odds) = \log\left(\frac{\pi}{1-\pi}\right) = latitude + longitude$$

- GAM Equation: $y = \beta_0 + \beta_1 x_1 + f(x_2) + \epsilon, \epsilon \sim N(0, \sigma^2)$

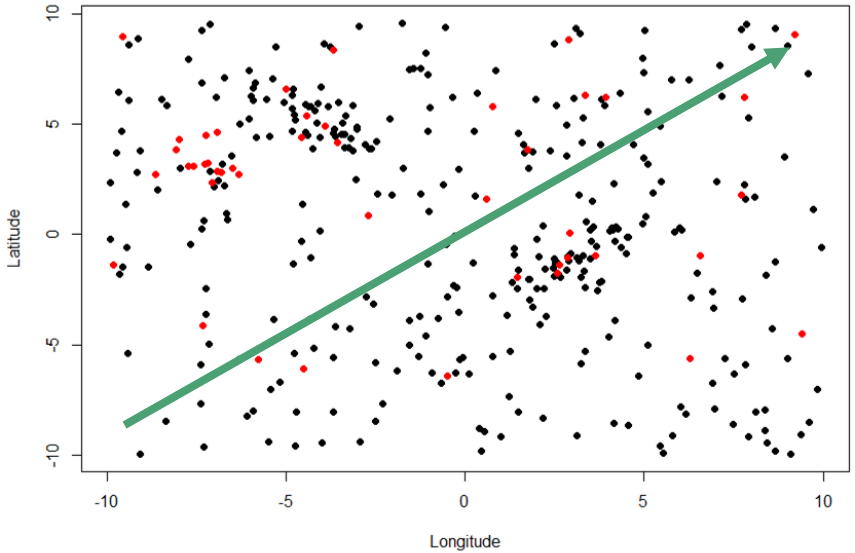
Linear component

Nonlinear component

$$\log(odds) = \log\left(\frac{\pi}{1-\pi}\right) = s(latitude, longitude)$$

Splines

- Linear regression assumes a linear relationship between predictors and outcomes
- Splines capture the nonlinear relationship and the interaction between the two



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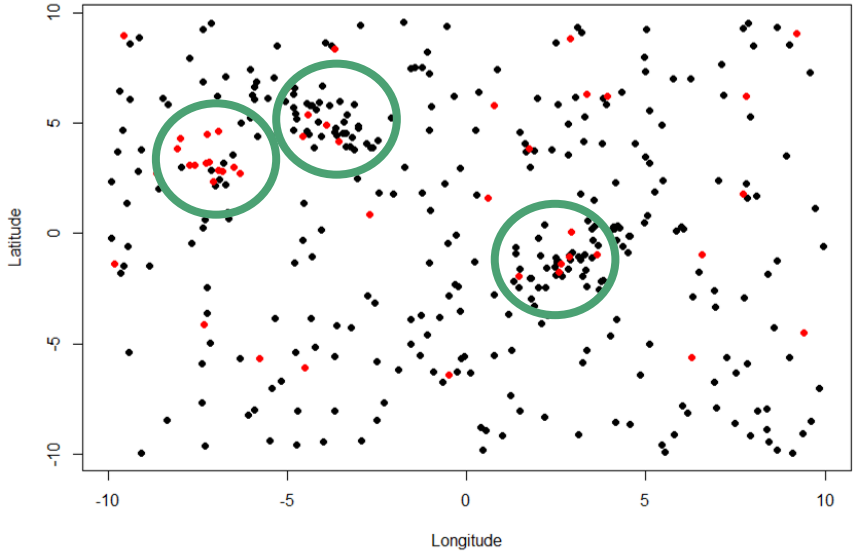
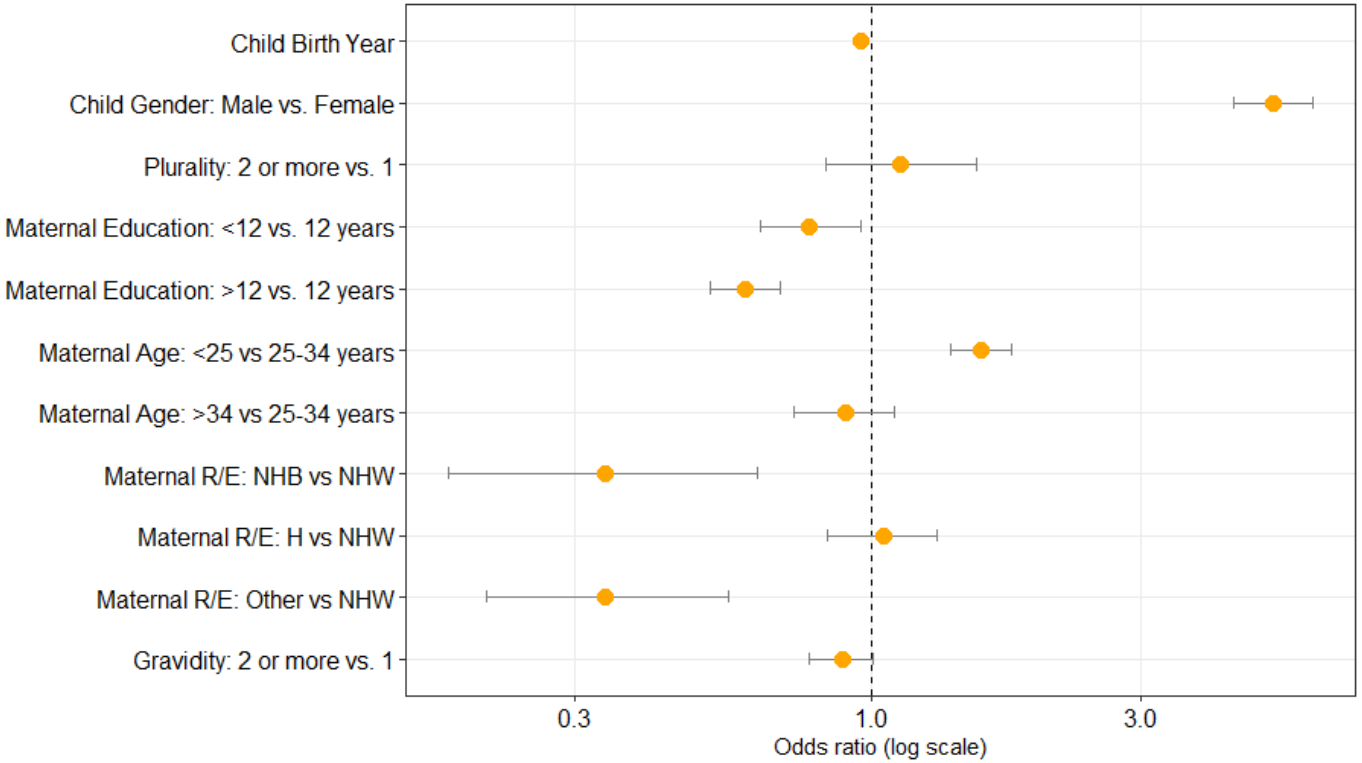


