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Descriptive Epidemiology of infantile hypertrophic pyloric stenosis in United States

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PhD, Microbiology

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2005

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An abstract of

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Abstract

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Background: Infantile hypertrophic pyloric stenosis, commonly referred to as pyloric stenosis (PS) is characterized by muscular hypertrophy of the pyloric sphincter, causing obstruction of the gastric outlet in the newborns. The epidemiology and etiology of PS is not well-understood, with previous reports differing on prevalence estimates and characteristics associated with PS. The aim of this study was to conduct a comprehensive, population-based investigation of descriptive epidemiology of PS in the United States (U.S.).

Methods: Population-based data for cases with PS (n=16,320), delivered during 1999-2005 and enumerated from 11 U.S. birth defects surveillance programs, along with data for all live births (n=8,390,584) within the same time period and catchment areas were used to estimate PS prevalence and associations with selected infant and parental characteristics. Adjusted prevalence odds ratios (aPORs) and 95% confidence intervals (CIs) were estimated using multivariable logistic regression analyses for all cases combined and for isolated cases (without other major birth defects).

Results: The prevalence (per 10,000 live births) for all PS cases combined (n=16,320) was 19.45 (95% CI=19.15, 19.75); the prevalence for isolated cases (n=14,548; 89% of total) was 17.33. After adjusting for selected infant and parental characteristics, male sex, preterm gestation (<37 weeks), and young parental age (<20 years) were observed to be associated with an increased risk, whereas low birth weight (<2500 grams), higher maternal education (>high school), and non-white race/ethnicity were associated with a reduced risk among all cases combined and isolated cases. Subgroup analyses by sex for all PS cases yielded similar results, and also showed a higher prevalence of low birth weight and low gestational age among females compared to males.

Conclusions: This is the first large, multi-state, population-based study in the US on the prevalence of PS and associated infant and parental characteristics, including paternal race and ethnicity. Our findings offer an improved understanding of the prevalence of PS and descriptive characteristics of this defect in a large, well-described population, providing a continuum of information between 1999 and 2010, and serving as a sampling frame for future detailed investigations of infant and parental environmental and genetic risk factors for PS.

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INTRODUCTION

Infantile hypertrophic pyloric stenosis, commonly referred to as pyloric stenosis (PS), is a condition characterized by an acquired narrowing of the pylorus in infants. The pylorus, consisting of pyloric antrum and the pyloric muscle, connects the stomach to duodenum. PS is the result of progressive hypertrophy of the pyloric muscle, which causes obstruction of the gastric outlet of pylorus (1). This obstruction produces forceful projectile post-prandial vomiting, which is usually non-bilious. PS usually presents from the first two-12 weeks of life, typically, in a previously healthy infant; peak prevalence occurs during the fifth week of life (2).

The exact cause of PS in infancy is unknown. A recent theory of causation proposed by Rogers (2006) posits that hyperacidity is a precursor to PS. Because PS infants are hypersecretors of acid, this hyperacidity becomes dangerously high due to failure of negative feedback between gastrin and gastric acidity within the first few weeks of life. Acid entering the duodenum causes contraction of the pyloric sphincter, and hyperacidity naturally leads to repeated pyloric sphincter contractions and sphincter hypertrophy. The repeated feeding of the vomiting PS infant produces feed-related sphincter contraction and plays a significant role in pathogenesis (3).

PS affects about 2-50 per 10,000 live births globally (4), is more common among males than females (5-7), and predominantly occurs (~93 %) as an isolated phenotype (5,6). Left untreated, PS can lead to dehydration, weight loss, metabolic alkalosis, and death in severe cases (8). Surgical treatment, using the Ramstedt pyloromyotomy technique, is the standard method of treatment for PS and generally has a good prognosis resulting in fatality rate of usually less than 1% (9, 10). Nonetheless, children that

received surgery for PS may suffer long-term gastrointestinal problems, with a greater risk of reporting chronic abdominal pain at long-term follow-up after surgery, compared to their siblings without a history of PS (11). Additionally, children with PS are likely to experience interference with activities and to seek medical attention (11), leading to hospitalizations, with an average charge of approximately US$13,000 per person per year (12).

Epidemiology

The occurrence of PS has been reported to range from 20 to 50 per 10,000 live births in the U.S. and Europe (9), but less so in other parts of the world (4). Reported prevalence estimates for PS have differed considerably by region and time (4, 13). Studies from the United Kingdom and Ireland reported a significant increase in PS prevalence over the past three decades (14, 15), whereas studies from Scotland (16), Sweden (17), Denmark (18), and U.S. (5,7) reported significant decreases during a similar time frame. We calculated the prevalence of PS using aggregate data reported by the National Birth Defects Prevention Network (NBDPN), based on ongoing surveillance in 31 states in the U.S. during the years 2006-2010. From our estimation, we noted that the most recent prevalence of PS was 19.0/10,000 live births (19). Additional studies from the U.S. report higher prevalence among infants born to non-Hispanic white mothers compared to those born to Hispanics, non-Hispanic Black, Asian, and Native American mothers (5,7, 20, 21). Reduced risk for PS has also been observed among most births or offspring of parents who are both non-white, as well as for those births of parents with mixed race-ethnicity (22).

Etiology

The etiology of PS is suggested to be multi-factorial, including environmental and genetic factors (23).

Environmental factors

Infant Factors: The occurrence of PS is significantly higher among males compared to females (4-5:1) (9, 21); however, there is no clear explanation for the male predominance (1). In addition, males show a higher rate of preterm births and higher rate of low birth weight compared to females, indicating intrauterine fetal growth restriction among male cases and differences in pathogenesis of PS in males and females (23, 24). Evidence for an association of PS with birth weight remains unclear. A large population based cohort study on PS cases born during 1983-1990 in New York State found a decreased risk for PS among infants with birth weights <1500 grams, but no difference in risk among infants with birth weights > 4250 grams, compared to infants in the referent group with birth weights from 2500-4250 grams (6). In contrast, a study of PS cases born during 1999-2002 in Texas reported reduced risk among infants with birth weights >4500 grams, but no difference in risk among infants with birth weights <1500 grams compared to those with birth weights from 3000-3499 grams (7).

There is inconsistent evidence regarding the relation between preterm birth and PS. Some studies reported positive association (23, 25, 26), whereas others reported no associations (7, 9). The increase in proportion of preterm infants with PS could be attributed to the increased survival of premature infants over the years due to improved medical support. The age at presentation of PS in preterm infants is less clearly defined

compared to age at presentation in full-term infants, typically the first two to 12 weeks of life. It has been suggested that preterm infants may present with PS at a later chronological age than term infants, because symptom onset may be more closely related to maturity as dated from conception than from birth or to some event experienced later by prematurely-born than full-term infants (9).

The occurrence of PS has also been reported to vary by season of birth; however, the evidence is inconclusive. Studies have shown a peak occurrence during summer (6, 27), spring-autumn (28), winter (29), or no influence due to season of birth (30). These differences may arise from inconsistencies in defining the months included in a season.

Among other infant factors, exposure to erythromycin and azithromycin in infants in the first two weeks of life has been reported to be associated with an increased risk of PS in some (31, 32), but not all studies (33). A higher occurrence of PS also has been described in children that were exposed to erythromycin during a pertussis epidemic (34).

The parallel decline in the incidence of PS and sudden infant death syndrome (SIDS) in Sweden during the 1990s led to the hypothesis that placing the child to sleep in a prone position is a shared risk factor for these two different conditions (17); however, subsequent studies indicated that, after the implementation of recommendations to put the child to sleep in supine position in various European countries, PS occurrence did not decline as expected (4, 16). Additionally, caesarean delivery has been associated with increased risk of PS (23, 25). It has been suggested that disturbances in the gut flora of infants born by caesarean section might be involved although the mechanism for how this could trigger the development of PS is unclear. Also, the delayed start of breast-feeding

associated with caesarean delivery could increase the risk of PS, as breast-feeding has been suggested to have a protective effect (25, 35, 36).

Maternal Factors: Maternal age has been associated with PS, with some reports showing women who were <20 years of age during their pregnancy had up to 40% higher risk of giving birth to babies with PS compared to mothers aged 25-30 years (13, 21, 23, 25). Associations between parity and PS have been reported with the risk of PS being highest among first-born infants and declining with increasing birth order (37, 23, 25); however, Krogh et al., (2012) reported no significant association between maternal age and PS after adjustment for birth order (23). PS has been reported to be inversely associated with maternal education, with women who have more than a high school education being less likely to deliver an infant with PS (6,7, 21).

Maternal smoking during pregnancy may contribute to the development of PS (21, 23, 25). A large Danish birth cohort study reported an increased risk of PS among infants of smoking mothers compared to those born to mothers who did not smoke, after adjustment for maternal age, marital status, sex of the child and birth order (38, 39).

Several other maternal factors have been examined in single studies. A population-based cohort study reported an increasing dose-response relation between pre-pregnancy body mass index (BMI) and risk of PS, after controlling for maternal age, race/ethnicity, education, smoking, marital status, and nativity (40). Findings from a recent population-based case-control study in Hungary suggested that cases with PS had a higher proportion of mothers diagnosed with hyperthyroidism or who used oral nalidixic acid pre-pregnancy, compared to control mothers of offspring without any birth defect

(41). Another recent study showed a dose-response relationship between pounds of pesticide used in maternal county of residence and occurrence of PS. Further subset analyses showed that the positive association between PS and county pesticide use was more likely for male infants from mothers who were white, aged 20-35 years, had high school or lesser education and smoked (21).

