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Sunny Xu Date

Prevalence and Descriptive Epidemiology of Congenital Hydrocephalus in Iowa, 2003–2011

By

Sunny Xu
Master of Public Health

Global Epidemiology

Vijaya Kancherla, PhD
Committee Chair

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By

Sunny Xu

Bachelor of Science
University of Michigan
2017

Thesis Committee Chair: Vijaya Kancherla, PhD

An abstract of
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Abstract

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Congenital Hydrocephalus in Iowa, 2003–2011
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Background: There is a paucity of contemporary information on the prevalence of congenital hydrocephalus (CH) and associated factors in the United States (US). We conducted a retrospective study using data from a Midwestern birth cohort to examine prevalence and descriptive epidemiology of CH**.**

Methods: We used population-based, surveillance data from the Iowa Registry for Congenital and Inherited Disorders to compare CH cases (n=244) with Iowa live births (n=353,805) delivered during 2003–2011. Cases were classified as isolated (no additional major birth defects) or multiple (one or more additional major birth defects). We used Poisson regression analysis to estimate prevalence per 10,000 live births and logistic regression analysis to estimate crude and adjusted prevalence ratios (cPRs and aPRs, respectively) and corresponding 95% confidence intervals (CI)s; aPRs were controlled for selected infant and parental characteristics.

Results: Overall, 83 (34%) of 244 cases were isolated. Among all cases, CH prevalence was 6.9 (95% CI=6.1,7.8). In crude analyses, we observed positive associations for males, plural pregnancies, and parental age at delivery (<20 or ≥35 years) and race/ethnicity; estimates for plural pregnancies and paternal race/ethnicity had CIs that excluded the null. Where data were available, findings were similar for isolated and multiple CH cases.

Conclusion: Our estimated CH prevalence in Iowa is comparable to other regions of the US. Our findings for some, but not all, infant and parental characteristics were comparable to previous findings. Future studies are needed to confirm prevalence patterns and associated factors among CH phenotypes.

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Table of Contents

Prevalence and descriptive epidemiology of congenital hydrocephalus in Iowa, 2003–2011

Sunny Xu[1], Vijaya Kancherla[1], Jonathan Suhl[2], Kristin M Conway[2], Paul A Romitti[2,3]

[1]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia

[2]Department of Epidemiology, College of Public Health, The University of Iowa, Iowa City, Iowa

[3]Department of Biostatistics, College of Public Health, The University of Iowa, Iowa City, Iowa

Abstract Word Count = 250 (Limit = 250 words)

Corresponding author:
Paul A Romitti, PhD
Departments of Epidemiology and Biostatistics
College of Public Health
University of Iowa
S416 CPHB
145 N Riverside Dr
Iowa City, IA 52242
(Tel) 319-384-1549
e-mail: paul-romitti@uiowa.edu

Running title: Prevalence and epidemiology of congenital hydrocephalus

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Key Words (up to 5): congenital hydrocephalus, epidemiology, prevalence, risk factors, population surveillance

1 | INTRODUCTION

Primary congenital hydrocephalus (CH) is characterized by impaired circulation and absorption of cerebrospinal fluid (CSF) in the ventricular system of the brain, beginning after 20 weeks of gestation (1, 2). Primary CH differs from acquired hydrocephalus, which occurs as a complication of extrinsic factors, such as neonatal infections or traumatic brain injuries (2, 3). Normally CSF, formed in the ventricles, travels through the ventricular system of the brain and is absorbed into the bloodstream (4). A physical blockage of CSF flow in the cerebral ventricles or functional impairment outside of the ventricular system in the subarachnoid space produces a buildup of CSF and leads to increased intercranial pressure (4, 5). CH is considered obstructive, when there is a point of blockage, or communicating, when there is free CSF flow (4).

CH can present as an isolated defect or co-occur with other birth defects, including neural tube or other central nervous system defects (2). Prevalence estimates for CH vary worldwide. A study using data from four European registries estimated prevalence of isolated CH at 4.8 per 10,000 live births (6), whereas a retrospective Danish cohort study estimated prevalence of isolated CH at 6.2 per 10,000 live births (7), and 11.0 per 10,000 live births for all idiopathic CH (8). Prevalence estimates in China have been reported as 5.0–8.3 per 10,000 live births for isolated CH (9-12), 6.1–20.3 per 10,000 live births for all CH (9-13), and a suggested decrease from 2005–2015 (11, 12). In a recently published systematic review and meta-analysis, the pooled prevalence of CH was estimated to be highest in Africa (14.5 per 10,000 live births) and Latin America (31.6 per 10,000 live births) with the lowest pooled estimates reported for the United States (US; 6.8 per 10,000 births) (14).