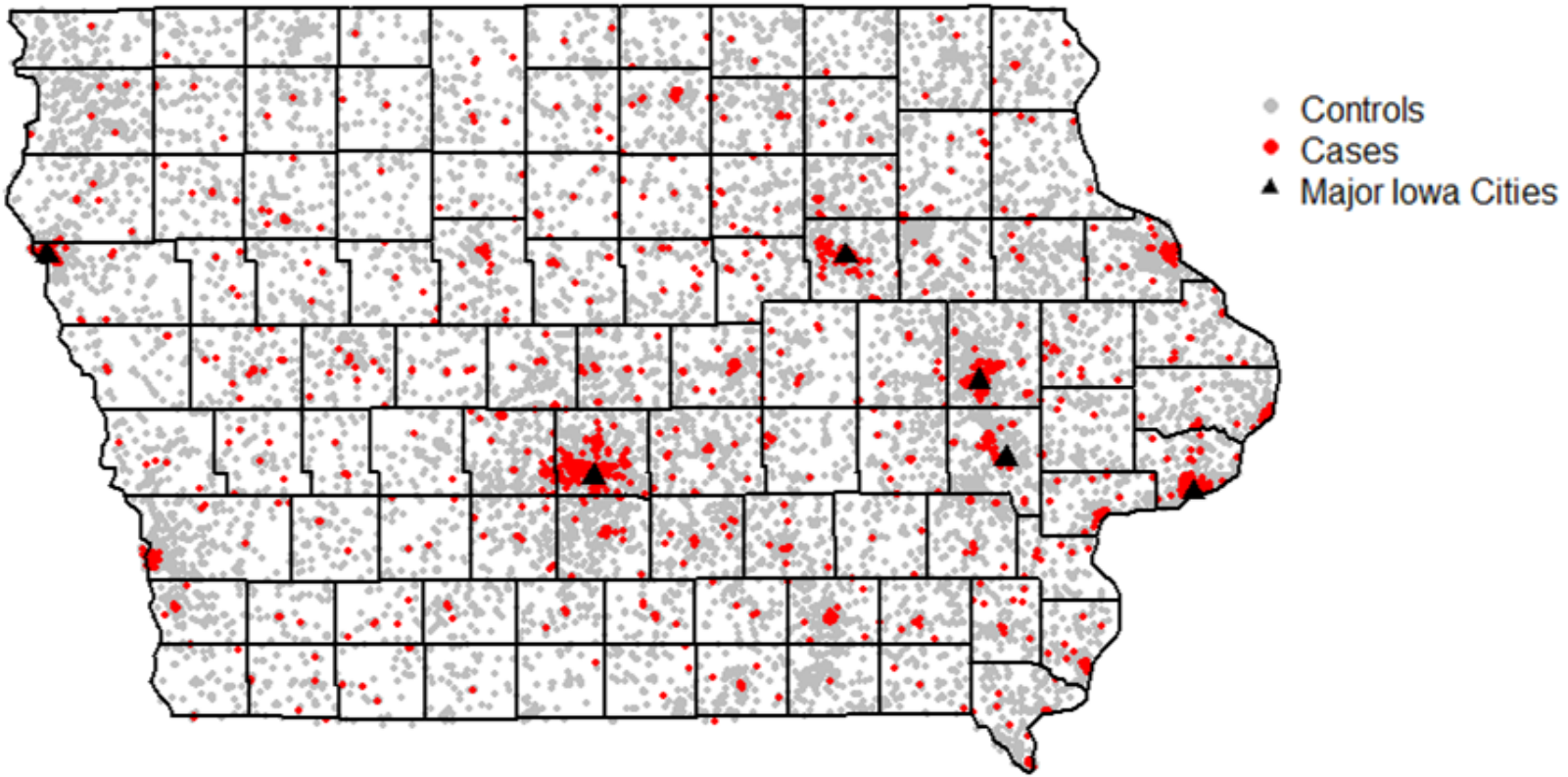
Results

Crude Odds Ratios with 95% Confidence Intervals



R/E = Race/Ethnicity, NHW = Non-Hispanic White, NHB = Non-Hispanic Black, H = Hispanic