Reported associations between maternal use of macrolide antibiotics, specifically erythromycin use late in pregnancy or two weeks after pregnancy, are mixed with some studies reporting an increased risk of PS (42, 32, 38) and others reporting no association (43, 44).

Paternal Factors: Few studies have examined associations between paternal risk factors and PS. Studies of associations between paternal age and PS have yielded inconsistent results (47, 48). A population-based birth defects study in California found higher risk of PS among offspring of fathers <29 years of age, with risk declining by 7% for every five-year increase in paternal age, and suggested to be attributable to an interaction of genetic factors with behavioral factors, such as the use of alcohol and recreational drugs (48). Conversely, a study using data from the British Columbia Health Surveillance registry did not report an increased risk of PS among infants of fathers 20-24 years of age or <20 years of age, relative to those 25-29 years of age (47). Association of other paternal factors, such as race/ethnicity and education with PS have not been reported.

Genetic factors

PS presents most often as an isolated phenotype, with more than 90% of cases occurring without other major structural birth defects; however, the occurrence of PS as part of genetic syndromes, suggests that genetic factors play a role in its etiology (45). Familial aggregation may occur in isolated PS, and there is a high concordance in monozygotic twins (13). A large Danish cohort study reported a 20-fold increase of PS among siblings of children affected with PS, and a six-fold increase in risk among monozygotic compared with dizygotic twins (49).

Given the strong familial tendency, attempts have been made to identify genetic loci for PS. Recent genome-wide linkage analyses have identified mutations on chromosomes 2q, 3p, 5q, 7p, 11q, 16p and Xq that may contribute to PS (50, 51, 52). Some of these regions harbor interesting candidate genes including glucagon-like peptide 2, nitric oxide synthase 1, motilin, and neuropeptide Y, which may help regulate smooth muscle tone and gastric motility (49). Other genes, such as those located on the Xq chromosome, may play a role in the male predominance of the disease.

In summary, the differing reports of prevalence and characteristics associated with PS suggest the need for a large study among a racially/ethnically diverse population with cases enumerated using systematic population-based surveillance methods and population-based data on live births to serve as a comparison population. The aim of this study was to conduct a comprehensive investigation of the descriptive epidemiology of PS, using data from 11 population-based birth defects surveillance programs in the U.S., covering over eight million births from 1999 through 2005. We also wanted to compare the prevalence estimates for the 11 States for the years 1999-2005 with the overall prevalence that we calculated for the 31 States from the most recent NBDPN report from

the years 2006-2010, and to see if there were any important deviations in the prevalence of PS overtime. Results from this study will offer an improved understanding of the prevalence of PS and descriptive characteristics of this defect in a large, well-described population that can serve as a sampling frame for future detailed investigations of infant and parental environmental and genetic risk factors for PS.

METHODS

Data source

The Pyloric Stenosis Work Group of the National Birth Defects Prevention Network (NBDPN) Data Committee sent out a call for collaboration to representatives from interested birth defect surveillance programs in the U.S. to participate in a population-based study of the descriptive epidemiology of PS. Only the programs that identified birth defects diagnosed among live births throughout the first year of life and those that could provide data for a subset of the years chosen for the study, i.e. from January 1, 1999 through December 31, 2005, were invited to participate. Infant data requested for PS cases were sex, month of delivery, year of delivery, gestational age, birth weight, plurality, additional defects diagnosed within first year of life, date of surgery (month and year only), vital status at 1 year of age. Maternal data requested were age at delivery, race and ethnicity, education at delivery, month and year of last menstrual period, pregnancy history (live births other than this birth now living; live births other than this birth now deceased; other terminations before 20 weeks; other terminations after 20 weeks); paternal data requested were age at delivery and race and ethnicity.

The Iowa Center for Birth Defects Research and Prevention (CBDRP), funded by the Centers for Disease Control and Prevention (CDC) served as the coordinating center for the project. Eleven NBDPN sites contributed data to the current study. Participating sites were the population-based birth defect surveillance programs in Arizona (AZ), Arkansas (AK), Colorado (CO), Florida (FL), Hawaii (HI), Iowa (IA), New York State (NY), North Carolina (NC), Oklahoma (OK), Texas (TX), and the CDC in Metropolitan

Atlanta, Georgia (GA). Data were sent from these states to the Iowa CBDRP electronically via secure file transfer or on electronic media via express mail. Data were provided for the years 1999-2005 from all the states except for Arizona (1999, 2000, 2003, and 2004), and North Carolina, (2003-2005), representing around 35% of the U.S. population.

Case enumeration and classification

Cases enumerated using the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) diagnosis and procedure code 750.5 or the CDC/British Pediatric Association code 750.51 for diagnosis of congenital hypertrophic pyloric stenosis (includes constriction, hypertrophy, spasm, stenosis and stricture of pylorus) were included in the study. Cases were classified as 'isolated' if the case did not have an additional, unrelated major structural birth defect. Cases that were diagnosed with a chromosomal or monogenic etiology (e.g. aneuploidy, chromosomal deletion syndrome) or at least one other major structural birth defect in a different organ system (e.g., spina bifida) were classified as non-isolated cases.

Controls

Birth registry vital records for each of the years included in the study period were used to retrieve information on the aforementioned infant, maternal and paternal characteristics for all the live births without PS.

Exposure Variables

Cases and controls enumerated were linked with birth certificate data from each participating state, and information on infant (sex, birth weight, gestational age, season and year of birth, plurality), maternal (age at delivery, race/ethnicity, education, parity, calculated as sum of number of previous live and non-live births) and paternal (age at delivery, race/ethnicity) characteristics were extracted.

Statistical analysis

Data were pooled across the 11 surveillance programs, and prevalence for PS per 10,000 live births was estimated for the birth period 1999 through 2005, using total number of cases in the numerator and total live births (including the cases) in the denominator. The 95% confidence interval around a prevalence estimate was determined using Poisson approximation method, per the following equation:

Lower limit = exp (log (pr) - 1.96*se)

Upper limit = exp (log(pr) + 1.96*se)

where pr = estimated prevalence, and

se (standard error for prevalence estimate) = 1/sqrt (no. of cases)

A test for trend to determine the difference in PS prevalence by phenotype (isolated and multiple cases combined, isolated only, and multiple only) and by sex (males, females) during the study period, was performed using Kendall Tau-b correlation test. Total live births delivered from January 1, 1999 through December 31, 2005 without PS were used as controls for comparison with cases.

Cases and controls were compared for selected infant, maternal, and paternal characteristics using the Pearson Chi square test Infant characteristics were sex (male,

female), gestational age at delivery (<37, ≥37 weeks), birth weight (<2500, 2500-3999, ≥4000 grams), season of birth (Winter if born during January through March, Spring if born during April through June, Summer if born during July through September, and Fall if born during October through December), plurality (singleton, twin or more), maternal and paternal age (<20, 20-34, ≥35 years), maternal and paternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, others), maternal education at delivery (<12, 12, 13-15, ≥16 years), and state of birth, using Pearson Chi square test (Table 1).

Both crude and adjusted prevalence odds ratios (PORs) and corresponding 95% confidence intervals (CIs) were estimated to investigate associations between PS and the aforementioned characteristics using logistic regression analysis. Multivariate analyses were performed using three approaches: Backward selection method, dropping covariates that were least significant (P value < 0.05), forward selection method, adding covariates that were most significant, and *a priori* model where covariates were selected if shown to be associated with PS in previous studies. Multicollinearity was examined for each model. Analyses were conducted separately for all cases combined (hereafter referred to as combined cases), isolated cases, non-isolated cases, male cases and female cases. All statistical analyses were conducted using SAS (version 9.4; SAS Institute, Cary, NC). The study was approved by the institutional review boards at each participating site, as well as those at the University of Iowa and Emory University.

RESULTS

Overall, a total of 16,320 PS cases and 8,390,584 live births were identified from the participating states during the seven-year study period. Of the PS cases, 89% (n=14,548) were isolated cases, and 82% were male infants, while 18% were female infants. A descriptive analysis of the infant, maternal, and paternal characteristics included in the study is shown in Table 1. Overall, there were significant differences between cases and controls with respect to the selected infant, maternal, and paternal characteristics (*P* values <0.05) except for season of birth (*P* value=0.26) and parity (*P* value=0.88); however, the estimates for parity were based on data available from only two of the participating states (North Carolina and Georgia). The most common birth defects found among multiple cases were atrial septal defects, ventricular septal defects, patent ductus arteriosis, and hypospadias.

The overall prevalence estimate (per 10,000 live births) for all PS combined was 19.45 (95% CI=19.15, 19.75), whereas the prevalence for isolated was 17.33 (95% CI=17.06, 17.62). The overall prevalence (per 10,000 live births) among males was 31.4 per 10,000 live births while that for females was 7.4 per 10,000 live births (Table 2). The prevalence was higher among infants that were male, had birth weight of 2500-3999 grams, had gestational age of less than 37 weeks, were born with multiple births (twin or higher), were born to parents that were non-Hispanic whites, less than 20 years of age at the time of delivery and mothers who had less than a high school education (Table 2).