CH accounts for approximately 58% of all childhood hydrocephalus deaths in the US (15); however, improvements in clinical and surgical care have reduced mortality associated with CH (15). If left untreated, CH may lead to early death and impact the neurological development and social wellbeing of the child (15). The most common treatment for CH is to insert a ventriculoperitoneal shunt in order to divert CSF away from the brain towards the abdomen to relieve the built-up pressure (5). Placement of a shunt has been associated with both infectious and mechanical complications (16) and may require multiple surgeries during a patient's life (17). Long-term outcomes of CSF diversion vary, ranging from children who have a near-normal quality of life to those who develop seizure disorders or report chronic headaches in adulthood (5, 18). Despite the potential for adverse outcomes, diversion typically is associated with some improvement in neuropsychological function (19, 20). Additionally, treatment interventions completed earlier in life are more likely to result in near-normal cognitive development (21).

Along with the morbidity and mortality associated with CH is the costs of care for affected individuals. A nationally-representative study of weighted hospital discharge data in 2003 for pediatric patients (ages 0-18 years) in the US reported that annual hydrocephalus-related health care accounted for nearly 40,000 admissions and 0.6% of all pediatric hospital admissions in that year, with estimated total hospital charges ranging from 1.4–2.0 billion dollars (22). Of these hydrocephalus-related admissions, approximately 5,000 were CH-related admissions (22). The study concluded that hydrocephalus is a chronic illness and that those affected have disproportionally increased health care expenditures, and a significantly increased risk of mortality, compared to their unaffected counterparts (22).

Reducing the burden of CH requires identifying risk factors for CH; studies suggest a multifactorial etiology (23). Etiological associations have been reported for familial transmission, as well as selected infant and maternal characteristics, and selected maternal exposures during pregnancy. Familial inheritance of CH is supported by recurrence within families (8, 24, 25), with recurrence risk estimates ranging from 4-12% (18). Of known genes, transmission has been found to follow X-linked (*L1CAM*, *AP1S2*) or autosomal recessive (*MPDZ, CCDC88C*) patterns of inheritance (4, 26). With regard to non-genetic factors, infant characteristics positively associated with increased risk of CH include male sex (2, 7, 9, 27), preterm birth (gestational age ≤37 weeks) (2, 7, 28), low birth weight (<2000g) (27, 28), and plural pregnancy (7, 9, 28-30). Maternal characteristics positively associated with an increased risk of CH include young (<20 years) or advanced (≥35 years) age at delivery (2, 9), non-Asian race/ethnicity (2, 27), low socio-economic status (27), and nulliparity (7, 31). Pregnancy-related maternal exposures positively associated with CH include use of antidepressants or alcohol during pregnancy (7, 25), lack of prenatal care (25), and chronic maternal health conditions, such as pre-exiting diabetes (2, 3, 7) and hypertension (2, 3).

Despite the morbidity, mortality, and costs of care for CH, contemporary, population-based data on prevalence and descriptive epidemiology of CH in the US are limited. Of the few population-based studies (27, 28, 32), the most recent estimate of prevalence of CH in the US was reported for the birth period 1991–2000 (27).

To address these gaps, we aimed to examine the prevalence of CH in Iowa from 2003 to 2011, using data from an active, population-based surveillance program. We also aimed to examine associations between selected infant and parental characteristics and CH.

As our findings are derived from a multi-source, population-based registry, they can inform resource allocation for programs aimed at providing treatment and services to CH cases. Findings from our study can be generalized to other regions in the Midwestern US with comparable populations.

2 | METHODS

2.1 | Human subjects approval

Our study protocol was reviewed and approved by the institutional review board at The University of Iowa.