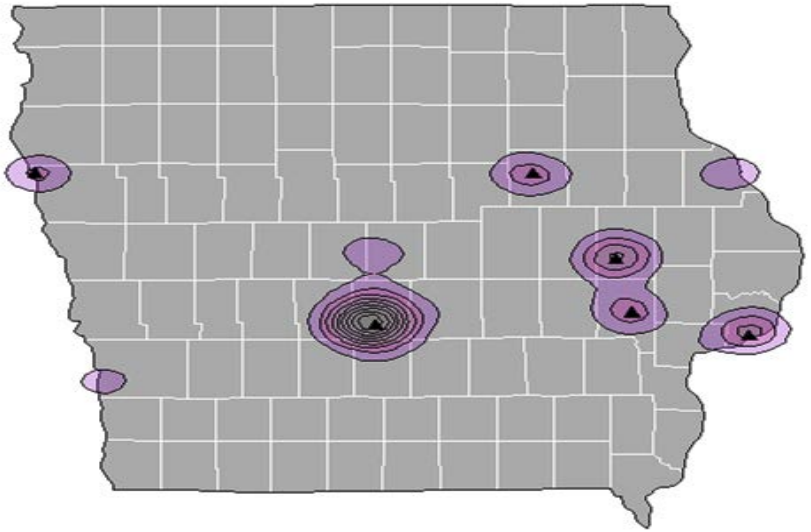
Cases and Controls in Iowa

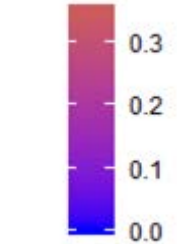


Based on 10% random sample of live births

Density Plots

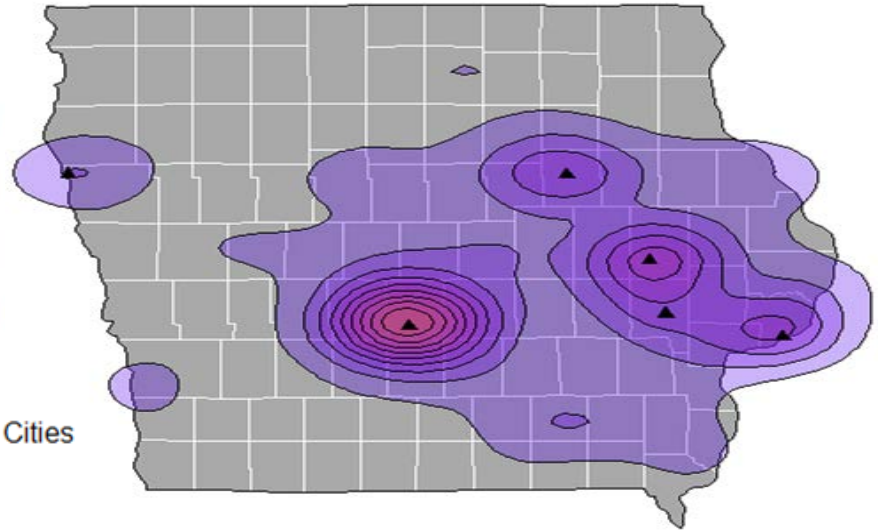
Controls (2001 - 2015)





▲ Major Iowa Cities

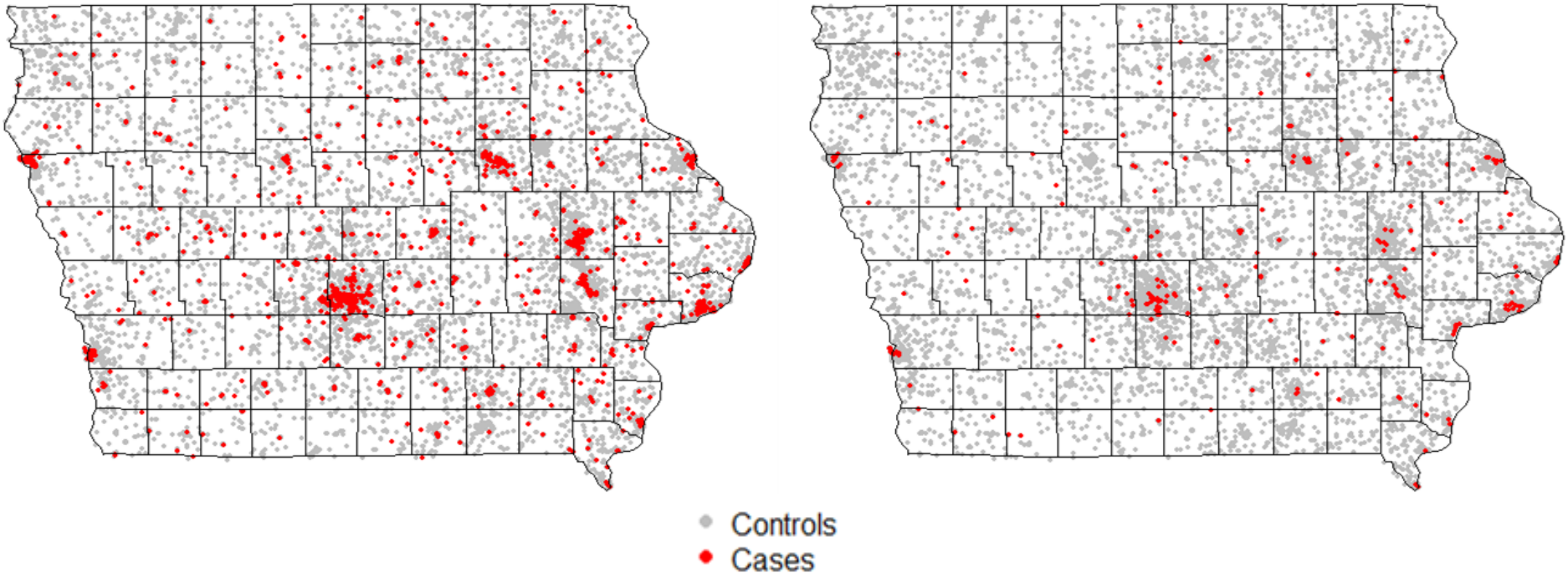
Cases (2001 - 2015)