The prevalence of PS by case categories in nine states (excluding AZ and NC, for which data was not available for the entire study period) did not differ significantly between the years of birth (*P* value=0.33, combined; 0.14, isolated) and was the lowest

during the year 2003 for combined and isolated cases, while it was highest during the year 2004 for all case categories (Figure 1). Likewise, the prevalence of PS by sex remained unchanged between the years of birth (*P* value=0.33, all combined male cases, isolated male cases, isolated female cases; 0.51, all combined females) (Figure 2).

Of all eleven states that contributed data for this study, Hawaii had the lowest prevalence (per 10,000 live births) (5.5; 95% CI=4.5, 7.0), whereas Iowa had the highest prevalence (31.6; 95% CI=29.6, 33.8). However, these estimates did not include data for all the years from two of the states (Arizona, data not available for 2001, 2002 and 2005; North Carolina, data not available for years 1999-2002) (Table 2). Sensitivity analysis performed after exclusion of these two states showed the same results as the main analysis, except that birth weight was not found to have a significant association with PS (*P* value=0.08) (Supplementary Table 1).

The unadjusted POR for males was about four-times that of females under all case categories (Table 3). The infants with birth weight less than 2500 g were at a lower risk among combined cases (cPOR=0.70, 95% CI=0.67, 0.75) and isolated cases (cPOR=0.60, 95% CI=0.57, 0.65), compared with the referent group who weighed 2500-3999 grams; however, no decrease in PS risk was observed for infants with birth weight >4000 grams, compared to the referent group for any of the case categories. Similarly, the risk of PS among infants with gestational age <37 weeks was slightly increased for combined cases (cPOR=1.16; 95% CI=1.11, 1.22), and near unity for isolated cases (cPOR=1.05, 95% CI=1.0, 1.11), compared to the infants with gestational age of ≥37 weeks. The season of birth did not show a significant association with PS (*P* value= 0.26), and no difference in risk for “winter”, “fall” and “summer” births compared to the referent “spring” births.

Multiple (twin and higher) births were at a slightly increased risk compared to singleton births (Table 3).

Maternal age <20 years at the time of delivery was associated with a higher risk (cPOR=1.33, 95% CI=1.28, 1.39) of PS, while maternal age of 35 years or older was associated with lower risk (cPOR=0.78, 95% CI=0.75, 0.82), compared to 20-34 years of age. Infants born to non-Hispanic black, Hispanic, Asians, Pacific Islanders, or Native American mothers had a lower risk compared to those born to non-Hispanic white mothers. Higher maternal education was associated with a significantly lower risk of PS. Compared to high school graduates (12 years of education), mothers with some college degree (13-15 years of education) or higher (16 or more years) education were less likely to have infants with PS. Paternal age <20 years at the time of delivery was associated with a higher risk, and non-White paternal race/ethnicity was associated with reduced risk of PS, compared to respective referent groups (Table 3). Using Georgia as the reference State (prevalence=13.6 cases/10,000 live births, 95% CI= 12.5, 14.9), only two states, Hawaii and Arkansas had a lower risk, while the remaining states had a higher risk of PS (Table 3). Sensitivity analysis performed after exclusion of these two states showed the same results as the main analysis with minimal changes in the estimates (Supplementary Table 1).

Sub-group analyses for all male cases, and all female cases were similar to those of the main analyses. However female cases were more likely to have low birth weight and preterm birth compared to the male cases (Table 4).

The PORs were adjusted for all variables shown in Table 1 except for parity and year of birth, using the variable formats shown in Table 5. In the full model, male sex,

low gestational weight, multiple births, and younger parental age were associated with an increased risk of PS, after adjusting for all other co-factors (except state of birth). On the other hand, birth weight less than 2500 grams or more than 4000 grams, higher maternal education attainment, and non-White race/ethnicity were associated with a reduced risk of PS. The reduced model, using backward elimination, produced the same results. An alternate reduced model, using forward selection approach, produced similar results, after adjusting for all variables except maternal and paternal race/ethnicity. For the *a priori* model, paternal characteristics were not included due to a large proportion of missing data, and gestational age was not included as there was a strong correlation between birth weight and gestational age (*P* value < 0.0001). As birth weight can be measured more accurately compared to gestational age, we decided to exclude the latter from our *a priori* model. Findings from *a priori* model were consistent with those from the other aforementioned models. Multi-collinearity was not detected in any of these models (Table 5).

DISCUSSION

The overall prevalence of PS during the seven-year study period in this multi-state population-based study was 19.4 cases per 10,000 live births. Approximately, 90% of the cases were isolated. Both crude and adjusted analyses supported a higher prevalence of PS among males, preterm (gestational age <37 weeks) and multiple births infants, and infants born to parents <20 years old and whose mothers had <high school education at delivery. A reduced prevalence was observed among low birth weight (<2500 grams) infants and infants born to non-white parents. No significant associations were observed with season of birth or parity.

Our overall prevalence estimates for the 11 States for the years 1999-2005 were similar to overall prevalence that we calculated for the 31 States from the most recent NBDPN report from the years 2006-2010. Comparison of our state-wise estimates with the most recent NBDPN estimates, showed that prevalence of PS has not changed considerably over the years for most of the states, but has increased by 2.3- and 1.5-folds for Arkansas and Oklahoma, respectively (3).

The male predominance of PS was consistent with previous population-based studies from the U.S. (5-7) and European countries (23, 25), which reported a four- to five-fold excess of PS among males. The significantly higher risk observed among preterm infants (<37 weeks), when adjusting for birth weight and other variables, was consistent with the all of the previous studies (6, 23, 25), as was the higher risk among cases of multiple births (5, 53).

Consistent with some of previous studies, an increased risk of PS was observed among infants born to mothers <20 years of age at delivery (13, 25) and a lower risk

among infants born to older mothers (5-7, 23). Our finding regarding association of younger paternal age (<20 year) with higher prevalence of PS were similar to those of a population-based study from Texas that showed a higher prevalence of PS among offspring of men < 20 years of age, after adjustment for maternal age, maternal race/ethnicity, and paternal race/ethnicity (55). These findings were also supported by results of the California Birth Defects study that reported paternal age <29 years to be associated with an increased risk of PS compared to paternal ages from 38-42 years (48), but contradicted those reported by the British Columbia Health Surveillance Registry that found no association between PS and paternal age when adjusted for maternal age and paternal race/ethnicity (47). The lower risk of PS among infants born to mothers with >high school education at delivery was supported by all of the previous studies (5, 7).

Our findings of association of PS with birth weight were not directly comparable to previous studies. We found a reduced risk among infants with a birth weight <2500 grams. However, some of the previous studies reported a modest increase in PS among infant with birth weights 1500-2499 grams (aPOR=1.05 and aPOR=1.12), but a decreased risk in PS among infants with birth weights <1500 grams (5, 6). These differences could be explained by the use of more granular categories of birth weight (<1500, 1500-2499, 2500-4250, ≥ 2450 grams) and also different referent groups (3000-3499 grams; 2500-4250 grams) than those used in our study. Additional studies reported an inverse association (23) or no association (25) between birth weight for gestational age and PS.

Our findings regarding differences in PS prevalence by maternal race/ethnicity were similar to those reported in previous studies. Other population-based, U.S. studies

examining PS prevalence from New York, California, and Texas, confirm our findings of lower prevalence among infants of non-Hispanic Black, Asian, and Hispanic mothers compared to those of non-Hispanic white mothers (5-7). Moreover, sub-group analyses of Hispanic and Asian infants in Texas showed a reduced risk of PS among infants with foreign-born mothers but not among those U.S.-born mothers. These findings could be attributed to differences in frequency of behavioral risk factors for PS, such as breastfeeding, or differences in frequency of ascertainment of mild cases of PS by race/ethnicity or nativity (7). The association between maternal place of birth and PS among infants of different racial/ethnic groups could not be determined in our study due to lack of information on nativity. The results from our study showed a lower risk among infants of non-white fathers, but there are no previous studies that have examined association between paternal race/ethnicity and PS. The lack of association between season of birth and PS in our study was consistent with some studies (30, 54), but not others which reported a peak occurrence during summer months (6, 27).

The lack of association between parity and PS in our analysis of limited data available from two states was consistent with some (7) but not with most other studies that found birth order of 2 or more to be associated with reduced risk compared to first born (5,6,25).

Our study has several strengths. This was the first multi-state, population-based study of PS in the U.S., using a large sample size of over 8 million infants representing 35% of the U.S. population. Previous studies on PS prevalence have focused on single states (New York, Texas, California). We were able to include all births with PS, using systematic methods of case ascertainment, with information on additional birth defects.

By excluding other defects diagnosed among cases, we estimated prevalence for isolated cases, in additional to all cases combined. Our study sample also consisted of racially/ethnically and demographically heterogeneous population, which improved representativeness of our study findings for the general U.S. population. Additionally, this is the first study examining the association between paternal race/ethnicity and PS.

A limitation of our study is that data obtained from birth records may not always be reliable and temporal variations occur in information collected on birth certificates. Additionally, the study was limited by analyses of only the demographic factors, with no data on other pre-conception and prenatal exposures, which may have given us valuable information on potentially important risk factors, such as smoking, history of chronic diseases, and medication use.

In conclusion, the findings from our descriptive study suggest that the risk of PS is associated with several infant and parental characteristics. Our study focused on major demographic variables to identify PS prevalence stratified by important infant and maternal characteristics. Our findings offer an improved understanding of the prevalence of PS and descriptive characteristics of this defect in a large, well-described population, providing a continuum of information between 1999 and 2010, and serving as a sampling frame for future detailed investigations of infant and parental environmental and genetic risk factors for PS.