2.2 | Case enumeration and classification

We obtained data on primary CH diagnosis among live births, fetal deaths, and elective terminations of pregnancies for birth defects for the years 2003–2011 from the Iowa Registry for Congenital and Inherited Disorders (IRCID). The IRCID uses population-based, active, multiple-source case finding and record abstraction to enumerate and confirm CH cases statewide. CH cases were classified and coded using the centers for Disease Control and Prevention/British Pediatric Association codes 742.300 (aqueductal stenosis), 742.310 (Dandy-Walker malformation), 742.320 (hydranencephaly), 742.380 (other specified hydrocephalus), and 742.390 (unspecified hydrocephalus). Cases of acquired CH were excluded. All primary CH cases were reviewed by a clinical geneticist and classified as isolated (no additional, major birth defects) or as multiple (one or more major birth defects in another organ system).

2.3 | Birth data

We obtained birth certificate data for selected infant and parental characteristics of all live births registered during 2003-2011 from the Iowa Department of Public Health.

2.4 | Infant and parental characteristics

We examined selected infant, maternal, and paternal characteristics among CH cases and all live births. Infant characteristics examined were sex (female, male), year of birth, and plurality (1, 2 or more). Infant gestational age and birth weight were not examined in this study since they are known to be highly correlated (33); additionally, there is literature that suggests adjusting for these variables will lead to biased estimates (34). Maternal characteristics examined were age at delivery in years (<20, 20–35, ≥35), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), education at delivery in years (<12, 12, >12), and parity (0, 1 or more). Paternal characteristics examined were age at delivery in years (<20, 20–35, ≥35) and race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other). Data were available for 98% of case infants, 90% of case mothers, and 75% of case fathers. Corresponding proportions of data on descriptive characteristics were available for all live births were 96%, 95%, and 83%. One observation for infant gestational age was recorded as zero and was considered a possible data entry error. The value was set to missing in the final analysis.

2.5 | Prevalence analysis

We estimated CH prevalence (per 10,000 live births) as the ratio of the number of CH cases to the number of live births for the birth period 2003–2011. A Poisson regression model with a log link function was used to estimate the average annual prevalence and corresponding 95% confidence interval (CI) for the study period. Prevalence was estimated

separately for each birth year for all CH cases. Additionally, prevalence was estimated for isolated and multiple cases individually for each birth year.

2.6 | Descriptive analysis

CH cases and live births were compared on infant and parental characteristics using the Pearson Chi square test. Analyses were conducted separately for all, isolated, and multiple cases. Variables selected for descriptive analyses were identified due to their reported associations in previous studies. Logistic regression analysis was used to estimate crude and adjusted prevalence odds ratios (cPR and aPR, respectively) and their corresponding 95% CIs to examine associations between CH and selected infant and parental characteristics; exact logistic regression was used when at least one category of a descriptive variable included <5 case mothers. Covariables were included in the multivariable model if the covariable was shown to be associated with CH in previous studies, or if there was a statistically significant association ($p<0.05$) observed between CH and the covariable. Multivariable analyses were conducted separately for all cases, isolated cases, and multiple cases. All analyses were conducted using SAS Software version 9.4 (SAS Institute Inc., 2013).

3 | RESULTS

3.1 | Prevalence analysis

Overall, 244 CH cases and 353,805 live births were identified during 2003–2011. Of the 244 CH cases, 83 (34%) were classified as isolated and 161 (66%) as multiple. Over the nine-year study period, the average annual prevalence (per 10,000 live births) of all CH cases was estimated at 6.9 (95% CI=6.1,7.8) (Table 1), being highest in 2011 at 9.2 (95%

CI=6.6,12.8) and lowest in 2007 at 5.1 (95% CI=3.4,7.9) (Figure 1). Prevalence was estimated at 2.4 (95% CI = 1.9,2.9) and 4.6 (95% CI = 3.9,5.3) among isolated and multiple cases, respectively.

3.2 | Descriptive analysis

Frequency and percent distribution of selected infant and parental characteristics for CH cases and all live births are presented in Table 2. Findings from crude analyses examining the association between CH and selected infant and parental characteristics are presented in Table 3. Among all cases, the cPRs were statistically significantly higher for pregnancies with a plurality >1 compared to a plurality of 1. The cPRs also were significantly higher for infants with non-Hispanic Black fathers compared to non-Hispanic White fathers. Additionally, for multiple cases, cPRs were significantly higher for plurality >1 and non-Hispanic Black mothers and fathers, compared to their referent categories. Furthermore, the cPRs indicated positive associations for males and parental age at delivery (<20 or ≥35 years), although these estimates had CIs that included the null. The cPRs for education at delivery and parity were close to null.