IHPS Cases by Gender

Males (2001 - 2015)

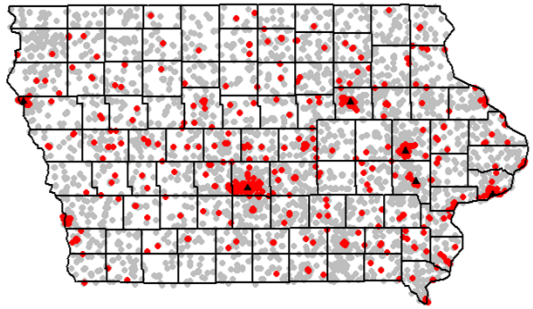
Females (2001 - 2015)



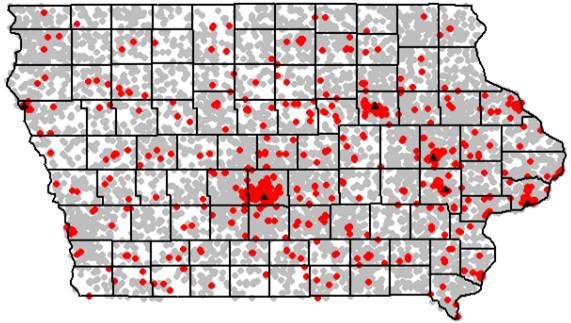
Based on 10% random sample of live births