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Table 1. Infant, maternal and paternal characteristics of Pyloric Stenosis cases and controls born between 1999-2005

Characteristics	All live Births (N= 8390584) n (%)	Controls (N=8374264) n (%)	All Cases (N=16320) n (%)	Chi sq[e] (*P* value)	Isolated Cases (N=14548) n (%)	Chi sq[f] (*P* value)	Non-isolated Cases (N=1772) n (%)	Chi sq[g] (*P* value)
Infant								
Sex								
Male	4298604 (51.23)	4285368 (51.17)	13236(81.66)	< 0.0001	11818 (81.84)	< 0.0001	1418 (80.34	< 0.0001
Female	4091779 (48.77)	4088809 (48.83)	2970 (18.33)		2623 (18.16)		347 (19.66)	
Unknown	201	87	114		107		7	
Birth weight (grams)								
< 2500	935890 (11.17)	934556 (11.17)	1334 (8.23)	< 0.0001	1025 (7.10)	< 0.0001	309 (17.51)	< 0.0001
2500 - 3999	6737670 (80.41)	6724196 (80.40)	13474 (83.13)		12165 (84.22)		1309 (74.16)	
≥ 4000	705690 (8.42)	704289 (8.42)	1401 (8.64)		1254 (8.68)		147 (8.33)	
Unknown	11334	11223	111		104		7	
Gestational age (weeks)								
< 37	863739 (10.29)	861829 (10.29)	1910 (11.70)	< 0.0001	1551 (10.66)	< 0.0001	359 (20.26)	< 0.0001
≥ 37	7481029 (89.16)	7466849 (89.16)	14180 (86.89)		12788 (87.90)		1392(78.56)	
Unknown	45816	45586	230		209		21	
Year of Birth								
1999	1126509 (13.63)	1124424 (13.63)	2085 (12.86)	< 0.0001	1860 (12.88)	< 0.0001	225 (12.47)	0.0004
2000	1156938 (13.99)	1154706 (13.99)	2232 (13.77)		2021 (13.99)		211 (11.95)	
2001	1067719 (12.91)	1065632 (12.92)	2087 (12.88)		1860 (12.88)		227 (12.86)	
2002	1073771 (12.99)	1071752 (12.99)	2019 (12.46)		1782 (12.34)		227 (13.43)	
2003	1300786 (15.73)	1298410 (15.74)	2376 (14.61)		2119 (14.67)		257 (14.56)	
2004	1313280 (15.89)	1310412 (15.88)	2868 (17.69)		2550 (25.50)		318 (18.02)	

Characteristics	All live Births (N= 8390584) n (%)	Controls (N=8374264) n (%)	All Cases (N=16320) n (%)	Chi sq[e] (*P* value)	Isolated Cases (N=14548) n (%)	Chi sq[f] (*P* value)	Non-isolated Cases (N=1772) n (%)	Chi sq[g] (*P* value)
2005	1228299 (14.86)	1225757 (14.86)	2542 (15.68)		2252 (15.59)		290 (16.43)	
Unknown	123282	123171	111		104		7	
Season of birth								
Winter	1988318 (24.05)	1984484 (24.05)	3934 (23.75)	0.26	3424 (23.79)	0.5	410 (23.48)	0.44
Spring	2016956 (24.40)	2012977 (24.40)	3979 (24.65)		3538 (24.58)		441 (25.26)	
Summer	2174503 (26.30)	2170169 (26.30)	4334 (26.83)		3849 (26.74)		485 (27.78)	
Fall	2087457 (25.25)	2083463 (25.25)	3994 (24.78)		3584 (24.90)		410 (23.48)	
Unknown	123350	123171	179		153		26	
Plurality								
1	8077511 (96.26)	8061551 (96.87)	15619 (96.39)	0.002	13938 (96.52)	0.018	1681 (95.29)	0.0125
2 or more	261259 (3.13)	260674 (3.13)	585 (3.61)		502 (3.48)		83 (4.71)	
Unknown	52155	52039	116		108		8	
Maternal								
Age at delivery (years)								
< 20	989687 (11.80)	987173 (11.79)	2514 (15.51)	< 0.0001	2253 (15.60)	< 0.0001	261 (14.79)	< 0.0001
20 -34	6262742 (74.65)	6250759 (74.65)	11983 (73.95)		10699 (74.09)		1284 (72.75)	
≥ 35	1136782 (13.55)	1135074 (13.56)	1708 (10.53)		1488 (10.30)		220 (12.46)	
Unknown	1373	1258	115		108		7	
Race/Ethnicity[a]								
Non-Hispanic White	3223500 (48.80)	3213982 (48.77)	9718 (58.95)	< 0.0001	8483 (58.98)	< 0.0001	1035 (58.77)	< 0.0001
Non-Hispanic Black	916164 (13.87)	914955 (13.88)	1209 (7.49)		1066 (7.41)		143 (8.12)	
Hispanic	2090796 (31.65)	2085870 (31.65)	4926 (30.51)		4387 (30.50)		539 (30.61)	
Other[b]	375261 (5.68)	374769 (5.69)	492 (3.05)		448 (3.11)		44 (2.50)	
Unknown	1784863	1784688	175		164		11	

Characteristics	All live Births (N= 8390584) n (%)	Controls (N=8374264) n (%)	All Cases (N=16320) n (%)	Chi sq[e] (*P* value)	Isolated Cases (N=14548) n (%)	Chi sq[f] (*P* value)	Non-isolated Cases (N=1772) n (%)	Chi sq[g] (*P* value)
Education (years)								
< 12	2025815 (24.45)	2021185 (24.44)	4630 (29.01)	< 0.0001	4161 (29.24)	< 0.0001	469 (27.13)	< 0.0001
12	2566792 (30.98)	2561336 (30.97)	5456 (34.19)		4843 (34.03)		613 (35.45)	
13-15	17363225 (20.97)	1732940 (20.95)	3285 (20.58)		2922 (20.53)		363 (20.99)	
16+	1957020 (23.62)	1954431 (23.63)	2589 (16.22)		2305 (16.20)		284 (16.43)	
Unknown	104732	104372	360		317		43	
**Parity*								
0	294414 (41.29)	294414 (41.29)	485 (40.72)	0.879	419 (40.28)	0.958	66 (43.71)	0.253
1	234663 (32.91)	234663 (32.91)	421 (35.35)		367 (35.288)		54 (35.76)	
2	115478 (16.19)	115478 (16.19)	198 (16.62)		173 (16.63)		25 (16.56)	
3	42967 (6.03)	42967 (6.03)	59 (4.95)		56 (5.38)		3 (1.99)	
≥ 4	25530 (0.30)	25527 (0.30)	28 (0.17)		25 (0.17)		3 (0.17)	
Unknown	1855	1855	0		0		0	
Paternal								
Age at delivery (years)								
< 20	306102 (4.22)	305298 (4.22)	804 (5.89)	< 0.0001	728 (5.98)	< 0.0001	76 (5.19)	0.001
20 -34	4998037 (68.89)	4988057 (68.88)	9980 (73.13)		8943 (73.40)		1037 (70.88)	
≥ 35	1950940 (26.89)	1948077 (26.90)	2863 (20.98)		2513 (20.63)		350 (23.92)	
Unknown	1135505	1132832	2673		2364		309	
Race/ Ethnicity[a]								
Non-Hispanic White	2859133 (51.15)	2851163 (51.13)	7970 (59.25)	< 0.0001	7124 (59.26)	< 0.0001	846 (59.04)	< 0.0001
Non-Hispanic Black	666215 (11.92)	665200 (11.93)	1015 (7.54)		892 (7.42)		123 (8.58))	
Hispanic	1756268 (31.42)	1752172 (31.42)	4096 (30.44)		3663 (30.47)		433 (30.22)	
Other[b]	308180 (5.51)	307807 (5.52)	373 (2.77)		342 (2.85)		31 (2.16)	
Unknown	2800867	2797922	2866		2527		339	

Characteristics	All live Births (N= 8390584) n (%)	Controls (N=8374264) n (%)	All Cases (N=16320) n (%)	Chi sq[e] (*P* value)	Isolated Cases (N=14548) n (%)	Chi sq[f] (*P* value)	Non-isolated Cases (N=1772) n (%)	Chi sq[g] (*P* value)
States								
Arkansas	261738 (3.12)	261526 (3.12)	212 (1.27)	< 0.0001	179 (1.23)	< 0.0001	33 (1.56)	< 0.0001
Arizona[c]	370886 (4.42)	370134 (4.42)	752 (4.51)		709 (4.87)		43 (2.03)	
Colorado	470460 (5.61)	469698 (5.61)	762 (4.57)		650 (4.47)		112 (5.29)	
Florida	1467979 (17.50)	1464373 (17.50)	3606 (23.70)		3119 (21.44)		487 (27.48)	
Georgia	353802 (4.22)	353321 (4.22)	481 (2.89)		427 (2.94)		54 (3.05)	
Hawaii	123237 (1.47)	123169 (1.47)	68 (0.41)		49 (0.34)		19 (1.07)	
Iowa	267593 (3.19)	266746 (3.19)	847 (5.08)		699 (4.80)		148 (8.35)	
North Carolina[d]	361105 (4.30)	360395 (4.30)	710 (4.26)		613 (4.21)		97 (5.47)	
New York	1762933 (21.01)	1759830 (21.01)	3103 (18.62)		2884 (19.82)		219 (12.36)	
Oklahoma	351771 (4.19)	350777 (4.19)	994 (5.96)		915 (6.29)		79 (4.46)	
Texas	2599080 (30.97)	2594295 (30.97)	4785 (28.71)		4304 (29.58)		481 (27.14)	