Our findings from multivariable analysis (data not shown) tended to reflect those from the crude analysis, except for the association with maternal race/ethnicity. Among all CH cases, the adjusted findings still revealed a significant positive association with multiple gestation (aPR=2.5; 95% CI=1.5,4.1) and having non-Hispanic Black fathers compared to non-Hispanic White fathers (aPR=1.8; 95% CI=1.0,3.1). Findings from multivariable analyses for multiple CH cases were similar to those of all cases. The aPRs were significantly higher for plurality >1 (aPR=3.6; 95% CI=2.2,6.2) and for non-Hispanic Black paternal race/ethnicity (aPR=2.3; 95% CI=1.1,5.0), compared to their respective

referents; there was a slight decrease in the magnitude of associations for plurality >1 and paternal race/ethnicity in the adjusted analysis compared to the crude models. Separate multivariable analysis was not conducted for isolated CH cases because no significant associations were noted in crude analysis.

4 | DISCUSSION

We used data from a population-based, birth defect surveillance program in the US to estimate the prevalence of CH, spanning a nine-year birth period from 2003–2011. Prevalence of CH (per 10,000 live births) was estimated to be 6.9, and ranged from 5.1 in 2007 to 9.2 in 2011. Prevalence of isolated and multiple CH (per 10,000 live births) were estimated to be 2.4 and 4.6, respectively. We did not observe statistically significant differences in prevalence by infant sex. Both crude and adjusted analyses showed an excess risk of CH in pregnancies with plurality >1 and among infants with non-Hispanic Black fathers compared to their respective referents. Prevalence of CH was higher among non-Hispanic Black mothers for multiple CH cases in crude analysis; however, this association did not persist after adjusting for plurality and paternal race/ethnicity. We did not observe significant associations between multiple CH cases and other selected maternal factors such as age at delivery, education at delivery or parity, nor for paternal age at delivery.

Our contemporary CH prevalence estimate of 6.9 per 10,000 live births is comparable to that reported in a population-based state-wide study in Utah between 1940–1979 (7.0 per 10,000 live births) (32). Our prevalence estimate exceeds that reported in the previous California study (1991-2000) (5.9 per 10,000 live births) (27), but is less than that reported in the previous Hawaii study (1986-2000) (10.4 per 10,000 live births) (28). We

attribute this variability in prevalence to the racial/ethnic distributions of cases and live births between the populations in Iowa, and those in California and Hawaii. There also may have been some differences in study methods between the states that could contribute to observed the variation. Prevalence estimates stratified by isolated and multiple CH cases were not reported in previous US studies; however, Utah (32) reported a greater proportion of CH cases with other major birth defects, consistent with what we observed in Iowa.

The direction of the association between plurality and CH observed in our study is consistent with previous studies (7, 9, 28-30); however, the magnitude of our estimate (aPR=2.5) was slightly lower than those previously reported (aPRs ≥3.0) (29, 30). CH cases with other major birth defects had a higher aPR for plurality compared to all cases combined in our analysis. In contrast to some of the previous studies that reported statistically significant associations with maternal age at delivery (2, 9), race/ethnicity (2, 27), and parity (7, 31), we did not observe any maternal factor examined to be significantly associated with CH. We did, however, observe positive, non-significant associations for younger (<20 years) and older (≥35 years) maternal age at delivery and for non-Hispanic Black mothers compared to non-Hispanic White mothers. Our finding of non-Hispanic Black paternal race/ethnicity to be associated with CH is a novel finding. This association should be further examined as our study had missing data on paternal race/ethnicity for 17% of all cases and 14% of all live births. The lack of significant associations observed for male sex, maternal age at delivery, or parity and CH in our sample is inconsistent with previous findings (2, 7, 9, 27). These inconsistencies may be related, not solely, to differences in case ascertainment, case inclusion criteria for other surveillance programs, or attributed to sample size.

There were some limitations in our study. We were able to focus only on non-inherited risk factors of CH, as we conducted a surveillance-based study. Nonetheless, a high proportion of data were available for selected infant (sex, plurality) and maternal (age at delivery, race/ethnicity, education, parity) characteristics for all and multiple cases. Another limitation is that births in Iowa are predominately to non-Hispanic White mothers (>80%), and hence our prevalence estimates are generalizable only to those regions, especially in the Midwestern US, that have a similar race/ethnic diversity as our study population. Lastly, our sample size of isolated CH cases was small (n=83) which made it difficult to assess risk factors that may be associated with development of isolated CH in multivariable analysis.