IHPS Cases by Maternal Age

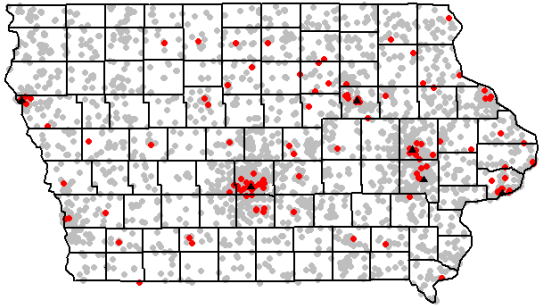
Under 25



25 to 34



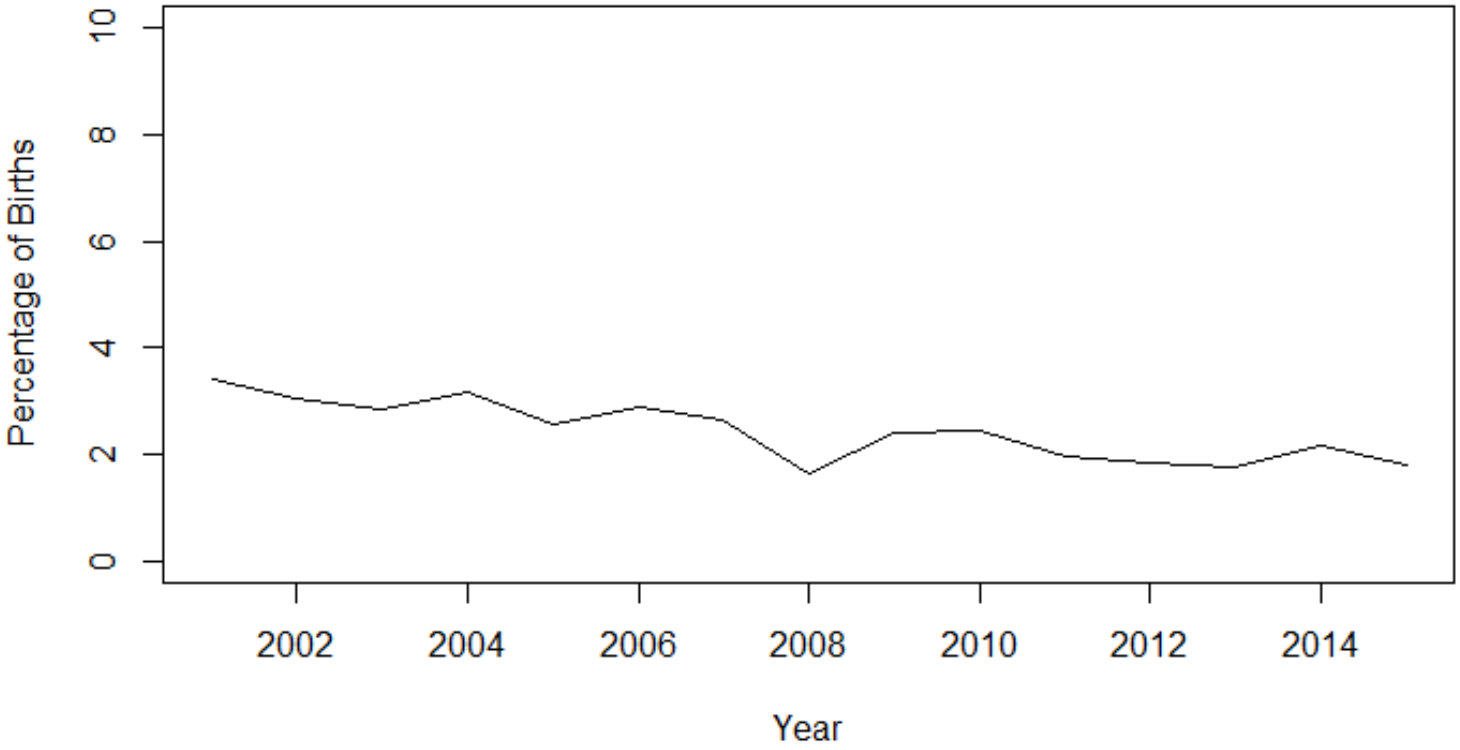
35 or Older



Controls
Cases
Major Iowa Cities

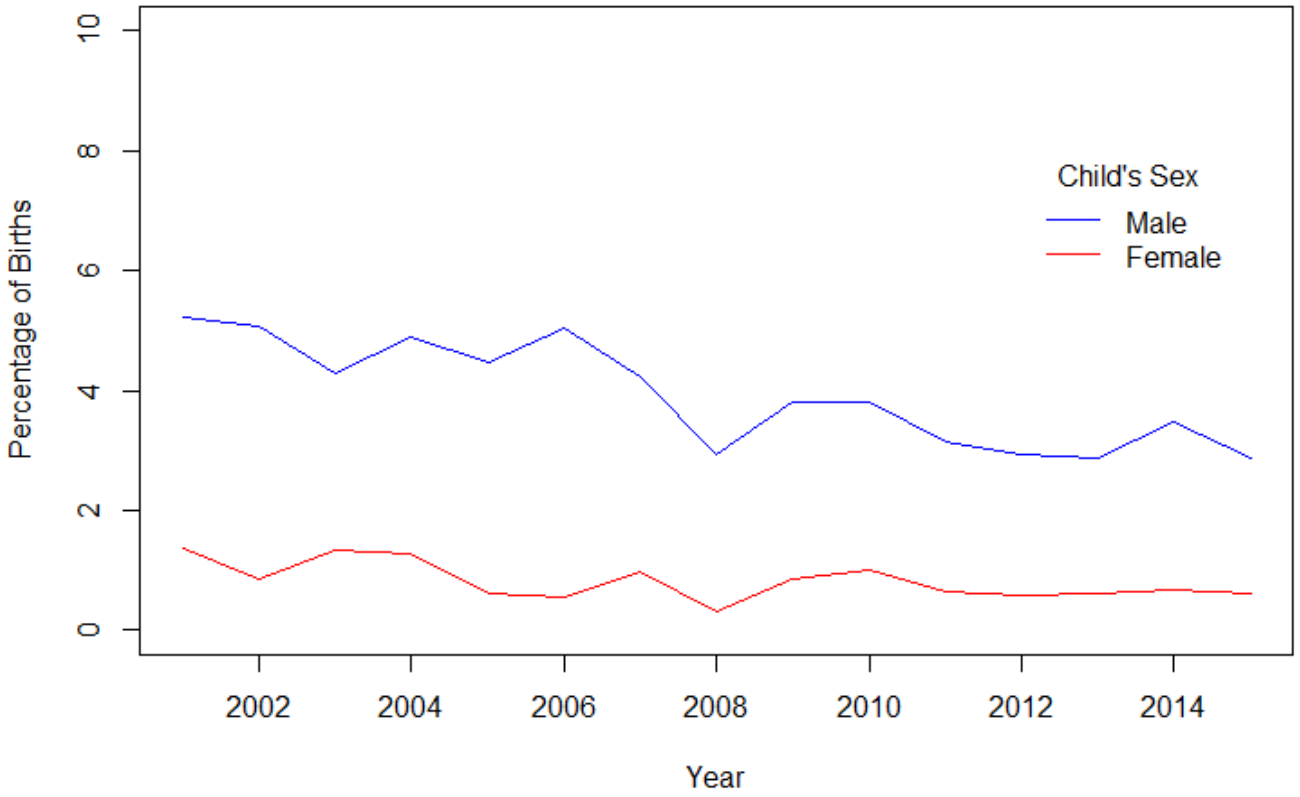
Based on 10% random sample of live births

IHPS Cases in Iowa



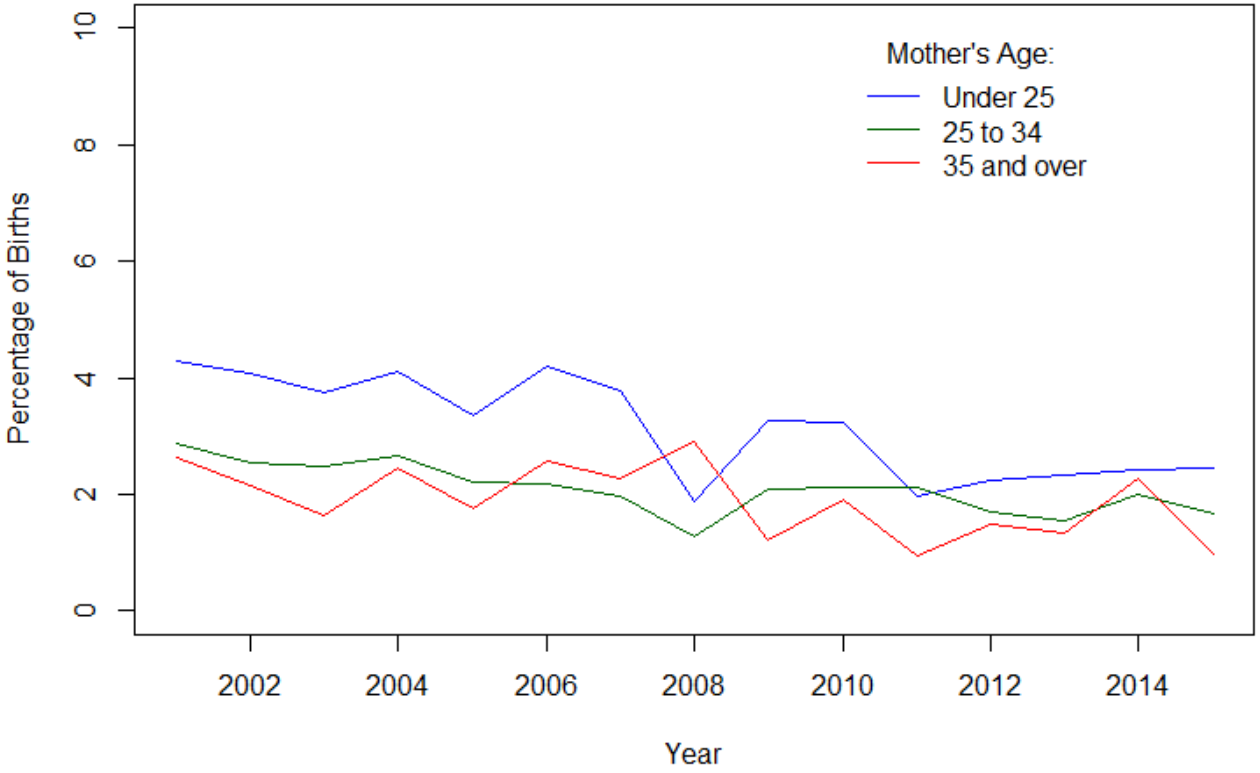
Based on 10% random sample of live births