N, total number ; n, frequency ; Chi sq, Chi-square test of association

[a] does not include data from New York

[b] includes Asians/Pacific islanders, native Americans, and other races/ethnic groups

[c] includes data from the years 1999, 2000, 2003, and 2004

[d] includes data from the years 2003-2005

[e] All cases vs. Controls

[f] Isolated cases vs. Controls

[g] Multiple cases vs. Controls

* includes previous live and previous non-live births from only two states (North Carolina and Georgia)

Table 2. Prevalence of pyloric stenosis among infants born between 1999-2005

Characteristics	All cases (N=16320) *Prev./10,000 live births (95% CI)	Isolated cases (N=14548) *Prev./10,000 live births (95% CI)	Non-isolated cases (N=1772) *Prev./10,000 live births (95% CI)
Overall	19.45 (19.15, 19.75)	17.33 (17.06, 17.62)	2.11 (2.01, 2.21)
Infant			
Sex			
Male	30.79 (30.27, 31.32)	27.49 (27.00, 27.99)	3.30 (3.13, 3.47)
Female	7.26 (7.00, 7.52)	6.41 (6.17, 6.66)	0.84 (0.76, 0.94)
Birth weight (grams)			
< 2500	14.25 (13.51, 15.04)	10.95 (10.30, 11.64)	3.30 (2.95, 3.69)
2500 - 3999	20.00 (19.66, 20.34)	18.05 (17.73, 18.38)	1.94 (1.84, 2.05)
≥ 4000	19.85 (18.84, 20.92)	17.77 (16.81, 18.78)	2.08 (1.77, 2.44)
Gestational age (weeks)			
< 37	22.11 (21.14, 23.13)	17.96 (17.08, 18,87)	4.15 (3.75, 4.61)
≥ 37	18.98 (18.67, 19.30)	17.12 (16.82, 17.42)	1.86 (1.77, 1.96)
Year of Birth			
1999	18.50 (17.73, 19.32)	16.51 (15.78, 17.28)	2.00 (1.75, 2.28)
2000	19.29 (18.50, 20.11)	17.47 (16.72, 18.25)	1.82 (1.59, 2.09)
2001	19.54 (18.72, 20.40)	17.42 (16.64, 18.23)	2.12 (1.86, 2.42)
2002	18.80 (18.00, 19.64)	16.59 (15.84, 17.38)	2.20 (1.94, 2.50)
2003	18.26 (17.54, 19.01)	16.29 (15.61, 17.00)	1.97 (1.75, 2.23)
2004	21.84 (21.05, 22.65)	19.42 (18.68, 20.18)	2.42 (2.17, 2.70)
2005	20.69 (19.90, 21.51)	18.33 (17.59, 19.10)	2.36 (2.10, 2.65)
Season of birth			
Winter	19.28 (18.68, 19.90)	17.22 (16.65, 17.80)	2.06 (1.87, 2.27)
Fall	19.72 (19.12, 20.35)	17.54 (16.97, 18.13)	2.19 (1.99, 2.40)
Spring	19.93 (19.34, 20.53)	17.70 (17.15, 18.27)	2.23 (2.04, 2.44)
Summer	19.13 (18.58, 19.73)	17.17 (16.61, 17.74)	1.96 (1.78, 2.16)
Plurality			
1	19.33 (19.03, 19.64)	17.25 (16.97, 17.54)	2.08 (1.98, 2.18)
2 or more	22.39 (20.65, 24.28)	19.21 (17.60, 20.97)	3.18 (2.56, 3.94)
Maternal			
Age at delivery (years)			
< 20	25.40 (24.43, 26.41)	22.76 (21.84, 23.72)	2.63 (2.33, 2.98)
20 -34	19.13 (18.79, 19.48)	17.08 (16.76, 17.40)	2.05 (1.94, 2.16)
≥ 35	15.02 (14.33, 15.75)	13.08 (12.44, 13.77)	1.93 (1.69, 2.21)

Characteristics	All cases (N=16320) *Prev./10,000 live births (95% CI)	Isolated cases (N=14548) *Prev./10,000 live births (95% CI)	Non-isolated cases (N=1772) *Prev./10,000 live births (95% CI)
Race/Ethnicity[a]			
Non-Hispanic White	29.52 (28.93, 30.12)	26.31 (25.76, 26.88)	3.21 (3.02, 3.41)
Non-Hispanic Black	13.19 (12.47, 13.96)	11.63 (10.95, 12.35)	1.56 (1.32, 1.84
Hispanic	23.56 (22.91, 24.23)	20.98 (20.37, 21.61)	2.57 (2.37, 2.80)
Other[b]	13.11 (12.00, 14.32)	11.94 (10.88, 13.09)	1.17 (0.87, 1.57)
Education (years)			
< 12	22.85 (22.21, 23.52)	20.53 (29.92, 21.17)	2.31 (2.11, 2.53)
12	21.25 (20.69, 21.83)	18.87 (18,34, 19.40)	2.39 (2.20, 2.58)
13-15	18.92 (18.28, 19.57)	16.83 (16.23, 17.45)	2.09 (1.88, 2.32)
16+	13.22 (12.73, 13.75)	11.78 (11.30, 12.27)	1.45 (1.29, 1.63)
Paternal			
Age at delivery (years)			
< 20	26.26 (24,51, 28.14)	23.78 (22.11, 25.57)	2.48 (1.98, 3.11)
20 -34	19.96 (19.57, 20.36)	17.89 (17.52, 18.27)	2.07 (1.95,2.20)
≥ 35	14.67 (14.15, 15.22)	12.88 (12.38, 13.39)	1.79(1.61, 1.99)
Race/Ethnicity[a]			
Non-Hispanic White	27.87 (27.27, 28.49)	24.91 (24.34, 25.50)	2.95 (2.77, 3.16)
Non-Hispanic Black	15.23 (14.32, 16.00)	13.39 (12.54, 14.29)	1.84 (1.55, 2.20)
Hispanic	23.32 (22.62, 24.05)	20.85 (20.19, 21.54)	2.46 (2.24, 2.71)
Other[b]	12.10 (10.93, 13.40)	11.09 (9.98, 12.34)	0.78 (0.54, 1.11)
States			
Arkansas	8.10 (7.08, 9.27)	6.84 (5.90, 7.92)	1.26 (0.89, 1.77)
Arizona[c]	20.27 (18.88, 21.78)	19.11 (17.76, 20.58)	1.16 (0.86, 1.56)
Colorado	16.20 (15.08, 17.39)	13.81 (12.79, 14.92)	2.38 (1.97, 2.86)
Florida	24.56 (23.77, 25.38)	21.24 (20.50, 22.00)	3.32 (3.03, 3.62)
Georgia	13.59 (12.43, 14.87)	12.07 (10.98, 13.27)	1.52 (1.17, 1.99)
Hawaii	5.52 (4.53, 7.00)	3.97 (3.00, 5.26)	1.54 (0.98, 2.42)
Iowa	31.65 (29.59, 33.85)	26.12 (24.25, 28.13)	5.53 (4.70, 6.50)
North Carolina[d]	19.66 (18.26, 21.16)	16.97 (15.68, 18.37)	2.68 (2.20, 3.28)
New York	17.60 (16.99, 18.23)	16.36 (15.77, 16.96)	1.24 (1.08, 1.42)
Oklahoma	28.26 (26.55, 30.07)	26.01 (24.38, 27.75)	2.24 (2.80, 2.80)
Texas	18.41 (17.90, 18.94)	16.56 (16.07, 17.06)	1.85 (1.69, 2.02)

*Prev., Prevalence; CI, confidence interval

[a] does not include data from New York

[b] includes Asians/Pacific islanders, native Americans, and other races/ethnic groups

[c] includes data from the years 1999, 2000, 2003, and 2004

[d] includes data from the years 2003-2005

Table 3. Unadjusted analysis of association between pyloric stenosis and selected infant, maternal and paternal characteristics