There are notable strengths to our study. Our study is based on data collected by a population-based surveillance program that uses active, multiple-source, case finding and record abstraction. This allowed for comprehensive case enumeration for live births, stillbirths, and elective terminations of pregnancies due to birth defects, which minimized underestimation of total prevalence of CH. Additionally, record data abstracted for each case were reviewed by a clinical geneticist.

In conclusion, our findings, based on a robust surveillance program, estimated the prevalence of CH to be within the range previously reported in other US population-based studies. Some, but not all, of our study findings were consistent with previously reported associations with infant and parental characteristics, perhaps owing to variations in case inclusion criteria, surveillance methods, and sample size. Our novel observation of a strong association with paternal non-Hispanic Black race/ethnicity may be of importance or may be a chance finding. Future studies with larger sample sizes are needed to examine the

prevalence and risk factors for CH using a longitudinal study design and include data for other risk factors that were not available to us in from birth certificate data.

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TABLES

Table 1. Prevalence, per 10,000 live births, of congenital hydrocephalus by birth year, Iowa 2003–2011

Birth Year	Annual Number of CH Cases[a]	Annual Number of Live Births	Prevalence of all CH cases per 10,000 live births (95% CI)	Prevalence of isolated CH per 10,000 live births (95% CI)	Prevalence of multiple CH per 10,000 live births (95% CI)
2003	21	38,139	5.5 (3.6, 8.4)	2.6 (1.4, 4.9)	2.9 (1.6, 5.2)
2004	20	38,368	5.2 (3.4, 8.1)	1.3 (0.5, 3.1)	3.9 (2.4, 6.5)
2005	34	39,275	8.7 (6.2, 12.1)	3.3 (1.9, 5.7)	5.4 (3.5, 8.2)
2006	29	40,592	7.1 (5.0, 10.3)	3.2 (1.9, 5.5)	3.9 (2.4, 6.4)
2007	21	40,835	5.1 (3.4, 7.9)	2.7 (1.5, 4.9)	2.5 (1.3, 4.6)
2008	35	40,219	8.7 (6.3, 12.1)	2.5 (1.3, 4.6)	6.2 (4.2, 9.2)
2009	22	39,659	5.6 (3.7, 8.4)	2.0 (1.0, 4.0)	3.5 (2.1, 6.0)
2010	27	38,514	7.0 (4.8, 10.2)	0.8 (0.3, 2.4)	6.2 (4.2, 9.3)
2011	35	38,204	9.2 (6.6, 12.8)	2.6 (1.4, 4.9)	6.5 (4.4, 9.7)
Total	244	353,805	6.9 (6.1, 7.8)	2.4 (1.9, 2.9)	4.6 (3.9, 5.3)

Abbreviations: CH=congenital hydrocephalus; CI=Confidence Interval.
[a]Includes live births, stillbirths, and elective terminations for birth defects.

Table 2. Infant and parental characteristics of congenital hydrocephalus cases and all live births, Iowa, 2003-2011

	All live births (n = 353,805)		**All CH cases (n = 244)**		**Isolated CH cases (n = 83)**		**Multiple CH cases (n = 161)**	
Characteristics	n	%	n	%	n	%	n	%
Infant								
Sex								
Male	181,095	51.2	133	54.5	45	54.2	88	54.7
Female	172,709	48.8	106	43.4	36	43.4	70	43.5
Missing	1	0.0	5	2.1	2	2.4	3	1.9
Plurality								
1	341,341	96.5	222	91.0	81	97.6	141	87.6
2 or more	12,464	3.5	22	9.0	2	2.4	20	12.4
Maternal								
Age at delivery (years)								
<20	29,829	8.4	24	9.8	6	7.2	18	11.2
20–35	280,110	79.2	182	74.6	63	75.9	119	73.9
≥35	28,519	8.1	25	10.3	11	13.3	14	8.7
Missing	15,347	4.3	13	5.3	3	3.6	10	6.2
Race/ethnicity								
Non-Hispanic White	298,380	84.3	203	83.2	73	88.0	130	80.8
Non-Hispanic Black	14,019	4.0	13	5.3	1	1.2	12	7.5
Hispanic	26,102	7.4	14	5.7	6	7.2	8	5.0
Other	11,158	3.2	12	4.9	3	3.6	9	5.6
Missing	4,146	1.2	2	0.8	0		2	1.2
Education at delivery (years)								
<12	50,269	14.2	31	12.7	10	12.1	21	13.0
12	81,711	23.1	56	23.0	15	18.1	41	25.5
≥12	219,450	62.0	146	59.8	55	66.3	91	56.5
Missing	2,375	0.7	11	4.5	3	3.6	8	5.0
Parity								
0	108,932	30.8	72	29.5	26	31.3	46	28.6
1 or more	235,414	66.5	149	61.1	51	61.5	98	60.9
Missing	9,459	2.7	23	9.4	6	7.2	17	10.6
Paternal								
Age at delivery (years)								
<20	8,520	2.4	7	2.9	1	1.2	6	3.7
20–35	238,196	67.3	138	56.6	50	60.2	88	54.7
≥35	54,260	15.3	39	16.0	17	20.5	22	13.7