IHPS Cases in Iowa



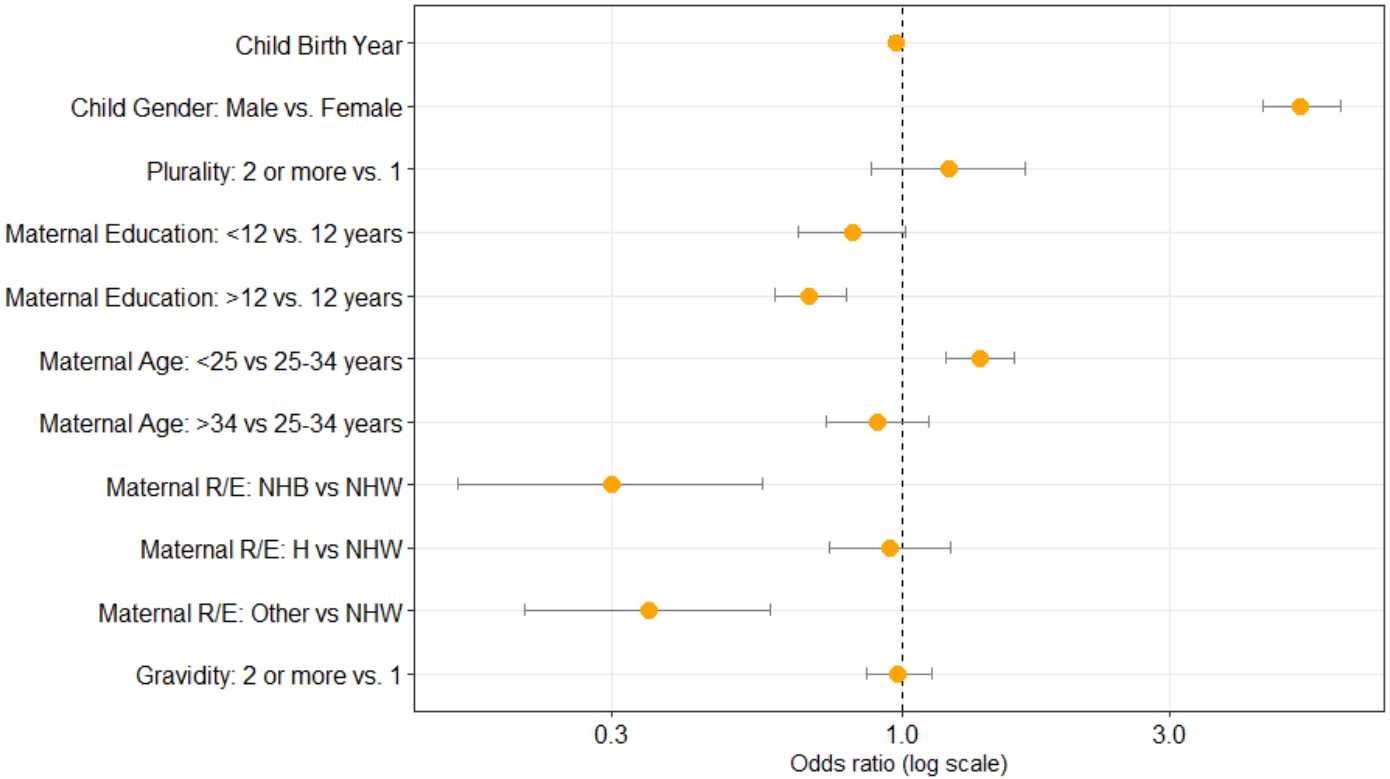
Based on 10% random sample of live births