Characteristics	All cases cPOR (95% CI)*	Isolated cases cPOR (95% CI)*	Non-isolated cases cPOR (95% CI)*
Infant			
Sex			
Male	4.25 (4.08, 4.42)	4.23 (4.12, 4.48)	3.90 (3.47, 4.38)
Female	Referent	Referent	Referent
Birth weight (grams)			
< 2500	0.71 (0.67, 0.75)	0.61 (0.57, 0.65)	1.70 (1.50 1.92)
2500 - 3999	Referent	Referent	Referent
≥ 4000	0.99 (0.94, 1.05)	0.98 (0.93, 1.04)	1.07 (0.90, 1.27)
Gestational age (weeks)			
< 37	1.16 (1.11, 1.22)	1.05 (0.99, 1.11)	2.23 (1.99, 2.51)
≥ 37	Referent	Referent	Referent
Year of Birth			
1999	Referent	Referent	Referent
2000	1.04 (0.98, 1.11)	1.06 (0.99, 1.13)	0.91 (0.76, 1.10)
2001	1.06 (0.99, 1.12)	1.05 (0.99, 1,12)	1.06 (0.88, 1.28)
2002	1.02 (0.96, 1.08)	1.00 (0.94, 1.07)	1.10 (0.92, 1.33)
2003	0.99 (0.93, 1.05)	0.99 (0.93, 1.05)	0.99 (0.83, 1.18)
2004	1.18 (1.12, 1.25)	1.18 (1.11, 1.25)	1.21 (1.02, 1.44)
2005	1.12 (1.05, 1.18)	1.11 (1.04, 1.18)	1.18 (0.99, 1.41)
Season of birth			
Winter	0.98 (0.94, 1.02)	0.98 (0.94, 1.03)	0.94 (0.82, 1.08)
Fall	Referent	Referent	Referent
Spring	1.01 (0.97, 1.05)	1.01 (0.96, 1.06)	1.02 (0.90, 1.16)
Summer	0.97 (0.93, 1.02)	0.98 (0.93, 1.025)	0.90 (0.78, 1.03)
Plurality			
1	Referent	Referent	Referent
2 or more	1.16 (1.07, 1.26)	1.11 (1.02, 1.22)	1.53 (1.22, 1.90)
Maternal			
Age at delivery (years)			
< 20	1.33 (1.28, 1.39)	1.33 (1.28, 1.39)	1.29 (1.13, 1.47)
20 -34	Referent	Referent	Referent
≥ 35	0.78 (0.75, 0.82)	0.77 (0.72, 0.81)	0.94 (0.82, 1.09)

Characteristics	All cases cPOR (95% CI)*	Isolated cases cPOR (95% CI)*	Non-isolated cases cPOR (95% CI)*
Race/Ethnicity[a]			
Non-Hispanic White	Referent	Referent	Referent
Non-Hispanic Black	0.45 (0.42, 0.47)	0.44 (0.41, 0.47)	0.48 (0.41, 0.58)
Hispanic	0.79 (0.77, 0.82)	0.80 (0.77, 0.83)	0.80 (0.72, 0.89)
Other[b]	0.44 (0.40, 0.48)	0.45 (0.41, 0.50)	0.36 (0.27, 0.49)
Education (years)			
< 12	1.07 (1.03, 1.12)	1.09 (1.04, 1.13)	0.97 (0.86, 1.09)
12	Referent	Referent	Referent
13-15	0.89 (0.85, 0.93)	0.89 (0.85, 0.93)	0.87 (0.77, 0.99)
16+	0.62 (0.59, 0.65)	0.62 (0.59, 0.65)	0.61 (0.53, 0.70)
Paternal			
Age at delivery (years)			
< 20	1.32 (1.22, 1.41)	1.33 (1.23, 1.43)	1.20 (0.95, 1.51)
20 -34	Referent	Referent	Referent
≥ 35	0.73 (0.70, 0.77)	0.72 (0.69, 0.75)	0.86 (0.76, 0.98)
Race/Ethnicity[a]			
Non-Hispanic White	Referent	Referent	Referent
Non-Hispanic Black	0.56 (0.52, 0.58)	0.54 (0.50, 1.57)	0.62 (0.52, 0.75)
Hispanic	0.83 (0.80, 0.87)	0.84 (0.80, 0.87)	0.83 (0.74, 0.93)
Other[b]	0.43 (0.39, 0.48)	0.44 (0.40, 0.50)	0.34 (0.24, 0.48)
States			
Arkansas	0.59 (0.51, 0.70)	0.57 (0.48, 0.67)	0.83 (0.53, 1.27)
Arizona[c]	1.49 (1.33, 1.67)	1.58 (1.41, 1.79)	0.76 (0.51, 1.13)
Colorado	1.19 (1.06, 1.34)	1.14 (1.01, 1.29)	1.56 (1.13, 2.16)
Florida	1.81 (1.64, 1.99)	1.76 (1.59, 1.95)	2.18 (1.64, 2.88)
Georgia	Referent	Referent	Referent
Hawaii	0.41 (0.31, 0.52)	0.33 (0.24, 0.44)	1.10 (0.60, 1.70)
Iowa	2.33 (2.08, 2.61)	2.17 (1.92, 2.45)	3.63 (2.66, 4.95)
North Carolina[d]	1.48 (1.29, 1.62)	1.41 (1.24, 1.59)	1.76 (1.26, 2.45)
New York	1.29 (1.18, 1.43)	1.36 (1.22, 1.50)	0.81 (0.60, 1.10)
Oklahoma	2.08 (1.87, 2.32)	2.16 (1.92, 2.42)	1.47 (1.04, 2.08)
Texas	1.35 (1.23, 1.49)	1.37 (1.24, 1.52)	1.21 (0.92, 1.61)

cPOR, Crude/unadjusted Prevalence Odds Ratio; CI, Confidence Interval

[a] does not include data from New York

[b] includes Asians/Pacific islanders, native Americans, and other races/ethnic groups

[c] includes data from the years 1999, 2000, 2003, and 2004

[d] includes data from the years 2003-2005

Table 4. Unadjusted and Adjusted analysis of association between pyloric stenosis and selected infant, maternal and paternal characteristics stratified by sex

Characteristics	Male cases cPOR (95% CI)	Female cases cPOR (95% CI)	Male cases aPOR[a] (95% CI)	Female cases aPOR[a] (95% CI)
Infant				
Birth weight (grams)				
< 2500	0.68 (0.64, 0.73)	0.91 (0.81, 1.02)	0.47 (0.43, 0.52)	0.69 (0.57, 0.84)
2500 - 3999	Referent	Referent	Referent	Referent
≥ 4000	0.85 (0.80, 0.90)	0.80 (0.77, 1.05)	0.79 (0.74, 0.85)	0.83(0.68, 1.01)
Gestational age (weeks)				
< 37	1.09 (1.04, 1.15)	1.37 (1.23, 1.52)	1.48 (1.38, 1.60)	1.76 (1.50, 2.05)
≥ 37	Referent	Referent	Referent	Referent
Plurality				
1	Referent	Referent	Referent	Referent
2 or more	1.14 (1.04, 1.25)	1.29 (1.08, 1.55)	1.36 (1.20, 1.54)	1.19 (0.93, 1.53)
Maternal				
Age at delivery (years)				
< 20	1.34 (1.28, 1.41)	1.26 (1.14, 1.40)	1.19 (1.10, 1.28)	1.01 (0.86, 1.20)
20 -34	Referent	Referent	Referent	Referent
≥ 35	0.78 (0.73, 0.82)	0.82 (0.73, 0.92)	0.91 (0.84, 0.99)	0.88 (0.74, 1.04)
Race/Ethnicity[b]				
Non-Hispanic White	Referent	Referent	Referent	Referent
Non-Hispanic Black	0.43 (0.40, 0.46)	0.53 (0.47, 0.61)	0.42 (0.36, 0.49)	0.44 (0.32, 0.60)
Hispanic	0.80 (0.77, 0.83)	0.81 (0.75, 0.88)	0.76 (0.70, 0.83)	0.89 (0.74, 1.06)
Other[c]	0.42 (0.38, 0.46)	0.55 (0.45, 0.67)	0.56 (0.48, 0.66)	0.63 (0.45, 0.88)
Education (years)				
< 12	1.07 (1.03, 1.12)	1.09 (0.99, 1.19)	1.04 (0.98, 1.10)	1.10 (0.97, 1.24)
12	Referent	Referent	Referent	Referent
13-15	0.89 (0.85, 0.93)	0.89 (0.80, 0.98)	0.84 (0.79, 0.88)	0.84 (0.74, 0.95)
16+	0.62 (0.59, 0.66)	0.61 (0.55, 0.68)	0.56 (0.53, 0.60)	0.55 (0.48, 0.63)
Paternal				
Age at delivery (years)				
< 20	1.31 (1.21, 1.42)	1.32 (1.11, 1.56)	1.12 (1.01, 1.24)	1.13 (0.90, 1.42)
20 -34	Referent	Referent	Referent	Referent
≥ 35	0.73 (0.70, 0.77)	0.75 (0.68, 0.83)	0.85 (0.80, 0.90)	0.87 (0.76, 0.99)
Race/Ethnicity[b]				
Non-Hispanic White	Referent	Referent	Referent	Referent
Non-Hispanic Black	0.53 (0.49, 0.57)	0.63 (0.55, 0.73)	0.81 (0.71, 0.93)	0.95 (0.73, 1.24)

Characteristics	Males cPOR (95% CI)	Females cPOR (95% CI)	Males aPOR[a] (95% CI)	Females aPOR[a] (95% CI)
Hispanic	0.84 (0.81, 0.88)	0.82 (0.75, 0.90)	0.95 (0.87, 1.03)	0.81 (0.68, 0.98)
Other[c]	0.41 (0.37, 0.47)	0.52 (0.41, 0.65)	0.72 (0.61, 0.85)	0.77 (0.55, 1.09)

cPOR, Crude/Unadjusted Prevalence Odds Ratio; aPOR, Adjusted Prevalence Odds Ratio; CI, Confidence Interval

aEach variable adjusted for all other variables in the model

[b]does not include data from New York

[c] includes Asians/Pacific islanders, native Americans, and other races/ethnic groups

Table 5. Multivariate analysis examining the association between pyloric stenosis and selected infant, maternal and paternal characteristics