Missing	52,829	14.9	60	24.6	15	18.1	45	28.0
Race/ethnicity								
Non-Hispanic White	252,449	71.4	171	70.1	65	78.3	106	65.8
Non-Hispanic Black	11,687	3.3	14	5.7	2	2.4	12	7.5
Hispanic	22,173	6.3	16	6.6	7	8.4	9	5.6
Other	8,121	2.3	8	3.3	2	2.4	6	3.7
Missing	59,375	16.8	35	14.3	7	8.4	28	17.4

Abbreviations: CH=congenital hydrocephalus

[a]One case infant with recorded gestational age of 0 weeks set to missing.

Table 3. Crude prevalence ratios and 95% confidence intervals for associations between selected infant and parental characteristics and congenital hydrocephalus, Iowa, 2003-2011

Characteristics	All CH cases cPR (95% CI)	Isolated CH cases cPR (95% CI)	Multiple CH cases cPR (95% CI)
Infant			
Sex			
Male	1.2 (0.9, 1.6)	1.2 (0.8, 1.9)	1.2 (0.9, 1.6)
Female	Referent	Referent	Referent
Plurality			
1	Referent	Referent	Referent
2 or more	2.7 (1.8, 4.2)	NC	3.9 (2.4, 6.2)
Maternal			
Age at delivery (years)			
<20	1.2 (0.8, 1.9)	0.9 (0.4, 2.1)	1.4 (0.9, 2.3)
20–35	Referent	Referent	Referent
≥35	1.4 (0.9, 2.1)	1.7 (0.9, 3.3)	1.2 (0.7, 2.0)
Race/ethnicity			
Non-Hispanic White	Referent	Reference	Referent
Non-Hispanic Black	1.4 (0.8, 2.4)	NC	2.0 (1.1, 3.6)
Hispanic	0.8 (0.5, 1.4)	0.9 (0.4, 2.2)	0.7 (0.3, 1.4)
Other	1.6 (0.9, 2.8)	1.1 (0.2, 3.3)	1.9 (0.9, 3.6)
Education at delivery (years)			
<12	0.9 (0.6, 1.4)	1.1 (0.5, 2.4)	0.8 (0.5, 1.4)
12	Referent	Referent	Referent
≥12	1.0 (0.7, 1.3)	1.4 (0.8, 2.4)	0.8 (0.6, 1.2)
Parity			
0	1.1 (0.8, 1.4)	1.1 (0.7, 1.8)	1.0 (0.7, 1.4)
1 or more	Referent	Referent	Referent
Paternal			
Age at delivery (years)			
<20	1.4 (0.7, 3.0)	NC	1.9 (0.8, 4.4)
20–35	Referent	Reference	Referent
≥35	1.2 (0.9, 1.8)	1.5 (0.9, 2.6)	1.1 (0.7, 1.8)
Race/ethnicity			

Non-Hispanic White	Referent	Referent	Referent
Non-Hispanic Black	1.8 (1.0, 3.1)	NC	2.5 (1.4, 4.5)
Hispanic	1.1 (0.6, 1.8)	1.2 (0.6, 2.7)	1.0 (0.5, 1.9)
Other	1.5 (0.7, 3.0)	NC	1.8 (0.8, 4.0)

Abbreviations: CH=congenital hydrocephalus; CI=confidence interval; cPR=crude prevalence ratio; NC=not calculated.

FIGURES

Figure 1.