IHPS Cases in Iowa



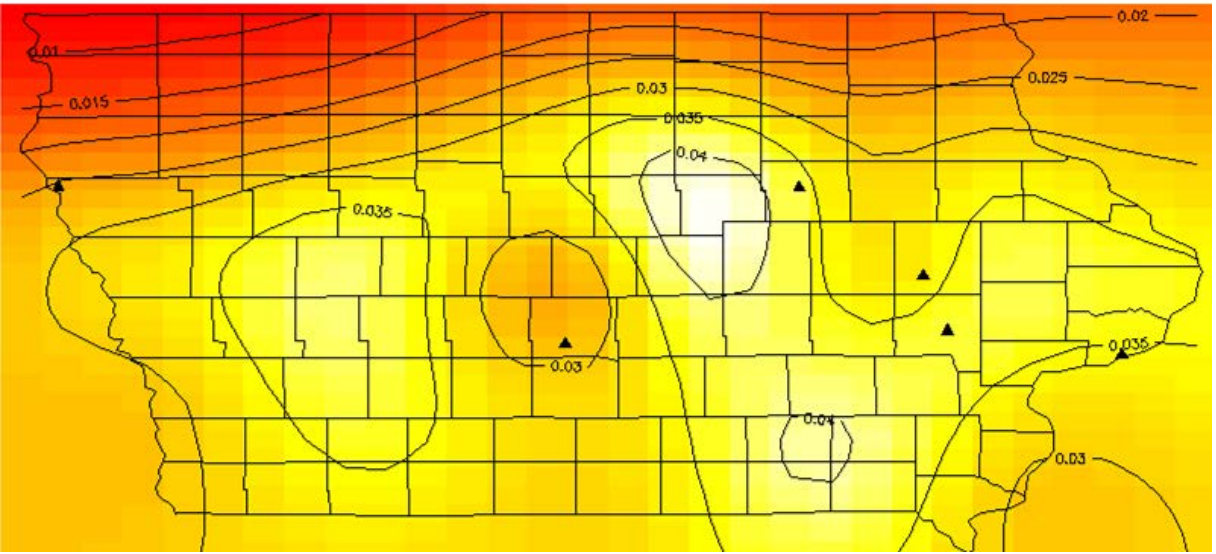
Based on 10% random sample of live births

Adjusted Odds Ratios with 95% Confidence Intervals

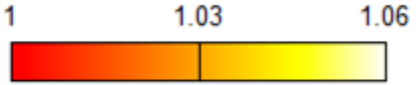


R/E = Race/Ethnicity, NHW = Non-Hispanic White, NHB = Non-Hispanic Black, H = Hispanic

GAM Results



Region	County
North Central	Grundy
South East	Davis, Jefferson, Van Buren, Wapello
West	Audubon



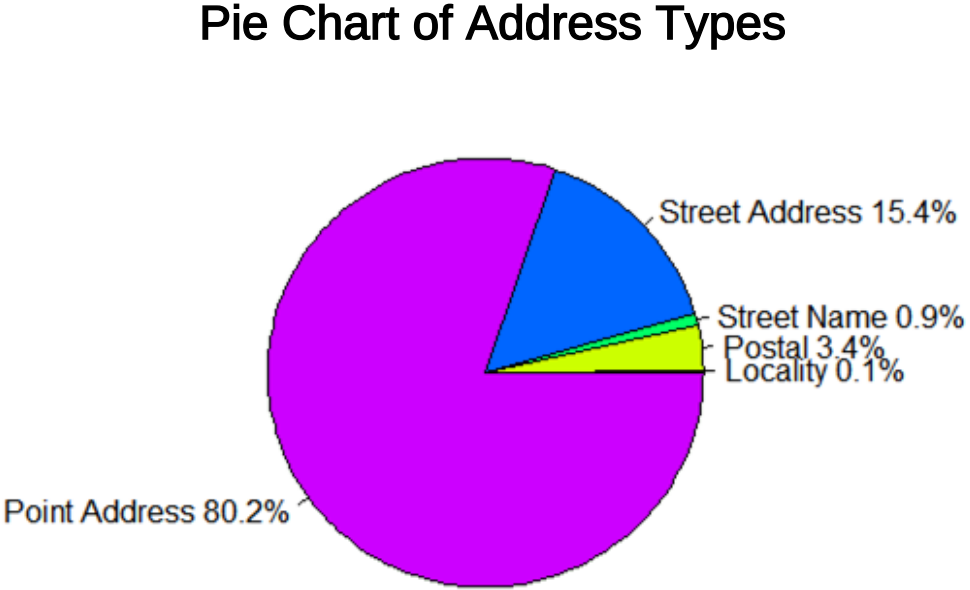
Odds

Limitations

- Missing data from paternal race/ethnicity and paternal age variables
- Some resident addresses coded to zip code centroid (3.5%)
- 10% random sample of controls used instead of full population

Strengths

- Large population-based dataset
- Case diagnoses confirmed by clinical geneticist
- Individual latitude and longitude point locations for most (96.5%) maternal residences



Conclusion

Based on the GAM Analysis

- IHPS cases decreasing linearly over time
- We can predict that Grundy, Wapello, Jefferson, Davis, and Van Buren have the highest odds of infants having IHPS

What may have contributed to the decrease in IHPS over time?

- Public health initiatives
- Surgery being moved from general surgeons to specialty surgeons
- Alternative treatments

What may have contributed to the hotspots?

- Agricultural exposures
- Unrecognized genetic factors

References

- Kapoor, R., Kancherla, V., Cao, Y., et al (2018). Prevalence and descriptive epidemiology of infantile hypertrophic pyloric stenosis in the United States: A multistate, population-based retrospective study, 1999–2010. *Birth Defects Research, 110*(2), 159-169. https://doi.org/10.1002/bdr2.1439
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- El-Gohary, Y., Abdelhafeez, A., Paton, E., et al (2017). Pyloric stenosis: an enigma more than a century after the first successful treatment. *Pediatric Surgery International*, 34, 21-27. doi:10.1007/s00383-017-4196-y
- Jobson, M., & Hall, N. J. (2016). Contemporary management of pyloric stenosis. *Seminars in Pediatric Surgery, 25*(4), 219-224. doi:10.1053/j.sempedsurg.2016.05.004

Thank you for your time!

Any Questions?