	All Cases			Isolated Cases			
Characteristics	**Model 1[1] (Full Model)**	**Model 3[3] (Reduced model 2) (Forward selection)**	**Model 4[4] (*a-priori* model)**	**Model 1[1] (Full Model)**	**Model 2[2] (Reduced Model 1) (Backward selection)**	**Model 3[3] (Reduced model 2) (Forward selection)**	**Model 4[4] (*a-priori* model)**
Infant							
Sex							
Male	4.33 (4.14, 4.52)	4.30 (4.12, 4.49)	4.26 (4.09, 4.43)	4.38 (4.18, 4.60)	4.38 (4.18. 4.60)	4.36 (4.16, 4.57)	4.30 (4.12, 4.49)
Female	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Birth weight (grams)							
< 2500	0.56 (0.52, 0.60)	0.55 (0.50, 0.59)	0.62 (0.59, 0.66)	0.48 (0.44, 0.52)	0.48 (0.44, 0.52)	0.44 (0.40, 0.48)	0.53 (0.49, 0.57)
2500 - 3999	Referent	Referent	Referent	Referent	Referent	Referent	Referent
≥ 4000	0.85 (0.80, 0.90)	0.85 (0.81, 0.91)	0.85 (0.81, 0.90)	0.83 (0.78, 0.89)	0.83 (0.78, 0.90)	0.84 (0.79, 0.90)	0.85 (0.80, 0.90)
Gestational age (weeks)							
< 37	1.40 (1.32, 1.49)	1.45 (1.36, 1.54)	n/a	1.32 (1.24, 1.41)	1.32 (1.24, 1.41)	1.40 (1.31, 1.49)	n/a
≥ 37	Referent	Referent	n/a	Referent	Referent	Referent	n/a
Season of birth							
Winter	0.96 (0.92, 1.01)	0.97 (0.92, 1.01)	0.97 (0.93, 1.02)	0.97 (0.92, 1.02)	n/a	0.97 (0.92, 1.02)	0.98 (0.93, 1.03)
Fall	Referent	Referent	Referent	Referent	n/a	Referent	Referent
Spring	1.01 (0.96, 1.06)	1.01 (0.96, 1.06)	1.00 (0.96, 1.05)	1.01 (0.96, 1.06)	n/a	1.01 (0.96, 1.06)	1.00 (0.96, 1.05)
Summer	0.94 (0.90, 0.99)	0.95 (0.90, 0.99)	0.96 (0.92, 1.00)	0.95 (0.90, 1.00)	n/a	0.96 (0.91, 1.01)	0.97 (0.92, 1.01)
Plurality							
1	Referent	Referent	Referent	Referent	Referent	Referent	Referent
2 or more	1.44 (1.31, 1.58)	1.40 (1.27, 154)	1.56 (1.43, 1.70)	1.52 (1.37, 1.68)	1.52 (1.37, 1.68)	1.48 (1.34, 1.64)	1.60 (1.46, 1.76)

	All Cases			Isolated Cases			
Characteristics	**Model 1[1] (Full Model)**	**Model 3[3] (Reduced model 2) (Forward selection)**	**Model 4[4] (*a-priori* model)**	**Model 1[1] (Full Model)**	**Model 2[2] (Reduced Model 1) (Backward selection)**	**Model 3[3] (Reduced model 2) (Forward selection)**	**Model 4[4] (*a-priori* model)**
Maternal							
Age at delivery (years)							
< 20	1.13 (1.06, 1.20)	1.13 (1.06, 1.20)	1.14 (1.1, 1.20)	1.12 (1.05, 1.20)	1.12 (1.05, 1.20)	1.13 (1.06, 1.21)	1.14 (1.09, 1.20)
20 -34	Referent	Referent	Referent	Referent	Referent	Referent	Referent
≥ 35	0.98 (0.92, 1.04)	0.97 (0.91, 1.03)	0.95 (0.90, 1.00)	0.97 (0.91, 1.04)	0.97 (0.91, 1.04)	0.95 (0.89, 1.02)	0.93 (0.88, 0.98)
Race/Ethnicity[a]							
Non-Hispanic White	Referent	n/a	Referent	Referent	Referent	n/a	Referent
Non-Hispanic Black	0.46 (0.40, 0.52)	n/a	0.40 (0.38, 0.43)	0.47 (0.41, 0.54)	0.47 (0.41, 0.54)	n/a	0.40 (0.37, 0.42)
Hispanic	0.80 (0.75, 0.85)	n/a	0.69 (0.66, 0.71)	0.80 (0.74, 0.85)	0.80 (0.74, 0.85)	n/a	0.68 (0.66, 0.71)
Other[b]	0.66 (0.58, 0.75)	n/a	0.57 (0.52, 0.62)	0.68 (0.59, 0.78)	0.68 (0.59, 0.78)	n/a	0.59 (0.54, 0.65)
Education (years)							
< 12	1.03 (0.98, 1.08)	1.02 (0.97, 1.06)	1.06 (1.02, 1.10	1.04 (0.99, 1.09)	1.04 (0.99, 1.09)	1.02 (0.98, 1.07)	1.07 (1.03, 1.12)
12	Referent	Referent	Referent	Referent	Referent	Referent	Referent
13-15	0.88 (0.84, 0.92)	0.89 (0.84, 0.93)	0.89 (0.85, 0.93)	0.87 (0.83, 0.92)	0.87 (0.83, 0.92)	0.88 (0.84, 0.93)	0.89 (0.85, 0.93)
16+	0.60 (0.57, 0.63)	0.64 (0.61, 0.68)	0.60 (0.57, 0.63)	0.60 (0.57, 0.63)	0.60 (0.57, 0.63)	0.65 (0.61, 0.68)	0.60 (0.57, 0.63)
Paternal							
Age at delivery (years)							
< 20	1.11 (1.02, 1.21)	1.15 (1.05, 1.25)	n/a	1.12 (1.02, 1.22)	1.12 (1.02, 1.22)	1.16 (1.06, 1.27)	n/a

	All Cases			Isolated Cases			
Characteristics	**Model 1[1] (Full Model)**	**Model 3[3] (Reduced model 2) (Forward selection)**	**Model 4[4] (*a-priori* model)**	**Model 1[1] (Full Model)**	**Model 2[2] (Reduced Model 1) (Backward selection)**	**Model 3[3] (Reduced model 2) (Forward selection)**	**Model 4[4] (*a-priori* model)**
20 -34	Referent	Referent	n/a	Referent	Referent	Referent	n/a
≥ 35	0.93 (0.88, 0.98)	0.79 (0.75, 0.82)	n/a	0.91 (0.87, 0.96)	0.91 (0.87, 0.96)	0.77 (0.73, 0.81)	n/a
Race/Ethnicity[a]							
Non-Hispanic White	Referent	n/a	n/a	Referent	Referent	n/a	n/a
Non-Hispanic Black	0.88 (0.79, 0.98)	n/a	n/a	0.84 (0.75, 0.94)	0.84 (0.75, 0.94)	n/a	n/a
Hispanic	0.85 (0.80, 0.92)	n/a	n/a	0.85 (0.79, 0.92)	0.85 (0.79, 0.92)	n/a	n/a
Other[b]	0.77 (0.68, 0.88)	n/a	n/a	0.78 (0.68, 0.90)	0.78 (0.68, 0.90)	n/a	n/a
States							
Arkansas	n/a	0.44 (0.36, 0.52)	n/a	n/a	n/a	0.40 (0.34, 0.50)	n/a
Arizona[c]	n/a	1.31 (1.13, 1.51)	n/a	n/a	n/a	1.55 (1.34, 1.80)	n/a
Colorado	n/a	0.91 (0.80, 1.03)	n/a	n/a	n/a	0.87 (0.76, 0.99)	n/a
Florida	n/a	1.39 (1.26, 1.55)	n/a	n/a	n/a	1.36 (1.21, 1.51)	n/a
Georgia	n/a	Referent	n/a	n/a	n/a	Referent	n/a
Hawaii	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Iowa	n/a	1.74 (1.53, 1.96)	n/a	n/a	n/a	1.61 (1.41, 1.83)	n/a
North Carolina[d]	n/a	1.10 (0.97, 1.25)	n/a	n/a	n/a	1.07 (0.93, 1.23)	n/a
New York	n/a	1.04 (0.94, 1.16)	n/a	n/a	n/a	1.09 (0.98, 1.22)	n/a
Oklahoma	n/a	1.34 (1.89, 1.51)	n/a	n/a	n/a	1.37 (1.21, 1.56)	n/a
Texas	n/a	0.99 (0.89, 1.10)	n/a	n/a	n/a	0.99 (0.89, 1.11)	n/a

[1]Adjusted for all the variables listed except States of birth

[2]Backward elimination on Model 1; not shown for All cases (same as Model 1)

[3]Adjusted for sex, birth weight, gestational age, plurality, season of birth, maternal age, maternal education, paternal age, state of birth
[4]Adjusted for sex, birth weight, plurality, season of birth, maternal age, maternal race/ethnicity, maternal education
[a] does not include data from New York
[b] includes Asians/Pacific islanders, native Americans, and other races/ethnic groups
[c] includes data from the years 1999, 2000, 2003, and 2004
[d] includes data from the years 2003-2005