Extra Slides: Justification

Correlation and Chi-Square Tests

Correlation test:

- Correlation between Maternal Age and Paternal Age
  - cor = 0.75
  - p-value < 2.2e-16

Chi-Square test:

- Independence between Maternal Race/Ethnicity and Paternal Race/Ethnicity
  - p-value < 2.2e-16

GLM/GAM comparisons (n = 49656)

GLM/GAM	Covariates	Space	Time
1. glm	*		
2. glm		X	
3. glm			X
4. glm	*	X	X
5. gam		X	
6. gam			X
7. gam	*	X	X

	1. glm	2. glm	3. glm	4. glm	5. gam	6. gam	7. gam
1. glm	NA	< 2.2e-16	NA	3.702e-09	NA	NA	5.263e-07
2. glm		NA	NA	< 2.2e-16	6.138e-05	1.026e-05	< 2.2e-16
3. glm			NA	< 2.2e-16	0.0387	0.9924	< 2.2e-16
4. glm				NA	NA	NA	0.0496
5. gam					NA	0.0210	< 2.2e-16
6. gam						NA	< 2.2e-16
7. gam							NA

* Gender, Plurality, Maternal Age, Maternal Education, Gravidity and Maternal Race/Ethnicity

Dropped Data and Unknowns

- Paternal age
  - 4757 missing data
- Maternal Education
  - 231 missing information
- Gravidity
  - 1218
- Maternal Race/Ethnicity
  - 83
- Paternal Race/Ethnicity
  - 9191
- Total Sample Size (49656)

Address Type Distribution

Locality: 64

Point Address: 39833

Postal: 1673

Street Address: 7638

Street Name: 448

Frequency Tables

Sex	Overall	Case - N(%)	Control - N(%)	OR (CI)
Male	25615	949 (3.7%)	24666 (96.3%)	5.16 (4.40, 6.07)
Female (ref)	24041	179 (0.7%)	23862 (99.3%)	

	OR (CI)
Birth Year	0.97 (0.95, 0.98)

Univariate Models

Sex	Overall	Case - N(%)	Control - N(%)	OR (CI)
Male	25615	949 (3.7%)	24666 (96.3%)	5.13 (4.37, 6.02)
Female (ref)	24041	179 (0.7%)	23862 (99.3%)	

	OR (CI)
Birth Year	0.96 (0.94, 0.97)

Plurality	Overall	Case - N(%)	Control - N(%)	OR (CI)
1 (ref)	47971	1085 (2.3%)	46886 (97.7%)	
2 or more	1685	43 (2.6%)	1642 (97.4%)	1.21 (0.88, 1.65)

Univariate Models

Plurality	Overall	Case - N(%)	Control - N(%)	OR (CI)
1 (ref)	47971	1085 (2.3)	46886 (97.7)	
2 or more	1685	43 (2.6)	1642 (97.4)	1.13 (0.83, 1.54)

*Percents may not sum up to or may exceed 100% due to rounding

Maternal Age	Overall	Case - N(%)	Control - N(%)	OR (CI)
< 25	13612	420 (3.1)	13192 (96.9)	1.37 (1.19, 1.58)
25 - 34 (ref)	30241	604 (2.0)	29637 (98.0)	
> 35	5803	104 (1.8)	5699 (98.2)	0.90 (0.73, 1.11)

Univariate Models

Maternal Age	Overall	Case - N(%)	Control - N(%)	OR (CI)
< 25	13612	420 (3.1)	13192 (96.9)	1.56 (1.38, 1.77)
25 - 34 (ref)	30241	604 (2.0)	29637 (98.0)	
> 35	5803	104 (1.8)	5699 (98.2)	0.90 (0.73, 1.10)

Maternal Education	Overall	Case - N(%)	Control - N(%)	OR (CI)
Less Than High School	5315	135 (2.5)	5180 (97.5)	0.81 (0.65, 1.01)
High School (ref)	10007	322 (3.2)	9685 (96.8)	
College	34334	671 (2.0)	33663 (98.0)	0.68 (0.59, 0.79)

Maternal Education	Overall	Case - N(%)	Control - N(%)	OR (CI)
Less Than High School	5315	135 (2.5)	5180 (97.5)	0.78 (0.64, 0.96)
High School (ref)	10007	322 (3.2)	9685 (96.8)	
College	34334	671 (2.0)	33663 (98.0)	0.60 (0.52, 0.69)

Univariate Models

Gravidity	Overall	Case - N(%)	Control - N(%)	OR (CI)
1 (ref)	15056	370 (2.5)	14686 (97.5)	
2 or more	34600	758 (2.2)	33842 (97.8)	0.98 (0.86, 1.13)

Univariate Models

Gravidity	Overall	Case - N(%)	Control - N(%)	OR (CI)
1 (ref)	15056	370 (2.5)	14686 (97.5)	
2 or more	34600	758 (2.2)	33842 (97.8)	0.89 (0.78, 1.01)

Maternal Race/Ethnicity	Overall	Case - N(%)	Control - N(%)	OR (CI)
Non-Hispanic White (ref)	43021	1017 (2.4)	42004 (97.6)	
Non-Hispanic Black	1238	10 (0.8)	1228 (99.2)	0.30 (0.16, 0.56)
Hispanic	3437	85 (2.5)	3352 (97.5)	0.95 (0.74, 1.22)
Other	1960	16 (0.8)	1944 (99.2)	0.35 (0.21, 0.58)

Maternal Race/Ethnicity	Overall	Case - N(%)	Control - N(%)	OR (CI)
Non-Hispanic White (ref)	43021	1017 (2.4)	42004 (97.6)	
Non-Hispanic Black	1238	10 (0.8)	1228 (99.2)	0.34 (0.18, 0.63)
Hispanic	3437	85 (2.5)	3352 (97.5)	1.05 (0.84, 1.31)
Other	1960	16 (0.8)	1944 (99.2)	0.34 (0.21, 0.56)

Univariate Models