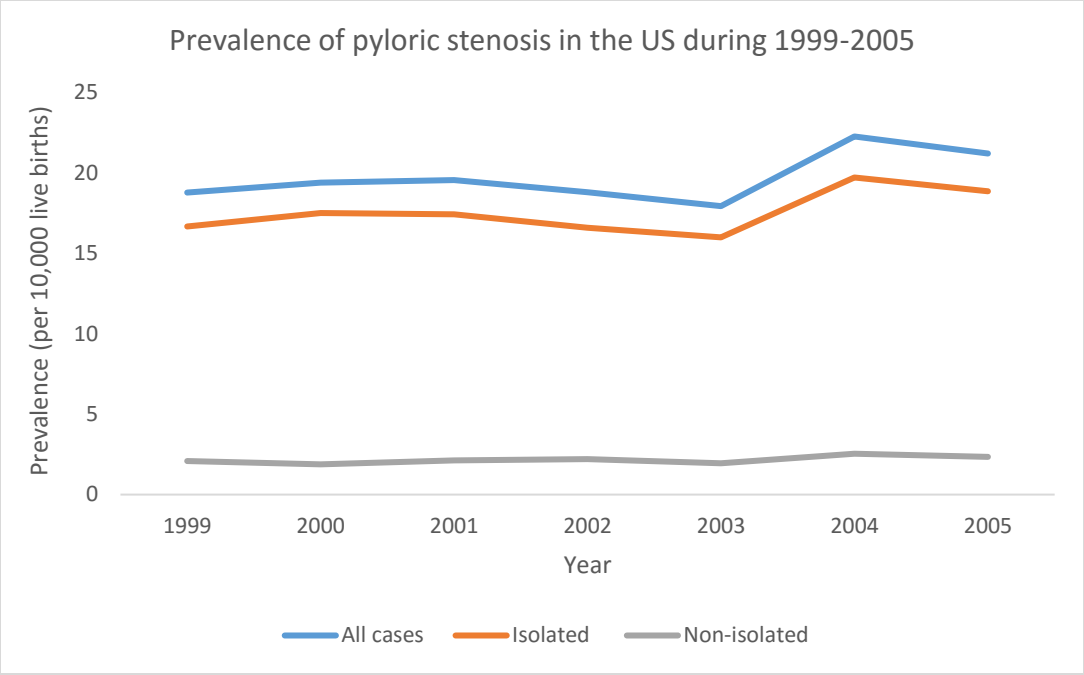

Figure 1. Prevalence of pyloric stenosis in the US during 1999-2005

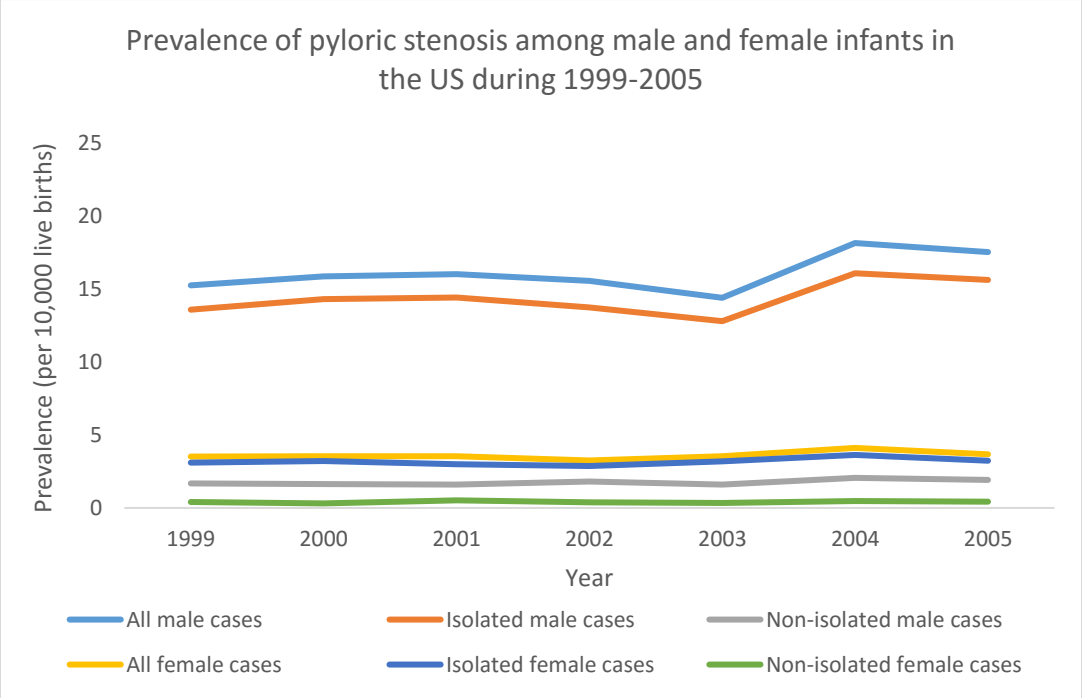

Figure 2. Prevalence of pyloric stenosis among male and female infants in the US during 1999-2005

Supplementary Table 1. Pyloric stenosis counts and unadjusted analyses for association with selected infant, maternal, and paternal characteristics for nine States between 1999-2005

Characteristics	All live Births (N= 7658593)	Controls (N=7643735)	All Cases (N=14858)	Chi sq* (*P* value)	All Cases cPOR* (95% CI)
Infant					
Sex					
Male	3924184	3912039	12145	<0.0001	4.27 (4.10, 4.46)
Female	3734339	3731629	2710		Reference
Unknown	70	67	3		
Birth weight (grams)					
<2500	611146	609941	1205	0.08	1.01 (0.95, 1.07))
2500 - 3999	6368655	6356235	12420		Reference
≥4000	674671	673438	1233		0.94 (0.88, 0.99)
Unknown	4121	4121			
Gestational age (weeks)					
<37	783619	781889	1730	<0.0001	1.16 (1.10, 1.22)
≥37	6830802	6817765	13037		Reference
Unknown	44172	44081	91		
Year of Birth					
1999	1034797	1032855	1942	<0.0001	Reference
2000	1068785	1066712	2073		1.03 (0.97, 1.10)
2001	1067719	1065632	2087		1.04 (0.98, 1.11)
2002	1073771	1071752	2019		1.00 (0.94, 1.07)
2003	1088929	1086976	1953		0.96 (0.90, 1.02)
2004	1096164	1093724	2440		1.19 (1.12, 1.26)
2005	1105259	1102915	2344		1.13 (1.06, 1.20)
Unknown	123169	123169			
Season of birth					
Winter	1811983	1808476	3507	0.133	0.97 (0.93, 1.02)
Spring	1839418	1835749	3669		Reference
Summer	1980962	1976992	3970		1.01 (0.96, 1.05)
Fall	1902993	1899349	3644		0.96 (0.92, 1.00)
Unknown	123237	123169	68		
Plurality					
1	7367621	7353299	14322	0.002	Reference
2 or more	239014	238480	534		1.15 (1.05, 1.25)
Unknown	51958	51956	2		

Characteristics	All live Births (N= 7658593)	Controls (N=7643735)	All Cases (N=14858)	Chi sq* (*P* value)	All Cases cPOR* (95% CI)
Maternal					
Age at delivery (years)					
< 20	898058	895775	2283	<0.0001	1.32 (1.26, 1.38)
20 -34	5710458	5699478	10980		Reference
≥35	1048919	1047328	1591		0.79 (0.75, 0.82)
Unknown	1158	1154	4		
Race/ethnicity[a]					
Non-Hispanic White	2848353	2839607	8746	<0.0001	Reference
Non-Hispanic Black	823141	822017	1124		0.45 (0.42, 0.47)
Hispanic	1890280	1885743	4537		0.79 (0.77, 0.82)
Other[b]	317649	317226	423		0.44 (0.40, 0.48)
Unknown	1779170	1779142	28		
Education (years)					
<12	1833825	1829628	4197	<0.0001	1.08 (1.03, 1.12)
12	2357086	2352070	5016		Reference
13-15	1580684	1577667	3017		0.90 (0.86, 0.94)
16+	1795256	1792839	2417		0.63 (0.60, 0.66)
Unknown	91742	91531	211		
Paternal					
Age at delivery (years)					
< 20	279977	279233	744	<0.0001	1.32 (1.23, 1.43)
20 -34	4545099	4535981	9118		Reference
≥ 35	1807242	1804576	2666		0.73 (0.70, 0.77)
Unknown	1026275	1023945	2330		
Race/ ethnicity[a]					
Non-Hispanic White	2532904	2525577	7327	<0.0001	Reference
Non-Hispanic Black	597471	596533	938		0.54 (0.51, 0.58)
Hispanic	1588483	1584710	3773		0.82 (0.80, 0.85)
Other[b]	264422	264091	331		0.43 (0.39, 0.48)
Unknown	2675313	2672824	2489		
States					
Arkansas	261738	261526	212	<0.0001	0.59 (0.51, 0.70)
Colorado	470460	469698	762		1.19 (1.06, 1.34)
Florida	1467979	1464373	3606		1.81 (1.64, 2.00)
Georgia	353802	353321	481		Reference
Hawaii	123237	123169	68		0.41 (0.31, 0.52)

Characteristics	All live Births (N= 7658593)	Controls (N=7643735)	All Cases (N=14858)	Chi sq* (*P* value)	All Cases cPOR* (95% CI)
Iowa	267593	266746	847		2.33 (2.08, 2.61)
New York	1762933	1759830	3103		1.29 (1.78, 1.43)
Oklahoma	351771	350777	994		2.08 (1.87, 2.32)
Texas	2599080	2594295	4785		1.35 (1.23, 1.49)

*Chi sq, Chi-square test of association; cPOR, Crude/unadjusted Prevalence Odds Ratio; CI, Confidence Interval

[a] does not include data from New York

[b] includes Asian/Pacific islanders, native Americans, and other races/ethnic groups